Evoked Potentials during Language Processing as Neurophysiological Phenomena

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Alas, here can't be a list. I'd forget somebody and could never forgive me. If you're reading this and think you should be listed here, you probably were in my thoughts as I was writing this and deserve to be on here. Granted, if you're reading the acknowledgements to my thesis, chances are you're my mom - in which case you *understand* - or my supervisor - in which case you'll be happy I didn't invest too much time in this I'd rather spend on orthography and triple-checking my references.

There are people whose birthdays I keep forgetting and who still call me on mine; who put up with me not calling for years, and still listen when I *do* call them all of a sudden; who see me every day, and put up with me still; who have the patience and tact when dealing with me I don't have in me to return; who accept all of my excuses and shortcomings and give me a second chance, and a fifth, and a seventh; who've indulged a seventeen-year old for decades; and honestly, I don't understand how they do it. And yet, if they were to stop, I'd complain, because I couldn't do without.

So - *thank you*.

Contents

1

BRAINS AND THE PERCEPTION-ACTION-LOOP

Neurons receive sensory data from afferent connections, deconvolute and transform it, and relay it to motor efferents, while constantly updating the connections determining this system. This basic structure allows a dragonfly to catch a subcentimeter target during a high-speed half-second flight, and a human to extract a speech signal from a noisy background, incrementally parse the unfolding sentence and respond by updating behavior and memory to be best equipped for future challenges of a dynamic environment. The major role of the brain can thus be described as implementing the perception-action-loop (Fuster, 2004; Fuster & Bressler, 2012). A key process in this cycle is the flow of information from low-level sensory cortices to temporal and occipital association cortices; then, information continues to flow along a caudo-rostral gradient. In this core process, posterior areas are better connected to, and primarily processing, sensory input, and central and anterior areas control output, but also an third important aspect of brain function: state control. Important recurrent connections and multi-level interactions happen along these pathways, facilitating memory persistence, temporal integration and hierarchical planning/control processes.

In simple organisms, the loop is quite trivial, with sensory afferents and motor efferents being closely connected. As organisms grew more complex, more and more of the brain became involved in another task than managing input and output: self-management. The complexity of the brain required a complex system of dynamically modulating brain states to be most appropriate to the current environment, by regulating attention and arousal.

The perception-action loop (See Figure 1.1) shows a basic spatiotemporal structure in the brain where feed-forward systems transmit and transform sensory input along a caudo-rostral gradient of increasing processing complexity (Bornkessel-Schlesewsky & Schlesewsky, 2013; Churchland & Sejnowski, 1988; Rauschecker & Scott, 2009) along a pair of pathways (the dorsal and ventral streams). In the other direction, top-down modulation of attentional focus, ressources and stream switching/reorientation stem from neuromodulatory input largely under control of the frontal cortex, travelling along an rostro-caudal gradient (Lee & Dan, 2012).

1.1 ELECTROENCEPHALOGRAPHY AND COGNITION

The first major technique for investigating the spatiotemporal structure of the neuronal activity underlying cognition was the Electroencephalogram (EEG). The methods applied in the present work are, at its heart, attempts to answer fundamental questions in brain research already present at the very

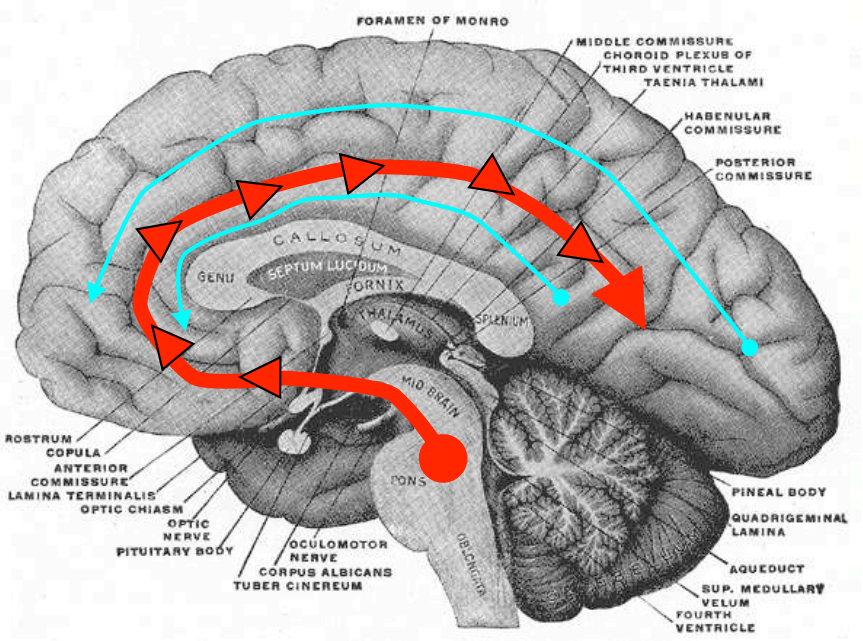

Figure 1.1: Rough schematic of the sensory feed-forward gradient (teal) and neuromodulatory state control gradient (red). Based on a public domain image.

beginnings of EEG investigations; how do systemic control and local processing interact to close the action-perception loop? Specifically, the present work implements contemporary signal processing mechanisms to examine the EEG during processing of and responses to language.

The first specifically language-related phenomenon, the N400 correlated with semantic processing, was demonstrated in 1980, by Marta Kutas and Steve Hillyard. The sensitivity of this component to semantic associations has been extensively studied, replicated and elaborated on in the following three decades (Kutas & Federmeier, 2011). In the 1990s, linguists became increasingly interested in the potential of applying the EEG method to the study of complex and subtle phenomena in the domains of structural processing, exemplified by Chomsky (1992):

> "There are certain states and properties of the brain which these theories exactly capture. The mental organs can also be viewed in other ways. For example, you can look at them in terms of cells or atoms. Or, more interestingly for the moment, you can look at them in terms of electrical activity of the brain, so-called Event-Related Potentials, ERPs. Now, rather surprisingly, there's some recent work which shows quite dramatic and surprising correlations between certain properties of the computational/representational systems of language, and of ERPs, Evoked Potentials. For the moment, these ERP measures have no status, apart from their correlation with categories of expression that come out of computational/representational theories. They're just numbers, picked at random. They don't have any, there's no relevant theory about them says look at these numbers

> and not at some other numbers. In themselves, in other words, they're curiosities. Still, it's interesting, because they do, there are correlations to rather subtle properties that have emerged in the attempt to develop computational/representational theories that explain the form and meaning of language. So that suggests an interesting direction for research, namely to try to unify these quite different approaches to the brain, to place each of them in an appropriate theoretical context, for the moment that's primarily a problem for the ERPs, but if you could pursue it, it could be quite an interesting direction, with lots of consequences." (Chomsky, 1992)

When, following the "semantic" N400, an ERP component responsive specifically to structural deviations was reported (Osterhout & Holcomb, 1992)[1], this "P600" was readily integrated into theories of language cognition. However, this step did not come in the form of the emergence of a theory of ERPs. Instead, ERPs are typically investigated in the form of a "zoo" of components (Luck, 2005), which researchers attempt to map onto concepts coming from other theories, such as structural computations in case of the P600. Thus, the "theory of ERPs" is generally not pursued as a neurobiological theory, but as the linking between surface phenomena and cognitive, psychological or linguistic atoms or constructs - attempts to locate (in time, but also space, that which has been argued to exist based on theoretical considerations.

1.2 OVERVIEW

This work proceeds as follows. First, a history of electroencephalography is given, with a special focus on the context and impact of the original discovery of the "Berger wave". This discussion will position key figures and developments in relation to the debate between systemic, holistic, procedural and dynamic accounts of brain work on one hand, and localised, atomic accounts on the other. I argue that the early history of the EEG can be understood as a clear example of a systemic phenomenon only visible to the holist's eye, as representing not the activity of a specific area, but system-wide *states*. However, it was quickly co-opted by localist researchers such as Wilder Penfield - very fruitfully, at that.
In the next chapter, mechanisms of controlling attentional state in response to the evaluation of input are described. Of crucial importance here are a number of anatomically defined systems, including the Dorsal and Ventral Attention Networks and the associated brain areas, but also a set of functionally defined, diffusely active systems: the neuromodulator projections spread throughout the brain. I then discuss how the EEG relates to these aspects of attention - functional, anatomical, chemical - by reviewing key components and positioning them with respect to these systems. I identify commonalities and substantial overlap between three "biphasic patterns", the ERN/P_E, the N2/P3 and the N400/P600. As an overarching framework, the Locus Coeruleus/Noradrenaline theory of the P3 (Nieuwenhuis, Aston-Jones, & Cohen, 2005) will be referred to as a model solution.
Then, I describe three of my studies which aimed to evaluate the fruitfulness of this theory of the biphasic patterns. The first employs Independent

1 The original stimulus sets employed in this study can however hardly be considered "subtle".

Component Analysis to argue that the brain systems active during sentence processing also activate during non-linguistic tasks. As a serendipitous finding, an early frontal negativity showing categorical sensitivity to semantic mismatches is observed. The second study replicates this latter finding in a novel sentence processing paradigm; the action-perception cycle is taken as the fundamental principle of brain activity. A range of exploratory analyses describe further task-related, domain-general systems shaping the EEG during sentence processing. The third study was very narrowly designed to test, using the paradigm developed in Study 2, if the P600 shows the same response alignment as does the domain-general P3 - a necessity if the two are to be associated via a common neurobiological foundation.
A final chapter discusses the implications and restrictions of these discussions and findings.

2

ELECTROENCEPHALOGRAPHY AND SYSTEMIC NEUROSCIENCE

2.1 BEFORE THE EEG: SYSTEMIC VERSUS LOCALISED BRAINS

The liver, the lungs, the spleen - some organs are made up of seemingly uniformly distributed cells all performing some systemic function. What about the brain? Following the pre-history of brain research (Gross, 1987), at the beginning of modern neuroscience stood the question of the localistic vs. holistic brain.

For the phrenologists, the idea that distinct parts of the brain hosted distinct cognitive aspects was given. To them, a criminal was a criminal, exhibited criminal behaviour, because the part of his brain supporting the "moral sense" was underdeveloped, also causing the overlaying cranium to be of disproportionate size. The phrenologist attempted to deduce individual cognitive and temperamental alignments from such cranial differences. The scientific basis for phrenology is usually traced to the "Cranioscopy" of the neuroanatomist Gall (Simpson, 2005; Zawidzki & Bechtel, 2004). Beyond such contributions to the philosophy underlying early neuroscientific research, he also introduced an influential method: using the newly developed *microtome*, he systematically cut the brain into thin slices, allowing following neuroanatomists, such as Paul Broca, to describe e.g. the fiber tracts connection brain areas.

Phrenology is now universally understood as a pseudoscience and even associated with "scientific racism" in popular culture; in Quentin Tarantino's "Django", the racist slave holder Candie applies phrenology to a black man as a sign for a cruel, uneducated past. Stephen Jay Gould characterises this approach as the *mismeasure of man* (Lewis et al., 2011). However, beyond this problematic aspect of his research, Gall developed neuroanatomic concepts and tools that are of crucial importance, including a focus on the cortical gyri, the grey matter, and slice-wise dissection of the brain. Furthermore, Jean Baptiste Bouillard, later famous as a mentor of Broca's, was strongly influenced by Gall (Simpson, 2005).

In opposition to such reductive and atomistic attempts to link physiology and cognition stood the *holistic* view on the organ of thought. The "aggregate field" of the brain was the concept at the heart of the holistic vision. Pierre Flourens (Yildirim & Sarikcioglu, 2007), experimenting with small animals such as frogs, disagreed with the phrenologist idea. In his animal studies, he was able to specifically damage certain low-level faculties by targeted lesions, such as breathing or motor balance. However, he was unable to specifically damage higher cognitive facilities such as memory or will.

When damaging the cortical hemispheres themselves, lesioned animals either appeared to continue behaving normally, if the lesion was small; or rather, stopped any behaviour whatsoever, if the lesion was large. Lesion size, not lesion location, seemed to determine the damage, seemingly disproving cortical localisation (Riese & Hoff, 1951). Flourens concluded that while simpler functions must be localised, the hemispheres and part of the brain stem work as a whole organ, where everything does everything, also called equipotentiality. In a similar experiment in 1881, Goltz had lesioned what was then already considered the motor cortex of a dog. The animal was still capable of walking, even running (Mundale, 2002).

Ironically, it has been argued (Hakosalo, 2006) that even the cross-sections of brain tissue introduced by Gall turned against the localist view when these thin slices were used to attack Meynert's localist perspective, which relied on insights gained from the older defibering technique.

A substantial argument for brain localisation came from the works of Paul Broca and Carl Wernicke, perhaps the early neurophysiologists best known to researchers of language. Operating in the middle and end of the 19th century, both had found individuals who, after a traumatic injury to the brain, exhibited distinct (and different) behavioural/cognitive impairments. Broca's patient Tan, with damage including what is now known as Broca's area in the left inferior frontal gyrus (lIFG), had extremely limited abilities to produce speech, but seemingly intact speech comprehension abilities. Broca interpreted this to mean that the lIFG hosted the faculty of speech. A tiny swath of cortex, he proposed, could allow a major, and distinct, human ability.

In a similar vein, Korbinian Brodmann undertook the task of cartographing the brain based on local cell type distribution. He found that the cortex was cytoarchitectonically compartmentalised, and gave each of these 52 compartments (in either brain hemisphere), spanning a few cm^2 in size, a number. Broca's area is found at Brodmann's Areas 44 and 45.

Further support came from stimulation studies in animals by Fritsch and Hitzig, who implemented early experimental work on the somatotopic motor homunculus (Riese & Hoff, 1951).

An important opponent of the localisation of speech to the lIFG, and localisation in general, emerged in Pierre Marie (Brais, 1992). Marie built on a large sample of over 100 aphasic patients to argue that the association between the lIFG and aphasia was not nearly as reliable as Tan had led Broca to believe (for a similar contemporary argument see Dronkers, Plaisant, Iba-Zizen, & Cabanis, 2007; Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004), and argued his point with so much vigour that he was finally met with ignorance or even outright hostility (including being challenged to a duel over a scientific publication). Beyond his unprofessional manners, Marie also found that Tan's brain featured extensive lesions, reaching far beyond just the lIFG.

One of Marie's arguments against brain localisation, especially of linguistic faculties, has recently been elegantly restated. Marie contended that a faculty so young and still rare as reading and writing could have hardly resulted in the evolution of a specific brain compartment dedicated to writing, a position echoed by recent work on the recycling of cortical maps (Dehaene et al., 2010). And if a filigrane and complex system such as reading, impossible for all animals, required no dedicated brain system, why should speech, or anything?

At the end of the 19th century, the question of the systemicity versus locality of brain function was still a major topic in the study of the nervous system, though the consensus began to become heavily weighted towards a localist view. The discussion began to include the fine structure of the brain, the cell level. The prevalent view had been that the nervous system was one continuous, interconnected organ. Ramon y Cajal presented the dissenting "neuron doctrine", according to which the nervous system was comprised of myriads of distinct cells - neurons; and at the contact points between these neurons, gaps. Indeed, Willhelm His observed such gaps (the synaptic cleft). Cajal was awarded with a Nobel prize in Physiology and Medicine in 1906, together with Golgi, who had been a holist and fierce opponent of the Neurone Doctrine, but whose preparation/staining methods had allowed Cajal's observations.

Even before his Nobel Prize, the portugese Cajal had been invited to Britain by Sir Sherrington to present this view, and his clear silver-staining pictures demonstrating the boundaries between individual central nervous system cells. Sherrington had been at the centre of the localist/holist debate from the beginning of his career. In the second half of the 19th century, British scientists formed a committee to settle the issue: was the brain a systemic whole, or could specific functions be attributed to specific locations? It was decided to surgically lesion one hemisphere of a dog brain and document the resulting behavioural changes. Sherrington was the student tasked with conducting the experiment. Observing that the dog's behaviour was *selectively* impaired, he published a report that demonstrated the hemispherization, and thereby, presumably, the localisation, of brain functions.

When Sherrington was invited to write Part III of the *Textbook of Physiology*, about the nervous system, he had to come up with a word for the boundaries between neurons that were known from Cajal. He decided on the word "synapse".

In 1932, Sherrington, together with Lord Adrian, was awarded with the next Nobel Prize for Medicine and Physiology, in part for his contributions to "cerebral localisation".

2.2 THE DISCOVERY OF THE EEG AND THE STUDY OF THE PHYSIOLOGICAL CORRELATES OF COGNITION

Sherrington's synapses not only connected neurons, they also implemented unidirectional boundaries, paving the way for the localisation of cognitive functions analogous to how metabolic functions had been localised to the body's organs. The "where" question became the primary focus of research on the central nervous system, and many important discoveries were made. Two decades after the neurone doctrine, the German physician Hans Berger (Millett, 2001) presented the first fruitful method allowing the investigation of the temporal and, eventually, the spatiotemporal dynamics of brain work.

Beginning his research at the turn of the 19th century, Berger, working in a psychiatric clinic, was not only the first person to record human scalp EEG, but also one of the first researchers on cerebral blood flow in relation to cognitive states. Investigating physiological correlates of mental states with human patients at the beginning of the 20th century, Berger assumed that the cerebral blood could be informative regarding brain activity. He proposed that the brain's metabolic requirements exhibit task-sensitivity. Then,

cortical blood flow, as measured by the pulsing of blood vessels, could give insight into cognitive mechanisms.

Therefore, Berger measured pulsation rates over post-surgical holes in the skull while his subjects were guided through various cognitive states (Gloor, 1994). Indeed, he found relations between state and pulsation rate, which he could connect to cognition-related brain metabolism. That neurons required oxygen to function had been established by Sir Sherrington in 1890. Thus, Berger's work was in fact amongst the early precursors of functional magnetic imaging research, which relies on the BOLD (Blood Oxygen Level-Dependent) effect of cognition/brain metabolism correlations.

Together with Brodmann, he also attempted a first study of psychopharmacology and cortical blood flow by administering cocaine to patients with skull resections.

Berger (1913) published his (modest) findings in a publication with a programmatic title for the following century of neuroimaging:

> "Über die körperlichen Äusserungen psychischer Zustände. Weitere experimentelle Beiträge zur Lehre von der Blutzirkulation in der Schädelhöhle des Menschen"
>
> About the physiological expressions of psychological states. Further experimental contributions to the science of blow flow in the human cranium. (my translation)

Berger's interest in measuring such physiological expressions of psychological states resulted from his understanding of the law of conservation of energy (Gloor, 1994; Millett, 2001). Descartes had assumed an immaterial mind influencing the body, but Berger rejected dualism. Yet if it was the physical brain that controlled the body, then, by Newton's law, these processes must result in the release of energy - and energy one should be able to measure. So Berger set out to study *"psychic energy"*. The expectation that energy expenditure by the brain should reflect in increased metabolism had originally inspired in the blood flow studies.

Berger was dissatisfied with the results of his observations of cortical pulsations, as well as with attempts to measure cortical currents in animals. At the age of 51, still fascinated by the possibility of measuring *psychic energy*, he began experimenting with electroconductive electrodes. On the 6th of July 1924, he first measured the current flow on the scalp of a young man, parts of whose skull had been resected months before on the suspicion of a tumor. Berger applied two electrodes to the scalp of the patient close to the resection, amplified the potential difference between the two electrodes, and translated this current flow into the writings of a mechanical pen. Berger expected to find current flow that he interpreted to represent neural activity - and indeed, he observed a systematic pattern which he was convinced represented the brain's activity (See Figure 2.1 for an example).

For these early recordings, he punctured the skin and periosteum of patients, which, as he writes, was only possible using local anaesthetisation. At first using zinc-steel electrodes, he later proceeded to using silver electrodes with silver chloride-coated tips giving him superior results; similar Ag/AgCI electrodes are still standard equipment in 21st century research. He switched between invasive needle electrodes and foil or flat electrodes. His initial subjects were instructed to trim their hair, or Berger attempted to

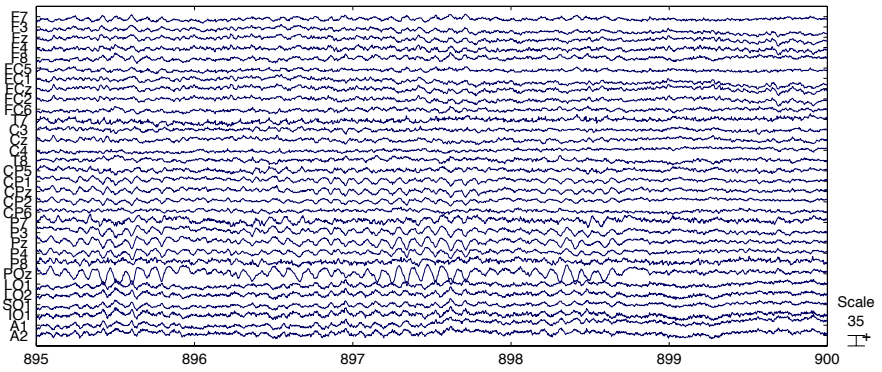

Figure 2.1: Example of α wave activity (see especially Channel POZ). Data has been cleaned of line noise and eye artifacts using ICA.

measure over hair-free sections, achieving impedances as low as 150 kOhm (Collura, 1993), much more, but within an order of magnitude of the often less than 10 kOhm typical of 21st century recordings.

At first exclusively experimenting with patients with partial skull resections, which there were many of in the wake of the first World War, Berger conducted the first human scalp EEG recordings using a bipolar montage, applying two electrodes at various scalp sites. First, he placed electrodes primarily at scalp sites where, after the patient had healed from surgery, only soft tissue covered the brain, but later, he reported that the EEG could also be recorded from the intact skull - allowing the recording of the brain activity of virtually any human being. The first non-resected subject whom he successfully recorded an EEG from was his own son Klaus. With more experience, he was able to abolish the invasive needle electrodes which had to puncture the skin and use non-penetrative electrodes instead. He measured multiple patients of his, preferentially displaying the potential between a forehead and a midoccipital electrode.

Already separated from his localist colleagues due to his interest in parapsychologic phenomena (Millett, 2001), his very basic setup necessarily necessarily had to treat the brain as a whole system; a bipolar montage results in only one time series for the potential difference between both electrodes. Berger described both the resting state of the brain, and its reaction to perturbations by an external event. His results consequently described a non-localized *temporal*, or, more specific, an *oscillatory* nature of brain activity - both because brain activity, as is better known today, is at least partly periodic, and because his techniques did not allow for any other finding; it was mostly blind to the spatial structure. The findings were quite different from what any localist might have looked for.

Berger had recorded the potential between just two electrodes, resulting in just one outcome: a single time series, reflecting the potential difference between the two electrodes. Since the discovery of the multichannel differential amplifier by Berger's contemporary and critic Jan Friedrich Tönnies in 1932 (Eccles, 1971), the EEG is commonly recorded with this system that compares the potential between multiple measurement and one reference electrode (or rather, the difference between electrode minus ground and reference minus ground). It would not make sense to arbitrarily assign one

of Berger's two electrodes the label "reference". His apparatus would simply sum the whole cortical activity in between two points, allowing only the broadest, most general and distributed processes to emerge. Berger noticed that the measurements did not change significantly if he moved one electrode. Underestimating the importance of referenced recording and volume conduction, Berger drew from this the conclusion that whereever he measured, the underlying cortex was engaged in roughly the same activity - that the brain was indeed to be viewed as one single quasic-atomic, wholistic complex.

Today, it is usually recommended (Schiff, 2005) to use a "quiet" reference electrode. But the differential amplifier comparing the electrode minus ground to the reference minus ground potential had not been invented yet, disallowing Berger from using any sites but scalp sites; if he used an arm or chest reference, he would always measure a signal that was heavily contaminated by ECG and EMG influence, and reflected cortical activity only to a small degree.

Berger was also the first to recognize and control the potential for heavy artifactual contamination of scalp-recorded EEG data, co-recording EKG traces and noting that a potential EEG correlate of seizure activity could also represent facial twitches.
He also investigated if the EEG was sensitive to respiration. Previously, Mosso (H. Berger, 1931a) had shown that regional blood flow was correlated with deep breaths (again analogous to later fMRI research); however, no such effect was found for the EEG.
Only after controlling for a range of possible aspects, Berger was finally convinced that his measurements actually represented brain activity and dared going public with his observations.

In 1929, Berger first published his findings *"Über das Elektroenkephalogramm des Menschen"*, and over the next two decades, he followed up with a series of "Mitteilungen" (Berger, 1929; H. Berger, 1931b; 1931a; including Berger, 1932; H. Berger, 1933a; 1933b; Berger, 1934; H. Berger, 1935a; 1935b; Berger, 1936; 1938). In the first "Mitteilung", his main finding concerned what he called the *"alpha"*/α rhythm. At rest, most of his subjects induced a periodic activity with a frequency of around 10 Hertz in his pen writer apparatus. This rhythm appeared wherever he placed his electrodes. However, when their resting state was perturbed, for instance by instructing them to perform calculations, or by a touch, the α rhythm disappeared, to be replaced by a faster rhythm Berger called "beta"/β. Berger assumed that it too reflected a cortex-wide state.

Like many of Berger's findings, this observation is still the subject of ongoing investigations. It is now well established (Pfurtscheller & Lopes de Silva, 1999) that critical task stimuli induce event-related desynchronisation of the α band (ERD), and concurrent synchronisation of the β band (ERS); a similar phenomenon, sometimes called "mu"/μ blocking (Makeig, Delorme, et al., 2004), occurs with motor-associated oscillations around 10 hz that are not strictly correlated with α before responses to critical events.

Berger (1929, p. 530) emphasised the difference between

> "*ständig vorhandenen Strom*, der von der Hirnrinde abgeleitet werden kann, und seinen *Veränderungen bei peripheren Reizen*" (emphasis Berger)

> *constantly ongoing electric current* that can be measured at the cortex, and its *perturbation by peripheral stimulation* (my translation)

This fundamental difference between "background" and "evoked/induced" activity is still at the heart of EEG research.

For the first decade after his discovery of the EEG, Berger was mostly ignored or perceived as an outcast by colleagues both at home and overseas. The then-current Sherringtonian psychophysiologic dogma still emphasized localized research, not systemic temporal patterns, and emphasised rationally-minded investigations of physiological phenomena, not seemingly metaphysical speculation. Berger's reports about whole-brain states as correlates of purely internal mental processes which he connected to parapsychological phenomena must have seen suspicious to his colleagues, who described psychophysiological processes of perception and movement and their relation to subsets of the central nervous system.

Thus, the research of Berger's contemporaries was by necessity primarily animal based, their primary goal, to localize brain functions, broadly in the vein of prior localist approaches, like Broca's localization of the faculty of speech by investigating the behavioral correlates of a spatial phenomenon, a brain lesion.

Berger however assumed that what he called the α rhythm, and what was, when first replicated, called the "Berger rhythm" by his colleagues (Adrian & Matthews, 1934), reflected non-centralized, systemic activity (though Walter, 1936 applys the name "Berger rhythm" to the EEG as a whole, distinct from α). He had proposed that every part of the cortex could exhibit the 10 hz oscillation, the brain working as an undivided whole (Berger, 1938):

> "Ich halte jedoch für eine Reihe von Untersuchungen die Ableitung yom Schädel als Ganzes für aufschlußreicher, da meiner Ansicht nach das menschliche Großhirn als einheitliches Ganzes tätig ist."
>
> I think however that for a number of investigations the measurement from the skull as a whole to be more informative, since in my opinion, the human cerebrum works as an undivided whole.
>
> (Berger 1938, p. 418, my translation)

He even performed the first spectral analysis of the EEG (H. Berger, 1931b; Dietsch, 1932), applying a Fourier transformation to recordings containing α waves.

Berger, who, by all accounts, was not especially informed about electrophysics, assumed that finding α rhythms at multiple scalp sites would be indicative of α rhythms being generated by the directly underlying brain sites. In addition to the double handicap of going against the mainstream (Riese & Hoff, 1951) while lacking a strong methodological base, the spread of Berger's ideas may have been hindered by his parapsychological leanings that again associated the anti-localist perspective with nonscientific approaches, in contrast to the dominant localist paradigm with its claim for scientific rigor.

Furthermore, previous recordings of the current flow directly at the exposed cortices of animals had not resulted in any activity as clearly regular as

Berger's α. This made his findings even harder to accept by the Sherringtonians, contributing to the fact that Berger found himself practically ignored by the international community for the first decade following his discovery (Borck, 2006; Haas, 2003), similar to the reception of Caton's earlier work on electrophysiology.

2.3 THE EEG IN THE HANDS OF THE SHERRINGTONIANS

Later researchers, especially Lord Adrian and William Grey Walter, connected the EEG to the Sheringtonian framework of brain localisation, performing spatiotemporal investigations of the EEG. The EEG especially gained credence from the localisation of brain tumors from δ wave activity - a conjunction of oscillatory research and localising research, the spatiotemporal dynamics of (in this case aberrant) neuronal patterns.

Localising tumors as sources of δ activity was proposed and realised in the 1930s by William Grey Walter (Bladin, 2006; Walter, 1936). Grey Walter measured the EEG using multiple electrodes and relayed their output into multiple oscilloscopes, thus painting a picture of the living brain's spectral topography (See Figure 2.2 for an example). He contributed findings that still influence contemporary understanding of the nature and source of the EEG. Based on his measurements, he concluded that multiple localised cortical rhythms contributed to the potential measured at scalp sites. The appearance of an unitary α rhythm is a result volume conducted mixing of these local phenomena.

Grey Walter also discovered one of the main non-oscillatory brain phenomena: the near-DC Contingent Negative Variation, a slow vertex-negative shift preceding expected events. In line with Berger's fascination with parapsychology, even Grey Walter's *Nature* paper about the CNV reported that the research had been funded in part by the *Parapsychologic Association of New York*, indicating that the EEG was still only partially a topic of serious scientific investigations.

Grey Walter had been preceded in his research by Lord Edgar Adrian, who had earlier received the Nobel prize together with Sherrington. He was the first to publicise, after some failed attempts, his replication of Berger's findings, giving them the credibility of a Nobel laureate (who had his own α waves recorded and printed).

Adrian traced the α rhythm to a fairly stable source in the occipital lobe, against Berger's assumption of systemicity, using early source localisation techniques. First, Adrian recorded consecutively with multiple placings of either two or four electrodes (leading to one or two signals at a time). He then analysed the α rhythm in the phase domain with the four-electrode, two-signal recordings, comparing different locations, and noticed that different sites did not show identical α phase. This he interpreted to indicate on one hand, the possibility of travelling waves originating in the occipital lobe; and on the other hand, connecting Berger's finding to the Sherringtonian localisation, as an indication of a distinct generator. Volume conduction by one specific source somewhere in between two sites could create the signal at both frontal and occipital electrodes.

Also, when he measured that in two patients with skull resections over the temporal cortex, the rhythm was especially restricted to the occipital parts,

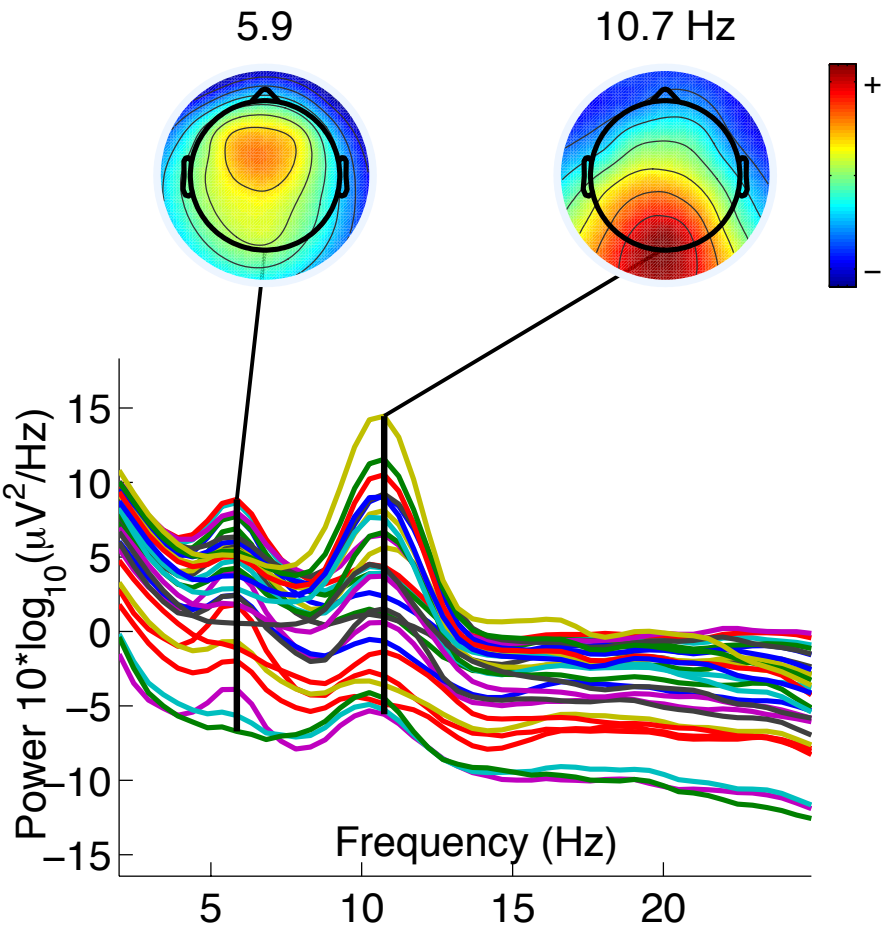

Figure 2.2: Example of the topography of α and θ oscillations from the same subject as in Figure 2.1. The occipital focus of the former and the clear mediofrontal center of the latter are clearly visible. Data has been mastoid referenced and cleaned of artifacts.

which he interpreted to result from the escape of an occipitally generated current through the hole instead of spreading to frontal sites. Finally, he measured that the amplitude of the α rhythm was at its maximum at occipital leads - a non-trivial task without a multi-channel differential amplifier. By carefully comparing the relative amplitude of α at multiple sites, he triangulated the rhythm to the occipital lobes, compatible with the fact that it was strongly modulated by the visual perceptions of the subject (it was already known at this time that occipital cortices were essential for vision); introduction of visual stimulation abolished α, especially "sharp contrasts nearer the central part of the [visual] field" (Adrian & Matthews, 1934, p. 368).

Importantly, Adrian had to combine both spatial and temporal measures to arrive at his conclusions; without the observed frontal-occipital phase inversion, his research would have been inconclusive. Grey Walter also relied on phase relations in his observations.

Adrian could also explain why direct recordings from the animal cortex had not produced the Berger rhythm: it was an *intermediate-scale* phenomenon, originating from the summed current flow of large neural populations, the convoluted activity of many neurons low-pass filtered by the distant electrode site. In contrast, the more localised direct recordings had primarily found the higher-frequency, less-regular output of smaller cell groups. Indeed, Adrian could show α by measuring the scalp EEG of a patient soon to undergo surgery for a suspected tumor, but when he applied the same electrodes directly to the exposed cortex at the equivalent locations during the operation (nowadays called Electrocorticography, or ECoG), he saw the same unstable high-frequency signal as was observed in animals.

A further, and probably the most, important field for the clinical application of the EEG became epileptology. In 1935, Lennox reported the first convincing ictal EEG, characterised by δ activity (Bladin, 2006). Ictal EEG is still considered a, or even the, major neurophysiological diagnostic tool in the diagnosis of epilepsy (Tatum et al., 2008).

Herbert Jaspers read the reports by Adrian and Berger, replicated their findings (Jasper & Carmichael, 1935), and decided on further investigations. This lead directly to Jaspers' and Wilder Penfields' successful fine-grained mapping of the human cortex using ECoG, including the somatotopic representation, and their groundbreaking work in the surgical treatment of epilepsy (Penfield, 1959; Vannemreddy, Stone, Vannemreddy, & Slavin, 2010).

Adrian also speculated that, because the relative amplitudes would change over time, multiple generators with distinct time course contributed to the scalp signal, turning on and off based on cognitive demands. He even had X-ray recordings of his subjects made, preceding the later use of EEG/MRI-coregistered source localisation; and implanted artificial sources in a recently deceased cadaver to estimate the reliability of his localisations.

Thus, while Berger had stressed the uniformity of the EEG at multiple scalp sites, Adrian and Walter exploited its non-uniformity at different electrodes. Electrodes, the sensors capturing the brain-generated signal, capture the mixed projections of broad patches of cortical systems to different degrees (Nunez & Srinivasan, 2010). Since even under the most reduced form of brain localism, not all of these systems can be assumed to be perfectly synchronised, and since synchronisation shows frequency dependence (higher

frequencies being more localised than lower frequencies), this mixing process works as a low-pass filter in the temporal domain (Duun-Henriksen et al., 2013), which primarily affects the spectrum above 20 hz. Higher spatial resolution allows, given an appropriate nature of the underlying system, not only to reconstruct the higher-frequency activity, but also to reconstruct what can appear as a broad, global, low-frequency pattern as a superposition of multiple underlying distinct, but interacting patterns stronger localised in space and time. Berger had recorded with one electrode-reference pair; Adrian with three or four simultaneous electrodes which he systematically moved around on his subject's heads; modern systems range from tens to hundreds of electrodes.

2.4 BRAIN BASIS OF ELECTROPHYSIOLOGICAL ACTIVITY

2.4.1 *Space: Network Scale and Levels of Analysis*

David Marr (Marr, 1982) famously proposed that cognitive investigations must take serious the issue of *levels*. This approach has often been understood as implying that an investigation of, for example, the computations performed in the process of e.g. perception can happen independently of an investigation at the algorithmic or implementation levels, and in fact each level *must* be analysed separately for knowledge to be gained (Poeppel, 2012; Poeppel & Embick, 2004).
This perspective has not been universally accepted (Churchland & Sejnowski, 1988; Elman, 1998). Even Marr's co-author Poggio (2012) has felt the need to specify that Marr's framework was not intended to afford the investigation of levels in isolation, but rather in integration.
However, any given neuroscientific method is only ever able to investigate brain activity at a certain *scale* (Churchland & Sejnowski, 1988; Churchland & Sejnowski, 1990), and smaller or larger systems may be inaccessible to this level. No analysis of only a single level can explain brain work or human cognition, or even the activity at this level alone (Bell, 2007). Events at one level can only ever be fully understood by putting it in context with events at the supervenient and the enclosed levels. Consequently, to understand the information contained in the EEG, a rough sketch of its relationship to brain organisation at other levels is required.

At the lowest (relevant) level, neurons generate the action potentials that relate input between afferent and efferent, and in doing so, generate electrical fields which are then picked up by the EEG (Kutas & Dale, 1997). However, single neurons are only of restricted interest and accessibility to EEG researchers, since due to their size, their contribution to the electric field measured at the scalp is lost in noise. The skull and the surrounding soft tissue greatly attenuate the electric fields inside the brain (by orders of magnitude), as had already been presented by Grey Walter (1936). More importantly, the surrounding neurons all generate their own electric fields. Furthermore, due to the spatiotemporal dynamics of action potentials, they will only rarely result in scalp-measurable effects. Rather, the EEG is most likely mostly sensitive to postsynaptic potentials (Niedermeyer & da Silva, 2012).
Consequently, what the EEG measures is primarily the degree of synchronisation in underlying groups, or networks, of large numbers of neurons.

Thus, it is less neural physiology, but neural connectivity and networking that is relevant for the shape of the EEG.

Pyramidal cells, the most important cell type in cortical grey matter, are conical cells with an at least partially straight axon along which spikes propagate. They are tightly interconnected, insofar as the average path length between cortical neurons might be as low as three (Freeman & Breakspear, 2007).

Locally, groups of 10s to 100s of neurons connect to form microcolumns (Buxhoeveden, 2002; Jones, 2000). At least in primary sensory areas, microcolumns show fine-grained feature-level sensitivity (Hubel & Wiesel, 1962). Only highly invasive methods allow investigations at this level. Beyond single neuron groups, the major unit at a mesoscopic level of the brain, at a mm^2 scale, are macrocolumns, consisting of hundreds of microcolumns.

On the macroscopic level, visible to current non-invasive research, the cortex is divided into areas (like Brodmann's Areas/BA's, based on cytoarchitectonic patterns), of which usually (depending on the employed mapping) a handful (52 in the case of BA's) are distributed across each of the cortical gyri and sulci. These in return make up the four brain lobes. The lobes are symmetrically arranged along the saggital plane, with one of each (frontal, parietal, temporal and occipital) in each hemisphere. The subcortical structure of the brain consists primarily of the limbic system and various nuclei, though these are rarely thought to directly reflect in the EEG due to their distance from the scalp (although they likely, as will be discussed later, establish an essential indirect effect). It is on the macroscopic level where most functional attributions to localised centres have been made. Brodman Areas, or subdivisions of BA's into a handful of parts, are usually the basic "unit" of brain localisation when neuroimaging findings are verbalised (beyond giving exact voxel coordinates, e.g. Talairach coordinates; predictions in brain imaging research are not formulated by referring to such sub-mm^2 - scale units, but to the broader, cm^2 - scale level BA's or BA divisions). Dehaene & Cohen (2007) propose the term *"cortical macromap"* for this level of investigation.

The most optimistic possible spatial resolution of the EEG has been estimated to also be at the cm^2 level (Churchland & Sejnowski, 1988; Makeig & Onton, 2012; Nunez, 2000; 2002). However, due to practical methodological concerns, especially with regards to realistic and individual head models and the fundamental indeterminacy of the problem (Acar & Makeig, 2010; Luck, 2005; Niedermeyer & da Silva, 2012; Nunez, 2000), a more realistic upper bound for localizing EEG effects is somewhere between the level of lobes and BA subdivisions/cortical macromaps. A recent comparison of coherence between intracranial and subdural electrodes (Duun-Henriksen et al., 2013) indicated smaller areas do not contribute significantly to the EEG.

It is then this level that has to be understood to properly interpret EEG data. Of course, higher-level phenomena must emerge from low-level systems; the activity vector of a macrocolumn must be the weighted sum of the activity vectors of its microcolumn members, and the activity of a BA must somehow emerge from the individual neurons and synapses it hosts. However, a complete model of brain dynamics from the lowest to the highest levels is far outside the possibilities of contemporary neuroscience (Bell, 2007). Furthermore, current research converges on the possibility of describing EEG phenomena mostly in reference to macroscopic phenomena while

still holding true to the principle of emergence by offering solutions realistic down to the neural level.

As noted, while the EEG is principally sensitive to action potentials, it is currently assumed that mostly dendritic input, post-synaptic potentials (PSPs), are reflected in the EEG, not axonal activity (Makeig & Onton, 2012; Niedermeyer & da Silva, 2012; Nunez, 2002). Roughly speaking, this means that the EEG may be most sensitive to the input to a brain region, less the output (though note the previous comments on network locality and the high interconnectedness of brain regions)[1].

Furthermore, most EEG recording should be dominated by cortical activity, primarily since subcortical sources are too far from the scalp to create a focused electric field (Hari, Parkkonen, & Nangini, 2010).
Finally, the EEG is usually assumed to reflect PSPs of cortical gyri. Due to the parallel alignment of neurons in the cortical sheet, perpendicular to the surface, the strongest sources of the EEG (in contrast to MEG) come from groups of gyral neurons, which receive sufficiently similar synaptic input to demonstrate synchronized PSPs, and are sufficiently close to the surface (other than sulci). Alternatively, different gyri receiving input from or being synchronized by a low-latency shared source may be considered functionally equivalent to a large group of adjacent neurons (Makeig & Onton, 2012). Consequently, sources of the EEG must not reliably reflect cytoarchitectonically coherent sources (brain anatomy), but functionally similar structures, or structures receiving similar shared (subcortical, thalamic . . .) input (brain function).

2.4.2 *Time: Synchrony and Coordination*

In one of the principal works of neuroscience in the 20th century, Donald Hebb (Hebb, 1949; Sejnowski, 1999) introduced the functional principle of cognition and brain dynamics: self-organization of groups of nerve cells representing associative learning. Hebb can be associated with the localist perspective (Brown & Milner, 2003); he criticized tests of general intelligence for patients with brain insults, assuming that localised lesions should result in specific, not general deficits. His self-organised cell assemblies lend themselves primarily to a theory of local interactions. Yet, the work of Berger had a "profound effect" (Hebb, 1949, p. 47) on him, and he assumed a primary role of functional neurophysiology in psychology.

Hebb proposed a function of neurons that has later been neuroanatomically confirmed as a guiding principle of neuronal behavior: spike-time dependent plasticity (Song, Miller, & Abbott, 2000). If the presynaptic neuron repeatedly fires before the postsynaptic neuron, meaning, if a neuron contributes to the firing of a downstream neuron, their synapse is strengthened; if the postsynaptic neuron reliably fires before the presynaptic neuron, the synapse is weakened, a process described by *Hebb's law*. Over time, associated cells then form cell assemblies, small, functional units of neurons all sharing excitatory connections.
Functionally, they reproduce associations learned by temporal/causal association.

1 The same probably holds for fMRI (Logothetis, 2002).

Local synchronisation can arise from such local connections, especially by inhibitory control (Wang, 2010); when the interneurons in a local system are thusly coordinated, increased neuronal activity will lead to an increased EEG signal at electrode sites sensitive to this system. However, quasi-local quasi-synchronisation can also arise via systemic mechanisms, such as subcortical drive. One brain function analysed in a systemic fashion is arousal and attentional modulation. The role of neuromodulators in regulating arousal and attention is discussed in detail in chapter 3.

While the brain is highly interconnected even at large distances, most connections are short and local. At the EEG-relevant mesoscale level, EEG-relevant units (like macromaps, groupings of macroscopic numbers of cells in the range of hundreds of millions to millions of millions of neurons or more) have been assumed to be both significantly synchronized at intermediate frequencies (1-20 hz) due to the propagation speed of neural activity (Makeig, Debener, Onton, & Delorme, 2004; Nunez & Srinivasan, 2010; Wang, 2010), and to be significantly distinct from surrounding areas.
Indeed, using combined micro- and mesoscopic measurements, Duun-Henriksen et al. (2013) observe that intermediate-frequency oscillatory coherence characterises medium-scale patches of cortex. At smaller scales, activity does not appear as synchronous oscillations, at least not in such frequency bands, and at larger scales, coherence is lost. Oscillatory coherence then appears as a systemic, emergent, mesoscopic phenomenon.

Either due to local or distant interactions, neurons, in response to environmental stimuli and task demands, form both local functional cell assemblies, and somewhat stationary local cell groups (Nunez, 2000), and these cell assemblies dominate cortical signal processing. Interestingly, local interactions in the form of Hebbian cell assemblies are unlikely to determine the event-related potentials (ERPs) aligned to critical events.
Action potentials are short-lasting in contrast to PSPs (Kirschstein & Köhling, 2009). By itself, this entails a lesser contribution to the scalp field, but it is also important in relationship to the scale of local connectivity. Large groups of neurons, large cortical patches, are required to fire in synchrony to result in a scalp field. Action potentials travel along the axon in a biphasic manner. Precise phase alignment of neurons however only occurs at small scales. The action potentials of large groups of neurons will therefore result in a near-zero potential at the scalp, as short-lasting action potentials, in their positive and negative phases, are slightly out of phase with each other. Then, as noted, longer-lasting post-synaptic potentials (PSPs) are assumed to be the source of the ERP (Elbert & Rockstroh, 1987; Kotchoubey, 2006; Niedermeyer & da Silva, 2012).
A generalisation of the relationship between the ERP at a certain site and the activity of the directly underlying tissue was proposed by Elbert & Rockstroh (1987). Synchronized excitation (EPSPs) of apical (long distance, white matter-crossing) dendrites and/or inhibition (IPSPs) of basal (short distance, cortico-cortical) dendrites cause a scalp-negative current flow. Inhibition of apical or excitation of basal connections cause a positive current flow. Local cell assemblies are comprised of apical and basal fibers. In cell assembly synchronisation, reflecting both apical as well as basal activity, the concurrent positive and negative current flows cancel each other out. In contrast, thalamocortical afferents exclusively consist of apical fibers. Consequently, thalamo-cortical afferents are probably the major contributor to the ERP. In contrast, thalamo-cortical and cortico-cortical *feedback loops* are assumed to

form the basis of oscillatory activity (Pfurtscheller, Lopes da Silva, & da Silva, 1999).

	EPSP	IPSP
Apical (long)	-	+
Basal (short)	+	-

Table 2.1: Schematic of which kind of action potentials (excitatory or inhibitory) reflect in scalp EEG phenomena of which polarity (Elbert & Rockstroh, 1987)

2.5 SYSTEMIC BRAIN MECHANISMS AND THE EEG

The first two Nobel Prizes for Medicine and Physiology of the 20th century are associated with the localist interpretation. Cajal and Golgi had shared the prize in 1904, but ultimately, Cajal's *Neuron Doctrine* prevailed over Golgi's interpretation of the brain as a continuous entity. Adrian and Sherrington, who shared the price in 1932, had both contributed significantly to the localist idea, and Adrian had even reinterpreted Berger's idea of the α rhythm as a holistic phenomenon by localising it to the occipital lobes. Both of them had conducted extensive experiments with local stimulation of nerves, resulting in specific effects.

The next Nobel Prize related to the CNS concerned the debate regarding the chemical versus the electrical nature of neural signal propagation (Langmoen & Apuzzo, 2007). The actual research preceded the EEG by decades. In 1936, Dale and Loewi shared the price for their discovery of neurochemical substances relaying nerve signals (Grant, 2006). Loewi, son of a wine merchant, demonstrated a clear systemic effect; as was known, vagus nerve stimulation slowed heart rate. Loewi collected the fluid surrounding a preparation of a heart after stimulation of the vagus nerve, and applied the fluid to a different preparation, where the heart rate also began to drop - without any direct, localized stimulation. Dale was the discoverer of the neurotransmitter and neuromodulator Acetylcholine/ACh (Brown, 2006). Von Euler received the Nobel prize in 1970 for his discovery of Noradrenaline/NE, which together with the later discovered Dopamine/DA belongs to the catecholamine class of neurotransmitters. Eventually, a wide range of neuromodulators was discovered, and neuromodulatory functions of "classical" transmitters were observed (Katz, 1999).

Prior to Von Euler's and Lowei's discovery, the neurophysiological community favoured the theory that synapses communicate via electrical signals (Lajtha & Vizi, 2008). In fact, John Von Eccles initially favoured it, too, and yet, it was him who helped establish the critical role of chemical transmission at synapses in the CNS (Eccles, Eccles, & Fatt, 1956), where neurotransmitters are released and activate receptors, either polarizing or depolarizing the target neuron, bringing it closer to or further away from its next spike - the basis of neural computation.

Dale's principle, termed so by Eccles, proposes that each neuron stores and releases only one transmitter, and is therefore either inhibitory or excitatory. Especially the second half of the principle has been called into question by the observation that the nature of a substance as excitatory or inhibitory depends on the target site, with specific receptors responding differently to various transmitters. However, neurotransmitters do more than contribute to direct/point-to-point, fast, excitatory or inhibitory synaptic signalling.

Dales' neurotransmitter substances clearly established the transmission of an action potential from one nerve to the other, across the synaptic cleft, via a chemical signal. Moreover, in their second nature as neuromodulators, they evoke a systemic effect, providing the mechanism behind Loewi's observation. Once released during an action potential, neurotransmitters may not only travel from the pre- to the post-synaptic neuron and thereby contribute to the general polarisation of the neurone, either bringing it closer to or away from spiking. They may also partake in *neuromodulation*, that is,

> "[a]ny communication between neurons, caused by release of a chemical, that is either **not fast**, or **not point-to-point**, or **not simply excitation or inhibition** ..."
>
> (Katz, 1999, p. 3)

A wide range of phenomena have been termed neuromodulatory, but primarily, it describes neural signalling that works not primarily by de- or repolarising the target, but by changing its activation profile, e.g. by making it more or less suspectible to (sometimes specific) inhibitory or excitatory post-synaptic potentials, and/or by changing its spontaneous firing rate. Such influence is called modulatory, compared to the primarily transmitting function of other neurotransmitters. Typically, aminogenic neurotransmitters, such as GABA and glutamate, primarily work in synaptic transmission, whereas the amines, especially the monoamines Dopamine, Noradrenaline and Serotonin, work as neuro*modulators* (Katz, 1999; Purves et al., 2004). However, most neurotransmitters can somehow be found in neuromodulatory roles.

The major sources of human neuromodulatory activity to the cortex stem from subcortical nuclei, some of which are specifically dedicated to implementing one of the neuromodulator systems of the CNS. By their synaptic distribution, these regions establish neuromodulatory systems that induce more or less systemic effects, broadly influencing anything between small cell groups up to vast stretches of the cortex to adapt its activation profile in the process of volume transmission of neurotransmitters. Volume transmission, in contrast to direct one-to-one neural connections, or "wiring" (Agnati, Zoli, Strömberg, & Fuxe, 1995), stems from the diffuse release and uptake of chemicals.

Another important aspect of neuromodulation, beyond this spatial aspect, is found in the different temporal profile. Classically, neuromodulators are thought to function via slow (G-protein coupled) metabotropic receptors (requiring secondary messengers). In contrast, the fast ionotropic receptors (neurotransmitter-gated ion channels) are assumed to reflect direct, instantenous signal transmission.

Neuromodulators are also slower regarding the offset of their effects. At local connections, neurotransmitter re-uptake, clearance of the substance from the synaptic cleft, may be near-instantaneous. In contrast, e.g. ACh turnover has been found to be slower at many CNS sites, leading to a spatially diffuse,

temporally transient effect. Generally, neuromodulators are usually found at some low, but non-zero concentration, baseline level, during every brain state, and neuromodulatory activity corresponds to the changing of this baseline rather than, in direct synaptic transmission, the introduction of a new substance into the synaptic cleft (Descarries, Gisiger, & Steriade, 1997).

The discovery of chemical transmission was a paradigmatic shift (Carlsson, 2001). Practically, it opened the field of neuropharmacology and the targeted manipulation of cognitive states, including drug treatments for mental disorders. Paradigmatically, it brought a resurgence of non-localist, systemic perspectives on brain functions.

An important role of neuromodulators in cortical state regulation is well established. Recently, systemic neuromodulator activity has been implicated in EEG and, increasingly, ERP neurophysiology. In this regard, electroencephalography is returning to its roots; to Berger's idea of a unifying brain pattern. In the following, systemic brain mechanisms will be discussed in more detail.
Later chapters of this text will discuss in detail recent proposals for a possible role of neuromodulators in the ERP correlates of higher cognition.

2.6 HOLISTS VS. LOCALISTS, REDUX

Avoiding this systemic nature of the event-related scalp EEG as reflecting subcortical input to the cortex, a phenomenon only observable at meso- and macroscopic levels, the decades after the World War II produced advances especially in the localist field of local field potentials and single-unit recordings. Regarding the holist/localist debate, in the end, localism won, at least since Penfield's extremely effective investigations (Penfield, 1959). Concurrently, a related, but distinct development happened in the cognitive sciences; inspired by Noam Chomsky, Fodor (1985)'s *modular mind* [though Fodor himself is a fierce opponent of vulgar brain localisation research, Fodor:1999vt] began to dominate the field, where cognition consisted of multiple distinct modules - each of which could, possibly and at least to some extent and with some overlap, be localised anatomically. With the introduction of the fMRI, the localism debate has firmly shifted away from the question of *if* brain functions are localised, to the question of *how and where* they are localised.

And yet, it took Berger's holistic beliefs to uncover the EEG. At first, the EEG was a German phenomenon, only later crossing the channel and the Atlantic (Rösler, 2005; Stone & Hughes, 2013). As Borck (2006) argues, compared to the amateur from Germany, many other labs in the United Kingdom or the United States were better equipped, better staffed, better educated, better suited to discover the EEG. α waves are simple to measure. Once they began looking for it, it took Adrian and Jaspers substantially less than Berger's decade to measure the EEG. But nobody found it *before* Berger, and even when he had published his findings, he was met with doubt. Borck (p. 453) writes:

> "For its coming into being, the EEG required a 'Kulturträger' from Germany, pursuing a holistic and speculative research program against the consensus among the international community of neurophysiologists."

It required the support of the established Nobel laureate Adrian, and possibly his reinterpretation of the "Berger rythm" as a local phenomenon, to convince the community of the importance of the observation. Yet, the EEG was, and is, evidence of non-focal phenomena in the brain, and the localist-leaning community was not out to discover non-focal phenomena. What exactly was special about Berger's understanding of the brain that allowed him to surpass his colleagues?

Berger wasn't a strict equipotentialist. He was a follower of Meynert, the "arch-localist" (Hakosalo, 2006; Mundale, 2002). He knew enough about the localisation of motor functions to record the EEG over the ipsi- and contralateral hemisphere while stimulating the hand, reporting a hemisphere-dependent desynchronisation over the motor cortices (H. Berger, 1933b), resembling what is now called μ *blocking*. Berger did assume a certain compartmentalisation of brain functions. Yet he also expected to find a governing meta-order, and when he found α, he was sure to have found

> "... im E.E.G. eine gerichtete, die Großhirnrinde beider Hirnhälften zu einem einheitlichen Ganzen zusammenfassende Tätigkeitswelle ..." (H. Berger, 1933b, p. 7)
>
> ... in the EEG an aligned action wave, integrating the cortices of both hemispheres into one united whole ...

To him, the brain was a system - with subdivision, but also macrophenomena and shared states across distinct areas.

While unable to hide his satisfaction over the late appreciation, when reviewing the work of Adrian and their localist interpretation, Berger was vehemently opposed to the idea that the EEG could reflect local phenomena:

> "Adrian und Matthews sind bei ihren schon oben erwähnten Untersuchungen über das E.E.G. des Menschen zu dem Ergebnis gekommen, daß die von ihnen in Übereinstimmung mit meinen Feststellungen gefundenen elektrischen Potentialschwankungen in der Hirnrinde selbst entstehen. Sie gelangen aber weiterhin zu der irrigen Annahme, daß sie im Occipitallappen entstünden." (H. Berger, 1935b, p. 448)
>
> Adrian and Matthews, in their above mentioned investigations concerning the human EEG, have concluded that the electrical potential fluctuations they have found in agreement with my work arise in the cortex itself. However, they arrive at the erroneous interpretation that they emerge in the occipital lobes.

He also explicitely refused the name "Berger waves", as Adrian had christened α, because such a term implied that they were just one example of an expression of a local phenomenon - visual processing. In contrast, Berger says about the α waves that they strike him as ...

> "... eine merkwürdige Zusammenfassung der so ausgedehnten und in ihrem anatomischen Bau reich gegliederten, wenn auch örtlich doch nur wenig verschieden gebauten Großhirnrinde mit ihren etwa 14 Milliarden Ganglienzellen zu einer einheitlich arbeitenden Ganzheit, wie sie uns im E.E.G. vor Augen tritt, die mich immer wieder mit Staunen erfüllt."

> "Schon bei der Besprechung der Wirkung einer motorischen Leistung auf das E.E.G. mußte ich auf die Einwirkung der Anspannung der Aufmerksamkeit auf die cerebralen Potentialschwankungen eingehen und darauf hinweisen, daß neben dieser die Muskeltätigkeit als solche am E.E.G. überhaupt nicht in Erscheinung tritt. Es zeigt sich eben immer wieder, das am menschlichen E.E.G. jede Anspannung der Aufmerksamkeit weitgehende Veränderungen hervorruft. Nach den schönen Versuchen von Ectors, Jasper, Jasper und Rheinberger und anderen liegen die Verhältnisse beim Tier ganz ähnlich. Die jedem Untersucher des E.E.G. sofort auffallende Tatsache, daß das E.E.G. ganz anders aussieht bei ein und demselben Menschen, je nachdem er die Augen offen oder geschlossen hat, und daß die Änderung des Zustandes der Augen fast sofort die entsprechende Veränderung am E.E.G. zutage treten läßt, war ja der Ausgangspunkt der falschen Annahme, daß die α-W. etwas mit dem Sehen zu tun hätten, im Occipitallappen entstünden und bei Blinden fehlten. Ich habe diese Annahme in früheren Mitteilungen widerlegt." (Berger, 1938, p. 424)

> ... a surprising integration of the so vast and in its anatomical structure richly differentiated, while locally only structurally marginal differing cortex with its approximately 14 billion ganglion cells into a coherently working unity, like we can see in the EEG, that again and again amazes me.

> Already when discussing the results of motor expressions on the EEG I had to mention the effect of arousal of attention on the cerebral potential fluctuations and on the fact that otherwise, muscular activity as such does not appear in the EEG. It becomes apparent again and again that in the human EEG, every arousal of attention induces wide-spread perturbations. Based on the beautiful experiments by Ectors, Jasper, Jasper & Rheinberger, the relation is quite similar in animals. The fact, becoming immediately noticable to anybody investigating the EEG, that the EEG appears fundamentally different in one and the same person depending on if their eyes are open or closed, and that changing the state of the eyes immediately reflects in corresponding perturbations in the EEG, has been the point of origin of the erroneous assumption that the α waves are related to seeing, originate in the occipital lobes and are missing in the blind. I have disproven this assumption in previously communicated letters. (My translation)

To Berger, α was a sign of a unifying, system-wide state all cortical compartments would be found in. Local brain centres would have dedicated functions, but they were all united in the general attentional state of the brain.

As noted, current work has associated specifically high-frequency *gamma*/γ oscillations (> 30 hz) with local computations, and low-frequency oscillations, like α and theta/θ, with wide-spread connections (Carandini, Nauhaus, & Carandini, 2012; Nunez & Srinivasan, 2006; Schroeder, Lakatos, Chen, Radman, & Barczak, 2009; von Stein & Sarnthein, 2000). Such a perspective was already foreseen by Berger:

> "In der aus den Aktionsströmen der einzelnen Nervenzellschichten sich zusammensetzenden und zu einem einheitlichen Ganzen verwobenen kennzeichnenden Spannungskurve des E.E.G. des Menschen findet die gesamte physiologische und psychophysiologische Arbeit der menschlichen Hirnrinde ihren sinnfälligen Ausdruck. Die α-W. des E.E.G. entstehen in der inneren Hauptzone der Rinde; sie entsprechen ihrer ständigen physiologischen Tätigkeit und zeigen bei allen allgemeinen Betriebsstörungen der Rinde deutliche Abänderungen. Gewisse β-W. mit einer Länge von 11-24 [msec], deren Ursprungsort wohl in den Zellschichten der äußeren Hauptzone zu suchen ist, entsprechen der psychophysiologischen Tätigkeit der Rinde; sie sind also als die materiellen Begleiterscheinnngen der psychischen Vorgänge anzusprechen." (Berger, 1936b, 187)

> In the potential waves of the human EEG, constituted of and integrating into a unitary whole the action potentials of individual nerve cell layers, one finds the index of the sum of the physiological and psychophysiological work of the human cortex. The α waves of the EEG originate in the inner main zone of the cortex; they correspond to its permantent physiological activity and show strong changes during all general perturbations of the workings of cortex. Certain β waves with a length of 11-24 msec, whose point of origin is most likely found in the outermost main zone, correspond to the psychophysiological activity of the cortex; they should also be called the material correlates of psychological processes.

In contemporary terminology, waves with a length of 11-24 msec (42-90 hz) correspond to high-frequency oscillations that would nowadays be called γ (see also Berger, 1938, p. 431; 1934, p. 541).

2.7 THE FUNCTION OF THE BERGER WAVE

However, Berger's main interest were consistently the larger, more reliable and more reliably sensitive α waves.

Berger did assume a local *origin* of α:

> "Diese Feststellung bestärkt mich ebenso wie die oben mitgeteilte Beobachtung in der Auffassung, daß im E.E.G. ein in ganz bestimmter Richtung über die Hirnrinde verlaufender Vorgang, eine fortschreitende Tätigkeitswelle, zum Ausdruck kommt . . . " (Berger, 1933, p.568)

> This observation, like the observation mentioned above, reaffirm me in my assumption that the EEG reflects a process spreading across the cortex in a specific direction, an ongoing activity wave . . .

Specifically, Berger assumed a frontal-to-occipital spread (in contrast to the more plausible occipital-to-frontal spread, Nunez, 2002). However, the local *origin* does not correspond to local *confinement*:

> "Das E.E.G. entsteht *allüberall* in der Großhirnrinde und stellt eine gerichtete Tätigkeitswelle der Großhirnrinde dar ..." (Berger 1935, p. 454).
>
> The EEG arises *everywhere* in the cortex and corresponds to a focused activity wave of the cortex ...

The spread of α results in the unification of the whole system into one meta-state. Mirroring later investigations confirming the low spatial resolution of EEG measures (Duun-Henriksen et al., 2013; Nunez & Srinivasan, 2010), Berger stated:

> "Der Mensch ist eben kein noch so zusammengesetzter physikalisch-chemischer Apparat, sondern eine psychophysische Ganzheit! Der Schlußfolgerung von Herrn Tönnies, daß es unmöglich sei, von dem uneröffneten Schädel des Menschen lokalisatorische Ergebnisse zu gewinnen, kann ich nun durchaus zustimmen." (Berger, 1934, p. 540)
>
> Man is not a constructed physical-chemical apparaturs, but a psychophysic whole! The conclusions of Mr. Tönnies about the impossibility of gaining localisatory results from the intact human skull I can surely agree to.

With these lines, Berger does not imply any metaphysic, parapsychological field corresponding to the human soul or spirit. Rather, Berger connected α to a quite specific and well-defined psychological phenomenon with rather clear physiological correlates: *attention and arousal*.

Concerning the EEG, he constantly mentions the

> "... innige Zusammenhang mit den Aufmerksamkeitsvorgängen, der wichtigsten psychophysischen Funktion." (Berger 1935, p. 454)
>
> ... strong relationship with attentional processes, the primary psychophysical function.

With the EEG, Berger provided the first, and in many ways possibly still only, method to study a direct, real-time correlate of the general state of the central nervous system of humans.

3

NEUROPHYSIOLOGY OF ATTENTIONAL STATE CONTROL

As Berger had deduced from his investigations of the α rhythm, attention and arousal are indeed aspects of brain function that are especially governed on a systemic level.

Arousal is the "ability to mobilize metabolic energy to meet environmental or internal demands on behavior" (Marrocco & Field, 2002, p. 223). Cortical arousal emerges as a relationship between the general environment of the organism and sustained levels of neuronal activity. The higher the arousal level, the more reactive the cortex is to external events, the stronger neural perturbations become coupled to external events, and the more likely is it that external events will result in motor behavior.

Attention is the focal equivalent to general arousal; it "is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought" (James, 1890, p. 403f). This selected stimulus is what cortical behavior is then tightly coupled to; it perturbs neural patterns and has a much higher chance of leading to motor behavior than stimuli outside the scope of attention.

The primary psychological examination of attention, including an associating with neurophysiological networks, is found in major reviews by Posner & Petersen (Petersen & Posner, 2012; Posner & Petersen, 1990). Three main components of attention are identified: the alerting, orienting, and execution networks.

The *alerting* system provides on-demand regulation of vigilance. Depending on the expectation of upcoming events requiring immediate processing and reactions, the reactivity of the brain is adjusted. For example, altering cues indicating significant consequences induce alerting; the circadian rhythm also influences arousal. This network is associated with the reticular formation.

Orienting is implemented by a cross-modal frontoparietal network. Orienting corresponds to the selection of sensory streams (modalities, locations, features) to be attended. A related concept is re-orienting, a process required when another stream than the currently attended stream carries significant information.

The last system has been identified as *detection* (Posner & Petersen, 1990) or *executive* function (Petersen & Posner, 2012). It corresponds to the system establishing target awareness and/or regulating the appropriate response to stimuli; this network is at least partially overlapping with the orienting network, with central processes of both action and awareness being instantiated in the mediofrontal cortex, including the cingulate gyrus.

3.1 MODELS OF AROUSAL AND ATTENTION

Computational models of arousal and attention refer to the concept of cortical responsitivity, or gain (Aston-Jones & Cohen, 2005; Krichmar, 2008; Tiesinga & Sejnowski, 2009). In this context, a gain function represents how sensitive a neural system is to external perturbations (Salinas & Thier, 2000; Servan-Schreiber, Printz, & Cohen, 1990). The gain function of neural systems observes a sigmoidal shape; output generally proportionally tracks inout, but low input does not fundamentally shape network properties, and under increasing drive, at a certain level of stimulation a ceiling is reached as the maximal output of the network (thresholded by refractory period dependent maximal firing rates). Gain modulation refers to the steepness of the slope between these two extremes. A high-gain system is unperturbed by many forms of weak stimuli (effectively blocking them off instead of relaying them further), and amplifies strong inputs; a low-gain system more faithfully relays weaker inputs, but requires stronger input to produce strong outputs (See Figure 3.1)[1]. Therefore, in a diffusion (Jepma, Wagenmakers, & Nieuwenhuis, 2012; Smith & Ratcliff, 2004) or dynamical system (Deco, Rolls, & Romo, 2009) model of decision making, high-gain systems are quicker to cross the decision threshold following relevant events. However, as a trade-off, they are more likely to overreact and more likely to ignore weak relevant inputs.

