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Development of an Experimental EEG Paradigm to Investigate Dysfunctions in Schizophrenia: Predicting the Sensory Consequences of One's Own Actions

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1 Index of Abbreviations

BOLD	Blood-Oxygen-Level Dependent
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EEG	Electroencephalography
ERP	Event-Related Potential
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th revision
fMRI	Functional Magnetic Resonance Imaging
SANS	Scale for the Assessment of Negative Symptoms
SAPP	Scale for the Assessment of Passivity Phenomena
SAPS	Scale for the Assessment of Positive Symptoms
SCID	Structured Clinical Interview for DSM-Disorders
SZ	Schizophrenia
SZP	Patient with Schizophrenia

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4 Introduction

4.1 Importance of Prediction Mechanisms

In our daily life we are faced with permanently changing situations generated by ourselves and by the environment. This, in turn, requires the capability of our brain to navigate all these experiences and filter out information since not everything happening reaches our awareness. As a complex process, sensory gating helps us understand and respond to the environment (Pynn & DeSouza, 2013). For appropriately reacting to changes in the environment, it is important to correctly attribute them. Therefore, it is necessary to be aware of the agency to actions and their consequences detecting the origin of them for discriminating self-generated from externally-generated events (Bansal et al., 2018). Just how important attributing agency is can be seen in the animal kingdom (Crapse & Sommer, 2008). Namely crickets show attenuated activity in specific neurons during chirping providing evidence for discriminating self-generated from external stimuli during behaviour at the cellular level (Poulet & Hedwig, 2006). Moreover, it is assumed that self-generated actions and their sensory consequences have no need of further cognitive processing which in turn saves metabolic resources and increases the efficiency of attention for external sensory stimuli (Frith, 1995).

It is generally assumed that distinction in self-generated and external actions is a result of knowledge about motor commands. Different internal models have been postulated such as the central monitor (Frith, 1992) and the internal forward model (Wolpert, 1997; Wolpert et al., 1995). With this in mind, these models can be used as a basis of sensory prediction of the motor command. Therefore, a copy of the motor command, more precisely an efference copy (Holst & Mittelstaedt, 1950), is generated to represent the predicted sensory consequences of the intended movement (Miall & Wolpert, 1996; Wolpert & Flanagan, 2001; Wolpert et al., 1995). Subsequently, the prediction is compared to the afferent sensory feedback, the actual sensory consequence (Blakemore, Wolpert, & Frith, 1998; Frith et al., 2000a). Thus, a match or mismatch results from the comparison: a mismatch is detected as a prediction error (Wolpert et al., 2011; Wolpert & Flanagan, 2001) and can help us with motor learning updating the predictions and adapting motor planning (Brooks & Cullen, 2019; Wolpert & Kawato, 1998). On the other hand, a match between predicted and actual sensory feedback leads to sensory attenuation which is well researched by a number of studies describing for example why we can't tickle ourselves (Blakemore et al., 1999; Blakemore, Wolpert, & Frith, 2000; Weiskrantz et al., 1971). Due to the match and resulting sensory attenuation, actions and their sensory consequences are experienced as self-generated whereas a mismatch results in attributing agency to external sources (Blakemore et al., 1999; Blakemore et al., 2002). Consequently, sensory consequences of one's own actions are

predictable and therefore do not require as much cognitive resources as external actions (Blakemore, Wolpert, & Frith, 1998; Frith, 1995; Pynn & DeSouza, 2013; Shergill et al., 2013).

Overall, prediction mechanisms occupy a central place in daily life in which it is important to classify actions and furthermore, attribute agency to understand the environment and responding adequately to it.

4.2 Principle of the Forward Model

Efficient perception of the environment and ourselves as part of it requires processes making predictions about changes which permanently happen (Pynn & DeSouza, 2013). Therefore, it's necessary to discriminate between self-generated and external changed situations (Bansal et al., 2018). Early on, Helmholtz (1925) identified the need of a cognitive mechanism for discriminating between moving objects in the environment and movement on the retina due to eyeball movements. Later on, Sperry (1950) suggested the model of corollary discharge presented by the motor command area to the sensory one for processing the sensory reaction to reafferent information. Finally, it is assumed by Von Holst and Mittelstaedt (1950) that there is a principle of reafference: simultaneous with the motor command, there is sent a copy, namely the efference copy, to sensory areas in the brain resulting in corollary discharge of the predicted input of the motor act. Thus, reafferent information, in other words the actual sensory input, as a consequence of self-generated movements is cancelled in the related sensory cortex (Ford et al., 2014)

Due to that suggested internal model, sensory processing is made: efference copy and corollary discharge are assumed to prepare the sensory areas for the reafferent feedback of one's own planned actions by making a prediction about action consequences (Cullen, 2004). This mechanism is shown in Figure 1. Moreover, it is also known as the forward model (Miall & Wolpert, 1996; Roussel et al., 2014; Wolpert, 1997; Wolpert & Ghahramani, 2000; Wolpert & Kawato, 1998). Consequently, the predicted feedback is compared to the reafferent sensory feedback and in case of a match, the further processing of the sensory consequences can be suppressed (Blakemore, Wolpert, & Frith, 2000). As a result, it is assumed that suppression of the response to the action feedback and attenuation of the reafferent signals (Weiss et al., 2011) increase the efficiency of attention focusing on external applied actions, so-called exafferent stimuli (Brooks & Cullen, 2019), in the environment (Pynn & DeSouza, 2013), for instance externally-generated tactile information (Bays & Wolpert, 2007; Blakemore, Wolpert, & Frith, 2000).

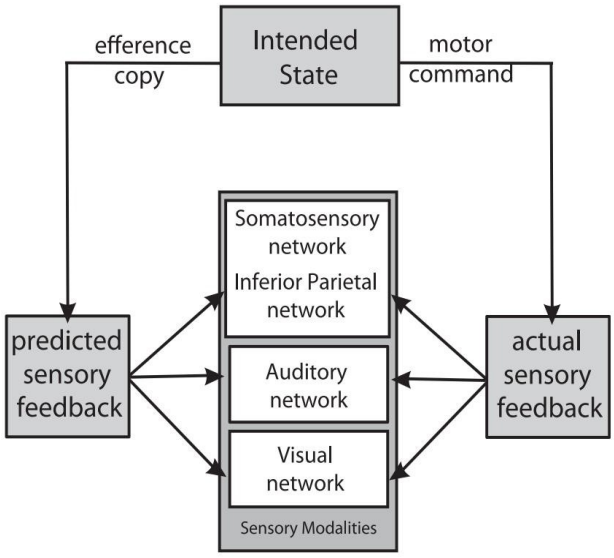

Figure 1 The Efference Copy Mechanism
Reference: Pynn & DeSouza, 2013, p.125

On the one hand, suppression of processing reafferent sensory consequences can be used to cancel inappropriate reflexes to predicted activities through preparing the sensory cortex (Cullen, 2004). On the other hand, an important function of the inhibition of the sensory activity is presumably making self-generated stimuli less surprising and therefore, allocating fewer resources which at the same time saves resources for external unpredicted stimuli (Pynn & DeSouza, 2013; Shergill et al., 2013; Wolpert & Flanagan, 2001). Reduction of cognitive load as a result of prediction mechanisms of self-generated actions is essential in our world of never ending external input (Bansal et al., 2018; Blakemore, Wolpert, & Frith, 1998) where one has to interact, adapt and fit in constantly. Moreover, the importance of suppression related to cognitive resources is shown by Ford et al. (2014) describing the correlation between the size of the match and suppression: the greater the one, the greater the other. Following, inaccurate predictions or even prediction errors are high-priced wasting metabolic resources. On this assumption, it plays a key role in human beings to have a brain working economically and processing efficiently with the aim of using resources exclusively for necessary stimuli (Ford et al., 2014).

Since the human brain must process and act on signals in different sensory modalities simultaneously, it is essential to use an internal forward mechanism not only for single modalities but also for the prediction of multisensory action consequences (Straube et al., 2017). For example, when we press a computer key there is somatosensory, auditory and visual feedback included. Thus, prediction of multisensory action consequences was already investigated in previous studies (Kemenade et al., 2016, 2017; Schmalenbach et al., 2017; Straube et al., 2017) and further, there is evidence for the facilitating effect

of multisensory information in perception (Ernst & Banks, 2002; Ernst & Bülthoff, 2004; McDonald et al., 2000). Therefore, Straube et al. (2017) assumed to have suppression in processing of both unisensory and multisensory predicted consequences in comparison to unpredicted consequences within the framework of one forward model creating multisensory predictions. Moreover, they presumed suppression to be even stronger in multisensory than in unisensory conditions which is a critical part in a highly multisensory environment.

Another key role in predicting environmental changes precisely plays the prediction of time, spatial information and intensity. Therefore, prediction mechanisms refer not only to the action itself but also to the temporal factor of the sensory consequences (Elijah et al., 2016; Hughes et al., 2013b). It has been assumed that prediction on the timing of actions is another function of the internal models in tool use contexts (Kilteni & Ehrsson, 2017b; Pazen et al., 2020) which has been shown by previous studies investigating the detection of temporal deviation (Arikan et al., 2019; Kemenade et al., 2016, 2017; Leube et al., 2003; Leube et al., 2010; Schmalenbach et al., 2017; Straube et al., 2017). Further, these models predict spatial information about the motor command which have to match with the afferent sensory feedback as well as the temporal prediction for sensory attenuation and the action being recognised as self-generated. The greater the temporal or spatial deviation from the predicted motor command, the less precisely is the prediction of the sensory consequences and therefore, the less attenuated is the sensation (Bays et al., 2005; Blakemore et al., 1999). Finally, a huge temporal or spatial deviation leads not only to less attenuation, but also to attribution of the action to another agent than oneself since the reafferent signal doesn't correspond to the predicted one (Blakemore et al., 1999; Farrer et al., 2008).

Overall, it is assumed that the result of the comparison between predicted and actual feedback of sensory, temporal and spatial action consequences is outside our awareness as long as there is no mismatch (Blakemore et al., 2002). Consequently, our attention can be focused on external changes in the environment without being distracted by self-generated intentions (Poulet & Hedwig, 2002; Pynn & DeSouza, 2013).

4.3 Prediction in the Sensory Systems

Environmental changes can be perceived by means of different senses. Therefore, there is need for prediction in each of the sensory systems.

As early as in the beginning of the 20th century, it has been assumed that there has to be a mechanism stabilizing our visual perception through moving the eyes permanently but not perceiving the world as moving (Holst & Mittelstaedt, 1950). Later on, it has been shown that an internal forward model is used for stabilization of the visual field (Duhamel

et al., 1992; Wurtz, 2008) and that it is necessary to have a stable visual world not only moving our eyeballs but also our head or body (Haarmeier et al., 1997).

Besides a stable visual world, the forward model is also fundamental to predicting the sound of one's own voice (Bansal et al., 2018; Ford & Mathalon, 2005; Pynn & DeSouza, 2013). Moreover, it is assumed that predicting auditory consequences is also important for self-generated vocalization or other auditory stimuli (Bansal et al., 2018; Eliades & Wang, 2005).

Not only prediction of visual and auditory consequences but also of somatosensory action feedback plays a key role in interacting with the environment. Therefore, it has been reviewed by Bansal et al. (2018) that it is essential to use a prediction mechanism and its function to prepare tactile, visuomotor and force processing domains. Further, these mechanisms can presumably be used to specify, update and adapt motor plans receiving reafferent feedback from self-generated actions, hence, it is also called motor learning (Brooks & Cullen, 2019; Shadmehr et al., 2010; Vaziri et al., 2006; Wolpert & Kawato, 1998). Overall, internal forward modelling is assumed to be crucial for sensorimotor integration (Wolpert et al., 1995).

4.4 Distinction between Self and Other and Sense of Agency

Another function and result of internal forward models using the motor command is the ability to distinguish between self-generated and external actions (Frith, 1992; Gallagher, 2000; Pynn & DeSouza, 2013; Wolpert, 1997; Wolpert et al., 1995). It is assumed that the prediction of self-generated actions matches the actual reafferent sensory feedback and therefore, the match allows us to identify actions as our own. In contrast, there is no efference copy for external actions preparing the sensory brain areas, and therefore, a mismatch presumably results in perception that the action of the experienced exafferent sensory consequence is externally produced (Blakemore et al., 1999; Blakemore, Smith, et al., 2000; Blakemore, Wolpert, & Frith, 2000, 2002). Since these externally-generated consequences contain new information for the brain, it is important for the interaction with the environment to be able to focus more intensively on processing these exafferent stimuli in comparison to predicted reafferent action consequences which have no need of further processing. Therefore, it is suggested that self-generated sensory feedback is attenuated for increased attention to external actions and changes in the environment (Frith, 1995; Pynn & DeSouza, 2013; Weiss et al., 2011).

Since the environment is changing constantly, it is essential to attribute agency correctly to react appropriately and control our actions as well as speech and thoughts (Bansal et al., 2018). With this in mind, the so-called sense of agency was reviewed by Haggard (2017): it has been described as the subjective awareness of experiencing our own

actions and their sensory consequences as self-controlled, thus, attributing agency to ourselves and further, allocating external changes correctly to extrinsic agents. Furthermore, it is not only important to identify direct action consequences as self-generated but also indirect consequences dependent on external devices used by ourselves (Ford et al., 2014). Subsequently, self-generated action consequences match the prediction and consequently, they are attributed to ourselves, but if there was a mismatch, the sense of agency is assumed to be reduced and the action is attributed to an external agent (Frith et al., 2000b; Synofzik et al., 2008). In other words, the more precise the prediction the greater the match and the greater the sense of agency and feeling of control (Farrer et al., 2008; Knoblich & Kircher, 2004; Leube et al., 2003). In addition, as long as there is no mismatch, this mechanism of self-awareness does not reach our consciousness (Blakemore et al., 2002; Gallagher, 2000). Finally, the sense of agency - based on sensory attenuation - helps us with social interactions and the feeling of responsibility in daily life (Gentsch & Schütz-Bosbach, 2011). Overall, these mechanisms for distinction between self and other are essential for perceiving our own actions as non-alarming and consequently, integrating ourselves appropriately in the environment (Bansal et al., 2018).

Distinction in the Sensory Systems

As a human being, we interact with the environment and our fellow men within different sensory systems. Therefore, it is important to take advantage of an internal forward model and its function of prediction in each of the systems for distinction between self- and externally-generated actions and as a consequence for perceptual stability.

In the auditory system, efference copy prepares the auditory cortex and therefore, one's voice as well as inner experiences like thoughts, inner speech and memories can be attributed to oneself (Creutzfeldt et al., 1989; Eliades & Wang, 2003; Ford & Mathalon, 2005; Houde et al., 2002; Mathalon & Ford, 2008). In addition, the internal forward model allows the prediction of sensory consequences for self-initiated sounds with external devices e.g. pressing a button (Ford et al., 2014; Ford, Roach, et al., 2007) and the correct agency attribution despite of uncertainties in frequency and onset (Baess et al., 2008). This is important since many of our daily interactions with the environment produce sounds that we do not exactly know at the moment of generation. Moreover, even physically-identical sounds can be attributed correctly to their agent due to different neural response and subsequent perception (Baess et al., 2011; Sato, 2008) as a result of the prediction mechanism. Consequently, distinction is crucial in the auditory system to interact correctly with the environment.

Attribution of sensations to distinguish between self-generated and external actions is also essential in the visual system. As in the auditory system, efference copy of the motor command for the eye muscles as well as the head position updates the visual cortex about the eye position and the object's retinal location for a stable visual world (Helmholtz, 1896; Sommer & Wurtz, 2008; Wurtz, 2008, 2018; Wurtz et al., 2011). In contrast, there is no prediction when movement of the eye is externally produced, for example with the finger pressing on the eye (Helmholtz, 1896), making stabilisation of the visual world is impossible. As a consequence, the object's retinal location changes and the world seems to move as there is no efference copy preparing the sensory areas in the brain and therefore, the visual change is attributed to an external agent. Thus, efference copy is necessary for correctly attributing visual sensation.