Gain is related to the signal-to-noise ratio; a high-gain state more clearly differentiates epochs containing stimuli from epochs not containing stimuli.

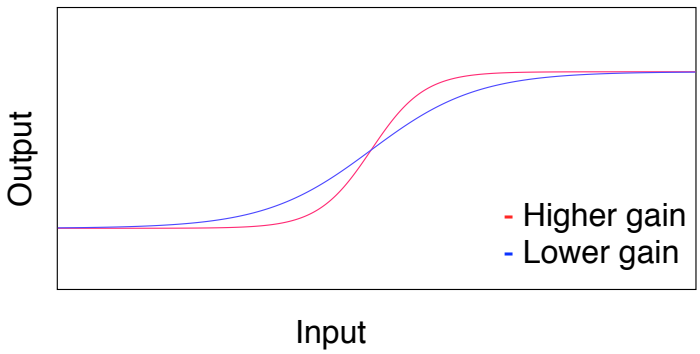

Figure 3.1: Example of gain functions. The blue sigmoid represents a low-gain state, the red sigmoid a high-gain state where strong input results in disproporitionally stronger output, and weak input in disproportionally weaker output, compared to the low-gain state.

Arousal control can be modelled as adapting general synaptic gain (Lee & Dan, 2012; Schiff, 2008). Attention control can be modelled as specific gain adaption (Tiesinga & Sejnowski, 2009). A highly aroused state is a high-gain state; a stimulus can be brought into the center of attention by gain modulation (Aston-Jones & Cohen, 2005; Hurley, Devilbiss, & Waterhouse, 2004), and held in the center of attention against external distractors by

1 This is assuming gain only modulates the slope. In many (possibly more realistic) models, gain also shifts the area under the curve of the gain function.

controling gain. Arousal and attention are thus both tonic states, but the transition between states can be rapid and phasic.

Another, related and overlapping framework describing these general phenomena describes behavior on an axis from exploratory to exploitatory (Aston-Jones & Cohen, 2005; Daw, O'Doherty, Dayan, Seymour, & Dolan, 2006; Doya, 2008; Yu, 2005). During exploratory states, brain patterns are highly sensitive to variances in external events; during exploitative states, behavior is guided by a focused set of available and acquired information, and the sensitivity to external variance is minimized. Exploratory states are states of high (tonic) general arousal, exploitative states correspond to focused attention (low tonic arousal, and strong phasic responses to attended stimuli).

As described by the *Yerkes–Dodson* law (Yerkes & Dodson, 1908), the relationship between performance and arousal follows an inverted U-curve - at least for non-simple tasks. Overly aroused and lethargic states both impair performance. This can be explained by referring to the gain curve (Servan-Schreiber et al., 1990); excessive gain increases the ratio of of false alarms to correct actions (worsening *d'*), but low gain states increase the number of misses (because the stimulus is not sufficient to activate the system past the threshold) and may increase reaction times (See Figure 3.2). Consequently, both focal (attention) and general (arousal) gain have to be adaptively modulated.

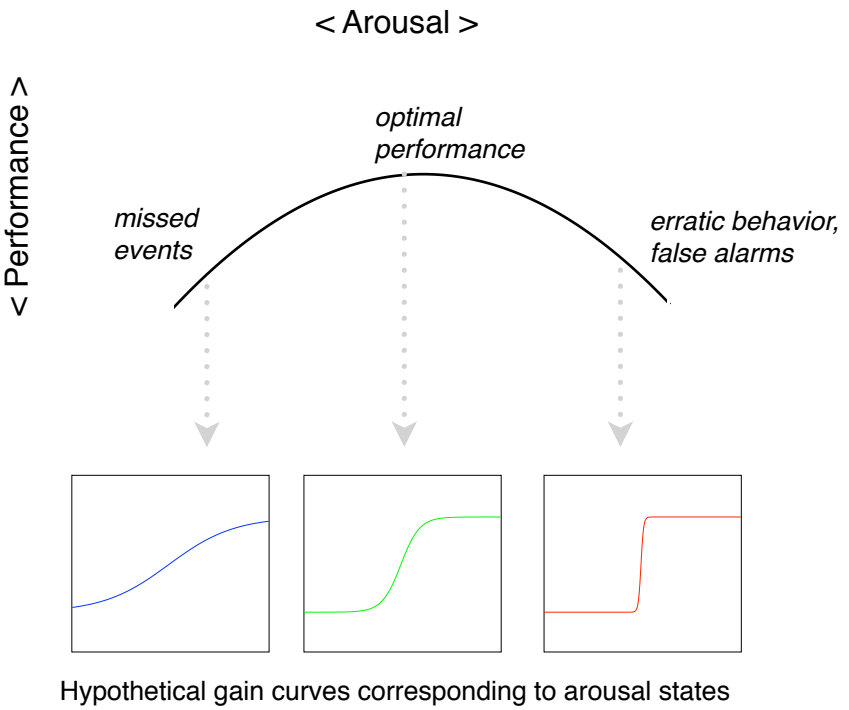

Figure 3.2: Example of how the Yerkes-Dodson law might relate to gain. Qualitative performance and hypothetical gain curves are shown as a function of arousal.

The key systems responsible for arousal and attentional control are of special importance to the sciences of brain and behavioral for several reasons: they are amongst the most important determinants of brain activity and behavior (Pfaff, Martin, & Faber, 2012); they are well-researched (Aston-Jones & Cohen, 2005; Corbetta & Shulman, 2002; Sara, 2009); they are one of the key phenomena where the relationship between non-invasive neurophysiological observations and behavior are relatively well-established (Corbetta, Patel, & Shulman, 2008; Nieuwenhuis et al., 2005); and these brain systems show both high baseline activity and high task-induced variance. Due these two latter aspects, they can be expected to dominate a vast range of neurocognitive findings, both because arousal and attentional reorientation are crucial aspects of task performance in experimental settings, and because systems with high baseline activity have a high chance of showing up as spurious findings, especially given the low experimental power typical for neuroscience (Button et al., 2013; Yarkoni, 2009).

Three main systems interact in the regulation of arousal: the cortex itself, especially frontal and parietal systems (Fox et al., 2005); the thalamus (Marrocco & Field, 2002; Schiff, 2008); and the brainstem, especially the reticular activation system (Funke & Eysel, 1993; Moruzzi & Magoun, 1949; Pfaff et al., 2012).

Berger already mentioned the possibility of connecting α to parts of these systems, including thalamocortical loops (Pfurtscheller et al., 1999):

> "Berze (...) sieht im Thalamus ein Zentrum, von dem aus der Tonus des Bewußtseinsorgans reguliert und der psychocerebrale Apparat, d.h. die Hirnrinde, ein- und ausgeschaltet werden kann. Es ist durchaus möglich, daß dies auch für den Ablauf des E.E.G. gilt." (Berger, 1933 p. 569)
>
> Berze sees in the thalamus a centre from which the tonus of the psychological organs is regulated and the psychocerebral apparatus, the cortex, is activvated and deactivated. It is surely possible that such a process also applies to the EEG.

The thalamus functions as the last pre-cortical relay station that most sensory information has to pass before it can be processed, establishing the thalamus as a gate for input to the cortex (McCormick & Bal, 1994). Thalamus relay cells regulate their firing dependent on the arousal of the subject, switching between tonic and burst firing modes (Sherman, 2001). The gating function of the thalamus gives it a critical role of setting the threshold for cortical excitability (Elbert & Rockstroh, 1987). Supporting a major role of the thalamus in the genesis of α, a subset of thalamic neurons have been found to fire bursts at the rate of the α rhythm (Vijayan & Kopell, 2012).

Anatomy and function of the reticular activation system were investigated by early EEG investigators (Lindsley, Bowden, & Magoun, 1949; Moruzzi & Magoun, 1949). It consists of a number of nuclei and networks in the brain stem. It controls cortical arousal via ascending pathways, including the primary neuromodulator systems, NE, DA, 5-HT, ACh, as well as e.g. histamine (Daw et al., 2006; Lee & Dan, 2012). Its lower aspect, the reticular formation, projects both to the cortex and to the spinal cord. The pons (the mid section of the brainstem) includes the noradrenergic Locus Coeruleus. In the lower brain steam, the medulla, Raphe's Nuclei contribute the serotoninergic projections to the cortex. The mesencephalon, the top of the brainstem, contains for example the Substantia Nigra and its dopaminergic projections.

Cortical projections of neurons from the subcortical neuromodulator systems are thought to not primarily excite or inhibit specific target neurons, but at least in part diffusely release chemical signals in a process of volume conduction (Hasselmo, 1995). In addition to their direct excitatory or inhibitory effects, neuromodulators, such as NE, DA, 5-HT and ACh (Gu, 2002), are thought to modulate the relationship between neurons at the release site and their presynaptic inputs. They may do this in part by changing the gain curves of the affected cortical neurons, and it is this aspect of neuromodulators that is by some researchers assumed to establish their critical role in attentional state control (Aston-Jones & Cohen, 2005).

Area	Location	Neuromodulator
Locus Coeruleus	Reticular formation (Pons)	Noradrenaline
Raphe's Nucleus (dorsal)	Reticular formation (Medulla)	Serotonin

Table 3.1: Major neuromodulator systems with ascending cortical projections in the brain stem

Area	Location	Neuromodulator
Nucleus Basalis	Forebrain	Acetylcholine
Substantia Nigra & VTA	Mesencephalon	Dopamin
(TM	*Hypothalamus*	*Histamine)*

Table 3.2: Major neuromodulator systems with ascending cortical projections outside the brain stem

3.2 THE VENTRAL ATTENTION-LOCUS COERULEUS NEXUS

3.2.1 *The Locus Coeruleus/Norepinephrine system*

3.2.1.1 *Anatomy*

The Noradrenaline/Norepinephrine (NE) system is possibly the best-mapped modulatory system. Its connection to arousal (Berridge, 2008) and attention/reorientation (Aston-Jones & Cohen, 2005; Bouret & Sara, 2005; Sara & Bouret, 2012) are well researched. All cortical NE stems from just one source: the Locus Coeruleus/LC ("blue spot") in the reticular formation (Foote & Morrison, 1987; Samuels & Szabadi, 2008), a small cluster (of only around 15.000 cells per hemisphere in humans) projecting widely to various areas of the cortex.

The main cortical targets of the LC are found in the frontal lobes, especially the cingulate cortex and the orbitofrontal cortex. Past the central fissure,

especially areas of the parietal lobes, like the TPJ and the posterior cingulate, receive dense innervations, with temporal areas being less densely innervated (Morrison & Foote, 1986). However, all of the cortex receives LC projections. The projections to frontal regions are substantially shorter than those to parietal, temporal and occipital regions, leading to shorter transmission latencies (see below).

LC projects to the cortex rather diffusely (Gatter & Powell, 1977). Only about 20-25% of LC cells project to only one or two cortical targets (Sakaguchi & Nakamura, 1987), and most show extensive cortical arborization.

One aspect of axonal innervation of multiple targets is axonal branching, or collateralization. LC projections to the cortex show extensive anterior-to-posterior/sagittal collateralization, but no coronal collateralization (Loughlin, Foote, & Fallon, 1982). Consequently, a single LC cell often innervates both frontal and e.g. occipital regions; however, it rarely innervates, for example, multiple frontal regions at the same time (Chandler & Waterhouse, 2012). These projections ignore cytoarchitectonic boundaries, so that a single LC cell will non-discriminately synapse in a part of the cortex exhibiting one cell distribution while also easily projecting to other areas with a different distribution; this has been interpreted to imply that LC projections do not show specificity regarding the functional localisation of their multiple targets.

On the other hand, individual LC cells rarely project to both cortical and subcortical targets (Losier & Semba, 1993).

At their target sites, LC neuron terminals rarely (possibly around 10-20% in the macaque) synapse, indicating a diffuse transmission mode via volume conduction (Lajtha & Vizi, 2008).

The LC also projects connections to many brainstem and other subcortical regions, including the Ventral Tegmental Area/VTA (DA), Dorsal Raphe's Nucleus/DRN (5-HT) and the substantia innominata, which hosts the pedunculopontine tegmental/PPT, laterodorsal tegmental/LDT and Nucleus Basalis of Meyert/NBM.
In the innominate, the LC is thought to inhibit inhibitory GABAergic neurons and excite excitatory ACh neurons (Szabadi, 2013). Another important connection lies in the integration between the LC and the limbic system. The LC builds strong excitatory projections to the hippocampus and (possibly reciprocal) the amygdala, serving again as the sole source of hippocampal NE. Furthermore, the LC projects strongly to the thalamus.
In sum, the LC exerts great influence on the cortex in key regions involved in such diverse and important functions such as memory, arousal, cognitive control and action. It also influences other neuromodulator systems.

Cortical innervation by the LC does not exhibit substantial layer specificity, with near-uniform distribution across all layers (Benavides-Piccione, 2005). The localisation of neurons with different projection targets throughout the LC shows some degree of organisation insofar that parts of the LC project preferably to limbic, others to cortical areas. Furthermore, LC neurons with specific projections are mainly located at the periphery, central LC neurons show the typical nonspecific, multiple projections (Fallon & Loughlin, 1982; Loughlin, Foote, & Bloom, 1986; Loughlin, Foote, & Grzanna, 1986). However, there seems to be no organisation regarding specific cortical projections (Sakaguchi & Nakamura, 1987).

Cross-species, conduction speed of LC activity to the cortex shows significantly less variance than conduction distance; while primate brains are larger, and LC-to-cortex axonal distances longer, than in the rat brain by orders of magnitude, conduction latencies vary by less than a factor of two due to increased myelination of projection fibers. Since myelination is costly, it can be assumed that maintaining short LC projection latencies was critical in primate evolution. Conduction latencies vary mostly by target site; in the monkey, LC-to-frontal cortex latencies are around 70 msec, LC-to-occipital ~100 msec (Aston-Jones, Foote, & Segal, 1985). Consequently, while phasic LC activity should affect most of the cortex rather uniformly, neuromodulation by the LC should show slight latency variations, increasing along a rostro-caudal gradient (in contrast to the primarily caudo-rostral gradient in sensory processing), for different brain areas. Bluntly put, a direct effect of phasic NE will influence the frontal cortex between 30-100 msec before occipital regions.

The innervation between the prefrontal cortex and especially the cingulate gyrus in the frontal cortex with the LC is *functionally* reciprocal, constituting one of the main cortical projections to the LC. The frontal cortex activates the LC via the NPg (Nieuwenhuis, De Geus, & Aston-Jones, 2010) or direct innervation (Gompf et al., 2010).

According to some studies (Aston-Jones, Ennis, Pieribone, Nickell, & Shipley, 1986), the LC receives strong direct input from only two areas: the nucleus prepositus hypoglossi and, mainly, from the nucleus paragigantocellularis/NPg in the medulla (Ennis, Aston-Jones, & Shiekhattar, 1992). This view is not uncontroversial, and some researchers assume richer input to the LC, including multiple subcortical and cortical sources (Counts & Mufson, 2012). Other direct sources may include the amygdala (Szabadi, 2013) and orexinergic input from the hypothalamus (González, Jensen, Fugger, & Burdakov, 2012). Other authors claim that VTA and the prefrontal cortex also affect the LC (Sara, 2009; Weinshenker & Schroeder, 2006).
Sara and Herve-Minvielle (1995) report that in the rat, the Locus Coeruleus receives inhibitory projections from FR2, which, together with the dorsal cingulate, forms the rat dorsomedial (pre)frontal cortex (Uylings, Groenewegen, & Kolb, 2003); this area is considered a sensorimotor area. In the Rhesus Monkey, retrograde labelling has implicated anterior parts of the cingulate (Porrino & Rakic, 1982, fig. 3).

While it is not unambiguously clear how restrictive the LC afferent system actually is, it is well known that the LC does react to cortical and other input. However, it has been argued (Aston-Jones, 2004) that this input stems from indirect, diffuse connections terminating near the LC (Luppi, Aston-Jones, Akaoka, Chouvet, & Jouvet, 1995).

The observation of a highly selective afferent system is interpreted to mean that the LC receives only highly processed input.

The LC is characterized by strong inhibitory autoconnectivity. This establishes its refractory period; following strong LC activity, the NE released in the LC itself inhibits and dampens LC activity while residual NE is metabolised (on the order of hundreds of milliseconds or even seconds).

LC activity is described in two basic modes: tonic and phasic mode. Tonic LC function, the average spiking rate (and therefore, NE release rate) over sustained periods, is associated with general arousal by influencing cortical tone and modulating the gain curve across the cortex. An increase in tonic

LC output characterizes, for examples, the transition from sleep to the awake state (Aston-Jones, Gonzalez, & Doran, 2007). It is correlated with EEG wide-band power (Aston-Jones & Bloom, 1981a).

Typically, LC neurons in tonic mode fire at a rate of 2 hz or less. A decrease in LC output raises the threshold for a stimulus to significantly perturb the cortex, decoupling the cortex from the environment, e.g. during sleep. Tonic LC mode is closely associated with the inverted U-curve relation between arousal and performance (Aston-Jones & Cohen, 2005).

Generally, tonic LC firing is correlated with arousal, sensory stimulation, and wide-band EEG amplitude (Foote, Aston-Jones, & Bloom, 1980), and optogenetic manipulations have established that excitation of the LC alone is sufficient to transition to the waking state (Carter et al., 2010).

Phasic LC firing, short bursts of multiple consecutive spikes within a window of tens of milliseconds, is a fast, sub-second latency reaction to discrete, acute events (Foote et al., 1980; Rasmussen, Morilak, & Jacobs, 1986). During such bursts, the (nonspecifically projecting) core cells of the LC fire simultaneously, without local specificity (Aston-Jones & Bloom, 1981b; 1981a; Loughlin et al., 1986); peripheral cells, showing more specificity, fire less uniformly. This implies that during a burst, the LC exerts its effect upon most of the cortex simultaneously, without the ability to target specific cortical sites.

3.2.1.2 *Function*

LC responses are triggered when freely behaving animals encounter novel objects during the exploration of their environment (Vankov, Hervé-Minvielle, & Sara, 1995), and when a salient, disruptive stimulus is first presented, an LC response follows. However, following repeated presentation, this response quickly habituates (Sara, Vankov, & Hervé, 1994). Noradrenaline levels have been measured to rise following conditioned cues (associated with negative reinforcers), regardless of cue modality, and regardless of if the cue elicited a response before conditioning (McQuade & Stanford, 2000), implying a sensitivity of NE to the *subjective* significance of stimuli.

Similarly, during oddball-task like paradigms, where rare targets and common non-targets are presented, LC responses follow stimuli when they belong to the stimulus class to which responses will be rewarded, or when they are reliable cues for important upcoming events (Aston-Jones, Chiang, & Alexinsky, 1991). When reward patterns change, LC bursts follow suit; LC activity ceases to follow nonrewarded stimuli (nontargets), and rewarded stimuli induce LC bursts. When activity in the NPc of the medulla is blocked, this LC response disappears.

At first, phasic LC activation was observed following stimulis presentation; however, when observing the LC in behavioral paradigms, a critical role in the modulation of behavior became apparent. LC bursts are better temporally correlated with the response to a stimulus than with the stimulus itself (Clayton, Rajkowski, Cohen, & Aston-Jones, 2004; Rajkowski, 2004); furthermore, only stimuli that are detected and categorized as task-relevant in that they require and result in a behavioral response are reliably followed by LC activation. Missed or ignored stimuli do not typically result in LC bursts.

Plasticity in the hippocampus likely depends on NE because hippocampal neurons only show long-term potentation under NE influence (Bouret & Sara, 2005; Lemon, Aydin-Abidin, Funke, & Manahan-Vaughan, 2009); consequently, the LC plays a crucial role in encoding memories (Sara et al., 1994; Tully & Bolshakov, 2010), establishing a double role in the response to novel stimuli. The LC reacts to novel stimuli, facilitating the encoding of stimulus nature, and is then silent to repeated stimulus presentation unless a reinforcing context exists.

Two main, mostly equivalent or overlapping proposals for the function of phasic LC activation have been proposed. On one hand, LC activation has been associated with dynamic gain regulation as a temporal filter following motivationally significant events (Aston-Jones & Cohen, 2005; Eldar, Cohen, & Niv, 2013; Nieuwenhuis et al., 2005). Alternatively, reset of cortical networks facilitating attentional reorientation has been proposed as the main role of the LC (Bouret & Sara, 2005; Sara, 2009; Sara & Bouret, 2012).

According to Aston-Jones, Cohen and Nieuwenhuis, the role of the phasic LC-NE response lies in the implementation of adaptive gain modulation in order to properly process critical events. In their view, the LC is activated when a stimulus has been categorized as being of high motivational significance, meaning that it is of importance to the current goals, intentions and activities of the subject. Crucially, the LC response is an endogenous response; it depends on the subjective significance of the stimulus, not on sensory aspects (Aston-Jones, Rajkowski, Kubiak, & Alexinsky, 1994).

The LC is only activated by cortical sources *following* this analysis process. The following systemic release of noradrenaline then facilitates the activation of an appropriate reaction due to the effects of noradrenaline on the gain of target sites.

Noradrenaline changes the ratio between spontaneous and induced spiking; higher NE levels suppress spontaneous firing and thereby increase the signal to noise ratio (Ego-Stengel, Bringuier, & Shulz, 2002; Foote, Freedman, & Oliver, 1975; Funke & Eysel, 1993, Funke:1993vz; Hirata, 2006; Kasamatsu & Heggelund, 1982; McCormick, 2002). The effect of NE on cortical SNR seems to be largely induced by inhibition of spontaneous activity while sparing evoked activity. It also induces a sharpening of tuning curves (Hirata, 2006).

Possibly, the lower load of spontaneous spiking, inhibited by NE, also increases the effect of postsynaptic potentials, leading to higher evoked activity, in addition to lower spontaneous activity (Kuo & Trussell, 2011). This further manifests in a functional increase in gain. However, this gain increase may be selective; NE may decrease horizontal, intracortical transmissions and increase inhibitory vertical feed-forward signals (Kobayashi et al., 2000). Beyond these effects on PSPs, it also depolarizes pyramidal neurons, raising the likelihood of synchronized, input-dependent action potentials while decreasing spontaneous spiking.

Bouret and Sara (2005) argue that the LC/NE signal functions as a neural interrupt signal following an event requiring a state transition. They propose NE resets cortical states, allowing the transition towards a new state. Prototypically, this reset allows reorientation towards a salient stimulus that may require a change in behavioral state, such as a response. Sara (2012) associates this view with the concept of the "truncated conditioned reflex" (Giurgea, 1989); this concept, which they adopt from the physiologist Ku-

palov, characterises an internal, *cortical* response (possibly followed by external, overt actions) to external stimuli.

Reorientation behavior must not be overt; a stimulus may be detected as belonging to a category that requires a change in cognitive state (mediated by NE release), yet this must not correlate with overt responses.

A connected, but possibly distinct role of NE is found in memory. NE facilitates retrieval (Bouret & Sara, 2005), but also encoding, especially of declarative/associative memory (Cahill & McGaugh, 1996; Ferry, Roozendaal, & McGaugh, 1999; Gelinas & Nguyen, 2007). A proposed mechanisms (Cahill & McGaugh, 1998; McIntyre, McGaugh, & Williams, 2012) lies in the LC/amygdala connection. Amygdalar coding of event emotional valence might be coded or signaled by LC NE, allowing the storage of highly arousing stimuli in long-term associative memory.

What is the neural basis of these functional phenomena? In the cortex, the main site where NE exerts its effect are α1-adrenoceptors (Samuels & Szabadi, 2008), which has been interpreted to mean that the primary direct action of NE in the cortex is excitatory. However, this stands in contrast to the observation that the primary effect of NE on cortical pyramidal neurons is inhibition of spontaneous activity (Foote et al., 1975; Funke & Eysel, 1993; Hirata, 2006). Direct (hyperpolarising/depolarising) and indirect (modulating) actions of NE also differ.
It has been argued that phasic NE release may activate α 1 and β receptors over apha 2 receptors, which are preferentially activated by tonic NE (Carter et al., 2010). α-adrenergic activation has been shown to excite (inhibitory) GABAergic neurons, inducing cortical IPSPs (Kawaguchi & Shindou, 1998) which may however be layer-specific (Salgado et al., 2010). Here, it contrasts with the effect of ACh (Kawaguchi, 1997; Kawaguchi & Shindou, 1998).
Three more mechanisms of NE firing are relevant:
NE contributes to spike persistence. Over time (on the scale of tens of milliseconds), neurons tend to reduce their firing in response to a given input. NE application has been shown to strongly attenuate this *spike frequency adaption* process, leading to persistent stimulus-induced spiking (Madison & Nicoll, 1986).
NE almost completely abolishes post-spike hyperpolarisation in many cortical neurons (Madison & Nicoll, 1986).
NE sharpens timing of evoked spikes (Sara & Bouret, 2012), leading to increased cross-trial evoked responses following sensory stimulation.

Another especially rich and neurophysiologically grounded proposal of how NE affects cognitive states is given in Arnsten's *dual state* model (Arnsten, 2000; Arnsten, 2011; Ramos & Arnsten, 2007). Due to differential receptor distributions, NE levels impact the frontal and posterior cortices differently. During moderate NE levels, the prefrontal cortex functions optimally and effectively instantiates top-down control. When NE is high, prefrontal coordination is impaired, but SNR in the rest of the cortex is improved, leading to a bottom-up, posterior-dominant state.

In sum, the effects of NE are complex. Various receptor types show divergent effects, and receptors are differently distributed across the brain. These effects may be non-linear, showing an inverted U-curve response. NE shows different effects at different time scales, with at times paradoxical tonic vs. phasic effects. NE may also differentially influence evoked vs. transient spiking, as well as showing differential effects on direct and indirect ef-

fects. While the precise effect of cortical NE is therefore complex beyond current understanding, researchers (Aston-Jones & Cohen, 2005; Sara & Bouret, 2012) roughly agree in the role of phasic activity of the LC/NE system in supporting cortex-wide effective reorienting and adaptive processes following critical events, increasing the *responsiveness to external stimuli* (Katz, 1999, p. 318) following top-down activation by its cortical (prefrontal/cingulate) afferents.

LC activity	Dominant receptor type	Gain	Cognitive State	Dominant Brain Area
low tonic	α 2	low	lethargic	posterior
phasic	α 1/β	high	reactive	prefrontal
high tonic	α 2	excessive	erratic	posterior

Table 3.3: Cortical function of various NE levels

3.2.2 *Detection and Control in the Cingulate: Function, Anatomical Accuracy and Precision*

The cingulate cortex, including the cingulate gyrus and sulcus, is a limbic module at the center of the cortex, under parietal and frontal lobes and above the corpus callosum. It has been implicated as a key system of the *executive* network in the proposal by Posner et al. (Petersen & Posner, 2012; Posner & Rothbart, 2007; Posner, Rothbart, Sheese, & Tang, 2007).

The cingulate cortex plays an essential role in the top-down modulation of attentional states based on external, especially the parts of it anterior of the rolandic fissure, in the frontal cortex. In the writings elaborating major theories, such as the Conflict Monitoring and the Feedback Learning theory as well as much of the literature on arousal and attention, the frontal brain area in focus is typically termed "ACC". This terminology is avoided by some researchers (Mueller, Makeig, Stemmler, Hennig, & Wacker, 2011; Ullsperger, Danielmeier, & Jocham, 2014) for reasons of anatomical ambiguity. They instead refer to modern cytoarchitectonical analyses (Vogt, 2005; Vogt & Palomero-Gallagher, 2011) arguing for a more fine-grained parcellation of the pre-rolandic cingulate gyrus. According to Vogt (2005; 2011), the cingulate anterior of the anterior commissure can be divided into the ACC and the MCC. The ACC consists of the pre- and subgenual anterior cingulate cortices (sACC/pACC). The mid-cingulate cortex/MCC consists of the anterior and posterior midcingulate cortex.
The parts of the cingulate in the posterior frontal cortex, especially the aMCC, but also possibly including parts of pACC and pMCC, are also referred to as the rostral cingulate zone/RCZ (Picard & Strick, 1996). A related terminology refers to this areas as the dorsal Anterior Cingulate/dACC; term-based activation maps (see the chapter on the anatomy of attention networks) for the term "dACC" are strikingly similar to the RCZ (See Figure 3.4).

Especially the RCZ has been argued to implement a key system in the modulation of attention: specifically, by monitoring performance and

assigning attentional ressources based on task demands (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; M. Ullsperger, Danielmeier, et al., 2014), for example following *"pre-response conflict"*, *"decision uncertainty"*, *"response errors"* and *"negative feedback"*, all of which the RCZ is highly sensitive to. Vogt (2005) assigns the role of *response selection* to the MCC - specifically, the aMCC is proposed to implement "fear avoidance", the pMCC "skeletomotor orientation". More anterior parts of the cingulate are assigned viceral, emotional roles.
The anatomically more adequate labeling is not consistently employed by even recent examples of the respective theories (Holroyd & Yeung, 2011; Yeung & Summerfield, 2012), who use the label ACC to refer to the "anterior portion of midcingulate cortex" (Holroyd & Yeung, 2012, p. 122). Their related, but distinct proposal (Churchland, 2013; Holroyd & Yeung, 2012) assigns the "ACC"/aMCC a role in sustaining behavior under stress, threat or distractors.
Due to the terminological inconsistency, many important papers do not make explicit to which part of the cingulate they refer. Consequently, it will be unavoidable to employ a rather rough terminology when discussing various, terminologically imprecise or even conflicting sources. The terms dACC/RCZ/MCC are used in the source literature rather interchangeably. I will restrict myself to the deliberately ambiguous label Medio-Frontal Cortex/MFC to approximately reproduce the anatomical implications of the source literature while avoiding incorrect or imprecise labels.
Whenever more specific anatomical claims are possible and intended, the more precise parcellation of Vogt (2005) will be employed. When, very broadly, an unspecifiable subset of the cingulate cortex anterior of the rolandic fissure - ACC and/or MCC - is intended, the term *pre-rolandic cingulate* will be used.

Regarding especially the electroencephalographic method, the appropriate terminological labelling is further complicated because all inverse models are approximations, and that ERPs necessarily summated comparatively broad activity loci. The relationship between the spatial synchrony required for scalp field generation and cytoarchitectonical boundaries is not clear. Intracranial measures are sensitive to similar, but different aspects of the electric field. While ECoG (Bonini et al., 2014; Wang, 2005) and co-registered fMRI/EEG (Debener, Ullsperger, et al., 2005) do indeed implicate the area around the RCZ in the generation of scalp negativities, the exact extent of the generators is hard to precisely estimate.

3.2.3 *Cortical Loci of Attention: Ventral and Dorsal Networks*

Beyond the general influence of noradrenaline on networks and neurons - what are the cortical systems that are influenced by the LC during state control? One main cortical target of LC projections has been identified and its workings associated with LC activity: the Ventral Attention Network/VAN.

The VAN is one of several resting-state networks identified by seeking correlations in the BOLD time series collected during the resting state (Lee, Smyser, & Shimony, 2012). It has been argued that the focus on resting-state networks in fMRI research was a paradigmatic shift away from a Sherringtonian framework (Raichle, 2009). To Sherrington, the brain was, like every nerve, primarily reactive (Sherrington, 1929); internal activity was depen-

dent on external activity. In contrast, resting-state networks are intrinsically connected and active regardless of task context.

Such resting-state activity had already been discussed by Berger:

> "Es kann leicht eine falsche Vorstellung erwecken, wenn das bei geschlossenen Augen im verdunkelten Zimmer bei möglichster geistiger Ruhe und Fernhaltung aller äußerer und, soweit auch durchführbar, innerer Reize aufgenommene E.E.G. als"Ruhekurve" bezeichnet wird. Die Potentialschwankungen entsprechen keineswegs einer Ruhepause der Gehirnarbeit, sondern sie sind ein Zeichen der weder durch äußere, noch durch innere Reize gestörten ständigen automatischen Rindentätigkeit."
> (Berger, 1938, 14)

> It can lead to wrong impressions when the EEG recorded with eyes closed, in a darkened room, during mental rest and avoidance of all external and, if possible, also internal stimulation, is called "resting wave". The potential fluctuations do not correspond to a pausing state of brain work, but are an index of constantly automatic cortical activity unperturbed by neither external, nor internal stimulation.

Amongst these networks are various sensory, motor and task-relevant networks; however, of primary concern for the regulation of attention are the VAN and the dorsal attention network/DAN (Corbetta et al., 2008; Ozaki et al., 2012; Shomstein, 2012; Shomstein, Lee, & Behrmann, 2010).

The dorsal network includes the inferior parietal sulcus/IPS and the superior parietal lobule/SPL, the dorsal prefrontal cortex/dPFC and the frontal eye field/FEF. The ventral network includes the temporo-parietal juncture/TPJ (especially on the right; rTPJ) between the inferior parietal lobule/IPL and the superior temporal sulcus/STS, the MCC or dorsal anterior cingulatedACC, the insula, the inferior frontal gyrus/IFG, and the posterior cingulate/PCC (Majerus et al., 2012). However, these results are only generally consistent across studies.

Across fMRI studies, these networks very commonly co-activate, as can be readily seen in large metanalyses such as *Neurosynth* (Yarkoni, 2011) (See Figures 3.3 and 3.4). Here, studies are automatically analysed for activation foci and key terms. Conflating over all other factors, papers mentioning the term "TPJ" show, trivially, with high probability, activity in TPJ, but also very often also show IFG and MFC activity; so do papers mentioning the term "dACC".

The DAN is thought to implement top-down or goal-driven attention. It protects mental focus on a specific information stream or stimulus against distractors and promotes aspects of the sensory input to the focus of processing. Prototypically, it is active in implementing spatial attention, where stimuli at a critical position are promoted and stimuli appearing at other sites are ignored. It is also assumed to maintain an attentional set of expected stimuli that require responses.

In contrast, the VAN implements bottom-up, stimulus-driven attention. It allows the detachment from a current focus of attention if another stimulus is sufficiently intrusive or has been judged to require reorientation. It also

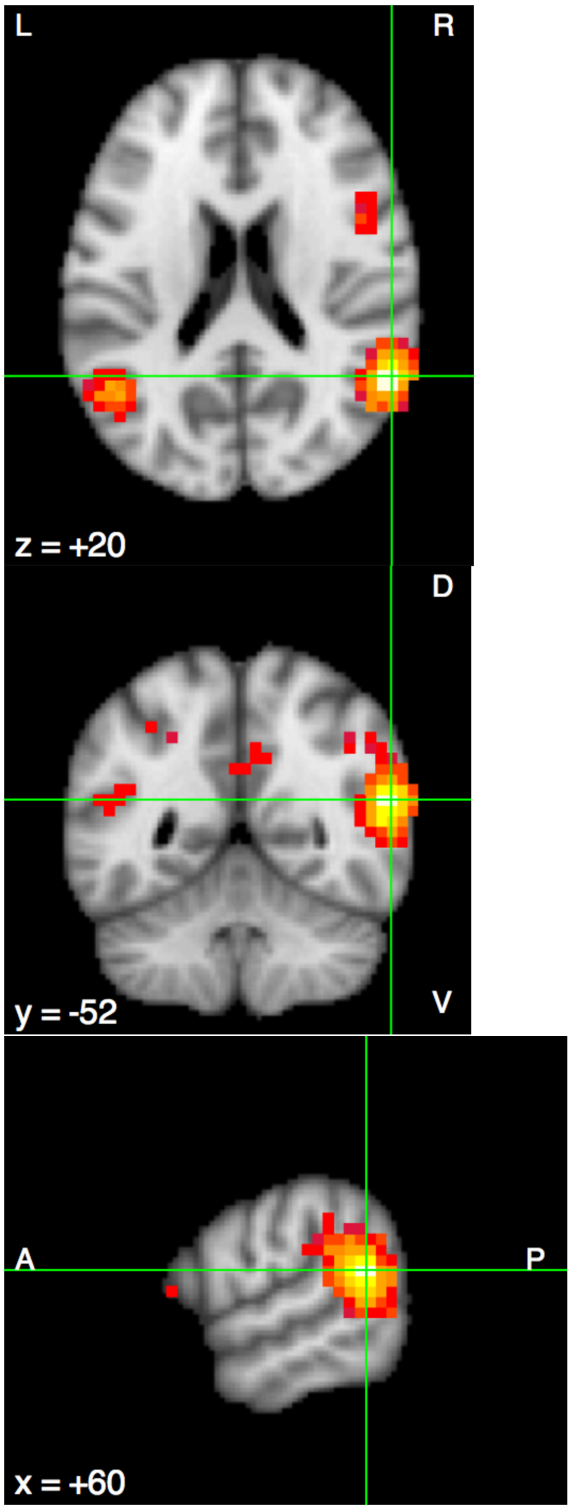

Figure 3.3: Term-based map of cross-study activations for the term "tpj" derived by the Neurosynth database (Yarkoni, 2011). The green coordinate vector shows the right TPJ region; further regions incluce IFG and cingulate cortex.

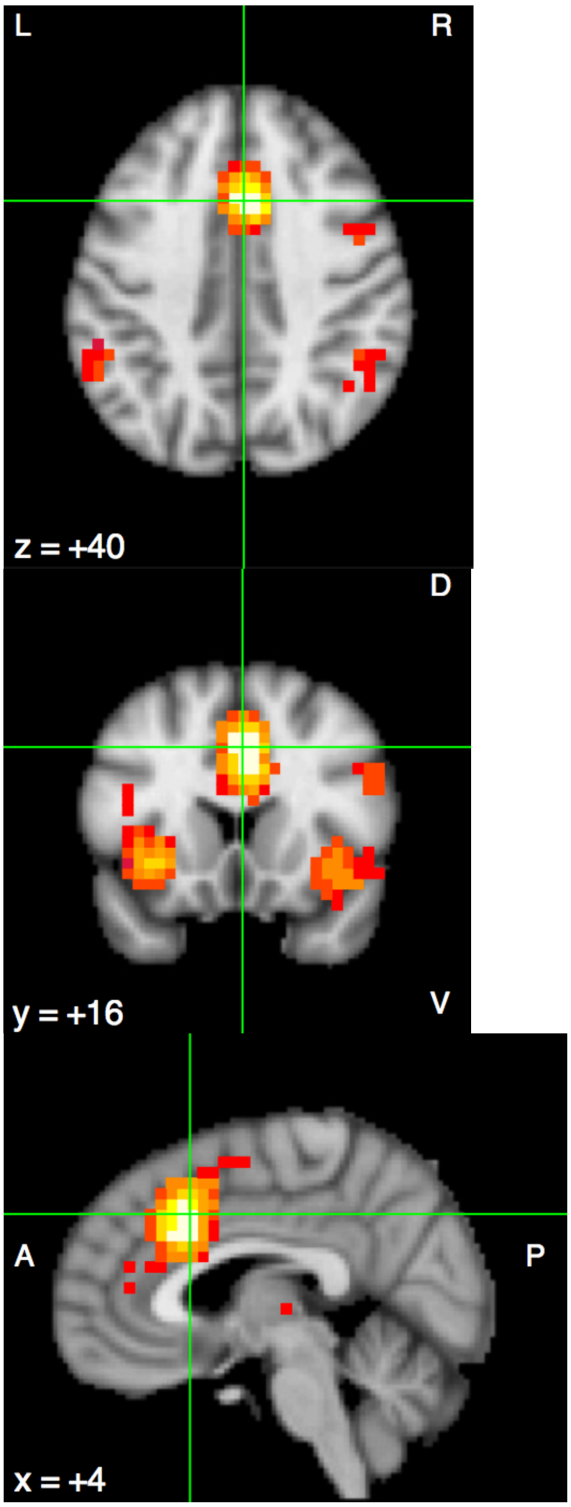

Figure 3.4: Term-based map of cross-study activations for the term "dACC" derived by the Neurosynth database. The green coordinate vector is focused on the dorsal parts of the cingulate, including MCC and pACC; further regions incluce IFG and TPJ.

functions as an alerting system, becoming active following cues that critical stimuli are upcoming (Clerkin et al., 2013). Importantly, it is active in *effective* reorientation - only stimuli that catch the subject's attention activate the VAN, indicating that attention-catching is mediated by the VAN, where the VAN interrupts any sustained attention and refocuses attention on the new stimulus. As noted, the TPJ is assumed to play the role of the *circuit breaker* here.
The amodal or supramodal (Davis, Downar, Crawley, & Mikulis, 2000; Macaluso, 2010) nature of this system has also been demonstrated by intracranial recordings (Chennu et al., 2013). These show a relative insensitivity of TPJ responses to the *type* of deviancy, with both spatial and frequency auditory Oddballs eliciting responses; however, these responses depend on attention, in that non-attended streams do not elicit them.

The role of the DAN therefore seems to correlate better with sustained, ongoing aspects of attention - distractor resistance and preparatory action. The VAN implements vigilance - it must be able to respond rapidly and temporally precise.

Using single-unit recordings of neurons in monkey IPL (Bisley, 2006), reorienting has been closely modeled. The population response to events at locations in the focus of attention shows higher contrast sensitivity; when reorienting occurs, contrast sensitivity switches towards another position, temporally correlated with the response.

Importantly, both of these networks reliably correlate with α oscillatory power (Sadaghiani et al., 2010). BOLD levels in the VAN correlate positively with α and β power, DAN BOLD Levels are negatively correlated with α and β power. These correlations include fMRI-identified regions not directly contributing to EEG-observable α, such as the medio-frontal/cingulate cortex and the thalamus.

The VAN receives extensive noradrenergic projections from the LC. Especially noteworthy are, again, the TPJ and the MFC. Macaque area 7 (a possible homologue of the human TPJ) receives exceptionally dense LC innervation (Divac, Lavail, Rakic, & Winston, 1977; Mesulam, Van Hoesen, Pandya, & Geschwind, 1977; Morrison & Foote, 1986). The TPJ is the brain region that is most reliably connected to reorientation behavior, becoming active to stimuli that effectively capture attention and generally, to targets regardless of overt response requirements. Also called Ventral Parietal Cortex, it is extensively connected to frontal and temporal areas (Cabeza, Ciaramelli, & Moscovitch, 2012). In the attention network account, it is assigned a role in bottom-up, stimulus-driven reorientation of attention (Corbetta et al., 2008). The pre-rolandic cingulate similarly reacts to targets and novelty, but also plays a key role in activating the LC and generally, in task control.

Functional imaging research also shows that the VAN is deeply interconnected with the LC/NE system. NE levels correlate with VAN activity (Hermans et al., 2011), and functional antecedents of VAN activity and phasic LC activity are highly similar. The temporal interdependence of VAN and LC responses, as well as overt reactions, has been demonstrated using combined EEG and fMRI (Walz et al., 2013); here, coupled brain steam and VAN activity predicted behavioral variability. A sketch of the mechanism of NE-facilitated reorienting following effectively attention-grabbing stimuli is therefore possible:

(1) the categorization of a stimulus as requiring a cognitive state shift

(2) activation of the LC by a frontal system including the MFC

(3) release of NE at target sites, including MFC and TPJ

(4) cortical network reset following NE-induced increases in responsitivity, including suppression of DAN focus

(5) response selection based on stimulus-response mapping, possibly supported by TPJ/medio-frontal cortex

The activation of LC responses by cortical drive comes from reciprocal connectivity with frontal regions. However, their basic purpose includes the modulation of activity in parietal, temporal, occipital and motor areas. In the following, the ventral and dorsal processing streams supporting perception and action in these areas will be discussed, including their relationship to the attention networks.

3.2.3.1 *Dual stream models and attention networks*

DAN and VAN nontrivially relate to the dorsal and ventral streams, two brain networks where sensory input arriving at primary sensory areas travels in a posterior to anterior direction along the brain's major fiber pathways, enabling both visual (Goodale, Westwood, & David Milner, 2004; Schneider, 1969) and auditory, including linguistic (Dick & Tremblay, 2012; Griffiths, Marslen-Wilson, Stamatakis, & Tyler, 2013; Kummerer et al., 2013), processing. In vision, the dorsal path crosses inferior parietal areas, towards motor and frontal areas, connected by the superior longitudinal fasciculus, especially its arcuate part; in audition, an analogue auditory stream originating in the primary auditory cortex has been established (Rauschecker, 1998; Rauschecker & Scott, 2009). The ventral stream travels along the temporal lobe towards the frontal lobe via fiber pathways including the extreme capsule and the uncinate fasciculus. Originally (Mishkin, Ungerleider, & Macko, 1983), it was proposed that the dorsal stream processes stimulus location to facilitate interaction, for example as *vision for action* or the "where" stream; multiple reinterpretations followed, such as that of a "how" path (Goodale & Milner, 1992). The ventral stream establishes stimulus/object identity, as in *perception for vision* or the "what" stream. While most research in this regard has a low temporal resolution (fMRI and lesion methods), ECoG recordings mapping ventral stream activity show strongly stimulus-locked activity, while dorsal stream electrodes show strongly response-locked activity (Chang et al., 2011); in such analyses, one of the areas to not exhibit exclusively response- or stimulus-locked activity is the TPJ.

Currently, the debate has acknowledged that the roles and even identities of the two streams are far from being fully characterized. Yet, the general association of the dorsal stream with spatial and motor aspects, and the ventral stream with stimulus perception and identity as well as memory systems, still reverberates in the research (McIntosh & Schenk, 2009; Milner & Goodale, 2008; Singh-Curry & Husain, 2009).

The dual-stream perspective has been extended to also include auditory processing (Rauschecker, 1998), where a dorsal temporal-to-frontal stream was

originally associated with spatial processing of sounds, and a ventral stream with recognition. Recently, the two-stream perspective has been embraced by researchers of speech processing (Hickok & Poeppel, 2004; Rauschecker & Tian, 2000). Here, the ventral stream has been associated with speech segment identification and the dorsal stream with speech/motor integration. The influential Hickok & Poeppel model (Hickok & Poeppel, 2007) assumes a ventral stream connecting, in that order, primary auditory areas, the medial temporal gyrus/MTG (Lau, Phillips, & Poeppel, 2008) as a locus of lexical association, the anterior temporal lobe/ATL as part of a system implementing combinatorial processing, and finally the IFG. The Rauschecker & Scott model (Rauschecker, 2012; Rauschecker & Scott, 2009) does not emphasize a role of the MTG. Conversely, the dorsal stream is primarily assigned a role in speech production by the Hickok & Poeppel model, travelling along the core of the TPJ, a region named Sylvian parietal temporal/area Spt and the inferior parietal lobe/IPL, both areas assumed to play a role in sensorymotor integration, and the premotor and motor cortex, reaching again the IFG.

The development of the VAN/DAN hypothesis, increasingly built on resting-state fMRI data, marks a major divergence from the original dual-stream hypothesis. Superficially, the two perspectives on the dorsal/ventral systems - in attention/reorientation; and in perception/action; - have little in common. However, the brain areas in question are partially overlapping, requiring the integration of both perspectives. Some attempts have been made to integrate the functional interpretations resulting from both models for the proposed roles of isolated regions important for both perspectives (Singh-Curry & Husain, 2009). However, no universally accepted model unifying all functions has so far emergent.

3.2.4 *At the Heart of the VAN: Controversial Perspectives on TPJ Function*

3.2.4.1 *Anatomy and Terminology*

The functional assignment of the general area termed TPJ here is not any less controversial than anatomical categories and terminology (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; Galaburda & Sanides, 1980). Parietal and temporal lobes meet at the end of the Sylvian fissure. The area directly adjacent to the end of the Sylvian fissure is sometimes (Hickok, Buchsbaum, Humphries, & Muftuler, 2003; Hickok, Okada, & Serences, 2008; Pa & Hickok, 2008) specifically denoted "area Spt" (Sylvian parietal temporal in the planum temporale). A wider, more general region, dorsally to the juncture, is the supramarginal gyrus/SMG, joined ventrally by the angular gyrus/AG (equivalent to BA 39), both together forming the ventral lobe or, alternatively, the inferior lobe/IPL of the parietal cortex. Some researchers (Nieuwenhuis et al., 2005) identify the parietal AG and SMG as subdivisions of the TPJ area; others (Husain & Nachev, 2007) add the posterior part of the superior temporal gyrus; others (Ciaramelli, Grady, Levine, Ween, & Moscovitch, 2010) identify the TPJ as a part of the SMG. Sometimes, the posterior superior temporal sulcus alone, or, conversely, the posterior inferior parietal lobule, is identified as the TPJ (Bzdok et al., 2013).

The temporal neighbours of this parietal cluster, frontal to the TPJ, ventral to the Sylvian fissue, is Wernicke's Area, a key brain region associated with

language, and connected to the locations most strongly associated with primary auditory (primary auditory cortex; frontal to Wernicke's Area) and lexical processing (MTG; ventral to Wernicke's Area). By some measures, Wernicke's Area and the TPJ overlap (Bogen & Bogen, 1975).

The TPJ also connects to the occipital lobe (at the lateral occipital gyrus) and dorsally to motor areas (the primary sensorimotor cortex in the parietal lobe).

The extensive connectivity of the TPJ includes areas associated with both the ventral and the dorsal streams (Cabeza et al., 2012; 2008), as well as fiber tracts associated with the dorsal stream, such as the arcuate, and ventral connections, such as the middle longitudinal fascicle and the extreme capsule (Dick & Tremblay, 2012; Dick, Bernal, & Tremblay, 2013). The TPJ is also connected to the hippocampus via the inferior longitudinal fasciculus. Its most extensive far-reaching cortico-cortical connection is to the cingulate, especially the ACC (Mesulam et al., 1977).

In sum, depending on how broadly the TPJ is defined, this brain region is located directly in between the areas associated with the brain's main sensory centres; here, temporal areas associated with hearing and speech, occipital areas associated with vision and parietal/motor areas associated with somatosensory processing meet. It is also connected to internal systems, including memory and somatosensory processing, and receives projections from brain stem nuclei modulating arousal/attention and learning and forward-oriented processing.

3.2.4.2 *Function: Multimodal Sensory Processing, Sensorimotor Hub, or ToM?*

In the following review of the functional correlates of TPJ activation, hemispheric lateralization will be ignored for the sake of simplicity. Generally speaking, attentional reorientation and Theory of Mind have been especially associated with right-lateralized activity (Corbetta et al., 2008; Saxe & Wexler, 2005), whereas language-related TPJ activity is often somewhat left-lateralized. A more specific investigation of hemispheric differences has recently indicated that the left TPJ is more sensitive to the subjective significance and the right TPJ to intrinsic salience/intrusiveness of stimuli (DiQuattro & Geng, 2011; Kucyi, Hodaie, & Davis, 2012), though the TPJ is bilaterally sensitive to task relevance (Downar et al., 2001a).

It may thus be not too surprising that the TPJ has been implicated in a near boundless variety of paradigms across all these sensory and internal systems, including purely auditory, visual, and somatosensory stimulation, leading to proposals focusing a multimodal (Downar et al., 2001b; Downar et al., 2001a; Matsuhashi et al., 2004), multisensory (Macaluso, 2010; Macaluso & Driver, 2005; Macaluso, Driver, & Frith, 2003) or domain-spanning (Bzdok et al., 2013) function. It is one of the most common findings in neuroimaging research (Yarkoni, 2011). Most such studies have been carried out using fMRI. Of special interest regarding unimodal stimulation is a recent study indicating that TPJ activity is a necessary precondition for the conscious perception of visual hallucinations induced by Transcranial Magnetic Stimulation of the occipital lobes (Beauchamp, Sun, Baum, Tolias, & Yoshor, 2012); only when TPJ γ power, as measured by ECoG, was high did TMS result in reports of visual percepts, implying

a role of the TPJ in relaying sensory information to networks supporting conscious experience.

The TPJ also specifically responds to multimodal integration. For example, the TPJ is implicated in the McGurk effect of integrating visual (lip movements) and auditory correlates of speech (Jones & Callan, 2003), though a more characteristic region might be the adjacent aspects of the superior temporal sulcus/STS (Nath & Beauchamp, 2012) that is also implicated in multisensory integration (Beauchamp, 2005), and in gesture/speech integration (Straube, Green, Jansen, Chatterjee, & Kircher, 2010). Processing combined tactile and visual stimulation also depend on the TPJ (Papeo, Longo, Feurra, & Haggard, 2010). Relying on lesion studies, the TPJ has also been implied in synaesthetic and metaphor comprehension (Hubbard & Ramachandran, 2003; Ramachandran & Hubbard, 2001), including comprehending linguistic metaphors accompanied by gestures (Straube, Green, Sass, Kirner-Veselinovic, & Kircher, 2012). Beyond this auditory/visual integration, area Spt at the core of the TPJ is also associated with acoustic/motor integration (Hickok et al., 2008).
Of special importance regarding the TPJ is the observation that this region is part of a restricted number of brain areas (Stein & Stanford, 2008) sensitive to sensory integration spanning more than two modalities (trimodal integration).
While the dorsal and ventral stream distinction is strongly based on a differential sensitivity to spatial versus identity information, the TPJ has, as noted before, been shown to be comparatively insensitive to this distincrion (Chennu et al., 2013), but strongly sensitive to attentional factors, indicating a supramodal role in directing attention to stimuli. In a related finding, the AG emerges as sensitive to amodal semantic processing, becoming active to both the picture of an apple and the written word "apple" (Fairhall & Caramazza, 2013).

In additions to such (partially low-level) multisensory integration processes, the TPJ has also been implicated in processing a more abstract category of human experience: the so-called Theory of Mind/ToM. In numerous studies (Callejas, Shulman, & Corbetta, 2011; Saxe & Wexler, 2005), the TPJ became active during tasks involving hypotheses about the current mental state of another person. A multi-facetted debate has emerged regarding the compatibility of such high-level, abstract features with a more basic role of the TPJ, especially in attentional reorientation (Callejas et al., 2011; Perner & Aichhorn, 2008; Scholz, Triantafyllou, Whitfield-Gabrieli, Brown, & Saxe, 2009). A nearly identical perspective emerges for the adjacent STS (Hein & Knight, 2008), leading to a characterisation as the "chameleon of the human brain".

Various researchers have attempted to integrate these two seemingly disparate findings (Cabeza et al., 2012), including both theoretical and methodological proposals. Proponents of a specific localisation of ToM in the TPJ argue for a subdivision of this area, with some parts being sensitive to ToM, others to reorientation paradigms (Mars et al., 2012); it has also been proposed that different parts of the TPJ are active in different networks, one internally-oriented ToM-sensitive and an external, stimulus-driven reorientation network (Bzdok et al., 2013). This claim is disputed by researchers observing substantial overlap in activation patterns across paradigms (Decety & Lamm, 2007; Mitchell, 2007) who argue that ToM-associated effects are an artifact of the attentional and/or memory demands of these paradigms (Cabeza et al., 2012; Callejas et al., 2011; Corbetta et al., 2008).

In a related finding, researchers associated with the ToM side of the debate (Young, Camprodon, Hauser, Pascual-Leone, & Saxe, 2010) have implicated the TPJ also in moral reasoning. Furthermore, the TPJ (and potentially associated areas, the posterior cingulate and precuneus) is very commonly found in studies of the semantic system (Binder, Desai, Graves, & Conant, 2009). It has also been associated with memory processes; specifically, the Attention to Memory/AToM model (Cabeza et al., 2012; Ciaramelli, Grady, & Moscovitch, 2008) wherein the TPJ implements attentional reorientation not only following external events, but also resulting from internal, memory-driven processes, such as remembering an important date. Potentially, the input from memory related areas, such as the hippocampus/MTG, is handled similarly by the TPJ as is external, sensory input. Consequently, the TPJ has also been identified as a region linking external (stimulus-directed) and internal (i.e. memory- or simulation/ToM - based) information (Bzdok et al., 2013); however, such a narrow proposal is incompatible with the wide range of findings establishing that the TPJ is also active in linking any two external streams.

In contrast to this heterogenous picture of a role of the TPJ in cross- and multimodal stimulus evaluation mostly based on fMRI-focused research, in lesion studies, the TPJ is specifically associated with spatial neglect (Husain & Rorden, 2003). Consistently, right TPJ lesions correlate with left-hemispheric spatial neglect, where subjects can fundamentally process stimuli in the left visual field, but do not become aware of them and cannot consciously interact with them.

While the TPJ is an important area in multiple major research programs - multimodal integration, dual-stream models of language, and attention - it is not easily integrated into any interpretation compatible across the resulting perspectives.

In the primary models of two processing streams in vision (Goodale & Milner, 1992; Milner & Goodale, 2008), the processing stream terminates at or near the IPL, and no detailed considerations regarding its role are made. However, the TPJ is of crucial importance in auditory perception/language and has consequently been assigned a major role in two-stream models of speech (Hickok & Poeppel, 2007).

Similarly, comparing two-stream and attention network accounts, the assumed function of inferior parietal regions, especially the TPJ, which plays a well-established and central role in the VAN, does not easily integrate with the dual stream model. For example, while spatial oddballs (stimuli whose location is unexpected) preferentially activate the dorsal and identity oddballs (stimuli whose inherent features are unexpected) preferentially activate the ventral stream, the TPJ is strongly activated by either kind of oddball (Marois, Leung, & Gore, 2000).

3.2.4.3 *TPJ: Dorsal or Ventral?*

As noted, in the VAN/DAN model, the TPJ is the key posterior center of the *ventral* network, corresponding not to top-down control, but to bottom-up responses.
But for proponents of dual stream accounts of speech processing (Hickok & Poeppel, 2004; Rauschecker & Scott, 2009), the TPJ is necessarily assigned a

role in the dorsal stream, since the dorsal path from primary auditory areas in the superior temporal lobe to frontal areas must pass the TPJ:

> The dorsal stream projects dorso-posteriorly involving a region in the posterior Sylvian fissure at the parietal–temporal boundary (area Spt)
> Hickock & Poeppel (2004, p. 67)

Problematically, the TPJ (more specifically: its subdivision area Spt), being a member of the dorsal speech stream, is primarily implicated in mapping between sensory and motor representations, and is thought to have a critical role in production, but only a supportive role in perception (Hickok et al., 2008); however, as discussed above, while the TPJ (and the pSTS) reliably activates during multimodal integration, this activation is far from being restricted to sensory-motor integration, but to purely sensory multimodal paradigms.
Current studies continuously observe that the TPJ remains in conjunction analyses of production and perception (Grabski et al., 2013). One recent study reports greater activity for covert compared to overt articulation (Andreatta, Stemple, Joshi, & Jiang, 2010). A meta-analysis (Bzdok et al., 2013) found that at least the right TPJ is at least as, or even more predictably active during "hearing" (there as defined by the BrainMap taxonomy as "The sense of hearing") than during speaking.

It has also been proposed that the relationship of the TPJ area might be in linking dorsal and ventral streams, since it receives information from multiple senses and is connected to fiber tracts associated with both streams (Karnath, 2001); for example, it may synthesise information about both the type and the location of an object, or, in the auditory domain, of associating the content of speech with speaker identification (Tian, 2001).
What all these accounts share is the interpretation of the dorsal system as implementing controlled, goal-oriented processes, and the ventral system as being stimulus driven and relevant to the categorization of sensory input, with the TPJ playing a role in cross-modal integration.

Two main forms of attempts to reconcile these disparate views seem possible. First, one perspective, possibly most compatible with the approach outlined by researchers such as Saxe and coworkers (Mars et al., 2012; Saxe, 2010; Scholz et al., 2009), assuming that a specific subdivision of the TPJ specifically implements ToM - related processes; or Hickok et al. (2008), who declare a specific sensitivity of area Spt to sensorymotor integration associated with the vocal tract; and possibly Corbetta (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Corbetta et al., 2008), who assumes a specific role of the right TPJ in stimulus-driven attentional reorientation.

Underlying such proposals are three components: first, a strong anatomical distinctness of brain areas; secondly, functional specificity of such areas; and thirdly, a high reliability and resolution of specifically fMRI to distinguish between specific functions and activations of specific brain areas. Such interpretations can be associated with a localist perspective on brain work.

Generally, it could be attempted to precisely model the specific functions of small, segregated brain patches by integrating a growing number of functional neuroimaging work, identifying the lowest common denominator for any brain area. At the end of such an approach, the broad area in question (the areas surrounding the end of the Sylvian fissure) would be segre-

gated into multiple subdivisions with specific, distinct, and different functions overlapping with aspects of cognition currently identified by cognitive theories (Hickok & Saberi, 2012).

Alternatively, a perspective that is less optimistic about anatomical separability[2], intuitions about cognitive categories and methodological precision is possible. In this view, the brain would not be seen as strongly segregated, and the function of adjacent regions would not be seen as similar, yet distinct. Rather, their function would be see as lying on a gradient; for example, the temporo-occipital regions would function similar to superior temporal regions, with more occipital regions being more important for visual, more temporal regions more important for auditory aspects of overlapping, interacting, similar, not strictly differentiable cognitive faculties.

Here, an estimation of a lowest common denominator for the whole TPJ complex would be the only possible outcome, and it should reflect the functional anatomical embedment of this region.

Specifically, the TPJ area is characterized by the following broad observations.

Anatomically, it is connected to both primary sensory and motor areas, both input and output systems, as well as metacognitive and memory areas; it also receives brain stem neuromodulatory signals, especially from the LC. Functionally, the TPJ is found in a wide range of stimulus integrative paradigms, including stimulus-driven reorientation, conscious perception, and multiple forms of uni- and multimodal integration.

Functionally, TPJ responses can be observed following events in two different time frames. Uni- and multimodal *integration* is presumably a sustained process, relaying continuously arriving sensory information. *Reorientation* is a punctualized process that necessarily results in the disruption of the integration of any currently attended sensory streams and may result in sustained attending to a new stream. In the VAN perspective (Corbetta et al., 2008), this punctualized process is a specific function of the TPJ - the TPJ as a "circuit breaker". However, a specific punctualized, phasic mode is already implemented by the Locus Coeruleus. A parsimonious explanation of TPJ effects in both reorientation and multimodal integration could depend less on the function the TPJ itself, but in the function of its surroundings. Potentially, the TPJ routes between the multiple sensory streams connected here depending on attentional demands. Interrupt signals from the LC following intrusive, significant events then implement a network reset (Bouret & Sara, 2005) in the TPJ, abolishing the current sensory link and allowing the TPJ to let a new setup form. The TPJ would then not have the function

2 One problematic aspect of typical fMRI analysis in this regard is that current statistical procedures in the Neyman-Pearson framework implement a systematic *under*estimation of the extent of activation (Gelman, 2013; Gelman & Price, 1999). Maps and reports of "statistical significance" are categorically masked by thresholding at a fixed, binary level such as "$p < .05$", which implies that an observation that would have had a very low probability of occurring if the region does not show a differential response to two task conditions, such as e.g. 7% probability of observing the data given exactly 0 difference, will typically be disregarded for the sake of "controlling type I errors". Consequently, statistical parameter estimates masked by significance cutoff thresholds present an overly narrow, segregated and separated representation of cortical activity - a lowest denominator, where only regions where a true zero effect is very unlikely are shown, and many regions where it is only *slightly* less unlikely (Rosnow & Rosenthal, 1989) are hidden (surely, following Rosnow & Rosenthal, God loves the map masked at $p < 0.06$ as much as the one masked at $p < 0.05$).
A similar argument has been presented by Klein (2010).

of implementing reorientation/"breaking circuits"; rather, a given sustained state of the TPJ might be equivalent to attending to a subset of the sensory (including memory-related) input, and attending to an alternative subset of input dimensions may require a network reset. The role of the "circuit breaker" would remain with the LC, able to somewhat focally reseting the state of specific cortical networks.

I propose that such a mechanism can explain a wide range of TPJ-related findings while being mostly derived from the already well-established functions of its neuronal environment, including its position as a hub between various primary sensory and internal processing associated areas and its integration in the LC system.

Due to its low spatial resolution, EEG research has traditionally not contributed much by itself to most of the discussion regarding functional anatomy. However, specifically phasic activation of the ventral system and the MFC/TPJ are responsible for some of the major ERP components, especially the P3, providing a further perspective on the attention system by allowing to noninvasively map the time course of attentional reorientation. The following chapters will discuss findings from this domain in detail.

3.3 MEASURING ATTENTION IN HUMANS WITH THE EEG

Anatomical and functional imaging studies have elaborated on the general anatomy of attention and cross-modal integration system, and single-cell and ECoG recordings in animals have established the temporal dynamics of LC activity. However, the precise spatiotemporal dynamics of reorientation in human cognition is not easily inferable from such methods. However, readily collectable physiological correlates of arousal and attention exists in measures of autonomous nervous system activity and the EEG/ERP.

The Orienting Response/OR, originally described by Russian researcher Sokolov, is a psychophysiological reaction following stimuli of sufficient "novelty, intensity, [and/or] significance" (Barry, 1990, p. 2). Regarding novelty, habituation results from stimulus repetition. Regarding intensity, the OR lies on a spectrum between insensitivity to low-intensity stimuli, and startle/pain responses to stimuli with extreme intensity. Significance is understood as the subjective importance placed on the occurrence of an event.

Various physiological effects, indices of the OR, follow novel, intense and significant stimuli, including the Galvanic Skin Response/GSR measured by skin conductance response/SCR, changes in blood volume and heart rate, pupil dilation, increases in respiration rate and EEG broad-band, especially α, power decrease (Barcelo, Hall, & Gale, 1995; Nalivaiko, Bondarenko, Lidström, & Barry, 2011). All these effects covary in temporal and intensity profiles.

This observation regarding the EEG during the OR is remarkably similar to Berger's view on α blocking. Berger wrote:

> "... findet man, daß der Schreckreiz, wie jeder Reiz, der die Aufmerksamkeit fesselt, zu einem Spannungsabfall und einem Ausfall der Hauptwellen des E.E.G. führt. Nach kurzer Zeit kehren dann die Hauptwellen wieder." (Berger, 1933, 6)

> One can observe that the surprising stimulus, like any attention-capturing stimulus, leads to a drop in current and a breakdown of the main waves of the EEG. After a short time, the main waves return.

The OR has been connected to the LC/NE system (Bouret & Sara, 2005; Counts & Mufson, 2012; Nieuwenhuis et al., 2010; Sara & Bouret, 2012). Anatomically, both the LC and the autonomous nervous system receive input from a common source, the nucleus paragigantocellularis/PGi (Pfaff et al., 2012), which is an area receiving strong projections from cortical sites such as the insula and the ACC. Lesioning the NE system can abolish the physiological correlates of the OR, such as the SCR (Yamamoto, Arai, & Nakayama, 1990). The relationship between LC function, pupil dilation and behavioral parameters, such as learning/memorization profiles following from gain regulation, has been extensively investigated (Eldar et al., 2013). However, this relationship is complex, with interactions over multiple time frames.

Interestingly, error monitoring and the OR share a number of physiological similarities, such as heart rate and pupil dilation effects (Wessel, Danielmeier, & Ullsperger, 2011) and a common association with the catecholamine system (DA and NE), though dopamine might play a more prominent role in error processing than NE (Mueller et al., 2011). Similarly, OR-like autonomous nervous system responses better correlate with NE-related than with DA-related ERP components (Hajcak, McDonald, & Simons, 2003).

EEG correlates of error processing have been linked to the MFC/RCZ (Debener, Ullsperger, et al., 2005), a major locus of cortex-LC interactions.

Consequently, an association of the OR and the physiological reactions to becoming aware of errors, mediated with the LC system, has been proposed (Ullsperger, Harsay, Wessel, & Ridderinkhof, 2010; Wessel, Danielmeier, Morton, & Ullsperger, 2012).

As noted, LC activation decreases broad-band EEG power, and the OR is characterized by a desynchronized cortical state (Barcelo et al., 1995). Berger had already observed that peripheral effects of the OR and parameters of the EEG correlate:

> "Die Untersuchungen der Latenzzeit dieser Psychoreaktion der Pupille stehen mit den Ergebnissen meiner Messungen über die Zeit, die verfliegt, bis die Hemmungswirkung sich am E.E.G. zeigt, in gutem Einklang. Die Veränderung am E.E.G. tritt nämlich erheblich früher ein." (Berger 1933, 563)

> The investigations of the latency of this psycho-reaction of the pupil are quite compatible with results of my measurements concerning the time until inhibitory effects show up in the EEG. The EEG perturbations appear substantially earlier.

Generally, α and broadband power become greatly attenuated before the other correlates of the OR, compatible with the effects of LC activation on arousal and broadband EEG power.

However, a further EEG measure of the activity of brain regions implementing the reorientation of attention has been proposed: the P3.

3.3.1 *The P3*

α blocking is sensitive to the subjective relevance of stimuli. In contrast, the earliest ERP effects were related to externally measurable parameters. Sensory stimulation resulted in strictly stimulus-dependent effects, including the evoked potential and the "exogenous" ERP components, such as the "vertex potential" including the N100/N1 (Davis & Zerlin, 1966; Davis, Mast, Yoshie, & Zerlin, 1966; Davis, 1939) and the following P200/P2, and C1/P1 (Spehlmann, 1965). Indices of movement include the CNV (Walter, Cooper, Aldridge, McCallum, & Winter, 1964) and the negative peak at movement onset/MRP (Gilden, Vaughan, & Costa, 1966). Exogenous potentials covary with various stimulus aspects inherent to the stimulus itself.