As well as in the auditory and visual system, the forward model also plays a key role in the somatosensory system. As with the other modalities, efference copy enables the prediction of self-induced tactile motor consequences to inform sensory brain areas (Blakemore et al., 2002) Thus, prediction facilitates the differentiation between the actions generated by ourselves and actions generated externally (Bays et al., 2006). Furthermore, self-initiated touch and movement are perceived as attenuated in comparison to external tactile stimulation which is necessary to distinguish between the two (Cardoso-Leite et al., 2010; Juravle et al., 2017; Kilteni et al., 2020; Weiss et al., 2011). Overall, predictive mechanisms are essential in each of the sensory systems to discriminate between self and other.

4.5 Intensity Perception and Sensory Attenuation

Prediction in the sensory systems results not only in discrimination but in less intense perception of self-initiated actions, a phenomenon called sensory attenuation (Roussel et al., 2014). For example, self-generated touch is perceived as attenuated and as weaker than externally produced or passive touch (Bays et al., 2006; Bays et al., 2005; Blakemore et al., 1999; Kilteni et al., 2020; Kilteni et al., 2019). Kilteni et al. (2020) assumed the lack of efference copy in passive and external touches to be the reason for experiencing them with stronger intensity than active touch since there's no prediction of sensory consequences resulting in attenuation.

Prediction in the somatosensory system is the reason why we can't tickle ourselves (Blakemore, Wolpert, & Frith, 2000; Claxton, 1975; Weiskrantz et al., 1971). In active tactile movements, efference copy results in dampened reafferent brain activity and therefore, the tactile stimulation is perceived as less intense and tickly. In passive movements, there is reafference including sensory information about the state of the body without the predictive efference copy and consequently, only little reduction in

ticklishness. In contrast, external exafferent stimulation induces neither efference copy nor reafference. Thus, the tactile stimulation is experienced as more intense and tickly than in the active and passive condition (Blakemore et al., 1999; Blakemore, Wolpert, & Frith, 1998; Shergill et al., 2005; Weiskrantz et al., 1971). Overall, the principle of efference copy and the resulting sensory attenuation explain the phenomenon why people are not able to tickle themselves.

Sensory attenuation is also shown when people try actively mimicking a given level of force which was presented to them externally first (Kilteni et al., 2018; Kilteni & Ehrsson, 2017a, 2017b). For example, force processing were demonstrated in a previous study: healthy subjects apply an increased amount of force due to sensory attenuation in active conditions in comparison to the given amount, in other words, subjects cannot correctly mimic the level of force (Shergill et al., 2003). Thus, sensory attenuation in the somatosensory system results in underestimating our self-generated amount of force.

As in the somatosensory modality, sensory attenuation has also been demonstrated in the visual and auditory sensory systems (Blakemore, Goodbody, & Wolpert, 1998; Cardoso-Leite et al., 2010; Hughes et al., 2013b; Roussel et al., 2013; Sato, 2008; Weiss et al., 2011). For example, Roussel et al. (2013) showed reduced contrast discrimination sensitivity for visual stimuli that were congruent to action-effect associations resulting from preactivation of sensory action-effects. Furthermore, self-generated stimuli have been shown to be perceived as darker than passively induced visual stimuli as a result of predictive mechanisms in a former study using functional magnetic resonance imaging (fMRI) (Lubinus et al., 2021).

In conclusion, the less precise and the less corresponding to the motor command in time, space and intensity the prediction is, the less the sensory attenuation and therefore, the greater the intensity of the perceived stimulus (Blakemore et al., 1999).

4.6 Neural Correlates of Prediction Mechanisms

Prediction mechanisms are not only demonstrated in adapted intensity perception with psychophysiological data but also on a neural level. Therefore, many studies have shown the electrophysiological correlates of sensory attenuation and the resulting feeling of agency, for example by comparing brain activity between self-generated and externally induced stimuli (Aliu et al., 2009; Blakemore et al., 2001; Blakemore, Goodbody, & Wolpert, 1998; Gentsch & Schütz-Bosbach, 2011; Hughes et al., 2013a; Martikainen et al., 2005; Schäfer & Marcus, 1973). So, these data show cortical processes resulting in attenuated neural response in active conditions, namely reduced event-related potential (ERP), by using electroencephalography (EEG) (Baess et al., 2008; Baess et al., 2009). Specifically, the N1 component of the ERP, the first negative deflection in EEG patterns

referring to the reference, peaks about 100 ms (therefore also known as N100) after the stimulus and is assumed to be suppressed in its amplitude as demonstrated in these studies. Overall, N1 suppression is seen as the neural effect of the internal forward model reflecting the cancellation of reafferent sensory consequences and by extension the prediction and distinction mechanisms.

Electrophysiological Data in the Sensory Systems

ERP responses for the auditory system regarding the forward model and sensory attenuation have been shown by many studies (Aliu et al., 2009; Baess et al., 2011; Baess et al., 2009; Creutzfeldt et al., 1989; Curio et al., 2000; Eliades & Wang, 2003; Ford, Gray, et al., 2007; Houde et al., 2002). Accordingly, there can be seen speech-induced suppression while speaking in the auditory cortex measured with the EEG in comparison to hearing recorded playbacks, for example as self-generated sounds via button press as well as altered or alien voice substituted for their own (Ford, Gray, et al., 2007; Heinks-Maldonado et al., 2005; Wang et al., 2014). Moreover, even in the absence of actual speech, inner speech induces a similar neural effect in the auditory cortex resulting in suppression of brain activity (Whitford et al., 2017). Therefore, it is assumed that also thoughts and inner speech produce an efference copy. Besides speech, there is another aspect in the auditory system: self-elicited tones, for example via manual button press, lead to suppression too (Baess et al., 2008; Ford et al., 2014; Ford, Roach, et al., 2007; Ghio et al., 2018; Martikainen et al., 2005; Sowman et al., 2012). In addition, uncertainty in frequency, quality and onset is tolerated, but suppression is still the largest when this information matches the prediction (Baess et al., 2008). Furthermore, an active movement not directly connected to the tone also results in action-dependent suppression of auditory processing. Thus, action-sound contiguity leads to attenuated cortical response without triggering directly the sound (Hazemann et al., 1975; Horváth et al., 2012; Makeig et al., 1996). Overall, sensory attenuation in the auditory system is shown for speech, thoughts, self-initiated and action-associated sounds in the EEG.

In line with findings for sensory attenuation in the auditory modality, there is given little evidence by previous studies for suppression of early visual components elicited by self-generated visual action consequences in comparison to externally-generated sensory consequences. For example, Gentsch & Schütz-Bosbach (2011) demonstrated reduced cortical brain activity to visual action effects when they are self-generated in comparison to externally induced effects. These results are congruent with findings of other authors using a movement-device with a button press and in addition, self-generated visual flashes by volitional eye movement (Mifsud et al., 2018). Unlike these previous results, there is other research which did not find early reduced activity. Moreover, some studies

demonstrated enhancement instead of suppression for different visual ERP components of self-generated visual action consequences (Csifcsák et al., 2019; Hughes & Waszak, 2011; Mifsud et al., 2016). Overall, results for early components in the visual system show inconsistency in electrophysiological brain activity.

In the somatosensory systems, results are in line with the auditory system and sensory attenuation. Response to self-generated movement is assumed to be attenuated in comparison to external touch demonstrated with electrophysiological data (Chapman, 1994).

Functional magnetic resonance imaging data

Further, many studies demonstrated sensory attenuation with neurophysiological data using fMRI. There is evidence from differences in blood-oxygen-level dependent (BOLD) signal, for example of the somatosensory cortex and the cerebellum, between self- and externally-generated sensory consequences (Arikan et al., 2019; Leube et al., 2003; Shergill et al., 2013; Straube et al., 2017). These differences in brain activity has also been shown for the question why we cannot tickle ourselves (Blakemore, Wolpert, & Frith, 1998). Furthermore, a mismatch between prediction and actual feedback is shown as increased activity in the fMRI (Kemenade et al., 2017). Overall, the specific neuroanatomic brain areas of the different sensory systems can be demonstrated more precisely with functional imaging data than with electrophysiological data. However, these two methods complement each other in understanding the neural correlates of prediction, specifically the sensory attenuation.

4.7 Prediction in Schizophrenia

Schizophrenia (SZ) is a chronic and severe mental disorder. The complex neuro-psychiatric illness is associated with a broad variety of so-called positive and negative symptoms. On the one hand, there are significant alterations in behaviour and perception usually not being experienced by healthy subjects which are known as positive symptoms. These include hallucinations and delusions as well as passivity experience, thought and ego disturbances (Andreasen & Olsen, 1982) and are mainly present in acute phases of the disorder. On the other hand, negative symptoms describe a reduced state in comparison to healthy behaviour, including mental and emotional states which particularly occur in the chronic phases of the disease. Specifically, there is anhedonia, flattening of affect, apathy and listlessness, impoverishment of speech as well as cognitive impairment, emotional and social withdrawal (Andreasen et al., 1990; Dilling & Freyberger, 2019).

Schizophrenia affects around 1% of the worldwide population (Gaebel & Wölwer, 2010) whereas the most common form is paranoid SZ. Moreover, the complex neuropsychiatric illness is among the Top Ten worldwide causing a high degree of disability as reviewed by the World Health Organization (2002). What is known is that lifetime prevalence is increased with familial exposure whereas the cause of the neuropsychiatric illness has not yet been conclusively clarified and seems to be multifactorial (see textbooks of Psychiatry for details).

The medical historical development in Germany started with Emil Kraepelin who first described the clinical symptomatology of SZ in 1896, the so-called 'dementia praecox'. Later on in 1911, Eugen Bleuler characterised the term schizophrenia and formulated the disorder as a group of schizophrenias with the differentiation from dementia. Finally, Kurt Schneider distinguished between first- and second-order symptoms in 1959 as a preliminary stage of today's definition and classification of SZ (Hofer & Fleischhacker, 2012; Schneider, 1959).

4.7.1 Disturbed Prediction Mechanisms in Schizophrenia

The positive symptoms of schizophrenia are thought to be a result, at least in part, of disturbed efference-copy mechanisms (Daprati et al., 1997; Franck et al., 2001; Frith, 1987, 1992; Kircher & Leube, 2003; Lindner et al., 2005; Shergill et al., 2005). Failures in the internal forward model system to generate efference copy and therefore, failures in transmission to sensory cortices and sensorimotor integration (= disintegration) has been proposed to cause psychotic symptoms and the neurological abnormalities associated with SZ (Bansal et al., 2018; Blakemore, Wolpert, & Frith, 2000; Feinberg, 1978; Ford & Mathalon, 2004, 2005; Frith, 1995). It is assumed that patients with schizophrenia experience these misperceptions because of an inability to predict sensory consequences. Consequently, cortical processes cannot be unconsciously adapted as in healthy subjects and therefore, there is no typical sensory attenuation in neural responses to expected self-induced stimuli (Blakemore et al., 2002; Leube et al., 2010). This dysfunction in the internal forward model causes not only wasting of metabolic resources but inappropriate attention and salience to sensory input generated by the patients themselves (Fletcher & Frith, 2009; Kapur, 2003; Pynn & DeSouza, 2013). Overall, deficits in self-monitoring and predictive mechanisms presumably result in symptomatology of SZ.

4.7.2 Sense of Agency in Schizophrenia

Patients with psychopathological symptoms of SZ have not only deficits in their sense of self wherefore the disorder is also called disorder of the self, but further disturbance in discrimination between own and other. Therefore, there is presumably dysfunction in the

internal monitoring system usually resulting in sensory attenuation for self-produced stimuli and in addition, allowing the brain to distinguish between self- and externally-generated sensory consequences (Blakemore, Smith, et al., 2000; Frith, 1992; Frith & Done, 1989). Moreover, the system normally enables one to identify actions, speech and thoughts correctly to their origin as long as there is no perturbance in prediction mechanisms (Bansal et al., 2018; Jeannerod, 2009). Abnormal predictions lead to a lack of awareness and attenuation of self-induced sensory consequences (Frith et al., 2000b). Further, they result in reduced sense of agency and therefore, cause false agent attribution (Blakemore et al., 2002) which is why SZ is also called disorder of agency. Consequently, it has been shown that in tasks requiring internal predictions, patients have difficulties in comparison to healthy subjects (Daprati et al., 1997; Lindner et al., 2005; Martinelli et al., 2017; Shergill et al., 2005; Shergill et al., 2014). Overall, it is assumed that patients with SZ misattribute self-generated sensory consequences to an external source or agent on the basis of perturbance in internal predictive mechanisms.

Correspondingly to pathomechanisms in prediction and in sense of agency, clinical signs in SZ include passivity experiences such as delusions of influence or alien control and ego disturbances (Leube & Pauly, 2008; Schneider, 1959). Patients with SZ feel like their self-generated actions and speech as well as thoughts and emotions are intended but controlled, influenced or initiated by external force, for example alien control, and isolated from the sense of will (Blakemore et al., 2002; Feinberg & Guazzelli, 1999; Frith, 2005; Wing et al., 1974). For example, Mellor et al. (1970) cite how a shorthand typist feels: ‘When I reach my hand for the comb it is my hand and arm which move, and my fingers pick up the pen, but I don't control them... I sit there watching them move, and they are quite independent, what they do is nothing to do with me... I am just a puppet who is manipulated by cosmic strings. When the strings are pulled my body moves and I cannot prevent it.’ (Mellor, 1970, p. 18). Thus, patients with SZ are aware of their goal, for example moving their hand, but identify an external source instead of themselves as the agent of the action and following sensory consequences.

4.7.3 Sensory Systems in Schizophrenia

It is assumed that the classification of self-induced sensory consequences as external occurs as disturbances of self and hallucinations in SZ (Frith, 1992). Hallucinations are erroneous perceptions and sensory experiences when awake without external input but perceived as real stimuli in relation to their properties. Further, the sensory input feels like being under external control isolated from the sense of will (Aleman & Haan, 1998; Slade & Bentall, 1988). Patients with SZ are presumably not aware of predicted consequences because of dysfunctional efference copy mechanisms and therefore, they cannot compare expected to actual sensory feedback. Hence, patients have difficulties

in attributing the agent to the action. Consequently, it is assumed that they experience self-generated stimuli as external ones, specifically as hallucinations (Bansal et al., 2018; Blakemore et al., 2002). First and foremost, hallucinations in SZ are most common for the auditory system with a lifetime prevalence of 64-80%, followed by the visual, subsequently the tactile and last but not least, the olfactory system (Andreasen & Flaum, 1991; McCarthy-Jones et al., 2017).

In the auditory system, misattributing inner speech as well as thoughts and memories to external sources cause the perception of externally-generated verbal stimuli occurring as hearing spoken voices, so-called auditory hallucinations, and thought-insertion in SZ (Feinberg & Guazzelli, 1999; Fletcher & Frith, 2009; Jeannerod, 2009; Pynn & DeSouza, 2013; Waters & Badcock, 2010). Further, there is evidence for self-monitoring deficits, especially speech-monitoring deficits, resulting in this positive symptomatology of SZ (Blakemore, Smith, et al., 2000; Daprati et al., 1997; Feinberg, 1978; Ford et al., 2008; Franck et al., 2001; Frith, 1995; Lindner et al., 2005). Moreover, first-rank symptoms in SZ psychopathology include for example commenting, dialogizing and commanding voices in the absence of a real speaker and are considered to be central to the disorder (Hoffman, 1986; Johnstone, 1991; Leube & Pauly, 2008; Schneider, 1959). Overall, auditory hallucinations are the most common with respect to the other modalities in SZ and they are seen as a result of misattributing one's inner voice.

In the visual system, hallucination often co-occurs with one of the other modalities in patients with SZ, especially with the auditory system (Bracha et al., 1989; Frieske & Wilson, 1966; Goodwin et al., 1971; Mueser et al., 1990; Waters et al., 2014). In patients with visual hallucinations, the world is assumed to be perceived as unstable during own eye movements due to disturbances in predictive mechanisms and visual processing dysfunctions resulting in the impression that self-produced (retinal) information comes from the outside (Butler & Javitt, 2005; Butler et al., 2008; Holzman et al., 1973; Lindner et al., 2005; Thaker et al., 1996; Thakkar et al., 2017). Moreover, mental images as produced during imagining or memorising are assumed to be attributed to external sources and therefore, they are perceived as real stimuli generated from the outside (Morrison et al., 2000). Thus, misinterpretation relying on abnormal prediction presumably causes visual hallucinations.

As with the visual and auditory modality, there are also tactile hallucinations in SZ, although not as often (McCarthy-Jones et al., 2017; Thomas et al., 2007). Consistent with the assumption of failure in prediction mechanisms and resulting deficits in self-monitoring, it is assumed that the attribution of self-produced movements and touch to an external agent cause the perception of being externally controlled and generated

(Blakemore et al., 2001; Blakemore et al., 2003; Frith, 1987, 1992; Frith et al., 2000a; Spence et al., 1997).

4.7.4 Intensity Perception in Schizophrenia

Self-generated touch and tactile stimuli as well as sensations of other sensory modalities are usually attenuated in the corresponding cortical sensory areas. This results not only in less brain activity and agency attribution to oneself, but further in a decrease in the feeling of intensity. For example, healthy subjects perceive a self-produced tactile stimulus as less ticklish and intense than an identical externally-generated one, whereas patients with positive symptoms as hallucination and passivity experience do not show a decrease in intensity rating (Blakemore, Smith, et al., 2000). Thus, it is assumed that there is reduced modulation of brain activity resulting in a dysfunction in sensory processing and attenuation in SZ (Bansal et al., 2018).

In line with the tickling task and the hypothesis that there is failure in prediction mechanisms in SZ, there is a further task underlining this: patients are more precise in mimicking an exact level of force, applied externally to them first. In contrast, healthy subjects apply an increased amount of force due to sensory attenuation causing underestimation of self-generated force (Shergill et al., 2005). Overall, in SZ there is presumably perturbance in the sensory attenuation of self-generated action consequences on the basis of failure in the forward model shown by the tickling as well as the force task.

4.7.5 Neural Correlates of Prediction Mechanisms in Schizophrenia

Reduced sensory attenuation in SZ is not only shown in sensory attenuation and behavioural data but in electrophysiological data. Therefore, study of eye movements gives evidence for neural correlates and dysfunction of prediction mechanisms and the failure of this system in patients with SZ (Thakkar & Rolfs, 2019).

In the auditory system, there is reduced N1 suppression in patients with SZ in comparison to healthy subjects during self-produced sounds, for example while speaking and moreover, during inner speech (Ford, Gray, et al., 2007; Ford & Mathalon, 2004, 2005; Ford, Mathalon, Heinks, et al., 2001; Ford, Mathalon, Kalba, et al., 2001a, 2001b; Ford et al., 2013; Ford, Roach, et al., 2007; Heinks-Maldonado et al., 2007). Parallel to these findings, there is also less suppression in self-induced sounds with an external device like a button press delivering a tone in SZ (Ford et al., 2014). Moreover, when it comes to auditory hallucinations, they are perceived as real acoustic stimuli in the corresponding brain areas, specifically the Heschl's gyrus, demonstrated in fMRI data (Dierks et al., 1999; Oertel et al., 2007). Thus, findings for the auditory modality are seen as a result of abnormal predictive mechanisms in SZ.

As with the auditory modality, abnormalities in sensory attenuation in SZ have also been shown in the somatosensory system, especially with neurophysiological functional imaging data using fMRI. For example, brain activity relating to self-generated tactile compared to external forces is increased in patients in comparison to healthy subjects (Shergill et al., 2014). Further, Leube et al. (2010) demonstrated worse detection of delayed visual feedback of own hand-movements and less attenuation in somatosensory cortical areas in SZ in comparison to controls and therefore, they assumed that this was a result of impaired efference copy. Overall, it is assumed that lesions in corresponding brain areas result in dysfunction of sensorimotor integration (Wolpert et al., 1998) and that following dysfunctional modulation of somatosensory activity results in perturbances of self-monitoring.

4.8 Study Goals

In our everyday life, we are constantly faced with changing situations in the environment and social interaction. Therefore, efficient perception of the environment and ourselves as part of it requires processes making predictions about the upcoming changes (Pynn & DeSouza, 2013). Furthermore, it's necessary to discriminate between self-generated and externally changed situations (Bansal et al., 2018). Moreover, it is assumed that self-generated actions and their sensory consequences have no need of further cognitive processing which in turn saves metabolic resources and increases the efficiency of attention for external sensory stimuli (Frith, 1995). Overall, the internal forward model is known as an important mechanism to interact in daily life.

Consequently, disturbed prediction mechanisms and failure in efference copy are assumed to be a reason for several symptoms of SZ, a chronic and severe mental disorder affecting around 1% of the worldwide population (Gaebel & Wölwer, 2010). Considering the high suicide rate of 10% and the high degree of disability as well as the huge economic costs as reviewed by the World Health Organization (2002), research is needed to serve both the health care system and patients suffering from SZ (Gaebel & Wölwer, 2010). Moreover, this demonstrates the importance of this work on dysfunctions in SZ. The disease is associated with a broad variety of so-called negative and positive symptoms, for example hallucinations and delusions. However, given that most of the prior neurophysiological research addressed the auditory and tactile systems, it is important to gain further scientific knowledge for the visual modality as well.

Against the outlined background, the main purpose of this work was the development of an experimental EEG paradigm to investigate efference copy based predictions in healthy subjects and patients with SZ. In the present study, we wanted to investigate prediction of self-generated versus external initiated actions and their sensory

consequences. Further, we intended to demonstrate intensity perception for active and passive conditions. Therefore, we decided to develop a behavioural intensity judgment task for the visual system since there are only few and incongruent results, in particular with patients. Following, we wanted to improve the experimental setup of an experiment designed for a healthy student sample to make it as suitable as possible for patients with SZ. Therefore, the sample of participants was divided into two parts. Firstly, healthy subjects participated in the extensive experiment with many trials, conditions and varying intensities of the test stimuli. Secondly, another sample of healthy subjects and a small group of patients fulfilled the task of the optimised experiment.

According to the aim of this work to achieve the development of a suitable experimental task, various sub-goals must be fulfilled. Firstly, we expected for the extensive experiment that in healthy subjects, the analyses of a selected number of trials (in visual trials with stimuli of the same intensity) will be sufficient to show that N1-ERPs have significantly lower amplitudes in the active conditions than in the passive. Secondly, we assumed that the second stimulus is perceived as more intense significantly more often in trials with visual stimuli of the same intensity in active conditions than in passive ones due to efference copy. With the main aim to develop an optimised experiment (more efficient, for example shorter overall duration, only visual condition, increased number of trials of the same intensity) for suitability of patients, we expected clearer N1-ERP and behavioural effects for the optimised experiment after changing the experimental setup of the extensive one. Finally, we suggested that patients are able to perform the optimised task well and do not find it too complicated. We expected this to be evidenced by the Post-Experiment Questionnaire.

5 Materials and Methods of the Extensive Experiment

5.1 Participants

We recruited N = 26 healthy students from the University of Marburg (Philipps-Universität Marburg) by a university mailing list, advertisements and word of mouth. Eighteen of the students were female. Ages ranged between 19 and 31 (M = 23.7, SD = 3.46). All students were right-handed by their own admission and depending on our experimental setup and construction. If the participants wore glasses, they were supposed to have them on. None of the participants wore a hearing aid. Before taking part in the experiment, participants were screened to ensure they met inclusion criteria. All participants had to be between 18 and 60 years old and were naïve to the purpose of the experiment. Exclusion criteria included a past or current mental disorder relating to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), a first-degree relative with SZ, regular use of psychoactive medications, history of drug or alcohol abuse or serious brain injury and further neurologic diseases compromising the central nervous system, for example epilepsy.

Before starting the experiment, all participants were informed about the procedure, had the chance to ask questions and gave their written informed consent according to the Declaration of Helsinki.

All participants obtained 30 euros for the EEG recording session as an expense allowance for an average time effort of 2.5-3 hours.

One participant's behavioural data were missing due to a technical error with the presentation software. These data couldn't be included but this participant could still be included in the EEG analyses. Therefore, 25 participants' data were included in behavioural analyses and 26 in EEG analyses.

5.2 Equipment

Participants sat in a darkened room. The experimental construction consisted of a 19" computer monitor running at 60 Hz with an ordinary keyboard. Next to that was placed the button box. Participants wore headphones by Sony.

EEG data were recorded from 32 active Ag/AgCl electrodes according to the international 10-20 system using an elastic cap (actiCAP, Brain Products GmbH, Germany) to mount the electrodes.

Experimental presentation was performed with Psychtoolbox (V 3.0.12) (Brainard, 1997) running on Octave (V 4.0.0) in Linux.

5.3 Task and Stimulus Material

The procedure outlined here was completed as part of a larger study also containing an auditory as well as a multimodal task. For the purposes of this study, only the visual task is described. The methods and dataset have been used and parts of it have already been published by Ody et al. (2023).

Instructions were displayed to the participants step by step on the screen. All participants were asked to do a short training session before applying the EEG cap to familiarise them with the task which consisted of 5 blocks of 5 trials each. If there were still any uncertainties about the experimental procedure, the participants could ask questions verbally after the training.

In order to fulfil the task, participants sat in front of a computer monitor in the darkened room. They had to lay down their right hand on the button box next to the monitor. The index finger was attached loosely to the button with a soft bandage. Two fingers of the left hand had to be placed on the “V” and “N” key of the keyboard. Additionally, the participants wore headphones for masking the sound of the button press with pink noise and for presentation of auditory stimuli.

Participants attended to visual stimuli displayed on the computer monitor and auditory stimuli delivered through headphones transmitting via Psychotoolbox. Active and passive movements were executed using a custom-made device, the button box. In active blocks, participants had to press the button which initiated a stimulus (grey circle), followed by a second stimulus. In passive blocks, the button was activated by compressed air by means of an electromagnet, pulling the participant’s finger down with the same trajectory. In both blocks, participants judged whether the first or second stimulus was more intense (brighter) by pressing one of the defined keys with their left hand. The key “V” means the first stimulus was perceived to be more intense, the key “N” had to be pressed when the second one was perceived to be more intense.

The structure of a single trial is shown in Figure 2.

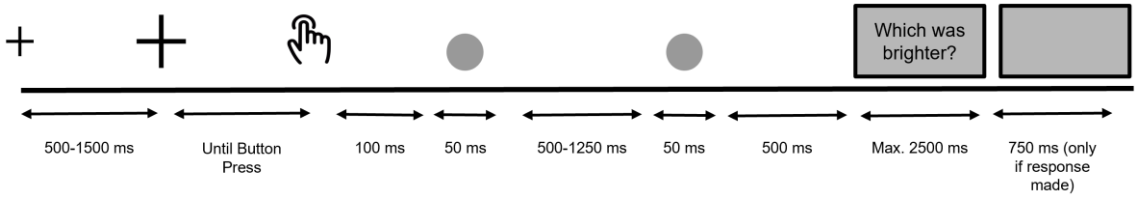

Figure 2 An Example of an Active Trial in the Extensive Experiment

In each trial, a black fixation cross appeared on the screen for a randomly selected duration of 500, 750, 1000, 1250 or 1500 ms which had to be fixated by participants. Followed by a larger fixation cross (= cue) in the same black colour, participants had to press the button actively by themselves in active trials. In passive trials, the cue indicated that the button would soon be activated. The button was activated after a jittered interval of 500-1250 ms in steps of 83 ms. The first (target) stimulus, a grey circle, was presented for 50 ms with a delay of 100 ms after the button press making the stimulus' appearance in both active and passive conditions predictable even though participants could not predict when their finger would move in the passive condition. So, the delay's function was matching temporal prediction between active and passive trials. After a randomly selected inter-stimulus interval with variable duration of 500, 750, 1000 or 1250 ms, the second (comparison) stimulus was presented for 50 ms. While the stimuli were presented, the fixation cross disappeared, but remained on screen during the interstimulus interval and the following 500 ms interval after the comparison stimulus. Afterwards, the participants had to judge the intensity of the stimuli. Therefore, the question appeared on the monitor: 'Welcher war heller?' ('Which was brighter?', in German). Deciding by pressing the "N" or "V" key on the keyboard, a response triggered inter-trial interval of 750 ms was made before the next trial followed. If the participant failed to response within 2500 ms, the next trial started automatically.

As part of the larger study procedure, the intensity of the visual stimuli varied too. The first visual stimulus was a 250-pixel circle and was always presented at a luminance of 11.42 cd/m², whereas the second (comparison) stimulus could have a luminance of 8.84, 9.94, 11.42, 12.69 or 14.04 cd/m². However, in order to address the hypothesis that the comparison stimuli should be judged as subjectively brighter more often in the active condition than in the passive condition, only trials in which both stimuli had identical luminance were used for analysis. Therefore, all reported analyses include only this subset of trials. Stimuli were presented on a fixed grey background with luminance of 3.40 cd/m². Luminance measurements were performed using an i1Display Pro photometer (X-Rite Pantone, Grand Rapids, USA).

In total, 100 active and 100 passive trials were presented for the visual condition. Trials were presented in mini blocks of 25. Since this work is part of a larger study containing an auditory and multimodal conditions as well, the total number of experimental trials was 800. Further, the experimental blocks of the different conditions were arranged pseudo-randomised in different order during the overall duration of the larger study achieving by varying the order of presentation (visual or auditory first), the order of unimodal and bimodal blocks within them and the starting action in each block (active or passive movement).

In addition, two blocks were included to control for motor activity in the ERP signal, presented after the experimental block. Identically to the experimental blocks, participants saw a fixation cross and made an active or passive button press. However, following the button press, there was a 1000 ms delay before the stimuli and question were presented. Each block consisted of 60 trials which in turn consisted of 30 active and 30 passive trials presented in mini blocks of 15 trials each. These conditions were included to control for differences in motor activity between the active and passive conditions. The activity related to the button press alone (without stimulus) can be subtracted from the ERPs in the experimental condition, minimising potential differences related to motor activity between the active and passive conditions. The 1000 ms delay was included to allow this activity to be captured without being affected by the task. However, the task was also included in order to ensure that participants remained engaged as in the experimental blocks. Due to the larger study design, half of the control block trials had the visual task while half had a similar task using auditory stimuli.

In total, the duration for the extensive experiment was 2.5-3 hours. This included about 15 minutes for the instructions and the training session and about another 30 minutes for applying the EEG cap. Afterwards, the experimental task counting 920 (800 experimental and 120 control) trials in total lasted about 1.5-2 hours. Finally, the removal of the EEG cap and washing of the hair was about 15 minutes.

5.4 EEG Data Acquisition and Preprocessing

EEG was continuously recorded from 32 electrodes (Fp1/2, F7/8, F3/4, Fz, FT9/10, FC5/6, FC1/2, T7/8, C3/4, Cz, TP9/10, CP5/6, CP1/2, P7/8, P3/4, Pz, O1/2 and Oz) at a sampling rate of 500 Hz and was referenced online to the electrode location Fcz. The ground electrode was placed on the forehead. Impedances were kept at 25 kO or below. The complete session was recorded online with BrainVision Recorder and the signal was amplified by a BrainVision amplifier (Brain Products GmbH, Germany).