The P3 is the original *endogenous* component. It was discovered by Sutton et al. (1965) in a paradigm investigating subjective uncertainty, averaging large numbers of EEG epochs from multiple trials to create Event-Related Potentials/ERPs. In some trials, a cue was reliably predictive of the actual stimulus. Compared to such trials, in trials where the nature of the stimulus could not be predicted, a large biphasic component pattern emerged. First, around 200 msec, a negative component peaked (N2), followed by a large, long-lasting positive peak with a broad, centro-parietal maximum. A number of mismatch-sensitive negative components were discovered in the context of the P3 (Ritter & Ruchkin, 1992), including the Mismatch Negativity/MMN (Butler, 1968; May & Tiitinen, 2010) as an index of automatic deviancy detection and the aforementioned N200/N2 often preceding the P3 as an index of deviancy detection in an attended stream.

In 1967, Sutton elegantly demonstrated the endogenous nature of the P300 when a P3 was observed to the informative omission of a stimulus (Sutton, Tueting, & John, 1967).

In the visual domain, the P3 can be defined as, following the P1 and P2 peaks, the third positive peak of the visually elicited potential. Alternative names include the "P300", because it usually peaks later than 300 msec after stimulus presentation, or the Late Positive Complex/LPC. Though the P3 was originally discovered in subject averages, it is also one of the few components visible in single EEG trials.

Sutton's finding instigated substantial research regarding the antecedents and function of the P3. Most importantly, as was already understood following Sutton's original experiment, the P3 is sensitive more to subjective than to stimulus-inherent factors. It is often found in contexts of surprisal, such as Sutton's study; however, highly expectable stimuli also often result in a P3. In fact, both interpretations may be applied to the principal P3 paradigm: the two-stimulus oddball paradigm. Here, subjects are presented with sequences containing repetitions of two kinds of stimuli, one of which is more common than the other. Typically, the rarer stimulus will have to be responded to manually, or a different response has to be given to either stimulus. The rare stimulus shows an N2/P3 pattern compared to the common stimulus: a negativity with a peak around 200 msec is followed by the P3. Two related paradigms elicit slightly different responses. In the typical 3-stimulus oddball design (Debener, Makeig, Delorme, & Engel, 2005; Polich & Margala, 1997; Squires, Squires, & Hillyard, 1975), a third class of stimulus is introduced: rare, novel stimuli that elicit a positivity with a sharper peak and a more frontal distribution than the rare target, called P3a or nov-

elty P3 to distinguish it from the typical posterior-central P3 (or contrastingly, "P3b"). In the go/no-go task (Pfefferbaum & Ford, 1988), responses are given to common targets and have to be inhibited to rare non-target stimuli; here, compared to the common targets, the rare non-target elicits a mid-central "no-go P3". A related paradigm is the continuous performance task, where targets are embedded in a non-predictable stream of non-targets; here, a monophasic P3 follows targets.

A number of loosely connected components includes: the P600 (Curran, 1999; Kutas, 1988; Rugg & Doyle, 1992), sometimes also called Late Positive Potential/LPP or LPC (Friedman, 2000; Rugg & Allan, 2000), a later-peaking positive component correlated with item recognition; the positive posterior Slow Wave often following the P3b (Loveless, Simpson, & Näätänen, 1987); and the LPP/LPC correlating with the emotional intensity of stimuli (Brown, Van Steenbergen, Band, de Rover, & Nieuwenhuis, 2012); and the far-frontal P3f (Delorme, Westerfield, & Makeig, 2007; Potts & Tucker, 2001) preceding responses. Other components sometimes associated with the P3 include the error positivity/P_E following conscious errors; recently, it has been shown that the P_E is best connected to conscious awareness of errors (Murphy, Robertson, Allen, Hester, & O'connell, 2012; Wessel et al., 2012). Finally, the syntactic positive shift/SPS or linguistic P600 (not to be confused with the earlier nomenclature for the memory-related P600) following linguistic deviancies (Osterhout & Holcomb, 1992) has been interpreted as a P3 (Coulson, 1998), a proposal that will be discussed in more detail below.

The role of the P3a in novelty detection or distractibility has been contrasted with a more general role in reorientation/attention-capturing following salient, but task-irrelevant stimuli (Barcelo, Escera, Corral, & Periáñez, 2006; Friedman, Cycowicz, & Gaeta, 2001; Parmentier, Elsley, Andrés, & Barcelo, 2011; Sawaki & Katayama, 2008), possibly by a frontal network (Debener, Makeig, et al., 2005; Wronka, Kaiser, & Coenen, 2012) centred on the cingulate cortex as a mediator of frontal responses to critical stimuli (Onton, Delorme, & Makeig, 2005).

In a combined fMRI/ERP study (Bledowski et al., 2004), overlapping source-localized ERP and fMRI activity to (non-novel) distractors were highly compatible with the DAN whereas targets reflected in VAN activity (note that in this study, the authors labelled a centro-posterior positivity following non-responded, non-novel stimuli as a "P3a").

The P3 is sensitive to various aspects of stimulus, task and subject state in its size, latency and scalp distribution. Generally, differences in scalp distribution are more often interpreted as implicating distinct components, since ERP components are assumed to be generated by spatially stationary brain systems whose activity varies more in time and strength than space (Makeig et al., 1999).

Two different questions concern the strength of the P3. On one hand, the nature of stimuli that do elicit a P3, compared to those that do not; on the other hand, what stimulus aspects modulate the size of the component (measured typically base-to-peak, sometimes as mean area or integral).

Extensive research has established a number of factors influencing P3 amplitude. Less probable/more surprising and more important/task relevant stimuli elicit a larger P3 (Nieuwenhuis et al., 2005; Polich, 2007). The only stimulus-inherent factor known to reliably influence P3 amplitude is stimu-

lus intensity. Generally, subjective factors are the main determinants of its amplitude, including probability, relevance and ease of categorization.

P3 latency roughly covaries with the latency of response execution in psychological paradigms requiring a response. However, in many simple tasks, the P3 peaks after the response (Makeig, Delorme, et al., 2004; Verleger, 1997). Using manual estimation of P3 latency in single trials, no correlation between response timing and P3 timing could be found (Ritter, Simson, & Vaughan, 1972). Yet, by computer-based measures of single-trial P3 latency (Gerson, Parra, & Sajda, 2005; Jung et al., 1999; Kutas, McCarthy, & Donchin, 1977), it has been shown that the P3 is reliably time-locked to behavioral responses on a per-trial basis, implying either a causative relation between or a common causer behind the P3 and actions.

Emphasizing speed of response over accuracy may decouple RT and P3 (Kutas et al., 1977), and increasing the coordinative complexity of the response does so reliably; however, stimulus-response incompatibilities do not (Nieuwenhuis et al., 2005; Verleger, Jakowski, & Wascher, 2005).

A set of motor sensitive ERP components is well known (including the CNV, MRP and ERN), but when stimulus-response mapping and response execution are straightforward, the P3 generally does not vary much in latency, size or distribution between passive paradigms, explicit-task paradigms with overt responses, such as button presses to targets, or without over responses, such as silent counting tasks (Oades, Zerbin, & Dittmann-Balcar, 1995; Salisbury, Rutherford, Shenton, & McCarley, 2001; Shucard, Abara, McCabe, Benedict, & Shucard, 2004; Starr, Aguinaldo, Roe, & Michalewski, 2003).

Furthermore, while the P3 is response aligned if an overt response is produced, in covert or task-free paradigms, a significant P3 can still be elicited, e.g. by the subject's own name in the sleeping or comatose state (Perrin, García-Larrea, Mauguière, & Bastuji, 1999; Perrin et al., 2005; 2006; van der Stelt & van Boxtel, 2008; Wesensten & Badia, 1988), and in attentive subjects, attended, intrusive, surprising stimuli elicit a comparable P3 regardless of if they are targets or non-targets (Oades et al., 1995).

When the decision about the response and the response itself are separated by a maintenance period, a P3 already follows the cue (Kok & De Jong, 1980; Luo & Wei, 1999; Praamstra, Meyer, & Levelt, 1994).

The specific cortical generators of the P3 are not known, but two aspects are commonly accepted. First, the P3 is assumed to be connected to the TPJ. TPJ lesions abolish the P3b and, often, P3a (Knight, Scabini, Woods, & Clayworth, 1989; Verleger, Heide, Butt, & Kömpf, 1994; Yamaguchi & Knight, 1991), though not in all studies (Ortiz Alonso, Fernández, Benbunnan, Maestu, & De Miguel, 1996). This finding does not necessarily imply that the TPJ generates the P3, especially since it is implausible that one region could project in distinct patterns resulting in both P3a and P3b distributions. With intracranial electrodes, P3b-like activity has been measured reliably especially near the TPJ, including in the IPL (Halgren et al., 1995; Smith et al., 1990).

With source localisation techniques applied to EEG data, P3a generators have been distinguished from P3 generators and localised in the frontal cortex, potentially including the dorsal anterior cingulate/dACC/MFC (Crottaz-Herbette & Menon, 2006; Debener, Makeig, et al., 2005; Tenke & Kayser, 2008; Wronka et al., 2012). Source localisation attempts have also

identified the TPJ region as accounting for much of the scalp-measured P3b (Makeig, Delorme, et al., 2004), compatible with findings from EEG-informed fMRI studies showing a wide-spread effect centered around the TPJ (Bledowski et al., 2004; Crottaz-Herbette & Menon, 2006; Menon, Ford, Lim, Glover, & Pfefferbaum, 1997). Event-related fMRI studies employing similar paradigms as P3 studies observe activity in the primary constituents of the VAN: the TPJ, MFC and IFG, and the insulae (Ranganath & Rainer, 2003).

Secondly, it is commonly accepted that the P3 is most likely not generated by just one local generator, but by one or more widespread cortical systems (Nieuwenhuis et al., 2005; Pineda & Westerfield, 1993). P3-like potentials have been recorded even in brain areas thought to not contribute to the scalp field during the P3, such as the hippocampus (Knight, 1996).

Functionally, beyond the original subjective probability hypothesis, the P3 has been interpreted to reflect stimulus categorization (Mecklinger & Ullsperger, 1993; Nasman & Rosenfeld, 1990) or attention to self-referential stimuli (Gray, Ambady, Lowenthal, & Deldin, 2004), following the observation of a larger P3 after presentation of the subject's own name or face.

The two traditionally dominant interpretations of the P3 differ primarily in their interpretation of the nature of expectancy as a P3 antecedent, and in the possibility of either memory focused, high-level "strategic" (Donchin & Coles, 1988, p. 366) vs. perception-action-loop focused, single-episode "tactical" interpretations of its functions.

In the **Context Updating model** (Donchin, 1981; Donchin & Coles, 1988; Polich, 2007), the P3 depends on the subjective probability and the task relevance of a stimulus, and the P3 follows stimuli requiring a change of the mental model of the environment: unexpected, high-utility stimuli. The P3 represents "strategic" processing; it indexes the control not of actions, but of behavioral strategies, by updating the mental model in memory. P3 amplitude correlates with the discrepancy between the previous and the target mental model, and P3 latency with the time it takes to process the stimulus (as demarcating the point where the necessity of a context update becomes apparent). Recently, the importance of memory representations as antecedents and targets of the mechanism behind the P3 within the Context Updating model has been emphasised (Polich, 2007).

An opposing view appoints the P3 a role in the more "tactical" **linking between** specific **perceptions and** specific **actions** (Verleger, 1988; Verleger et al., 2005). In this framework, the P3 is thought to demarcate the point of closure of one cycle in the perception-action loop.

From these models, highly conflicting interpretations emerge especially regarding the response-aligned nature of the P3. Verleger assumes that the P3, indexing the transition from a processing to a reaction state, must be aligned equally well to stimulus as to response. To Polich/Donchin, response alignment can be considered an artefact of the fact that stimulus evaluation usually precedes response execution.
While the Context Updating model is quite popular (as evidenced by over a thousand citations to Polich's review from 2007 by Google Scholar), it has found strong and, in my opinion fundamentally destructive, opposition (Verleger, 2010), and does not warrant much further discussion.
Verleger (1988) especially argues that the theory of the P3(b) as tracking the

degree of unexpectedness/surprise of a stimulus is untenable for two reasons. First, in e.g. the Oddball paradigm, truly unexpectable events elicit a P3a, not a P3b, indicating that the P3b to targets, which are more expectable than new tones, does not simply index their respective unexpectedness. Secondly, other components, especially the N400 (that will be discussed below), parametrically index the degree to which certain events are surprising. The N400 may be a component directly reflecting expectability, being modulated by behavioral significance; the P3 seems to be a component directly reflecting behavioral significance, modulated by expectability.
Donchin & Coles (1988) respond to these claims by claiming that expectancy is only indirectly relevant for the P3 in that it correlates how strong the stimulus is incompatible with the current model of the context, as well as being based on the inconsistency is of sufficient "weight" to license updating the model; however, this reference to the "weight" fundamentally reshapes their model as one where the P3 marks internally motivated task significance, not perceptual predictability.
Verleger also, referencing Goodale and Milner (1992), attempts a preliminary association of the P3 with the ventral and dorsal processing streams, where response-locked aspects of the P3 correspond to the dorsal "how" stream and stimulus-locked aspects to the ventral "what" stream.

3.3.2 *The LC/NE-P3 Hypothesis*

A more recent proposal assigns an even more "tactical" role to the P3. Nieuwenhuis et al. (Nieuwenhuis, 2011; 2005) propose that the P3 is connected to phasic LC activation. The P3 resembles the functional and anatomical context of the LC/VAN. It follows effectively attention-grabbing stimuli regardless of their modality, but dependent on their subjective relevance. The assigned function in this model is establishing a temporal filter; the LC responds with a phasic burst to certain stimuli. At its wide-spread cortical and possibly sub-cortical target sites, NE then increases cortical gain, creating a brain state that is biased towards effectively reacting to the stimulus in question, for example by translating stimulus categorization into action. Coincidentally, affected neurons also depolarize in synchrony across the cortex, leading to a scalp-measurable P3.

Primary sources (Madison & Nicoll, 1986) indicate that around half of the measured pyramidal cells respond to NE by hyperpolarization, one quarter with depolarization and another quarter with an initial hyperpolarization followed by a depolarization.
It is not known if a possible primary depolarising effect of NE on pyramidal cells dominates during the P3, or if the P3 is instead caused by hyperpolarization, or alternatively by the increased spiking rate due to the gain increase. In this regard, remember that NE seems to decrease the total spiking rate due to the sharpening of the gain curve, which decreases spontaneous spikes more than it increases evoked activity (Funke & Eysel, 1993). If, as noted, NE strengthens inhibitory post-synaptic potentials to pyramidal cells (Kobayashi et al., 2000), this may result in a scalp-positive field as by the mechanism proposed by Elbert & Rockstroh/Kotchoubey (Elbert & Rockstroh, 1987; Kotchoubey, 2006). Alternatively, a known hyperpolarizing effect of NE on pyramidal cells (Hasselmo, 1995; Madison & Nicoll, 1986) would also be compatible with the Elbert & Rockstroh/Kotchoubey proposal.

Anatomically, the P3 is overwhelmingly compatible with the action of LC-released NE at specific sites, especially those with dense NE innervation, such as the TPJ and the MFC.

The manifold of P3-associated topographies has been connected to a systemic release of NE by Nieuwenhuis et al. with the proposal that brain areas more invested in certain paradigms will also be more strongly affected by NE. I conclude that this proposal could imply that within a single participant, single trial-activation of different brain areas during a P3 will always show approximately the same relative latency, dependent on the length of LC differentiation, if it is the primary depolarizing effect of NE that induces the P3; more generally, finding that across trials, the latencies at which multiple manifestations of the P3 peak different in areas are stable with regards to each other (but not necessarily to stimulus onset), this would strongly imply an underlying common source such as LC drive. Conversely, if it was found that the P3 reflects in activity that has different latencies in different areas within a single trial, and that these latencies vary between trials, this could either imply that the indirect neuromodulatory effect results in the P3 and that different brain areas show independently variable activation foci within trials, or that the P3 does not depend on the LC phasic effect in all areas, but only in those where cross-trial within-site latency variance is small.

More generally, the LC/NE theory makes a general prediction about the spatial distribution of the latency of the P3. Sites to which the NE projections are comparatively short, such as the orbitofrontal cortex, should show early, and posterior sites, with long conduction distances, should show late P3 effects. As noted, in the monkey, these latency differences have been estimated to be around 30 msec between frontal and occipital areas (Aston-Jones, Foote, et al., 1985), a number that can be expected to be slightly higher in the larger human brain. However, if the P3 peaks simultaneously at distant sites, or with significantly greater and variable delay at posterior compared to anterior sites, or if frontal sites peak after posterior sites, the LC/NE-P3 theory would require extensive modifications.

An interesting external validation of an inherent prediction of the LC/NE-P3 model comes from research using Independent Component Analysis/ICA to investigate the time course of spatially stationary, synchronized brain systems. As noted, the NE innervation of the cortex begins in the ventral prefrontal cortex and proceeds along a caudo-rostral gradient. Therefore, innervation of the frontal lobe is accomplished with substantially shorter fibers than in the rest of the brain; longer fibers connect the LC to the TPJ than to the MFC. Consequently, event though axonal conduction speed is fast, it can be predicted that under a phasic LC burst, frontal brain areas will be impacted slightly before posterior, temporal and parietal regions. Visual inspection of data reported in one study (Makeig, Delorme, et al., 2004) implies that the far-frontal subcomponent of the P3, the P3f that is likely generated in areas of the frontal lobe with short fiber connections to the LC, peaks slightly before the parietal, TPJ-associated P3b. Here, in a way compatible with predictions derived from the LC/NE-P3 model, top-down, meta-cognitive arousal/state switches quickly propagate through the cortex on a rostro-caudal gradient, compared to the caudo-rostral gradient more common for bottom-up, stimulus-driven processes (Bornkessel-Schlesewsky & Schlesewsky, 2013; Fuster, 2004; Van Essen & Maunsell, 1983).

Like the phasic LC response, the P3 is temporally coupled to overt responses, and habituates depending on the novelty/surprisal value and the utility of the stimulus. While the precise temporal structure of short-term cortical NE signaling is not known, the stimulus-measured latency of the P3 is roughly of the same magnitude as the expected arrival of NE at the cortex.

Extensive studies by Pineda and colleagues have established that the monkey equivalent of the P3, induced by a variant of the oddball paradigm, is indeed connected to the LC system. Lesions of the LC attenuated or abolished the P3 to a degree correlated with the damage to the LC (Pineda, Foote, & Neville, 1989), as did application of the NE agonists clonidine (Pineda & Swick, 1992; Swick, Pineda, & Foote, 1994). Other components tended to stay unaffected by the pharmacological manipulation.

Monkeys demonstrated P3 effects with different scalp topographies between a visual and an auditory oddball paradigm. A pharmacological intervention targeting the NE system attenuated both components (Pineda & Westerfield, 1993). This observation supported the proposition that the P3 is a systemic effect induced by the impact of diffuse neuromodulator systems at multiple cortical sites, dependent on task demands.

These results could be repeatedly replicated in humans; pharmacological manipulations of the NE system influence P3 amplitude (Halliday et al., 1994; Joseph & Sitaram, 1989) and show similar influences on the human P3 and the monkey homologue studied by Pineda and colleagues (Pineda, Westerfield, Kronenberg, & Kubrin, 1997).

The OR is trivially integrated into the LC/NE-P3 model (Nieuwenhuis et al., 2010). In addition to their connection to the phasic LC response, the P3 and the OR both depend less on stimulus-inherent characteristics such as stimulus complexity, but on its subjective significance (Barcelo et al., 1995).

Amongst the other aspects of the OR, α blocking has been most extensively associated with the P3. Temporal and functional (Sergeant, Geuze, & Winsum, 1987; Sutoh, Yabe, Sato, Hiruma, & Kaneko, 2000; Yordanova & Kolev, 1998; Yordanova, Kolev, & Polich, 2001), and to a lesser extent spatial (Intriligator & Polich, 1994; Yordanova et al., 2001) similarities and correlations between P3 and α blocking have been extensively documented. The onset and magnitude of P3 and α blocking covary, and show similar scalp distributions. Like α blocking, the magnitude of the P3 depends on the distance between eliciting events (Gonsalvez et al., 1999; Gonsalvez & Polich, 2002).

Similar correlations between single-trial skin response/SCR and P3 have been reported (Knight & Scabini, 1998; Matsuda, Nittono, & Ogawa, 2013; Rushby & Barry, 2007). The P3 also shows an inverted U-curve relationship with pupil dilation and reaction times consistent with the LC/NE-P3 model (Murphy, Robertson, Balsters, & O'connell, 2011).

Furthermore, the P3 habituates similarly to the LC response (Vankov et al., 1995): it decreases when the subject disengages from the task, but can be maintained even over prolonged sessions if necessary (Fjell et al., 2007; Lammers & Badia, 1989; Pan, Takeshita, & Morimoto, 2000; Polich & McIsaac, 1994; Ravden & Polich, 1998). Interestingly, covert P3s seem more resistant to habituation than P3s during tasks with an active motor component (Lew & Polich, 1993), indicating that sensory-to-motor linking can become more automatic than memory updating. The P3 to task-irrelevant, repeated events

whose salience depends on their surprise value habituates (Hirano, Russell, Ornitz, & Liu, 1996).

The LC-NE/P3 theory also provides an explanation of the attentional blink phenomenon by means of the refractory period of the LC (Nieuwenhuis, Gilzenrat, Holmes, & Cohen, 2005). Events of the kind that elicit a P3, such as rare targets in a rapid visual stream, are often followed with a slight lag by a time window of relative insensitivity. Target stimuli appearing in this time window tend to be missed. In the LC-NE/P3 model, this can be explained by the inability of the LC to produce another phasic response to the second target due to autoinhibition.

The LC-NE/P3 model is also compatible with the role of NE as a circuit breaker/network reset switch (Bouret & Sara, 2005). It marks the transition from one (such as a perceptive, or expectative) brain state to another (often motor- or memory-oriented) state. Contrary to attempts of further segregating the P3 component complex, the antecedents of multiple iterations of the P3 can be integrated under this explanation, including the sensitivity to novelty and task-switching (Barcelo et al., 2006).

The LC/NE-P3 account is far from being established without doubt. Some of its predictions have turned out to be wrong (Nieuwenhuis, van Nieuwpoort, Veltman, & Drent, 2007). As will be discussed in detail below, other neuromodulators have also been associated with the P3. The precise effect of NE at cortical targets and the exact time course of this effect are as of yet unspecified, and some criticism regarding the observed ERP effects and the speed of the supposedly underlying catecholamine system have been articulated (Lapish, Kroener, Durstewitz, Lavin, & Seamans, 2007; Warren, 2011). The specific answer of these LC/NE perspective to such arguments is as of yet outstanding. However, amongst the candidates for the explanation of the ERP, the neuromodulator proposal is an extremely attractive candidate due to its reductive potential.
Within the proposal initiated by Nieuwenhuis et al., all peripheral and EEG (OR; including SCR, cardiovascular events and pupil dilation), ERP (P3), anatomical (VAN) and behavioral (state switching following subjectively significant events, associated with tight P3/reaction time coupling) aspects of attention/arousal have become connected. In this framework, neuropsychological measures of cortical activity are directly associated with a neurophysiologically plausible mechanism. This mechanism is systemic; the P3 is not defined by the activation of a specific neural generator (though typically, major contributions from TPJ and/or MFC can be estimated), but by a diffuse subcortical drive affecting multiple brain systems.

A small number of other ERP components have, a large number haven't been similarly integrated. In the following, I will present the other main neuromodulator systems, a number of other ERP components, and alternative proposals for the generation of the ERP.

3.4 FURTHER NEUROMODULATO SYSTEMS

3.4.1 *Dopamin/DA*

3.4.1.1 *Neurochemistry*

Dopamin belongs to the catecholamine family (in part a subdivision of the monoamine family), as does NE. DA is obtained from its precursor L-DOPA and is converted into NE by Dopamine β-hydroxylase, and will even activate NE receptors to a small degree. Like NE, DA has been reported to increase neural gain/SNR (Johnson, Palmer, & Freedman, 1983; Kroener, Chandler, Phillips, & Seamans, 2009; Servan-Schreiber et al., 1990; Thurley, Senn, & Luscher, 2008).

Dopamine administration can induce behavioral arousal (Boullin, Adams, & Boulay, 1978). However, while NE is primarily associated with (long term, arousal and short term, attention) state and behavioral control, DA is primarily associated with learning and reward. Regarding behavioral control, DA is associated with motivation, and approaching and goal-directed, structured behavior. While NE is associated with declarative memory, DA also plays a critical role in procedural memory (Molina-Luna et al., 2009) and working memory. DA also induces a hyperpolarizing effect thought to stem, at least in part, from its effects on adrenergic receptors (Hasselmo, 1995).

3.4.1.2 *Anatomy*

CNS DA projections primarily emerge from two subcortical basal ganglia nuclei in the brain stem, travelling along three major pathways (Purves et al., 2004).

The nigrostriatal pathway, connecting the substantia nigra and the striatum, is mainly implicated in higher motor control. The mesolimbic pathway contains DA projections from the Ventral Tegmental Area/VTA and the pars compacta of the Substantia Nigra (SNc) to limbic systems including hippocampus, amgydala and thalamus, and is critical in learning and memory in a mechanism that is well-investigated (Lisman & Grace, 2005). The mesocortical pathway connects the VTA and SNc to the cortex. In contrast to the extensive noradrenergic innervation of the cortex, DA therefore reaches only selected areas (Foote & Morrison, 1987). DA density is extensive in prefrontal and anterior cingulate areas, and falls off rapidly across an rostrocaudal gradient. The temporal lobe is only weakly innvervated (including the enthorinal cortex), and little to no innervation reaches parietal and especially occipital lobes, though DA fibers in monkey area 7 have been reported (Foote & Morrison, 1987).

In the cortex, DA is thought to mediate adaptive control of behavior based on procedural learning. However, the majority of DA projections target the basal ganglia, especially the striatum.

The VTA, one nucleus providing the primary limbic and cortical DA signaling, hosts only 5000 neurons in humans, but strongly influences multiple systems due to its diffusive release/volume conduction ability (Arias-Carrión, Stamelou, Murillo-Rodríguez, Menéndez-González, & Pöppel, 2010).

The VTA and SNc collateralize less diffusely than the LC, with many DA projections reaching exclusively cingulate or prefrontal cortices (Loughlin & Fallon, 1984). Frontal DA often shows a rather low rate of synapses, indicating diffuse projection, possibly via volume conduction (Lajtha & Vizi, 2008); however, the rates are higher (20-40% in the macaque) than those for LC/NE.

Again, as with the LC/NE system, both tonic and phasic modes of activation must be considered (Dreher & Burnod, 2002; Schultz, 2007).

The peripheral and motor, as well as clinical, properties of the DA system will not be discussed here.

3.4.1.3 *Function*

A simple gain modulatory effect of DA in the frontal cortex is broadly compatible with some observations, such as DA agonist effects on semantic priming (Angwin et al., 2004; Copland, McMahon, Silburn, & de Zubicaray, 2009; Pederzolli et al., 2008; Roesch-Ely et al., 2006). Rising DA levels increase priming effects at short latencies (compatible with increased responsitivity to stimuli whose percept is strong due to their recency), but greatly attenuate priming over longer latencies (compatible with an attenuation of weak, decayed signals).

Tonic DA levels have been argued to set the baseline from which phasic signals emerge; the lower tonic levels are, the more impactful phasic signals become due to a higher base-to-peak distance (Grace, 1991).

In recent proposals similar to the dual-state model of NE, tonic DA, or alternatively, switching between tonic and phasic modes, is associated with regulating network stability and maintaining memory or action intentions against interference in the frontal cortex (Bilder, Volavka, Lachman, & Grace, 2004; Dreher & Burnod, 2002; Durstewitz & Seamans, 2008; Holroyd & Yeung, 2012), often associated with areas receiving extensive dopaminergic projections, such as the MFC and the orbitofrontal cortex/OFC.

DA levels	Dominant receptor	Gain	Memory Trace stability
low	D2	low	flexible
moderate	D1	moderate	stable
high	D2	excessive	instable

Table 3.4: Dual-state model of frontal DA

The different sensitivities of the two primary DA receptor types, D1 (including D5) and D2 (including D3 and D4), are of crucial importance in such models. D2-type receptors are primarily activated by low and high, D1-type receptors by moderate DA concentrations. In the dual-state model of DA function (Durstewitz & Seamans, 2008), DA signalling switches between a stable, D1-receptor dominated state facilitating exploitative behavior, and a D2-receptor dominated, unstable, receptive, explorative state. In the (high-gain) D1-dominated state, a focused percept or memory trace is protected

against distraction, but behavior becomes inflexible due to deep wells/local minima in the energy/attractor landscape of the frontal cortex. In a (low-gain) D2-dominated state, multiple cell assemblies representing multiple parallel, competing patterns are concurrently active and the energy landscape is more shallow.

In a related proposal (Holroyd & Yeung, 2012), the MFC enforces behavior with long-cycle reward contingencies against distractors when DA levels are high (a D1 dominated state) against competing action plans with short-term reward contingencies.

Recently, theories have begun to focus a gene polymorphism with high relevance to the catecholamine system (Durstewitz & Seamans, 2008; Mueller et al., 2011; Osinsky, Hewig, Alexander, & Hennig, 2012): the Val158Met polymporphism regulating catechol-O-methyltransferase/COMT expression. Regarding DA, this gene influences specifically prefrontal DA levels because the controlled enzyme breaks down DA so that Val genotypes show substantially faster DA catabolism than Met genotypes. Consequently, due to different DA level baselines, the phasic-to-tonic distance differs between genotypes. For example, a nonlinear response function to the DA agonist levodopa/L-DOPA has been observed between skeptics and believers regarding paranormal phenomena, with L-DOPA decreasing response sensitivity (d') in skeptics, but increasing it in believers (Krummenacher, Mohr, Haker, & Brugger, 2010).

Phasic dopamine has been associated with temporal difference, or reward, prediction error signalling by comprehensive research (Hollerman & Schultz, 1998; Schultz, 2007; 2010; Schultz, Dayan, & Montague, 1997). In many paradigms, the measured DA signal is proportional to the difference between the reward predicted and the reward received, especially in tasks where rewards can be temporally predicted. Unpredicted rewards, as well as unpredicted stimuli cueing upcoming rewards, elicit a strong burst that correlates in amplitude with the unexpectedness of the reward. Predicted rewards as well as cues for non-rewarded events do not elicit a DA response.

Omission of a highly expected reward leads to a phasic depression in baseline DA activity shortly following the time point where the reward was expected (Schultz et al., 1997). Unexpectedly early or late administration of rewards that were strongly expected to occur (but at a different time point) also lead to a positive signal. As the temporal lag between cue and reward events grows, which presumably entails an increasing uncertainty of the time point of the expected reward, responses to eventual reward administration become stronger (Fiorillo, Newsome, & Schultz, 2008; Kobayashi & Schultz, 2008). Cues indicating likely, but not certain rewards induce firing proportional to the subjective probability of a following reward (Fiorillo, Tobler, & Schultz, 2003). Furthermore, DA neurons show a slight transient ramping up of activity following a cue indicating an upcoming reward.

It is commonly assumed that DA codes value, not simply expectedness; unexpected aversive (for example, noxious) stimuli lead to depression, as do cues predicting aversive events. The interpretation of DA as coding *signed* prediction errors is essential for most theories. However, as will be discussed in more detail below, recent investigations have shown that some DA neurons code unsigned unexpectedness, leading some researchers to emphasise the role of novelty in dopaminergic signaling (Redgrave & Gurney,

2006) and emphasising the role of surprisal-based learning and attention (Oliveira, McDonald, & Goodman, 2007; Roesch, Esber, Li, Daw, & Schoenbaum, 2012).

Both the positive and the negative signal have a short latency (not much more than 100 msec). Optogenetic activation of GABAergic neurons in the VTA have identified them as the cause of the negative signal, and also demonstrated aversive conditioning by optogenetic activation of these neurons (Tan et al., 2012).

While some researchers argue that due to its time course, DA bursts are unlikely to influence movements directly following responses the burst eliciting stimulus (Arias-Carrión et al., 2010), others argue that DA may play an important role in acute response selection (Schultz, 2007), and at least some DA neurons have shown response-locked behavior similar to LC cells (Bouret, Ravel, & Richmond, 2012).

Temporal prediction error signalling is thought to be an essential aspect of self-organised learning in neural networks by reinforcement learning (Bayer & Glimcher, 2005). Some modelling work (Ashby & Casale, 2003) has indicated the feasibility of the DA signal instantiating just such a reinforcement learning procedure, given that a main effect of DA may be gain modulation.

Recently, optogenetic tools have allowed to show a causal association between VTA activation and reward prediction error reinforcement learning via increased positive conditioning by stimuli under concurrent optogenetic excitation of the VTA (Kim et al., 2012; Steinberg et al., 2013).

Problematically, it has been argued (Jocham & Ullsperger, 2009; Lapish et al., 2007) that the depressive aspect of the DA system (phasic inhibition following outcomes worse than expected) is too slow to accurately signal a temporal prediction error. The clearance rate of extracellular DA is probably rather on the order of seconds than on the millisecond precision rate required for an accurate temporal prediction error learning system. If DA levels do not decay to or close to baseline levels in short time, inappropriate stimuli may be associated with raised DA levels and become positively reinforced; similarly, the dip stemming from phasic inhibition may be too slow to become associated with the stimulus.
Consequently, it has been suggested that e.g. co-release of glutamate by DA neurons may impact fast-spiking interneurons in the PFC to transmit the phasic error signal to the cortex (Lapish et al., 2007). Alternatively, the frontal cortex might be the source, not the target of the DA error signal by MFC projections to GABAergic neurons in the DA system (Jocham & Ullsperger, 2009). This signal may be used as a top-down modulation of frontal cortex DA levels, leading to a D1-dominated mode that might be more focused and less error-prone. The error signal in the MFC (ERN; see the chapter on the ERN) may be generated by GABA, glutamate or acetylcholine (Wang, 2005).

Optogenetics has supported that DA neurons of the VTA co-release glutamate under physiological conditions, at least to subcortical targets (Tecuapetla et al., 2010).

Beyond many similarities, some significant differences between the anatomy and proposed functional roles of the DA and LC/NE systems exist. First, while the VTA/DA system is connected to primary sensory processes (Comoli et al., 2003) and shows very short response latencies, no extensive in-

nervation of cortical areas beyond the frontal cortex exists (Berger, Thierry, Tassin, & Moyne, 1976). An exception might be the rhinal cortex of the temporal lobe, an area associated with the hippocampus. In contrast, the other major neuromodulator systems, including the LC, each innervate basically all of the cortex.

Secondly, DA and NE signalling differ in that most DA neurons code subjective value, NE neurons subjective significance. Both DA and NE respond strongly to stimuli enabling rewarded behavior; they differ in that the firing of most DA neurons is depressed by noxious stimuli (Ungless, 2004), even though aversive stimuli are highly significant (significance is sometimes described as sign-neutral value). Consequently, the DA system has been mostly implicated in reward-based learning and motivation, in contrast to the significance-based state control by the LC/NE system.

However, some researchers have expressed doubt in the predominant reward prediction error theory (Bromberg-Martin, Matsumoto, & Hikosaka, 2010; Redgrave & Gurney, 2006; Redgrave, Gurney, & Reynolds, 2008). Their concerns are focused on two observations: first, the phasic DA signal could be too early to reflect a completed evaluation of the degree to which a stimulus fulfils a prediction (Redgrave, Prescott, & Gurney, 1999). Secondly, DA neurons also respond to presumably valence-neutral, new stimuli, similar to the OR (Crescimanno, Sorbera, Emmi, & Amato, 1998); however, with regard to this criticism, it can be argued that novelty can be rewarding in itself, and the OR is not reliably modulated by DA antagonist administration. Thirdly, some neurons in the DA system give positive signals (firing rate increases) to noxious stimuli. This later observation had at first been questioned on the basis that not all neurons in the VTA/SNc are necessarily dopamine carriers, and that neurons who become excited by noxious events show different spike wave forms than dopaminergic neurons (Ungless, 2004). Recent studies (Brischoux, Chakraborty, Brierley, & Ungless, 2009; Valenti, Lodge, & Grace, 2011) have claimed that at least a subpopulation of most likely dopaminergic basal ganglia neurons code valency-neutral significance, similar to LC/NE neurons (though see Fiorillo, 2013).

A majority of DA neurons however spikes preferentially following stimuli with positive value (Brischoux et al., 2009; Mirenowicz & Schultz, 1996; Schultz, 2002), whereas LC neurons react strongly to both rewarding events and aversive events, such as a cross-species agressor (Levine, Litto, & Jacobs, 1990) or pain (Ennis et al., 1992), so much that a report of LC neurons reliably responding specifically only to non-noxious stimuli was noteworthy in 1981 (Aston-Jones & Bloom, 1981a).

A related, but distinct model (possibly more compatible with valence-neutral, unsigned surprisal coding by the DA system) explores the role of DA and the VTA/hippocampus loop in memory encoding (Lisman & Grace, 2005) dependent on stimulus novelty[3]. Area CA1 of the hippocampus is thought to function as a "comparator", establishing if the external events signalled by the cortex (including the entorhinal cortex) correspond to the prediction supported by area CA3 based on previously encountered and processed events. This process manifests in an early decrease in local field potential/LFP in the hippocampus ("N85"). Novel stimuli are then relayed to the VTA. The VTA responds to this novelty signal with a phasic

3 Interestingly, Francis Crick had proposed a very similar function for the Locus Coeruleus as a network telling the brain "what to remember" rather than a specific encoding or perception system (Crick, 1989).

DA signal to the hippocampus, roughly coincidental with a further LFP depression ("N300"). DA then allows for long-term potentation/LTP to occur, resulting in the encoding of novel and salient stimuli.

The VTA response to stimuli also inducing an OR, such as the opening of a door in a previously closed-off room, habituates over time, with a roughly similar, but often slightly earlier latency compared to LC activity (Rasmussen, Strecker, & Jacobs, 1986). Following the stimulus eliciting an OR, during the transient α desynchronization, DA firing is transiently strongly depressed (Steinfels, Heym, Strecker, & Jacobs, 1983).

3.4.1.4 *P3*

Antecedents of P3 and VTA/DA phasic activity (following salient and/or unpredictable events) are similar, as are their characteristics regarding habituation, timing and possibly a response-locked status. Proponents of the context-updating model (Polich, 2007) propose the (inappropriately named) "dual-transmitter" model of the P3, where the P3a reflects frontal dopaminergic action, compatible with extensive DA innervation of frontal and especially cingulate cortex, whereas the P3b depends on NE. It has been argued (Nieuwenhuis et al., 2005) that DA is unlikely to play a role in the generation of the P3 based on an observation of an intact P3 following lesioning of the VTA in rats (Ehlers & Chaplin, 1992; Ehlers, Wall, & Chaplin, 1991). However, a DA-induced effect manifesting in a scalp P3a could, if at all, emerge from cortical areas with strong DA innervation - which excludes most of the cortex but for the frontal lobe. However, in the study in question, frontal electrodes did not show a P3-like effect even in sham-lesioned control animals. Any deductions regarding a frontal effect in humans based on rats not showing a frontal effect with or without lesions is questionable.

Evidence for an involvement of the DA system in the P3 indeed exists. Polich (2007) reviews mostly indirect evidence comparing populations likely differing in the integrity and activity of their DA systems, who consequently also show different P3s. However, direct pharmacological manipulations of the DA system in humans do indeed strongly and selectively influence the P3a (Kähkönen et al., 2002). DA- and NE-related genes both influence the P3 in non-trivial ways (Liu et al., 2009). Specifically, multiple large-scale studies have shown that the COMT polymorphism influences frontal aspects of both target- and novelty-related P3 effects (Gallinat et al., 2003; Heitland, Kenemans, Oosting, Baas, & Böcker, 2013; Marco-Pallares et al., 2010). However, COMT-based interpretations must reflect the fact that DA and NE metabolism are inherently linked. Yet, the COMT polymorphism seemingly does not influence the P3*b* in the two-tone Oddball paradigm (Bramon et al., 2006; Marco-Pallares et al., 2010; Spronk et al., 2013), implying that an explanation based on e.g. reduced COMT-type modulated NE availability may not be sufficient.

A similarity between the effects of NE and cortical DA release on the scalp ERP is indicated by an unusual source. Dopamine-ß-hydroxylase - deficient populations produce no NE. It is assumed that normally noradrenergic neurons store DA instead. Such patients have been found to produce a regular P3 (Jepma et al., 2011). If normally noradrenergic LC cells release DA instead of NE in the typical context causing LC phasic bursts, and the same P3 potential as usually is found, a highly similar effect of DA and NE on the

aspects of neural function that influence the ERP can be deduced, assuming the LC/NE model is approximately true regarding the P3. Consequently, DA, which is released in the frontal lobe, may induce a P3a. Parkinson patients show no P3a, while the P3b is partially intact (Polich, 2007). DA antagonist Sulpiride shows a nonlinear relationship with oddball-evoked P3 that is compatible with an inverted-U function of DA (Takeshita & Ogura, 1994).

In sum, while far less extensively elaborated than the LC/NE-P3 connection, an associated (though not necessarily exclusive) between frontal, especially ACC, sources of the P3a and their dopaminergic innervation is plausible, and may explain certain differences between prototypical P3b and P3a activity, especially regarding their topography. This entails the possibility of a neuromodulatory basis behind the distinctive classes of P3-like positivities, with far-frontal (Delorme et al., 2007) and parietal P3-like activity being associated with the LC/NE that is most specifically associated with effective reorientation and reaction initiation, and anterio-medial P3a associated with the VTA/DA system that corresponds more with evaluative functions and long-term task control.

An entailment of this proposal would be that not all P3 iterations must show a spatiotemporal structure consistent across participants. If P3f and P3b result from phasic LC activity projected to frontal and, slightly (~30 msec) later, temporo-parietal regions/TPJ, their relative positive peak latencies should be stable within participants and trials, and typically tightly coupled to response; but if anterior areas such as the MFC receiving dense VTA innervation elicit a distinct P3a under the influence of DA, this effect must not necessarily show the same latency relative to the NE-related P3 effects within participants and trials, and not the same degree of stable response-locking.

3.4.2 *Acetylcholine*

3.4.2.1 *Neurochemistry*

Acetylcholine/ACh is not a catecholamine, but its primary action at target sites is again often claimed to be an increase in signal-to-noise ratio (Funke & Eysel, 1993, Sato:1987tp). Specifically, in more recent proposals, it has been argued to function by increasing response gain (Disney, Aoki, & Hawken, 2007; Soma, Shimegi, Suematsu, & Sato, 2013) via two pathways (Soma, Shimegi, Osaki, & Sato, 2011): by multiplying the output to strong stimulation via fast ionotropic nicotinic receptors, and via decreased interneuron feedback (Zinke et al., 2006) by slow, metabotropic muscarinic receptors.

Regarding PSPs at pyramidal cells, ACh induces slow depolarization (Hasselmo, 1995; Madison & Nicoll, 1984; Madison, Lancaster, & Nicoll, 1987).
In the thalamus, ACh works even more directly via excitation: it drastically increases spontaneous firing, while only mildly enhancing evoked firing (Hirata, 2006), potentially even decreasing SNR. Here ACh may stand in contrast to the gain-enhancing effect of thalamic NE that is mainly produced by reducing spontaneous firing without excessive attenuation of evoked responses (McCormick, 2002; McCormick & Bal, 1994).

The response gain modulation acts differently between cortico-cortical and thalamo-cortical projections. When investigating the effect of ACh on intact

thalamocortical preparations, it was found that in auditory (Hsieh, Cruikshank, & Metherate, 2000), somatosensory (Michael Erik Hasselmo & Cekic, 1996a) and visual (Kimura, Fukuda, & Tsumoto, 1999) cortex, ACh excites thalamocortical and inhibits cortico-cortical circuits. There, ACh greatly inhibits intracortical transmission and mildly increases thalamocortical transmission, leading to substantial net boost of the importance of thalamocortical connections. Specifically, ACh decreases inhibitory interneuron feedback circuits, specifically in layer I of the cortex (possibly via muscarinic receptor activation), and increases feed-forward activity from the thalamus to afferent layers (via nicotinic receptor activation). It thereby influences receptive fields in the thalamus (Hirata, 2006).

A contemporary review of the specific functional effects of ACh (Picciotto, Higley, & Mineur, 2012) proposes that as a neuromodulator, the mechanisms of ACh are partially similar, partially highly different than for the catecholamines. In the cortex, similar to the neuromodulatory effects of NE and DA, ACh selectively enhances responses to events requiring direct reactions while decreasing responses to less significant sensory input. By increasing thalamo-cortical connections, but decreasing excitatory cortico-cortical transmissions (Hasselmo & McGaughy, 2004; Katz, 1999), ACh impairs the spread of patterns throughout the cortex and their stability and increases the susceptibility of the cortex to bottom-up influence.

In sum, ACh may increase the response to important external input compared to ongoing internal patterns possibly incongruent with the sensory input. It has thus been associated with stimulus detection (Parikh & Sarter, 2008) and "switching to the input mode" (Sarter, Hasselmo, Bruno, & Givens, 2005, p. 5), but also switching between retrieval and encoding (Hasselmo & Sarter, 2010), just as the P3 (Verleger et al., 2005) and the LC/NE system (Aston-Jones & Cohen, 2005) have been associated with switching to an output mode. In a related function, for neurons contributing to visual processing, ACh also reduces spatial integration (Roberts & Thiele, 2008), i.e., the radius of space a neuron is sensitive to, in a matter that is highly similar to that induced by the cognitive process of sustained attention.

3.4.2.2 *Anatomy*

The number of neurons projecting ACh to the cortex is significantly higher than for LC/NE neurons, and innervation density is higher than for any other neuromodulator system (Lajtha & Vizi, 2008). Consequently, ACh projections to the cortex are universal and even more extensive than those from the LC/NE system (Foote & Morrison, 1987). They emerge primarily from the Nucleus Basalis of Meynert/NBM. Some cortical projections also originate from the medial septal nuclei.

Projecting subcortically, the basal forebrain nuclei PPT and LDT (probably tonically) control the tone of the DA network (Picciotto et al., 2012); increased ACh levels here increase the likelihood of burst firing in the VTA, but decrease tonic activation in the NAc, which in sum increases the relative (baseline-to-peak) magnitude and therefore, possibly the effectivity of phasic VTA signaling.
NBM afferents include the LC (Fort, Khateb, Pegna, Mühlethaler, & Jones, 1995).

Junctional complexes are even rarer for cortical ACh projections than for the LC system, at 10-15% synaptic contacts by some (Lajtha & Vizi, 2008) estimates; though see Sarter et al. (2009). While as universal as LC projections and also showing nonspecific arborization indicative of a primarily diffuse, volume conductive function (Descarries et al., 1997), individual ACh neurons project to specific cortical sites (Aston-Jones, Shaver, & Dinan, 1985; Bigl, Woolf, & Butcher, 1982; Koliatsos et al., 1988), and show less diffuse connectivity than LC neurons (Price & Stern, 1983). Single neurons within the NBM project to the cortex so that each neuron drives only small (mm^2 scale) patches of the cortex (Katz, 1999), with no neurons projecting to widely dispersed areas, such as projecting simultaneously to both frontal and parietal areas. Furthermore, NBM projections to the cortex are distinctly localized in different populations within the NBM (Mesulam & Geula, 1988; Zaborszky, 2002; Zaborszky, Buhl, Pobalashingham, Bjaalie, & Nadasdy, 2005), indicating that the NBM has the ability to rather selectively target specific cortical sites. Consequently, it has been proposed that the NBM selectively modulates cortical sites where a mismatch between predictions and input is found (Katz, 1999).

Innervation density increases along a path (Mesulam, Hersh, Mash, & Geula, 1992) consisting of

- upstream (direct afferent) primary sensory cortices
- downstream primary sensory cortices
- unimodal associative areas
- multimodal associative areas
- paralimbic areas (e.g. cingulate)
- limbic areas

Finally, in contrast to uniformly fast-conducting LC neurons, ACh neurons show somewhat more variable, nonuniform ranges of latencies to their cortical targets (Aston-Jones, Shaver, et al., 1985).

As noted, it is commonly argued that like other neuromodulators, cortical efferents of cholinergic neurons do not synapse extensively, but release ACh diffusely (Descarries, Aznavour, & Hamel, 2004; Descarries et al., 1997). Consequently, it was traditionally assumed that ACh is released systemically throughout the cortex (Sarter & Bruno, 1997). However, recently, it has been proposed that direct, junctional transmission, not volume conduction, is a primary mode of cholinergic action in the cortex (Sarter et al., 2009), and it has indeed been shown that ACh contributes fast synaptic transmission (Goyal & Chaudhury, 2013; Roerig, Nelson, & Katz, 1997) and that ACh levels are raised following attended, attention-requiring stimuli with an onset latency of a second or less (Parikh & Sarter, 2008). These raises were observed to be localized; while ACh levels in the prefrontal cortex tracked cue presentation, no ACh response was observed in the motor cortex. Note how the NBM/ACh projection system differs here form the nonspecific, systemic LC/NE system.

Still, it is unknown what the fastest time scale of cholinergic modulation of cortical processing is. As noted, researchers have proposed sub-second

effects of phasic LC/NE activity on the scalp ERP; it is not implausible that such fast effects may also exist for the ACh system, but no direct empirical evidence exists. In this regard, it may become important that a majority of NBM neurons may be able to co-release glutamate, with the glutamate EPSP showing the characteristically fast ionotropic response, a slower ionotropic effect of ACh on nicotine receptors, followed by a further multi-second, slow cholinergic effect at metabotropic muscarine receptors (Allen, Abogadie, & Brown, 2006).

However, recent investigations have provided additional evidence for an extremely high temporal and spatial precision of cholinergic neuromodulation (Muñoz & Rudy, 2014). Optogenetic and fast pressure injection have presented further evidence in favour of a temporally precise and low-latency effect of phasic ACh signals.
Activation of muscarinic receptors via fast pressure injection has demonstrated an inhibitory effect faster than 300 msec (Gulledge, 2005; Muñoz & Rudy, 2014). This is surprisingly faster than might have been expected for the supposedly slow metabolic muscarinic system; however, while it is on the right order of magnitude for typical ERP effects, it might be some 100 msec too slow to realistically contribute to the ERP, especially considering that this effect reflects the direct application of ACh, whereas in the behaving organism, additional delays follow from stimulus classification, activation of the NBM, and conduction delays before the neuromodulatory signal reachers the cortex. However, further *in vivo* experiments could better clarify the potential role of phasic muscarine receptor activity on the ERP.

Beyond simply measuring the latency of NBM neurons or the response profile of target neurons under ACh application, recent investigations (Muñoz & Rudy, 2014; Pinto et al., 2013) using optogenetic activation of NBM neurons and consecutive measurement of their cortical targets, have demonstrated that the time course of NBM neuromodulation is of extremely low latency. Network reorientation following less than 200 msec after optogenetic activation of the NBM was observed, a signal well fast enough to support temporally precise processes.

Regardless of the importance of direct synaptic transmission of ACh, it is generally in line with other research indicating a higher specificity of ACh projections compared to the LC/NE system. While some researchers argue that the cortical impact of the ACh system is also nonspecific, diffuse and nonlocalized (Lucas-Meunier, Fossier, Baux, & Amar, 2003), but it has been shown that unimodal (visual, auditory) sensory stimulation specifically increases ACh levels in the associated (temporal, occipital) sensory areas (Fournier, Semba, & Rasmusson, 2004; Jiménez Capdeville, Dykes, & Myasnikov, 1997; Laplante, Morin, Quirion, & Vaucher, 2005), and it is generally assumed that NBM activity utilizes the topographical resolution allowed for by its internal structure and distinct projection system (Fadel, 2011; Klinkenberg, Sambeth, & Blokland, 2011). This localized top-down control at modality-specific cortical sites may be mediated by frontal areas (Rasmusson, Smith, & Semba, 2007).

3.4.2.3 *Function*

Confusingly, the primary function of ACh is typically given as playing a role in "attention" (Klinkenberg et al., 2011; Sarter et al., 2005), a terminology un-

satisfactorily broad and similar to descriptions of the LC/NE system. However, crucial differences can be found regarding the two forms of attentional modulation by the two systems. Similar to NE, high ACh levels increase the influence of thalamic afferents over the cortical landscape, whereas low ACh leves emphasize intracortical, recurrent connections (Wester & Contreras, 2013), setting the brain into an "input mode" (Sarter et al., 2005, p. 5). This facilitation of thalamic afferent activity may be induced by nicotinic, intra-cortical suppression via muscarinic receptors (Hasselmo, 1999).
ACh has a critical function in sustaining attention, with lesions of the NBM greatly impairing this capacity, especially regarding the detection of targets of low sensory salience (Sarter et al., 2005). This deficit does not result from primary sensory deficits. Functionally, this has been associated with effortful top-down processes of e.g. distractor inhibition. Specifically, ACh increases the response to stimulus features that are task-critical and focused, and decreases responses to defocused features (Sarter & Bruno, 1997). Thus, ACh implements a modality- and feature-specific amplification of input, or top-down orienting (in contrast to stimulus-driven re-orienting) to certain dimensions, locations or streams (Hasselmo & Sarter, 2010). Within the focused stream, it performs contrast enhancement and improves discrimination (Devore & Linster, 2011), possibly by the sharpening of tuning curves that results from decreases e.g. spatial integration in the visual domain (Roberts & Thiele, 2008). ACh in the visual cortex increases contrast sensitivity, but may decrease movement direction sensitivity (Bhattacharyya, Veit, Kretz, Bondar, & Rainer, 2013).

Single-unit recordings of PPT neurons have observed tonic increases following cues and phasic responses to rewards (Okada, Nakamura, & Kobayashi, 2011). The sustained attentional control function of ACh has been associated with the posterior parietal cortex (Broussard, 2012; Broussard, Karelina, Sarter, & Givens, 2009; Bucci, Holland, & Gallagher, 1998). The auditory cortex may have the ability to directly control the cholinergic modulation of its auditory afferents (Schofield, 2010; Schofield, Motts, & Mellott, 2011), allowing the auditory cortex to exert top-down control of its input.

Compatible with a role of ACh in attenuating intracortical and facilitating thalamocortical processes, the role of hippocampal ACh in memory has been delegated to a complex, "biphasic" role in facilitating (afferent-dependent) encoding, but inhibiting (cortico-cortical) retrieval and consolidation (Hasselmo & McGaughy, 2004; Micheau & Marighetto, 2011), likely mediated by its role in modulating hippocampal θ rhtyhms (Douchamps, Jeewajee, Blundell, Burgess, & Lever, 2013; Hasselmo, 2006). Targeted impairment of the ACh system has even been shown to improve retrieval or recognition (Winters, 2006).
In the model of ACh function championed especially by ACh researcher Hasselmo (2010; Katz, 1999) focuses on the observation that ACh shows differential effects in memory retrieval and memory encoding, supporting encoding while inhibiting retrieval. Here, it is assumed that

> [m]odulation determines strength of external information relative to internal prediction
>
> ...
>
> This raises the question of how the output of the network is suppressed during a mismatch event (for learning of the new information), whereas the same output of the same network can

> guide behavior consistently in the absence of a mismatch. This is where other effects of neuromodulators become very important. In addition to changing the strength of synaptic modification, these neuromodulators might also change the relative influence of internal predictions and input from the external environment. Under most conditions, internal predictions dominate and guide behavior, but when there is a sufficient mismatch, external input could be allowed to dominate, and the internal predictions would be suppressed. (Katz, 1999, p. 330)

As noted, this system may contrast with the effect of NE specifically in its localisation, being location and therefore modality specific. ACh may therefore specifically modulate areas of mismatch between internal predictions and incoming environmental information (Michael Erik Hasselmo & Cekic, 1996b). Quoting the proposal at length,

> These differences in the anatomical distribution of synapses from a single modulatory neuron could reflect important functional differences between the different modulatory systems involved in learning and memory. The level of noradrenergic modulation may be set by environmental conditions which require a general global change in sensitivity to external stimuli. For example, in a novel environment, an animal may go into a state of fear in which the sensitivity of response to all modalities of stimulation are enhanced to speed its reaction time and escape from danger. These same properties of modulation would enhance the learning of a wide range of stimuli. In contrast, the local distribution of cholinergic innervation could reflect a more local modulation on a column-by-column basis. This could allow selective sensitivity to modalities or categories which are relevant to a specific behavior. For example, an animal may be in a familiar environment, so that its noradrenergic tone would be low, but it might encounter an unfamiliar odor. In this context, cholinergic modulation might be enhanced only in those cortical subregions important for evaluation of the novel odor. Thus, one could imagine a system in which some cortical regions were dominated by internal predictions, with little response to external stimuli. All columns or subregions which matched this internal prediction would remain in a low modulatory state. However, if a specific column or subregion had external input which did not match this prediction, these could individually go into a state of higher cholinergic modulation—suppressing the internal influence from other cortical regions and enhancing the sensitivity to external input. A network of this type would allow learning in a more selective manner—focusing on those aspects of stimuli not matching the current expectation. (Katz, 1999, p. 340)

All in all (see Figure 3.5), the anatomy of the ACh system and the observed effects of ACh are compatible with a role in relatively precise orienting to specific sensory streams, induced by prefrontal signalling causing topical ACh release at stream-dependent processing sites. It shifts brain activity towards being dominated by a specific attended sensory stream, facilitating the processing and encoding of information from this stream; and in turn suppresses intra-cortical activity and thereby, retrieval and predictive and consolidating processes. In contrast to DA, the ACh system innervates sen-

sory cortices and is not value- or action- oriented, but detection-oriented, and in contrast to the LC, this innervation may become selectively active only to specific streams.

Recently, optogenetic tools have become available, allowing researchers to specifically target the cortical projections of the NBM (Kalmbach, Hedrick, & Waters, 2012). Activation of the NBM via surface illumination induced similar LFP desynchronisation as tail pinches or electrical NBM stimulation. Such methods may allow a more precise investigation of the effects of ACh *in vivo*.

3.4.2.4 *P3*

ACh has been repeatedly implicated in P3b generation. In multiple oddball studies, the P3b was strongly reduced or completely absent following application of the potent ACh antagonist scopolamine[4](Curran, Pooviboonsuk, Dalton, & Lader, 1998), and in some (Hammond, Meador, Aung-Din, & Wilder, 1987; Meador et al., 1987; 1993) furthermore partially restored by anticholinesterase inhibitors/AChEIs (which increase ACh levels). The ACh agonist nicotine has been observed to increase P3 amplitude (Knott et al., 2011), although this manipulation also affected earlier components.

In other studies, no direct effect of scopolamine (Douglas D. Potter et al., 2000a) or nicotine (Warbrick et al., 2012) on the oddball P3b was found, and in one, the oddball P3 effect was not impacted by scopolamine, but both targets and non-targets displayed a more negative ERP (Douglas D. Potter et al., 2000b). In a study employing both visual and auditory continuous performance tasks/CPT, scopolamine slightly reduced the P3 only in the auditory CPT (Knott, Harr, & Ilivitsky, 1999). In a recognition memory study, scopolamine impaired performance, but did not attenuate the recognition P3 (Potter, Pickles, Roberts, & Rugg, 1992).
Thus, in specific studies, scopolamine strongly attenuated the P3, whereas it did little to affect it in other studies.

In most of these studies, impairments of the ACh system also correlated with substantial behavioral deficits, whereas nicotine tended to improve performance. Furthermore, since an important function of the ACh system is in target detection, it might be that any effects on the P3 induced by manipulating this system stem from impairing the processing systems that feed the categorization-dependent mechanism behind the initiation of the P3. This perspective is further supported by the observation that AChEIs, which primarily increase tonic levels, restored the P3; possibly, target detection, which is critical for the P3, but is not the process directly marked by the P3, is impaired by ACh depletion, and restoring tonic ACh levels restores the P3 indirectly via restoring target detection processes.
As noted, the ACh system is innervated by the LC system and during an LC phasic response, NE release in the NBM could be expected to result in co-released ACh.
However, fundamentally, the very drastic effects of scopolamine on the P3 observed at least in some studies imply a significant association between the P3 and ACh. The specific nature of this connection has yet to be investigated.

4 Hans Berger had already investigated the effects of scopolamine on the EEG, observing that it blocked α (H. Berger, 1935a).

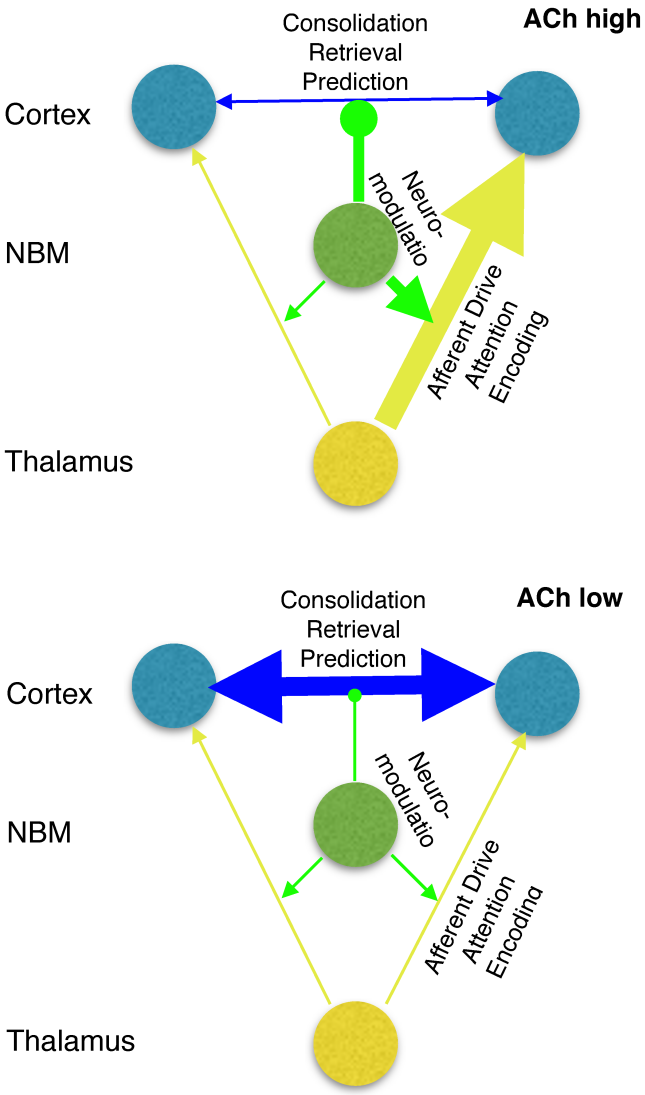

Figure 3.5: Diagram of the proposed function of ACh in the thalamus-cortex-NBM triangle. Pictured is spatially localised ACh action, affecting specific cortical sites processing a specific input stream. Blue arrow: intra-cortical (inter-columnar, specifically intra-lobular) activity. Green arrow: (muscarinic) inhibitory and (nicotinic) excitatory ACh action. Yellow arrow: bottom-up afferent activity. Thicker arrows correspond to stronger activity. Top: high ACh levels, corresponding to facilitation of activity from specific input streams and relative suppression of intra-cortical activity. Bottom: low ACh levels, corresponding to a brain mode dominated by intra-cortical activity and predictive processing. Partially based on Hasselmo (Hasselmo, 2006).

3.4.3 *Serotonin*

3.4.3.1 *Neurochemistry*

Serotonin/5-HT is possibly the least understood neuromodulator (Cools, Nakamura, & Daw, 2010; Cools, Roberts, & Robbins, 2008). 5-HT is a monoamine like the catecholamines, but in contrast to ACh, DA and NE, it is commonly observed to *lower* the evoked-to-background activity ratio/gain/SNR (Funke & Eysel, 1993; Hurley et al., 2004). It induces hyperpolarization in pyramidal cells (Hasselmo, 1995). However, more complex, non-linear, context- and stimulus-dependent effects are also observed (Hurley & Hall, 2011).

Conventionally, improved SNR/increased gain are used more or less synonymously with generally improved cognition; consequently, it might be questionable why brains would ever deliberately be in any other mode but a high-gain mode, or even deliberately down-regulated gain.
Modelling work has shown that, by a process termed *stochastic resonance*, cortical noise may actually support the detection of weak signals (Traynelis & Jaramillo, 1998; Wiesenfeld & Moss, 1995).
Another possibility is that, as an inverse of the proposed effects of high gain on decision making, lowering gain could postpone perceptual categorization or behaviorally relevant decision making in the face of uncertain environmental information, decrease approaching behavior and instant reactions, and increase cortico-cortical analytic processes and multi-stream integration. For example, in a diffusion model, 5-HT could functionally raise the decision threshold; in an energy landscape/attractor state model, it could flatten the environment or allow transitioning out of local optima, allowing reevaluation and reconsideration (Deco et al., 2009).

3.4.3.2 *Anatomy*

Cortical 5-HT supply is provided by the Nucleus of Raphe, especially the dorsal Raphe's nucleus/DRN (Purves et al., 2004). It projects extensively to all of the cortex. Projection density falls off slightly along an rostro-caudal gradient (Michelsen, Schmitz, & Steinbusch, 2007). In this and other ways, the cortical efferent projection topography of the DRN resembles other neuromodulator systems. For example, IPL, spanning much of the greater TPJ region, is innervated by the LC, the NBM and the DRN (Divac et al., 1977).

These projections may be topographically organized within the DRN, without extensive collateralization across areas at least in motor, sensorimotor and visual areas (Waterhouse, Mihailoff, Baack, & Woodward, 1986); frontal and subcortical collateralization may be specific (Waselus, Valentino, & Van Bockstaele, 2011). Limbic, sublimbic and associated areas, including hippocampus, amygdala and MFC, receive dense innervation.

Frontal neurons projecting to the DRN often simultaneously project to the VTA. Terminals are more often synaptic than for the LC/NE system (Lajtha & Vizi, 2008), though still not dominant (30-45%).

Different genotypes of 5-HTTLPR are associated with decrease or increase 5-HT transmission (Canli & Lesch, 2007).

3.4.3.3 *Function*

Inhibition, not activation, of the 5-HT system causes behavioral arousal (Nitz & McNaughton, 1999). DRN neurons concentrate their firing following visual or auditory stimuli, leading to an evoked response without an increase in total spiking rate as a biphasic short peak-sustained pause pattern (Heym, Trulson, & Jacobs, 1982). This effect seems to depend neither on novelty, as it does not quickly habituate (Rasmussen et al., 1986), nor on significance, as it follows conditioned and unconditioned stimuli alike. This effect is faster and more temporally focused than that of DA and especially NE neurons. Amongst the Raphe, only DRN neurons exhibit this behavior, and those DRN neurons who respond to one stimulus modality also respond to other modalities (Trulson & Trulson, 1982).

Serotonin is associated with behavioral inhibition (Schweighofer, Tanaka, & Doya, 2007). 5-HT neurons increase their tonic firing rate during periods of awaiting both reward and sensory events (Miyazaki, Miyazaki, & Doya, 2011), and this mechanism is necessary for withholding preemptive responses during such waiting periods (Miyazaki, Miyazaki, & Doya, 2012). During overwhelming aggressive encounters, such as by the human experimentator or by a larger conspecific, DRN activity is increased in the tree shrew, but offensive, aggressive conspecific behavior correlated with decreased DRN firing (Walletschek & Raab, 1982).

Serotonin neurons so far have also presented themselves as a heterogenous population. Some DRN neurons tonically code reward, unlike DA neurons that phasically code the difference between predicted and received reward (Nakamura, Matsumoto, & Hikosaka, 2008). Clockwise-spiking DRN neurons are phasically excited, bursting DRN neurons phasically inhibited by noxious stimuli (Schweimer & Ungless, 2010). Some DRN neurons preferentially encode reward, others movements, others sensory events (Ranade & Mainen, 2009).

5-HT has been modelled as signalling a (phasic-acute, but more strongly tonic-average) punishment signal, roughly as the inverse analogue of the VTA/DA system (Cools et al., 2010), reinforcing aversive behavior and inhibitory control (Cools et al., 2008).

While I am not aware of any previous suggestions in this regard in the literature, or specific empirical tests examining such a proposal, it seems possible in the light of the effects of increased SNR in neural networks discussed above that beyond its role in reward signalling and behavioral inhibition, 5-HT signalling follows perceptual uncertainty and facilitates analysis of stimuli that are not easily categorizable. Possibly, by raising the decision threshold, weak signals, previously suppressed interpretations or subordinate associations may become gradually available.