EEG preprocessing was performed with the EEGLAB toolbox (Delorme & Makeig, 2004). Therefore, the raw continuous EEG was downsampled to 250 Hz offline and high-pass filtered at 0.5 Hz. Further, a notch filter was applied to remove 50 Hz line noise and its harmonics (100, 150, 200, 250 Hz) from the PREP pipeline using cleanLineNoise (Bigdely-Shamlo et al., 2015). Additionally, bad channels were rejected and interpolated by identifying via artefact subspace reconstruction (Chang et al., 2018). The resulting EEG data were rereferenced to the average of two mastoid electrodes (T7/8). Then, we implemented automatic ICA-based artefact detection and rejection by using AMICA (Palmer et al., 2012). Finally, data were low-pass filtered at 20 Hz and an additional artefact identification and rejection procedure was implemented with the

ft_artifact_zvalue (z = 12) from the Fieldtrip toolbox (Oostenveld et al., 2011). Using this method, 8.42% trials were rejected due to containing artefacts.

5.5 Data Analysis

All analyses were done with custom-made MATLAB scripts (R2020a MathWorks, Sherborn, Massachusetts). Further, for all analyses an α level of .05 was considered as statistically significant. For all *t*-tests, we reported Cohen's *d* as a measure of effect size.

N1-ERP Analysis

For N1-ERP analysis, we selected only visual trials where both stimuli had the same intensity. In total, there were 40 trials (20 active and 20 passive).

EEG were bandpass filtered between 0.5 and 20 Hz using a Butterworth filter and then segmented from 300 ms before to 400 ms after the button press and from 300 ms before to 400 ms after the onset of the fixation cross at the start of the trial. The data were then subjected to a baseline correction using the period 200 ms before the onset of the fixation cross at the start of the trial. Next, the mean activity per participant, channel and time point was calculated for each condition. The activity in the active and passive control conditions was then subtracted from the active/passive experimental conditions. The ERP was averaged across channels O1, O2 and Oz.

For statistical analysis, peak values were extracted by identifying the most negative value of the ERP across all conditions. Then, a time window of 24 ms around the centre value were defined and all the values within this window were averaged per participant and per condition. These peak values were then entered into paired samples *t*-tests.

Behavioural Analysis

Performance in the intensity judgement task was assessed by examining the proportion of trials in which the stimulus of interest was perceived as darker than the second stimulus. Since the luminance of the target stimulus was held constant throughout the experiment, any change in perception of brightness would reflect purely perceptual differences. While conventional analyses considered changes in the comparison stimulus, for example by using different contrast values for visual letter stimuli (Roussel et al., 2013), we selected only those trials with identical brightness. The proportion of trials in which participants answered 'second stimulus brighter' were calculated for each participant and condition. The proportion of '2^{nd} brighter' responses was compared between the active and passive conditions with a paired samples *t*-test. Trials in which no response was given were excluded from the analysis (2.1%).

5.6 Ethics Proposal

The experiment was approved by the ethics committee of the University of Marburg (AZ 40/20) on 03/06/2020 and was performed in accordance with the Declaration of Helsinki of 1975.

6 Results of the Extensive Experiment

In the following sections, the results of the selected trials (with the same intensity) from the extensive experiment are presented. Firstly, we show the analyses of EEG data and secondly, the behavioural data of healthy subjects are demonstrated. The analyses aim to identify whether there is a significant difference in the N1-ERP amplitude between active and passive conditions as well as in the behavioural task judging which stimuli was brighter.

6.1 N1-ERP Suppression in Healthy Subjects

Figure 3 demonstrates the mean ERP amplitudes to visual stimuli (A) and the topographical scalp plots (B) for healthy subjects. In Figure 4, the distribution of N1 peak values is shown for active and passive button press for healthy subjects. For the visual stimuli (see Fig. 3, Fig. 4), N1 was suppressed for visual stimuli in the active condition in comparison to the passive one. Mean N1 peak values in active trials (M = 0.63, SD = 3.29) were smaller than in passive trials (M = -1.11, SD = 3.11). The difference was significant ($t(25)$ = 2.24, p = .034, Cohen's d = 0.44).

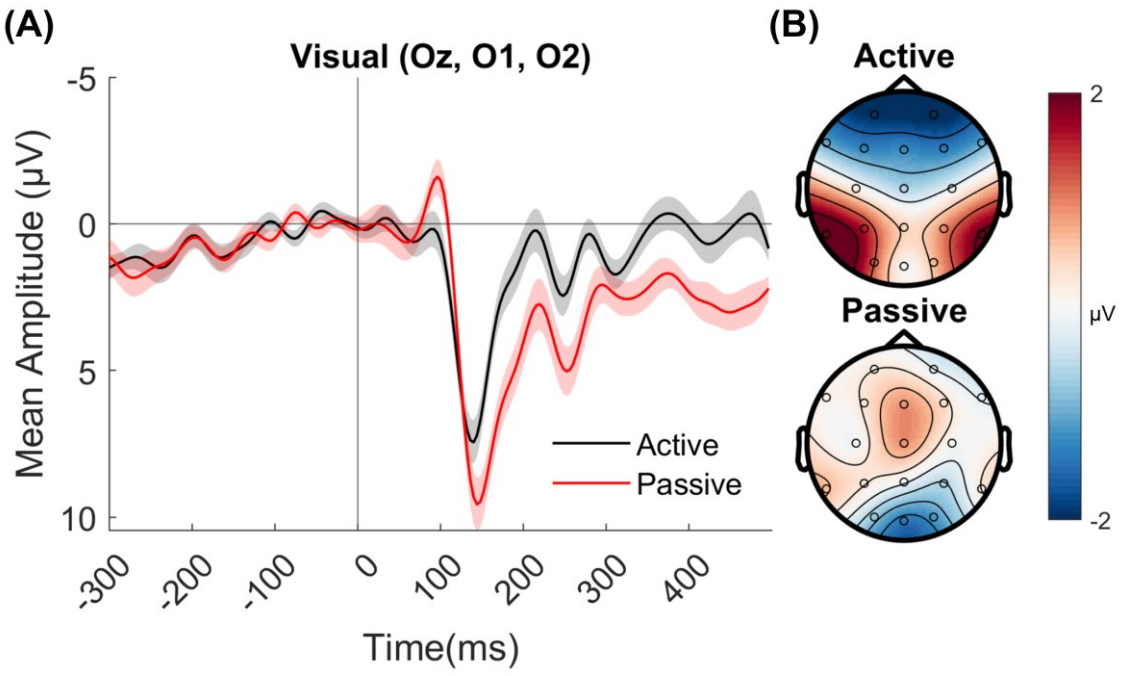

Figure 3 N1-ERP Suppression in Healthy Subjects in the Extensive Experiment
(A) Event-related potential (Mean Amplitude (µV)) to visual stimuli following an active or passive button press for healthy subjects; black line: active condition; red line: passive condition; shading around the lines: standard deviation; 0 ms: button press (B) Scalp topography maps for suppression of N1 amplitude (84-108 ms) for healthy subjects

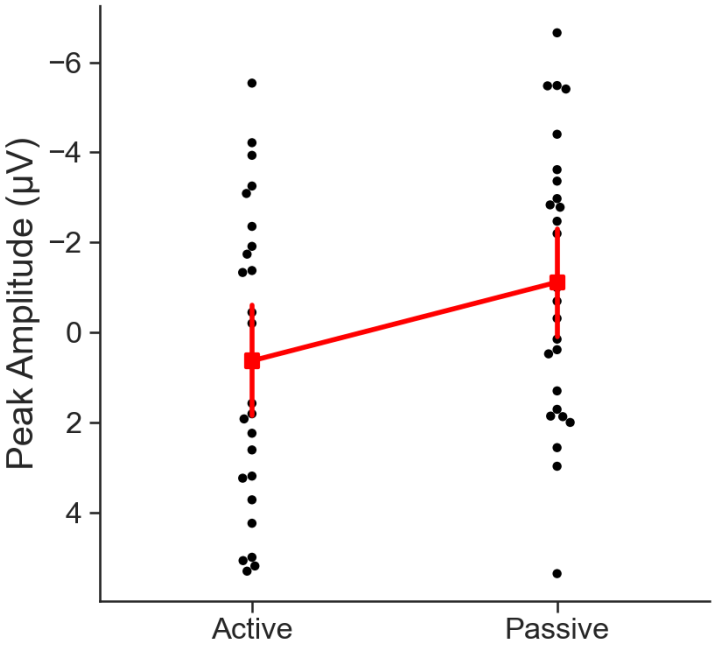

Figure 4 N1 Peak Values in Healthy Subjects in the Extensive Experiment
Distribution of N1 peak values (Peak Amplitude (µV)) for active and passive trials of a button press and visual stimulus in healthy subjects; error bars represent bootstrapped confidence intervals

6.2 Intensity Perception in Healthy Subjects

Figure 5 shows the result of the behavioural task judging whether the first or second visual stimulus was brighter. This figure demonstrates the percentage response '2nd brighter' while comparing active and passive trials for stimuli with the same intensity. Statistical results show no significant difference ($t(24) = -0.78$, $p = .443$, Cohen's $d = -0.16$) between the active ($M = 78.60$, $SD = 11.25$) and passive conditions ($M = 80.90$, $SD = 15.49$).

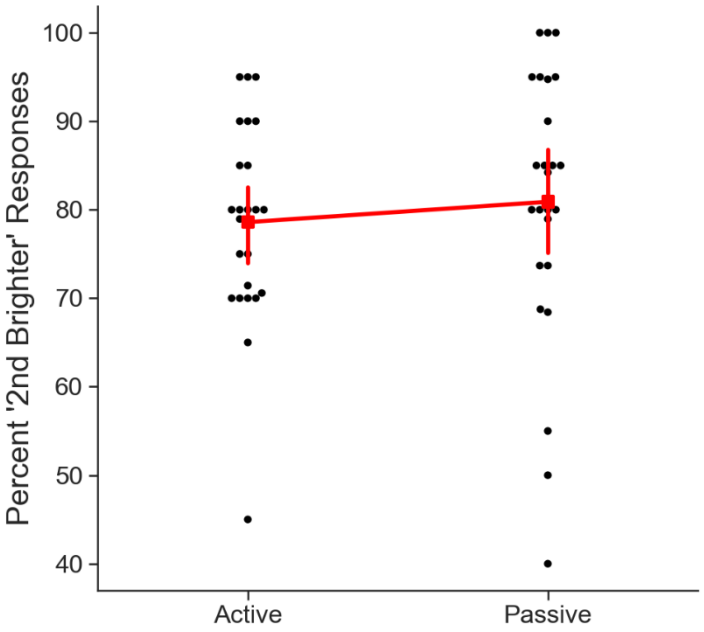

Figure 5 Intensity Perception in Healthy Subjects in the Extensive Experiment
Percent '2nd brighter' responses for active and passive trials in healthy subjects; error bars represent bootstrapped confidence intervals

7 Discussion of the Extensive Experiment

As outlined in the introduction, the main objective of this study was the development of an experimental EEG paradigm to investigate efference copy based predictive mechanisms in SZ regarding the processing of visual consequences of one's own actions. In the present study, we investigated prediction of self-generated versus externally-generated actions as well as intensity perception in the visual sensory system. Therefore, participants completed a computer experiment including an active or passive button press and a subsequent question about intensity of succeeding visual stimuli. With the aim of experimental development, the study was divided into two parts. Firstly, there was a sample of healthy subjects participating in the extensive experiment. Secondly, another sample of healthy subjects and a small group of patients fulfilled the task of the optimised experiment. In the following section, the analyses of a specific subset of trials (of the same intensity) from the extensive experiment is discussed, as the basis for the optimised experiment. We observed a significant difference for N1-ERP suppression in the active condition in comparison to the passive one. However, we found no significance in the behavioural task judging intensity in active and passive trials.

7.1 N1-ERP Suppression in Healthy Subjects

The results of EEG data in the extensive experiment showed significantly suppressed N1 peak values for visual stimuli in the active condition in comparison to the passive one. The present findings are generally consistent with previous research for the sensory systems. It has to be noted, that N1 suppression is mostly presented for the auditory system (Baess et al., 2008; Ghio et al., 2018; Martikainen et al., 2005), followed by the tactile system (Chapman, 1994).

For the visual system, previous studies showed incongruent results for the mean N1 amplitude. Our findings are parallel to the results of previous research describing suppression for the mean N1 amplitude. Namely, Gentsch & Schütz-Bosbach (2011) observed sensorimotor attenuation for self-generated effects as well as we did by using a movement-device with a key press and resulting visual stimuli. Further, Mifsud et al. (2018) showed N1 suppression in frontocentral sides especially for self-generated visual flashes by volitional eye movement besides actively button-press generated effects. Moreover, they demonstrated the relation between sensory attenuation and the strength of association between the type of motor action like saccades or a button press and the sensation, a flash. In particular, they showed greater N1-ERP suppression associated with eye-movements than with the button press, arguing that eye movements are more often and highly associated with visual sensations in comparison to hand movements.

Hence, it can be discussed that for our experimental task in the extensive experiment, we might get better results connecting the visual stimuli to eye movements instead of a button press. Furthermore, reduced brain activity in the visual sensory cortex was additionally supported by Lubinus et al. (2021) using fMRI and demonstrating reduced BOLD activity for self-generated visual stimuli in comparison to externally induced sensory consequences.

On the other hand, it should be noted that some previous studies did not find suppression for early activity in the sensory cortex. Thus, some studies demonstrated enhancement for different visual ERP components in the active condition in occipital electrodes (Csifcsák et al., 2019; Hughes & Waszak, 2011; Mifsud et al., 2016), for example by using a chequerboard stimulus. Furthermore, enhanced BOLD activity was demonstrated in the auditory cortex during self-initiated tones using fMRI (Reznik et al., 2014). It can be discussed that these results might reflect general predictive mechanisms but not in particular the internal forward model and the mechanism of an efference copy. Due to this described incongruency in previous studies and the fact that there is only little research in the visual domain, we decided to focus on the visual sensory system. Further, we wanted to investigate whether we can find common results for the forward model in the visual system as with robust findings for the auditory modality.

While previous results for the visual system are diverse, however, the suppression effects in early components of the primary visual response we demonstrated are seen as a result of the internal forward model and its function of prediction for self-generated actions. By using efference copy, sensory consequences of one's own actions can be predicted (Wolpert et al., 1995). In case of a match between predicted and reafferent sensory feedback, there is sensory attenuation (Blakemore et al., 1999). In other words, there is no need for further cognitive processing which in turn saves metabolic resources (Frith, 1995). Furthermore, this internal prediction mechanism, the so-called forward model, allows to distinguish between self-generated and external actions and therefore, attributing actions to their correct agent (Blakemore, Wolpert, & Frith, 2000; Frith, 1992). According to the theory of the forward model, our study is in line with prior research demonstrating the electrophysiological equivalents of sensory attenuation and sense of agency, in particular the N1-ERP suppression.

7.2 Intensity Perception in Healthy Subjects

The results of the behavioural task in the extensive experiment showed no significant difference between the active and passive condition when it comes to judging which of the two visual stimuli was brighter. This finding stands in contrast to the understanding

of sensory attenuation that self-initiated actions are perceived as less intense than external ones.

Considering the somatosensory system, self-generated touch is perceived as attenuated and as weaker compared to an externally produced or passive one (Bays et al., 2006; Blakemore et al., 1999; Weiskrantz et al., 1971). Parallel findings for sensory attenuation are demonstrated for the auditory system, for example the perception of self-generated sounds (Weiss et al., 2011). Sensory attenuation has been seen as a result of a match between predicted and sensory reafferent feedback. In this case, sensory activity is assumed to be cancelled (Bays & Wolpert, 2007).