However, it is so far not known if the 5-HT is even capable of specific phasic responses to complex stimuli in a highly sensitive manner. Available evidence examines phasic responses to extremely simple, typically unconditioned stimuli, or mostly tonic increases during conditioning contingent behavior.

3.4.3.4 *P3*

5-HT may have some impact on the P3 (Hansenne, Pitchot, Papart, & Ansseau, 1998), though any such effect is likely to be small or spurious (Kenemans & Kähkönen, 2011). No specific interaction or mechanism has so far been proposed.

3.4.4 *Other neuromodulator systems*

A range of other neuromodulator systems shape brain activity. The above discussion focused on the catecholamines and ACh as the prototypical brain stem systems, stemming from a small set of subcortical nuclei and influencing vast amounts of the cortex. Other important neuromodulatory phenomena include the histamine system (Haas, Sergeeva, & Selbach, 2008), with a neuroanatomical base roughly comparable to those discussed, but also phenomena such as the neuromodulatory effects of classical neurotransmitters, such as Glutamate (Katz, 1999). Neuroactive hormones, including sex hormones such as the androgens testosterone and DHT (Anon, 1970), act on the androgen receptors in an neuromodulatory fashion (Crockett & Fehr, 2014). However, these systems have not been implicated with regards to the specific events of phasic bursts which may be critical for the punctuated, targeted control of attentional state, reflecting in the ERP.

3.4.5 *Summary*

All neuromodulators seem to play a dual role in phasic facilitation of appropriately reacting and adapting to punctual, often surprising and/or critical events, and in tonically setting long-term neuronally and behaviorally adaptive processes. ACh, NE and DA increase gain and sharpen tuning curves; ACh primarily increases evoked, NE decreases spontaneous firing; 5-HT decreases evoked activity compared to spontaneous activity. ACh, NE and 5-HT innervate most of the cortex; DA selectively innervates the frontal lobe. ACh and 5-HT could show topographical organisation of cortical projections at the subcortical source, and compartmentalisation of projections at target sites, with ACh specifically being likely to exert highly selective activation of specific cortical sites; NE is likely general and universal, with uniform temporal and spatial distribution of phasic activity. NE and DA play a role in approaching, arousal and action, ACh in attention and perception (Andrianov, 1995), 5-HT in aversion, inhibition and waiting. NE, ACh and DA are all associated with encoding, NE and DA with consolidation and retrieval of memories. The LC system unidirectionally modulates all other neuromodulator systems, while in itself receiving only little external input. The approximate locations of the respective systems, as well as the broad extent of their cortical (not including subcortical and limbic) projections, is shown in Figure 3.6.

Based on this elaboration, the role of neuromodulation in the perception-action-loop can be understood in more detail than in the introductory sketch (see Figure 3.7). Frontal and pre-frontal areas exert cognitive control, request neuromodulatory activity and direct attention in sensory processing; neuromodulator systems, including the brain stem, affect both sensory and frontal

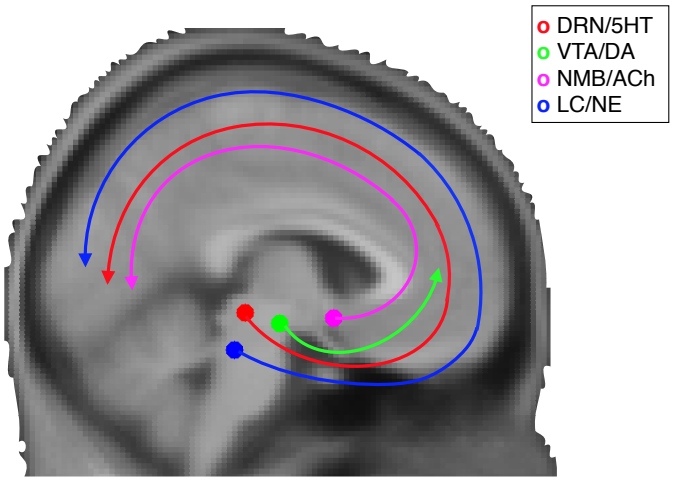

Figure 3.6: Location of the major neuromodulatory nuclei projected onto the MNI standard brain. Red: LC/NE. Green: VTA/DA. Blue: DRN/5-HT. Pink: NBM/ACh.

cortices (Lee & Dan, 2012). Within the neuromodulator, recurrent connections are prevalent, with the LC at the bottom of this network, affecting all other systems, but receiving only limited external input.

Investigating the specific and differential purposes of the various neuromodulator networks in detail, Nieuwenhuis et al. (2005) have proposed that NE instantiates a temporal window of attention; in a continuous stream of sensory inflow, phasic LC bursts select a temporal window so that information presented in this window is promoted to more likely influence behavior. ACh, in contrast, in its role as implementing e.g. spatial attention, has been associated with selecting temporally simultaneous alternatives (2010), as shining an attentional "spotlight" that selectively illuminates only a part of the sensory input. Consequently, the differential functions of the NE and ACh systems, both of which are deeply fundamental for what cognitive science subsumes under "attention", may possibly be described as *syntagmatic* attention for the LC/NE system (where time points in the stream/sequence of temporal events are selected), and as *paradigmatic* attention for the NBM/ACh system (which may select between parallel alternativerepresentations or patterns).

The best elaborated model for explaining focused attention-related EEG and ERP effects in reference to neuromodulation is provided by the LC/NE-P3 theory, but DA might play a role in generating the P3a and impairments of the ACh system can have a significant impact on the P3b.
Considering the direct effect on membrane potential (and ignoring for now the more complex effects on e.g. evoked and induced spiking), NE and DA release may be expected to result in scalp-positive, ACh in scalp-negative deflections due to the hyperpolarisation/depolarisation they induce.

System	Source	Cortical Targets	Collateralization	Function
NE	LC	universal	Extensive (??)	Syntagmatic Attention
DA	VTA/SN	frontal	?	Approaching/ RPE learning
ACh	NBM	universal	Reduced (Sagittal)	Paradigmatic Attention
5-HT	DRN	universal	?	?

Table 3.5: Summary of neuromodulator projections to the cortex

System	Effect on membrane potential	Modulation of cortico-corticular vs. thalamo-corticular transmission	Effect on tuning curves
NE	Hyper-polarization	Strong inhibition of cortical transmission, thalamic excitation (receptor dependent)	Sharpening
DA	Hyper-polarization?	Highly receptor dependent	?
ACh	Depolarization	Inhibition of cortical transmission, strong thalamic excitation	Widening
5-HT	Hyper-polarization	Complex	Shifting

Table 3.6: Summary of effects of neuromodulators on action potentials/PSPs

The P3 was originally found in a biphasic pattern including a preceding N2. In the following, this as well as two further biphasic patterns of the ERP will be discussed and it will be discussed probable neuromodulatory systems behind their generation.

3.5 THEORIES OF THE ERP

Excited by the discovery of the original endogenous component, a range of follow-up experiments intended to specify the role of the P3 established a "zoo" of further ERP components (Luck, 2005; Ritter & Ruchkin, 1992). As noted, these components initially appeared especially interesting because they behave quite differently from the exogenous potentials. Exogenous,

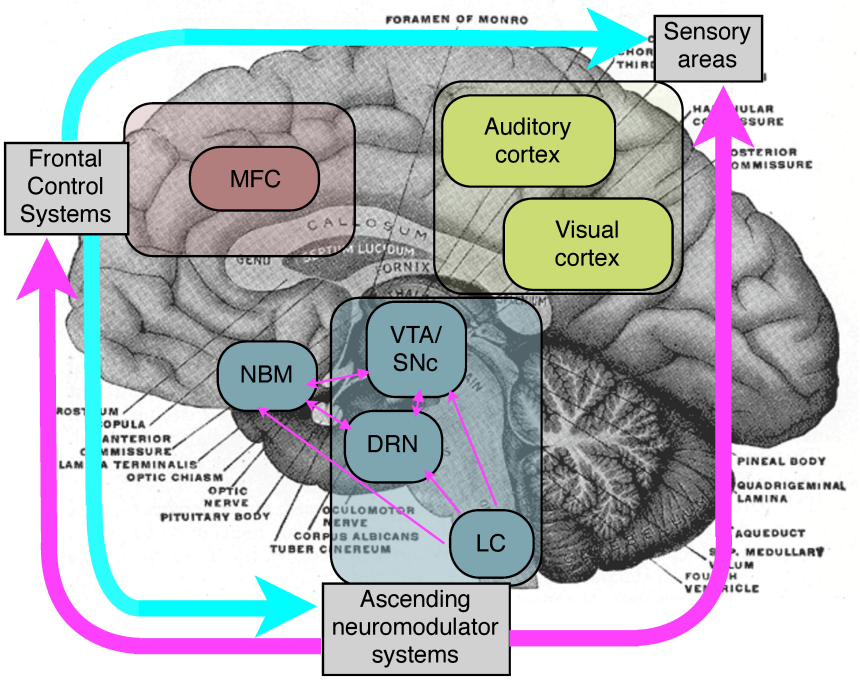

Figure 3.7: Diagram of major ascending and descending projections in the action-perception loop. Pink arrows: neuromodulator projections. Teal arrows: cortical projections. Rounded boxes: anatomical areas. Grey rectangles: large functional areas. Anatomical labels are placed vey roughly anatomically correct, primarily preserving relative over absolute placement. Partially based on Lee (2012).

strictly stimulus-locked, feature-dependent components likely relate to low-level perceptual processing; their generation has often been associated with fast, local mechanisms such as the phase resetting of local neuronal populations (Makeig et al., 2002). In contrast to this potentially oscillatory, stimulus-induced activity, a phasic origin has been proposed for later components (Barry, 2009), potentially of neuromodulatory origin for at least some of these late components (Nieuwenhuis et al., 2005; de Rover et al., 2011). Interestingly, an endogenous negativity is often followed by a positivity that appears better time-locked to the subjects' response time in averaged ERPs; more complex paradigms and stimulus categories, such as the semantic content or structure of speech, induce later negativities and positivities. The three most important of these biphasic patterns will be discussed here: the N2/P3 following paradigms with comparatively simple perceptual matching requirements, the response-locked ERN/P_E related to error commission, and the N400/P600 following recognition memory or linguistic mismatches.

Specifically, it will be investigated if these three biphasic patterns of a mismatch-sensitive negativity and a reaction/adaption-facilitating positivity can be associated and even identified with each other. A similarity between some (Coulson, 1998; Holroyd, 2004; Polich, 1985) or all (Kotchoubey, 2006) of these components has been noticed before.

However, here, it will be attempted to link these components in reference to underlying neuromodulatory systems. For this purpose, first, a discussion of a potentially oscillatory component in the generation of these potentials will be discussed, embedded in a discussion of the temporal properties of ERP components.

The study of ERP components, their differential sensitivity, antecedents and shapes, which precludes their usage for the studying of cognitive functions, has been termed "ERPology" by Steve Luck (2005).

3.5.1 *ERP and Oscillations*

3.5.1.1 *Time sensitivity and phase sensitivity*

The EEG is a time-sensitive method. This entails both the option of fine-grained investigations into the temporal structure of processes, and the necessity to precisely correlate measurements with events. These properties become potentiated when dealing with averaged EEG signals time-locked to events of perturbations, the Event-Related Potentials.

The phenomena Berger observed were visible on a single-trial level. Adrian mentioned that when he perceived a stimulus or committed an action, his "Berger rhythm" disappeared, giving way to the faster β waves. Tumour activity and sleep stages were also visible from observation of the ongoing EEG signal with the naked eye. However, soon it became clear that much of the ongoing activity was not directly interpretable. Researchers therefore may have been inclined to enter a framework wherein much of the observed EEG could be considered as noise for the purpose of the researcher. This noise could not be easily filtered out because the problem was underconstrained; to separate signal from noise, the nature of the signal had to be known, yet the intermixing of noise and signal prohibited knowing the signal. Therefore, averaging analysis was developed. The underlying

assumption was that activity not correlated to stimulus events would not systematically correlate with stimulus timing, whereas stimulus-relevant activity would. By simply averaging over multiple presentations, the relevant features would be enhanced, noise attenuated.

The assumption that the background or the not strictly task-related signal is simply a reflection of dendritic noise is no longer upheld. Still, the ongoing EEG contains more as of yet uninterpretable than informative signal, even after ongoing attempts to analyse it (Makeig, Delorme, et al., 2004; Makeig et al., 2002). The averaged EEG, however, quickly resulted in interpretable findings, including the N100/N1 (Davis, 1939), the aforementioned CNV (Walter et al., 1964) and the P300/P3 (Sutton et al., 1965).

The N100/N1 is a typical feature of the averaged EEG, or an "Event-related potential (ERP) component" (components most important to language/sentence processing will be discussed in detail in the following section) that appears, at sites where it is maximal, as a negative peak approximately 100 ms after the presentation of most forms of discontinuous stimuli. The P300/P3 is a late (at least 250 ms, but up to 1000 or more ms after stimulus onset) component dominating both the ERP after critical stimuli requiring reorienting behaviour, as well as the ERP time-locked to this behaviour. The CNV is best observed when time-locking to expected actions or events. Originally, the preferred nomenclature for ERP components gave the scalp polarity and the peak latency (in relation to the time-locking point), however, multiple aspects of the task, like stimulus complexity (Verleger, 1997) and modality (Kretzschmar, Bornkessel-Schlesewsky, & Schlesewsky, 2009; Kutas & Federmeier, 2011) and the recording technique, like the chosen reference (Dien, 1998; Luck, 2005), can influence these measures. Luck (2005) describes the N100/N1 as the first negative, the P300/P3 as the third positive peak of the ERP; however, earlier negative peaks can be found in certain paradigms, and in continuous presentation, the P3 often emerges as the first and only positive peak. In the following, the term P3 will be used to generally refer to the whole cluster of ERP components, but especifically to the dominant centro-posterior aspect often called the P3b, and where an observation is restricted to any specific iterations (e.g., P3a), this will be specified.

This already highlights that the first critical choice to be made in averaging EEG data is to which time point the individual trials should be aligned. The response-locked ERP exhibits different criteria than the stimulus-locked ERP. Some stimulus-locked features, like the N1, disappear completely in response-locked data; the P3 is visible in both, but shows a different scalp topography and waveform, indicating that different aspects of the components are temporally better aligned to stimulus or to response.

Other possible time-locking points have been used, for example, the disambiguation point or the Category Violation Point (Hagoort, 2003), or the first fixation time point in studies of natural reading combining EEG and eye tracking (Kretzschmar et al., 2009).

Fundamentally, every study of EEG data using the averaging method requires time locking points. The averaging process not only greatly attenuates activity fully unrelated to the task, but also task-related activity that is not significantly phase-locked to a specific time-point has been exhaustively discussed (Cohen, 2011; Makeig, 1993). For example, μ and α blocking (e.g., the decrease of 10 Hz rhythms following stimulus presentation and preced-

ing a reaction) do not show strict phase alignment; the onset of the 10 hz amplitude drop is somewhat reliably related to stimulus onset, but its phase is not consistent with regards to the stimulus, especially not across multiple oscillatory cycles. Oscillatory blocking by itself is therefore not an ERP feature.

Phase-locked activity, like ERPs, are called "evoked", non-phase - locked changes, like α/μ blocking, are called "induced" (for a recent discussion, see Bastiaansen, Mazaheri, & Jensen, 2012).

An event that shows some, but not perfect temporal alignment to the time-locking point will still show up in the ERP, but its shape will be influenced by the temporal jittering. For example, if the response follows quickly after the stimulus, response-locked components will also appear in the stimulus-locked ERP, but they will appear broader, flatter. This is especially critical if response times differ between two conditions, leading to different degrees of jitter.

Consequently, signals whose phase and latency are relatively consistent compared to the time-locking point will determine the ERP. But even though the mathematical antecedents of the appearance of a component in the ERP are mostly understood, which brain processes actually emerge is an open question. In the following, I will discuss the main proposals about the origin of phase-locked EEG perturbations.

The phase-reset model proposes that ongoing oscillations can be reset by critical events, leading to sufficient phase consistency; here, the ERP emerges out of a reshaping of the ongoing EEG. The neurochemical model proposes that phasic neuromodulator activity roughly time-locked to critical events affects large neural populations at once. The asynchronous amplitude modulation model highlights that stimulus-induced amplitude shifts in non-phase consistent non-mean zero ongoings oscillations show up as low-frequency ERP components.

As a preface, I will note that especially by proponents of the phase-reset model (Makeig et al., 2002; Roehm, 2005), a so-called "classical" model is often alluded to. I have not been able to find a citation for this view; even though proponents of the phase-reset model argue it to be the default, I have not been able to produce a source, or found them to provide a source, that actually explicitly makes the claims attributed to this "classical" model. Consequently, this "classical" model is not discussed under its own subheading.

The "classical" model is not truly a model by itself, but rather simply a restating of the mathematical background given above, with some elaboration about its neural underpinnings, as well as the addition of some aspects that are attributed to the classical view for which I have been unable to find any support in the literature by anyone, including the sources cited as representing the "classical" view. It may be true that for example in the first years of EEG research, many researchers assumed a lot of the EEG reflected true cortical noise; however, this seems to be not an issue for ERP researchers, who are generally aware of the existence of non-random, functionally relevant non-time locked phenomena in the EEG.

For example, Makeig et al. do not cite any literature when they claim that "(m)ost electroencephalographic (EEG) studies" follow the "classical model" (Makeig et al., 2002). Klimesch et al. (2007) (p. 1013) state that the "Evoked model" predicts that the ongoing EEG represents "random noise", and that,

consequently, "EEG oscillations do not serve a specific function". I have not found this claim in the literature cited by Klimesch et al. (2007). It seems to result from a misunderstanding of the terminology of other researchers. For example, Luck (2010) states that "by averaging together many trials of the same type, the brain activity that is consistently time-locked to the stimulus across trials can be extracted from other sources of voltage (including EEG activity that is unrelated to the stimulus and non-neural sources of electrical noise". On one hand, the term "noise" here refers to non-neural current flow. Moreover, measured noise is such a thing only in relation to some intended measure, and calling an aspect of a data set "noise" does not imply that it is truly random; but rather, not in an interpretable way related to the critical measure. If an EEG researcher averages multiple trials to improve the "signal-to-noise" ratio, he does not imply that the ongoing EEG is actually noise, but rather, that he is not concerned with certain aspects of the data, without claiming the lack of a potentially neurocognitive origin thereof. In fact, α blocking/ERD, well-known since Berger, is generally understood to relate to cognition even by researchers who necessarily, when averaging across trials, lose this aspect of their data due to its lack of inter-trial phase coherence. Consequently, it may be considered *noise* for the purpose of the experiment, without an implication that e.g. the generating process is truly random and/or independent of cognition. Consequently, some popular introductions (Rugg & Coles, 1995) use the term noise in the quotative ("noise"/"noise"), and those who don't often precede their discussion of noise and averaging by pointing out that multiple methods existing to interpret electrical brain activity, and that following sections refer to attempts to extract time-locked activity (Hillyard, 2009; Kutas & Dale, 1997).

As another example, Klimesch et al. (2007, p. 1013) claim that only according to the "Evoked model", "Evok. comp. are generated by localized neural activity", and that therefore, "Dipole source analysis yields meaningful results". In contrast, at least two strictly evoked models of certain ERP components (Holroyd, 2004; Nieuwenhuis et al., 2005; Warren, Tanaka, & Holroyd, 2011) assume a fundamentally systemic origin where neuromodulators affect multiple sites roughly in parallel, but with a distinct time course. Major proponents of a phase-reset model (Delorme, Palmer, Onton, Oostenveld, & Makeig, 2012; Makeig, Debener, et al., 2004), however, argue that oscillatory activity can be successfully localized in theory and practice. They assume that while synchronised firing spreads over the scalp, it can be accurately described as being focused at certain brain areas, or "sources".

3.5.1.2 *The phase reset model*

The phase-reset model goes back at least 4 decades (Sayers, Beagley, & Henshall, 1974) and has been championed by a number of research groups. It is commonly elaborated in opposition to a roughly sketched alternative explanation usually termed the "classical view" which I, as mentioned above, have so far only seen described in papers unequivocally favouring the phase-reset model. This "classical view" is presented as containing the assumption that the ERP results from the event-induced appearance of an independent, fixed activation pattern, orthogonal to the ongoing EEG, in single experimental trials.

In contrast, the phase-reset model proposes that ERP components result from the reshaping of the ongoing EEG. As noted, ongoing oscillations (like

α and β waves) will average out to zero in the ERP if they are not sufficiently phase correlated to the time-locking point, meaning, trials show uniform distribution of phase. However, inter-trial phase coherence can result in parts of an ongoing oscillation showing up in event-locked averages if the event rearranges the ongoing phase to be non-uniform; for example, by causing the oscillation to "reset", meaning, immediately transitioning to oř (or another value identical across trials) at a fixed time after the event. If for example an α oscillation is "reset" quickly following the stimulus in a significant proportion of trials, an ERP very much like the N1/P1 and the following "α ringing" might appear.

The primary implication of the phase-reset model, and the major difference to other models, is the strong dependence of the ERP on the ongoing EEG. One model of Event-Related Brain Perturbations (Makeig, Debener, et al., 2004), "Event-Related Brain Dynamics", assumes that at least significant aspects of both the ERP, and of the ongoing brain activity, can be described as a combination of evoked quasi-oscillatory components (including the far-frontal P3f, Delorme et al., 2007), and the reorganisation of the phase of ongoing oscillations (including the N1/P1 (Makeig et al., 2002) and the ERN (Luu, Tucker, & Makeig, 2004)). The Klimesch model (Klimesch, Hanslmayr, Sauseng, & Gruber, 2006; Klimesch et al., 2007) assumes that the reset of ongoing α may explain at the very least the N1/P1 complex. Roehm (2005) further proposed that phase resets in delta/δ and θ bands could produce late linguistic components, like the N400 and the P600.

3.5.1.3 *EEG oscillations: causes and functions*

The assumed neurophysiology behind ERP components and the cognitive function attributed to them in the phase-reset framework are deeply intertwined with contemporary interpretations of cortical oscillations. That the EEG shows strong oscillations has been known for nearly a century now, but recently, increasing evidence has become available linking oscillations directly to cognitive function.

The researchers Pfurtscheller and Lopes da Silva have extensively researched the relation between evoked and oscillatory activity (Pfurtscheller, 1992; Pfurtscheller et al., 1999; Pfurtscheller, Stancak, & Neuper, 1996; da Silva & Gon\c calves, 2008). While usually not cited as opponents to the phase-reset model, they have contributed important models of the relationship between brain activity and the EEG that includes a proposition of fundamentally different networks for oscillatory and for evoked activity. They attribute the ERP to afferent drive, whereas oscillations are attributed to local main neuron - interneuron interactions possibly driven by thalamo-cortical loops (see also Wang, 2010).

While different neuronal circuits are responsible for different forms of activity, it has been shown (Lopes da Silva, 1991) that one brain area can, depending on cognitive states, produce different oscillations, showing α during some aspects of the task, and β during others. Consequently, it is hypothesised that α, like Adrian (1934; 1935) had assumed decades earlier, marks an idling of sensory brain areas, while the related μ (a near-10 hz rhythm with bilateral central maxima) marks idling of motor areas.

However, perhaps in contrast to such a passive interpretation of brain oscillations, it has been demonstrated that the timing of a sensory event

relative to the phase of ongoing oscillations influences perception (Beck, 1965; Busch, Dubois, & VanRullen, 2009; Mathewson et al., 2011; VanRullen, Busch, Drewes, & Dubois, 2011). Specifically, stimuli that reach the subject during α peaks are more likely to be detected, those at α troughs more likely to be missed. Furthermore, pre-stimulus α power correlates negatively with detection. Building on these findings, Mathewson et al. (2011; 2012) proposed that α may not represent passive, but active idling: cortical areas are set to oscillate strongly to block incoming stimuli while the subject intends to be in an exploitative, action-oriented or internally-focused state, where external stimulation has to be controlled to allow motor or cognitive operations to occur unperturbed.

That the phase of EEG oscillations not only correlates with cognitive states, but can seemingly be targeted to allow the appropriate states to co-occur with expected events, has been supported by recent discoveries using ECoG in animals. Lakatos et al. (2008) found that low, quasi-oscillatory components preferentially align one receptive "phase" with critical stimuli that are sufficiently expectable in time. Furthermore, these brain states predict improved behaviour compared to the non-receptive "phase" during stimulus presentation. Thus, low-frequency oscillations allow for temporal predictions (Arnal & Giraud, 2012).

It has been proposed (Schroeder & Lakatos, 2009) that this coupling between negative low-frequency phase and cortical responsitivity is mediated by a recently discovered oscillatory hierarchy, where low-frequency phase is connected to high-frequency (γ; beyond 30 hz) amplitude (Canolty et al., 2006). This result is also compatible with an interpretation of γ not as an oscillation, but simply a measure of spiking rate (Burns, Xing, & Shapley, 2011), possibly reflecting excitability.

This oscillatory hierarchy has also been demonstrated during language processing (Canolty et al., 2007), where, depending on task demands (visual or spoken language), different low-frequency networks control high-frequency amplitude. This observation may be related to the finding that Locus Coeruleus activity is locked to slow wave phase so that LC cells are most likely to fire during the transition from down- to up state, roughly compatible with the optimal induction of phasic LC activity by a stimulus arriving during the down state and the arrival of LC-released Noradrenaline at cortical targets (supporting target processing) during the up state (Sara & Bouret, 2012). Consequently, pre-stimulus Ventral Attention Network activity predicts subsequent memory recall of the stimulus (Wen, Yao, Liu, & Ding, 2012), compatible with the facilitation of memory processes by frontal noradrenaline (Bouret & Richmond, 2009; Sara & Bouret, 2012).

Altogether, these results support a role of the large- to intermediate scale oscillatory brain activity that is detectable by the EEG in controlling the gating of sensory information.

A slightly different perspective is found in the works of Klimesch (Klimesch, 2012; Klimesch et al., 2007). Here, α is also thought to gate between excitation and inhibition; however, it plays a major, more active role not only in the gating of sensory information, but also in memory access, where high α inhibits irrelevant memory during memory retention, and low α facilitates memory access (see also Palva & Palva, 2007).

3.5.1.4 *Phase reset: experimental evidence*

METHODOLOGICAL CAVEATS IN TIME-FREQUENCY ANALYSIS Time-frequency analyses can identify the time course of power and phase modulations. Theoretically, the resolution in the frequency band is restricted on the upper end by the sampling rate according to the Nyquist-Shannon theorem, which implies that only frequency bands up to half of the sampling rate can be represented. The closer to the sampling rate, the more serious aliasing distortions occur (see also Wijnants, Cox, Hasselman, Bosman, & Van Orden, 2013). However, the sampling rates possible with contemporary equipment easily go beyond any oscillations that can be reasonably expected in the EEG.

At the lower end, the spectral resolution is theoretically restricted by the length of the time window, but in practice, in typical ERP/time-frequency research (in contrast to research on near-DC slow fluctuations, conducted using different methodology), the necessary high pass filters restrict the reasonably interpretable window to above one or 0.5 hertz, and investigations of low frequencies are in danger of contamination by filter or analysis window border effects as well as artifacts (drifts or gross motor movements).

Due to the uncertainty principle, there is a trade-off between temporal and spectral resolution in time-frequency decompositions; using Fast Fourier or wavelet transformations, activity can be precisely located either in space or in time.
They can be applied to the averaged data, netting the time-frequency characteristics of the evoked signal, but losing non-phase locked activation; when applied to un-averaged data, they illustrate the so-called induced (temporally correlated, but not phase locked) activity.

To evaluate the data in favour of and against the phase reset model, it is critical to understand that non-oscillatory and oscillatory effects will reflect as having energy in certain frequency bands following frequency and time-frequency analyses, like Fourier or wavelet transformations (Mäkinen, Tiitinen, & May, 2005; Yeung, Bogacz, Holroyd, & Cohen, 2004; Yeung, Bogacz, Holroyd, Nieuwenhuis, & Cohen, 2007). Furthermore, Fourier transformations specifically are well-known to induce high-frequency artifacts due to what is called *Gibb's phenomenon* (Gibbs, 1898; 1899; Hewitt & Hewitt, 1979).

In data containing both ongoing oscillations with uniform phase distribution, and a time-locked evoked signal, time-frequency and frequency analysis techniques will pick up the power in strictly evoked components, which reflects not an oscillatory nature, but the slope and peakedness of the curve. At the time of the evoked component, while the ongoing oscillation has uniform phase, leading to insignificant phase coherence, the evoked signal present in single trials biases the decomposition towards the phase of the evoked component. The detection of frequency band power or inter-trial phase coherence by wavelet or Fourier transformations is therefore not a sufficient index of oscillatory dynamics.

As a similar problem, the temporal filtering of non stationary data (including data containing evoked components), as is commonly done with EEG/ERP data, results in apparently oscillatory activity by spreading the spectral power of a stationary signal in time. This problem is most critical near the edges of filters; problematically, filters used in typical ERP research are indeed close enough to the critical frequencies to cause distortion effects

(Acunzo, Mackenzie, & van Rossum, 2012; Kappenman & Luck, 2010; Luck, 2005; Rousselet, 2012; Widmann & Schröger, 2012, VanRullen:2011dw; Yeung et al., 2007)). High-pass filters primarily dampen components. This, in turn, can potentially delay and attenuate ERP peaks and ERP peak differences between conditions, especially once the pass band extends beyond 1 hz. More problematically, a low-pass filter with a pass band at 10 hz, common for visually smoothing signals (Rousselet, 2012), will severely distort typical ERP waveforms, including artificial "oscillatory" activity and both artificially early peaks and artificial differences between conditions, and even a 20 hz filter can time-shift effects. Acausal filters induce artefacts both before and after a filtered wave, whereas causal filters only distort the signal following a wave or peak, but distort the waveform itself significantly more than acausal filters (Widmann & Schröger, 2012).

FINDINGS A number of predictions have been generated from the phase-reset model and tested, including: lack of stimulus-induced power increase, similar scalp topography/generators of ongoing EEG and ERP, and increased stimulus-locked inter-trial phase coherence/concentration. However, all of these measures are now understood to be problematic (Sauseng et al., 2007; Yeung et al., 2004; 2007), lacking the ability to reliably differentiate phase reset from a purely additive component.

The relation between pre-stimulus ongoing EEG and the ERP seemed at first to provide the major aspect where critical implications of phase resetting can be tested. Originally, it was assumed that if the ERP emerges from a modulation of the ongoing EEG, then the spectral power, especially in a narrow band around the dominant frequencies of the ongoing EEG, should be equivalent pre-stimulus and post-stimulus, whereas there should be significant post-stimulus inter-trial phase coherence. However, if an evoked component appears in addition to the otherwise ongoing (not reset) EEG, both a power increase and phase coherence should be observed, since an evoked component still has power in certain frequency bands. In return, a pure phase reset model must predict that when no pre-stimulus ongoing oscillation with sufficient power is found, no ERP can result, since the modulation of a weak signal will not result in a strong signal.

Some researchers have indeed found evidence regarding this prediction. In some experiments, single-trial post-stimulus EEG power was found to not be greater than pre-stimulus power (Makeig et al., 2002), indicating phase reorganisation. Others (Barry, 2009; Jervis, Coelho, & Morgan, 1989; Mäkinen et al., 2005) found that post-stimulus power was greater than pre-stimulus power, indicating an additive/evoked effect.

Moreover, there is an important cofound: the known disappearance (desynchronisation) of the "Berger rhythm" upon stimulation. Since it is known that a large decrease in the dominant rhythm of the ongoing EEG follows stimuli of the kind commonly used in experiments, such recordings are cofounded with regards to pre-to-post - stimulus - comparisons of spectral power.

However, the Berger rhythm is a scalp phenomenon. As discussed, it emerges as the volume conducted mix of several cortical sources at the scalp as the dominant pattern in the scalp EEG, whereas it is often not found in direct cortical readings. Shah et al. (2004) recorded directly from the visual cortex and observed that a significant, domineering evoked com-

ponent appeared after stimuli, larger than the usually negligible ongoing pre-stimulus activity. Even in single trials, the evoked response was readily visible, but no oscillatory activity was observable. These findings may not trivially generalise to the ERP since they were recorded in animals, and the findings were restricted to superior cortical layers. In contrast, in human subjects, multi-cycle phase locking without concurrent power increase has been reported (Rizzuto et al., 2003).

Other researchers have tried to restrict the analysis of time-locked synchronisation by only considering frequency bands that are actually distinguished by steady, observable in the ongoing EEG (Pfurtscheller et al., 1999); some researchers therefore restrict research into ERS/ERD to α and β bands, since in almost all recordings on awake subjects, at most these two clear spectral peaks appear.

However, oscillations may be ongoing and still not appear in the raw scalp recordings (Sauseng et al., 2007). Certain brain systems may show clear θ peaks which is in the summed EEG dominated by the larger α peak, but θ oscillations still react to cognitive stimuli (Onton et al., 2005). Similarily, the μ rhythm has generally been assumed to only characterise a minority of individuals (Niedermeyer, 1999; Pineda, 2005), but using ICA, recent attempts have identified reliable μ components in most subjects (Makeig et al., 2002)

Further attempts to support or attack the phase-reset model have mostly highlighted that current techniques cannot differentiate a phase-reset from an evoked model. A number of elaborate analyses (Luu et al., 2004; Makeig et al., 2002) purportedly showing that phase reset of frontal-midline θ lies at the heart of the error-related negativity have been presented, including single-trial phase sorting, single-trial amplitude sorting and the comparison of the scalp topography of ongoing and averaged EEG. However, when applying the same methods to simulated data containing either an evoked, or a phase-reset component, Yeung et al. (Yeung et al., 2004; 2007) found that these methods result in the same findings for either data set, and therefore do not reliably indicate phase resetting.

The dependence of post-stimulus phase on pre-stimulus phase has also been used to distinguish the positions; it has been argued that a dependence would support (Klimesch et al., 2007), but also that dependence would disprove (M. L. Risner et al., 2009; M. Risner et al., 2009) the phase reset model. Both positions have been met with criticism (Klimesch, Sauseng, & Gruber, 2009; Ritter & Becker, 2009).

Since phase reset necessarily perturbs the phase of the ongoing EEG, the degree of phase stability of α after stimulus has been investigated (Mazaheri, 2006); a high degree of phase stability was interpreted to indicate a lack of phase reset.

In a review, Sauseng et al. (2007) summarise some of the problems of trying to prove or disprove the phase-reset model. They conclude that by itself, empirical observations have so far not produced sufficient evidence for either view; however, they claim that phase-reset models allow nontrivial predictions not afforded by the evoked model. For example, they cite Roehm et al. (2005) as studies where time-frequency analyses show higher sensitivity to cognitive processes and phenomena. However, as noted, time-frequency methods like the wavelet transformation are by their nature not evidence of oscillatory activity, but simply deconvolute the spectral structure of a signal. If a component is found to carry energy in the θ band, this finding does

not necessarily connect it to an underlying, independent θ oscillation, but primarily quantifies its shape. While time-frequency analyses may show improved sensitivity compared to the ERP, this is not necessarily tied to the assumptions of the phase-reset model.

Often, phase reset models have specifically attempted to connect intrinsically stable oscillatory bands identifiable from a clear peak in the EEG spectrum, such as α and possibly β/θ, to fast, early, sharp exogenous components related to sensory processing (Barry, 2009; Makeig et al., 2002). The P3 has been argued to represent mostly δ/sub-θ, low-frequency activity by Klimesch et al. (2000), distinct from ongoing α or θ oscillations.

However, a specific role oscillations has also been proposed in higher cognitive functioning and late ERP components, including the P3 as the averaged result of single-trial θ and/or δ phase concentration (Başar-Eroğlu, Demiralp, & Schürmann, 1992; Başar-Eroğlu, Karakaş, & Schürmann, 2001; Schürmann, Başar-Eroğlu, & Kolev, 2001), and of three-cycle α (Schack & Klimesch, 2002) or θ (Delorme et al., 2007) bursts.

The most extensive recent work on brain oscillations and a form of higher cognitive function, linguistic processing, has probably been presented by Bastiaansen and coworkers (Bastiaansen & Hagoort, 2006; Bastiaansen, Magyari, & Hagoort, 2010; Bastiaansen et al., 2012; Bastiaansen, Van Berkum, & Hagoort, 2002; Hagoort, Hald, Bastiaansen, & Petersson, 2004; Wang, Zhu, & Bastiaansen, 2012), including the sensitivity of δ, θ, α, β and γ oscillations to semantic integration. However, they have generally deemphasized phase information and therefore, the relation between ERP components and brain oscillations. Similarily, the recent work on a possible connection between θ phase and acoustic speech amplitude envelope (Ghitza, Giraud, & Poeppel, 2013; Giraud & Poeppel, 2012; Luo & Poeppel, 2007; 2012) is not connected to evoked components.

However, both approaches have implied that certain ongoing oscillations, especially θ and α, may be sensitive to linguistic processing.

The contribution of phase reset of δ and θ to late linguistic components (N400 and P600) has resulted in the finding that different linguistic processes reflect differently in time-frequency analyses (Roehm et al., 2005; Roehm, Bornkessel-Schlesewsky, & Schlesewsky, 2007). Yet these analyses were restricted to measures shown to be equally sensitive to phasic as well as to phase-reset systems by the investigations of Yeung et al.

3.5.1.5 *Alternative models linking oscillations and ERPs*

Three alternative perspectives on an association between oscillations and ERPs have been proposed recently: the Travelling Wave model (Alexander et al., 2013; Klimesch, Hanslmayr, Sauseng, Gruber, & Doppelmayr, 2006) according to which a non-stationary evoked α oscillation spreading from occipital sites reflects as an ERP in the trial averages; the Firefly model (Burgess, 2012), according to which multi-band frequency slowing results in the complex ERP structure; and the amplitude modulation of asymmetric/non-zero mean oscillation theory of evoked potentials (van Dijk, van der Werf, Mazaheri, Medendorp, & Jensen, 2010; Mazaheri, 2006; Mazaheri & Jensen, 2008; Nikulin et al., 2007), which derives low-frequency ERP components from power shifts in non-phase locked higher-frequency oscillations.

The asymmetric amplitude modulation model/AAMM of ERP generation highlights an important aspect of the mathematics of periodic activity that is often ignored when describing the preconditions of the emergence of the ERP. Uniform phase distribution across trials results in a zero mean potential only if the oscillations are symmetric around zero. If oscillations are however net positive or negative, amplitude modulations will induce baseline shifts. For example, if the ongoing α activity sums up to a positive value, then a time-locked, but not phase-locked decrease in α power will lead to a negative shift in the average.

The difference between this view and a model assuming non-oscillatory, evoked activity behind the ERP are subtle, but significant; mainly, the asymmetric amplitude modulation model assumes that the resulting ERP is shaped not by the sum of similarly shaped component found in single-trials, where the potential time course of single-trial evoked responses looks like the potential time course of the averaged ERP; but rather, that the time course of the ERP mirrors the single-trial amplitude modulation time course (the time course of single-trial ERD/ERS).

Since amplitude shifts of α, e.g. ERD/ERS, are well established, finding α to be non-zero mean would strongly indicate the possibility that α ERD/ERS may contribute to the evoked potential. Indeed, recent investigations (Mazaheri & Jensen, 2010) indicate that just this is the case. As noted, α blocking and the P3 share many parameters (Yordanova et al., 2001); in the AAMM, a causal relationship from α ERD to the P3 could be established, though the original elaborations of the model do not preferentially refer to the P3. This proposal does not necessarily conflict with the LC/NE-P3 model, since the exact nature of how cortical NE induces the P3 is open for investigation. If cortical NE causes α blocking, it may be that P3 and LC/NE are linked by AAMM. Fundamentally, the AAMM model makes very specific, testable predictions regarding a dependence of components on α asymmetry and, to a lesser extent, power. However, it must be noted that for many components, AAMM is an unlikely explanation due to the different topography of mostly occipital α and e.g. the frontal P3a or far-frontal P3f.

Recently, a further unconventional model of deriving late potentials from oscillatory reordering has been described (Burgess, 2012). The "Firefly" model describes how the ERP could arise from frequency slowing, but it has so far not been extensively reviewed, discussed or tested.

3.5.1.6 *Summary*

Fundamentally, no unambiguous test of the phase reset model, being able to falsify it, exists, since all measurable phenomena exhibited by a phase resetting system are also exhibited by a purely phasic system working independently of ongoing oscillations. Further models linking late ERP components to oscillatory reorganisation have not been subjected to extensive tests yet.

In contrast, the extensive physiological background between explanations of late ERPs as reflecting phasic activations of neuromodulator systems leads to testable predictions. From a Popperian or Lakatosian stand point (Lakatos, 1970), the "neuromodulator model of ERPs" is the more progressive research programme as long as it is not disproved.

However, the phase reset model still holds considerable appeal. The existence and functional nature of multiple brain oscillations is well established,

and certain ERP components show behaviour highly compatible with oscillatory phenomena. An attractive solution could be found in a mixed approach: early exogenous components might at least partially stem from phase reorganisation, later endogenous components from phasic neuromodulator activity. Furthermore, the interaction between oscillations and neuromodulators (such as e.g. encoding being coordinated by hippocampal θ and ACh) might become of interest in this regard.

3.5.2 *The ERP as Threshold Regulation*

Two interesting unified accounts of ERP effects come from Elbert & Rockstroh (Elbert, 1992; Elbert & Rockstroh, 1987) and Kotchoubey (2006). The accounts are similar enough to warrant a shared discussion.

3.5.2.1 *The electrophysiology of scalp polarity*

Both accounts rest on the premise that the scalp-negative components represent both a common underlying physiological as well as functional background, and the scalp-positive components another. As noted above, Elbert & Rockstroh connect scalp-negative and positive ERPs to apical EPSPs and IPSPs, respectively - as does Kotchoubey. Kotchoubey specifically assumes that ACh and Serotonine are responsible for these EPSPs to superficial apical dendrites, and thereby, scalp negativities. In contrast, GABA is thought to mediate the inhibitory activity resulting in scalp positivities.
ERP effects do not appear tagged as "positive" vs "negative". They always reflect differences between reference and measurement electrode. Dipoles trivially project dipolar. However, tangential dipoles (in folds between gyri and sulci) and deep sources are generally argued to contribute little to the ERP by both groups. As Elbert (1990) argues, deep sources can be expected to contribute less to the EEG scalp fields than superficial (cortical) sources simply due to their distance. Tangential dipoles similarly contribute little to the scalp field because they must project through large amounts of brain tissue and cerebrospinal fluid. However, this assumption may seem questionable when considering the MMN, which seems to be generated by a dipole in the posterior temporal lobe and shows a strong frontal peak in the scalp ERP.
Yet, these researchers propose a shared underlying mechanism for surface ERP positivities and another mechanism for surface ERP negativities.

Generally, for all of the following, it must be kept in mind that attempts to generalize ERP components based on (dominant) scalp polarity are only viable insofar as the dominant sources of the scalp ERP are actually found in the required structural arrangement. How far this assumption is warranted is an open question.

3.5.2.2 *The function of the ERP*

SURFACE NEGATIVITIES Negativities are proposed to reflect feedforward expectations (Kotchoubey) and cortical excitation (Elbert & Rockstroh), increased sensitivity to cortical input. The role attributed to surface negativities as laid out by Kotchoubey is roughly equivalent to the construction and checking of forward models. They reflect stimulus-evaluative processes,

including preparatory processes (such as the CNV) and mismatches between expected and perceived events (such as the MMN). They also include the construction of appropriate expectations (similar to the Context Updating attributed to the P3 by Polich & Donchin). Ressources are put in place based on event demands.

SURFACE POSITIVITIES To react to stimuli, encode stimuli into memory, or *pick up* on perceived and processed information for the purpose of acting on them, a reduction of cortical thresholds is advantageous, which is implemented by inhibitory PSPs to the cortex. Kotchoubey proposes that resources prepared during negativities are consumed in this phase. Feedback processes happen during this phase, and irrelevant information is suppressed.
Apical IPSPs result in a positivity (such as the P3). The underlying inhibitory threshold regulation supports memory encoding, action selection and task performance. In the process of each *"perceptual act"* (Kotchoubey, 2006, p. 48), positivities and negativities constantly alternate. Thereby, Kotchoubey proposes that the quasi-oscillatory nature of the ERP in *"negative-positive cycles"* reflects the cortical instantiation of perception-action loops.

	Physiology	Function	Correlates
Negativity (CNV, MMN, N400)	Excitation of apical dendrites (ACh & 5-HT?)	Feedforward expectations (Kotchubey) Cortical excitability (Elbert & Rockstroh)	Memory updating, stimulus processing, attention & anticipation
Positivity (P1, P3, P600)	Inhibition of apical dendrites	Feedback processes, inhibition/dysfacilitation	Control, Action selection

Table 3.7: Key elements of the component-unifying proposals by Kotchubey/Elbert & Rockstroh

3.5.3 *Relationship between the models*

3.5.3.1 *Threshold regulation and the LC/NE model*

In some respects, both of the proposals elaborated upon in the above subchapter resemble essential aspects of the LC/NE model.
Kotchoubey proposes that the inhibitory feedback processes during positivities allow the suppression of irrelevant information and the selection of appropriate actions - a line of thought strikingly similar to the "temporal filter" proposed in the LC/NE model. Key functional aspects of the role assigned to scalp positivities by Elbert & Rockstroh are fundamentally identical with the LC/NE understanding of the P3. A key passage will be quoted at length:

> A threshold control mechanism of this kind would provide the brain with the ability to interrupt ongoing activity, when relevant

> information was received. If thresholds were set high consequent upon the presentation of relevant information, ongoing activity would drop to a low level instantaneously, and activity would survive only in those elements pertaining to the concept associated with the encourage circulation of activity throughout the brain. Such interruptions would generate positive waves ...
> (Elbert, 1990, p. 241)

The proposed *"interrupt[ion] of ongoing activity"* strongly resembles the *"network reset"* role of NE release (Bouret & Sara, 2005), the condition on perceived relevance overlaps with the antecedent condition of subjective significance (Nieuwenhuis et al., 2005), and the suppression of non-salient and facilitation of strong signals is equivalent to the proposed gain control function of NE.
However, a key difference between both proposals rests in the fact that Nieuwenhuis et al. (2005, p. 516) assume a fundamentally incompatible underlying physiological mechanism: *"NE may produce a prolonged depolarization of cortical neurons that would increase their responsiveness"*.
Problematically, to my understanding, too little is known about the cortical effects of NE and the activity underlying the ERP to decide between these incompatible physiological accounts.

3.5.3.2 *Phase reset and the LC/NE model*

The relationship between the proponents of neuromodulator and phase reset models has often been controversial, with researchers defending neuromodulator models arguing for methodological inconsistence in phase reset research (Holroyd, HajiHosseini, & Baker, 2012, for discussions of phase reset model methodology by proponents of neuromodulator models; Yeung et al., 2004; 2007), and researchers defending phase reset models interpreting neuromodulator models as "classical" (Cohen, Wilmes, & van de Vijver, 2012). However, some researchers propose that neuromodulator release may induce oscillatory responses (Makeig & Onton, 2012) or that oscillatory and phasic/neuromodulator perspectives may coexist (HajiHosseini & Holroyd, 2013; Holroyd et al., 2012).
At least in the core LC/NE model however, the ERP effects in question are fundamentally of a non-oscillatory nature (although they show quasi-periodicity due to the alternation of activation and refractory periods).

3.5.3.3 *Phase reset and threshold regulation*

The phase reset and threshold regulation models may stand in fundamental opposition in that Elbert & Rockstroh assume that the ERP stems from thalamic feedforward processes, while cortical oscillations have been attributed to feedback loops. Furthermore, threshold regulation is assumed to represent a modulatory, additive effect with regards to ongoing activity instead of a remodelling.
However, similarities can be found in that oscillations and phase alignment are increasingly connected to active gating between insensitive and receptive states (Canolty et al., 2006; Mathewson et al., 2011), resembling the thresholds proposed by Elbert & Rockstroh.
Some proponents of the phase reset model (Makeig, Delorme, et al., 2004)

have indeed proposed that non-oscillatory phenomena may be adequately captured by threshold regulation, in parallel to distinct oscillatory effects.

3.6 FURTHER ERP COMPONENTS: THE COMPONENT ZOO

3.6.1 *N2/P3*

3.6.1.1 *Anatomy and antecedents*

The N2 has been extensively discussed in older (Pritchard, Shappell, & Brandt, 1991) (Ritter & Ruchkin, 1992) and recent (Folstein & Van Petten, 2008) reviews.

In the original P3 study (Sutton et al., 1965), the large positive deflection was preceded by a smaller negative peak in some subjects. Later, this component was found found again in an early oddball-like study (Squires et al., 1975); rare ($p < 0.1$) stimuli elicited a significant N2, regardless of perceptual aspects of the stimulus. A similar component was found in other studies investigating unexpected stimuli (Courchesne, Hillyard, & Galambos, 1975). It can either be described as a negative peak around 200 msec after stimulus onset ("N200"), or as the second negative peak of the ERP ("N2") after the N1 or, in difference images, the MMN (Luck, 2005). Both definitions are problematic; later N2 effects are found, including clear N2 effects around 300 msec (Holroyd, Pakzad-Vaezi, & Krigolson, 2008), and in many cases, the N2 emerges as the third, first or even only negative peak. Especially in early studies, terminological and paradigmatic confusion with the MMN can be found. Commonly, the primary difference between the two is automaticity of processing; an N2 is found for expectancy mismatches, incongruences or deviancies in an attended dimension of an attended modality (an attended stream). The MMN (previously called the "N2a") is automatic and only depends on perception, not awareness (Pritchard et al., 1991; Ritter & Ruchkin, 1992); it is also earlier and has a fixed polarity with dual peaks at frontal and occipo-temporal sites, compatible with a focused generator in both temporal or visual lobes. A further similar component is the transient posterior, often lateralized N2pc as an index of attention allocation in visual search (Luck, 2005).

The N2 has a somewhat variant topography between various tasks, being found with frontocentral, parietocentral and temporal/occipital maxima (Pritchard et al., 1991). The anterior N2 is often associated with the mediofrontal cortex[5], specifically the MCC/MFC (Crottaz-Herbette & Menon, 2006; Huster, Westerhausen, Pantev, & Konrad, 2010; Nieuwenhuis et al., 2003a; van Veen & Carter, 2002), especially by researchers associating the N2 with aspects of meta-cognition or cognitive control. It is often used as an index of "ACC"/MCC activity (Baker & Holroyd, 2011; Yeung & Nieuwenhuis, 2009), even without attempts at source localisation/inverse modelling.
While the MMN may lead to similar effects at mediofrontal electrodes, source localisation typically dissociates these two components.

Another possibly associated component is the N450 or Stroop N4 (Badzakova-Trajkov, Barnett, Waldie, & Kirk, 2009; Hanslmayr et al., 2008;

5 See the subchapter on the anatomy of the cingulate gyrus for a brief discussion of the anatomical ambiguity of this terminology.

West & Bell, 1997), a later negativity elicited during incongruent stimuli in the Stroop task that has also been located to the MFC. In the Stroop task, a word denoting a color is printed in a different color, interferring with the subject's ability to correctly name the font color due to interference from the meaning of the automatically read word.

An N2 has also been observed in the go/no-go task (Nieuwenhuis et al., 2003a), which is fundamentally an inverse oddball task where common stimuli are responded to and responses are inhibited to infrequent stimuli.

Furthermore, the N2 is found in the Sternberg tasks to items not in the memory set (Kotchoubey, Jordan, Grözinger, Westphal, & Kornhuber, 1996), and a similar component is found when participants must update their task set (Brass, Ullsperger, Knoesche, Cramon, & Phillips, 2005), with frontal activity preceding parietal activity.

Often (Folstein & Van Petten, 2008; Yeung & Nieuwenhuis, 2009), researchers dissociate specifically between, and assume different cortical mechanisms for response conflict-related ERN effects found when subjects are required to commit to a response choice, versus those where subjects are to primarily classify stimuli. However, many paradigms such as the Oddball paradigm show similar N2 effects both with and without over responses, and the pattern of difference responded and passive presentation is not clear. For this reason and the ideal of parsimony, such component classes will be treated differently only where they must.

Generation of the N2 depends not simply on physical deviancy of attended stimuli, but on deviance in an attended dimension of the stimulus. For example, when words were classified depending on their physical size, deviants elicited an N2; when they were judged on their semantic category, physical deviancy did not elicit an N2, but semantic deviancy elicited an N400 (Deacon, Breton, Ritter, & Vaughan, 1991).

In many paradigms, the topography of the N2 depends not on factors such as task complexity or stimulus novelty, but on stimulus modality - however, with an important caveat.

Within one study (R. Simson et al., 1977), auditory oddballs evoked a parietal component compatible with temporal generators, visual oddballs resulted in an occipital peak. A somatosensory N2 is found at sites ipsilateral to stimulation, compatible with an ipsilateral representation of body functions (Kekoni, Hämäläinen, McCloud, Reinikainen, & Näätänen, 1996). Intracranial measures have found highly specific N2 locations compatible with a precise modality-dependent generator (Allison, Puce, Spencer, & McCarthy, 1999; McCarthy, Puce, Belger, & Allison, 1999; Puce, Allison, & McCarthy, 1999), including face sensitive acitivity in the fusiform gyrus. Some studies show distinct changes in N2 in topography by changing parameters even within one sensory modality. In one study, face oddballs (faces of one sex being presented rarer, tens of face stimuli in total) resulted in an occipital N2 compatible with a generator in the fusiform gyrus (Warren et al., 2011). Such effects are compatible with a generation of the N2 by brain areas responsible for the processing of the respective modality (e.g., faces being processed in the fusiform gyrus). However, in this same study, color oddballs (one of two colors being less frequent) resulted in a central N2 compatible with a topography compatible with a cingulate generator. In another study (Lange, Wijers, Mulder, & Mulder, 1998), visual attention to binary

deviations of color or location (or their combination) also resulted in a central N2 localized to the ACC/MCC; yet, visual features such as location and color are not typically thought to be processed in the mediofrontal cortex. In other simple Oddball paradigms (Debener, Makeig, et al., 2005), the N2 is also often found with an anterior location.

Furthermore, the finding of anterior, possibly MCC-generated N2s in more abstract processes, such as the Flanker task, have lead to a disinterest of modality-specific generators of the N2 in favour of a focus on the anterior N2. In the Flanker task, subjects are presented with a central target to be attended and responded to, and surrounding "Flanker" items that may either be compatible or incompatible with the central target. Incompatible trials feature an N2 (Fritzmannova et al., 2009; Heil, Osman, Wiegelmann, Rolke, & Hennighausen, 2000; Kopp, Rist, & Mattler, 1996).

Typically, the no-go N2 shows the same frontal topography compatible with a possible generator in the MCC. The topography of the go/no-go N2 can also change with stimulus modality (Simson et al., 1977) in exactly the same way it does during an oddball task with the same stimuli (Simson et al., 1977).

To further complicate the issue of the nonstationary topography of the N2, it is likely that the component is mixed with an overlapping MMN and/or N2pc (Folstein & Van Petten, 2008) with their own respective topographies, and may often interfere with a concurrent P2. The auditory MMN results in a frontal negativity (likely projected from a dipole in temporal regions pointing anterior), but the equivalent (unattended sequence mismatch) visual component shows a posterior topography (compatible with a dipole in occipital cortices).

A highly informative finding regarding the relationship between modality-specific, topographically variable N2 effects and the invariant, MFC-generated, sometimes, but not always cognitive control-associated N2 was provided by a study employing fMRI-informed dipole analysis of data to study the precise stimulus-locked spatiotemporal dynamics of brain activity during an auditory and a visual oddball task (Crottaz-Herbette & Menon, 2006). As noted, they report P3a-like activity in the MFC, P3b-like activity generated by multiple posterior areas including areas in (SMG, IPL) and near the TPJ, including sensory areas, and a heterogenous, but systematic pattern of N2 effects. Following rare oddballs in either modality, an early MMN-like activity is generated in low-level areas (calcarine gyrus in the visual, Heschl's gyrus in the auditory domain). A large negative potential in the MFC peaks shortly after these effects. The P3-like effects follow the MFC activity, including the areas generating the MMN effects.

The authors propose that primary sensory areas detect modality-corresponding sensory deviations (corresponding to the MMN) and signal such activations to the MFC (eliciting the N2). The MFC then instantiates top-down modulation, including of posterior areas (P3). In the framework of the LC/NE-P3 perspective, this last step would of course correspond to activation of the LC via the cingulate-medulla pathway, and NE release in frontal areas including the MFC and posterior regions especially around the TPJ.

An important difference between the Flanker and Stroop paradigms in which they differ from Oddball and no-go paradigms is that the former features inherent stimulus incongruences. In a Flanker task, the target to

be attended is presented simultaneously with incongruent distractors. In a Stroop task, printed color and word meaning information are available simultaneously. In contrast, Oddballs are defined in their relation to a previous sequence; even single-stimulus P3 paradigms (Polich & Margala, 1997) contrast an event with a previous event-free span. Simultaneous presentations generally result in the anterior, ACC/MCC-associated topography.

The two possible N2 topographies in sequential effects can be subsumed as a modality-dependent (often posterior) effect (including the N2pc) and an anterior effect similar to the simultaneous N2 and P3a. Task complexity does not trivially predict if the modality-dependent or the anterior N2 topography will emerge; in tasks complex due to inhibition of prepotent responses or maintenance of a large memory set of targets to which individual stimuli have to be matched, the N2 is preferentially anterior, but in paradigms with perceptually or conceptually assignments, the N2 is often modality-dependent. Folstein & Van Petten (2008) associate the anterior N2 with control and the posterior N2 with attention-related processes.

Sometimes (Pritchard et al., 1991), the anterior and posterior N2s are assigned different names, with the anterior, novelty-associated N2 being called N2b (in contrast to the anterior P3a), and the posterior N2 termed N2c. However, central or anterior (N2b-like) rather than posterior N2 (N2c-like) effects are both found in simple expectation violation paradigms, such as unexpected continuations of well-known melodies or scale-inconsistent notes in a musical scale (Besson & Macar, 1987), and even within the same paradigm dependent on the attended dimension of the stimulus (Simson et al., 1977; Simson et al., 1977; Warren et al., 2011).

Unlike the P3, the N2 does not readily habituate, even in paradigms where P3 habituation is observed (Ravden & Polich, 1998).

The N2 is typically displayed as as stimulus-locked component. Problematically, no sophisticated analyses of an RT-locked nature of the N2 exist. Early studies (Ritter, Simson, Vaughan, & Friedman, 1979; Towey, Rist, Hakerem, Ruchkin, & Sutton, 1980) report a strong correlation between N2 and RT. However, these pioneer studies employed highly problematic methods: N2 peaks were hand-picked, and raw trials were analysed, possibly leading to substantial confounding by offset of P2 and onset of P3. In another study, the RT-locked N2 was smaller than in the stimulus-locked ERP (Nieuwenhuis et al., 2003a). ERPimages imply a stimulus-locked N2 component in a rotation task and a flanker task (Hoffmann & Falkenstein, 2010).

3.6.1.2 *Function*

Originally, the N2 was understood as a correlate of subjective surprisal. Paradigms evoking an N2 generally contain a component of various forms of mismatches and incongruences.

As noted, the first debate regarding its nature was concerned with the question of automaticity. Negative ERP components were observed following sequence violations/improbable events in both attended and unattended domains. Ultimately, attentiveness became the major distinction between the earlier, automatic, occipo-temporally generated MMN and the attention based, modality-variable N2 (Pritchard et al., 1991; Ritter & Ruchkin, 1992).

Some reviews (Patel & Azzam, 2005) argue that the N2 is sensitive not to expectancy violations, but to stimulus discriminability. However, the N200 is very large in very simple paradigms, such as the Oddball paradigm (Squires et al., 1975), and significantly smaller in complex tasks such as the Eriksen Flanker task that are often specifically used to observe sufficient error trials.

In the previous two decades, the debate concerning the role of the N2 was mainly concerned with a possible role in cognitive control. First, it was proposed to reflect response inhibition (Falkenstein, Hoormann, & Hohnsbein, 1999) due to its appearance on no-go trials. However, this view entails that 1. the component is fundamentally different from the oddball N2 or any two-choice N2, which may be undesirable, 2. the component should mostly covary with motor behavior. Especially the later prediction has been refuted.

The N200 to no-go trials depends on no-go probability. Some studies varied the ratio of go and no-go stimuli. When no-go stimuli are rare, an N2 is observed that however falls off in amplitude as the probability of no-go stimuli is increased. At 80% (Donkers & van Boxtel, 2004; Nieuwenhuis et al., 2003a) and 75% (Bruin & Wijers, 2002) probability, no-go stimuli no longer elicit an N2. Instead, at least in some studies (Nieuwenhuis et al., 2003a), a more negative ERP is found for rare go stimuli. This is not surprising since an 80% no-go trial task is virtually identical to a 20% target oddball task - though it should be noted that surprisingly, in high-probability no-go tasks, rare go stimuli often do not elicit an enlarged N2, different from the comparable contrast in an oddball task. Similarly, in equiprobable tasks, the N2 is often more negative for 50% no-go than for 50% go tasks (Nieuwenhuis et al., 2003a, Donkers2004; Pandey et al., 2012).

Compatible with a sensitivity of the N2 to incongruence or improbability, when investigating sequence effects in an equiprobable condition, go/no-go and oddball tasks become nearly indistinguishable (Smith, Smith, Provost, & Heathcote, 2010).

Contrasting a go/no-go and a go/GO task, where GO stimuli required not the inhibition of responses, but an especially forceful response, the less prepotent stimulus was reported to elicit an N2 even though both stimuli are responded to (Donkers & van Boxtel, 2004). However, the study used an especially drastic filter (2-12 hz bandpass) and did in fact observe differences in the N2 between GO and no-go conditions, so that it may not be trivially interpretable.

Still, the interpretation of the no-go N2 as a marker of response inhibition has been abolished. The previous findings are still roughly compatible with a finding that the N2 marks surprisal or expectation violation. However, the successor to the response inhibition theory have been two related theories of cognitive control rather than mismatch/expectation theories (Folstein & Van Petten, 2008): the conflict monitoring theory (Botvinick, Cohen, & Carter, 2004; Nieuwenhuis et al., 2003a; Ridderinkhof et al., 2004; Yeung & Nieuwenhuis, 2009) and the feedback learning theory (Holroyd, 2004; Holroyd, Nieuwenhuis, Yeung, & Cohen, 2003), two related models by partially overlapping researcher groups that have begun to converge into one paradigm (Holroyd & Yeung, 2012). According to the conflict monitoring theory, the MFC registers the simultaneous activation of multiple incompatible responses following a stimulus, and recruits additional attentional ressources to deal with this conflict. The feedback learning model assumes that the N2 is generated by the MFC in response to unexpected

outcomes, mirroring the dopamine signal to events that are worse than predicted (Schultz et al., 1997), and that its absence is induced by a dopaminergic signal to the MFC causing a scalp-positive ERP by the disinhibition of MFC motor neurons.[6]

Oddball or no-go N2 effects are explained by the conflict monitoring theory with regards to the prepotent response/non-response induced by the common tone/go-stimulus. In the feedback learning theory, they induce an N2 due to being unpredicted.

3.6.1.3 *N2 and P3*

The major difference in the antecedent conditions of the N2 and P3 is that the N2 shows gradual sensitivity to contextual stimulus identifiability, the P3 shows (mostly) binary sensitivity to stimulus category probability. For example, in a Continuous Performance Task/CPT, all items are equally common; yet targets elicit a P3b. For example, a task with the random presentation of 25 letters, 20% of which were designated targets and 80% nontargets (Breton, Ritter, Simson, & Vaughan, 1988), yielded an equally strong P3 as a two-letter task; the N2 was manipulated by this difference. Comparing the repeated presentation of a single, highly-probable male and a single rare female name with a list of randomly alternated male names and a single rare female name shows the same P3 to either rare condition (Kutas et al., 1977). Perceptual overlap between background and target strongly influences N2, but not P3 amplitude (Smith & Douglas, 2011).

The N2 shows large variance in topography, the P3 is comparatively stable. Generally, the N2 varies more with aspects of the stimulus in its context, the P3b more reliably with the subjective significance of the stimulus.

Generally, in the N2/P3 biphasic pattern, the N2 is most likely associated with stimulus-identificatory processes and the P3 with the reaction to the properly categorized stimulus, such as overt responses, memory updating or stream switching.

3.6.1.4 *Neurophysiology; possible neuromodulatory cause*

An initial candidate for neuromodulation of the N2 lies in the DA system, and indeed DA has been implicated in the conflict N2. Neuropharmacological inventions relating the DA system to the N2/P3 complex have resulted in indecisive vidence. Novelty-induced N2 and P3 have been found to be more negative (corresponding to N2 facilitation and P3 attenuation) by the DA agonist Apomorphine (Rangel-Gomez, Hickey, van Amelsvoort, Bet, & Meeter, 2013). DA antagonist Sulpiride was found to enhance N2 amplitude (Takeshita & Ogura, 1994) and displayed a nonlinear effect on the P3 - with P3 attenuation for subjects with a large pre-treatment component, and N2 attenuation for subjects with small pre-treatment P3s. A further downside for a straight association between the N2 and the DA system is that it might disallow connecting anterior and posterior N2 effects, since the DA system does not directly innervate possible key generators of the posterior N2.

A possible neuromodulator behind the whole range of N2 phenomena must fulfil a range of criteria.

6 See the chapter on possible neurophysiological foundations of the ERN for a critical discussion of the plausibility of this proposal from a low-level physiological perspective.

- It must allow for the variable topographies based on modality observed for the N2, including posterior generators.

This criterion likely excludes DA (since it is only marginally observed at posterior sites) and possibly NE (since NE does not allow for topographical flexibility; although Nieuwenhuis et al. (2005) argue that not differential NE release, but differential NE usage may result in differential topographies between conditions). In contrast, ACh and, possibly, 5-HT show differentiated topography.

- It must possibly correlate with demands for additional attentional ressources or perceptual discrimination.

This criterion biases towards ACh,[7] which has been associated with sharpening tuning curves and attentional focus.

- It must operate on a subsecond, probably millisecond time scale.

To date it is unknown how fast volume conducted or synaptic neuromodulation truly functions. A possible mechanism by which the release of such a neuromodulator may result in a scalp-negative potential must exist. Arguably, inhibition of basal cortico-cortical connections and facilitation of apical thalamo-cortical connections, as is known for ACh, may provide for such a mechanism, in that it is just such a pattern that should result in a scalp-negative potential. However, it could also be argued that if the ERP effect of NE is a scalp positivity, 5-HT, which exerts nearly opposite effects to NE, may also induce such a scalp-negative potential.

All in all, based on the anatomy and function of the system compared with characteristics of the component, the ACh system may be the best candidate for a neuromodulator behind the N2.

Acetylcholine may allow processing focused on current stimuli while suppressing interference from prior context (Müller & Singer, 1989), possibly supporting bottom-up based stimulus processing when stimuli are incompatible with such context. This mechanism may operate on a time scale of tens or 100s of msec. The association of the N2 with stimulus-pattern establishment and the P3 with perception-action linking maps well onto the proposal (Andrianov, 1995) that ACh connects to perceptory-evaluative and NE/DA to behavioral neuronal processes. However, so far, no clear empirical evidence regarding this proposal has been presented. However, two studies (Clark, 2005; Fisher et al., 2010) have demonstrated drastic effects of ACh modulations (via nicotine) on mismatch-sensitive ERPs, eliciting earlier and stronger MMN effects in attention/mismatch paradigms.

The anterior, MFC-related N2 has been correlated with partial θ synchronisation (HajiHosseini & Holroyd, 2013) using wavelet estimation of θ ITC. Interestingly, the θ rhythm is likely projected by the pre-rolandic cingulate under the inhibitory influence of ACh (Bland & Oddie, 1998; Wang, 2005). The cingulate cortex receives ACh via the medial basal-cortical pathway (Selden, Gitelman, Salamon-Murayama, Parrish, & Mesulam, 1998).

A related, but quite distinct theory investigates the N2/P3 as part of a necessarily, not incidentally biphasic pattern by reassigning the role of the LC/NE

7 The overlap between the requirements of a mismatch detection/resolution system and the ACh system has been noted by Jocham & Ullsperger (2009).

system in the N2/P3 wave. Warren (Warren, 2011) proposes that the N2 results from LC/NE phasic bursts, and the P3 corresponds to the refractory period following bursts. Indeed the N2/P3 wave shows a highly similar shape and time course (considering conduction delays) as LC response/refraction single-unit measurements. Topology differences of the N2/P3 are an essential aspect of this theory (Warren et al., 2011). As noted, Warren demonstrated that the oddball N2 varies in topology systematically with varying stimulus modalities, such as a maximum over P8, compatible with generators in the fusiform gyrus, to face oddballs. He proposes that following NE release, brain areas most engaged in processing the respective stimulus are more affected by NE and produce the largest response. At such target sites, NE enhances stimulus processing by its gain-increasing properties.