As shown by previous research, sensory attenuation and adapted intensity perception is also suggested for the visual system. Cardoso-Leite et al. (2010) investigated whether the prediction mechanism really makes a change in sensory perception or whether it leads to a response bias. They assumed that self-generated actions lead to changed perception of the learned action effects. Furthermore, Roussel et al. (2013) used a contrast discrimination task for the visual system. They showed reduction in discrimination sensitivity for stimuli being congruent to action-effect associations. Therefore, they suggested that sensory attenuation and following intensity perception results from preactivation of learnt sensory action-effects. In contrast to our study, they used different contrast values for the visual letter stimuli and investigated the contrast discrimination, whereas we investigated the intensity perception of stimuli presented with the same luminance. Therefore, the only difference between the conditions was the modality of action (active or passive) and as a result, the presence or absence of an efference copy, on which effects we wanted to focus. Furthermore, it has to be discussed that it has been probably too difficult to judge which of the stimuli was brighter, considering the performance of participants in the behavioural task. In fact, there were no differences in intensity between the stimuli, but this was to the unbeknownst of the participants. Hence, further studies for the visual sensory attenuation could include stimuli with not only the same intensity but differences in the level of luminance. However, for the purpose of this work, we wanted to focus on stimuli with the same intensity, whereas the larger study also contains different luminance levels.

Overall, it has to be noted that most of the previous studies investigating sensory attenuation and following intensity perception concentrate on the auditory and tactile sensory system. This in turn shows the importance of this study, which considers the visual system.

7.3 Discussion of the Methods

The results of the extensive experiment showed significance for the N1-ERP suppression but not for the behavioural task. Consequently, it is important to discuss the methods of the task for the development and optimisation of further experiments which is the main purpose of this work.

Sample of Healthy Subjects

Participants of the extensive experiment were all healthy subjects. Most of them were students from the University of Marburg. For the extensive experiment, we wanted to investigate whether the experimental setup and task is easy to complete and whether we should make changes for patients and further studies. Therefore, we chose the number of participants as well as the criteria for inclusion and exclusion based on previous studies (Bays et al., 2006; Ford, Mathalon, Kalba, et al., 2001b).

Task

Since this work is part of a larger study, the number of experimental trials was 800. In addition, there were 120 control trials after the experimental blocks. This overall number of trials was chosen because other studies showed stable effects using trial numbers in this area or a bit less (Baess et al., 2008; Gentsch & Schütz-Bosbach, 2011; Kemenade et al., 2016; Mifsud et al., 2018). However, we assume that the overall duration of the study was too long, especially when it comes to patients completing the task. For the extensive experiment, we observed that participants were visibly fatigued at the end of the experiment. Therefore, we decided to strongly reduce the overall duration of the task for the optimised experiment. In addition, we planned to ask the participants in the optimised experiment by means of a questionnaire how they perceived and experienced the experiment.

Furthermore, the larger study contained conditions of auditory and multimodal stimuli as well. Therefore, the experimental blocks switched a few times during the overall duration. This requires participants to regularly adjust to a new experimental situation, which might lead to confusion and inattention for the behavioural task. Further studies could try to focus on only one sensory condition for stable results.

For the purpose of this work, we analysed only trials with visual stimuli of the same intensity. Due to that, there were very few trials (40 in total, 20 active and 20 passive trials) of interest in the experimental setup of the larger study. However, our selected number of trials was sufficient to show that N1-ERPs have significantly lower amplitudes in the active conditions than in the passive. In order to improve the signal to noise ratio, further studies could extend the number of trials with stimuli of the same intensity.

Additionally, a larger number of trials could be able to show significant results for the behavioural task. However, we were able to show significant results with our selected number of trials revealing N1-ERP suppression.

Moreover, we wanted to control the factor of time in the experimental task. Since there was a button press before the stimulus appeared, there was always temporal prediction (vs. just a stimulus task without a button press). Hence, the only difference between active and passive conditions should have been the presence or absence of an efference copy. Other studies included a condition which was temporally unpredictable and without participants' input like Mifsud et al. (2018) and compared the effects. However, we wanted to make the active and passive condition as comparable as possible to focus on the effects of the efference copy mechanism.

Furthermore, another temporal aspect could be changed for better comparability in further studies. In our extensive experiment, the passive button latencies after the cue were predefined in jittered intervals. For optimising the experimental setup, the time interval between the cue and button press in passive conditions could be adapted to the time interval in active ones. Consequently, the conditions would be even more comparable than in the extensive experiment, which contains temporally predictable stimuli but not precisely matched between active and passive conditions.

Analysis

Another point that should be noted is the choice of the localisation of electrodes for the EEG analysis. For example, Mifsud et al. (2018) measured the mean N1 amplitude across frontocentral electrodes in contrast to our study. This in turn is similar to Gentsch & Schütz-Bosbach (2011) and Schäfer & Marcus (1973). We decided to analyse the N1 amplitude across occipital electrodes Oz, O1 and O2 in accordance with previous research investigating the influence of prediction mechanisms on visual ERPs (Mifsud et al., 2016). For better source localisation, the combination of EEG with anatomical Magnetic Resonance Imaging (MRI) can be considered for further studies as used before in a study regarding the auditory domain (Wang et al., 2014). However, we wanted to focus on the temporal benefit of EEG combined with the level of comfort in accordance with the aim of developing a task which is suitable for patients as well.

7.4 Limitations

Despite the significant findings we found for N1-ERP suppression in the visual system, it is important to mention some limitations.

Due to the fact that this work is part of a larger study, we cannot exclude that the other conditions not considered in our analyses effected our results. Consequently, the

optimised experimental task requires to contain only trials of the visual modality, presented at the same level of luminance.

Furthermore, the EEG as a neurophysiological research tool has its limits. Especially, the spatial resolution is not as high as fMRI can achieve. Therefore, anatomical accuracy is not as precise as well. Further studies might implement both tools in one experimental setup to go more in detail about the structures and moreover, to combine the temporal advantage of EEG with the spatial one of the fMRI.

However, this work is important to achieve further evidence on the electrophysiological correlates of prediction mechanisms, especially for the visual system since most of the studies focus on the other sensory modalities.

7.5 Intermediate Conclusion

In conclusion, we showed significant electrophysiological effects with regard to the prediction of sensory consequences of self-generated visual stimuli in a few selected trials (40 in total, 20 active and 20 passive trials) with the same intensity. We demonstrated significant N1-ERP suppression in active conditions in comparison to the passive ones in healthy subjects. Despite the methodologically low spatial resolution of EEG, this finding goes in line with prior research on prediction mechanisms and internal forward models. In contrast to our expectations for the behavioural task, we did not find a significant difference between the two conditions. This stands in contrast to the understanding of sensory attenuation that self-initiated actions perceived as less intense than external ones.

With the results in mind, we found different aspects we wanted to change for the optimised experiment. Especially against the background of the main purpose of this work: the development of an EEG paradigm to investigate dysfunctions in SZ. Therefore, the optimised experimental task requires not only trials of exclusively the visual modality and a larger number of trials with stimuli of the same intensity, but foremost, a shorter overall duration for better suitability for patients. Last but not least, we suggested improving the level of difficulty of the extensive setup to make the task easier to complete for participants, especially for patients.

8 Introduction of the Optimised Experiment

With respect to the results and limitations of the analyses of the selected trials of the extensive experiment, we made changes for the optimised experiment in two ways. Firstly, we implemented changes for the comfort level of the experimental setup. Therefore, we shortened the overall duration by, among other things, presenting fewer trials as well as fewer conditions by focusing on the visual condition presented with the same intensity. Secondly, we improved the difficulty level of the behavioural task. For this purpose, we made changes in the methods referring for example to the luminance, size and duration of the stimuli.

For assessing the suitability of the experimental task for patients, we implemented a Post-Experiment Questionnaire.

Study Goals

The main purpose of this work was the development of an experimental task that is suitable and easy to complete for patients with SZ. Therefore, we firstly expected clearer N1-ERP and behavioural effects in healthy subjects for the optimised experiment than in the extensive one after changing and optimising the experimental setup. We predicted larger N1-ERP effects as well as behavioural effects by altering the time intervals and shortening the overall duration, changing the presentation format and last but not least, by focussing on the visual condition only. We wanted to explore the results descriptively in the first place. Secondly, we performed statistical comparison to test the specific hypotheses. However, we were aware that results are not directly comparable due to the differences in the experimental setups and samples.

Finally, we suggested that patients are able to perform the optimised task well and do not find it too complicated. We expect this to be evidenced by the Post-Experiment Questionnaire. For example, we assumed that patients were able to concentrate well for the entire duration of the experiment as shown by high ratings in question number 1 and low ratings in question number 17. Moreover, we expected that patients understood the task well by our explanation and did not find it too complicated to complete it as demonstrated by high ratings in question number 4, 6, 8, and 9, and low ratings in question number 7 and 10. In order to make a comparison with the healthy subjects, we also evaluated their questionnaires. We expected them to be able to perform the task at least as well as the patients.

9 Materials and Methods of the Optimised Experiment

9.1 Participants

We recruited N = 24 healthy students from the University of Marburg in the same way as we did it with the students participating in the extensive experiment. Sixteen of the participants were female. Ages ranged between 18 and 34 (*M* = 24.96, *SD* = 4.53).

For the patients group we describe data from N = 5 patients with DSM-IV schizophrenia (F25.9, F20.5, F25.2, F20.0, F20.0) recruited from the university hospital in Marburg, university mailing lists, advertisements and word of mouth. All of the patients were male. Ages ranged between 33 and 59 (*M* = 46.6, *SD* = 11.26). In a preceding interview, we rated SZ symptoms (see Table 1) using the Scale for the Assessment of Positive Symptoms (SAPS) as well as the Scale for the Assessment for Negative Symptoms (SANS), the Scale for the Assessment for Passivity Phenomena (SAPP) and the Structured Clinical Interview for DSM-Disorders (SCID) (Andreasen, 1983, 1984; First, 2014; Spence et al., 1997). In order to include patients in the study, hallucinations or ego disorders had to be present in the lifetime. Therefore, patients had to score at least two points in one of the corresponding domains of SAPS (SAPS 1: Hallucinations, SAPS 2: Delusions). In total, there are five domains of SAPS, of which the first two are the relevant ones and are therefore listed in detail. The first domain of SAPS (Hallucinations) includes the following items rated from 0 (absent) to 5 (severe): Auditory Hallucinations, Voices Commenting, Voices Conversing, Somatic or Tactile Hallucinations, Olfactory Hallucinations, Visual Hallucinations and the Global Rating of Severity of Hallucinations. The second domain of SAPS (Delusions) contains the following items, also rated from 0 (absent) to 5 (severe): Persecutory Delusions, Delusions of Jealousy, Delusions of Sin or Guilt, Religious Delusions, Somatic Delusions, Ideas and Delusions of Reference, Delusions of Being Controlled, Delusions of Mind Reading, Thought Broadcasting, Thought Insertion, Thought Withdrawal and the Global Rating of Severity of Delusions. In deviation from the actual procedure of the scores, these were again explicitly collected for lifetime. We decided to do this because we did not only want to include patients who were currently suffering from the corresponding symptoms from the hallucinations or ego disorders category, but because we wanted to better represent the entire population of patients with SZ, which also includes well-treated, even symptom-free patients.

Table 1 Patients' Symptoms in Two Weeks/Lifetime
SZP = Patient with Schizophrenia; first value = two weeks / second value = lifetime

	SZP1	SZP2	SZP3	SZP4	SZP5
SAPS total	0/23	7/13	8/27	27/27	7/36
SAPS 1 *Hallucinations*	0/9	0/0	0/0	1/1	3/12
SAPS 2 *Delusions*	0/14	7/13	2/21	17/17	4/24
SANS total	3/30	4/13	2/24	34/34	9/4
SAPP	0/0	0/2	0/0	0/0	0/2

All participants were right-handed by self-report and had normal or corrected-to-normal vision. None of the participants wore a hearing aid. Before taking part in the experiment, participants were screened to ensure they met inclusion criteria. All participants had to be between 18 and 60 years old and were naïve to the purpose of the experiment.
Exclusion criteria for healthy subjects included a past or current mental disorder relating to the DSM-IV, a first-degree relative with SZ, regular use of psychoactive medications, history of drug or alcohol abuse. Healthy subjects as well as patients were excluded for serious brain injury and further neurologic diseases compromising the central nervous system, for example epilepsy.

All participants obtained 20 euros for the EEG recording session as an expense allowance for an average time effort of 1.5-2 hours (1 hour shorter than the extensive experiment). Patients received an additional 20 euros for the interview, which included a time effort of 1-1.5 hours.

The bureaucratic part was identical to that in the extensive experiment.

9.2 Equipment

The equipment in the optimised experiment of our study was exactly the same as in the extensive one described in 'Materials and Methods/5.2'. In addition, participants wore ear plugs during the main experimental and control trials.

9.3 Task and Stimulus Material

All participants first read the instructions (see appendix 1.1) explaining the experimental task. Thus, we were able to ensure that all of the participants got the same instructions. Furthermore, it made the task clearer in comparison to the instructions presented step

by step on the screen as in the extensive experiment. Moreover, the written instructions had the advantage that participants can refer back to them, unlike instructions presented on the screen. Following, participants were asked to do a short training session after applying the EEG cap to familiarise them with the task by completing 10 trials of each type active, passive and quick, counterbalanced across participants. The quick condition wasn't focus of this work and therefore, was not analysed.

In order to complete the task, participants sat in front of a computer monitor in the darkened room. The experimental setup was the same as in the extensive experiment. The participants wore headphones to perceive a recurring tone as well as ear plugs for masking the sound of the button press with pink noise adaptable to participants' individual loudness perception. We chose to do that in the optimised experiment to achieve similar effects in noise cancelling and button press masking.

Participants attended to visual stimuli displayed on the computer monitor transmitting via Psychotoolbox. For the optimised experiment, we decided to present only visual stimuli to the participants. In contrast, we used auditory and multimodal conditions in the extensive experiment in addition to the visual condition as part of a larger study. We made this change to focus on the visual domain because of the fact that this is the least well-studied sensory domain. Therefore, we can have a higher number of visual trials without an extension of the overall duration. Moreover, we assumed that switches between the conditions might confuse the participants. As a result, the optimised task was presumably easier to complete than the extensive one.

It must be emphasised that by presenting only visual stimuli, the overall duration of the optimised experiment with 336 experimental trials (112 active, 112 passive, 112 quick) was clearly shorter than that of the extensive one counting 800 experimental trials. Furthermore, active and passive movements were executed using the button box, the same one used for the extensive experiment. The task was identical to that in section 'Materials and Methods/5.3/Task'.

In contrast to the extensive experiment, in the optimised study design the circles always were the same luminance. However, participants were not told about that.

The structure of a single trial is shown in Figure 6.