In this model, then, the nonspecific topography of LC projections and the specific topography of the N2 are unified, as in the LC/NE-P3 model by Nieuwenhuis et al., by the assumption of universal NE release, but local evoked potential increases.

The model is appealing in part because it entails testable predictions. For example, N2 and P3 should always be temporally coupled.

3.6.2 *ERN/Pe*

3.6.2.1 *Anatomy and antecedents*

The ERN was discovered in 1989/90 (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1990; Gehring, Goss, Coles, Meyer, & Donchin, 1993; Gehring, Liu, Orr, & Carp, 2012), independently by two teams (Falkenstein and Coles/Gehring). When time-locking to the moment of response commission, the average of erroneously answered trials shows a sharp negative peak very close to reaction time compared to correctly answered trials. The ERN has been very convincingly linked to the MFC via ERP source localisation using dipole estimation (Dehaene, Posner, & Tucker, 1994) and LORETA (Roger, B e nar, Vidal, Hasbroucq, & Burle, 2010), fMRI studies (Ridderinkhof et al., 2004; Ullsperger & von Cramon, 2001) and fMRI/EEG co-registration (Debener, Ullsperger, et al., 2005). Specifically, in the MFC, the rostral cingulate zone/RCZ, between BA32, BA24, BA8 and BA6, has been identified as being sensitive to errors.

A related component is the feedback-related negativity or feedback-ERN (fERN) (Holroyd, Coles, & Nieuwenhuis, 2002) that is found following feedback indicating incorrect response (in feedback-locked, not response-locked data) and a highly similar component reflecting feedback indicating punishment such as monetary losses (Gehring, 2002). (f)ERN-like effects have also been observed in response to observing the errors of others (Miltner, Brauer, Hecht, Trippe, & Coles, 2004).

The ERN is part of a biphasic pattern quite similar to the N2/P3 (Davies, Segalowitz, Dywan, & Pailing, 2001) since it is often followed by a large positivity, the P_E (Overbeek, Nieuwenhuis, & Ridderinkhof, 2005), that is associated with both anterior and posterior topographies, with the anterior generator likely overlapping with the (MFC-associated) generator of the ERN (Herrmann, Römmler, Ehlis, Heidrich, & Fallgatter, 2004) and the centroparietal aspect resembling a P3b. The P_E reflects error awareness (Endrass,

Klawohn, Preuss, & Kathmann, 2011; Murphy et al., 2012; Shalgi, Barkan, & Deouell, 2009; Wessel et al., 2011), unlike the ERN, which is mostly insensitive to error awareness (Shalgi et al., 2009). It also correlates with the autonomous nervous system consequences of error commission, wich largely resemble the orienting response (Hajcak et al., 2003). TPJ (including STS, IPS and AG) also shows activation in a conjunction analysis of error and novel-stimulus trials (Wessel et al., 2012), compatible with an overlap between P_E and P3.

An influential research programme (Cohen, Wilmes, & van de Vijver, 2011; Luu et al., 2004; Luu, Tucker, Derryberry, Reed, & Poulsen, 2003) has associated the (f)ERN with pre-rolandic cingulate - generated frontal-midline θ phase reset instantiating cortical synchronization for the purpose of applying consequences of error processing across the brain.

Recently, evidence is converging on similarity, overlap, or even identity regarding the negative ERP components associated with error, feedback and novelty and stimulus mismatch/incongruence processing. *Predicted* negative feedback was shown to result in an attenuated or absent fERN in multiple studies (Chase, Swainson, Durham, Benham, & Cools, 2011; Holroyd et al., 2003). A similar finding was obtained in fMRI research: the MFC is usually activated by error or negative feedback trials, but when error probability becomes high, the MFC is instead activate by rare, unexpected positive feedback (Jessup, Busemeyer, & Brown, 2010), compatible with a sensitivity of the MFC-generated error signal not simply or even primarily to errors, but to prediction mismatches. ERN and N2 reflect in the same Independent Components and show overlapping activation in the fMRI (Wessel et al., 2012), and fERN and ERN in the same Principal Components (Potts, Martin, Kamp, & Donchin, 2010) and Independent Components (Gentsch, Ullsperger, & Ullsperger, 2009). Microelectrode recordings show that the same areas of the MFC respond to errors and to novelty (Wang, 2005). ERN and Stroop N2/N450 similarily interact with COMT genotype, and are correlated within individuals (Osinsky et al., 2012). Such findings emphasise the cofound that typically, erroneous response and negative feedback events are also rare events (compared to correct response and positive feedback events), and that the underlying system may not be selectively or primarily sensitive to errors, but to e.g. conflict or expectedness.

However, some findings differentiate conflict/mismatch potentials emerging from the medial frontal cortex, often within different divisions of the pre-rolandic cingulate, e.g. using fMRI (Ullsperger & von Cramon, 2001) or source localisation (Gehring & Willoughby, 2004); yet it is uncontroversial that all these mediofrontal, MFC-associated negative potentials at least partially overlap in cognitive antecedents, neural substrate, and function.

3.6.2.2 *Function*

Two recent main theories of the ERN have received detailed neurophysiological grounding.[8] Consequently, discussing the proposed function of the ERN includes discussing its neurophysiology, and they will therefore be presented in detail in the chapter on the neurophysiology of the ERN. Both of these theories associate, or even identify, the ERN with the fERN and the N450, and at least the MFC-generated iterations of the N2. Both of them

8 For a comparison with two further theories, see Gehring (2012).

have already been noted in the discussion of the N2. The conflict monitoring theory (Botvinick et al., 2004) assumes that the MFC monitors conflict between multiple response options and signals a requirement for attentional ressources, in turn generating the ERN; the feedback learning theory (Holroyd, 2004; Holroyd et al., 2002) assumes that a phasic reward prediction error signal in the DA system is relayed to the MFC, generating the ERN.

At the heart of many theories regarding the ERN, including the conflict monitoring and the feedback learning theories (Gehring et al., 2012), is the idea of the ERN resulting from a comparison between motor representations of the correct and the actual response. Consequently, the ERN would be expected to be sensitive not simply to the correctness of the response, but also to the difference between such representations.

Multiple studies (Arbel & Donchin, 2011; Bernstein, Scheffers, & Coles, 1995) have indicated that the size of the ERN is directly sensitive to the degree of the mismatch between the correct and the actually executed, incorrect response (e.g., when the correct response would have been right hand-right finger, left finger-left responses eliciting a larger ERN than right hand-left finger).

The generation of the ERN close to or within regions of the frontal lobe associated with motor control (including near the Supplementary Motor Area/SMA at the MFC) is highly compatible with such a general proposal. More specific questions concern the actual function of the mismatch detection, and the specific anatomical association of the various functions (e.g., which brain system is the detector, which the receiver of the error signal?). A tactile Oddball paradigm has, as discussed in the previous chapter, been found to elicit N2 effects compatible with generators near the SMA (Kekoni et al., 1996), indicating that mismatches in the somatosensory domain indeed reflect in an ERP component similar to the ERN.

A crucial question in this regard is how close the association between the ERN and the fERN is assumed to be, since the fERN results from the processing of typically visual (sometimes auditory) stimuli, not somatosensory information. Specifically: does the ERN directly reflect the degree of mismatch between expected and received somatosensory representations (as is assumed for e.g. the MMN), or does it reflect an evaluation of the degree of mismatch regarding e.g. the need for task adaptions it may indicate? Does it directly reflect the process of detection and resolving mismatches, or instead the importance of detected mismatches? Only the former interpretation of the ERN is compatible with the explanation of incongruence negativities as reflecting representation stabilisation under side-stream interference (see the discussion in the chapter concerning the N2).

As noted, some proposals of ERN generation assume that it represents a conflict between the actually activated and the intended motor response. From this perspective, the degree of the difference between an efference copy (Niziolek, Nagarajan, & Houde, 2013) and motor feedback reflect in motor-associated areas as the ERN, similar to how, in the Oddball paradigm, the difference between the memory copy of the common tone and the afferent firing pattern representing the actual input causes a mismatch negativity or N2. Evidence for a role of directly motor-associated areas comes from recent intracranial data in humans (Bonini et al., 2014), where the SMA and partially dorsal cingulate areas, but not the core RCZ showed error sensitiv-

ity, although no direct measurements of the RCZ from this experiment were presented.

One theory of medial frontal cortex action showing especially close match with the idea of percept/representation conflict as inducing these components is the predicted response-outcome model/PRO (Alexander & Brown, 2011). It partially corresponds to the observation that at least some components of the RPE learning system show, as described above, *unsigned* sensitivity to prediction errors (Roesch et al., 2012; Wessel et al., 2012). In the PRO model, it has been explicitly modeled how cingulate activity could reflect the difference between the outcome predicted to follow an action, and the outcome that actually occurs, with large overlap with experimental data (Ullsperger, Fischer, Nigbur, & Endrass, 2014). PRO especially stresses the importance of the unexpected non-occurrences of predicted outcomes of actions. However, not all negativities occur in the context of overt responses, as in the case of the N2.
Ullsperger et al. (M. Ullsperger, Fischer, et al., 2014) argue that unpredicted events that are *potentially* action relevant are of a similar status. In the action-perception cycle, action does not necessarily refer to motor output; as research on the P3 has shown, nonovert reorientation, such as in the "truncated reflex", is not fundamentally different in its neurophysiological antecedents than overt responses.

This proposal then resembles stimulus conflict theories of the N2 (and, as will be discussed later, the N400). From a perspective of incongruence negativities as reflecting conflict between representations, one question becomes pressing: what conclusions can be derived regarding valence or conflict processing from paradigms that inherently confound errors, low probability and negative valence? For example, the findings of an ERN-like effect while observing errors performed by others is confounded by the fact that errors as performed by artificial subjects who were modeled to behave like real subjects (Miltner et al., 2004) will be rarer than correct responses, and thereby novel. Furthermore, positive feedback will be more common, and positive feedback cues more predictable, than negative feedback and their associated cues. Negative feedback can be predicted to elicit an fERN-like anterior negativity simply on account of being unpredicted. One important test of this hypothesis is provided by studies sometimes delivering inappropriate feedback, such as randomly and rarely performing correctly performed trials, where subjects are expected to predict positive feedback, with negative feedback. From the perspective of incongruence negativities as being highly sensitive to stimulus predictability, it is quite unsurprising that unexpectedly *positive* feedback (when subjects expect negative feedback) elicits an N2-like negativity (Ferdinand, Mecklinger, Kray, & Gehring, 2012; Oliveira et al., 2007), or, assuming fMRI data can be integrated with ERP data, that observing the errors of others leads to similar BOLD responses in the MFC if subjects are rewarded or punished for the errors of others (de Bruijn, de Lange, von Cramon, & Ullsperger, 2009; Walton, Devlin, & Rushworth, 2004).

In sum, an association or identity between ERN, fERN and N2, or at least a neurophysiologically comparable and functionally similar underlying system, remains an attractive, but so far unproven perspective. Many questions remain to be answered in this regard.

The association of the P_E with the P3(b) is less controversial than any attempts to associate these negativities. Interpreting the error positivity as

a P3b following error detection (Overbeek et al., 2005; Ridderinkhof, Ramautar, & Wijnen, 2009; Steinhauser & Yeung, 2010) allows a fairly straightforward explanation of this phenomenon. This proposal also connects well to the LC/NE theory of the P3 as reflecting LC response to motivationally significant events, such as errors.

3.6.2.3 *Neurophysiology; possible neuromodulatory cause*

The Conflict Monitoring theory (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Botvinick et al., 2004; Nieuwenhuis et al., 2003b, Carter:2007uf; Ridderinkhof et al., 2004; Yeung & Nieuwenhuis, 2009) proposes that certain scalp-negative ERP components, especially the ERN and the medio-frontal N2, are generated by the MFC when it detects response conflict and initiates additional resource mobilisation (see Figure 3.8). Specifically, errors are thought to be generated when an alternative response impulse is activated by (typically side-stream) stimuli (e.g. flanker incompatible distractors or Stroop word meaning). The MFC, as the conflict monitor, detects such multiple active, conflicting responses, in the process generating the ERN, and activates the lateral prefrontal cortex/lPFC as the cognitive control system, which then assigns additional attentional resources to the systems governing the current task. Importantly, it is thought that conflict of *responses*, not e.g. conflict of stimulus representations is what the MFC is sensitive to. Response conflict can be understood as a subtype of representational conflict, in that responses are represented as e.g. efference copies; thus, response conflict sensitivity is a more specific prediction than representation conflict sensitivity, in that it excludes e.g. mismatches between representations of visual stimuli and predictions for such stimuli.

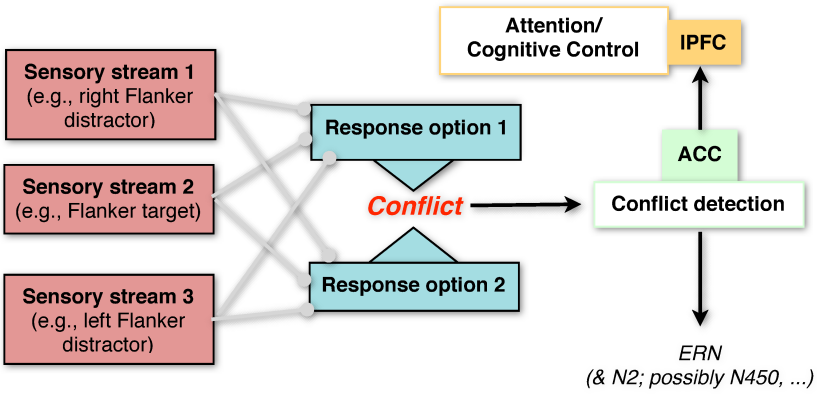

Figure 3.8: Diagram of conflict monitoring account. Filled boxes: brain areas. Boxes with colored borders: function of respective brain area. Filled boxes with black borders: representations. Arrows: causation. Lines ending in circles/squares: neural excitation/inhibition. Roughly following Joachm & Ullsperger (2009).

One important aspect of the conflict monitoring model is its implementation as a connectionist/PDP computational model (Nieuwenhuis, Yeung, & Cohen, 2004; Yeung & Nieuwenhuis, 2009), allowing the comparison of simulated and empirical data and novel predictions, for example, regarding

lesioning the system or increasing the concurrent cognitive load as well as the precise time course of cognitive control.

Recently, an intriguing comparison of simulated and empirical data has been used to argue against the conflict monitoring model (Burle, Roger, Allain, Vidal, & Hasbroucq, 2008). Using EMG, "partial" errors (trials where the EMG showed activation of the incorrect movement shortly before executing the correct movement) were investigated with regards to the temporal alignment of the ERN. While the conflict monitoring computational model implementation predicted that conflict would be highest reliably right before the execution of the actual response, the ERN on partial errors was found to be stimulus aligned. Such a finding is potentially better compatible with a model assigning *percept*, not *response* conflict to the mediofrontal negativity in this case.

The feedback-learning or reward prediction error reinforcement learning model of the ERN (Baker & Holroyd, 2011; Holroyd, 2004; 2004; Holroyd et al., 2002; 2002) concerns partially the same functions and brain systems, but assigns them differently (see Figure 3.9). Here, it is not the MFC that detects errors. Instead, the DA system detects and relays errors, in alignment with the proposed temporal prediction error model proposed based on single-unit data in animals (Schultz et al., 1997); these error signals correspond to the difference between the predicted and the received value of the event, and are relayed to the MFC via its dopaminergic innervation. The MFC, not the lPFC then uses this error signal to adapt behavior to current task demands.

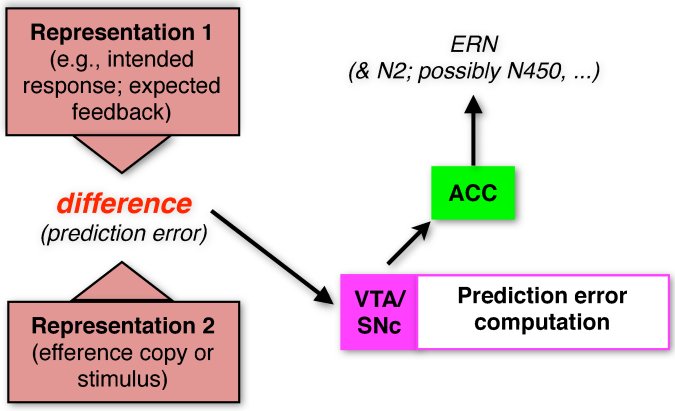

Figure 3.9: Diagram of reward prediction error account. Filled boxes: brain areas. Boxes with colored borders: function of respective brain area. Filled boxes with black borders: representations. Arrows: causation. Lines ending in circles/squares: neural excitation/inhibition. Roughly following Jocham & Ullsperger (2009).

Since the ERN is thought to mirror the phasic DA signal observed by Schultz et al., surprising events of positive value were predicted to elicit positivities. Indeed, stimuli cueing positive reward were found to be marked by a "reward positivity" (Holroyd, Krigolson, & Lee, 2011), and positive feedback elicited a similar positivity (Holroyd et al., 2008).

As noted in the discussion of the DA system, one substantial problem in the connection of the (f)ERN to the DA system is based on the consideration that

the DA signal, especially negative signals, phasic dips, are slower by orders of magnitude than both the observed ERP and the necessary temporal precision required to correctly associate stimuli and their reward contingencies (Lapish et al., 2007). DA neurons show slow baseline firing rates, and DA clearance rates are low; in the frontal lobe, extracellular DA is mostly governed by COMT-mediated catabolism. However, it is not precisely known what the time course of phasic DA decreases will be in vivo in the frontal cortex. Consequently, if it truly is the role of the DA system to detect errors, the transmission of these errors to the MFC likely is not implemented by a negative, passive dopaminergic signal. It has then be proposed (Jocham & Ullsperger, 2009) that other neurotransmitter/neuromodulator systems may be responsible for the ERN signal, a system fast and spatially focused enough to induce ERN-like effects. Possible sources include the ACh system that is assumed to be reasonably localised, or co-release of glutamate by DA neurons. Notably, such a system likely still could not model the ERN as the scalp-measured mirror of the phasic dip following prediction errors, since negative signals probably do not afford sufficient temporal precision for the proposed function nor the morphology of the component. Consequently, Jocham & Ullsperger (2009, p. 56) hypothesize that the role of DA is "setting the background of cortical excitability upon which other, fast acting neurotransmitters" act. Evidence compatible with such a proposal was provided in a study applying Independent Component Analysis to establish that the ERN shows a nonlinear, inverted-U dependence on COMT genotype and sulpiride (a DA agonist) administration (Mueller et al., 2011), both of which should influence tonic DA levels.

In inversion of the RPE model, Jocham & Ullsperger (2009) propose that the (f)ERN is generated in the MFC and signals errors to the DA system, either directly or indirectly (e.g. via the lateral habenula). This signal inhibits the DA system, causing a dip in frontal DA levels, shifting the frontal cortex towards a D1-receptor dominated state more resistant to error-inducing distractors.

In sum, while there exists ample evidence regarding genes relevant to the DA system and pharmacological manipulations targeting catecholamine levels (including NE) influencing the ERN, reviewed by Ullsperger (2010), the ERN may not be a direct reflection of phasic DA. It may instead be connected to focused ACh transmitted to the MFC via the medial pathway and/or to co-release of Glutamate by dopaminergic neurons signalling errors. Alternatively, the ACC, possibly activated by ACh or other neurotransmitters, may be the source, not the goal of the error signal, signalling errors to the DA system in order to modulate frontal DA levels in a top-down fashion.

The proposal of ACh transmissions to the MFC is congruent with the idea that ACh responds to modality-dependent systems processing critical targets; here, the two conflicting streams consist of the intended and the actual motor response. However, it should be noted that in the MCC and ACC, nicotinic receptor densities are comparatively low; only the muscarinic M_2 receptor is richly expressed in the MCC (Palomero-Gallagher, Vogt, Schleicher, Mayberg, & Zilles, 2009).

A possible identity of the P3 and P_E would reduce the question of a possible neuromodulatory origin of the P_E to the question of the neuromodulatory origin of the P3. However, even independently of that, the P_E has been associated with the NE system (Frank, D'Lauro, & Curran, 2007).
If anterior aspects of the P_E can be associated with the DA/P3a system, and

parietal aspects with the LC/NE-P3(b), these aspects of the P_E should doubly dissociate between paradigms, predictable by an earlier P3a or P3b. Due to the refractory nature of the LC/NE activation, P3s should not be able to reliably follow each other in short time intervals, so that a parietal response-locked P_E should not directly follow stimuli requiring a stimulus-induced P3b in single trials (though two concurrent P3b effects could appear in the averaged ERP as the sum of two stimuli eliciting a P3 with a certain probability).

3.6.3 *N400/P600*

3.6.3.1 *Anatomy and antecedents*

At the end of the 1970s, in the wake of research following the discovery of the P3 by Sutton and coworkers (1965), Mary Kutas and colleagues (including Steve A. Hillyard and Emanuel Donchin) conducted a series of experiments on the P3 to linguistic stimuli (Kutas & Hillyard, 1980a; Kutas & Van Petten, 1988), at first focusing on word lists (Kutas et al., 1977), but later branching into sentences. In an experimental pre-test, Kutas observed a novel ERP effect following a word that was semantically anomalous in the given context, such as "He shaved off his mustache and eyebrows". In a series of carefully conducted experiments where participants were presented with sentences shown word by word, with the last word being either congruent, or highly improbable and anomalous, such as "He spread the warm bread with butter/socks", the finding was confirmed (Kutas & Hillyard, 1980b; 1980c). Following the anomalous word in contrast to control words, in the time window where a P3 was expected, the ERP showed a centro-parietal negativity peaking around 400 msec, followed by a late, prolonged P3b-like potential peaking later than 600 msec (Kutas & Hillyard, 1980b, fig. 1b–c). These potentials were later termed the N400 and the P600, respectively, forming the biphasic pattern elicited primarily by high-level linguistic processing. Typically, visually evoked N400/P600 components are observed in the ERP time-locked to the onset of critical words, though ERPs time-locked to critical positions within a word (Hagoort, 2008), or the word prior to the critical word if parafoveal preview is possible (Kretzschmar et al., 2009), are also used. However, spoken and signed words also elicit N400 effects (Kutas, Neville, & Holcomb, 1987, where however a strong late positivity was found only in the written modality). Kutas did not show much interest in the late positivity, partially because it showed great interindividual variance (Kutas & Hillyard, 1980b), partially because she quickly began considering it simply a delayed P3, also noting its dependence on task factors (Kutas et al., 1987, p. 328).

In retrospect, an N400/P600-like pattern had already been observed in a previous study (Kutas & Donchin, 1978, fig. 2); word lists, just like the sentences used by Kutas et al. (Kutas & Hillyard, 1980b; Kutas & Hillyard, 1984), show a high, gradient sensitivity of N400 amplitude to word expectability, with contextually evoked or repeated words showing a reduced N400 compared to novel or contextually unlicensed words. Even in that early study, the N400 was sensitive to both phonological (e.g. rhymes) and semantic (e.g. synonyms) overlap between word and context. Generally, the N400 shows near-perfect correlation to the local "cloze probability", or expectability, of a word, with less expected words eliciting stronger (more negative)

N400 effects.
Interestingly, it is primarily the amplitude of the N400 that tracks e.g. expectability *within paradigms*, and not latency (Kutas & Federmeier, 2011). N400 amplitude therefore correlates with reaction time. Repeated presentation of the same item also does not shorten N400 latency for low repetition rates (<4) of presentations, but attenuates N400 amplitude (Besson, Kutas, & Van Petten, 1992); massively repeated presentation (>20) shortens it slightly, on the order of 50-100 msec (Renoult, Wang, Calcagno, Prévost, & Debruille, 2012). Here, it contrasts strongly with reaction time or the P3, which shows latency sensitivity to the complexity of processing within paradigms. However, the latency of the N400 is sensitive to e.g. stimulus complexity *between paradigms*, so that the N400 peaks later when the relevant dimension is a complex, abstract one such as sentence-level semantics, than when it is a simple one, such as word frequency (Barber & Kutas, 2007).

While the N400 shows direct sensitivity to contextual word-level expectedness, it is insensitive to some global features, such as sentence truth value. For example, the N400 does not differ much between a wrong sentence, such as "A robin is a vehicle", and its true, negated opposite, "A robin is not a vehicle", in contrast to true affirmative sentences such as "A robin is a bird" and false negated sentences such as "A robin is not a bird" (Fischler, Bloom, Childers, Roucos, & Perry, 1983), often being more sensitive to word-level associations than to overarching semantic structure. Interestingly, phonologically legal, but nonexistent non-words (pseudowords) elicit an N400 effect, possibly reflecting search processes (Bentin, McCarthy, & Wood, 1985; Deacon, Dynowska, Ritter, & Grose-Fifer, 2004; Holcomb & Neville, 1990), but illegal non-words do not. But generally, presumably stable associations between words play the, or at least a, major role in N400 amplitude.

However, multiple cases are known where the difference between a contextually expectable and a contextually not licensed word reflect in an N400 even if such context is not of a simple word association, or even generally linguistic, nature. In sentences contradicting autobiographical memory (Fischler, Bloom, Childers, Arroyo, & Perry, 1984, no LPC) of a participant (such as "I go to bed late" provided by an early rising participant) or general world knowledge (Hagoort et al., 2004, no LPC), the violating word result in an N400. Overarching context can gradually influence incongruent, unexpected words to not elicit an N400 (Nieuwland & Van Berkum, 2006). For example, at the beginning of a story, assigning mental dispositions to inanimate objects, such as by sending a yacht (instead of a sailor) to a therapist, elicits an N400/P600 pattern. However, if this assignment is repeated throughout the story, the N400/P600 disappears. Elaborate contexts (Van Berkum, Zwitserlood, Hagoort, & Brown, 2003) can also induce N400 effects in sentences that do not show an N400 if presented in isolation (but only a small, if any, P600; see their Figure 6). Finally, so-called "borderline anomalies" have been reported to result in a small N400, even though critical (incongruent) words did not differ in simple association strength (Tune et al., n.d.).

Similarly, while the overall N400 effect to individually unexpected words does not habituate, the N400 to specific sentences quickly habituates to the repeated presentation of the same sentence (Besson et al., 1992). Instead, a recognition positivity P600 is found at the 3rd presentation. Such habituation resembles "fast mapping" (Markson & Bloom, 1997) processes. Indeed, compatible with its association with temporal structures and an assumed

hippocampal component and the *complementary memory systems* theory (McClelland, 1998), the N400 indexes single-instance fast mapping forms of word learning (Borovsky, Elman, & Kutas, 2012).
The N400, unlike the P3, also persists during the attentional blink (Luck, Vogel, & Shapiro, 1996), supporting an automatic, subconscious nature of the component.

However, recently, it has also been shown that massively repeated presentation of a very small set of words (as few as 4) can result in reliable N400 effects (for example, distinguishing primed and unprimed, or concrete and abstract words) if an explicit instruction requires subjects to reliably process semantic aspects of critical words (Renoult & Debruille, 2011; Renoult, Brodeur, & Debruille, 2010; Renoult et al., 2012); specifically, by asking them for judgements which require semantic processing.

Generally, like for the N2, N400-like effects have been observed in multiple modalities, with the topography of the N400 often changing based on task modality. In a previously mentioned study, Besson & Macar (Besson & Macar, 1987) compared mismatches in word meaning and sequences in multiple other modalities and found that a clear N400/P600 pattern was only found for semantic mismatches; sequence mismatches in other modalities elicited an N2/P3 pattern. Subtle mismatches between remembered and presented facial features elicited an N400 with a more occipital topography (Olivares, Iglesias, & Antonieta Bobes, 1999; Olivares, Iglesias, & Rodriguez-Holguin, 2003). Short video clips could also induce N400/P600-like potentials (Sitnikova, Holcomb, Kiyonaga, & Kuperberg, 2008). Comparing mismatches between words and following natural sounds congruent or incongruent with the words, an N400 with a highly similar morphology and topography to the word N400 was found (Cummings et al., 2006). Substituting words in sentences with either congruent or incongruent pictures (such as a picture of a sock) elicited an N400-P600 effect similar to that for congruent vs. incongruent words (Nigam, Hoffman, & Simons, 1992). N400-like effects, often with slightly different topographies and without a clear P600, have also been reported e.g. for music (Koelsch et al., 2004) and cartoons (Cohn, Paczynski, Jackendoff, Holcomb, & Kuperberg, 2012), as well as for incongruent actions, e.g. illegal Basketball moves (Proverbio, Crotti, Manfredi, Adorni, & Zani, 2012)

Recent studies increasingly report that pre-semantic stimulus properties strongly influence the N400. A word's neighbourhood density, as measured by Coltheart's N (though see Yarkoni, Balota, & Yap, 2008), measures how many words a word is orthographically very similar to (such as *boat* vs. *boot*). Stronger than word frequency, this factor influences the N400 to words as well as phonologically legal non-words (Laszlo & Federmeier, 2009; Laszlo & Plaut, 2012); words and such pseudowords with more nearest neighbours, and with more high-frequency neighbours, induce a larger N400. Such a sensitivity to formal aspects is, at least superficially, surprising for conceptual accounts of the N400.

Within the linguistic domain, grammatical violations, such as verb-tense or determiner-noun mismatches, were also found to show the prominent N400-P600 pattern, albeit with a slightly different, less temporal, topography (Hagoort & Brown, 1999; Kutas & Hillyard, 1983). N400 effects also sometimes index non-prototypical (Van Valin, 2005) thematic roles (Bornkessel, Fiebach, & Friederici, 2004; Frisch & Schlesewsky, 2001) or unexpected animacy (Nieuwland, Martin, & Carreiras, 2013; Szewczyk &

Schriefers, 2011), and have consequently become associated with thematic reanalysis (Bornkessel-Schlesewsky et al., 2011), e.g., a reevaluation of a previous functional interpretation of a noun. Sometimes, certain morphosyntactic violations are specifically associated with a negativity in the N400 window with a left-anterior distribution (Osterhout & Mobley, 1995). Originally, a specific *early* left-anterior negativity/ELAN was also observed, but this effect has been shown to suffer heavily from methodological cofounds (Steinhauer & Drury, 2012), making the interpretation of many studies problematic. For example, an ELAN was reported for violations in Japanese sentences - even for subjects who spoke no Japanese (Mueller, Hahne, Fujii, & Friederici, 2005, fig. 2–4).

THE LATE POSITIVITY FOLLOWING THE N400 was rarely mentioned or statistically evaluated in earlier studies, although it is readily observable in ERP plots. Interest in language-evoked late positivities only emerged when further studies presented a substantial late positivity to grammatical violations. A large, late sustained centro-parietal positivity was observed when subjects encountered the deviating element of syntactically incongruent, "garden-path" sentences in a sentence acceptability judgement experiment (Osterhout & Holcomb, 1992), and a smaller LPC was found when subjects encountered grammatical violations in a task-free paradigm (Hagoort, Brown, & Groothusen, 1993). Osterhout named the component P600, Hagoort "Syntactic Positive Shift/SPS", with the former title becoming established.

P600 effects tend to be late and centro-parietal, though a wide range of findings, including earlier and more frontal components, can be found (Friederici, 2012; Molinaro, Barber, & Carreiras, 2011).

Small P600-like effects have been reported not only for syntactic violations, but also for syntactic complexity or pragmatic processes (Burkhardt, 2007). Beginning with some initial observations (Hoeks, Stowe, & Doedens, 2004; Kolk, Chwilla, van Herten, & Oor, 2003) large number of studies (Bornkessel-Schlesewsky & Schlesewsky, 2008; Brouwer, Fitz, & Hoeks, 2012 for reviews) also observe a P600 in some sentences, called **"reversal anomalies"** or "semantic P600 effects", where syntactic and semantic cues seem to differentially inform thematic role assignment. As an example: *The cheese ate the mouse.* To make matters worse, earlier researchers of such sentences were surprised to not observe an N400 in many of these sentences. Later research has indeed produced N400 effects in certain reversal anomalies (Bornkessel-Schlesewsky & Schlesewsky, 2008), dependent on the specific constructions and parsing strategies permitted by the language employed.
Generally, the magnitude of an N400 effect is readily accounted for by the well-known spreading activation-like nature of the component; combinatorics aside, the degree to which a word in one condition is less contextually supported by, for example, overlap of semantic features than in the control condition determines most of the N400 amplitude.

Fundamentally, any interpretation of these reversal anomaly effects in terms of theoretically motivated notions such as syntax or semantics is problematic. It is unclear how, utilising which information in which step, subjects actually process such sentences online. No direct mapping between ERP components and theoretically motivated linguistic domains exists, and current attempts at such a mapping are called into question by these very sentences. More psychologically-motivated approaches (Alday, Schlesewsky, &

Bornkessel-Schlesewsky, 2013; MacWhinney, Bates, & Kliegl, 1984) stress the dynamic reliance of processing on the integration of all relevant cues. A demarcation between cue types, assigning some of them (such as position) a categorically different status (e.g., "syntax") than others ("semantics"), is not nearly as reasonably supported by these ERP findings than in the theoretical domain. Even currently, a decade after the initial observation of the phenomenon, researchers struggle to come to terms with it; and the problem is not an aspect of mind and behavior that has to be resolved, but that the supposed instrument of investigation appears ill constructed.

The P600 is highly sensitive to task instructions. In studies presenting the same stimuli both under instructions to somehow actively respond to stimuli (e.g., judge acceptability via button press), or to simply passively attend to the stimuli, the P600 is significantly attenuated, and sometimes even absent, for trials without overt responses.
When the same sentences are presented under instructions of rating semantic coherence, the P600 is greatly attenuated when compared with instructions for rating correctness (Hahne & Friederici, 2002). The P600, but not the N400 following certain thematic or animacy violations is also greatly attenuated when comparing passive reading to acceptability judgements (Geyer, Perlmutter, Holcomb, & Kuperberg, 2006; Kolk et al., 2003). This effect of P600 attenuation without lack of an explicit task is also found in coherent short texts (Osterhout, Allen, McLaughlin, & Inoue, 2002).
Haupt and colleagues (Haupt, 2008; Haupt, Schlesewsky, Roehm, Friederici, & Bornkessel-Schlesewsky, 2008) have investigated such task effects in detail comparing a wide range of presentation modalities, including comparatively naturalistic modalities such as coherent prose short stories presented auditorily, and both acceptability as well as content memorisation tasks. They found that following subject-object reanalyses, an N400 effect (for the object-before-subject order that is legal, but disprefered in German) effect is a stable finding, but the P600 depends highly on task demands.

The P600 is also sensitive to the overall frequency of syntactic violations (Coulson, 1998; Coulson, King, & Kutas, 1998; Hahne & Friederici, 1999), becoming greatly attenuated or absent when errors become common. It has also been argued (Coulson et al., 1998) that the P600 is significantly greater to highly salient structural manipulations than to subtle phenomena. Subjects who do not judge a certain construction as (e.g. syntactically) anomalous also do not show a P600 (Osterhout & Mobley, 1995).

In sum, the P600 is sensitive to exactly the same factors as the P3b, especially salience, task significance, probability. It also strongly resembles the recognition P600 in more but name. The recognition P600 follows recognised stimuli, and the sentence P600 follows a word that identifies the sentence it is a part of to as belonging to a typically small set of critical experimental trials.

Even more so than the N400, P600 effects are found in virtually every modality/domain ever studied, especially since it is impossible to differentiate P3 and P600 effects. No clear morphological difference between the two exists; the P3 is the late positivity, the P3b its centro-parietal, task-sensitive iteration peaking not before 300 msec, and the P600 is a component featuring all these properties, but being preferentially observed in linguistic contexts.

A number of studies (Hagoort, 2008; Osterhout, McLaughlin, & Bersick, 2004) also report a dissociation between the negative and the positive waves,

such that semantic anomalies preferentially often only elicit an N400, syntactic violations only a P600.

3.6.3.2 *Function*

The observation of such a dissociation has led to several proposals (Friederici, 2011; Hagoort, 2008; Osterhout et al., 2004; Ullman, 2001) where the N400 reflects some form of semantic processing and the P600 syntactic processing. As shown, it become clear that neither component is exclusively sensitive to linguistic processing. Rather, the argument goes: the significance of the N400/P600 *during language processing* refers to the processing of its meaning and structure. In the other direction, the N400 is thought to refer to the modality independent processing of some more general form of what emerges as semantics in language, and the P600 to general rule-based or structural processing.

It is of course only from the perspective of the P600 as a distinct index of syntactic processing that "reversal anomalies" become puzzling. To begin with, influences of global plausibility on N400 amplitude are typically small, while the N400 is strongly influenced by word-level associations (Fischler et al., 1983; Kutas & Federmeier, 2011). Consequently, sentences where only the order, not the content of positions preceding the critical word are manipulated are not expected to show an N400 in the first place (Brouwer et al., 2012; Hoeks et al., 2004); for example, such as in the sentences employed by Kim & Osterhout (Kim & Osterhout, 2005):

- The hearty meal was *devouring* the kids.
- The hearty meal was *devoured* by the kids.

Consequently, specific aspects of language specific parsing strategies, e.g. depending on word order, become critical determinants of N400 effects in such paradigms (Bornkessel-Schlesewsky et al., 2011), as N400 effects based on e.g. combinatorial factors are highly construction- and interpretation-specific.
In contrast, many of such sentences are highly salient in being ill-formed and surprising, and in many cases, such as Kim & Osterhout (2005), task-critical (here, the task was an acceptability judgement).As elaborated on by Bornkessel-Schlesewsky et al. (2011), the late positivity may therefore be straight-forwardly interpreted as a P3-like component.

One early question in the discussion concerning the N400 that still reverberates in current debates concerns the situation of the N400 between the two extreme poles of an automatic spreading-activation access system based largely on form versus a system concerning the controlled processing and integration of lexical concepts. Word lists induce N400 effects: a "primed" word, one following a similar or related word, shows a smaller N400 than an unprimed word. A "dumb" automatic access explanation seemed feasible. In order to falsify this view, masked priming studies were conducted (Brown & Hagoort, 1993), showing that masking primes attenuates or even abolishes the N400. However, subsequent studies demonstrated masked priming under reduced stimulus-onset asynchrony (Deacon, Hewitt, Yang, & Nagata, 2000), and the N400 occurs during the attentional blink to words that do not reach awareness (Luck et al., 1996). Lexical accessibility still seems a primary determiner of N400 strength so that "facilitated lexical access" models (Lau et al., 2008) are still popular.

In contrast to the N400, which occurs during the attentional blink to items subjects are not aware of, the P600 is not elicited when syntactic violations occur during an attentional blink. However, an earlier negative potential has been reported to distinguish structural violations presented during the attentional blink without subject awareness (Batterink & Neville, 2013).

Overlap between the N400 and the N2, as well as the P600 and the P3, has been repeatedly discussed. The N400 and the N2 resemble each other (Deacon et al., 1991; Polich, 1985; Pritchard et al., 1991); other, related early proposals, such as Kutas and coworkers themselves (Kutas & Hillyard, 1980b), hypothesised (and, eventually, rejected) the N400 might be the result of an attenuated P300 for a less expected event. N400 and N2 are both sensitive to mismatches between preceding (and, in case of e.g. the N450, simultaneous) items and the target in a gradient fashion; both show a topography that often reflects specific putatively underlying brain systems in a modality-dependent fashion; and both are often, though not always, followed by a late positivity that is assumed to be more controlled and task-sensitive in nature. However, fundamentally, the N400 is sensitive to concept-level incongruences, whereas the N200 is sensitive to percept-level incongruences (and the MMN possibly to feature-level mismatch).

A recent extensive review by Mary Kutas and Kara Federmeier (Kutas & Federmeier, 2011) proposes that accumulating findings concerning the N400 do not answer the question of if it reflects pre- or post-lexical processing; rather, the nature of the N400 demonstrates that such questions result from an improper understanding of the nature of conceptual processing, conflating theoretical concerns with neurobiological realities. Instead of allowing the decision between theoretically motivated models, the N400 allows an exploration of how the brain constructs meaning. According to this proposal (Kutas & Federmeier, 2011, p. 639), the N400 reflects brain activity in a time window where information from simple, unimodal streams reflecting perceptory analyses submerges in multi-modal, including memory, processes that result in neural patterns representing *meaning*.

The N400 is thought to reflect the difference between the pre-stimulus neural landscape in the networks implementing the brain's understanding of meaning, and the additional neural firing required for the additional semantic features that need to be activated in order to accommodate for the current stimulus. This process is parallel to, and at times even partially predates, word recognition, in that meanings are activated over time as stimulus information becomes available in a feed-forward, spreading-activation manner.
For example, higher word frequency decreases the N400 because the semantics associated with high-frequency words will show higher baseline firing, and a larger Coltheart's N induces a larger N400 because neighbour meaning will also become activated to some degree. Such sensitivity of the N400 to formal features may be surprising to post-lexical/integrationist accounts of the N400. Another example for such sensitivity to formal features is the enlarged N400 to orthographic errors (Kim & Lai, 2012).

Phrased differently: according to Kutas & Federmeier (2011), the N400 reflects a time period wherein neural attractors from primary sensory systems influence the state of a complex, multimodal conceptual system whose fluctuating energy landscape is shaped by short- and long-term memory. Consequently, the N400 reveals more about the pre-stimulus brain state than about the processing of the word itself.

A related framework has resulted from connectionist modelling of meaning representation (Elman, 2004). Words have classically been understood as the objects of rule-like language operations (as is reflected by the hypotheses that words are either the objects of integration processes or the objects of retrieval processes). Instead, they may also be seen as the *agents* of language operations, with words actively inducing activity in semantic memory. ERP-based and modelling-based research has converged into a connectionist model of the N400 representing word-induced perturbations of semantic representation space (Laszlo & Plaut, 2012).

The interpretation of the P600 fundamentally depends on its possible association with the P3. Under an interpretation of the P600 as one P3-like potential, it is less a puzzle to be solved and more a reliable indicator of stimulus salience, significance or intrusiveness. Furthermore, from the perspective of the LC/NE-induced P3 representing reorienting (Corbetta et al., 2008), state change/network reset (Bouret & Sara, 2005), the closing of one perception/action cycle (Verleger et al., 2005) or as following decision processes (Nieuwenhuis et al., 2005), the P600 marks a transition point during the processing of a linguistic stream.

Consequently, what the P600 has taught researchers is that, while many syntactic and some semantic violations are highly intrusive and break up ongoing processing (remember that during the attentional blink following the P3/P600, semantic integration is severely impaired), encoding the event as surprising and incongruent, many semantic phenomena, where only the first half of the biphasic pattern is found, rather tend to challenge subjects to pursue an interpretation of a superficially anomalous sentence.

Such continued processing then leads to the restructured state of the conceptual system where a repeated or similar anomaly does no longer reflect in an increased N400.

Compatible with such a view, the N400 reflects expectedness violation strength in a gradient manner, whereas the P600 has been found to respond in a binary fashion to the strength of a violation. In a study comparing weak and strong violations ("The eye consists of the pupil, the iris and the [retina/eyebrow/sticker]"), both kinds of incongruences elicit a (graded) N400, but only the strong violation elicits a P600 (van de Meerendonk, Kolk, Vissers, & Chwilla, 2010) - compatible with a breakdown of interpretation at this point (note that van de Meerendonk propose that the P600 reflects the reanalysis following such a breakdown, not the transition itself).

However, extensive controversies surrounded the interpretation of the P600 as a distinct component versus its interpretation as a P3 (Coulson, 1998; Coulson et al., 1998; Gunter, Stowe, & Mulder, 1997; Osterhout, 1999). While agreeing on the fact that the P600 resembles the P3 in its scalp topography and latency, and in being sensitive to factors of task relevance and salience, proponents of an interpretation of the P600 argue that the double dissociation between syntactic and semantic violations establishes a functional difference between the P600 as a specific index of syntactic violations and the P3 as a general, amodal component.

I argue that the literature is far less homogenously in favour of the proposed double dissociation. An overwhelming amount of literature, beginning with the very first reports of an N400 (Kutas & Hillyard, 1980b), shows the biphasic pattern including the P600. The positive part of this pattern is reliably influenced by the degree of task significance, salience and intrusiveness of

the eliciting item, and is generally compatible with the antecedents and functional entailments of the P3.

3.6.3.3 *Neurophysiology; possible neuromodulatory cause*

The linguistic N400 is commonly assumed to be generated by a rather distributed network with a focus in the temporal lobe and the TPJ, possibly centered around the medial temporal gyrus/MTG (Lau et al., 2008) and/or the posterior temporal cortex, with some contributions from frontal areas. Most of these findings come from lesioning, fMRI and EEG/MEG source localisation (Curran, Tucker, Kutas, & Posner, 1993; Halgren et al., 2002) techniques and are therefore either indirect and/or imprecise.
Data on non-linguistic N400 effects is not extensive enough to allow a localisation typology.
Intracranial EEG data, the most direct evidence, stands in contrast with attempts to associate the semantics-sensitive scalp effect with a single, focal source, such as the MTG. Well-known, but also recent intracranial data (Elger et al., 1997; Guillem, N'Kaoua, Rougier, & Claverie, 1995; Nobre & McCarthy, 1995; Trébuchon, Démonet, Chauvel, & Liegeois-Chauvel, 2013) has repeatedly indicated that the N400 manifests in multiple parts of the temporal and, partially, parietal lobes at the same time, roughly following the extension of the ventral stream. Especially the MTG and the ATL (McCarthy, Nobre, Bentin, & Spencer, 1995) have been implicated by these findings. Simultaneously, the N400 may even manifest in the frontal cortex beyond the sylvian fissure, e.g. in the IFG. Although they are unlikely to contribute to the scalp ERP, N400-like effects (AMTL-N400) are also readily observed in the hippocampus (Grunwald et al., 1999; Klaver et al., 2005; Lisman & Grace, 2005), indicating concurrent, or even identical, activity in cortical-temporal and hippocampal regions. Generally, the N400 can be assumed to involve large parts of the brain, spanning substantially more than just one cortical BA (Van Petten & Luka, 2006), but essentially focused on the temporal lobe. Differential bihemispheric contributions have been extensively reported (Meyer & Federmeier, 2007; Wlotko & Federmeier, 2013).

Lesion studies of the P600 have shown highly heterogenous results. In a puzzling finding, two similar samples of aphasic patients with lesions including in the basal ganglia were reported to show, or not show a P600 (Friederici, von Cramon, & Kotz, 1999; Frisch, Kotz, Cramon, & Friederici, 2003). Performance on one task involving complex syntactic processing (Frisch et al., 2003, violation sentence accuracy) was at chance level in these participants, indicating syntactic processing was strongly impaired; in these patients, no P600 could be found. In contrast, in a task where the partially overlapping population scored highly (Friederici et al., 1999), a P600 was observed. A distinct sample of patients with lesions including Broca's area (Wassenaar, Brown, & Hagoort, 2004) was also found to have a greatly attenuated P600. In both cases, P3 responses in a simple auditory Oddball task were unimpaired. It has been argued that a dissociation between simple Oddball P3 and sentence P600 indicates separate underlying processes. However, the P3 most likely follows target detection (Nieuwenhuis et al., 2005); if subjects lack the capability to accurately detect targets, such as blind people during a visual Oddball (Groppe, 2007 proposed this example), no P3 is expected, but this tells little about the P3 itself. Furthermore, a heterogenous finding such as impaired P600 generation in one group of Broca's aphasics and one group

of Basal Ganglia patients (who also were aphasic) is highly compatible with an amodal, distributed underlying system, such as has been proposed for the P3.

fMRI studies of syntactic violation processing, where P600 effects are most commonly reported, often (Friederici & Kotz, 2003; Kuperberg et al., 2003) find increased activation in SMG and IFG (often left-lateralized) for syntactic violations. While (l)IFG and TPJ are often implicated in language processing, they also form the heart of the VAN identified with the P3 (Corbetta et al., 2008); furthermore, current studies on syntactic processing in naturalistic contexts (Brennan et al., 2012) and proposals on the neuroanatomy of language processing (Bornkessel-Schlesewsky & Schlesewsky, 2013; Hickok & Poeppel, 2004; 2007) do not assume that the syntactic aspects of language processing (in contrast to e.g. error detection) are simply localisable to TPJ and/or (l)IFG. Instead, a critical role in combinatorial processing is assumed for the anterior temporal lobe/ATL in many recent proposals (Brennan et al., 2012).

A possible neuromodulatory basis of the P600 obviously depends on the association with the P3; if the current proposal of an identity is correct, the P600 reflects VAN activation by phasic LC signals (and possibly DA activity). It could be studied in more detail if the far-frontal P3f is also active in passive comprehension tasks eliciting a P600.

A phasic neuromodulator behind the N400 has, to my knowledge, not been proposed so far. Different purine and amino acid neurotransmitters have been assigned tentative roles in semantic unification (Baggio & Hagoort, 2011). Ullmann (Ullman, 2001; 2005) has proposed that ACh may be of critical importance in the declarative memory system behind the N400; however, he does not propose a phasic ACh signal may cause the N400. Yet, the functional role of the N400, its distinct connection to memory, its distributed origin showing topographical modality sensitivity and its association with the N2 make it possible to speculate about a similar role of ACh in the N400 as has been proposed for the N2 and ERN.

ACh innervation of the temporal lobe is dense, especially in the entorhinal cortex that gates between hippocampus and temporal cortex. It comes from the lateral pathway emerging in the NBM. ACh in the temporal lobe supports bottom-up transmission and the short-term *encoding* of information (Hasselmo, Fransen, Dickson, & Alonso, 2000) while inhibiting cortico-cortical connections, presumably significantly influencing the preexisting state which with the stimulus interacts. Potentially, this inhibitory effect on cortico-cortical interactions and the facilitation of bottom-up feed-forward transmission could strengthen the stimulus against an incongruent context, allowing the establishment of stimulus-driven over expectation-driven states.

As noted, ACh has been proposed to bias processing towards sensory/bottom-up signals in the face of a conflict/mismatch between internal (cortical, predictive, top-down) and environmental (bottom-up, sensory) activity (Michael Erik Hasselmo & Cekic, 1996b; Katz, 1999). This view is compatible with the present proposal regarding the earlier mismatch/incongruence negativities in that the size of the N400 correlates to the resistance of the pre-stimulus stable-state energy landscape of the conceptual system to the new attractor. A current landscape shaped by prior information in conflict with the current event/word presents more interference (conflicting attractors/local minima). However, Kutas assumes that the N400, rather

than representing a mismatch effect, generally mirrors activity in this access/integration period, including during events where integration is facilitated and works rather flawlessly.

N400 effects in other modalities and with other topographies could also possibly be related to the wide-spread, differentiated projection system of the NBM.

It is known that one pathway by which ACh functions, for example, induces plasticity, is via its facilitation of NMDA signalling (Markram & Segal, 1990; Sabatino, Cromwell, Cepeda, Levine, & La Grutta, 1999). NMDA receptor activation induces Hebbian learning during LTP (Katz, 1999).
An inhibitory effect of Ketamine on the intracranial hippocampal N400 equivalent (Grunwald, 2008; Grunwald, Lehnertz, Heinze, Helmstaedter, & Elger, 1998) implies a role of NMDA receptors in the N400, similar to hypotheses resulting from considerations of the temporal scale of NMDA signalling (Baggio & Hagoort, 2011). Ketamine, but not manipulations of GABA signalling, also reduces the amplitude of N200 (Watson et al., 2009) and MMN (Kenemans & Kähkönen, 2011). A potential connection between a fundamentally NMDA-related N2/N400 and an ACh system modulating NMDA-dependent EPSPs seems therefore possible; however, other neuromodulators, including 5-HT, also influence NMDA signalling. Furthermore, GABA rather than NMDA has been associated with the ERN (Jocham & Ullsperger, 2009).

Phasic DA is unlikely to play much of a role in the N400, even though the basal ganglia innervate the temporal lobe (Middleton & Strick, 1996) and DA levels influence word processing (Copland et al., 2009; Roesch-Ely et al., 2006); the DA system does not extensively project to the temporal lobe and TPJ, where the N400 is most likely generated.

Phasic NE has been proposed as the source of the negative component of the biphasic pattern (Warren, 2011), but the common dissociation between N400 and P600 is problematic for this proposal.

Not enough is known about phasic 5-HT to hypothesize about a role in the N400. However, it should be noted that 5-HT projections innervate the temporal lobe (Savli et al., 2012), with a left-hemispheric bias in auditory areas (Fink et al., 2009), compatible with a role in a left-lateralized temporal language system. 5-HT is also known to interact with songbird song, in both perceptory/motoer and social aspects (Hall, Sell, & Hurley, 2011; Hurley & Hall, 2011).

3.6.4 *Input-mismatch negativities: a Bayesian perspective*

What is the similarity between the negative components of these biphasic patterns? What, if any, is the similarity in the underlying function of N2, ERN, N400?

A primary conflict is found in the fact of how directly the components represent stimulus processing. Kutas & Federmeier assume the N400 reflects the activation of semantic features by the stimulus, in a process of information extraction. In contrast, the Conflict Monitoring account of the ERN/N2 assumes that it reflects a top-down observatory process following and monitoring the distinct mechanism of stimulus processing. In the Kutas & Federmeier model, the N400 reflects likely temporal lobe activity as meaning

is constructed in this part of the brain; in the Conflict Monitoring model, the N2/ERN reflect MFC activity after some other (e.g. vision-related or somatosensory) part of the brain has processed the (e.g. visual, somatosensory) stimulus. In the N400 model, the N400 directly reflects the difference between pre-stimulus semantic activation in the temporal lobe and post-stimulus activation; in the Conflict Monitoring account, the difference between e.g. the representations of two activated responses does not directly reflect in an ERP component, but the signalling of the difference by another area does.

Although I will attempt as much of a synthesis as possible in the following, I generally assume that the difference is irreconcilable. Either one (or both) of the competing accounts is fundamentally wrong, or the components do not share a fundamental similarity. However, I propose that at least computationally, a great deal of similarity in the assumed underlying processes can be captured by a model of optimal inference using multiple information sources, which also can be used to model the ERP response.

3.6.4.1 *Optimal inference*

Bayes' rule (Gelman et al., 2013; Kruschke, 2010) describes how the probability of some event $P(A)$ given some evidence $P(B)$, the so-called posteror probability of A, can be computed, as long as the prior probability of A and B and the likelihood of B given A, $P(B|A)$, are known as well. By Bayes' rule, the higher the prior on A (the more probably the event is in the first place), the lower the prior on B (the less insensitive the observation of the evidence), and the higher the likelihood, the higher the posterior probability. Often, this will be used to infer a model M given some evidence/data D, as in equation (1).

$$(1)\quad P(M|D) = P(M) \times \frac{P(D|M)}{P(D)}$$

Here, M is some model to be inferred, D is some observed data; for example, a cognitive or neural process M generating some measure D. $P(M)$ is the prior probability of the model so that models that the inferential system is biased towards assigning higher posterior probabilities to models that are more likely to begin with. $P(D)$ is the prior probability of the data so that data that is less likely is more informative than data that has a high chance of occurring in the first place. $P(D|M)$ is the likelihood of the data given the model - for example, how is the observed data D under the assumption of a known generator function M.

An attractive feature of Bayesian inference is that evidence from multiple sources can be trivially combined by mere multiplication of the posterior probabilities, or by informing the prior (which is in many cases mathematically equivalent). A reduced approximation of utilising some sensory data and some other information stream, such as sensory information from another modality, or memory, in the process of Bayesian inference of the likely state of the world given some observed data/sensory input, can be constructed as in equation (2):

$$(2)\quad P(\text{world}|\text{sensory input, other information source}) = P(\text{world}) \times \frac{P(\text{sensory event}|\text{world})}{P(\text{sensory event})} \times \frac{P(\text{other information source}|\text{world})}{P(\text{other information source})}$$

The *marginal probability* of an inferred state is given by the posterior probability for this state divided by the posterior probabilities over all other states; the more likely alternatives, the less likely the candidate, and the less likely the alternatives, the more likely the candidate. The candidate with the highest posterior probability may then be selected as the most likely state of the world, given the available information sources, whereby the posterior also gives the believability of this outcome.
In a drift diffusion-like model, where information accumulates over time, the posteriors change in time, and a candidate may be selected once its marginal probability crosses a certain threshold.

Bayesian models of cognition and brain work have become prominent in the last decade, including in the domains of language learning (Chater & Manning, 2006; Chater, Tenenbaum, & Yuille, 2006) and language processing (Norris, 2013; Norris & McQueen, 2008), movement and the action/perception cycle (Körding & Wolpert, 2006; Wolpert, Ghahramani, & Jordan, 1995), and as the general principle of brain work and the ERP (Friston, 2005).
As these and other works discuss, Bayesian computations can often be readily approximated by neurally plausible neural networks.

3.6.4.2 *Bayes and the N2*

A basic proposal of how to model the Flanker N2 using Bayesian principles has been proposed by Angela Yu (Yu, 2005; Yu, Dayan, & Cohen, 2009). Equation (3) presents a simplified sketch of a similar Bayesian account, where the stimulus is to be inferred using two noisy information sources - the input of a neural population N_1 mostly coding information from the middle location of the visual presentation, but also, to a lesser degree, partially from the flanker locations; and the input of neural populations N_2 mostly coding lateral, but also coding central information (here simplified as only one population, though accurately, two populations should be used to model both left and right flankers).

$$(3)\quad P(item|N_1,\ N_2) = P(item) \times \frac{P(N_1|item)}{P(N_1)} \times \frac{P(N_2|item)}{P(N_2)}$$

Within a trial, information from N_1 and N_2 is assumed to accumulate over time, e.g. as a clearer visual representation is constructed. For each possible item (e.g., in a typical Flanker task, either the target or the alternative), the $P(item)$ then changes over time, until one candidate receives enough support to cross the selection threshold.

The model contains the information required for computing the conflict per trial. Given that the true $P(item)$ is identical in most Flanker paradigms, and consequently, the prior for either *item* will also be identical, the remaining terms are simply the respective likelihoods divided by the sensitivity - meaning, by how much the evidence biases either information source towards either item. In the case of an incompatible Flanker trial, the evidence from N_2 argues towards one item (the flanker), and the evidence from N_1 for another (the target).

Since in the flanker task, probabilities for either item will usually be symmetrical, and items are equiprobable, conflict is approximated by equation (4).

$$(4)\quad conflict = |\ P(N_1|item)\ | - |\ P(N_2|item)\ |$$

This model is far less informative than e.g. the neural network the Conflict Monitoring model is implemented in, or the full proposal by Yu, but highlights the relevant dynamics; conflict reflects the contrast between the information coming from multiple information sources.
Consequently, the N2 could be expected to correlate with the posterior probability as given by equation (3), as well as the marginal probability, and, entailed by this, the degree of mismatch between the two information sources as given by equation (4).

3.6.4.3 *Bayes and the N400*

A reduced approximation of utilising sensory data in the process of Bayesian inference of word meanings could be formalised as

$$\text{(5)}\quad \mathrm{P}(word|\mathrm{sensory\ input}) = \mathrm{P}(word) \times \frac{\mathrm{P}(\mathrm{sensory\ event}|word)}{\mathrm{P}(\mathrm{sensory\ event})}$$

This equation entails that more frequently activated word meanings (high $\mathrm{P}(word)$) should have higher posterior probabilities; consequently, the known importance of word frequency in lexical processing is entailed by the equation.
Words that are likely to have generated the observed sensory data should have higher posterior probabilities; this entails that e.g. misspelt words or sensory noise should decrease the posterior probability of words. Finally, sensory events that are very common should result in lower posterior probabilities; for example, nearest neighbourhood size (*Coltheart's N*) should negatively impact posterior probabilities, assuming sensory input is noisy (both due to neuronal noise, as well as due to visual noise and the token/type distinction, whereby one word form can be instantiated by multiple scribes or speakers in multiple contexts).

Similarly, Bayesian inference of word forms based on context could be formalised as in equation (6).

$$\text{(6)}\quad \mathrm{P}(word|\mathrm{context}) = \mathrm{P}(word) \times \frac{\mathrm{P}(\mathrm{context}|word)}{\mathrm{P}(\mathrm{context})}$$

This equation is less straight forward and possibly less intuitive than the previous one. It implies that, again, word prior probability should correlate with posterior probability. It also implies that words that are more likely to result in the given semantic context will have higher posterior probability, especially if the (semantic) context is improbable.

In the Flanker task, the prior probability of all items is typically equal and does not change throughout the experiment - and especially not based on the context. In contrast, words in congruent texts become expectable based on the semantic context, and readers and listeners, as the N400 clearly shows, use such information.
In a previous proposal implementing a Bayesian Reader (Norris, 2006; 2013; Norris & McQueen, 2008) roughly equivalent to equation (5), Norris et all. proposed that the prior on each word might not only depend on word frequency, but might be modulated by e.g. contextual expectations. Simply inserting equation (6) into the term representing the prior on words ($\mathrm{P}(W)$) in (5) nets equation (7) describing the posterior probability of a given word by combining evidence from two information sources.

$$\text{(7)}\quad \mathrm{P}(word|\mathrm{context}, \mathrm{sensory\ \ event}) = \mathrm{P}(word) \times \frac{\mathrm{P}(\mathrm{context}|word)}{\mathrm{P}(\mathrm{context})} \times \frac{\mathrm{P}(\mathrm{sensory\ event}|word)}{\mathrm{P}(\mathrm{sensory\ event})}$$

In this equation, the posterior probability of a word, given some evidence (some sensory event and some semantic context), depends on the prior probability of the word (likely closely correlated with an estimate of its frequency), the overlap between a forward model of the word form and the actual sensory input divided by the global probability of such a sensory input, and a term describing how much more probable the current context would be, given the word, compared to its base probability.
It thereby captures well-known properties of the N400. Large N400 effects can be primarily understood as situations where meanings suggested by current sensory input, such as word forms heard or seen, contrast with meanings suggested by memory/semantic context; these two information streams can be weighed against each other in this model of optimal inference of word meaning.
The N400 increases with increasing neighbourhood size, and decreases with word frequency and contextual fit. The N400 is also enlarged by recognizable, but misspelt words, i.e., words that largely, but not completely correspond to a contextually expectable word, such as "He ate the ceke" (Kim & Lai, 2012), corresponding to a lower likelihood of $P(word|sensory\ event)$.

Of course, in contrast to the typically equiprobable targets in the Flanker task, words have highly divergent prior probabilities, and are usually ambiguous. Furthermore, in contrast to the highly restricted number of possible items in the Flanker task (where the prior probability of all other items is at, or close to, 0), a large number of words exists and may appear in most contexts. Consequently, the relative evidence in favor of one word corresponds to the ratio between the evidence in favor of this word divided by the evidence in favor of all other words. Since the prior probability of the sensory input side of the evidence is shared by all candidates, only the prior on words $P(word)$ and the relative likelihood functions $P(evidence|word)$ are relevant, yielding equation (8). The prior on words $P(word_x)$ for each word x includes the respective contextual expectability for that word.

$$(8)\quad P(word_i|evidence) = \frac{P(word_i)\times P(evidence|word_i)}{\sum_{j=0}^{j=n}[P(word_j)\times P(evidence|word_j)]}$$

The model roughly corresponds to Kutas & Federmeier's understanding of the N400 corresponding to the inference of meaning based on combining information streams, both contextual and sensory evidence. Kutas implies such a connection between meaning inference and Bayes/optimality herself: comprehension "requires a common mechanism for evidence combination across different parts of the linguistic processing system, and probability theory (with Bayes' rule) is a natural, even optimal, fit" (Kutas, Delong, & Smith, 2011, p. 195).
Kutas & Federmeier however argue that the N400 corresponds to the activation of individual semantic features as meaning is dynamically constructed. Consequently, optimal inference should result in different degrees of activation across the semantic feature space. The evidence in favour of a particular semantic feature would then correspond to equation (9).

$$(9)\quad P(meaning|context, sensory\ event) = P(meaning)\times\frac{P(context|meaing)}{P(context)}\times\frac{P(sensory\ event|meaning)}{P(sensory\ event)}$$

The degree to which its activation should increase, compared to all other semantic features, to optimally reflect the state update suggested by the stimulus is described by equation (10).

$$(10)\ P(meaning_i|evidence) = \frac{P(meaning_i)\times P(evidence|meaning_i)}{\sum_{j=0}^{j=n}[P(meaning_j)\times P(evidence|meaning_j)]}$$

Again, conflict may exist between the evidence in favour of a word meaning or an individual semantic feature coming from contextual versus sensory evidence, as well as their respective prior. For a given (word) meaning, conflict between these information sources would then correspond to the absolute value of the difference between all information sources, including sensory input and the semantic context, given by equation (11).

$$(11)\ conflict =\mid P(meaning) - \left[\mid \frac{P(input|meaning)}{P(input)} - \frac{P(context|meaning)}{P(context)} \mid\right] \mid$$

The total conflict for all meanings would then correspond for iterating this process over all candidates, as in equation (12)[9].

$$(12)\ total\,conflict = \sum_{i=0}^{i=n} \mid \left[\frac{P(input|meaning_i)}{P(input)} - \frac{P(semantic\ context|meaning_i)}{P(context)}\right] \mid$$

In the connectionist model of Elman (2004, fig. 1), I expect conflict to correspond to a higher energy of the *hidden layer* receiving input from both the context and the input layer.
A similar account of the N400 as reflecting the mismatch between bottom-up and top-down information has been previously proposed (Lotze, Tune, Schlesewsky, & Bornkessel-Schlesewsky, 2011). However, the present approach can be readily extended to reflect conflict between e.g. two bottom-up sources of information, such as in the Stroop task (which elicits an N400), such as in equation (13).

$$(13)\ conflict =\mid P(color) - \left[\mid \frac{P(word\ form|color)}{P(word\ form)} - \frac{P(color|meaning)}{P(color)} \mid\right] \mid$$

Sentence-level or combinatorics-based influences on the N400 (Bornkessel & Schlesewsky, 2006; Haupt et al., 2008) are not directly accounted for by this rough model, but may presumably be easily, and even necessarily, integrated by fleshing out the semantic forward model; fundamentally, combinatorics *do* influence meaning comprehension, so parsing strategies will reflect in semantic memory, the basis for semantic priors and forward models in predictable ways. What has not been accounted for by such an information-based model are cross-modal influences not directly informing meaning inference, such as effects of attention or sensory characteristics irrelevant to meaning (Kuipers & Thierry, 2011), or subject state, such as effects of induced emotions (Federmeier, Kirson, Moreno, & Kutas, 2001). Furthermore, extensive investigations regarding the specific contributions of the two hemispheres to the N400 and the underlying processes (Federmeier, Wlotko, De Ochoa-Dewald, & Kutas, 2007) may present an opportunity to spell out the proposal.

3.6.4.4 *Optimal inference and complementary accounts of input negativities*

Equations (4) and (12) show how similar conflict emerges even in a simplified model of optimal inference, where multiple sources of information are combined. The model is agnostic with regards to the substantial difference between the perspective laid out by Kutas & Federmeier, where the N400 directly reflects stimulus processing, and the Conflict Monitoring model,

9 The prior on meaning probability has been left out for reasons of simplicity.

where ERN and N2 reflect processes following stimulus processing.
In the following, two alternative proposals will be made: first, how the Conflict Monitoring account of N2/ERN could be integrated under a representation/stimulus conflict perspective such as the Kutas & Federmeier of the N400. Then, how the N400 could be accounted for under a model similar to the Conflict Monitoring proposal.

THE N2 AND STIMULUS CONFLICT The conflict monitoring theory has proven effective in explaining much of the findings regarding the anterior N2 as a reflection of regulating ressources to the task in the MFC. I have however not been able to find any elaboration regarding non-anterior effects. I argue that it is possible to associate most known N2 findings, including those explained by the conflict monitoring account, under one common interpretation: stabilisation of neuronal patterns representing a stimulus encountered during processing stimuli in an attended stream under interference by alternative attractors from simultaneous or parallel streams (side-stream interference).

In the Bayesian analysis outlined above, this would simply reflect that to reconcile two conflicting information sources in the brain somehow requires cortical activity that reflects in a scalp negativity. For example, neuromodulatory attenuation of contextual evidence (as cortico-cortical transmission) and strengthening of thalamo-cortical, sensory event-related activity could be implemented by a neuromodulatory (e.g. ACh) impulse. Alternatively, in the face of conflict between expectations ($P(context|model)$) and observations ($P(sensory\ event|model)$), an increase of cortical noise could raise the relative decision threshold, leaving more time for additional evidence to accumulate before a decision regarding stimulus significance is made - possibly also instantiated by neuromodulatory (e.g. 5-HT) signalling.
Of course, while such possibilities are suggested to be possible in light of the discussed findings, they are far from proven; however, spelling them out could result in testable models.

This proposal is not entirely incompatible with the Conflict Monitoring or Feedback Learning accounts. The Conflict Monitoring theory focuses on the detection of response conflict and attentional ressource allocation for the purpose of selecting the appropriate response. For example, conflict is high when two different streams (such as flanker target vs. flanker distractors, or the memory trace activating the prepotent response to the common stimulus vs. the appropriate to the rare current stimulus) activate competing responses. However, an N2 is also observed in paradigms without a motor response. The conflict monitoring model is rather uninterested in such situations; but here, too, conflict exists - conflict between two competing stimulus representations. The Conflict Monitoring theory then deals with the topography of the N2 by focusing on likely MFC-generated N2 effects and assuming that this component does not reflect task- or modality-specific processes, but rather a domain-general, meta-cognitive system; consequently, it has little to say regarding N2 effects compatible with generators in modality-specific brain systems (such as the fusiform face-sensitive N2).

The Feedback Learning theory places an important focus on stimulus predictability/expectedness and stimulus valence. Here, less predicted stimuli induce a prediction error signal. While more similar to the idea of stimulus establishment under side-stream interference behind the N2 in its antecedents, it mainly focuses on the purpose of the N2 as the correlate of a

dopaminergic teaching signal. Similar to the conflict monitoring theory, the Feedback Learning theory associates the N2 with domain-general, modality-independent processes.

In simultaneous tasks, the two streams can either be different spatial locations (in the Flanker task) or two different modalities (print color versus word semantics in the Stroop task). In sequential tasks, the two streams consist of the memory trace(s) stemming from the previous sequence, and the current stimulus. The N2 could result from the difficulty of establishing the representation of the target stimulus under interference from competing objects.

The main difference between such a proposal and the Conflict Monitoring theory is that in the Conflict Monitoring theory, it is response representations competing with each other; in the present proposal, stimulus representations compete.

This proposal makes the prediction that in paradigms where no simultaneous conflict exists, an N2 should depend on the difference between the current item and the strength of a representation by the previous stream; for example, in the simple Oddball paradigm, the memory trace elicited by the repeated Oddball is strong, resulting in a substantial mismatch N2 to the target.

While in the Oddball task, the single rare target stimulus elicits an N2 in contrast to the single common non-target, the similar Continuous Performance Test/CPT is not known to reliably elicit an N2. In the CPT, one target is presented amongst an unpredictable stream of multiple stimuli. However, two variants do elicit an N2: in the A-X CPT, a cue ("A") has to be followed by a target ("X"), often resulting in an N2 (Beste et al., 2010). In CPT studies featuring predictive instead of nonpredictive sequences (1, 2, 3, . . . , with a fixed target unrelated to the sequence), a substantial N2 is observed (Zordan, Sarlo, & Stablum, 2008).

As noted, in a go/no-go task, across modalities, the N2 is larger if common and rare stimuli are more similar to each other (Nieuwenhuis et al., 2004). This has been suggested to imply that the N2 depends on task complexity and thereby reflects some measure of cognitive control. However, another explanation is likely. In the specific study, the printed or spoken letter F was used as the common go stimulus, and the rare no-go stimulus was either a T or an S (spoken or printed). Auditorily, F is more similar to S than to T, but visually, T and F are more similar. However, auditory perception necessarily functions incrementally. Both F and S (pronounced as letters; "es" and "ef") begin with the same two phonemes, /ʔɛ/. They only differ in their last phoneme. Consequently, the identical beginning of the no-go F may have in fact strengthened the active representation of the common go S, only to mismatch more strongly once the final consonant, discriminating F from S, is encountered. This conflict between an initially supported F expectation and the actual S may have resulted in a stronger effect. Since F and T differ initially, no such garden path could result. This explanation is also compatible with the finding that visually, the difference between F and T seems to have begun earlier than between F and S; in the measured time window, no-go T was actually not more negative than go F.

In contrast, printed letters can be processed as units. In this study, the printed F-S contrast was only marginally weaker than the F-T contrast.

Under this interpretation, the study is also compatible with a stimulus representation conflict model. S in the context of F activates the largely overlapping memory trace of F, leading to substantial stimulus representation conflict. No such activation of the trace by the current stimulus results in the F/T set.

Supporting evidence comes from a highly similar study (Smith & Douglas, 2011). Subjects were presented with similar and dissimilar pairs of common and rare tones (1000/2000 and 1000/1100 hz) and common and rare spoken letters (F/S vs. F/J). The F/S contrast again induced a larger N2 than the F/J contrast, compatible with the priming of the common non-target by the onset of S, but not J. However, the rare tone did not elicit a significantly different N2 between similar and different tone pairs. Simple tones do not show the same initial perceptual overlap, so no priming of the incorrect representation by the current target could exist.

I understand this proposal (See Figure 3.10) as a sketch of a generalisation of the Conflict Monitoring account that gives up predictive specificity (by referring exclusively to motor output-related phenomena) in order to account for more data and allow the association of most scalp-negative, mismatch-sensitive ERP components.

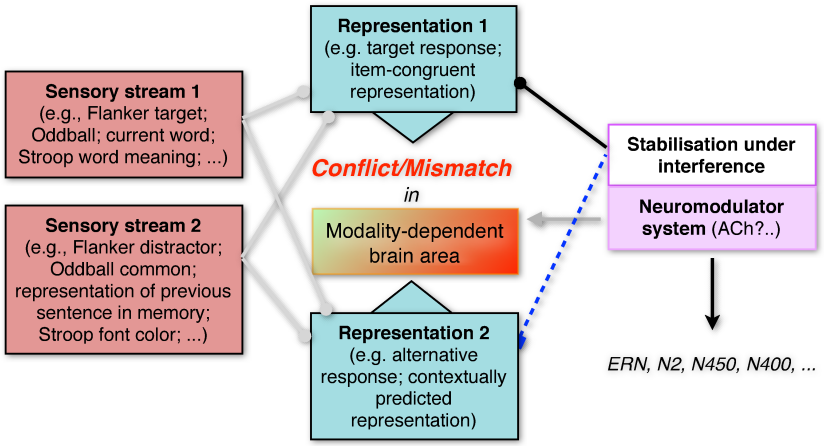

Figure 3.10: Diagram of representation conflict account. Boxes with colored borders: function of respective brain area. Filled boxes with black borders: representations. Arrows: causation. Black/blue lines ending in circles/squares: excitation/inhibition.

A recent proposal is also roughly compatible with the idea of the N400 representing such attenuation of side-stream interference; it comes from several studies associating the N400 with the inhibition of inappropriately activated representations (Debruille, 2007; Shang & Debruille, 2013).

THE N400 AND CONFLICT MONITORING The similarities between the Conflict Monitoring account and the Kutas & Federmeier model include:

1. A sensitivity to the degree of difference between the evidence for an entity to be inferred from different information streams

2. Specifically, a sensitivity to the mismatch between semantic information suggested activated by current sensory input (e.g. word forms) and semantic context/memory

3. Trial-to-trial adaptions following a process initiated by the system reflecting in the scalp negative ERP

Amongst the differences stands that under the Conflict Monitoring, but not the N400 account,

1. the ERP does not directly reflect stimulus-induced activity, but a meta-process; consequently,

2. the difference signal signals the degree/quantity of the required adaptions (the need for additional control), it does not directly reflect its kind/quality

3. the ERP stems not from brain areas directly processing the stimulus, but from a control/monitoring system

What if the N400 *also* was an indirect marker of conflict detection, indicating adaption requirements, as described by the Conflict Monitoring model? A conflict monitoring account has already been proposed for the P600 (Frenzel, Schlesewsky, & Bornkessel-Schlesewsky, 2011; van Herten, Chwilla, & Kolk, 2006; Kolk et al., 2003), and generally, a certain degree of conflict sensitivity can be accounted for by most accounts of the N400. However, the Conflict Monitoring model does fundamentally differ from any understanding of the (centro-parietal, language-related) N400 by arguing that the ERP reflects not the actual processing, but a distinct, supervising process.

Such an account is well believable for the N400. The purpose of the process underlying the N2/ERN is thought to be signalling a need for adaptions, and indeed, the single-trial magnitude of the components have been reported to correlate with concurrent adaptions. The N400, too, tends to be followed by adaptive processes. A verbatim repetition of an incongruent, N400-eliciting sentence leads to a strikingly distinct ERP pattern, a greatly attenuated or absent N400 followed by an LPC, compared to the verbatim repetition of non-anomalous sentences that do not elicit an N400 (Besson & Kutas, 1993). While it is sometimes claimed that the N400 does not habituate, this is only true when looking non-discriminatively at a variety of sentences presented over the course of an experiment; in contrast, exact repetition of items reliably leads to an attenuation of the N400, indicating that the eliciting items are processed differently after the first encounter. The N400 seems to precede an adaptive process. However, this process depends on some degree of semantic processing or meaning inference (Laszlo & Plaut, 2012; Renoult & Debruille, 2011).
It thus seems conceivable that the N400

- follows the detection of conflicts, possible between different information sources (e.g., semantic context vs. sensory input)

- reflects a signal of the need for adaptions following the detection of such conflicts

- is accompanied by an adaptive process that somehow renders the system more robust to following conflicts of this kind, such as an adaption of forward models (e.g., those of the form $P(context|meaning)$)

- does not, consequently, directly reflect actual semantic processing

The main benefit of such an account is that it would allow the integration or at least association of N400 and N2/ERN while preserving the extensive evidence and modelling in favour of the Conflict Monitoring model.
The main drawback lies in the fact that it is a more complex model - conflict sensitivity of the N400 could directly reflect the conflict between e.g. two information streams, instead of representing an additional process. It is therefore harder to falsify (being able to account for all N400 data while also accounting for some other possible data).
The dominant open question in this regard is that the neural machinery proposed to account for the N2/ERN does not readily map onto the known generators of the N400. So while the function and computations behind the Conflict Monitoring model may be shared for all these components, a different neural machinery than that proposed previously must account for either just the N400, or for all the components.
One possible solution here may be a neuromodulator signal allowing adaptive processes. Indeed, all major neuromodulators have been proposed to support or even directly induce short-term adaptive processes, like attentional sharpening, and long-term processes like memory encoding and plasticity.

THE N400 AND ACH Since ACh has been proposed to potentially underly the N2/ERN (Jocham & Ullsperger, 2009), a concise discussion of the role of ACh in adaptive processes under the light of this proposal follows.
Short-term adaptive processes include attentional reorienting, which ACh has been proposed to support (Hasselmo & Sarter, 2010; Sarter, Gehring, & Kozak, 2006; Sarter et al., 2009). As was discussed in chapter {#acetylcholine}, ACh sharpens cortical sensitivity, partially by changing the balance between bottom-up and top-down streams, and modulates tuning curves. It thereby implements an "attentional spotlight" function, whereby much input is de-emphasised, relatively emphasising a specific input stream. This process may allow the re-balancing between multiple sources of evidence in optimal inference of meaning, as in equation (11).
Indeed, models of ACh propose that it may be guided by prediction errors to control the balance between top-down and botton-up information streams (Doya, 2002; Hasselmo & Schnell, 1994; Yu & Dayan, 2003). As a related function, ACh has been proposed to transition between an encoding-dominant mode, where memory is dominated by sensory input, and a retrieval-dominant mode, where memory retrieval dominates (Doya, 2002; Hasselmo & Bower, 1993; Hasselmo & Schnell, 1994).

Doya (2002; Uddén, Folia, & Petersson, 2010) proposes that an ACh signal implements the learning rate of a reinforcement learning system. While this proposal mostly reflects tonic, not phasic signalling, it is quite compatible with the present scenario. An ACh signal implementing a raised learning may be the appropriate reaction to a surprising stimulus, such as a contextually unexpected word. Fast, neuromodulatory facilitated learning may then support the quick association of the word with the context.

However, even if a common neurochemical signal may underlie both N400 and N2/ERN, the neural substrate affected by this signal must still be assumed distinct, at least in many cases (when the N400 can be assumed to reflect largely temporal activity), although this would allow a parsimonious treatment of N450 and N2 that aligns the N450 and N400.
Primarily, the signal should reflect the modality of the task; the temporal lobe may be the locus of the required adaptions in a sentence processing task, as might be, for some reason, a mediofrontal system in many typical psychological paradigms.

3.6.5 *Summary*

A pair of three ERP components, each constituting a biphasic pattern, was described. The N2/P3 follow simple stimuli, with the N2 being sensitive to stimulus-induced incongruence and conflict, and the P3 modulating reactions. The ERN/P_E emerge time-locked to errors and reflect error/conflict detection and error awareness/adaption mechanisms, respectively. The N400/P600 are found to meaningful stimuli, essentially as late-latency correlates of the N2/P3 in a more complex domain; the N400 is especially sensitive to interpretable incongruences, the P600 may reflect mode switching following intrusive events such as strong semantic or syntactic violations. In all cases, the negativity can be described as representing stimulus-induced, perceptory processes, the positivity state-switching, perception-to-(re)action processes.
This perspective is broadly compatible with the threshold regulation model (Elbert & Rockstroh, 1987; Kotchoubey, 2006), where scalp-negative ERPs reflect input-sensitive processes and scalp-positive ERPs output-facilitatory processes.
In the following two tables, characteristic features of these positivities and negativities are summarised.

An interplay of DA, NE, ACh and possibly 5-HT could implement the functions associated with these components and cause the generation of the ERP. However, so far, far to little data is available to argue strongly in favor of any specific model.

A common underlying neuromodulatory system would provide an extremely simple, powerful explanatory mechanism - in two directions. Knowing which neuromodulators underlie the biphasic pattern would solve many of the questions surrounding the specific components; on the other hand, this association would allow to study the underlying system easily, by simple tasks and non-invasive methods.
Possibly, scalp positivities, such as the P3, P_E and P600, could reflect broad state changes supported by catecholaminergic signals. A centro-parietal, strongly task-sensitive topography could specifically reflect NE-dominant action, especially affecting major hubs of the VAN, such as the TPJ, and a mediofrontal positivity could reflect a dopaminergic signal. N400, N450, and the shorter-latency negativities could possibly reflect modality-dependent signalling for the requirement of short- or long-term adaptions, possibly mediated by a neuromodulatory signal such as ACh.

	N2	ERN	N400
Paradigms	Flanker Oddball	Performance Errors	Sentence processing (& other conceptual mismatches)
Space	Various	Mediofrontal (MFC)	Temporal/parietal (MTG, TPJ)
Time	between RT and stimulus	RT-locked	350+ msec post stimulus (latency stable within modalities)
See also	N450	FRN, CRN	LAN

Table 3.8: scalp-negative ERP components

However, Occam's Razor must not become Occam's Broadsword. The proposed associations require the reality check of overlapping neurophysiology between neuromodulator system and ERP component. Regardless of how well any given model accounts for previously collected data, it must generate new, testable hypotheses, and these hypotheses must be put to the test (Dienes, 2008).
Especially for sentence processing, a language-specific or at least computation-specific core of certain ERP components is often assumed. Such claims are incompatible with a generalized interpretation of late ERP components. In the following, the language-associated component pair will be investigated in a series of experiments, using modern EEG analysis techniques. I will attempt to connect sentence processing-related ERP components primarily to the N2/P3 and the VAN/LC/NE system.

	P3	P_E	P600
Paradigms	Flanker, Oddball	Performance Errors	Sentence processing (& other structural mismatches)
Space	Centro-parietal (incl. TPJ)	Centro-parietal	Centro-parietal
Time	RT-locked	RT-locked	< 500 msec
See also	P3a, P3f	-	SPS

Table 3.9: scalp-positive ERP components

4

EXPERIMENTS

The following collection of studies all contribute to one question: to which extent the language-relate ERP may be interpreted in the framework presented in the background section. Two main themes have emerged:

- The ERP, especially its late components, has been associated with supramodal, high-level functions such as state regulation, mismatch/conflict detection, and attentional allocation

- Instead of a large "zoo" of components reflecting the activity of specific localised neural systems during modality-specific processes, much of the endogenous ERP might stem from a discrete, limited set of subcortical projections of neuromodulator systems implementing such functions

As noted, in much of neurolinguistics, the ERP is understood as a mix of temporally stable, spatially variable components, each of which is distinct from each other, reflecting specific processes, often of a high-level linguistic nature. Components follow each other in a serial fashion, each reflecting stages or steps in more or less modularised processing chains. Little consideration is given to the physiological plausibility of such a process.
As an example for such work, in one proposal, the overall activity in the "N400 window", e.g. 350-550 msec post stimulus onset, is assumed to reflect "binding" of conceptual entities (Hagoort, 2008). Activity in earlier or later time windows is then attributed to different components, regardless of the existence of any clear morphological features such as peak, even if an "N200" activity covaries with e.g. N400 activity.
In contrast, investigations of the detailled behavior of the temporal dynamics of ERP components (Kutas & Federmeier, 2011; Kutas et al., 1977; Makeig, Delorme, et al., 2004) implies that some components indeed appear stimulus-locked, with a rather invariant latency, but that others show high variance. On the other hand, while components may often show little stability in latency within paradigm and subjects, their localisation may be rather stable, or at least predictable. Yet, neuromodulator theories of ERP components (Nieuwenhuis et al., 2005) assume that it is not always specific, distinct, localised brain systems generating specific ERP components, but rather, that subcortical projections induce systemic, diffuse activities with topographies depending on e.g. paradigm modality. It is highly unlikely for such diffuse subcortical projections to implement specific high-level linguistic processes; rather, they may signal very general processes, such as e.g. arousal state change or conflict signalling across modalities.
Some radical proposals entail a significant reduction of the "component zoo" (Elbert & Rockstroh, 1987; Kotchoubey, 2006), trying to subsume many

components under just two cortical processes; input-related processes often resulting in scalp-negative, and output-related processes resulting in scalp-positive components.

Much work is still required to develop, implement and test such a reduced framework in contrast to the dominant view of ERP components during language processing. Three contributions follow. Studies 1 and 3 primarily investigate how far a component typically associated with high-level linguistic processing, the P600 or "Syntactic Positive Shift", may rather reflect general reorientation following the detection of significant events by the VAN/LC/NE system. Study 2 investigates similarities and differences in two mismatch-sensitive negativities.

4.1 METHODS

Two techniques must be discussed in detail since they are 1. rarely used in studies of language processing and 2. prominently employed across all three studies. Both refer back to one of the core features of the EEG: accurate representation of temporal dynamics.

4.1.1 *ERPimages*

ERPimages present a straight-forward method of displaying single-trial dynamics in the light of the low SNR and temporal variance inherent to EEG data. ERPimages (Jung et al., 1999) are constructed by plotting stacked individual trials, aligned to some common reference point (e.g. the event the potential is related to, such as stimulus onset), and color-coded for potential (e.g., warmer colors representing more positive, colder colors more negative time points). After the application of visual filtering, ERP features become visible since such a display contains all the information given by the ERP. However, it also includes additional information about single-trial variance (high-amplitude outlier trials appearing more clearly); furthermore, the signal may be sorted by various additional time markers. For example, aligning to stimulus onset and sorting by response onset makes visible the relative alignment of components to stimulus or response timing. The visual inspection of ERPimages is a straight-foward and generally uncontroversial process; latencies of the secondary event are plotted on top of the EEG data. Then, the relative similarity of ERP features to the curve resulting from the plot of the sorting variable versus parallel to the alignment point can be estimated. In contrast, no commonly accepted method of quantifying such results has so far been developed. Still, ERPimages have become extremely helpful in investigating response- versus stimulus alignment (Debener, Ullsperger, et al., 2005; Makeig, Delorme, et al., 2004).

The sorting variable must not necessarily be a time point; trials may also be sorted by data characteristics such as amplitude in a specified time window, reaction time to a follow-up task or some other continuous measure.

One important aspect of regular ERPimages is that like ERPs, they only visualise neural events roughly time-locked and phase consistent with regards to the alignment and sorting events. Oscillatory phenomena with random phase after sorting do not reliably survive the filtering and become lost to SNR. However, the temporal dynamics of oscillatory processes may be

investigated by plotting the spectral power instead of the raw EEG; and by sorting trials by phase, phase-variant phenomena may become visible (Makeig, Debener, et al., 2004).

4.1.2 *Independent Component Analysis*

Establishing which EEG features are constituted by similar or different underlying systems is not trivial in part due to the *inverse problem*. It is generally assumed that ERP components can be considered distinct if they are projected by different stationary brain system (Coulson, 1998; Coulson et al., 1998; Osterhout, 1999). Conversely, two ERP components can be considered identical if they are projected by the same underlying system.

Of course, under models such as the LC/NE explanation of the P3, a component's identity is not identifiable with regards to specific neuronal generators (which may vary depending on task modality). In fact, the P3 is known to be both spatially and temporally distributed, including early far-frontal, and late parietal aspects. The N400, too, has been associated with a system that is non-stationary both in time and space; not only between paradigms (showing modality-sensitive generators), but also within trials (spreading from unimodal to multimodal systems).

Beyond such modern conceptualisations of late ERP components as widespread, temporally developing patterns however, the inverse problem acts as a fundamental boundary for associating ERP components based on their spatial structure. At the scalp, the electric field results from the mixing of various underlying generators. The deduction of the underlying generators from measured field properties is an ill-defined problem.

In the inverse problem, an inverse solution, an attemptf to deduce an underlying system from its observed properties, is met by the problem that typically, no unique solution exists for explaining the data by a model. Concerning ERP effects, the topography of an electric field measured on the scalp could be created by a magnitude of source configurations. Consequently, similar/identical topographies do not clearly associate ERP components. It is, however, generally assumed that different topographies dissociate components; how reliable this assumption is has not been convincingly argued. It has in fact been demonstrated (Urbach & Kutas, 2002) that significant differences in visually or statistically estimated scalp distributions of effects may result not from different underlying generators, but may be due to various other factors, such as differences in generator strength between conditions.

As a specific example of the inverse problem, source localisation of components is unreliable (Acar & Makeig, 2013). Dipole localisation techniques attempt to localize sources by selecting the location minimizing the unexplained variance; however, the lack of reliable forward models implies a lack of reliability of this procedure. Similar constraints apply to current source density or beamformer methods (Michel & Murray, 2012; Michel et al., 2004).

A different approach to the identification of brain components is provided by Independent Component Analysis/ICA (Bell & Sejnowski, 1995; Makeig, Bell, Jung, & Sejnowski, 1996; Makeig, Jung, Bell, Ghahremani, & Sejnowski, 1997).
The primary evaluation criterion for filter weights is the higher-order sta-

tistical independence of sources. Over repeated iterations, ICA attempts to converge to a solution where statistical dependencies between sources are minimized. The spatial filters (sets of sensor weights) resulting from ICA can then be used to filter the original time series of the data, resulting in the time series of the spatial filters. As a result, spatially stationary, distinct information components of the EEG signal can be investigated for their temporal dynamics.

One form of ICA, the natural gradient-based Infomax ICA, is often applied to EEG data where it exploits the extreme temporal resolution of the EEG signal by iteratively seeking for temporal correlations across sensors (electrodes) and estimates appropriate sets of sensor weights to isolate spatially stationary information sources within a signal assumed to contain, or be composed of, multiple mixed sources. It seeks to establish spatial filters of the EEG as sets of electrode weights by tracking temporally coherent signals.
Run separately for each subject, Infomax ICA typically is applied to specifically pre-processed data, including the rejection of gross, non-stereotypical (spatially unique or moving) artifacts, high-pass filtering and sphering. it then repeatedly randomises the temporal order of data point (nullifying, in contrast to some other forms of ICA, any kind of time-lagged correlation) and calculates the entropy, i.e., the shared information/statistical dependence across components. Filter weights are slightly adjusted based on this measurement, and the procedure is repeated for a high number of steps.

ICA has been used to separate different brain systems within EEG data, establishing spatially coherent centers of activity with distinct, unique temporal profiles. For example, the P3f could be successfully separated from nearby ocular activity (Delorme et al., 2007).

An important property of most forms of ICA of EEG data is that it is a bottom-up process driven entirely by temporal correlations. Spatial considerations do not inform the learning mechanism. Yet, ICA tends to recover spatially coherent sources (Delorme et al., 2012), a property that has been taken to imply that it recovers scalp traces of coherent centers of neuronal activity, possibly on the level of multiple macrocolumns (Makeig & Onton, 2012). By focusing on temporally correlated activity of spatial structures within the EEG, ICA fundamentally follows the original tradition of Berger, who had searched for a temporal unity of the brain in investigating its time series.
Yet, ICA of the EEG does not implement an inverse solution, since it seeks temporal coherence without regards for spatial structure. In theory, ICs may be spatially disjunct; for example, some ICs combine temporally tightly correlated activity from distant sources in the occipital lobes of both hemispheres. However, most sources are consistent with a single dipole or a coherent current source. Indeed, inverse modelling may be applied to the resulting filters (Acar & Makeig, 2013), estimating a source whose projection would be consistent with the observed sensor weighting. Such inverse solutions may be more sensitive than source modelling of ERP peaks, and have shown impressive correlations with simultaneously recorded fMRI data (Debener, Ullsperger, et al., 2005).

A final, straight-forward application of ICA is the removal of artifacts. Especially eye movements are easily separated and corrected by ICA, surpassing many alternatives (Jung et al., 2000); in contrast, high-frequency myogenic

(McMenamin et al., 2010) or certain MRI-based artifacts (Debener et al., 2007; Ullsperger & Debener, 2010) may not be trivially corrected via ICA.

4.2 STUDY 1

Given the properties discussed above, ICA might allow an interesting investigation of the question of how the N400/P600 can be integrated with the N2/P3 and ERN/P_E. Specifically, EEG data showing language-evoked N400/P600 effects can be decomposed using ICA, and the time series of the Independent Components/ICs most important for the N400 and P600 can then be investigated following other, non-linguistic events. One analysis comparing the Independent Components derived from the data in a linguistic task and from a non-linguistic Oddball task (Groppe, 2007) had already found that one common central-midline cluster accounted for much of the linguistic P600 and the Oddball P3. However, in that study, the analysis was focused specifically on this cluster, and the main investigation concerned activity during different tasks, not linguistic and non-linguistic activity during one and the same task.

An investigation of IC activation by linguistic and non-linguistic stages of the same task was attempted here by applying ICA to a previously reported data set (Kretzschmar, 2010). In that study, the authors report an early positive component following congruent and late positive components following incongruent sentence endings. Here, it was investigated if these positivities could be associated to the same Independent Components, and if these ICs also show sensitivity to non-linguistic aspects of the task.

Though the general theoretical framework and the entailed predictions regarding this experiment might in principle allow the prediction of the present findings, it must be stated that the following analyses can only be considered exploratory since the methods were repeatedly adjusted during the application of the ICA method - which is unconventional and untested in the domain of sentence processing research. Reported inferential statistics have to be considered from that perspective.

4.2.1 *Material and procedure*

4.2.1.1 *Material*

Kretschmar (2010) had presented subjects with 160 antonym sentences, each hosting a content word and its antonym (80 items; condition Ant), or a content word and a word semantically related to its antonym (40 items; condition Related), or two unrelated words (Roehm, Bornkessel-Schlesewsky, Rösler, & Schlesewsky, 2007, had already presented these stimuli in the visual domain). For example, subjects were presented with sentences such as in 4.1.

Sentences were presented over loudspeaker, preceded by a fixation cross. Slightly less than 1 second after sentence end, the fixation cross disappeared, and approximately 1 second later, a visual response cue (a question mark) was presented, advising subjects to indicate via button press if the previous sentence had been a true or a false statement.

Importantly, antonym words were highly predictable (cloze probability > 0.9). This was so because typically, words have only one antonym. Therefore, subjects could reliably solve the task by matching the semantic representation of the two potential antonyms, or they could achieve a highly reliable

	Example	Condition
a.	Das Gegenteil von schwarz ist weiß. “The opposite of black is white.”	ANT
b.	Das Gegenteil von schwarz ist gelb. “The opposite of black is yellow.”	MIS (related)
c.	Das Gegenteil von schwarz ist nett. “The opposite of black is nice.”	MIS (unrelated)

Figure 4.1: Example Stimuli Study 1.

guess by checking if the last word of the sentence matched a prediction that could have been built up at the position of the antonym target (“black” in the example).

4.2.1.2 *Procedure*

EEG was recorded from 64 channels using a Brain Products BrainAmp, at a sampling rate of 500 Hz, ground electrode at C2 and mastoid reference. The montage included 4 EOG electrodes (LO1, LO2, IO2, SO2). 30 right-handed native speakers of German (15 female; mean age: 24) were measured. Statistical analysis of behavioral measures and detailed scalp ERP analyses are reported elsewhere (Kretzschmar, 2010). In the prior analysis of this study, one subject was rejected from prior analyses due to a large number of artifacts. Artifact correction via ICA allowed the inclusion of this participant.

4.2.2 *EEG preprocessing*

For the present reanalysis, using standard analysis methods for ICA-based research of EEG data, participant data was processed using EEGLAB (Delorme & Makeig, 2004). EEG was average referenced under reconstruction of the mastoid reference, high-pass filtered at 1 hz to increase stationarity, non-stereotypic artifacts were rejected automatically using a Kurtosis statistics (Delorme, Sejnowski, & Makeig, 2007), epoched and subjected to AMICA Independent Component decomposition (Palmer, Kreutz-Delgado, & Makeig, 2006; Palmer, Makeig, Delgado, & Rao, 2008). The derived filters where then applied to raw data, which was then high pass filtered at .5 hz, allowing the use of the ICA weights in less extremely filtered data. Equivalent dipoles were calculated for individual ICs using the DIPFIT plugin (Oostenveld & Oostendorp, 2002). Then, data was re-referenced to linked mastoids.

ICs with non-dipolar distributions (more than 15% unexplained variance for the best-fitting dipole) and ICs with dipoles outside of the head volume were excluded. This procedure removed 1379 ICs, including most blink and motor artifact ICs, leaving 541 ICs representing all 30 subjects.

For the selected ICs, ERPs and spectra were computed, and the default kmeans clustering algorithm was used to cluster ICs across subjects based

on similarity in all relevant measures (absolute gradient of scalp map, weight 20; spectrum, dipole coordinates, and ERP, weight 1). 15 clusters resulted.

4.2.3 *Primary outcomes*

4.2.3.1 *Analyses*

First, mean scalp ERP by subject at electrode CPz (filtered and cleaned of both nonsterotypical, rejected and stereotypical, ICA corrected artifacts) for congruent and all incongruent endings was compared with a two-sample paired *t*-test compatible with the parameters used in the reference analysis (Kretzschmar, 2010). The purpose of this was simply to establish that the present, slightly different processing could replicate the main observations from the previous analysis. Therefore, one electrode showing both P3, N400 and P600 responses in the previous analysis was chosen.

Next, the primary clusters relevant for the P3-like effect were to be identified using the EEG envelope (Debener, Makeig, et al., 2005). In three time windows chosen to approximate the end of the typical N400 and P600 windows (0-500 msec past onset of critical words, 500-1200 msec past onset, 0-1200 msec past onset), separately for all words, congruent words, incongruent words, and the difference between congruent and incongruent words, it was calculated how much of the maximally negative and positive scalp sensor ERP the activity of each cluster back-projected to each electrode could explain, and clusters were ranked by their contributions.

Then, to test the clusters identified as the main contributors to the word-locked ERP for sensitivity to nonlinguistic events, ERPimages time-locked to either response execution or word onset were plotted for the main contributing clusters, and a within subjects, two-sample, two-tailed *t*-test was used to compare the subject mean ERP between word-onset locked and response locked activity in a 100 msec time window centered around the response.

4.2.3.2 *Results*

At electrode CPz, the mean ERP was more positive for Antonym trials in the early time window ($t(29) = 8.22$, $p < 0.001$, 95% CIs = 2, 3.32 ţV) and more positive in the later time window ($t(29) = -3.17$, $p = 0.0036$, 95% CIs = -1.128, -0.243 ţV). On first sight, this replicates the original findings after substantially different preprocessing: an early pattern, possibly reflecting a combined P3 and N400, for congruent and incongruent words, respectively, and a late P3/P600 for incongruent words.

However, visual inspection of the ERP plots in the present and the original analysis indicate a baseline difference between Antonym and all incongruent conditions (See Figure 4.2) that resembled the later difference in the late positivity. After applying a baseline correction (-250 to 0 msec; see Figure 4.3), no reliable difference between mismatches and matches in the later time window can be detected anymore ($t(29) = 0.26$; $p = 0.79$).
These discrepancies with the previous results were surprising. Since a number of analysis parameters had been changed, the analysis was

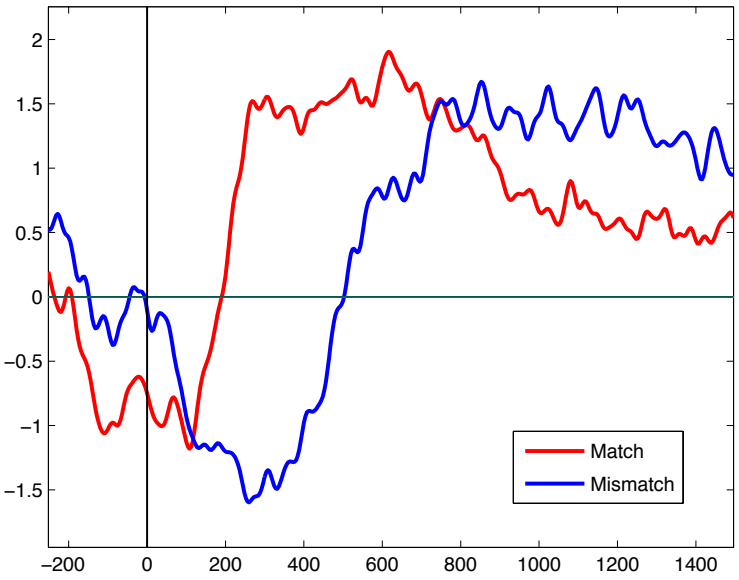

Figure 4.2: ERP for congruent and incongruent words at electrode CPz, no baseline.

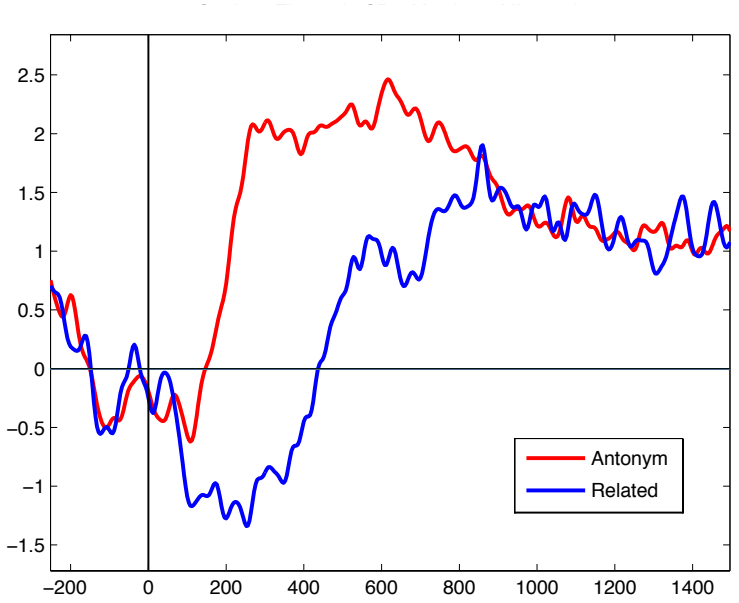

Figure 4.3: ERP for congruent and incongruent words at electrode CPz, short baseline.

repeated after manipulation of these parameters. For example, it is possible that the early, strong P3 for the congruent condition might have been impacted by the filter, inducing a pseudo-baseline effect by "smearing" the P3 into the pre-stimulus window. Furthermore, the original study did not conflate both incongruent conditions in this analysis. Consequently, data for all three conditions separately was reprocessed using a .1 hz filter (less than in the reference study), both with a short (250 msec; see Figure 4.4) and a long (750 msec; Figure 4.4) baseline. However, in neither of these analyses, a difference in the late window between congruent and incongruent conditions could be found. A substantially later effect (> 1s) somewhat resembled the expected late positivity.
Still, the incongruent condition did display a late positive component. As noted, visual inspection of the reference study indicated a similar phenomenon (Kretzschmar, 2010, p. 113), in that no baseline was applied, but the pre-stimulus ERP shows the same difference between conditions as the late time window. It is well established that a late positivity can be observed in this paradigm (Roehm, 2005), so the *existence* of a late positive *component* here is the default assumption; however, in the present data set, this *effect* of a *difference* between congruent and incongruent conditions in the time window of the P6-like component might not be reliably detected.

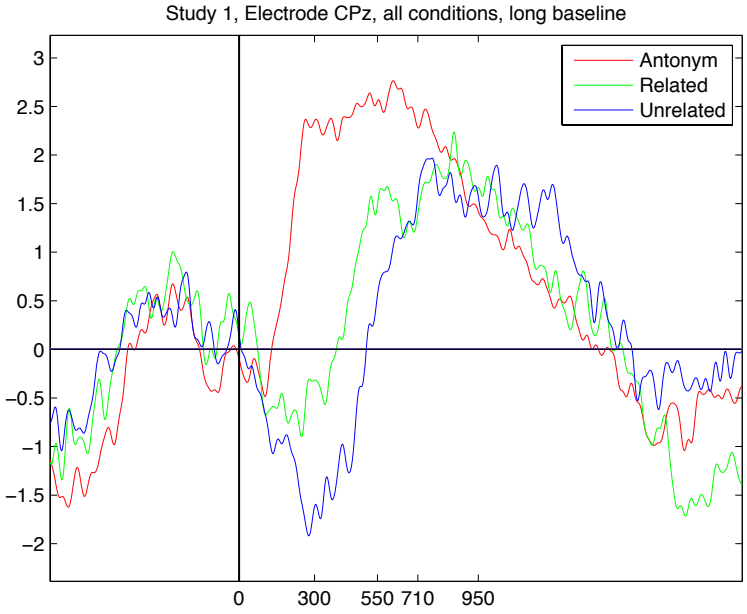

Figure 4.4: ERP for congruent and incongruent words at electrode CPz, short baseline.

Since the primary analysis goal of assigning the late positive *component* to brain sources was independent of the existence of reliable differences, this was the next step of the exploration.
Analysis of cluster contributions to the sensor-level ERP by ERP envelopes resulted in a fairly homogenous picture. An overview of all cluster contributions is given in Figure 4.6. The location of all cluster's estimated mean dipoles is given in Figure 4.7. One centro-parietal cluster dominated most time windows and comparisons. It was termed "P3b" due to the similarity

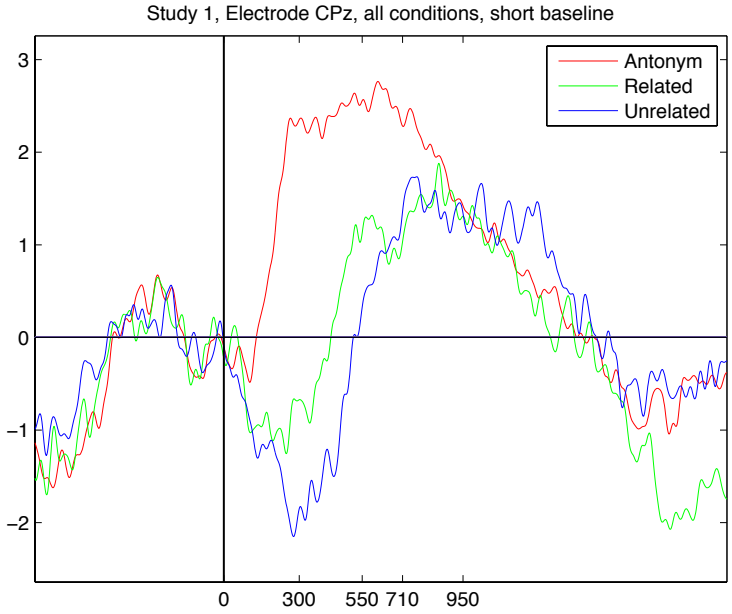

Figure 4.5: ERP for congruent and incongruent words at electrode CPz, long baseline. X axis gives the time windows employed in the initial analysis.

of its scalp map (spatial filter weights by electrode) to the topography of a P3b.

	pvaf (Percentage of variance accounted for by cluster) for time window/condition ...									
	0-1200 after word onset			0-600 ms after word onset			600-1200 ms after word onset			0-1200 ms
Cluster	ANT	MIS	ANT+MIS	ANT	MIS	ANT+MIS	ANT	MIS	ANT+MIS	ANT-MIS
P3b	**45**	**36**	38	**44**	**39**	**32**	**47**	31	40	**48**
Left Occ	15	24	22	20	17	22	8	36	23	16
Middle Occ	38	32	**39**	36	22	30	42	**45**	**45**	28
Right Occ	17	17	20	19	11	19	15	28	22	10
Range others	-5 to 19	-5 to 15	-1 to 20	-7 to 14	0 to 8	0 to 13	-2 to 24	-20 to 22	-3 to 24	-7 to 14

Figure 4.6: Contributions of clusters to the ERP in various time windows and conditions.

The "P3b" cluster alone (See Figure 4.8) accounted for more than 38% of the variance in the long-window (0 to 1200 msec post onset) ERP to all critical words combined, as well as 47% of the variance in the difference between ANT and MIS in this time window. Approximately 35% of both the positive signal in the early time window for ANT conditions and the negative signal for MIS conditions, and of the positive component in the late time window, were accounted for by this cluster.

Three occipital clusters (left, right and midline occipital; see Figure 4.9) explained between 20 and 40% of the variance for all these comparisons. However, their projection to electrodes CPz and Pz in the time window of positive, P3-like components was mostly negative, so they did not contribute to a positive component measured at centro-parietal electrodes.

Cluster	X	Y	Z	Nearest grey matter
P3b	-5	-36	18	Posterior Cingulate
Right Occipital	23	-64	2	Right Lingual Gyrus
Central Occipital	-4	-64	7	Cuneus
Left Occipital	-26	-60	-2	Left Lingual Gyrus
Frontal Midline	3	19	16	Anterior Cingulate
Left Frontal	-34	12	21	Left Insula
Right Frontal	37	9	12	Right Insula

Figure 4.7: Locations of cluster mean dipoles in Talairach coordinates; labels as by Talairach web client.

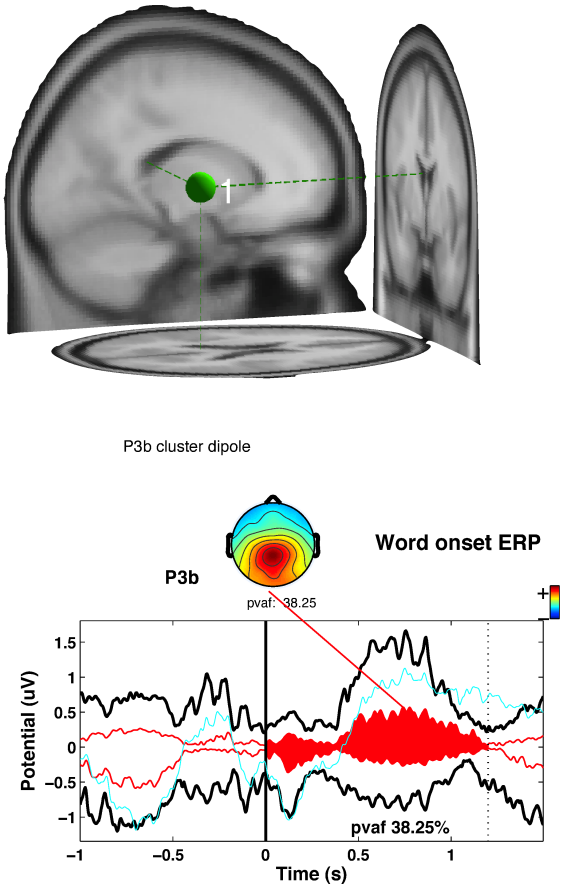

Figure 4.8: Top: estimated cluster mean dipoles for the P3b cluster projected onto the MNI standard brain. Bottom: ERP envelope and back-projected contributions of P3b cluster, for all conditions time-locked to word onset. Black line shows maximal and minimal ERP values. Filled red area shows total variance explained by occipital clusters. Teal line shows electrode CPz. Scalp map of cluster shown at top, percentage of variance accounted for by this cluster below.

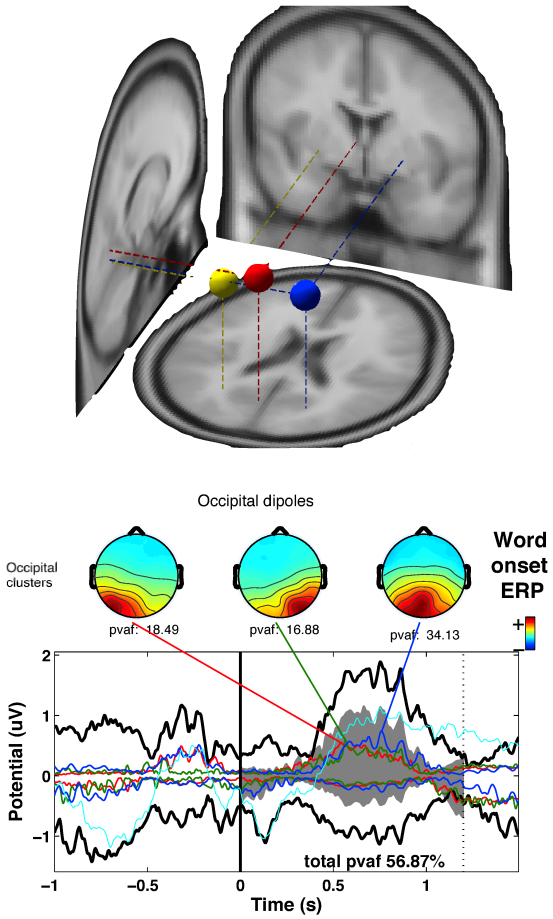

Figure 4.9: Top: estimated cluster mean dipoles for left occipital, right occipital and middle occipital clusters, projected onto the MNI standard brain, Bottom: ERP envelope and back-projected contributions of occipital clusters, for all conditions time-locked to word onset. Black line shows maximal and minimal ERP values. Filled grey area shows total variance explained by occipital clusters. Teal line shows electrode CPz. Blue, red and green lines show cluster maxima. Scalp map of cluster shown at top, percentage of variance accounted for respective clusters below; total variance accounted for by the sum of all clusters shown within ERP envelope plot.

The centro-parietal and occipital clusters together accounted for over 90% of the variance in the critical word-locked ERP. Other clusters accounted for less than 10% of the variance. This means that most of the relevant *positive component* activity could be traced back to the P3b cluster (since the occipital clusters did not project positively to central and parietal electrodes in this time window).

Consequently, it was this cluster that was selected for a test of response-locked activity. ERPimages (See Figure 4.10) and statistical investigation of response-locked effects indicated a response-locked peak of the cluster ($t(25) = 3.86$, $p < 0.001$; 95% CIs = 0.98 to 3.25).

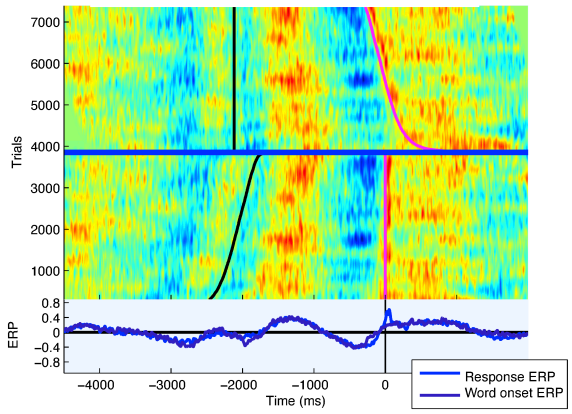

Figure 4.10: ERPimage of the P3b cluster, all conditions, time-locked to either critical word onset (black vertical line) or RT (pink vertical line), sorted by RT. RT- and word onset-aligned ERP at the bottom.

The P3b cluster mean dipole was located nearest to the posterior cingulate. Occipital clusters were located to the occipital lobe.

4.2.3.3 *Interim discussion*

One centro-parietal cluster accounted for the majority of the word-evoked ERP when analysed in multiple time windows and conditions. A number of further components were active, but contributed only marginally to typical word ERP components.

The main contributing cluster for the word-locked ERP also showed significant task-related activity.

The P3b cluster was not localized to the TPJ by equivalent dipole analysis, but instead, possibly near the posterior cingulate. The posterior cingulate receives strong noradrenergic input from the LC, and coactivates with the LC in certain paradigms (Payzan-LeNestour, Dunne, Bossaerts, & O'Doherty, 2013). However, it is equally likely that dipole analysis did not appropriately allocate the possibly widely distributed sources of this effect.

4.2.4 *Secondary and exploratory analyses*

A couple of further clusters of interest became apparent from investigating the other ICs active during word processing. These clusters were not in-

cluded in the focus of the original hypotheses; however, they either showed striking and surprising patters, or were referred to by secondary hypotheses, or are relevant because they demonstrated task-critical, but likely not language-specific functions during the linguistic task. Thus, the following is an exploration of the question of domain-general, task-critical systems contributing to and shaping the ERP during language processing tasks.
Measures, including methods and the associated results, for the exploratory investigations of these further sites of interest are reported here.

4.2.4.1 *Analyses of frontal clusters*

MEASURES One frontal-midline cluster with a topography previously associated with frontal-midline θ and the MFC/aMCC (Onton et al., 2005); and a left- and a right-frontal cluster. The cluster mean dipole of the frontal-midline cluster indicated a location in the cingulate cortex, possibly the pACC, aMCC or pMCC (See Figure 4.11 and 4.12).

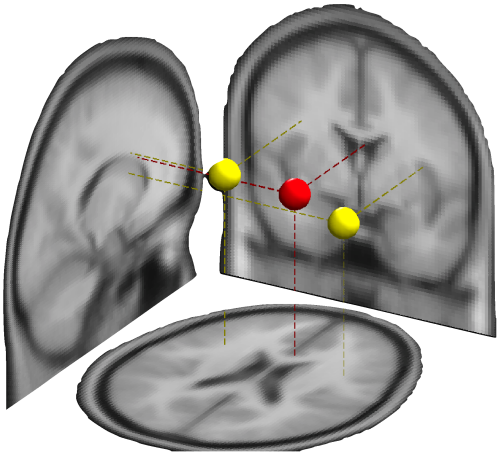

Figure 4.11: Cluster mean dipoles for frontal-midline (red) and left/right-frontal (yellow) clusters projected onto the MNI standard brain.

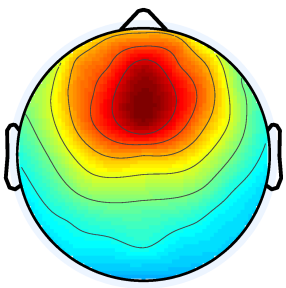

Figure 4.12: Scalp topography of frontal midline cluster

The frontal-midline cluster exhibited an N2/P3 - like pattern to words (See Figure 4.13). Visually, it seemingly distinguished between congruent and incongruent words (with an N2 for incongruent words), but not between related and non-related incongruent words. Consequently, frontal-midline cluster, within-subject ERP mean amplitude back-projected to electrode Fz

was compared in the time window of the N200 (100 to 200 msec after word onset). Contingent upon a positive finding, individual conditions were then to be compared with each other using paired, two-tailed *t*-tests.
Since visual inspection had indicated no differences between the two mismatch conditions, and classical frequentist hypothesis tests don't allow accepting the nil-null hypothesis of no differences, a default Bayesian paired *t*-test (Rouder, Speckman, Sun, Morey, & Iverson, 2009) was employed to calculate the Bayes Factor for subjects means of the differences. For this, a standard JZS cauchy prior, centered on 0, with a width of .5 standard deviations, was employed.

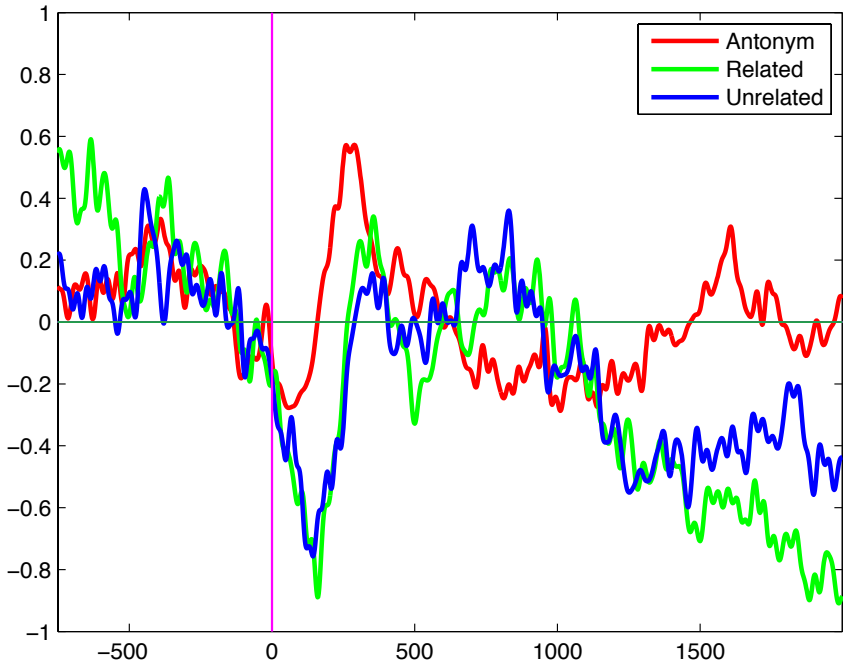

Figure 4.13: ERP at the frontal-midline cluster back-projected to electrode FCz, by condition, time-locked to critical word onset

The left- and right-frontal clusters were investigated in their differential responses to stimulus and behavioral reaction. An ERP to the disappearance of the fixation star was investigated using a *t*-test comparing the mean ERP in the P2 window following fixation star offset after back-projecting the clusters to electrodes F3/F4, respectively. Here, cue-locked ERP was compared to word-locked ERP (cue locking trials also synchronised them with regards to fixation star offset, since the fixation star reliably disappeared 1 second before response cue presentation).

RESULTS Concerning the frontal-medial cluster, the main ANOVA indicated a substantial N2 effect ($F(2,44) = 10.341$, $p < 0.001$, $\eta^2_p = 0.3$). According to the individual follow-up ttest comparisons, the ERP was significantly more positive for expected antonyms than for both mismatch conditions (Related Incongruent vs. Antonym: $t(22) = 4.58$, $p < 0.001$, 95% CIs: 0.36, 0.97; unrelated Incongruent vs Antonym: $t(22) = 3.55$, $p = 0.0018$, 95% CIs: 0.23, 0.88), but no difference was found between the two types of incongruences ($t(22) = -0.67$, $p > 0.5$, 95% CIs: -0.46 to 0.23).
The Bayes Factor strongly favoured the hypothesis of a difference between

matches and mismatches (BF H_1 over H_0: > 1000), but moderately favoured the hypothesis of no differences comparing the two kinds of mismatches with each other (BF H_0 over H_1: 4.3).
These results are also presented in table form below.

Test	Measure	95% CI lower	Effect size	95% CI upper	Test statistic	*p*
CONDITION	η^2_p	0.32	**0.42**	0.58	$F(2,44)=16.25$	<.0001
Match vs. Mismatch	*g*	0.93	**1.13**	1.54	$t(22)=6.6$	<.0001
Related vs. Non-related		-0.51	-0.10	0.30	$t(22)=-0.47$	.6

Table 4.1: Results mediofrontal cluster ERP Study 1

The left- and right-frontal clusters showed a diverse pattern. During word processing, a positive component was visible that did not differ between congruent and incongruent words. Between word offset and response cue presentation, and compatible with a P2-like component reacting to the disappearance of the fixation star, a further positive peak was observed. To the response cue itself, no clear component was observed, but a negative peak showed up as response-locked in ERPimages (See Figure 4.14).
The P2-like component following fixation star disappearance was statistically reliable ($t(35) = 3.68$, $p < 0.001$, 95% CIs: 0.19 to 0.68).

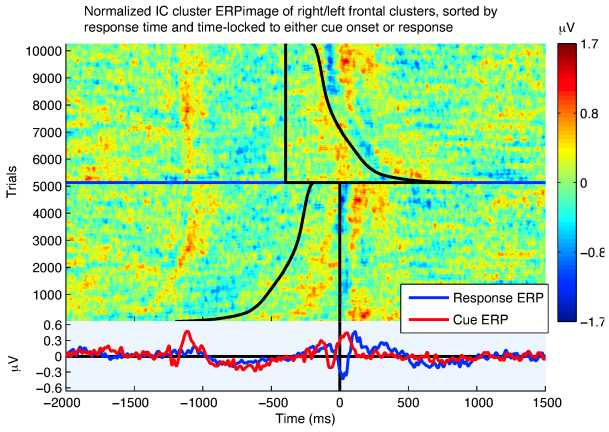

Figure 4.14: ERPimage of the left- and right-frontal cluster, all conditions, time-locked to either response cue onset (left vertical line) or RT (right vertical line), sorted by RT. RT- and cue-aligned ERP at the bottom.

4.2.4.2 *Time-frequency decomposition*

In the form of the blocking of the Berger wave, there is, beyond the P3, another EEG feature coinciding with the Orienting Response. If the late positivity observed in this study is a P3, and if the P3 indexes, here and otherwise, an OR, α blocking should be observed following the critical words. In order to test this, a time-frequency decomposition was conducted using standard measures.

MEASURES For Antonym and Unrelated Non-Antonym conditions, the time-frequency characteristics of the signal in the form of the Event-Related Spectral Perturbations/ERSP were estimated via wavelet decomposition (Delorme et al., 2007; Makeig, 1993). For this, the sigal was divided into 90 evenly spaced frequencies between 0.75 and 30 hz. Trials were analysed in a window spanning from 1.5 seconds before to 2.5 seconds after the onset of critical words, and for each frequency, the mean of a 500 msec long pre-stimulus baseline subtracted from each point using a single-trial baseline (Grandchamp, 2011).

RESULTS For either condition, a low-frequency (below 5 hz) phasic peak coincided with the peak of the ERP. Wide-reaching α and β ERD dominated the ERSP in both conditions (See Figure 4.15), compatible with the α ERD expected from an OR.

INTERIM DISCUSSION The frontal-midline cluster, resembling ICs previously associated with the mediofrontal cortex (Onton et al., 2005), demonstrated an N2-like component to unexpected endings. By itself, finding an N2 is not unexpected. What was surprising was the lack of a difference of this component between related and non-related words. Later processing by temporal and temporo-parietal areas, reflected in the N400, shows graded sensitivity to just such a contrast (Federmeier & Kutas, 1999; Kutas & Federmeier, 2011), and indeed, for the present antonym paradigm, a graded N400 has been reported using the same stimuli (Roehm, 2005).

This observation entails a few surprising considerations. First, the frontal brain system reflected by this IC cluster should operate rather independent of the primary linguistic system around the temporal lobes. Otherwise, a graded sensitivity would have been expected. This in turn entails the ability of frontal sites to match input words with words from the memory focus, without the subject recently having perceived the word in memory. Subjects could only find the actual input mismatching with a prediction of the correct antonym, which means that temporal sites likely implementing word representation must have constructed the prediction in an extremely short time span and relayed them to the frontal system. Then, the frontal system directly matches the memory trace with the actual input, potentially in part via thalamic efferents. This direct processing in the frontal lobe is also to be expected due to the extremely short latency of the N2-like effect, leaving little time to relay highly preprocessed information from the auditory cortex to the frontal system.

However, it is likely that if the frontal system functions as described here, its memory span must be highly limited, and work on a low-level, feature matching basis. Neither was the N2 modulated by word relatedness, as

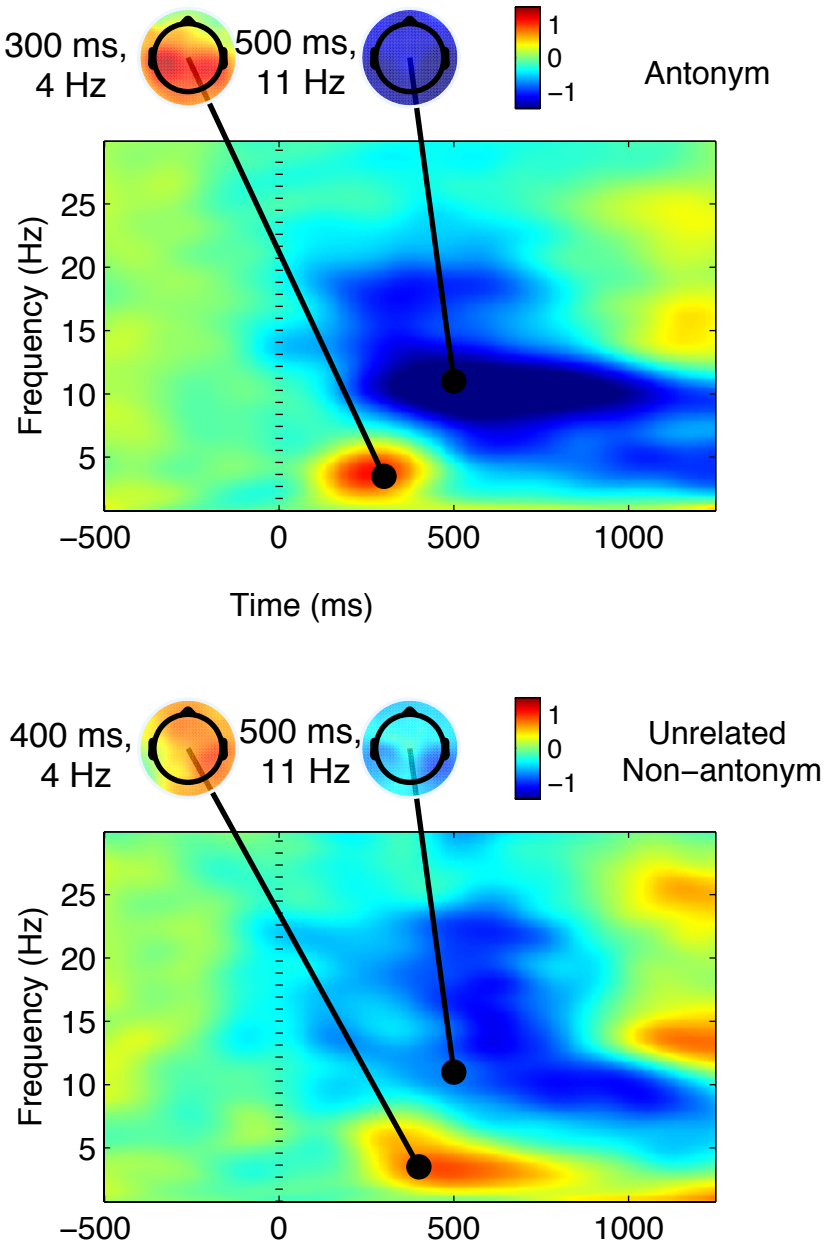

Figure 4.15: ERSP time-locked to onsets of critical words for Study 1, averaged over all subjects, trials and channels. Scalp topography for selected features is given.

would have been expected from a system with access to concept-level information deeper than feature level; nor is it likely that a "mental lexicon" - like system is redundantly implemented by both medio-frontal and temporal sites since reports of frontal contributions to sentence-level semantic integration usually focus on the lIFG (e.g., Lau et al., 2008).

However, while limited in scope, it can be assumed to operate in a cross-domain, multimodal fashion. In the present experiment, sensitivity to auditory prediction mismatches was observed, establishing input from both long-term memory stores and direct auditory pathways. Previously, anterior cingulate activity, or generally, brain systems with a similar spatial profile as the current IC cluster, have been found especially in low-span cross-modal mismatch paradigms.

The mediofrontal cortex becomes activated by the stroop task, where visual color and lexical information clash. It also responds stronger to two-stimulus Oddball paradigms where e.g. only one out of two colours is the deviant (Warren et al., 2011), than to open-set processing (such as the gender of a face, which rests on multiple probabilistic semantic features). This indicates a limited ability of this system to perform deeper processing, but also the sensitivity to conflicts between multiple input streams of different modalities.

The left- and right-frontal clusters could potentially reflect specific motor control[1]. Positivities followed events that possibly activated response impulses that were then to be suppressed: to critical words that allowed the selection, but not execution of the appropriate response; and to the disappearance of the visual fixation star, as the last perceptual event before the awaited visual response cue. The response cue in turn did not elicit a positivity, but a negativity was found right at response execution.

Possibly, scalp-positive activity of this cluster then reflects inhibitory, negative activity disinhibitory activity, instantiated in a temporally precise manner. This is compatible with a range of findings regarding IFG (Swann et al., 2009), MFG and the insulae (Swick, Ashley, & Turken, 2011), as well as with the role of these areas in the control of sequential behavior. Whereas Broca's area and associated sites are often implicated in high-level linguisti processing (Grodzinsky & Santi, 2008; Rogalsky & Hickok, 2011), in the present study, the signature of this possibly related system was more compatible with temporally precise modulation of motor impulses, in line with many non-linguistic studies of behavioral control, including the role of the (r)IFG in the ventral attention network (Corbetta et al., 2008) and response inhibition (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Aron, Robbins, & Poldrack, 2014).

The α blocking visible in the ERSP was a necessary entailment of the interpretation attributed to the late positivity, and corroborates the association with the P3 via the OR.

4.2.5 *Discussion*

In this reanalysis of a previously reported data set, ICA allowed the fine-grained analysis of multiple task-sensitive brain systems active during the

1 This interpretation was proposed by Jasmin Kzlrmak.

processing of words and the initiation of task-critical responses. As an exploratory study, its primary results were congruent with, but not exclusively decisive in favour of the idea that the N400/P600 pattern is closely tied to the N2/P3; main clusters were active both during the P3 and during the execution of the response, and α blocking followed critical events, as would be required under the LC/NE-P3 theory.
The analyses further highlighted a set of frontal systems with surprising properties in task control and cross-modal memory focus.

4.3 STUDY 2

A follow-up study aimed to further investigate the unexpected nature of the sensitivity of a frontal brain system to unexpected words. The basic question investigated here is: how sustainable is the assumption of fundamental common underlying principles for mismatch-sensitive scalp negativities? More specifically, regarding the domain of language processing, how viable is it to associate observed negative peaks with a general mismatch detection mechanism of the action-perception cycle, in contrast to the various theories assigning components to hypothesised structural computations?

In the first study, a frontal midline IC cluster, likely reflecting anterior or mid-cingulate activity, showed a surprisingly early negative deflection highly similar for both related an non-related unpredictable words, but not for expected words. Possibly, this effect might indicate a sensitivity of the mediofrontal cortex to stimulus conflict if the target set is very small. Therefore, the experiment was constructed in order to test a differential sensitivity of this frontal system to stimulus mismatch in closed-set, but not open-set tasks.

The primary focus of the experiment related to a difference between tasks solvable in reference to a restricted list of items, for example, by matching the current stimulus to a specific prediction, and tasks requiring modality-specific, multidimensional matching processes with a large or unrestricted set of relevant items. In the previous study, the main surprising finding had concerned the differential sensitivity of the frontal negativity in contrast to the N400. The N400 shows gradual sensitivity to the predictability and goodness-of-fit of the stimuli it is sensitive to, e.g. word meaning (Federmeier & Kutas, 1999; Kutas & Federmeier, 2011). The less expectable or congruent a word is, the harder it is to access and/or integrate, the larger the energy required to reconfigure the pre-stimulus energy landscape of the conceptual system to appropriately accommodate for the stimulus information, the larger the N400. For example, consider the contrast (Federmeier & Kutas 1999, p. 473)

> "They wanted to make the hotel look more like a tropical resort. So along the driveway, they planted rows of [palms/pines/tulips]."

In contrast to "palms", a large N400 is elicited by "tulips", a smaller one by "pines". Interestingly, the expectability of the correct target modulated within-category violations (here, "pines"), but not between-category violation or correct target waveforms; when the correct target was highly constrained, i.e., predictable, within-category violations elicited a smaller N400 than in low-constraint conditions.

In contrast, the observed early, N2-like effect likely generated by the demonstrated binary sensitivity in a contrast where using the same (Kretzschmar, 2010) and other (Roehm, 2005) data sets previous researchers had found gradient sensitivity of the N400. Compared with a correct antonym sentence such as "The opposite of black is white", a strong N2 was elicited by "… of black is salty", but also a statistically and visually indistinguishable effect for "… of black is yellow". Note again that all these sentences were highly constraining, with nearly 100% cloze probability (i.e., the word "white" is reliably predicted by subjects as the correct continuation of the sentence fragment "The opposite of black is …").

A somewhat similar effect had been observed in an Oddball experiment comparing two modalities (Warren et al., 2011). When subjects had to evaluate if one out of 40 possible presented faces was male or female, faces belonging to the gender that was less commonly presented elicited an N2 pattern possible with generators in the fusiform gyrus. When subjects attended the color of stimuli (stimuli were either yellow or blue), the N2 appeared earlier and was maximal at medio-frontal sites, which the authors described as compatible with a generator in the mediofrontal cortex. While the fusiform gyrus is highly face sensitive and likely processes facial characteristics, the MFC is generally neither implicated in color nor word processing.
The N2-like component observed in this study ("anterior N2"), also compatible with a generator in the mediofrontal gyrus, possibly the aMCC, pMCC or even pACC, thus resembles this previous finding in showing binary stimulus conflict sensitivity.