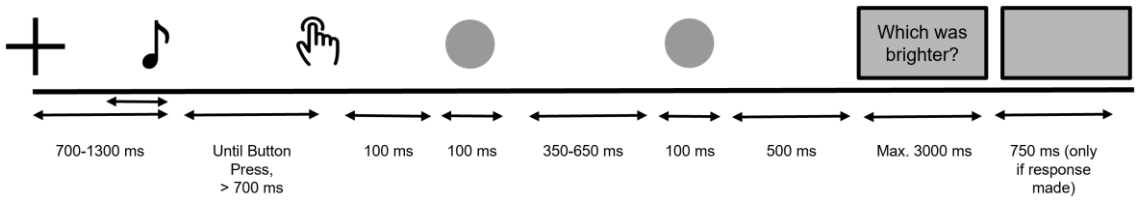

Figure 6 An Example of an Active Trial in the Optimised Experiment

In each trial, a black fixation cross of 40 x 40 pixels appeared on the screen for a randomly selected duration of 700-1300 ms in steps of 100 ms. In the optimised experiment, we changed the duration range of the fixation cross. Thus, the overall duration was shorter than for the extensive experiment by shortening the maximum duration. Moreover, we extended the minimum duration of the cross to give more preparation time to the task after the appearance of the fixation cross at the start of the trial. Next, a 1000 Hz tone (= cue) was presented for 100 ms over the headphones simultaneously with the cross. In our extensive experiment, there was a second cross (20 x 20 pixels) which was bigger than the first one (12 x 12 pixels). In the optimised experiment, we decided to increase the duration of the cross and make it a fixed size. Firstly, we did this to ensure there would be no extra visual activity that could affect the ERP of interest. Secondly, a larger cross is presumably more comfortable to look at for the overall duration. Instead of an enlarged second fixation cross, in the optimised experiment the tone indicated that participants were now free to press the button in active trials. The button press could be made 700 ms after the tone at the earliest to ensure that participants not only react to the cue intentionally as a reflex but decide to press the button voluntarily (Rohde & Ernst, 2012). Within the 700 ms time limit, the monitor was saying ‘Zu schnell. Versuchen Sie es erneut’ (‘Too quick. Try again’, in German) and the trial was repeated. For the passive condition, the button was activated after predefined button latencies in the extensive experiment. We decided to record time values between the cue and active button press in the optimised experiment. Therefore, we were able to shuffle passive button press latencies. Consequently, the two conditions in the optimised experiment were more comparable in timing. Further, in case of a time interval over 2500 ms in the active condition, any value for the subsequent passive one was 2500 ms. This was chosen in case someone did not press the button, for example because they were not attentive to the trial. Stimuli were presented with a delay of 100 ms after the button press for 100 ms, 50 ms longer than in the extensive experiment. This was done to make it easier to compare the intensity of the stimuli and judge which of the two were brighter. Compared to the extensive experiment, a shorter inter-stimulus interval was used (350-650 ms in steps of 50 ms). This was made for an easier comparison of the two stimuli and also to decrease the overall experimental duration. While the stimuli were

presented, the fixation cross disappeared, but remained on screen during the interstimulus interval. Afterwards, there was another interval of 500 ms before the participants had to judge the intensity of the two grey circles. Therefore, the question appeared on the monitor: 'Welcher war heller?' ('Which was brighter?', in German) deciding by pressing the "N" or "V" key on the keyboard, a response triggered inter-trial interval of 750 ms was made before the next trial followed. If the participant failed to respond within 3000 ms, the trial was repeated automatically. In the extensive experiment, the next trial started automatically if participants missed a response for longer than 2500 ms. We decided to extend the time range to 3000 ms. The duration was increased with the assumption of firstly, patients might need longer. Secondly, we ensured the same number of trials for all participants by repeating the trial instead of starting the next trial in case patients missed a lot of answers due to being unsure. Thus, the task should be easier to complete for patients in the optimised experiment. Descriptive statistics are reported in the results.

In this optimised experiment, unbeknownst to participants, the intensity of the stimuli didn't vary. The circles were presented at 700 pixels, larger than the ones in the extensive experiment in which we had a circle of 250 pixels in accordance with previous studies, where they for example used a 100-pixel area of interest (Mifsud et al., 2018). The visual stimuli were displayed at a luminance of 84.55 cd/m², brighter than in the extensive experiment. These changes were done to make the task clearer and the experiment easier to look at for a long time. Moreover, the luminance in the optimised experiment is more similar to prior research. For example, Mifsud et al. (2018) displayed their flashes with a mean luminance of 100 cd/m². In our study, both stimuli were presented on a fixed grey background with luminance of 3.40 cd/m² as in the extensive experiment.

In total, the experiment consisted of 336 trials divided in four blocks, which in turn consisted of two mini-blocks. Thus, each experimental block consisted of 84 trials which in turn consisted of two mini blocks of 28 active, 28 passive and 28 quick. Each mini block condition had 25 experimental trials with identical brightness and three catch trials. In catch trials, the second stimulus had a lower luminance of 28.45 cd/m². Catch trials were inserted to ensure that participants stayed attentive, as done by previous research as well (Roussel et al., 2013). Therefore, they were inserted into the trial sequence at random. By counting the number of experimental visual trials with the same intensity, the optimised experiment consisted of 200 trials for our analysis. In comparison to the extensive experiment, we increased the number of trials presenting visual stimuli with the same intensity five times in the optimised experiment. Active blocks were always presented before passive blocks. Between each block as well as each mini-block, the subjects had the opportunity to take a short break by their own decision.

In addition, two motor-only blocks were included to control for motor activity in the ERP signal. These blocks were always presented after the experimental blocks. Participants pressed the button in the typical paradigm but this time there wasn't a following stimulus. Each block consisted of 84 trials which in turn consisted of mini blocks of 28 active, 28 passive and 28 quick trials. Instead of a stimulus, the fixation cross remained on screen for a variable interval (1650-1950 ms in steps of 50 ms). The duration was chosen to be approximately the same length as an experimental trial. After this interval had passed, the cross disappeared for 750 ms, the same as the inter-trial interval in the experimental conditions. This interval also served as visual feedback that the trial was complete. This motor-only activity can then be subtracted from the ERPs in the experimental conditions to further minimise any differences between the active and passive conditions supposing the participants were engaged in the same way as in the experimental conditions. We decided not to include the task into the control blocks to make the overall duration of the procedure shorter. However, we focused only on the motor activity, thus we were able to give up the task in those blocks.

After finishing the experimental task, patients were asked to complete a questionnaire (see appendix 1.2) about the experiment.

In total, the duration for the optimised experiment was 1.5-2 hours. Consequently, the optimised experiment was about 1 hour shorter than the extensive experiment. The overall duration included about 15 minutes for the instructions and the training session and about another 30 minutes for applying the EEG cap. Afterwards, the experimental task counting 504 (336 experimental and 168 control) trials in total lasted about 0.5-1 hour and completing the questionnaire about another 5 minutes. Finally, the removal of the EEG cap and washing of the hair was about 15 minutes.

In Table 2, we listed the changes for the optimised experiment versus the extensive experiment. Some of the changes referred to the comfort level of the experimental setup, whereas others were made for improving the difficulty level of the behavioural task.

Table 2 Changes for the Optimised versus the Extensive Experiment
Act = active condition, Aud = auditory condition, Exp = experiment, Pass = passive condition, Ppts = participants, Vis = visual condition

	Extensive Experiment	**Optimised Experiment**
Instructions	- instructions presented step by step on the screen - additional words by mouth after the training if necessary	- written instructions
Training Session	25 = 5 blocks of 5 trials each	30 = 10 act + 10 pass + 10 quick
Pink Noise	- same for all ppts	- adjustable - plus ear plugs
Conditions	- act, pass - vis, aud, multimodal	- act, pass - only vis
Cue	fixation cross followed by an enlarged fixation cross (= cue) - 1st: 12 x 12 pixels - 2nd bigger: 20 x 20 pixels - duration: 500-1500 ms in steps of 250 ms	fixation cross + tone (= cue) - bigger size: 40 x 40 pixels - tone: 100 ms 1000 Hz - duration: 700-1300 ms in steps of 100 ms
Blocked Time after the Cue in Active Conditions	no time limit on button press	700 ms blocked after the cue ('too quick' → trial repeat)
Time between Cue and Passive Button Press (= Passive Button Press Latency)	jittered intervals of 500-1250 ms in steps of 83 ms	shuffled time values of the recorded active time values - time interval > 2500 ms in an active trial: any value for the subsequent passive trial was 2500 ms

	Extensive Experiment	**Optimised Experiment**
Circles (= Stimuli)	- 50 ms - 250 pixels - luminance of 11.42 cd/m² - fixed grey background with luminance of 3.40 cd/m²	- longer: 100 ms - bigger: 700 pixels - brighter: luminance of 84.55 cd/m² - fixed grey background with luminance of 3.40 cd/m² - included catch trials with lower luminance of the 2nd stimulus: ppts presumably remain attentive
Inter-Stimulus Interval	duration: 500-1250 in steps of 250 ms	shorter: 350-650 ms in steps of 50 ms
Missed Response (Which was brighter?)	> 2500 ms → next trial	> 3000 ms → repeat trial
Experimental Trials in Total	- larger exp: 800 = 4 x 200 (200 = 100 act + 100 pass: 50% vis 50% aud; mini blocks of 25) - larger exp vis: 200 = 100 act + 100 pass - same intensity vis: 40 = 20 act + 20 pass → only few trials with the same intensity in the vis	- 336 = 4 x 84 (84 = 3 x 28 act/pass/quick; mini blocks of 28: 25 trials of same intensity: act, pass, quick + 3 catch trials) - same intensity vis: 200 = 4 x 50 = 100 act + 100 pass → increase of same intensity vis overall trials: 40 → 200 → decrease of experimental overall trials: 800 → 336

	Extensive Experiment	Optimised Experiment
Control Trials	- 2 x 60 (60 = 30 act + 30 pass: 50% vis 50% aud; mini blocks of 15) - delay of 1000 ms after button press before stimuli and question appears	- 2 x 84 (84 = 28 act + 28 pass + 28 quick) - no stimuli, no question → fixation cross remains on the screen for a variable interval (1650-1950 ms in steps of 50 ms) - after this interval: the cross disappeared for 750 ms, the same as the inter-trial interval in the experimental conditions
Trials in Total	920	504
Experimental Duration	1.5 - 2 hours	0.5 - 1 hour
Overall Duration	2.5 - 3 hours	1.5 - 2 hours

9.4 EEG Data Acquisition and Preprocessing

For EEG data acquisition and preprocessing, we used the same strategy as for the extensive experiment described in section ‘Materials and Methods/5.4’.

9.5 Data Analysis

Analysis of the N1-ERP and behavioural data was exactly the same as in the extensive experiment described in section ‘Materials and Methods/5.5’. Catch trials as well as the quick trials in the optimised experiment were not analysed. Thus, there were 200 trials (100 active and 100 passive) in total for analysis.

For the analysis of the N1-ERP, 12.9% trials were rejected due to containing artefacts for healthy subjects, whereas 10.5% trials were rejected for patients.

For the comparison of effects in the extensive and optimised experiment in healthy subjects, we did a dependent samples *t*-test to test whether the effects (active-passive) for the single experiments are different between the experiments.

Post-Experiment Questionnaire

The responses of the Post-Experiment Questionnaire were entered in Excel 2019. Scores between 1 and 5 were assigned to each participant using a verbalised Likert

scale of odd numbers (I totally agree = 5, I agree = 4, Neutral = 3, I disagree = 2, I totally disagree = 1) and without scale points.

10 Results of the Optimised Experiment

The results in the following sections relate to the difference in the N1-ERP amplitude between active and passive conditions as well as in the behavioural task judging which stimuli was brighter in the optimised experiment. On the one hand, we show the EEG and behavioural data in healthy subjects. On the other, we describe the differences in effects between the extensive and optimised experiment. Consequently, we present the results of the Post-Experiment Questionnaire showing the performance of patients in the optimised experiment and finally, we demonstrate patients' data as an outlook.

10.1 N1-ERP Suppression in Healthy Subjects

Figure 7 demonstrates the mean ERP amplitudes to visual stimuli after pressing the button actively or passively (A) and the topographical scalp plots referring to N1 suppression (B) for healthy subjects. In Figure 8, the distribution of N1 peak values is shown for active and passive button press for healthy subjects. As presented in these figures (see Fig. 7, Fig. 8), N1 was suppressed for visual stimuli in the active condition in comparison to the passive one. Statistical results show that the mean of N1 peak values in active trials (M = 1.65, SD = 3.03) was smaller than in passive trials (M = -0.65, SD = 1.69). The difference was significant ($t(23) = 4.08$, $p < .001$, Cohen's d = 0.83).

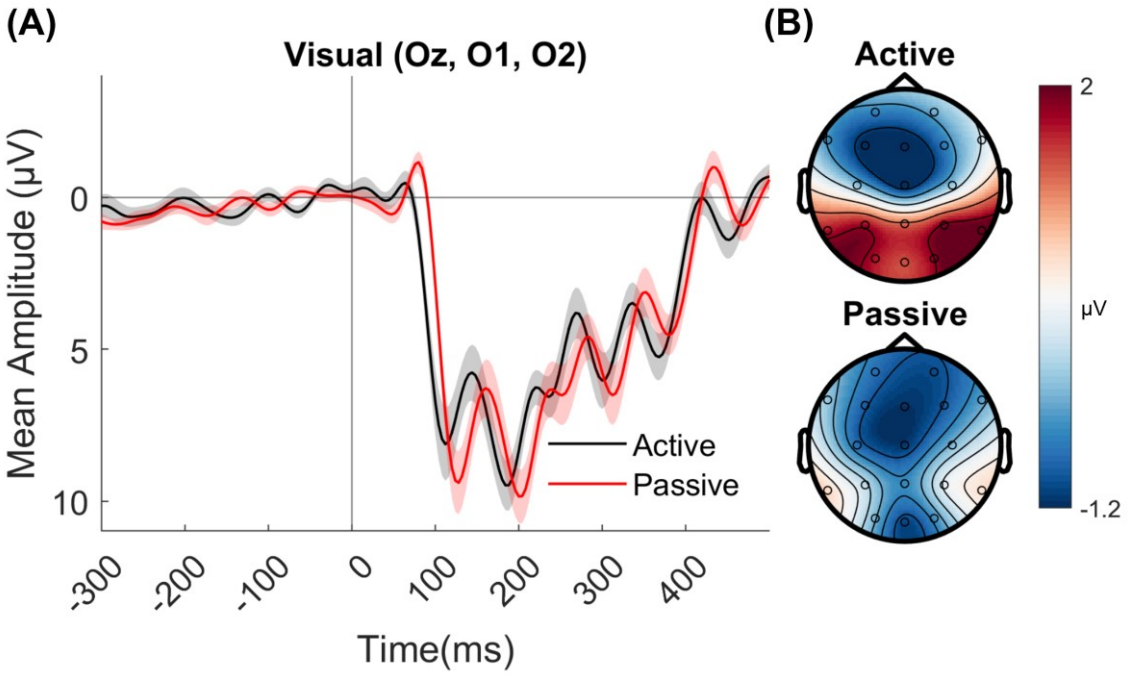

Figure 7 N1-ERP Suppression in Healthy Subjects in the Optimised Experiment
(A) Event-related potential (Mean Amplitude (µV)) to visual stimuli following an active or passive button press for healthy subjects; black line: active condition; red line: passive condition; shading around the lines: standard deviation; 0 ms: button press (B) Scalp topography maps for suppression of N1 amplitude (68-92 ms) for healthy subjects

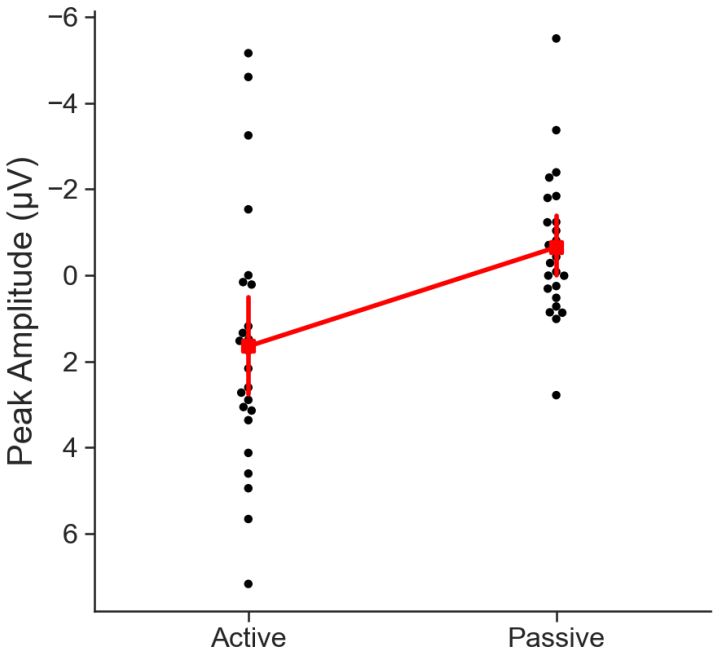

Figure 8 N1 Peak Values in Healthy Subjects in the Optimised Experiment
Distribution of N1 peak values (Peak Amplitude (µV)) for active and passive trials of a button press and visual stimulus in healthy subjects; error bars represent bootstrapped confidence intervals

10.2 Intensity Perception in Healthy Subjects

Figure 9 plots the result of the behavioural task judging whether the first or second visual stimulus was brighter. This figure demonstrates the percentage response '2nd brighter' while comparing active and passive trials for stimuli with the same intensity. Statistical results show no significant difference ($t(23) = 0.06$, $p = .948$, Cohen's $d = 0.01$) between the active ($M = 75.21$, $SD = 15.35$) and passive conditions ($M = 75.07$, $SD = 15.94$).