Both findings combined could be explained under the assumption that the frontal brain system whose activity it reflects has access to, or maintains, a very restricted set of working memory focus (Jonides et al., 2008), and can perform a simple pattern-matching process. The anterior N2 would result from the mismatch between the item in the memory focus and the actual input, with a binary sensitivity to the degree of difference between input item and memory focused item.

Interestingly, while the expectation in the Oddball task by Warren et al. could have been induced by perceptory processes, as a memory trace of a recent (and repeated) event, in the sentence presentation experiment, the expected target was not recently perceived; rather, it must have been retrieved from lexical long-term memory, based on the prediction induced by the previous antonym word. In contrast, the input item with which the prediction is matched was perceived; consequently, the anterior N2 here was sensitive to a mismatch between an item retrieved from long-term memory and the current stimulus. In the experiment by Warren et al., a memory trace from prior repeated presentation mismatched with the current stimulus. This matching process must have been fast; possibly, direct thalamic projections to cingulate cortex may be involved.

The specific primary goal of this second study was then to test this hypothesis. Was the classification of the anterior N2 in Study 1 as showing binary stimulus conflict sensitivity correct? This question was especially interesting from the perspective of the possibility of associating linguistic and non-linguistic negative mismatch potentials, possibly for mismatch potentials whose non-linguistic iterations are well researched.

4.3.1 *Material and procedure*

4.3.1.1 *Material*

Stimulus material was chosen in order to distinguish between incongruences in closed-set and open-set tasks. An anterior N2 was expected only for closed-set incongruences.

The previous study differentiated between predictable correct, related unpredictable incongruent and non-related unpredictable incongruent input. Consequently, a design was chosen including unpredictable correct words.

Sentence material was created by first collecting possible categories (hyperonyms) and category members (hyponyms). Then, to investigate if an item allowed or disallowed a specific prediction, questionnaires were used. 40 native speakers of German were given a list of German hyperonyms followed by 1-3 hyponyms, e.g. "To the category 'animals' belong lions, snakes and..." or "To the category 'olympic medals' belong bronze, silver, ...". (loosely translating the German original). For closed-set categories, only hyperonyms that had just 2 to 4 hyponyms were selected; for open-set items, words were selected from categories where more than 5 members could easily be found. Subjects were asked to name another member of the category. For 50 categories, a majority of subjects gave identical responses (cloze probability median: 100%, mean: 90%, range: 71-100). From these, 100 closed-set sentences were constructed by using each category twice, but reversing the order of category members (e.g., "To the category olympic medals belong [bronze, silver, and gold/gold, silver, and bronze]"). Closed sets consisted of 2 to 4 members. Syllable length-matched lists of open-set sentences were then created, using categories where subjects had not named one item more than 20% of the time; it was ensured that the most common named item were never selected for open-set sentences.

Sentences were read by a theatre actress who was instructed to speak lively and articulate, and recorded in .wav format, 44khz sampling rate. Sentences were constructed by first recording a carrier sentence containing the hyperonym and the first few (1-3) hyponyms, followed by the phrase "... and dummy", e.g. "The category 'animals' contains for example lions, snakes, and dummy". Target sentences were constructed by reading them in order in word lists alternating the phrase "and dummy and", e.g., "... dummy and buffalo and dummy and gold and dummy ...". Sentences were then cross-spliced using the free software Audacity by cutting the "dummy" phrase and replacing them with the "and" plus the following hyponym. The purpose of this cross-splicing procedure was to ensure that the speaker did not subconsciously introduce perceivable cues into mismatch sentences based on their own understanding of the incongruent nature of the sentence, while also minimising the possibility of unnatural transitions.
The same target words were each used in match as well as mismatch sentences. In the cross-spliced sound files, onsets of the actual noun were measured and later used to create ERP triggers.
The procedure was used to create both correct and incorrect sentences. For 200 correct sentences, the correct hyponym was adjoined to its hyperonym carrier sentence; then, for each hyperonym carrier sentence, a hyponym was chosen at random and also adjoined to create a mismatch sentence of the same category.

From the resulting 400 sentences, multiple item sets were created each containing 60 closed correct sentences (C+), 60 open correct sentences (O+), and 40 closed (C-) and 40 open (O-) incorrect sentences. Across all lists, every item was presented approximately equally often in correct as in incorrect variants. Sentence order was randomized within each category (within open and within closed lists), and stimulus lists were created using either first 100 open and then 100 closed set sentences (each with 60 correct and 40 incorrect in random order), or closed first, followed by open.
Such a blocked presentation is rare for neurolinguistic experiments, where usually, participants are kept in ignorance about the true nature of the manipulation, sentences are presented fully randomised, and it is hoped that

a "natural" listening condition is created. This was not attempted in this study. The aim was the investigation of how the brain allocates ressources to specific predictions and to general expectations, and it was ensured that participants were able to dedicated their attention fully to these two strategies, one optimal for one block of 100 sentences, the other optimal for the other block.

A set of example sentences in the original German, followed by a loose English translation, is given below (4.16). The critical target word is highlighted.

	Example	Condition
a.	Zur Kategorie Möbel gehören Schreibtisch und Sessel. "To the category furniture belong desk and armchair."	Open Match
b.	Zur Kategorie Möbel gehören Schreibtisch und Oma. "To the category furniture belong desk and grandma."	Open Mismatch
c.	Zur Kategorie Großeltern gehören Opa und Oma. "To the category grandparents belong grandpa and grandma."	Closed Match
d.	Zur Kategorie Großeltern gehören Opa und Sessel. "To the category grandparents belong grandpa and armchair."	Closed Mismatch

Figure 4.16: Stimuli Study 2.

Stimulus presentation was controlled by the Presentation software (Neurobs).

4.3.1.2 *Procedure*

It is unlikely that the previous observation of an anterior N2 are trivially compatible with the conflict monitoring model, as far as it is primarily concerned with *response* conflict monitoring. No overt response was to be performed. However, it is possible that a response was already selected during this stage, only to be executed later (at the response cue), and that conflict between congruent-appropriate "yes" and incongruent-appropriate "no" responses were activated by, respectively, the prediction for the input and the actual input.

In order to test this possibility, it was decided to instruct subjects to respond directly after the critical position, rather than waiting for a response cue. As previously described (Burle et al., 2008; Yeung et al., 2004), on correctly answered trials, response conflict should be maximal right before response execution. Consequently, if the anterior N2 reflects response conflict, not stimulus conflict, it should appear reaction time-locked rather than stimulus locked. However, if it represents stimulus conflict, a stimulus-locked component would be expected.

Upon arrival, participants filled in a questionnaire establishing their suitability as test subjects. They were then instructed that they would hear 200 sentences spread over 20 blocks of 10 items each, either the first or the second 100 with closed categories allowing only one possible option for the

last category member. They were told they should press a button as soon as they knew if the sentence was correct or incorrect. Half of the subjects had been instructed to press the left button to indicate congruent and the right to indicate incongruent sentences; the other half received the reverse assignment.

They were instructed to react both accurately and fast.

Subjects were instructed to watch a computer screen, on which a neutral smiley face was presented. Then, a sentence was played. When the subject had pressed the button, the smiley face was replaced with either a laughing or a sad face to indicate if the correct button had been chosen. Then, the next sentence was played.

After every 10 sentences, a feedback screen presented accuracy and mean response time of the last block were presented, as well as a laughing, neutral, sad, or a euphoric smiley, corresponding to 1-2, 3-4, 6-10 or 0 wrong responses on the last block.

Subjects were able to rest for as long as they wanted during this feedback screen. One session lasted for approximately 2 hours including EEG setup and the actual experiment. 20 subjects were measured, all right-handed native speakers of German between 20 and 30 years of age, and financially compensated for their assistance.

EEG was collected at 500 hz sampling rate using a 64 channel Brainproducts setup (Brainamp and Brainvision Recorder) with Ag/AgCI electrodes, mastoid reference and earlobe ground.

To my knowledge, such a procedure, including overt responses during sentence presentation, is novel, or at least rare in sentence processing research. In contrast to most psychologists, neurolinguists conducting research on sentence processing typically separate critical stimuli and response cues by asking subjects to inhibit judgement responses until a cue following the last word of the sentence. It is generally hoped that this will remove e.g. motor or "task-related" potentials from the sentence manipulation itself.

However, such an approach can be considered fruitless since the P3 reliably occurs to events that allow the selection of the response, even if the response choice has to be maintained in memory until a response cue is presented, as has been demonstrated by multiple paradigms separating critical event and response cue (Kok & De Jong, 1980; Luo & Wei, 1999; Praamstra et al., 1994).

In fact, given that is is well known that both the N400 (Kutas & Federmeier, 2011) and the P600 (Coulson, 1998) are highly sensitive to task factors, and it is impossible to remove decision-making and response-selection related activity from certain paradigms, it can be argued that it is beneficial to, rather than failing to remove such activity, include measurements allowing for its precise localisation in time.

4.3.2 *EEG preprocessing*

Offline, following our previous studies and standard procedural, data was loaded into EEGLab (Delorme & Makeig, 2004), average referenced including reconstruction of the reference channel, filtered using a 0.5 hz butterworth high pass filter, resampled to 125hz, and epoched around critical

word onset markers, excluding trials with incorrect responses and gross paroxysmal artifacts. To these epochs, extended Infomax ICA was then applied using EEGLab defaults, and 1300 (20x65) ICs extracted. Using the BEM 3-shell model of the DIPFIT plugin, estimated equivalent dipoles were calculated for each IC. For further artifact processing, non-dipolar ICs (more than 15% residual variance) were omitted from IC analysis, and their contribution to the EEG was subtracted before raw scalp ERPs were calculated to reduce artifactual activity. For the remaining 720 dipolar ICs, response-locked ERPs and spectra (3-40hz) were calculated. ICs were clustered across subjects using the default kmeans algorithm in EEGLab with the parameters "spectra" (3-35hz, weight: 1, dimensions: 10) and "scalp map" (map gradient, weight: 20, dimensions: 20). The default number of clusters, 37, was accepted, resulting in multiple brain and artifactual clusters.

4.3.2.1 *Cluster identification*

One cluster was identified to represent a similar mediofrontal brain system as in the previous study, with a mean scalp map resembling the cluster showing an N200 there (See Figure 4.17).

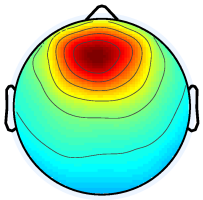

Figure 4.17: Mediofrontal cluster topography.

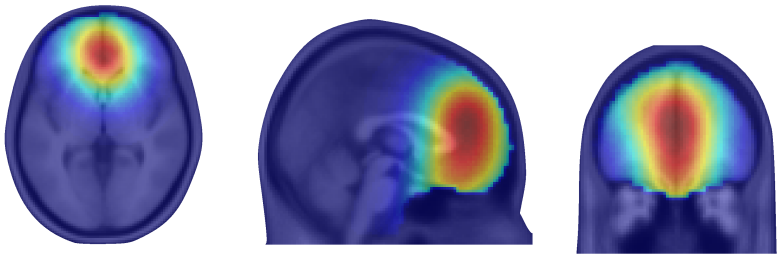

Figure 4.18: Mediofrontal cluster dipole densities.

Mean dipoles (See Figure 4.17) of the cluster were indeed located to frontal regions, with the center between aMCC and pACC (Talairach: X = 0, Y = +38, Z = +6). In addition to the source localization - based association of this cluster with the ACC/MCC, similar to previous findings (Onton et al., 2005), the purported mediofrontal cluster had a clear spectral θ peak (See Figure 4.19), around 6.5 hz.

The cluster housed 26 ICs representing 16 of our subjects. Following standard procedures (Makeig, Delorme, et al., 2004), the cluster was manually pruned to comprise 20 ICs from 17 subjects (two subjects did not show a clear frontal-midline IC, two had two plausible candidates; one IC was added that automatic clustering had assigned to a different cluster) for the

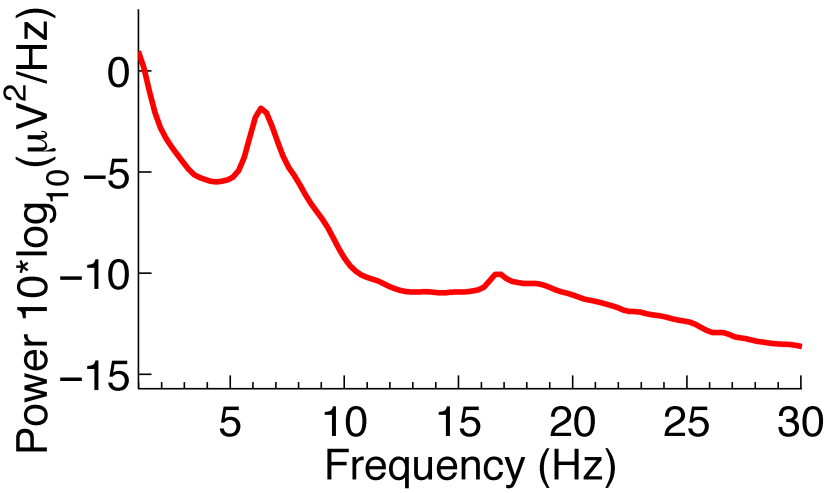

Figure 4.19: Mediofrontal cluster spectrum. Strikingly similar to the frontal midline θ effect in Figure 2.2.

sake of physiologic plausibility.[2] Clustering using the semi-automatic CORRMAP plugin (Viola et al., 2009) netted comparable results.

Importantly, this implies that only 18 of 20 subjects contributed to anterior N200 activity investigation, since only in these could a cluster resembling the previous findings be unambiguously identified; however, other measures (concerning behavioral and N400 data) were calculated on the full data set.

Further clusters were analysed for secondary and exploratory analyses, and will be described independently below.

4.3.3 *Primary outcomes*

4.3.3.1 *Methods and results of confirmatory analyses*

BEHAVIORAL MEASURES Error rates and reaction times to all four stimulus categories were collected and mean reaction times submitted to a 2x2 within-subjects repeated measures ANOVA along the factors "PREDICTABLE" (levels: Yes/No) and "CORRECT" (levels: Yes/No) using the MES Effect Size toolbox (Hentschke & Stüttgen, 2011), and η^2_p was estimated as a standardized measure of effect size. CIs for this measure were estimated from a bootstrapping procedure involving 1000000 permutations. Values for the population parameter of RTs by condition compatible with the data were estimated by the 95% Confidence Intervals per condition. Values for the population parameter of significant group differences were estimated as the 95% CI of mean differences. Since msec are easily relatable, the raw values were estimated instead of standardized effect sizes.

2 While automatic clustering of ICs is a problematic tool, manual selection could induce bias. However, on retrospective exploration, the N200 effect was already present with the fully automatic clustering, so manual pruning did not significantly influence the results.

ERP MEASURES For all 4 conditions, the ERP at the mediofrontal cluster was back-projected to electrode AFZ to capture the anterior N200; then, the raw scalp ERP measured at electrode Pz was collected to investigate N400 effects. This was done because back-projection allows easier cross-subject comparison and solves the problem of IC polarity ambiguity in the case of the ICA data; for the scalp data, using the raw electrode data avoids the problem of having to pick ICs to represent the N400.
As noted, scalp electrode data was artifact corrected by subtracting non-dipolar ICs, but neither data was low pass filtered. Data was baseline corrected using a pre-stimulus baseline from -250 to 0 ms.

The scalp ERP for electrode Pz and the IC cluster ERP for the mediofrontal cluster were subjected to statistical analysis in the N200 time window. Mean amplitude in a window from 150-250 ms after stimulus onset was calculated and a 2x2 within-subjects repeated measures ANOVA along the factors "PREDICTABLE" (levels: Yes/No) and "CORRECT" (levels: Yes/No) was used to investigate the anterior N200 effect, comparing O+, O-, C+ and C- conditions. For the ANOVA, using the MES effect size toolbox (Hentschke & Stüttgen, 2011), η^2_p was estimated for the overall design using 1000000 permutations. Since ERP voltage differences, especially of ICA-derived data, is far from being easily relatable, significant interactions were resolved and the magnitude of the respective condition differences quantified by the same procedure (as a standardized effect size measurement). For pairwise comparisons, Hedges' g (a type of Cohen's d, Cohen, 1992; Hentschke & Stüttgen, 2011) was chosen as the test statistic of choice.
Furthermore, I calculated the Bayes Factor (Dienes, 2008; Rouder et al., 2009) for the contrasts C- vs C+ and O- vs O+. Classical frequentist inferential hypothesis tests are not able to confirm a hypothesis, such as a nil-null hypothesis of no difference, because they compute the probability of data under the hypothesis, p(D | H), not the probability of a hypothesis given the data, p(H | D). Consequently, they may never establish that two observations are in fact identical. In contrast, Bayesian statistics evaluate and contrast the probability of specific hypotheses. Since one critical prediction in this experiment was that there would be no difference in the anterior N2 between open-set mismatches and open-set matches, Bayesian statistics seemed appropriate.
The Bayes Factor was calculated from F statistics using a default Bayes Factor method (Wetzels, Grasman, & Wagenmakers, 2012). A JZS cauchy prior centered on 0, with a width of .5 SD, was employed.

Mean amplitude from 350-450 ms at electrode Pz was subjected to the same procedure to investigate the N400 effect, and the scalp topography of condition differences was plotted for the mean ERP in this time window.

All calculations were also subjected to a non-parametric permutation test with 100000 permutations (as implemented in EEGLAB's *statcond* function).

Stimulus onset-locked, RT-sorted ERPimages as well as response-locked, RT sorted ERPimages (Jung et al., 1999) were calculated for back-projected mediofrontal cluster single trial activity, as well as for the EEG at electrode Pz.

BEHAVIORAL RESULTS Replies to matching and predictable sentences were faster than to mismatching and unpredictable sentences. **Mean** RTs in msec and 95% CIs by condition were Open/Match = 719 < **772** < 826

, Open/Mismatch = 777 < **822** < 867, Closed/Match = 463 < **522** < 581, Closed/Mismatch = 556 < **606** < 656.
Results demonstrated significant main effects for the comparison between predictable and unpredictable sentence contexts ($F(1,19) > 100$, $p < 0.0001$; η^2_p and 95% CI = 0.6 < 0.7 <0.9) and between correct and incorrect sentences ($F(1,19) > 60$, $p = 0.0001$, η^2_p and 95% CI = 0.75 < 0.8 <0.9), but the interaction failed to reach significance ($F(1,9) = 3.56$, $p = 0.07$).
RTs for open-set sentences were slower than for closed sentences by 198 < **233** < 268 msec (mean and 95% CIs of mean). Matches were responded to faster by 85 < **67** < 47 msec.

ERP RESULTS The mediofrontal cluster did not show a difference between open-set congruent and incongruent items. However, closed-set mismatches were significantly more negative than closed-set matches. This claim is based on the outcome of the ANOVA on the anterior N2.

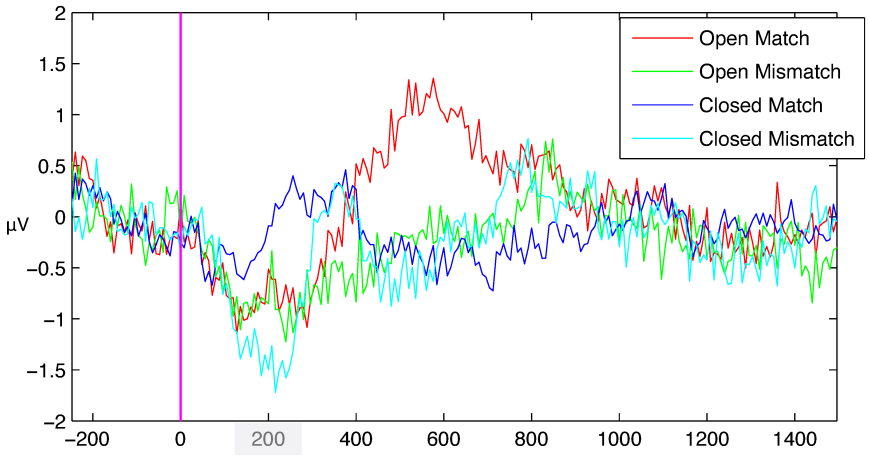

Figure 4.20: ERP of mediofrontal cluster back-projected to AFz by condition. In grey: time window of N2.

For the mean ERP in the N2 window from the mediofrontal cluster (see Figure 4.20), open and closed-set sentences did not differ reliably ($F(1,16) = 0.08$, $p > 0.5$, η^2_p and 95% CI = 0 < **0** < 0.3). In contrast, a statistical difference between matching and mismatching sentences was found ($F(1,17) = 9$, $p = 0.008$, η^2 and 95% CI = 0.17 < **0.36** < 0.64). However, it was driven by a highly significant interaction between the factors ($F(1,17) = 8.7$, $p = 0.008$, $\eta^2 = 0.02$ < **0.3** < 0.67).

Investigating the nature of the interaction, open-set matching and mismatching sentences (O+ vs O-) did not show a statistical difference ($F(1,17) = 0.3$, $p = 0.58$, $\eta^2_p = 0$ < **0.02** < 0.28). In contrast, mismatches from the closed sets (C-) had significantly lower mean amplitudes than closed-set matches (C+) had ($F(1,17) = 13.1147$, $p = 0.0023$, η^2_p and 95% CI = 0.24 < **0.45** < 0.67).
The permutation test confirm a significant main effect for "PREDICTABLE" ($p < 0.01$), a significant interaction ($p < 0.01$) and a significantly lower amplitude for predictable, incorrect/C- compared to predictable, correct/C+ trials ($p < 0.001$).
These results are also presented in table form below.

Test	Measure	95% CI lower	Effect size	95% CI upper	Test statistic	p
O/C	η^2_p	0	0	.30	$F(1,16)<.1$	.77
+/-		.17	**.36**	.64	$F(1,16)=9$	<.01
Interaction		.03	**.30**	.67	$F(1,16)=6.7$	.01
Closed (+/-)	g	.70	**1.20**	1.80	$t(16)=3.6$	.002
Open (+/-)		-.34	.15	.77	$t(16)=.55$	>.5

Table 4.2: Results mediofrontal ERP Study 2

The Bayes factor favoured the H_0 of no difference over H_1 when comparing alternative sets (BF 0 over 1: 3.65), and strongly favoured H_1 over H_0 when comparing closed sets (BF 1 over 0: 25).
Importantly, these measurements estimated that the difference between closed match (C+) and closed mismatch (C-) sentences, visible as an N2 in the plots, is reliably large, with even the *lower* bound of the effect size estimate indicating a strong effect, and the main estimate of η^2_p = 0.45 indicating that almost half of the variance in the N2 was explained by the experimental manipulation.
Furthermore, while the evidence for this must be considered only moderately strong (with BF > 3 usually being considered adequate), possibly due to the low number of data points, the Bayes Factor indicates that there is no reliable difference between open matches and mismatches in the MFC N2.
The combined results of the Bayes Factor analyses of the mediofrontal ERP for studies 1 and 2 are presented in table form below.

Study	Test	Difference?	Bayes Factor
1	antonyms vs. non-antonyms	Yes	>1000
	related vs. non-related non-antonyms	No	4.3
2	closed match vs. closed mismatch	Yes	25
	open match vs. open mismatch	No	3.65

Table 4.3: Bayes Factor for the hypothesis that the anterior N2 is equal (H_0) or unequal (H_1)

In contrast, the N400 was stronger for open-set items and for closed-set incongruent items than for closed-set congruent items.
Representing the N400, at electrode Pz (See Figure 4.21), a main effect for both factors was observed (PREDICTABLE: F(1,19) = 59, p < 0.0001, η^2_p and

CIs = 0.62 < **0.76** < 0.88; CORRECT: F(1,19) = 38, p < 0.0001, η^2_p = 0.46 < **0.67** < 0.85), as well as a significant interaction (F(1,19) = 9, p = 0.005, η^2_p = 0.1 < **0.33** < 0.63), with the ERP more negative for open-set/"O" than for closed-set/"C" trials, and for mismatch/"-" than for match/"+" trials. The N400 effect showed a typical centro-parietal localisation (See 4.22). These results are also summarized in table form below.

Test	Measure	95% CI lower	Effect size	95% CI upper	Test statistic	p
O/C	η^2_p	.62	**.76**	.88	F(1,19)=60	<.001
+/-		.46	**.67**	.85	F(1,19)=38	<.001
Interaction		.10	**.33**	.63	F(1,19)=9.5	.006
Closed (+/-)	g	.80	**1.37**	2.10	t(19)=5	<.001
Open (+/-)		.25	**.50**	.89	t(19)=3.5	.02

Table 4.4: Results N400 Study 2

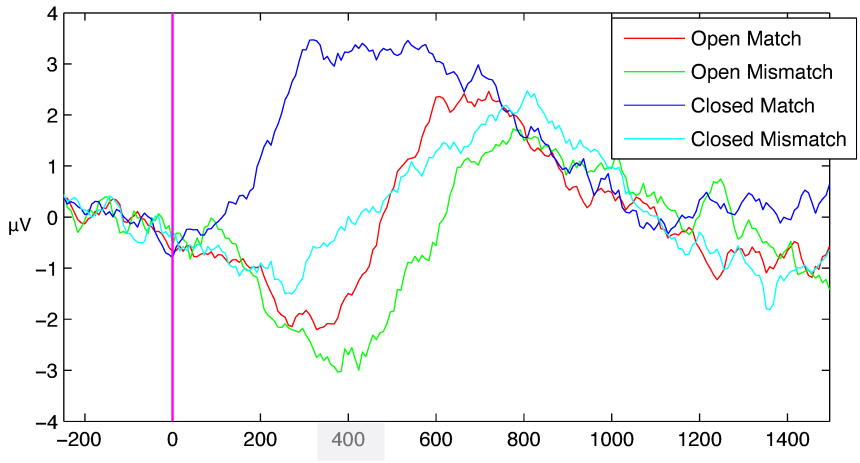

Figure 4.21: ERP at Pz by condition. Grey highlight: time window of N400.

In the ERPimages, the N200 effect appears as a straight, vertical blue line, following the single-trial stimulus onset with a fixed latency, and not varying in latency with single-trial response latency, indicating a stimulus-locked, not response-locked effect (See Figure 4.23).

In contrast, ERPimages of Pz data revealed a stimulus-locked N400 effect and a response-locked late positivity (See Figure 4.36).

4.3.3.2 *Interim discussion*

As predicted, the mediofrontal cortex differentiated between closed-set congruent and incongruent, or predicted and prediction-violation words, with an N200, but not between open-set congruent and incongruent words.

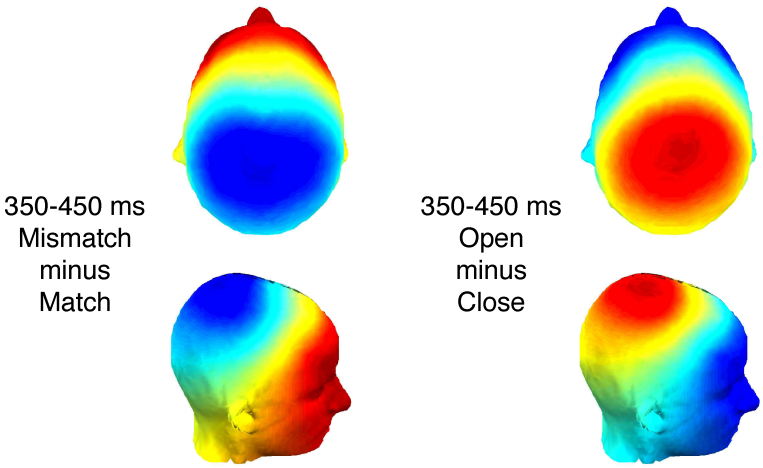

Figure 4.22: Topography of N400 differences.

Specifically, the obtained Bayes Factors indicated that the data strongly favoured a difference in the anterior N2 for closed-set mismatches, and moderately supported the equivalence of the N2 for open-set mismatches with open-set matches.
The later N400 effect showed the expected gradient sensitivity.
Furthermore, the anterior N2 was stimulus-, not response-locked. The N400 was stimulus-, the P600 response-locked.

4.3.4 *Secondary and exploratory analyses*

As in the first study, a range of further patterns in the data became of interest for the question of nonspecific, task-related influences on the ERP during sentence processing. Some of these concerned secondary predictions following the first study. Others concerned specific questions emerging from observations in this study.

After the clustering process, it became clear that two clusters strongly resembled the left and right-anterior clusters observed in the previous study (See Figure 4.25). These clusters were further investigated to explore if the previous hypothesis of these clusters as reflecting specific motor inhibition and disinhibition could be confirmed.

Two midline clusters were found (See Figure 4.24), of which one cluster resembled the P3f cluster reported previously (Delorme et al., 2007; Makeig, Delorme, et al., 2004), and one exhibited a topography that has commonly become associated with the ERN (Debener, Ullsperger, et al., 2005). Both of these clusters were compatible with a location in the cingulate cortex (roughly corresponding to the sACC and pACC/pMCC and SMA). These clusters were therefore subjected to further analyses, both of an exploratory as well as confirmatory nature. The main questions were if previous task-specific effects could be replicated; if they would behave consistently with the entailments of the LC/NE-P3 hypothesis; and if any further specification of the mediofrontal cluster might emerge from comparison with the central cluster.

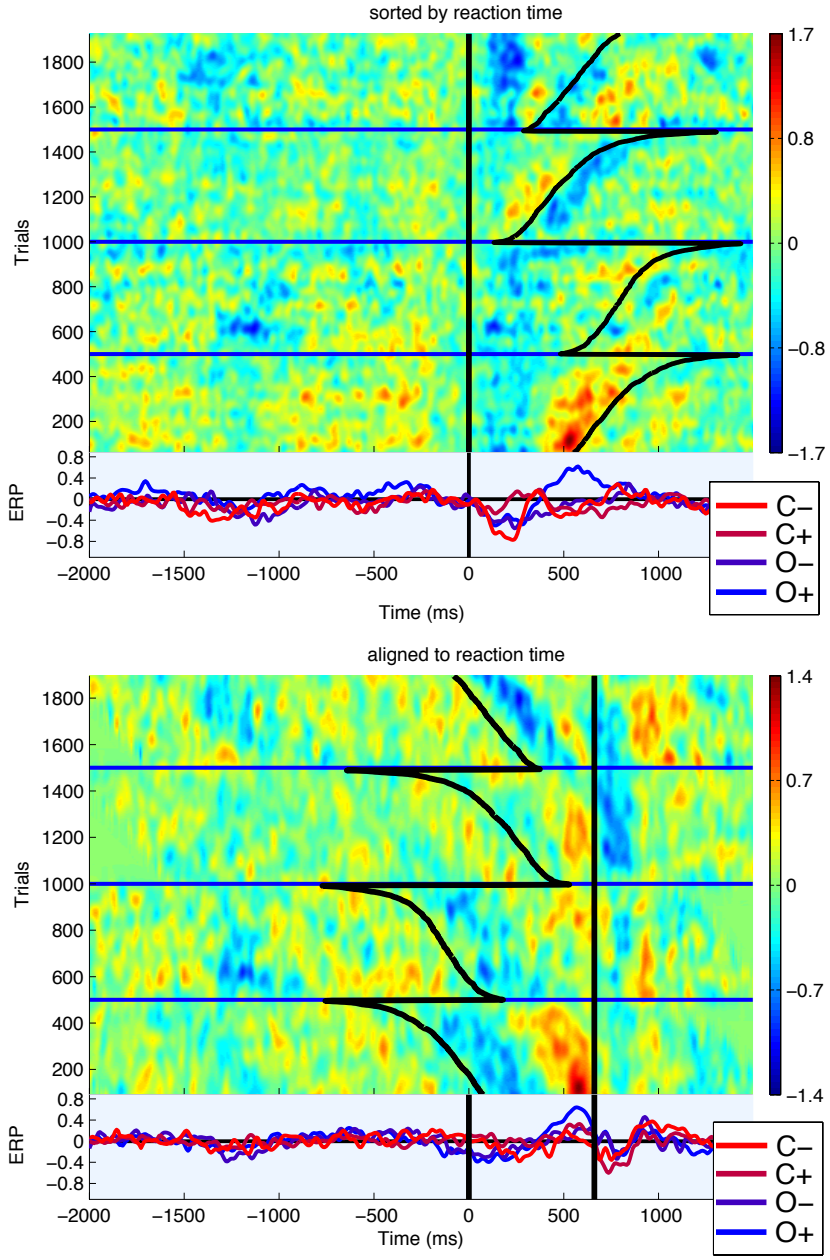

Figure 4.23: ERPimages of mediofrontal cluster back-projected to electrode Fz, split by condition, sorted by RT. Top: aligned to word onset. Bottom: aligned to response. At the bottom of ERPimages, the respective ERP is shown.

In contrast to the mediofrontal cluster already investigated in detail, neither of these clusters demonstrated a spectral peak in the θ range.

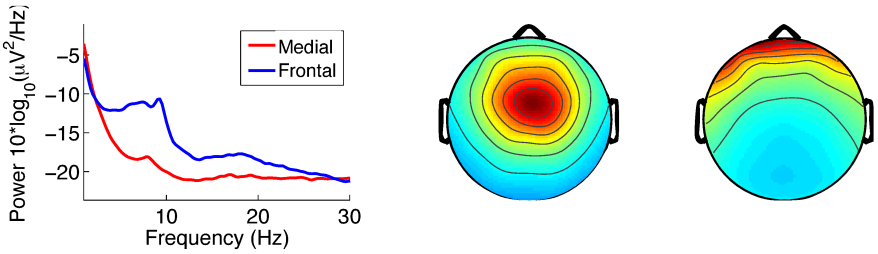

Figure 4.24: Scalp maps and mean spectrum of midline clusters. Left topography: central midline cluster. Right; far-frontal cluster.

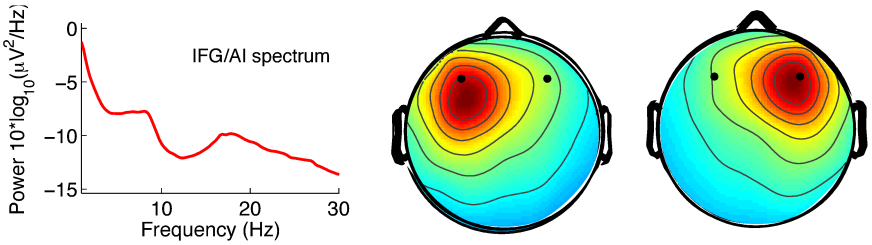

Figure 4.25: Scalp maps and mean spectrum of left- and right-frontal clusters. Since data for both clusters was concatenated, only one spectrum from the concatenated data was calculated.

4.3.4.1 *Right/left frontal clusters*

RESEARCH QUESTIONS/HYPOTHESES In the previous study, it had been tentatively hypothesised that two right- and left-frontal clusters represent lateralized motor control, projecting a scalp-positive ERP during inhibition of associated movements, and a scalp-negative ERP during disinhibition.

In this study, half of the subjects had to respond with the left, half with the right hand to incongruent words; the respective other hand was assigned to indicate congruent sentences. Presumably, in such a two-choice task, subjects first initiate a general response process and then select the specific response. I expected that the hemisphere ipsilateral to the eventually executed button press would show a positivity, indicating inhibition of this hemisphere's motor targets. Conversely, the hemisphere contralateral to the button press should show a negativity, indicating disinhibition.

METHODS Cluster mean dipoles were calculated as before.

Correctly answered trials were concatenated into two main categories with several subdivisions. Right-frontal cluster activity of subjects with right=congruent assignment when the left button was pressed (right, contralateral, congruent), their left-cluster activity during right button presses (left-contralateral, incongruent), as well as activity of right-frontal clusters of left=congruent assignment subjects during left button presses (right-contralateral, congruent) and their left-frontal activity during right

button presses (left-contralateral, incongruent) were pooled as contralateral activity trials. Right-frontal cluster activity during right button presses of left-congruent and right-congruent assignment subjects (right-ipsilateral, incongruent; right-ipsilateral, congruent) and left-frontal activity during left button presses for left-congruent and right-congruent assignments (left-ipsilateral, congruent; left-ipsilateral, incongruent) were pooled as ipsilateral activity trials.

This established a 2x2x2 design with the factors in/congrunent X ipsi/contra X left/right. ERPs were calculated for all 8 conditions by back-projecting cluster mean activity to electrodes F3 and F4 (for left- and right-frontal clusters, respectively). An unpaired ANOVA (due to uneven number of subjects per cluster) was applied to the mean ERP in an 80 msec window centered at the cluster ERP peak.

Then, ERPimages were calculated concatenating trials into two conditions, cluster activity ipsilateral and contralateral to button press, and sorted by RT and time-locked either to response or to stimulus onset.

The same measures were repeated for electrodes F3 and F4 in place of back-projected cluster activity.

In a further exploratory, hypothesis-free analysis, a time-frequency decomposition comparing ipsi- to contralateral activity was computed. For this, concatenated single trials were subjected to wavelet analysis, extracting 65 frequencies evenly distributed from 0.35 to 30 hz, in a window from -4500 msec before to 2500 msec after stimulus, with one wavelet cycle at the floor frequency, increasing by 50% with every frequency step. Event-related spectral perturbations (Makeig, 1993) were calculated by subtracting the single-trial spectral mean across the whole epoch from every individual time point, and phase-locking index was calculated as the consistency of phase per time/frequency point across trials (Tallon-Baudry, Bertrand, Delpuech, & Pernier, 1996). Then, for both measures, the difference between these two values was computed.

RESULTS 18/17 subjects contributed 24/30 to the left-frontal and right-frontal clusters. The mean dipole Talairach coordinates were X = -28, Y = 18, Z = 21, for the LF and X = 32, Y = 28, Z = 17 for the RF cluster. These coordinates locate the clusters close to the inferior or middle frontal gyri, but also the insulae (See Figure 4.26).

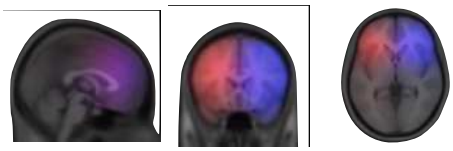

Figure 4.26: Dipole density estimates for the left and right-frontal clusters projected onto the MNI standard brain.

The ANOVA showed a main effect of "contra/ipsilateral"; the IC mean ERP amplitude (see Figure 4.27) at sites contralateral to button press were more negative than for sites ipsilateral to button press ($F(1,63) = 4$, $p < 0.049$; post-hoc unpaired, two-tailed t-test comparing the mean of all ipsilateral with the mean of all contralateral trials: t (34), $p = 0.001$, 95% CI: -3.19, -0.94).

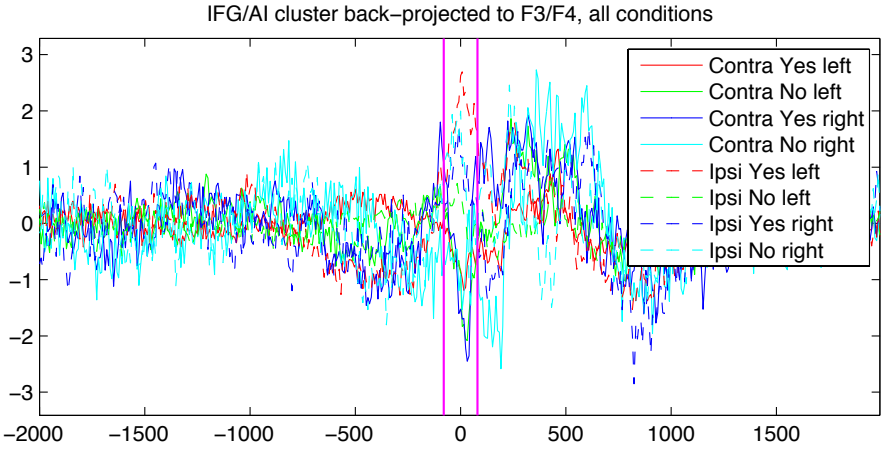

Figure 4.27: ERP for the left and right-frontal clusters back-projected to electrodes F3 and F4, all conditions.

The 3-way interaction approached significance ($p < 0.08$), but no other comparison was indicated to hold a noticeable effect (all $p > 0.2$). The ERP showed a sharp positive peak around button press for ipsilateral activity, and a following negative peak for contralateral activity; both peaks were followed by a slower, broader positive wave. All these effect appeared strictly response-locked in ERPimages (see Figure 4.28).

For scalp electrode data, the ERP was also more negative for contralateral than for ipsilateral activity, but not significantly so ($p > 0.1$ for all main effects and interactions). For both conditions, the ERP was dominated by a CRN-like negative peak right after response execution (See Figure 4.29).

The transient negative dip at ipsilateral sites was also weakly apparent in stimulus-locked ERPimages (data not shown).

Time-frequency decomposition (See Figure 4.30) was dominated by a pattern of β desynchronization before and synchronization after stimulus execution that did not differentiate between conditions. Response execution was also, for both conditions, preceded by evoked θ activity (power increase and phase locking) and a small amount of α ERD. No reliable differences in higher frequency bands during response execution could be observed.

INTERIM DISCUSSION Unlike scalp electrodes, IC cluster activity, congruent with apriori hypotheses, strongly differentiated between ipsilateral and contralateral activity. When movement execution occurred contralateral to the cluster, cluster activity showed a sharp, response-locked negative peak, which had been predicted to mark motor disinhibition. At ipsilateral sites, a slightly earlier positive peak was found, compatible with inhibition of the incorrect response shortly before execution of the correct response.

Such spatially distinct lateralization of response control-related processes is not unexpected, but so far undocumented. In the present data sets, it was only made visible via ICA decomposition and automatic clustering.

Surprisingly, conditions did not differ in the time-frequency domain, indicating that either β-band ERD/ERS is a broad and diffuse process affecting multiple sites simultaneously, or that superficially similar β activity marks both inhibition and disinhibition.

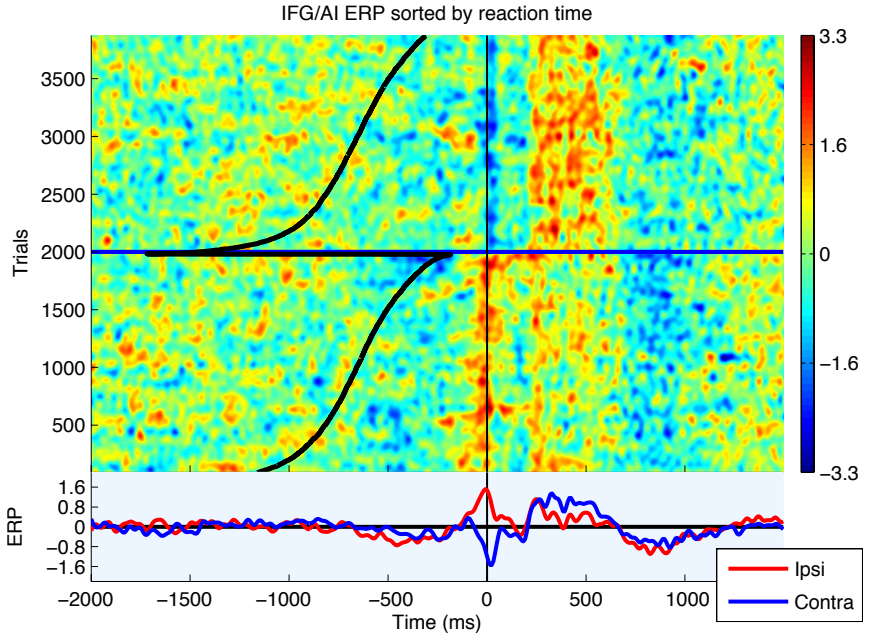

Figure 4.28: ERPimage for the left and right-frontal clusters back-projected to electrodes F3 and F4, all ipsilateral (contra) and contralateral (top) conditions combined. Bottom: ERP for ipsi- (red) vs. contralateral (blue) activity.

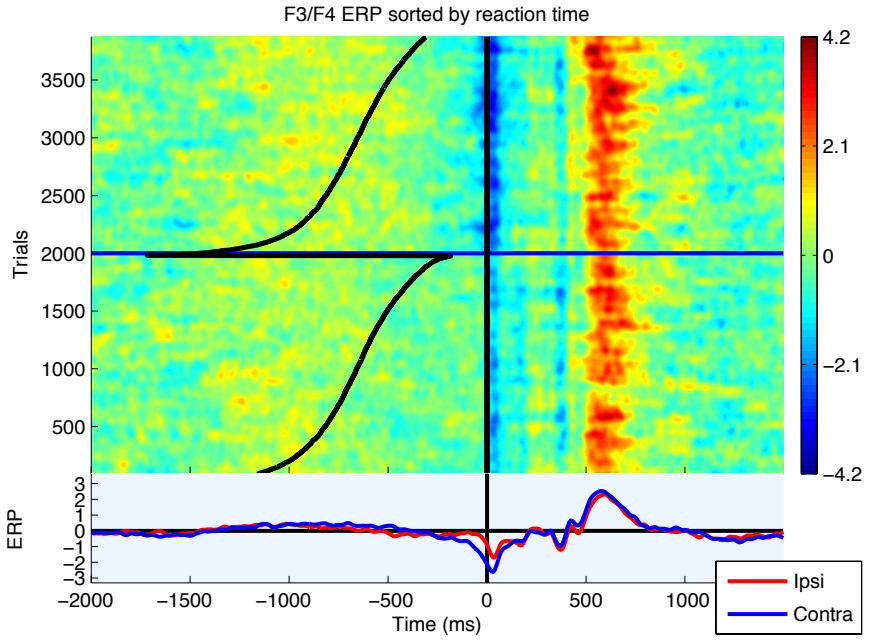

Figure 4.29: ERPimage for the left and right-frontal electrodes F3 and F4, all ipsilateral (contra) and contralateral (top) conditions combined. Bottom: ERP for ipsi- (red) vs. contralateral (blue) activity.

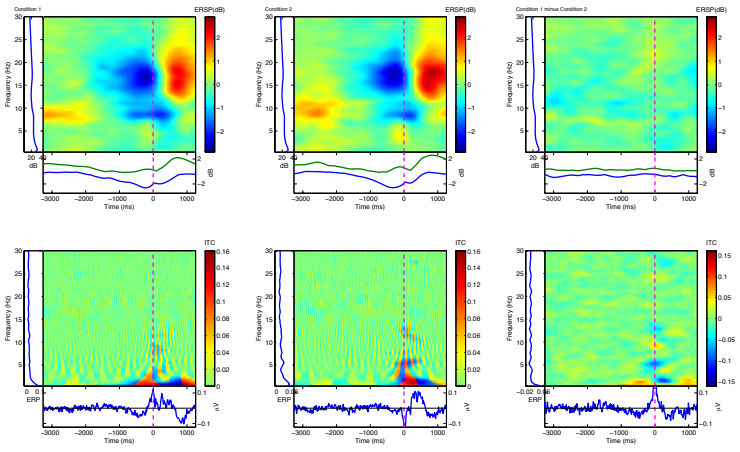

Figure 4.30: Time-frequency decomposition for ipsilateral (left) and contralateral (middle) activity of the lateral-frontal clusters, back-projected to F3/F4, and their difference (right). Top: ERSP. Bottom: ITC, including phase (left and middle), color-coded so that red marks coherently positive, blue coherently negative phase. Time series under time-frequency plots showing time course of maximal frequency, spectra to the right of time-frequency plots showing spectrum.

4.3.4.2 *Centro-medial and far-frontal clusters*

RESEARCH QUESTIONS/HYPOTHESES The anterior N2 cluster resembled previous findings (Onton et al., 2005) in the EEG/ICA-based literature in multiple regards. It shows a fronto-medial topography, a spectral peak in the θ range (6 hz), and its mean dipole was found in the dorsal anterior cingulate cortex. However, another, more centro-medial cluster has also been associated with the cingulate cortex, especially the rostral cingulate zone (Debener, Ullsperger, et al., 2005). Possibly, these two ICs could be functionally identical, with MCC activity reflecting either in a fronto-medial or a centro-medial topography. Alternatively, these two qualitatively different IC types could reflect different subdivisions of the cingulate cortex (pACC/aMCC/...); or one could reflect the mediofrontal cortex, the other a related brain area. And especially intuitive explanation would be that a more posterior topography closer to the motor cortices and the SMA reflects response conflict, whereas more anterior topographies reflect aMCC/pACC activity associated more with stimulus conflict. However, this intuitive analysis would have to be confirmed with more anatomically reliable measures.

In the present study, the incongruence/expectation violation - related N2 had been demonstrated at the fronto-medial, θ-peak cluster. However, in RT-sorted and RT-locked ERPimages, no CRN-like component could be observed. The CRN is typically, if it is observed, found at the same ICs as the ERN (Hoffmann & Falkenstein, 2010; Wessel et al., 2012), with a centro-medial distribution like the present centro-medial cluster.

Investigating the typical properties of the ERN-generating system could help integrate the observed anterior N2 finding into the larger research programme into the nature of the frontal control circuits.

A number of aspects of the CRN-exhibiting cluster are relevant; it should show a larger response-locked negative peak on error than on correct trials, and the magnitude of this ERN might correlate with post-error slowing (Overbeek et al., 2005; Wessel et al., 2011).

Also, in the previous study, various P3a-like components were observed at frontal-midline ICs, with varying latencies.

Furthermore, the far-frontal component cluster resembling the previously reported P3f (Delorme et al., 2007; Makeig, Delorme, et al., 2004) allows a testing ground for the proposal that if the LC/NE system causes the P3, the different conduction delays of frontal and parietal projections of the LC should result in earlier P3 peaks at frontal than at parietal sites.

Consequently, the respective timing and temporal alignment of negative and positive components were to be visualized.

METHODS Dipoles of centro-medial and far-frontal cluster ICs were computed and dipole density plots constructed.

Correctly answered open-set congruent, incongruent, closed-set congruent and incongruent, as well incorrectly answered trials were plotted in RT-sorted and stimulus-or RT-aligned ERPimages for centro-medial cluster ICs after back-projection to electrode FCz, where the ERN is maximal.

RT-sorted ERPimages were calculated for the back-projection of the P3f cluster to the right suborbital electrode. Furthermore, to compare P3f activity to the centro-parietal P3b, the mean ERP for electrode Pz was calculated after the removal of artifactual ICs.

Post-error slowing was calculated by subtracting, for every trial, the RT on trial n+1 from the RT on trial n. It was then correlated with single-trial ERN amplitude as the mean ERP in a 25 ms window centered around the negative peak for the centro-medial IC.

Since all of these explorations can be considered fully explorative, inferential statistics would be of little value. Consequently, results will be provided descriptively, qualitatively, and statistical analyses were restricted to effect sizes.

RESULTS The centro-medial and far-frontal clusters represented 17 and 18 out of 20 subjects, with 20 and 30 ICs, respectively. Mean estimated dipoles (See Figure 4.31) of the centro-medial cluster were compatible with a location in the rostral cingulate zone, and the source of the P3f cluster was found in the ventral prefrontal cortex, possibly the ventral anterior cingulate cortex or the orbitofrontal cortex.

The response-locked ERP of the centro-medial cluster (See Figure 4.32) demonstrated a sharp negative peak that was more negative for incongruent than for congruent trials (t = 2.2, 95% CI: 0.0690, 0.8346 µV), and more negative for incorrectly than for correctly answered trials (t = 1.7, 95% CI = 0.0065, 1.5174 µV). The low statistical validity of the ERN effect is likely attributable to the low number of total errors committed.

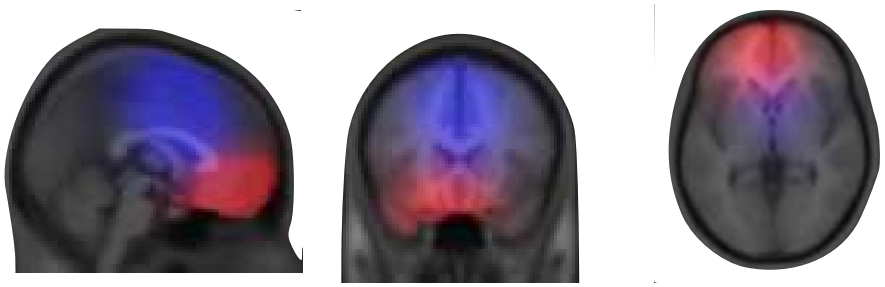

Figure 4.31: Dipole density estimates for the far-frontal (red) and centro-medial (blue) cluster projected onto the MNI standard brain.

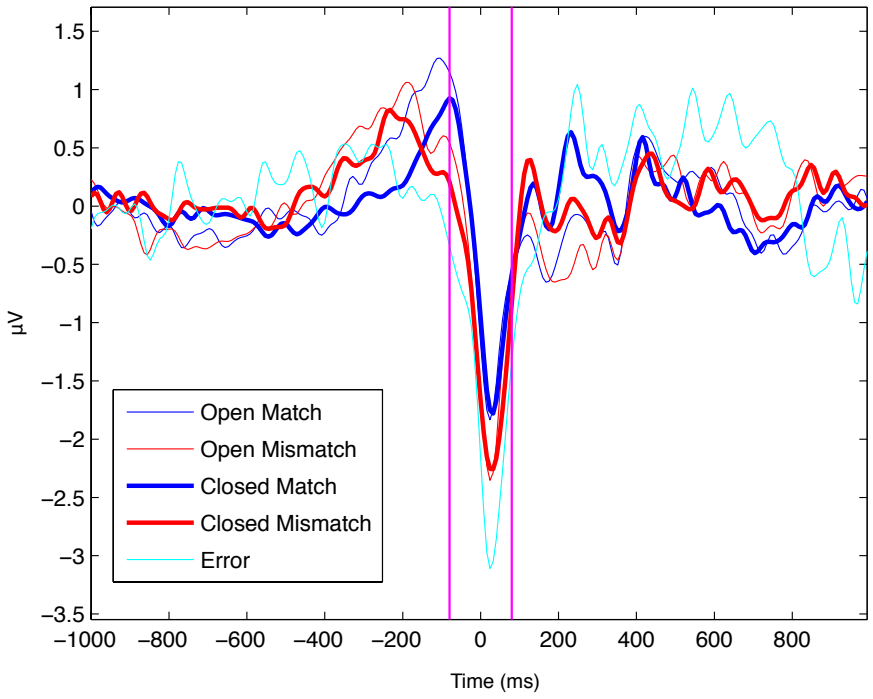

Figure 4.32: Response-locked ERP for the central-midline cluster back-projected to FCz.

Post-error slowing showed weak, but significant *positive* correlation with IC cluster amplitude in the ERN window (95% CI for skipped Pearson's r = 0.0407 < 0.2386), but the EEG at electrode FCz (-0.2867 < 0.0625) did not. Since only a low number of 161 artifact-free error trials were available, this value may not be reliable. Furthermore, the present paradigm featured substantially longer inter-event times, and substantially more complex stimuli, than typical for paradigms measuring PES. Consequently, the present investigation regarding the ERN must not be overestimated.

In ERPimages of the centro-medial cluster (See Figures 4.33 and 4.34), a positivity was visible for all four conditions, but appeared neither strictly response- nor stimulus-locked. Instead, it showed per-condition RT alignment, peaking later for the slow open- than for the fast closed-set trials, but within conditions, it appeared stimulus-locked. Furthermore, this positivity did not show temporal alignment with neither the P3f nor the positive peak at electrode Pz. In contrast, the response-locked negativity (CRN/ERN) is visible as a strictly RT-locked in both images.

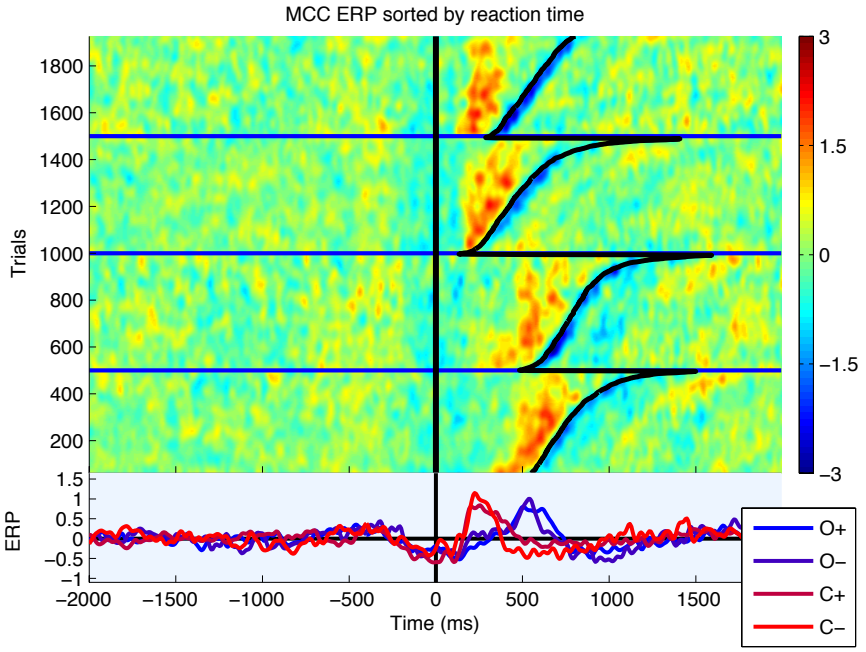

Figure 4.33: ERPimage of RT-sorted trials for the central-midline cluster back-projected to FCz, concatenated for all subjects, split by condition.

P3f ERPimages (See Figure 4.35 demonstrated a response-locked low-frequency pre-response positivity. It reliably peaked before the P3 at electrode Pz. In contrast, the positivity at Pz was strictly response-locked (See Figure 4.36).

INTERIM DISCUSSION The P3f cluster exhibits behavior congruent with that previously observed (Delorme et al., 2007; Makeig, Delorme, et al., 2004). Its response-locked positivity (P3f) reliably precedes the centro-parietal positivity (P3b). In this, it was compatible with an entailment of the LC/NE-P3 theory - that due to conductance delay, frontal areas, innervated

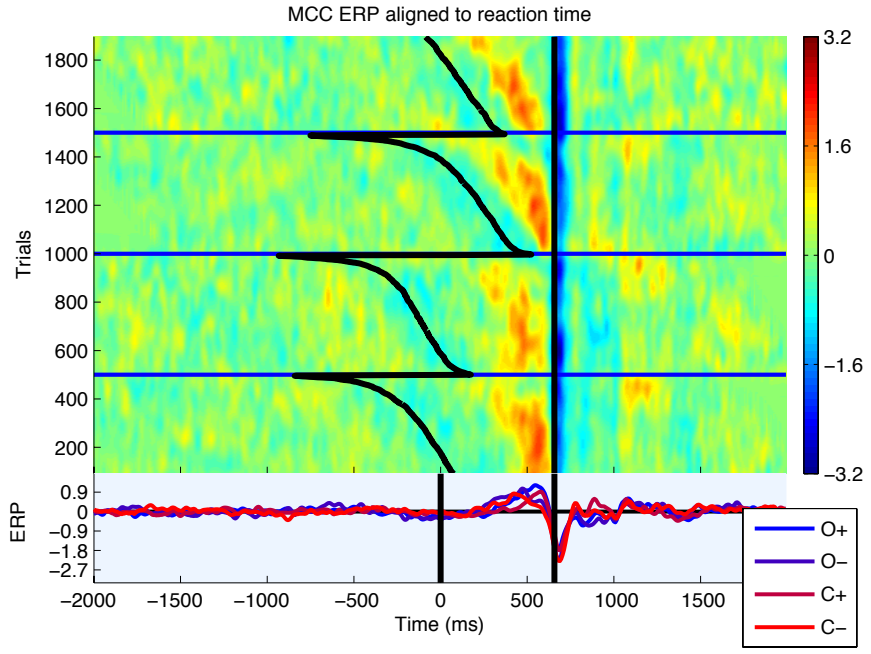

Figure 4.34: ERPimage of RT-sorted trials for the central-midline cluster back-projected to FCz, concatenated for all subjects, split by condition, aligned to RT.

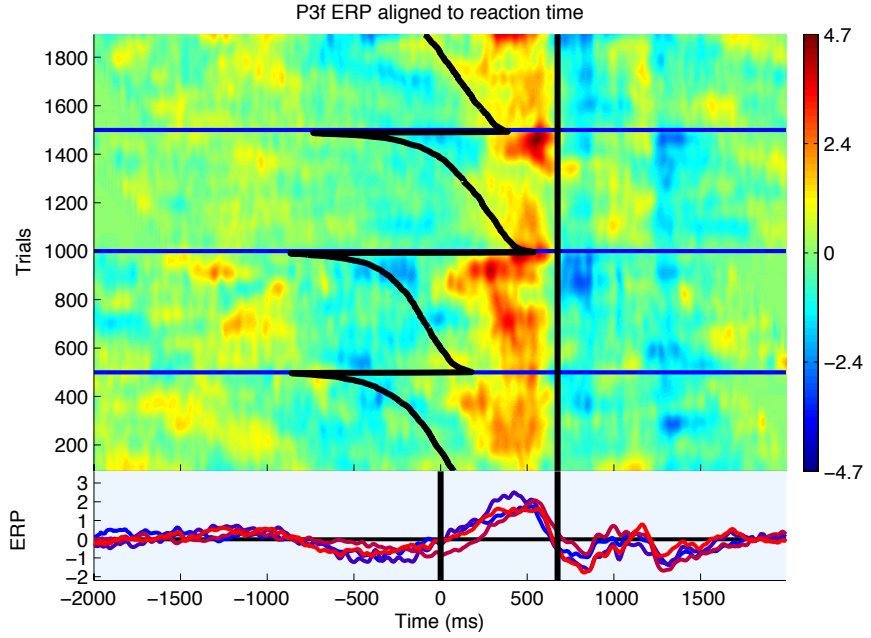

Figure 4.35: ERPimage of RT-sorted trials of the P3f cluster back-projected to an infraorbital electrode, concatenated for all subjects, split by condition, aligned to RT.

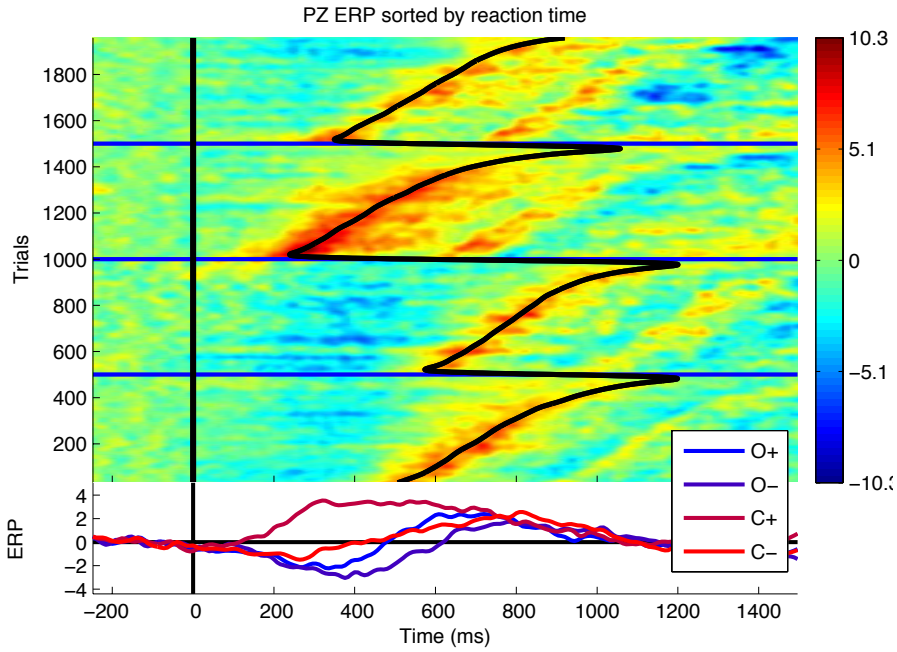

Figure 4.36: ERPimage of RT-sorted trials at electrode Pz, concatenated for all subjects, split by condition.

by shorted connections, should become affected by phasic NE before more posterior sites.

The centro-medial cluster demonstrated the CRN and ERN expected for a cluster representing the rostral cingulate zone. It did not contribute an incongruence N2. Furthermore, it projected a positive ERP component that varied in latency with condition, but was not aligned with RT in single trials. It is congruent with both source localisation and function that this IC cluster represents a different aspect of the medio-frontal conflict-sensitive network than the anterior cluster. In its topography, it resembles IC clusters often reported to show ERN effects in many studies (Debener, Ullsperger, et al., 2005; Gentsch et al., 2009). Potentially, this cluster reflects conflict-related activity in motor-associated areas, such as response conflict and response errors. The more frontal area could then reflect different kinds of conflict, such as stimulus conflict. However, some studies have reported an ERN with similar topographies (Mueller et al., 2011)[3] or overlap between stimulus and response conflict (Wessel et al., 2012).

The finding of two task-sensitive positive components with differential temporal alignment is surprising and potentially partially at odds with the LC/NE-P3 model. Depending on how exactly the model is understood, the effect of NE should influence the cortex not necessarily at the same time in every brain area, but with stable latencies between brain areas within subjects. However, it has been observed before that e.g. in inter-subject analyses, where P3b is strongly correlated to RT (Conroy & Polich, 2007), P3a covaries only weakly or not at all with RT.

3 In the data described by Mueller et al. (2011), in addition to the mediofrontal ERN cluster, a second, more posterior, centro-medial cluster was observed that also demonstrated response conflict sensitivity (Erik Mueller, p.c.). However, in this cluster, no interaction was observed for the pharmacological intervention/genotype, possibly indicating less importance of DA signals at this site.

A variety of post-hoc interpretations are compatible with this finding. The positivity at this location, possibly reflecting the rostral cingulate zone, might be influenced not primarily by the LC/NE system, but by another neuromodulator system, such as the DA system, or might not depend on neuromodulator systems at all. Alternatively, Nieuwenhuis et al. (2005) have proposed that the timing of the scalp ERP effect depends not only on the arrival of LC/NE at the cortex, but also on the brain processes that NE facilitates. Potentially, NE might facilitate brain processes with independent within-trial temporal alignment - a weaker, less constraining, but possibly physiologically required hypothesis.

4.3.4.3 *Time-frequency analysis*

Oscillatory components have been primary indices of attentional effects since the discovery of the EEG. Due to the availability of response timing during sentence processing, the temporal characteristics and relationship to ERP components of oscillatory activity for this data set were explored to investigate their nature.

METHODS Finally, a time-frequency decomposition was conducted. First, for each subject, trials from all conditions were concatenated and, for each channel, individually subjected to wavelet decomposition (epochs centered on RT, with a 4 sec pre to 2 sec post RT window; 1 wavelet cycle at the lowest frequency, increasing by 50% for every frequency step; 120 evenly spaced frequencies between 0.5 and 30 hz; ERSP computed relative to a whole-epoch baseline; ERSP time-warped to the mean of subject RT). The ERSP data was normalized to individual subject reaction times by time-warping each ERSP image to the mean RT. For this procedure, the "timewarp" parameter of the "newtimef.m" function of EEGLAB was used, which interpolates and stretches/squeezes the ERSP between two alignment points to correspond to a fixed length.

Furthermore, the time course of α and β ERS/ERD was investigated estimating α and β band ERSP and sorting trials by response, separately per condition, and plotting the result as ERPimages.

AAMM Then, in order to test the proposal that low-frequency components of the ERP may be related to amplitude modulations of asymmetric α oscillations (Mazaheri & Picton, 2004) noted in the prior discussion of alternative oscillatory models, ERPimages were sorted by the degree of α oscillation asymmetry using methods described previously (Mazaheri & Jensen, 2008)[4]. Data were band-pass filtered around the α frequency (8-12 hz), time points of local maxima and minima were extracted, and the coordinates used to look up the magnitude of the respective peaks in unfiltered data. The sum of all maxima and minima was used as the amplitude asymmetry for a given trial.

RESULTS All-channel time-frequency decomposition (See Figure 4.37) indicated three main features. An evoked peak of θ activity with a dual, frontomedial and bilateral parietal topography was found; concurrently, β ERD time-locked to response execution, followed by β ERS was found with a

4 Ali Mazaheri kindly agreed to sharing his scripts for the estimation of AAMM.

maximum bilaterally over motor cortices; and α ERD preceded, α ERS followed response execution.

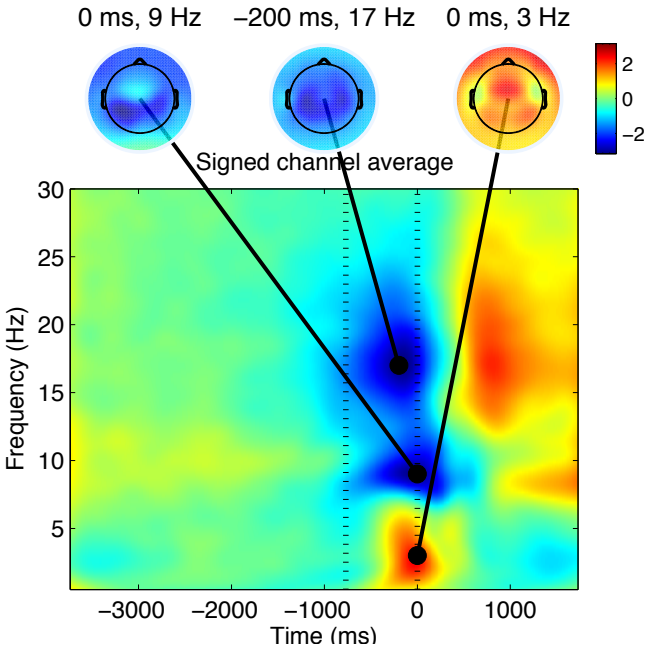

Figure 4.37: Time-Frequency decomposition averaged over all trials. Color denotes change from baseline in dB. Topographic maps of time-frequency features were selected manually; imaged is the (spatially smoothed) ERSP per channel at the highlighted time/frequency point. The left vertical dotted line displays the mean onset of critical words, the right dotted line indicates RT.

ERPimages (See Figures 4.38 and 4.39) demonstrated that α and β ERD lasted only right after RT, quickly synchronizing again after the execution of the motor response had been completed, and before feedback presentation.

AAMM In response-locked, asymmetry-sorted single trials, amplitude asymmetry was estimated in three time windows: pre-stimulus, post stimulus and across the whole window. In neither analysis was the magnitude of the response-locked positivity at Pz substantially affected (See figure 4.40). The present data do not support an association of AAMM and the P3.

4.3.5 *Discussion*

The present investigation of the spatiotemporal dynamics of brain activity during a sentence judgement task has replicated previous findings from simpler paradigms, such as the ERN/CRN, a late, response-locked positivity; and those from prior neurolinguistic research, such as a graded N400 sensitive to conceptual expectability, and a task-sensitive P600 to deviations.

The main finding concerns the anterior N2. As predicted, an anterior N2 was found only when a specific prediction could be made, but this prediction was violated. This finding confirmed the prediction formulated based on the

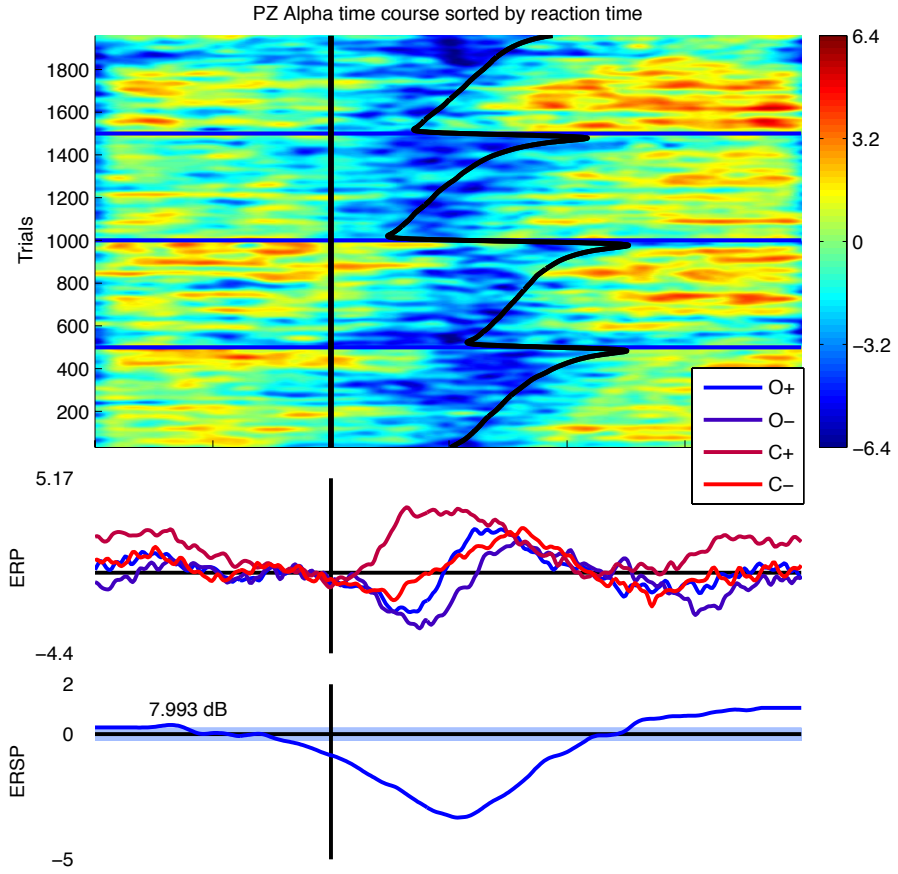

Figure 4.38: Top: plot of single-trial α ERSP sorted by reaction time, split by condition. Middle: ERP split by condition, base-lined from -250 to 0 msec before stimulus onset. Bottom: α ERSP time course.

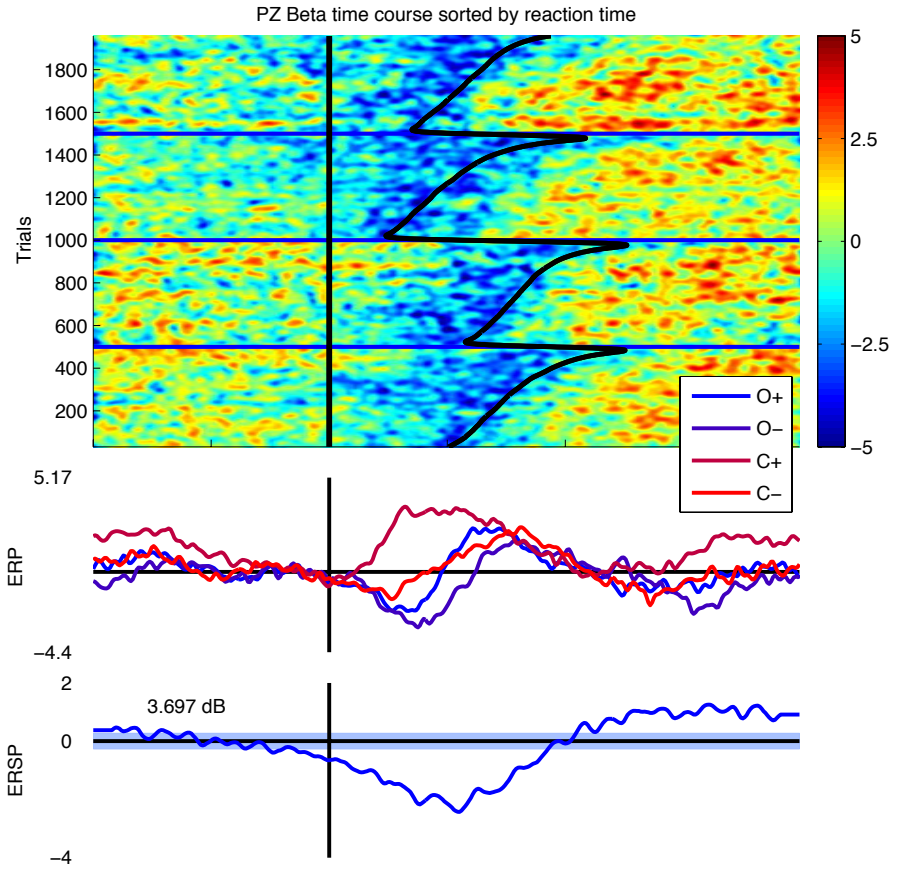

Figure 4.39: Top: plot of single-trial α ERSP sorted by reaction time, split by condition. Middle: ERP split by condition, base-lined from -250 to 0 msec before stimulus onset. Bottom: α ERSP time course.

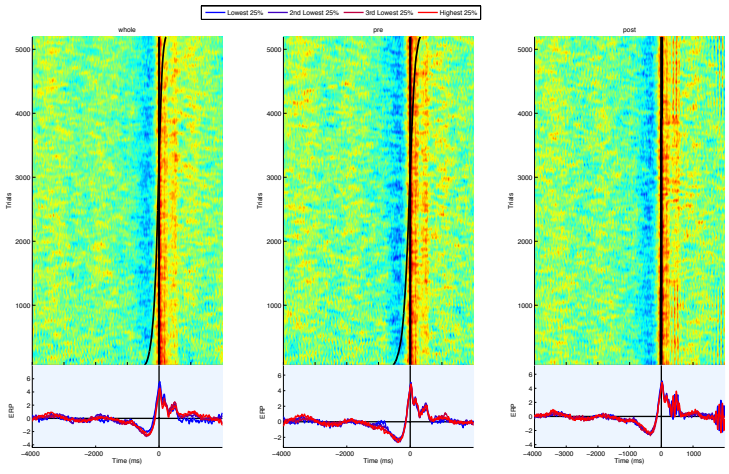

Figure 4.40: ERPimages, sorted by pre-stimulus (middle), post-stimulus (right) and whole-window α asymmetry. Bottom: ERP for 4 bins of the highest, lowest and intermediate degrees of AA.

previous study, where it was hypothesised that the mediofrontal cortex was sensitive to incongruences between one input stream and a highly focused set of specific representations.

However, the brain system sensitive to specific prediction violation was distinct (as separated by ICA) from the action control system projecting ERN/CRN activity. Empirically, this finding superficially conflicts with careful and methodologically well-reasoned reports regarding the identity between error- and novelty-related IC clusters (Wessel et al., 2012). Theoretically, it is compatible, but not directly deduced from a perspective on the ERN/N2 where both represent conflict between expected and actual events, one in the somatomotor, the other in the external, sensory domain.

A large-scale meta-analysis of over 1000 fMRI studies (Torta & Cauda, 2011) has indicated that mediofrontal activity for functions such as memory, attention and language are largely overlapping, but a cluster responsive to action execution is found somewhat more caudally. Indeed, the cluster reported for action execution was largely overlapping with the present ERN/CRN-projecting centro-medial cluster. The clusters sensitive to language, memory, attention and other domains were located in between the observed fronto-medial N2 cluster and the action execution cluster. Note that the action execution cluster, on order of being more caudal, was located closer to the motor cortex, which however might be due to measurement, or even simply labelling, error (presumably, action execution activates the motor cortex, including the parts adjacent to the MCC).

It is therefore conceivable that different (possibly overlapping) functional subsections of the mediofrontal cortex provide different cognitive functions, for example, that a region more integrated into memory processes responds to incongruences between predictions and sensory input, and another section to incongruences between intended and actual actions, e.g. by matching afference copies. Specifically, more frontal parts of the mediofrontal cortex, such as the pACC or aMCC, could reflect stimulus conflict; more posterior motor-adjacent areas such as pMCC, close to the SMA, could reflect response conflict.
However, since all these analyses must be considered tentative, hypotheses based on these findings require confirmatory testing.

Interestingly, the strongly action-sensitive centro-medial cluster projected an action-preceding, but not stimulus-locked positivity. This positivity might be associated with the P3a.

It could be hypothesized that the difference in activation patterns between IC clusters reflects the influence of different neuromodulator systems, with different time courses; possibly, e.g. the two catecholamine projections, DA and NE, differ in their strength and time course regarding various frontal systems.

4.4 STUDY 3

A final study was conducted aiming to confirm a central prediction emerging from the previous analyses: the identity of the late positivity following structural, e.g. syntactic and morphosyntactic deviancies, and the P3. The first study had indicated that the ICA-derived brain systems dominating the ERP during the late positivity elicited by a semantic deviancy were also active during the following visual response cue. The second study had demonstrated that the late positivity during the detection of semantic matches and mismatches was response locked. However, as noted, the P600 had traditionally been specifically associated with syntactic deviancies by researchers, and the difference between semantic and syntactic deviancies has often been seen as a reliable criterion to distinguish the two. The present review of the functional overlap between the P3 and the P600, including the sensitivity of the "syntactic" P600 to task factors and semantic deviancies, suggests one radical interpretation: the P3/P600 distinction can mostly be regarded as a historical artefact. Yet, the assumption of the identity between P3 and P600 allows falsifiable predictions, and beyond literature surveys, the preferred interpretation should be established by empirical tests.

In the LC/NE-P3 theory, the P3 marks an essential step in the action-perception loop; it corresponds to a break, where environmental events are so incompatible with the current behavioral pattern that a fundamental reorganisation of cognition and behavior has to be initiated. The P3 marks the phasic NE response that supports the transition of the cortex into a new state, for example, by upregulating cortical gain (Aston-Jones & Cohen, 2005), interrupting network patterns (Bouret & Sara, 2005) or by shifting the frontal/posterior balance (Ramos & Arnsten, 2007). Possibly, it corresponds to VAN activation, marking stimuli so intrusive that they capture attention and induce reorientation, including behavioral shifts.

This temporal correlation between the timing of the P3 and behavioral shifts, stemming from the underlying variable of NE perturbing the cortex, can be exploited experimentally. Specifically, if the P600 induced by morphosyntactic mismatches is, like the P3, an effect of LC/NE activity, it should show the same response-time alignment that the P3 exhibits in nonlinguistic paradigms.

This testing of the nature of the P600 as having the same role in the action-perception cycle as the P3 requires an experimental paradigm unused in the neurolinguistic study of sentence processing (with the exception of Study 2 in the present work): collecting response times while the subject comprehends sentences.

Typically, subjects are instructed to inhibit overt response until after the end of each presented sentence:

> "Subjects were instructed to wait until the"?" cue before responding. This delayed response was designed to reduce any contamination of the ERP waveform by response sensitive components such as the P300 (Donchin & Coles, 1988)."
> (Kuperberg et al., 2003, p. 288)

However, it is well established that while the person waits, the brain doesn't; the P3 happens at the time when response selection becomes possible, no matter if the response is executed immediately or after a delay period (Kok, 1988; Luo & Wei, 1999; Praamstra et al., 1994). Consequently, prohibiting immediate responses does little to avoid "contamination" by the P3. Instead, it

only removes the information about the timing of the P3. If the late positivity following syntactically deviant structures is caused by the same LC/NE network as the P3 following response selection, it should show the same RT alignment.
This does not entail that intentions to respond should be a necessary precondition of such positivities. The reorientation response follows any stimulus of sufficient salience that *might* be action relevant. However, if it actually does become action relevant, the facilatory effects of phasic neuromodulation on response selection should induce RT/ERP correlations.

For this purpose, a study was constructed presenting syntactic manipulations in a judgement paradigm where subjects were instructed to respond directly when they had come to a decision regarding the well-formedness of the sentence. It was predicted that only one late, centro-parietal positive component would follow syntactic violations, and that it would be response aligned. Specifically, it was assumed that this component would show stronger inter-trial coherence of low-frequency oscillations when time-locking trials to response than to stimulus, and that an estimate of single-trial positivity latency would show a strong correlation with RT on the same trial.

4.4.1 *Pre-registration*

Since the extensive theoretical background and the clear findings from the previous study allowed precise predictions, hypotheses, outcomes and a sketch of the analysis process were pre-registered (Wagenmakers, Wetzels, Borsboom, van der Maas, & Kievit, 2012) in a public clinical trial database before data collection started. Consequently, no data were collected before the main hypotheses had been made publicly available. The pre-registration protocol is found in the *Deutsches Register für klinische Trials* under the ID DRKS00004596, and a copy of the original experimental protocol is given in the appendix.

4.4.2 *Material and procedure*

4.4.2.1 *Material*

200 German sentences were constructed (see 4.41), following the scheme already used in Study 2 (example a.). All sentences introduced a hyperonym and then listed two of its members. Semantic violation sentences (c.) were constructed by exchanging hyponyms between sentences, where both the first and the second hyponym could be switched. Morphosyntactic violation sentences (b.) were constructed by exchanging determiners before hyponyms.

Since in German, nouns agree in gender with their determiner, this induced a morphosyntactic mismatch that could be detected on the noun following the exchanged determiner. Such gender mismatches have previously been shown to elicit P600 effects in the auditory domain, even in task-light or free paradigms (Hagoort & Brown, 2000).

Exchanges were conducted so that determiners of either of the three German genders were presented equally often.

	Example						Condition
a.	Zur Kategorie To the category	Getränke drinks	gehören belong	die Fanta the.fem Fanta.fem	und and	das Wasser. the.neut water.neut	*Control*
	"Fanta and water belong to the category drinks."						
b.	*Zur Kategorie To the category	Getränke drinks	gehören belong	der Fanta the.masc Fanta.fem	und and	das Wasser. the.neut water.neut	*Morphosyntax*
c.	*Zur Kategorie To the category	Getränke drinks	gehören belong	die Qualle the.fem jellyfish.fem	und and	das Wasser. the.neut water.neut	*Semantics*
	"Jellyfish and water belong to the category drinks."						

Figure 4.41: Stimuli Study 3.

Furthermore, as an exploratory feature, "double violations" were introduced, where sometimes (20 cases each), a morphosyntactic violation was followed by an additional semantic violation, or vice versa.

Since the stimulus preparation process in the previous study had suggested that the trained speaker seemed able to read incongruent sentences in a neutral tone, were recorded in their entirety by a trained speaker who was instructed to maintain a normal intonation even for deviant sentences. Intonation was monitored, and sentences that felt inappropriately articulated were re-recorded.

4.4.2.2 *Procedure*

Subjects were instructed to attend to the sentences carefully, and respond by a button press (left hand/right hand, incorrect/correct, counterbalanced across participants) once they were confident in their judgement regarding if the currently presented sentence was well-formed or deviant. Subjects were told to respond both accurately, and quickly.

Sentences were presented via loudspeakers. At the beginning of each trial, a neutral smiley face was presented that changed to a frowny or cheerful smiley once the participant had given an incorrect or correct response. Then, after a two-second interval, the next sentence was presented.

After every 20 sentences, a feedback screen interrupted sentence presentation, giving subjects the chance to rest for a while. The feedback screen informed participants about their average reaction time and accuracy.

Stimulus presentation was again controlled by Presentation (Neurobs).

Meanwhile, subject EEG was recorded in a montage of 33 Ag/AgCl electrodes using a Brainproducts Brainamp. The setup, placed according to the 10/20 convention, included a mastoid reference, earlobe ground, and 6 EOG electrodes.

Data of 20 participants was recorded, all right-handed native speakers of German, three men; mean age 24.75, range 21-42.

4.4.3 *EEG preprocessing*

EEG data was processed in EEGLAB (Delorme & Makeig, 2004). Data was band-pass filtered between 0.1 and 40 hz, downsampled to 100 hz, decomposed into independent components using AMICA (Palmer et al., 2006) after temporary high-pass filtering (ICA was computed on 1 hz filtered data and decomposition matrices were then applied to less radically filtered data), epoched around critical stimuli, re-referenced to linked mastoids, and incorrectly answered and artifactually contaminated trials were excluded (using the automatic kurtosis method provided by EEGLAB). Blink and HEOG ICs were identified using CORRMAP (Viola et al., 2009), and subtracted from the data.

4.4.4 *Primary outcomes*

4.4.4.1 *Measures*

ERPs were constructed by averaging trials time-locked to control, semantic and morphosyntactic violation noun onsets, respectively. ERPs at critical electrodes were plotted using ERPLAB. To further highlight the spatiotemporal dynamics of the ERP, butterfly difference ERPs were constructed by subtracting the mean of all control trials separately from the mean of all syntactic and all semantic violation trials, and plotting the topography in the N400 and P600 time windows.

For following single-trial analyses, single-trial difference waves were created by subtracting the mean of all control trials per participant from every single violation trial individually.

Using these difference trial waves, temporal alignment of the expected late positivity was measured threefold.

RT bin averages (Poli, Cinel, Citi, & Sepulveda, 2010) were constructed by sorting individual trials of individual subjects by RT and selecting the data between the 5th and the 95th RT percentile. Then, 4 RT bin quartiles were constructed per participant, and the trials in each bin averaged to construct (20 * 4) 80 RT bin ERPs. A leave-one-out jackknife procedure (Kiesel, Miller, Jolic oe ur, & Brisson, 2008) was used to construct 80 jackknife averages (each consisting of the mean of 19 subject ERPs), still corresponding to the 4 RT bins. Then, positivity latencies for each ERP were estimated by the fractional area latency method (Kiesel et al., 2008; Luck, 2005); for this, all values below 0 were set to 0, and the integral of the ERP was calculated between 0 and 2000 msec after stimulus onset. The resulting jackknifed latency estimates were subjected to a repeated-measures ANOVA, with latency as the dependent and RT quartile bin as the independent variable, to obtain an F value. This F value was corrected for the considerable underestimation of within-group variance introduced by the jackknife technique (Ulrich & Miller, 2001).
The corrected F value was used to calculate the Bayes Factor for the hypothesis of zero differences. For this, a default Bayes Factor ANOVA (Wetzels et al., 2012) was employed. A standard JZS prior, centered at zero, with a width of .5 standard deviations, was used.

Secondly, data from individual trials at electrode Pz were subjected to wavelet decomposition, using 2 wavelet cycles at the floor frequency, increasing by 50% for every frequency step with increasing frequency. Data was analysed between 0.5 and 8 hz in 30 evenly spaced frequency steps. The ITC was calculated independently for data time-locked to the response and to the onset of critical nouns, and subjected to a two-sample, paired Bayesian *t*-test with stimulus- vs. response-locked nature of trials as the independent and the mean of all estimated frequencies in a 50 msec window centered around the P600 peak as the dependent variable.

Furthermore, correlations between single-trial P600 latency and RT were estimated repeating the Woody filter procedure (Woody, 1967) previously proposed by e.g. Kutas et al. (1977). Only trials with less than 1500 msec RT were used, and again, electrode Pz was investigated. Furthermore, in a window following the onset of the feedback smiley (100 msec post button press), the mean ERP was subtracted from each individual trial to avoid the chance of selecting the necessarily RT-locked potential evoked by the feedback.

To apply the Woody filter, for every participant, the mean of all stimulus-locked violation difference trials was used as a template. Data was low-pass filtered at 6 hz. Then, for every individual trial, the time point of the best correlation between the template and the trial was calculated in a 500 msec window from 500 to 1000 msec after critical noun onset. Trials were then latency shifted to their time window of best fit with the template, and the mean of all shifted trials was used as the new template. This procedure was repeated iteratively for 100 times for every individual participant.

Then, for the morphosyntactic violation difference trials, a robust Pearson's correlation was calculated between single-trial RT and the latency shift (i.e., time point of best overlap with the template) at the last iteration as an estimate of positivity latency, using the Robust Correlation toolbox (Rousselet & Pernet, 2012). The same procedures were repeated for the N400 time window (50-500) on semantic violation trial data. Furthermore, a robust simple linear regression, implemented in MATLAB, was also added, attempting to predict positive peak latency based on RT.

RESULTS Visual inspection of Butterfly ERPs indicated an N400, followed by a P600 for semantic violation trials (see Figure 4.42) and a P600 for syntactic violation trials (see Figure 4.43), both with a typical centro-parietal topography. No reliable LAN effect is visible.

ERPimages (see Figures 4.44 and 4.45) showed a strongly RT-aligned late positive component for both semantic and morphosyntactic violations, as well as a stimulus-aligned N400 for semantic violations. Comparing RT- versus stimulus-aligned ERPs, the low-frequency component of the ERP did not differ substantially between the two (as would be expected for low-frequency components), but a higher frequency component appeared only for RT-locked activity.

Jackknife-estimated latencies strictly increased over RT quartile bins (see Figure 4.46). The Bayes Factor ANOVA comparing latencies by RT quartile bin strongly favoured the hypothesis of a significant difference between conditions (BF H_1 over H_0: 25:1). This finding indicated that the data strongly supported an increase of ERP latency with increasing RT.

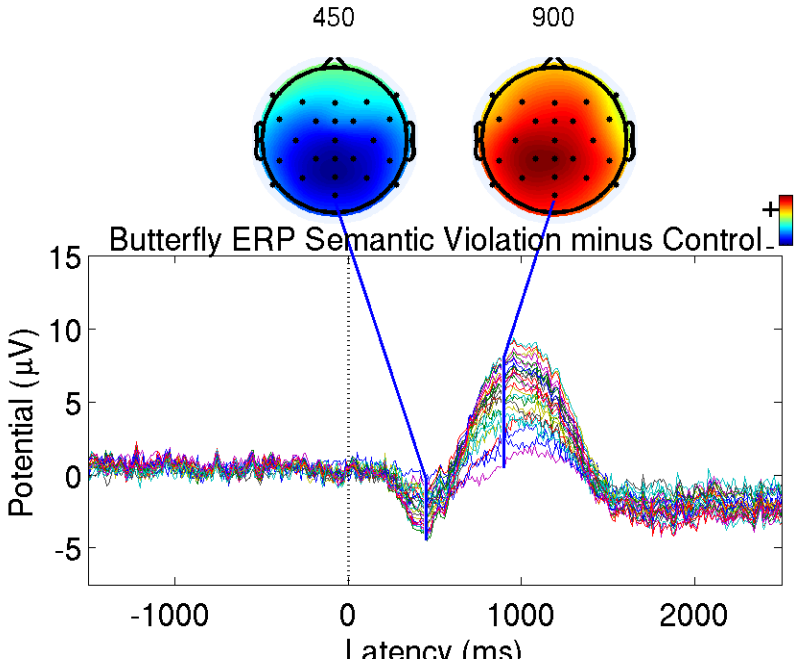

Figure 4.42: Butterfly ERP for semantic violation difference trials, showing all channels with topographic maps at selected locations (N400, P600)

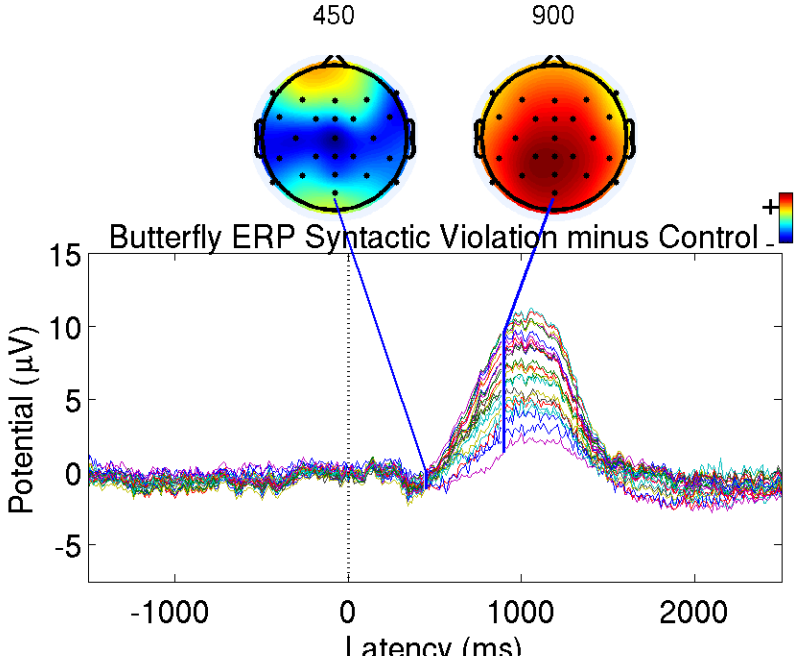

Figure 4.43: Butterfly ERP for morphosyntactic violation difference trials, showing all channels with topographic maps at selected locations (missing LAN/N400, P600)

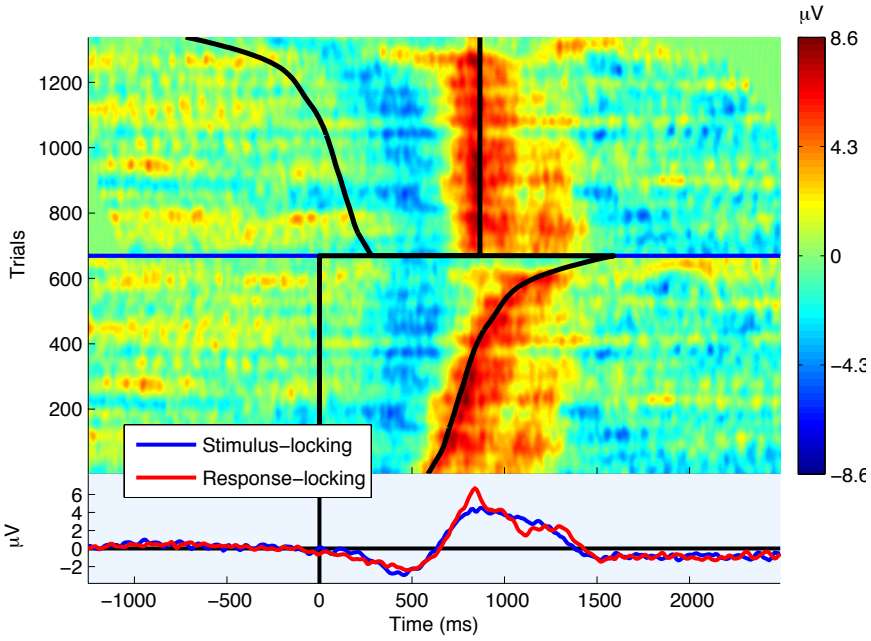

Figure 4.44: ERPimage for semantic violation trials, electrode Pz, showing the same data both RT-aligned (top) and stimulus-aligned (bottom). The left black line shows stimulus onset, the right black line shows RT. At the bottom, stimulus-locked (blue) and RT-locked (red) ERPs are shown.

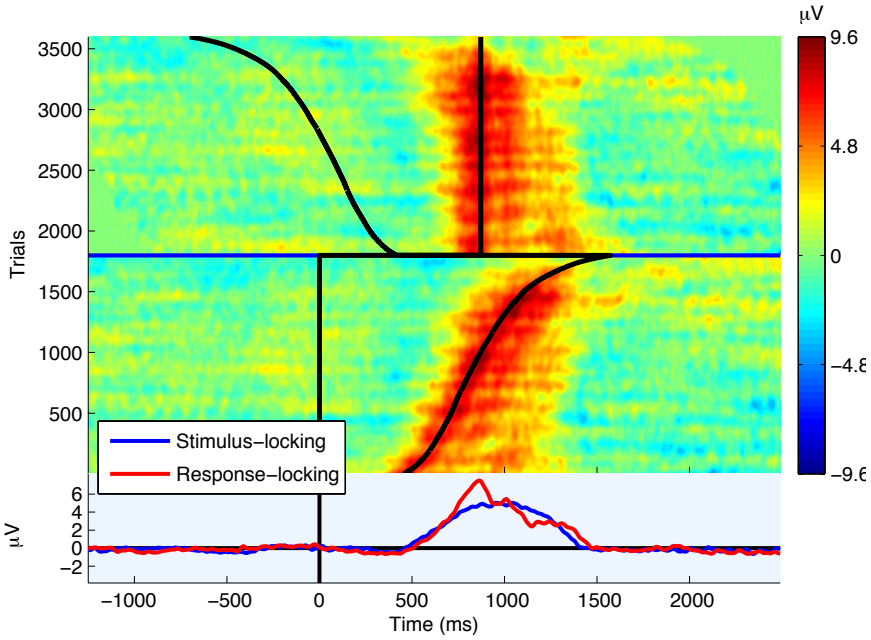

Figure 4.45: ERPimage for morphosyntactic violation trials, electrode Pz, showing the same data both RT-aligned (top) and stimulus-aligned (bottom). The left black line shows stimulus onset, the right black line shows RT. At the bottom, stimulus-locked (blue) and RT-locked (red) ERPs are shown.

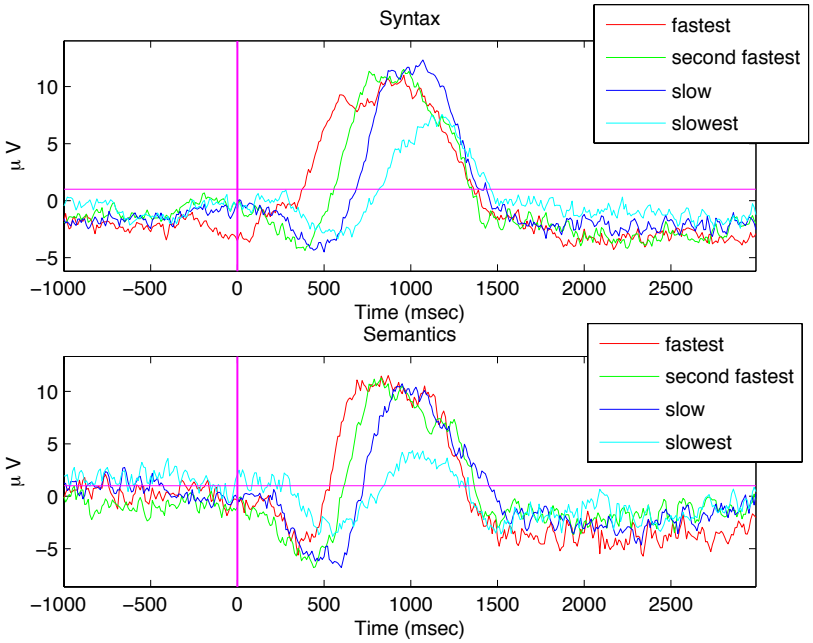

Figure 4.46: ERPs at Pz for syntactic (top) and semantic (bottom) violation difference trials (mean minus control), binned by RT into quartiles.

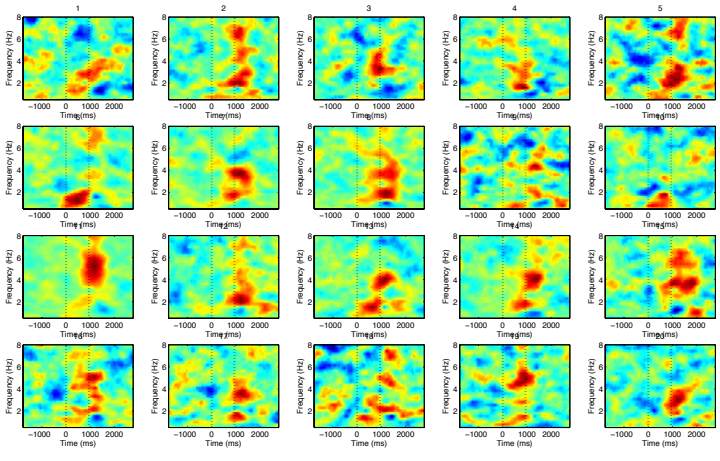

Figure 4.47: Time-frequency plot of low-frequency ITC differences at Pz, RT-locked minus stimulus-locked data, for each subject. Warmer colours: greater ITC for response-locked condition

The Bayesian two-sample *t*-test analysis of stimulus- versus response-locked ITC (see Figure 4.47) overwhelmingly favoured the alternative hypothesis over the null hypothesis (BF(0 | 1) = 1:263). The conventional analysis was in agreement with this finding, indicating that ITC was larger for response- than for stimulus-locked data ($t(19) = 4.933$, $p < 0.0001$, 95% CI = 0.036, 0.078).

These results imply that the response-locked data showed significantly stronger inter-trial coherence of low-frequency phase than stimulus-locked data, indicating response alignment at least of the low-frequency components of the P600.

The correlation between single-trial RT and Woody filter estimated positivity latency was strongly positive (correlation coefficient $r = 0.74$; 95% bootstrapped CI of correlation coefficients: 0.7244, 0.7690). The robust linear regression also presented RT as a significant predictor of positive component latency (constant: 82, slope: 0.76, standard error of the slope: 0.017, $R^2 = 0.538$, $p < 0.0001$). These calculations imply that single-trial RT is a stable predictor of single-trial positive component latency.

The correlation between estimated N400 latency and RT was not significant (95% bootstrapped CI of correlation coefficient: -0.0583, 0.0799). Consequently, in ERPimages, the N400 appeared as a straight line in stimulus-locked plots, implying stimulus alignment, not RT alignment of the N400.

Results of statistical analyses are also presented in table form.

Measure	Contrast	95% CI lower bound	Mean	95% CI upper bound
Method: Woody Filter estimated latency and RT	Syntactic violations: late positivity	.50	**.63**	.73
Unit: correlation coefficient (*r*)	Semantic violations: late positivity	.42	**.59**	.72
	Semantic violations: N400	-.02	.09	.12

Table 4.5: Results of Study 3 - RT/Component Latency Correlations

Measure	Contrast	95% CI lower bound	Mean	95% CI upper bound
Method: Low-frequency phase coherence	Syntactic violations: RT- versus onset-aligned trials	.05	**.08**	.12
Unit: ITC difference (ratio)	Semantic violations: RT- versus onset-aligned trials	.06	**.09**	.12

Table 4.6: Results of Study 3 - Inter-trial coherence

4.4.5 *Discussion*

The present study aimed to confirm the prediction that the late positivity following syntactically deviant items would be time-locked to RT. Conventional ERP analyses revealed an expected N400/P600 pattern for semantic and a P600 for morphosyntactic deviancies. Various single-trial analysis techniques indicated strong reaction-time locking of the single late positive component following syntactic, but not the N400 following semantic violations.

Low-frequency components of the P600 showed stronger inter-trial phase coherence in response- than in stimulus-locked data. Single trial RT and Woody-filter estimated P600 latency were strongly correlated; no correlation was found for the N400.

Importantly, no stimulus-aligned positivity could be observed, only the RT-aligned positivity. These findings confirm the (pre-registered) predictions derived from the interpretation of the N400/P600 pattern as one iteration of the biphasic pattern, similar to the N2/P3, with the P600 likely reflecting LC/NE phasic activation. In contrast, finding the P600 not response aligned would have strongly disfavoured the association of the P600 with the P3 and the LC/NE system.

While the present study thus strictly speaking failed to falsify the interpretation of the P600 as an aspect of LC/NE function, the findings do not necessarily contradict the perspective of the P600 as a distinct component. It is possible that an interpretation of the P600 as a distinct component could still accommodate the present findings. For example, it could be argued that syntactic analysis and acceptability decision times on one hand, and decision times and reaction initiation are probably strongly coupled, leading to a correlation of RT and P600 caused by a common cofound. Alternatively, it could be argued that even though in this task, syntactic analysis necessarily took place, a true P600 was not elicited due to various possible reasons such as a task focused on judgement over interpretation.

However, most importantly, the present paradigm did not elicit a P600 distinct from the RT-aligned, clearly P3-like positivity. This implies that either

the P600 is not a reliable, but only a circumstantial correlate of syntactic anomalies; or that the P600 behaves like a P300. Furthermore, while distinct-component theories of the P600 could, by post-hoc additions to their model, accommodate for the present findings, the LC/NE-P3 theory actually predicts these results.

A further important specific prediction can be made that directly contradicts key understandings of the P600-as-syntactic analysis perspective. Under that assumption, the P600 should covary with successfully detected and processed syntactic anomalies. Consequently, sentences eliciting P600 responses should be understood, and the P600-eliciting element correctly integrated. Conversely, if the P3, and consequently, the P600, reflect mode and/or stream switching, the opposite can be predicted. Typically, before a P600, the subject will be engaged in perceiving and interpreting the current sentence. A large P600 should then index a process of at least temporarily disengaging from the perception/interpretation manoeuvre towards some alternative, and the words falling exactly under the P600 curve should be poorly recollected and integrated. Potentially, the sentence as a whole may not be interpreted deeply, or not at all, given that P600-eliciting stimuli often contain major incongruences rending them impossible to coherently integrate.

On a minor note, the study also contradicted a prediction of the adapted LC/NE-P3 theory by Warren (2011). There, N2 and P3 are always necessarily assumed to occur together, since both reflect two aspects of LC phasic bursts. However, in this study, the contrast between semantic and syntactic violations showed that a positivity can appear without a negativity; the semantic violation condition also shows that the P600 is not temporally aligned to the N400, as would be predicted from a biphasic pattern.

5

CONCLUSION

The EEG does not easily lend itself to fine-grained investigations of subtle phenomena, of small-scale networks, of slow or transient processes. What it has always, since Berger's first *Berichte(n)*, provided are biomarkers of systemic cognitive states measured right from the CNS. And it might be that the EEG is specifically sensitive to such measurements. More localized, small-scale techniques may be insensitive to systemic, large-scale phenomena.

5.1 CROSS-LEVEL NEUROLINGUISTICS

Researchers have attempted to use the EEG to study subtle phenomena such as different stages of language processing. While it can be doubted how powerful of an instrument the EEG, especially the ERP, is in this regard, it is well-suited to investigate state changes induced by processing in this and other modalities. Connecting the large-scale, cross-areal events of the EEG to neuromodulator systems might allow the investigation of these powerful guiding mechanisms of human cognition. One necessary precondition for the scientific exploitation of the EEG for this purpose is to further "ER-Pology" so as to clearly associate various EEG/ERP markers with specific neurophysiological substrates. It may not be even possible to associate theoretically, or even behaviorally, deduced assumptions regarding cognitive functions with the EEG. As Kutas & Federmeier (2011) argue, the N400 is not easily mapped to various psycholinguistic constructs. Rather, the manifold observations regarding the N400 imply that non-neuronal concepts such as lexical access, lexical integration, even a mental lexicon, may be inappropriate when one no longer allows themselves the comfortable shielding from biological reality that an approach oriented along Marr's levels (1980) allows.

When ERPs become associated not with cognitive phenomena, such as lexical access, attentional reorienting, or syntactic reanalysis, but with neurophysiological phenomena such as phasic norepinephrine release, gain regulation or blocking of cortico-cortical transmission concurrently with facilitation of thalamo-cortical transmission, the concept of the ERP must be fundamentally reconsidered. Subtle differences in susceptibility to certain theoretically motivated, but not necessarily cortically instantiated phenomena do not necessarily inform a productive research program. Instead, empirically valid, measurable concepts must stand in the center of such research programmes. In other words: Marr's division is only partially sustainable (Churchland & Sejnowski, 1988; Elman, 1998).

Poeppel & Embick (Poeppel, 2012; Poeppel & Embick, 2004) have argued that cognitive realities must inform and even determine neurobiological research. If e.g. linguistics identifies a phenomenon on Marr's *computational level*, a computation that the brain must be capable of considering the observed phenomena, then neuroscience could be challenged to identify the neural basis of this computation. I do not consider such an approach to be sustainable. Historically speaking, projecting supposed cognitive primitives into neuroscientific data has not lead to clarity, but to biased interpretations and reifications of concepts whose "neural reality" is uncertain or doubtful. When the P600 was originally observed, it was seen as a confirmation of the reality of two distinct aspects of language, syntax and semantics. From this perspective, the observation of "reversal anomalies" was tremendously confusing. Had researchers remained at a more descriptive level, or restricted their explanations only to what could have been neurobiologically grounded, much confusion could have been avoided.
Cortical processes must be viewed on their own level. Contra Poeppel & Embick (Poeppel, 2012; Poeppel & Embick, 2004), a bottom-up approach, where the more empiric sciences are given primacy, is appropriate.

5.2 OCCAM'S RAZOR AT THE COMPONENT ZOO: ERP*OLOGY* AS NEUROBIOLOGY

The assumption that many ERP components can be subsumed under one biphasic pattern has allowed a number of predictions that have found empirical support over the three experiments discussed in this work. To paraphrase the proposal again:

- The biphasic pattern consists of a negativity followed a positivity
- The two components play different roles in the action/perception-loop: the negativity reflects incongruences between multiple attended streams (such as memory/predictions and various sensory streams, or intended versus executed motor patterns), the positivity supports the transitioning of the cortex to an appropriate state following the evaluation of the incongruent event
- The N2/P3, the ERN/P_E and the N400/P600 are all instances of this basic system, and can be evoked by events requiring cognitive adaptions in multiple domains, leading to various topographies and latencies for the effects
- Neuromodulator systems, such as LC/NE and VTA/DA for the positive component, and possibly NBM/ACh for the negativities, may cause the biphasic pattern
- ACh may support the encoding of unexpected events in the attended stream against interference from competing streams
- NE and DA support cortical and behavioral adaptions

5.2.1 *P600 and P3*

One entailment of this perspective is that all CNS and ANS correlates of the P3 should also apply to the P600. Some of these predictions were tested

in Studies 1 and 3. Exploring for the first time ICA to EEG data recorded during spoken sentence processing, Study 1 demonstrated that the Independent Components dominating the ERP following linguistic deviations are also systematically active during non-linguistic aspects of the same task. Exploring for the first time the response time alignment of EEG phenomena during sentence processing, Study 3 demonstrated that the positive component following (morpho)syntactic mismatches shows the same reaction time alignment as is known from the P3 and P_E.

Further predictions can be deduced from this model that go beyond the usual correlations of the P600 with various aspects of the task. The P600 should, *to the same degree as a P3 of similar latency*, magnitude etc., covary with heart rate, SCR, α desynchronisation and of course NE levels (even though these may not be accessible to reseachers), and manipulations of and genotype differences within the catecholamine system. Consequently, when subjects take part in both typical P3 and typical P600 paradigms while such measures are recorded, the resulting variables should show be correlated within subjects, and correlate with P600 as well as with P3 amplitude. The P600 should also behave similarly with regards to the attentional blink, memorisation and current behavioral state. Pharmacological interventions should interact in the same way for the P600 and P3, and should depend on phenotypic variation in the same way. Should methods of measuring LC activity using fMRI or measuring NE levels using MR spectroscopy improve, LC BOLD levels and MR-estimated NE levels should behave similarly for P3 and P600.
Neither of these factors should depend on direct response execution during sentence presentation, but rather interact with direct response execution in the same way the P3 does. Also, if the response-preceding P3f is not strictly dependent on the initiation of overt movements, if it is consequently also found in paradigms without direct overt responses, it should show the same within-trials within-subjects latency in regards to the parietal P3 as during overt responses.
Of course, the strictest test, combined EEG and single-unit recordings, will hardly ever become possible since single-unit brain stem recordings are never performed on animals capable of human speech. The optimal paradigms for eliciting a P3 comparable to a P600 has yet to be established. A high-latency, complex, but certainly non-linguistic task must be identified.

Psychologists are generally open to the idea of identifying similar components, and the P_E is rather uncontroversially accepted as a P3(b). Neurolinguistic researchers however are often opposed to the idea of associating P600 and P3 (Frisch et al., 2003; Osterhout, 1999). A number of arguments in opposition to the proposed association on the grounds of the present findings could be voiced.

It could be argued that the observed effect in Study 3 is simply a P3 elicited by target detection. However, the fact that the subjects correctly recognized morphosyntactic mismatches implies that they processed the linguistic structure at least to this level. However, no component clearly distinct from the P3 was seen. Consequently, either the observed positivity is a P600, in which case the P600 behaves like a P3 with regards to reaction time alignment; or the P600 is not a reliable correlate of syntactic incongruence processing.

As noted, neurolinguistic researchers often attempt to separate task-specific ERP components from sentence processing by postponing response execution after e.g. sentence presentation. However, typically, the time point where a decision can be made about the appropriate response is still within the sentence. As previous studies have shown, the P3 is rather coupled to response selection than to response execution; postponing the response does not delay the P3 (Kok & De Jong, 1980; Luo & Wei, 1999; Praamstra et al., 1994).

It has been argued (Osterhout, McLaughlin, Kim, Greenwald, & Inoue, 2004) that the P600 shows specific sensitivity to syntax, distinguishing it from the P3; semantic violations, so it is claimed, are not typically followed by a P600. This claim seems incompatible with much of the surveyed data. From the first N400 (Kutas & Hillyard, 1980b), followed by its (weak, but visible) late positivity, to the repeated finding of "reversal anomaly" P600 effects, the P600 often follows semantic violations. More importantly, its appearance is predictable based on the salience and intrusiveness of the semantic deviation (van de Meerendonk et al., 2010). Here it precisely mirrors the P600 to syntactic violations. Task relevance of deviations enhances the P600, task irrelevance attenuates it (Haupt, 2008; Osterhout, McKinnon, Bersick, & Corey, 1996). In this light, the finding of P600 effects in conditions without an explicit task mean little; the P3 is also found to intrusive stimuli without being made task relevant (Perrin et al., 2006).

Nevertheless, there seems to exist a certain asymmetry between semantic and syntactic violations. It is possible that sequences that are hard, but possible to interpret elicit mostly an N400, since subjects attempt to integrate semantically, continue lexical access etc.; sentences that are not further interpreted after the point that has afforded a decision about the next appropriate action (such as no longer attending to the speech stream and preparing the execution of the selected response) elicit mostly a P600, for example, when subjects abort the semantic interpretation of a sentence after having run into a garden path (as was potentially observed by e.g. Osterhout & Holcomb, 1992).

Of course, it is not trivial, but definitely possible to test numerous predictions derivable from the association between the P600 and the LC/NE system. Some have been attempted here, future investigations may support or weaken the simple model proposed here.

5.2.2 *N2, ERN and N400*

The general mismatch sensitivity of late scalp-negative ERP components was investigated in detail, and one aspect of the theoretical discussion emerged clearly: dependence of component topography on task modality. Whereas high-level matching processes (semantic processing) resulted in centro-posterior components, simpler, feature-level mismatches reflected, as in the study by Warren et al. (2011), in a different topography, pointing at different generators. Somewhat surprisingly, the anterior mismatch component observed in Study 2 did not show characteristics of response conflict - it dissociated from RT in time and the ERN in space - but rather stimulus conflict. This divergence asks for further investigations into the precise functions and sub-domains of the frontal system connected to anterior parts of the cingulate.

Generally, the question of how far the N400 directly reflects, as commonly assumed by neurolinguistis, stimulus-evaluative processes, or may rather resemble the N2 as understood by neuropsychologists, opens up some fundamental questions regarding the specific nature of this component that more or less single-handedly started the field of neurolinguistics and the neuroscientific investigation of sentence and meaning processing. The possibility that the N400 may, similar to the N2, be an *indirect* signal demands further attention.
A topographically flexible, mismatch- and prediction error-sensitive signal may, as discussed, best demonstrate a neuromodulator system showing a similar topographic specificity. As noted, Acetylcholine may be a promising candidate for further research.

5.3 TPJ, CINGULATE, AND LATERAL AND PRE-FRONTAL CORTICES ACROSS DOMAINS

The first and second studies supported a perspective on the function of a network in the mediofrontal cortex as a main hub in a frontal system controlling narrow-focus cross-modal stimulus representations. The finding, twice observed to linguistic stimuli here, of a binary sensitivity to incongruences between a single item held in memory focus and the actually incoming sensory data must be replicated with different methods, and validated in other domains but language. It is furthermore of great importance to disentangle a possible fine-grained subdivision of the pre-rolandic cingulate between action/somatomotor afference-related incongruence control, possibly in the pMCC; and non-motor, perceptual incongruence, possibly related to hippocampal θ, in the aMCC and/or pACC.

Furthermore, the possibility of independent time courses of the different neuromodulator systems projecting to the pre-rolandic cingulate, such as a dopaminergic P3a and a noradrenalinergic P3f/P3b, must be further investigated.

Studies 1 and 2 also investigated a temporally precise and hemisphere specific correlate of action control at lateral frontal sites. Of special interest might be the relation between the negative, disinhibition-associated component and the morphologically similar CRN/ERN.

The EEG also allows a special perspective on the activation of an attention network with one main hub in the TPJ. Phasic and tonic activity of the TPJ, only the former dependent on LC drive, may become visible in quite distinct paradigms. Fundamentally, a unifying principle of TPJ functioning (possibly as a hub of cross-modal, multi-stream routing and integration) is necessary. One contribution the EEG might provide here is to track the specific time course of phasic activity even on a single-trial level, which might allow differentiating phasic and tonic activity patterns of the TPJ.

5.3.1 *Localism vs. Holism one last time*

A certain fundamental incompatibility exists between two dimensions of cortical state control discussed here. On one hand, TPJ, cingulate, lIFG and other brain areas are assigned specific roles in state control - in the VAN, the TPJ integrates to reorient towards critical events, the cingulate detects

conflict; and the DAN implements top-down control, distractor resistance and focus. On the other hand, these very same functions are assigned to neuromodulator systems, who are defined not by their place, but by their chemistry. Noradrenaline supports reorientation, Acetylcholine supports top-down, focused attention, just as the VAN and DAN do. A similar argument could be made regarding brain oscillations.
The issue cannot be reduced to simple codependency- by assuming that for example the impact of NE at the TPJ induces reorientation. Acetylcholine is specifically domain-specific, but also cortex-wide available. The cholinergic "attentional flashlight" may illuminate specific cortical processing as required. In the LC/NE theory (and in the interpretation of the Context Updating model by Polich (2007)), it is specifically cortex-wide action, not restricted to the TPJ, that induces reorientation. What does it mean for both a systemic, qualitatively defined system, as well as a localised, positionally defined system to implement similar functions?

5.4 OUTLOOK: NEW RESEARCH METHODS FOR OLD QUESTIONS

The studies reported herein employed a number of methods, paradigms and metascientific practices new to linguistic research. Single-trial analyses (using ERPimages, Woody filters and phase consistency estimates), Independent Component Analyses, and within-sentence behavioral measures are new to sentence processing research, but allow a more representative perspective on e.g. the control of action during speech processing, and the nature of the EEG correlates of speech processing.

However, as noted, the present methods must be combined with further novel techniques, such as measures of ANS activity (SCR, pupil dilation, heart rate), fMRI co-registration, and ultimately, neuropharmacological interventions. Fundamentally, it must be understood which level of CNS activity the EEG is sensitive to; and this entails not only what it is insensitive to (such as small-scale and localized, or transient, long-lasting or temporally jittered phenomena), but also regarding the systemic measures that so far only Berger's waves properly demonstrate. Attempts to study higher cognition in the form of the interpretation of complex, abstract, meaningful structures and representation must not shy away from using supposedly low-level psychophysiological explanations, paradigms, tools and knowledge. Language may be a phenomenon including abstract phenomena such as recursion (Jackendoff & Pinker, 2005) and complex computations, but it is implemented by the same brain allowing rats to learn running mazes, and it is used to control actions and behavior (Barsalou, 1999), it surprises and startles, and will therefore reflect in such systems.

What is to be gained for knowledge of language from such research? First, and most importantly, a significant cofound of such studies may be better controlled. If what was assumed to mark syntactic processing turns out to mark general surprisal, the interpretation of data changes.

In sum, ignorance and unfounded optimism of researchers of language processing regarding possibly cofounds of their results by domain-general, low-level systems such as state control via neuromodulation must, and can be avoided. But knowledge of such systems may benefit research of language competence, listening as well as learning.

Secondly, language processing and especially learning are strongly modulated by state-wide phenomena such as arousal and affect (Krashen, 1981; 1985), and by measuring the specific interaction between systemic and specific factors, these interactions may be fruitfully investigated and potentially beneficial contexts identified. However, for this, the two must first be teased apart, their respective markers clearly identified and delineated. Should such integration become possible, benefits for investigating, monitoring and even boosting understanding and learning of language and data from other complex, abstract representational systems may also become available. It is known that neuromodulators gate learning (Ullman, 2005), both explicit, declarative learning of words (Knecht et al., 2004) and implicit, procedural learning of structure (Uddén et al., 2010), and that such systems may be targeted. Preceding such targeted interventions, measuring brain system interactions may allow the fast prediction of intervention efficacy, and their on-line guidance.

Finally, as has been shown in Study 2, research focused on comparatively low-level or general phenomena, such as Conflict Monitoring, may in fact benefit from research undertaken in a wholly different paradigm. Here, a supposedly stimulus conflict-related component was observed where a naive view might have expected response conflict. High-level, specific processes such as syntactic analysis differ from low-level tasks; for example, animal research almost always entails (implicit) conditioning and reward contingencies, whereas human subjects may be explicitly instructed, leading to different strategies and, presumably, brain systems. Thus, they have the potential to highlight different aspects of the low-level, general components active for all such tasks. Possibly, high-level paradigms such as linguistic tasks more clearly or more quickly allow the identification of the contained low-level phenomena, and more readily allow testing of the resulting hypotheses.

6

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6.1 GLOSSARY

ACC *Anterior Cingulate Cortex*; ambiguous term. Typically refers to some subset of the frontal parts of the cingulate gyrus. See dACC; MCC; MFC; pre-rolandic cingulate cortex.

In the four-part parcellation of Vogt (2005), the ventral, prefrontal parts of the cingulate cortex, including the pregenual and subgenual ACC.

ACH *Acetylcholine*; Neuromodulator released by e.g. the NBM; associated with focused attention (Hasselmo & Sarter, 2010; Zaborszky et al., 2013).

DA *Dopamine*; Neuromodulator released by VTA and SN_{pc}; associated with approaching behavior, novelty and reinforcement learning (Lisman & Grace, 2005; Schultz et al., 1997).

DACC *dorsal Anterior Cingulate Cortex*; terminology employed by some researchers to refer to the limbic aspect of the posterior mediofrontal cortex, including what is called MCC and parts of the pACC in the four part parcellation of the pre-rolandic cingulate (Vogt, 2005).

DAN *Dorsal Attention Network*; brain system supporting top-down focus (Corbetta et al., 2008)

ERN *Error-related Negativity*; ERP component peaking right after error commission at frontal- or centromedial sites (Gehring et al., 2012).

ICA *Independent Component Analysis*. A Blind Source Decomposition technique that maximises independence between components (Bell & Sejnowski, 1995).

IFG *Inferior Frontal Gyrus*; holds a control function in various time-critical faculties, such as speech (as a target of the dorsal stream important for speech production) and reorientation (as part of the VAN).

IPL *Inferior Parietal Lobe*; overlaps with the TPJ (Singh-Curry & Husain, 2009)

LC *Locus Coeruleus*; brain stem nucleus; extensive cortical NE projections (Aston-Jones & Cohen, 2005; Bouret & Sara, 2005).

LC/NE-P3 MODEL *Locus Coeruleus/Noradrenaline-P300 theory*; proposal that the P3 results from phasic activity of the LC following motivationally salient events (Nieuwenhuis et al., 2005).

MCC *Mid-cingulate Cortex* (Vogt, 2005); usually largely coextensive with RCZ and dACC.

MFC *Medial Frontal Cortex*; rough anatomic label centered around the MCC.

MMN *Mismatch Negativity*. ERP component following sensory deviants in simple, predictable sequences (May & Tiitinen, 2010).

N2 *N200*; ERP component sensitive to surprisal and conflict, peaking around 200 msec post-stimulus, often at frontal sites (Folstein & Van Petten, 2008).

N400 Also sometimes *N4*; ERP component sensitive to incongruent events in streams carrying meaning (Kutas & Federmeier, 2011).

NBM *Nucleus Basalis of Meynert* in the Basal Forebrain; extensive cortical ACh projections (Hasselmo & Sarter, 2010; Zaborszky et al., 2013).

NE *Noradrenaline/Norepinephrine*; Neuromodulator released by the LC; associated with behavioral shifts following salient events (Aston-Jones & Cohen, 2005; Bouret & Sara, 2005).

P3 *P300*; ERP component sensitive to salient, critical events (Nieuwenhuis et al., 2005; Polich, 2007). Includes subcomponents P3b, P3a and P3f.

P3b; sometimes referring specifically to the parietal, task-critical instance of the P300.

P600 Also sometimes *P6*; ERP component following deviant and/or task-critical items, often in sentences (Coulson et al., 1998; Osterhout & Holcomb, 1992). Possibly a P3.

PE *Error positivity*; ERP component following an ERN (Falkenstein et al., 1999; Ridderinkhof et al., 2009). Likely a P3.

RCZ *Rostral Cingulate Zone*; conflict- and control-associated mediofrontal brain area; usually largely coextensive with MCC and dACC.

RPE *Reward Prediction Error*; the (signed) difference between a prediction and an event (Schultz et al., 1997).

SN *Substantia Nigra*; often specifically the *pars compacta* (SN_{pc} or SN_c); dopaminergic nucleus (Lisman & Grace, 2005; Schultz et al., 1997).

TOM *Theory of Mind*; the ability to infer the mental states of others; often associated with the VAN (Saxe & Wexler, 2005)

TPJ *Temporo-Parietal Junction*. A broad, ambiguous anatomical label referring to the inferior or ventral parietal and, partially, posterior temporal and temporo-occipital cortices surrounding the end of the sylvian fissure. Often includes the Angular and Supramarginal Gyrus; also sometimes parts of the posterior Superior Temporal Gyrus (Cabeza et al., 2012).

VAN *Ventral Attention Network*; brain system including IFG, TPJ and dACC, supports bottom-up, stimulus-induced reorientation; associated with the P3 (Corbetta et al., 2008)

VTA *Ventral Tegmental Area*; dopaminergic nucleus (Lisman & Grace, 2005; Schultz et al., 1997).

α *Alpha oscillation*; ~10 hz EEG rhythm dominating the posterior scalp at rest (Niedermeyer & da Silva, 2012; Wang, 2010).

β *Beta oscillation*; 15-25 hz EEG rhythm associated with focus and behavior (Niedermeyer & da Silva, 2012; Wang, 2010).

γ *Gamma oscillation*; >30 EEG rhythm associated with high-level integrative processes (Niedermeyer & da Silva, 2012; Wang, 2010).

δ *Delta oscillation*; <3 hz EEG rhythm associated with sleep (Niedermeyer & da Silva, 2012; Wang, 2010).

θ *Theta oscillation*; 3-8 hz EEG rhythm associated with focus and memory (Niedermeyer & da Silva, 2012; Wang, 2010).

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7

APPENDIX

7.1 PRE-REGISTRATION FOR STUDY 3

All scripts relevant for the fulfilment of this pre-registered procedure are available online at https://github.com/jona-sassenhagen/Charybdis

Studienprotokoll zur Studie

Reaktionszeit-Alignment später positiver ERP-Komponenten für linguistische Abweichungen ("P600")

Jona Sassenhagen

I. Übersicht

1. Titel der Studie

Reaktionszeit-Alignment später positiver ERP-Komponenten für linguistische Abweichungen ("P600")

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3. Zusammenfassung

In dieser Studie wird das EEG von Versuchspersonen gemessen, während sie per Knopfdruck während der Präsentation auditiver Sätze über die Richtigkeit dieser Sätze entscheiden. Untersucht wird, ob ERP-Effekte, die bekanntermaßen auf sprachliche Abweichungen folgen, zeitlich stärker mit Wortpräsentation oder dem bewertenden Knopfdruck korrelieren. Damit soll untersucht werden, ob es sich bei diesen ERP-Effekten um Korrelate sprachspezifischer Stimulusverarbeitung, oder um generelle reorientierungsrealierte Effekte.

4. Hintergrund

Die Studie soll untersuchen, ob gewisse Gehirneffekte, die auf sprachliche Verletzungen folgen, höherkognitive linguistische Verarbeitung oder generelle Prozesse reflektieren.

Die P600-Komponente des ERP wird von machen Forschern (Hagoort et al., 1993, Friederici et al., 1995) als ein Marker syntaktischer Prozesse, von anderen (Coulson et al., 1999, Kretzschmar et al., 2010) als eine späte P300 (einen generellen Effekt von Zustandswechseln) verstanden. Die P300 wird mit Noradrenalinausschüttung des Locus Coeruleus assoziiert (Nieuwenhius et al., 2005), was auf Stimuli, die Reorientierung erfordern, folgt und zeitlich stärker mit der Reorientierung als mit dem Stimulus korreliert.

5. Experimentsübersicht

Teilnehmer werden Sätze hören, die Abweichungen enthalten, die bekanntermaßen eine P600 auslösen, während ihr EEG aufgezeichnet wird, und sollen auf Abweichungen per Knopfdruck reagieren.

Teilnehmer werden aus den Studenten der Universität Mainz ausgesucht.

Unsere Haupthypothese betrifft das Reaktionszeitalignment der positiven Komponente nach delektierten Abweichungen. Wir erwarten, dass Komponenten, die generelle kognitive Zustandswechsel reflektieren, zeitlich strikt mit dem Knopfdruck korrelieren, während Komponenten, die die Analyse des Stimulus indizieren, zeitlich stärker mit dem Stimulus-Onset korrelieren.

Die P600 wird in Form einer positiven ERP-Welle etwa 600 ms nach Abweichungen erwartet.

II. Design und Durchführung

1. Vorbereitung und Ablauf

Versuchspersonen wird bei Eintreffen im Labor ein Fragebogen betreffend EEG-relevanter persönlicher Angaben sowie die Anleitung überreicht. Während diese bearbeitet werden, wird das EEG-Setup appliziert.
Im Labor stehen Getränke und Snacks bereit.
Nach Abschluss der Aufzeichung wird Versuchspersonen die Gelegenheit gegeben, sich die Haare zu waschen.

2. Aufnahmetechnik

Das EEG der Studienteilnehmer wird mit einem Brainproducts Brainamp und der Software Brainproducts Brainvision Recorder aufgezeichnet. Teilnehmern wird eine Standard-Elektrodenkappe appliziert; weiterhin werden suboritale Augenelektroden platziert. Kontakt wird durch ein hautneutrales konduktives Gel hergestellt.
Antworten werden über einen Standard-USB-Controller aufgegeben.

3. Stimuli

Pro Versuchsteilnehmer 200 Sounddateien, 100 korrekte Kontrollen und 100 teilweise syntaktische oder semantische Verletzungen; pseudorandomisierte Listen; präsentiert mit der Software Presentation.
Stimuli werden in 20 Blöcken á 10 Sätzen präsentiert. Nach jedem Block wird eine Pause initiiert, deren Länge Teilnehmer selbst kontrollieren.

4. Teilnehmer

Gesucht werden mindestens 15 gesunde rechtshändige Muttersprachler des Deutschen. Erfahrungsgemäß (zb. Kutas & Hilyard 1980) sind ~12 Teilnehmer bei der gegebenen Anzahl an Messpunkten ausreichend, allerdings würden, wenn die logistischen und finanziellen Bedingungen gegeben sind, weitere (optimal 20+) Teilnehmer aufgezeichnet. Sollte während der Aufnahme festgestellt werden, dass die Daten eines Teilnehmers technikbedingt nicht verwendbar sind, könnten Nacherhebungen nötig sein.
Potentielle Ausschlußkrieterien sind neurologische Vorbefunde sowie eine hohe Fehlerquote.

III. Auswertung

1. Datenvor- und Hauptverarbeitung

Daten werden mit der EEGLAB-Software und bereits vorliegenden speziellen Matlab-Skripten verarbeitet werden. Zur Vorverarbeitung werden Rohdaten Tiefpass-gefiltert (0.5 hz Butterworth Hochpass-Filter), epochiert, mittels Independent Component Analysis zerlegt und ICA-artefaktkorrigiert. Danach werden pro Bedingung Reaktionszeiten, ERPs und ERPimages berechnet. Als statistische Tests werden *repeated measures* - ANOVA auf die Reaktionszeit/den Mittelwert der ERP-Amplitude im der kritischen Komponente entsprechenden Zeitfenster verwendet.

2. Primärer Endpunkt

Single-trial - Alignment der P600-Komponente entweder zum Onset des kritischen (syntaktisch abweichenden) Worte oder zur folgenden Reaktionszeit (RT) soll folgendermaßen gemessen werden: EEG - Epochen, zentriert um den Onset abweichender Worte, werden mit ERPimages (Jung et al., 2001) dargestellt und nach Reaktionszeit sortiert. Im Mittel (ERP) dieser Epochen wird eine positive ERP-Komponente etwa 600 ms nach Onset erwartet. Für RT-sortierte ERPimages zeigen sich Stimulus-relatierte Effekte als vertikale Linien (parallel zum Stimulus-Onset). RT-korrelierte Effekte zeigen sich als dem

Verlauf der Reaktionszeit folgende Kurven.
Wir werden diese Effekte primär auf centro-parietalen Elektroden beobachten (Pz und Nachbarn).

3. Sekundärer Endpunkt

Wir werden außerdem das Onset-/RT-Alignment anderer Sprach-relatierter ERP-Komponenten (N400, LAN, N2) untersuchen, sowie eventuelle Attentional Blink - Phänomene (ein zweites kritisches Ereignis während der P300 des vorherigen) und Effekte für semantische vs. syntaktische Abweichungen in ihrer Skalptopologie untersuchen.

IV. Abschluss

4. Zusammenfassung

In dieser Studie soll gezeigt werden, ob durch sprachliche Verletzungen evozierte späte Positivierungen sprachspezifische oder generelle Prozesse reflektieren, in dem ihre eventuelle zeitliche Koppelung an die Reaktionszeit auf single trial - Ebene untersucht wird. Dazu wird ein Standard-EEG während der Präsentation kurzer Sätze durchgeführt.

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7.3 EIGENSTÄNDIGKEITSERKLÄRUNG

Hiermit versichere ich, dass ich die vorgelegte Dissertation mit dem Titel

Evoked Potentials during Language Processing as Neurophysiological Phenomena

selbst und ohne fremde Hilfe verfasst, nicht andere als die in ihr angegebenen Quellen oder Hilfsmittel benutzt (einschließlich des World Wide Web und anderen elektronischen Text- und Datensammlungen), alle vollstandig oder sinngemaß ubernommene Zitate als solche gekennzeichnet sowie die Dissertation in der vorliegenden oder einer ahnlichen Form noch keiner anderen in- oder auslandischen Hochschule anlasslich eines Promotionsgesuches oder zu anderen Prufungszwecken eingereicht habe.

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