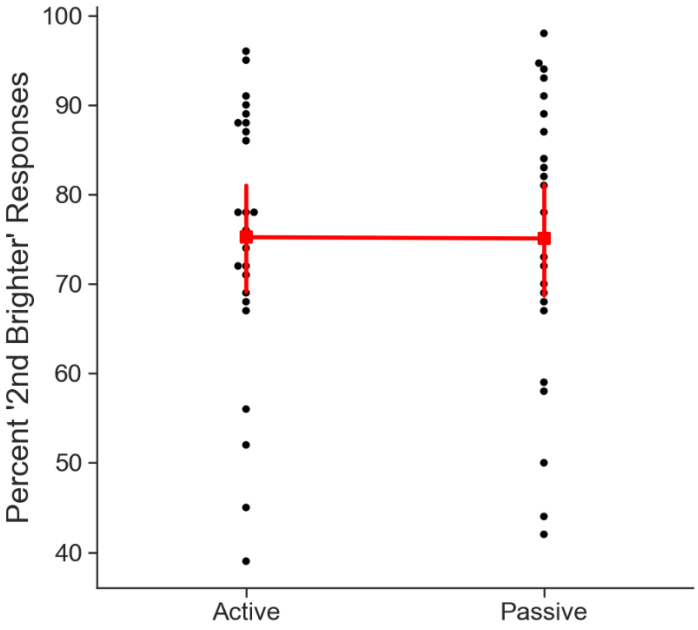

Figure 9 Intensity Perception in Healthy Subjects in the Optimised Experiment
Percent '2nd brighter' responses for active and passive trials in healthy subjects; error bars represent bootstrapped confidence intervals

10.3 Comparison of Effects in the Extensive and Optimised Experiments

As a result of the changes we made for the optimised experiment, we expected clearer N1-ERP and behavioural effects than for the extensive experiment. Following, we show statistical results in this section. Firstly, we describe data for the N1-ERP suppression effects. Secondly, data of the behavioural task is described.

Electrophysiological Data

Statistical results showed no significant difference ($t(48) = 0.57$, $p = .573$, Cohen's $d = 0.16$) between the mean of N1 peak values in the extensive experiment ($M = 2.3$, $SD = 2.76$) and optimised experiment ($M = 1.75$, $SD = 3.98$).

Behavioural Data

For the behavioural task, the statistical results showed no significant difference ($t(47) = -0.67$, $p = .507$, Cohen's $d = -0.19$) between the mean of percentage '2nd brighter' responses in the extensive experiment ($M = -2.3$, $SD = 14.76$) and optimised experiment ($M = 0.14$, $SD = 10.26$).

10.4 Performance of Patients Fulfilling the Optimised Experiment

In Table 3, the responses of the Post-Experiment Questionnaire are presented. Following, some items are highlighted. Patients rated the duration of the experiment as neutral but in the end, they were not able to concentrate as well (see questions no. 1, 2,

17). As shown in the table, they all understood the task (see questions no. 4, 6, 7, 8) and the setup was easy for them (see questions no. 9, 10, 13). The participating patients all tolerated the process of applying and wearing the EEG cap during the experiment (see questions no. 18-24).

Table 3 Post-Experiment Questionnaire of Patients
Responses of N = 5 Patients with Schizophrenia; SZP = Patient with Schizophrenia; I totally agree = 5, I agree = 4, Neutral = 3, I disagree = 2, I totally disagree = 1; MODE = value for mode, MAX = maximum value, MIN = minimum value

Question Number	SZP 1	SZP 2	SZP 3	SZP 4	SZP 5	MODE	MAX	MIN
1) I was able to concentrate well for the entire duration of the experiment.	5	4	5	3	2	5	5	2
2) The experiment was too long.	2	3	3	3	4	3	4	2
3) There were enough breaks.	4	4	4	4	3	4	4	3
4) The tasks were well explained to me.	5	4	5	5	4	5	5	4
5) The tasks between the breaks were too long.	3	2	3	2	3	3	3	2
6) I always understood what was required of me.	5	4	5	4	4	4	5	4
7) The experiment was too complicated for me.	1	1	1	3	2	1	3	1

Question Number	SZP 1	SZP 2	SZP 3	SZP 4	SZP 5	MODE	MAX	MIN
8) The instructions were very clear and I understood what I had to do.	5	5	5	4	4	5	5	4
9) I could easily remember which key had which meaning.	5	5	5	4	4	5	5	4
10) There were too many different keys I had to operate.	2	1	1	2	2	2	2	1
11) I was able to sit comfortably during the experiment.	3	4	4	4	1	4	4	1
12) I couldn't tell the difference between brightness of the circles.	3	4	3	2	2	3	4	2
13) I often pressed the wrong button by mistake.	2	3	2	4	2	2	4	2
14) Not all circles were equally bright.	3	4	5	4	4	4	5	3
15) I often had to guess at the answers because I wasn't paying attention.	2	3	2	3	2	2	3	2
16) I was often unsure of the answers.	4	4	3	4	2	4	4	2

Question Number	SZP 1	SZP 2	SZP 3	SZP 4	SZP 5	MODE	MAX	MIN
17) In the end, I couldn't concentrate as well.	3	5	1	4	4	4	5	1
18) It took too much time to apply the EEG electrodes.	2	2	4	2	2	2	4	2
19) The (EEG) preparation took too long.	2	2	3	2	2	2	3	2
20) The EEG electrodes distracted me from the task at hand.	2	2	1	2	2	2	2	1
21) I did not mind having the EEG electrodes applied.	4	4	4	2	4	4	4	2
22) The preparation made me tired.	3	2	2	2	4	2	4	2
23) The EEG cap bothered me during the investigation.	2	2	1	2	2	2	2	1
24) The EEG cap was uncomfortable.	3	2	3	2	4	3	4	2
25) I would participate in another experiment.	5	4	5	4	4	4	5	4

10.5 Performance of Healthy Subjects Fulfilling the Optimised Experiment

In Table 4, the mode and range values of the responses of the Post-Experiment Questionnaire of healthy subjects are presented. The responses are similar to the items we highlighted for patients. It can be said that the healthy subjects perceived the EEG

preparations and wearing the EEG cap as less disturbing in comparison to the patients (see questions no. 18-24). See appendix 15.3 for full details of the responses to the questionnaire.

Table 4 Post-Experiment Questionnaire of Healthy Subjects
Responses of N = 24 Healthy Subjects; I totally agree = 5, I agree = 4, Neutral = 3, I disagree = 2, I totally disagree = 1; MODE = value for mode, RANGE = value for range

Question Number	MODE	RANGE	Question Number	MODE	RANGE
1)	4	3	14)	5	2
2)	2	2	15)	2	3
3)	5	3	16)	4	3
4)	5	1	17)	4	4
5)	2	2	18)	2	3
6)	5	1	19)	2	2
7)	1	1	20)	1	2
8)	5	2	21)	5	4
9)	5	1	22)	1	3
10)	1	3	23)	1	2
11)	4	3	24)	1	3
12)	3	2	25)	5	2
13)	2	3			

10.6 N1-ERP Suppression in Patients with Schizophrenia

Figure 10 demonstrates the mean ERP amplitudes to visual stimuli after pressing the button actively or passively (A) and the topographical scalp plots referring to N1 suppression (B) for patients. In Figure 11, the box plot shows the distribution of N1 peak values for active and passive button press for patients. As presented in these figures (see Fig. 10, Fig. 11), N1 means showed the expected effect direction with lower peak in the active condition (*Mdn* = -0.1975) than passive condition (*Mdn* = -0.4762). Due to the small sample size, we used Wilcoxon Signed-Rank tests for patients' results in this and the following section 10.7 to increase statistical power. However, this difference was not significant ($Z = 0.135$, $p = 1$, $r = 0.067$).

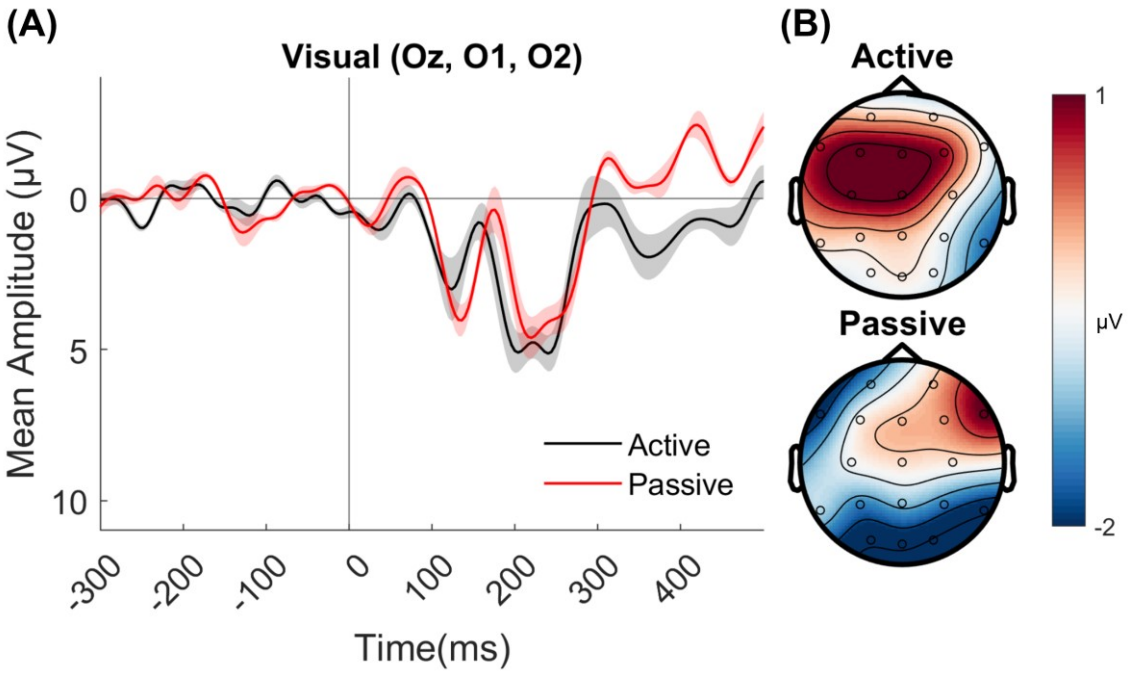

Figure 10 N1-ERP Suppression in Patients in the Optimised Experiment
(A) Event-related potential (Mean Amplitude (μV)) to visual stimuli following an active or passive button press for patients; black line: active condition; red line: passive condition; shading around the lines: standard deviation; 0 ms: button press (B) Scalp topography maps for suppression of N1 amplitude (60-84 ms) for patients

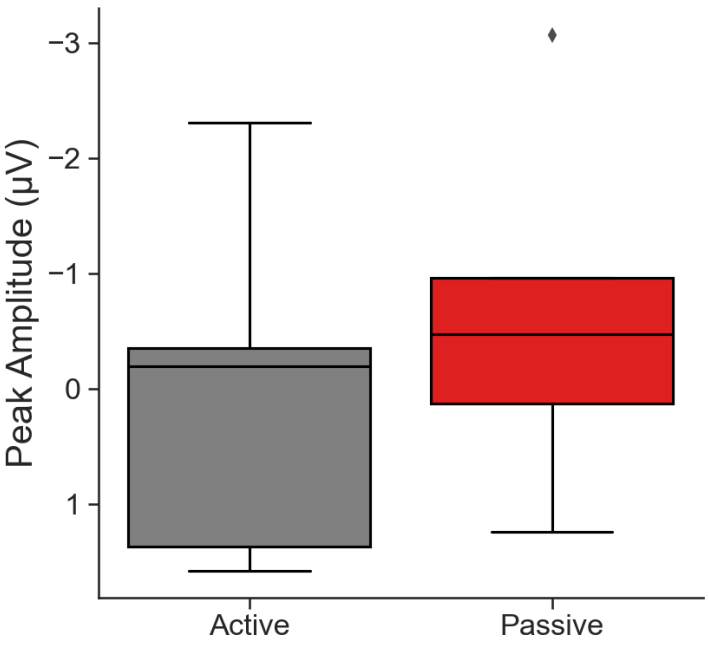

Figure 11 N1 Peak Values in Patients in the Optimised Experiment
Distribution of N1 Peak Values (Peak Amplitude (μV)) for active and passive trials of a button press and visual stimuli in patients; ♦ = outlier

10.7 Intensity Perception in Patients with Schizophrenia

Figure 12 shows the result of the behavioural task judging whether the first or second visual stimulus was brighter. This box plot demonstrates the percentage response '2nd brighter' while comparing active and passive trials for stimuli with the same intensity. Statistical results show no significant difference (Z = 1.214, p = .313, r = 0.6) between the active (*Mdn* = 73) and passive conditions (*Mdn* = 65).

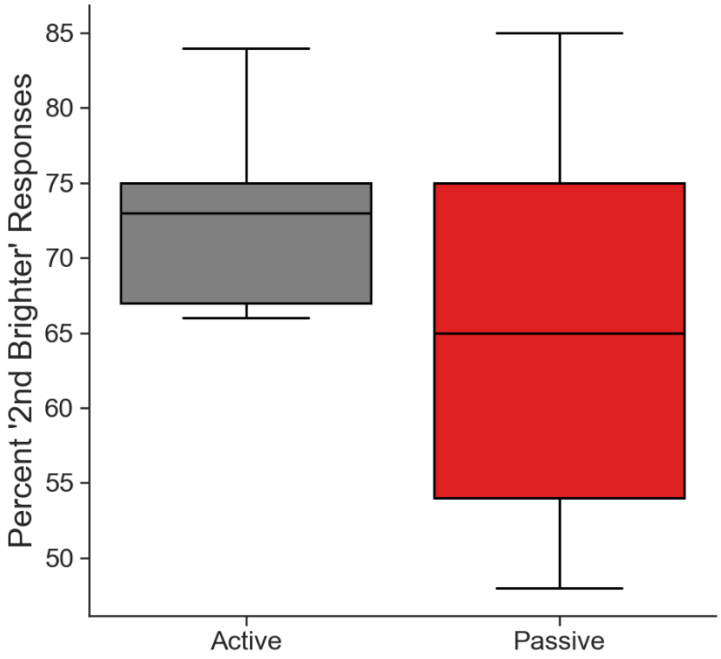

Figure 12 Intensity Perception in Patients in the Optimised Experiment
Percent '2nd brighter' responses for active and passive trials in patients

10.8 Repeated Trials in the Optimised Experiment

If participants missed a response for 3000 ms, the trial was repeated automatically. As a result, an average of 1.13 trials per participant were repeated (*SD* = 2.29) with a range from 0 to 11. An average of 0.4 trials per patient were repeated (*SD* = 0.55) with a range from 0 to 1.

11 Discussion of the Optimised Experiment

As outlined in the introduction, the main objective of this study was the development of an experimental EEG paradigm to investigate dysfunctions in SZ regarding the prediction of sensory consequences of one's own actions. Participants completed the same task as described for the extensive experiment except for few changes. The sample was divided into two parts: firstly, there were again healthy students and secondly, a small group of patients completed the task. In the following section, the optimised experiment is discussed with regard to the changes we made in the experimental setup. Moreover, the performance of patients and the outlook of patients' data are discussed as well. Consistent with the extensive experimental results, we observed a significant difference for N1-ERP suppression in the active condition in comparison to the passive one. However, we still found no significance in the behavioural task judging intensity in active and passive trials. Contrary to our hypothesis, we found no significant difference between the extensive and optimised experiment in terms of the means of N1-ERP peaks and the behavioural task. However, with the optimised experiment we were at least able to replicate the N1-ERP suppression suggesting the general validity of the approach. Finally, patients as well as healthy subjects were able to perform well and did not find it too complicated, as evidenced by the Post-Experiment Questionnaire.

11.1 N1-ERP Suppression in Active Conditions in Healthy Subjects

The results of EEG data in the optimised experiment showed significantly suppressed N1 peak values for visual stimuli in the active condition in comparison to the passive one.

These findings are in line with the extensive experiment as well as with prior research, as discussed in section 7.1 for the extensive experiment.

11.2 Intensity Perception in Healthy Subjects

The results of the behavioural task showed still no significant difference between the active and passive condition despite the optimising changes we made. As described for the extensive experiment, this finding stands in contrast to the understanding of sensory attenuation that self-initiated actions are perceived as less intense than external ones. In spite of many changes and approaches for improvement in comparison to the extensive experiment, we found no significance. Therefore, further studies require some more changes in the experimental setup optimising the task.

11.3 Comparison of Effects of the Extensive and Optimised Experiments

We found no significant difference for the EEG data and behavioural task between the extensive and optimised experiment.

Broadly speaking, it is difficult to compare directly the effects between the extensive and optimised effect since we changed the experimental setup for the optimised task. Moreover, the sample size was different for each experiment. Nevertheless, the results of comparing the effects between the extensive and optimised experiment stand in contrast with our expectations. On the one hand, we expected larger N1-ERP suppression for the optimised experiment in comparison to the extensive one. For example, the luminance and size of the visual stimuli were really low in the extensive experiment. Thus, we suggested a difference in neural activity by extending these parameters for the optimised experiment. On the other, we expected to get clearer results for the behavioural task for the same reasons, but they were still not significant.

While we did not find significance between active and passive trials for the behavioural task in the single experiments, we did not expect to show a difference for the comparison between the results of the two experiments. In contrast to these findings, patients tended to recognize the difference in intensity in accordance with the Post-Experiment Questionnaire. It should be noted that participants did not know that there was no difference in intensity except for the catch trials. Therefore, we do not know whether the responses in the questionnaire are due to sensory attenuation as we expected it or due to the inserted catch trials. However, in the behavioural data there was not significant difference in the single experiments as well as for comparison between the extensive and optimised experiment. Hence, the methods of the experimental setup should be discussed after the optimising changes again to figure out aspects which can be changed for further experiments.

11.4 Performance of Patients Fulfilling the Optimised Experiment

The results of the Post-Experiment Questionnaire showed that patients were okay with the duration of the optimised experiment but by the end, they were not able to concentrate as well. Furthermore, they all understood the task. Our first outlook on patients' electrophysiological and behavioural data presents no statistically significant results. In other words, we found no significant difference neither for N1-ERP suppression nor for the behavioural task in the active condition in comparison to the passive one. In relation to the small group of patients, the results may be clearer with a larger sample size. However, the development of an EEG study which is suitable for patients with SZ was successful regarding the Post-Experiment Questionnaire data.

Post-Experiment Questionnaire Data

In accordance with the Post-Experiment Questionnaire, patients rated the duration of the study as neutral, but the concentration decreased towards the end of the experiment. The experimental setup was easy for the patients and further, they all understood the

task. Overall, the participating patients all tolerated the process of applying and wearing the EEG cap during the experiment, while the healthy subjects felt even less disturbed. Generally speaking, the Post-Experiment Questionnaire showed the suitability of the task for patients as well as for healthy subjects. This is what we expected from the changes we made for the optimised experiment due to the main purpose of this work to develop an experimental task for patients.

As a consequence, further studies could shorten the overall duration of the study even more. Another option would be to include more breaks between the experimental blocks, for example by shortening the number of one block by maintaining the number of total trials (see question number 5). However, patients rated the number of breaks as enough (see question number 3).

The Post-Experiment Questionnaire was designed as a verbalised Likert scale of odd numbers and without scale point. It has to be noted that participants might tend to choose the middle as an escape category.

N1-ERP Suppression in Active Conditions in Patients with Schizophrenia in the Optimised Experiment

Electrophysiological data for the sample of patients with SZ showed no significant difference for the N1-ERP suppression between the active and passive condition. This finding is in line with former studies. For the auditory system, it has been shown less suppression for speech-related N1-ERPs in patients with SZ (n = 7) than in controls showing suppressed N1-ERPs for speech in comparison to playback (Ford, Mathalon, Heinks, et al., 2001). It can be discussed, that their sample as well as our sample of patients (n = 5) was too small to have enough power to detect a difference if indeed there is one. Consequently, a greater sample can be required. However, even with a larger sample (n = 27), patients showed less N1-ERP suppression for talking than healthy controls did (Ford, Gray, et al., 2007). Additionally, another study demonstrated reduced N1-ERP suppression for patients (n = 26) when using a button press delivering a tone (Ford et al., 2014). According to the authors, these findings about the neurophysiological difference in N1-ERPs between patients and controls provide evidence for dysfunctions on efference copy in patients with SZ (Ford, Mathalon, Heinks, et al., 2001).

Intensity Perception in Patients with Schizophrenia in the Optimised Experiment

We found no statistically significant results for the behavioural task comparing the active and passive trials. As described for the EEG data, patients' data were not focused in this work. Nevertheless, we did not expect significance for the difference in active and

passive conditions since we did not find any significance in the single experiments with healthy subjects as well.

11.5 Discussion of the Methods

Since we found no significant difference for the results between the extensive and optimised experiment, further changes should be made.

Sample of Healthy Subjects

As well as before, in the optimised experiment healthy subjects were mostly students from the University of Marburg testing the experimental setup and task before the sample of patients with SZ completed it. We decided to recruit again a similar number of healthy subjects to make the optimised experiment comparable to the extensive one (N_{Ext} = 27, N_{Opt} = 24; Ext = extensive experiment, Opt = optimised experiment). In order to achieve better comparability, further studies could match participants between extensive and optimised experiments in age and gender and moreover, with the sample of patients as well.

Sample of Patients with Schizophrenia

It has to be noted that all of the patients were male. This aspect should definitely be considered if one wants to align the results with the conditions of patient care. Moreover, it should be thought about the age range if one wants to compare the results to realities of everyday health care. We chose the age of 18-60 years for inclusion to the study in accordance with previous studies (Ford, Mathalon, Kalba, et al., 2001b) and due to the experimental setup using a computer.

The recruitment of patients was difficult since we chose strong inclusion criteria. We excluded many patients due to abuse of medication, drugs and alcohol while doing the first screening. For investigating neural correlates of prediction mechanisms, we wanted to exclude additional factors, aside from SZ, which might influence the results. Therefore, none of the patients had current abuse of the named substances. This criterion has to be discussed since substantial abuse is frequent in SZ. Due to that, including patients with abuse might represent the total population of patients with SZ better. In contrast, results might become less generalisable while having stricter criteria. However, we wanted to be as sure as possible not to have any influence of these substances on the results.

Another point that should be noted for the recruitment of patients is the conduction of the SCID. For the small sample of the patients, two research assistants conducted the interviews. On the one hand, this might lead to different ratings of the patients' responses in the standardised interview. On the other, personal differences in interviewing can be

balanced by two different conductors of the interviews. However, in everyday health care, there are different investigators as well and therefore, this represents the clinical reality better.

The sample size of patients might be considered too small to see reliable statistical results. Since this work is part of a larger study, there will be data from 24 patients with SZ in total, similar to previous studies (Kemenade et al., 2016). However, for the purpose of this work, the patients' EEG and behavioural data are only recorded for an outlook whereas the focus was the development of an EEG study and its experimental setup.

Task

The experimental set up and the task was easy to understand and well explained to the patients in accordance with the Post-Experiment Questionnaire data. Therefore, the written instructions in the optimised experiment provide all information to complete the task well.

Furthermore, there were only very few repeated trials in the optimised experiment. Thus, we conclude that the changed time limit of 3000 ms to give a response is fairly enough for participants both healthy subjects and patients.

For the optimised experiment, we extended the duration of visual stimuli displayed on the computer monitor from 50 ms to 100 ms. While considering prior research, this time value should be fine. For example, Mifsud et al. (2018) chose a duration of 33.33 ms for their flashes. However, a longer appearance of the stimuli might lead to better behavioural results. In a study of multisensory facilitation, van Kemenade et al. (2016) presented their first stimulus for 1 s. Therefore, further studies might extend the duration of stimulus presentation even longer. For this reason, fMRI might be a more suitable method for combining with behaviour in future studies. However, we chose this time interval based on prior research as well as for the factor that with EEG, we can assess short time intervals by recording brain activity time-synchronously.

Even though our selected number of 40 trials was sufficient to reveal N1-ERP suppression for the extensive experiment, we decided to enlarge the number for the optimised experiment to 200 experimental trials with visual stimuli of the same intensity. On the one hand, we did this in order to improve the signal to noise ratio. On the other, besides many other changes for the optimised experiment, we expected a difference in results for the behavioural task. Since there was only the visual condition in the optimised experiment, we could include more trials per condition and still keep it a reasonable length.

In addition, it should be noted that participants might get inattentive to the task by displaying visual stimuli of only the same intensity all the time. This is why we decided to insert catch trials in accordance with prior research (Reznik et al., 2015; Roussel et al., 2013). However, we wanted to focus on visual stimuli of the same intensity against the background of the development of an experimental study which is suitable in the overall duration for patients.

Last but not least, participants were able to sit as comfortably as possible to complete the task of the extensive experiment. Due to a fixed position of the button box and keyboard, the distance between the computer monitor and the eyes were always different between the participants. It could be argued that it is necessary to control that factor. For example, Mifsud et al. (2018) used a distance of 60 cm, van Kemenade et al. (2016) used a distance of 54 cm in front of the computer screen. Considering that our behavioural task did not show the expected results after optimising changes, further studies could try to combine the level of comfort and a fixed distance between the eyes and the computer monitor. However, we tried to make the task as comfortable as possible for the participants.

11.6 Limitations

The results of the optimised experiment cannot be applied to the total population of patients suffering from SZ by referring to a small sample of only five patients in the extensive experiment. Therefore, the larger study in which this work is framed might be more transferable in terms of content by including 24 patients with SZ in total and matching patients with healthy controls as well.

11.7 Importance

As outlined in the introduction and reviewed by the World Health Organization (2002), SZ is a chronic and severe mental disorder resulting in huge economic costs and a high suicide rate of 10%. Against that background and the fact that the neuropsychiatric illness is among the Top Ten worldwide causing a high degree of disability, the importance of research on SZ is demonstrated. The disorder affects around 1% worldwide (Gaebel & Wölwer, 2010) and therefore, requires clinical and scientific effort for investigating the pathomechanisms and appropriate treatment. For example, EEG could help to find the right frequency in transcranial direct current stimulation (tDCS). It has been suggested that efference copy mechanisms and action-outcome monitoring in patients with SZ can be improved by using this method (Straube et al., 2020). In order to address scientific progress as the basis for clinical treatment, the main purpose of this work was the development of an experimental EEG study which is suitable for patients. This work concentrated on the visual system since this is the least

well-studied sensory domain whereas visual hallucinations are the second most common after auditory hallucinations. By identifying several problems in the extensive experiment, we found solutions for the experimental task of the optimised task. As a result, patients with SZ suited the experiment as generally speaking, evidenced by the Post-Experiment Questionnaire.

11.8 Outlook

Considering the main objective of this work, there are further optimisation approaches for ongoing research to make the experiment even more suitable for patients. Furthermore, they might achieve more robust effects and therefore, gain broader understanding about the development of symptoms of the disease. However, this work provides insight into how to develop a suitable experimental task for patients with SZ, which plays a key role in designing experiments in every future study with participating patients.

Furthermore, we expect that the larger study in which this work is framed will be able to give further insight into the psychopathology in the visual domain in SZ due to a larger sample size. Moreover, in the larger study we want to investigate whether patients with SZ show impaired predictive mechanisms in the visual system as it has been shown in the auditory system since there is only little research for this sensory domain. These findings might gain broader understanding about symptoms in SZ as well.

11.9 General Conclusion

The results of this work strengthen former electrophysiological studies describing N1-ERP suppression in active conditions in healthy subjects. This finding refers to the extensive as well as to the optimised experiment. For the small sample of patients in the optimised task, we found no significant difference between the conditions which presumably requires a larger number of participants suffering from SZ for a robust effect. The effect of N1-ERP suppression was not larger in the optimised experiment after the optimising changes. However, the EEG effects go in line with prior research on prediction mechanisms including the forward model and its efference copy.

For the behavioural task in which participants were asked to judge the intensity of the two visual stimuli, we did not find a significant difference between the active and passive condition, neither for healthy subjects nor for patients. This finding was the same for the extensive as well as for the optimised experiment. This stands not only in contrast to our expectation of more robust effects after several changes for the optimised task, but to the understanding of sensory attenuation in general. Intensity perception is seen as an adaptable construct which depends on the agent of the actions we perceive. Thus, self-initiated sensory consequences are assumed to be perceived less intensely than

external ones. Since we found no significance, further changes and studies are needed to show more robust effects for the visual system whereas most of the former studies focus on the other sensory modalities.

Overall, the Post-Experiment Questionnaire showed that generally speaking, patients suited the task in the optimised experiment. This is what we expected from the changes we made after the extensive experiment since many of them were made in relation to the level of comfort. In conclusion, the main purpose of this work, namely the development of an experimental EEG study which is suitable for patients with SZ, was successful.

12 Summary

Background

Prediction mechanisms are crucial for efficient perception of the environment and ourselves as well as for discrimination between self-generated and external changed situations. Known as the internal forward model, an efference copy of the motor plan prepares the sensory areas for the reafferent feedback of one's own planned actions. In case of a match between predicted and actual sensory feedback, further processing of the sensory consequences can be damped. This can be seen in suppressed N1-ERP amplitudes in EEG as well as attenuated intensity perception in behavioural data. Moreover, agency for self-generated actions can be attributed correctly by means of this mechanism, whereas external actions cannot prepare the sensory cortex with efference copy and therefore are identified as externally-generated. Dysfunctions in the prediction mechanism for self-generated actions result in a mismatch in the internal forward model, which in turn results in external attribution of agency as well as abnormal neurophysiological and behavioural correlates. Disturbed prediction mechanisms and failure in efference copy are suggested to be a reason for several positive symptoms of schizophrenia like sensory hallucinations and passivity experiences.

Hypotheses/Objective

In the first part of our study, we investigated efference copy based predictions in healthy subjects in an extensive button press experiment. We hypothesised that the analyses of a selected number of visual trials with the same intensity will be sufficient to show N1-ERP suppression in active conditions. We expected that the second stimulus is perceived as more intense significantly more often in active conditions. With the main aim to develop an optimised and suitable experiment for patients, we hypothesised clearer N1-ERP and behavioural effects after changing the experimental setup in the second part of our study by altering the time intervals, shortening the overall duration, changing the presentation format and focussing on the visual condition only. Finally, we suggested that participants are able to perform the optimised task well. We expected this to be evidenced by the Post-Experiment Questionnaire.

Material and Methods

Participants pressed actively or passively a button followed by visual stimuli displayed on a computer monitor. Consequently, they judged whether the first or second stimulus was brighter by pressing one of the defined keys. For the total duration of the experiments, we recorded EEG. Additionally, participants were asked to complete a questionnaire about the optimised experiment to assess the performance and suitability.

Results

For both experiments, we found significantly smaller N1 peak values in active trials than in passive conditions in healthy subjects. The difference between the two experiments themselves was not significant. Behavioural data for intensity perception showed no significant difference, neither in the individual experiments nor in comparing the two. In patients with schizophrenia, we found no significant results for the optimised experiment. However, patients as well as healthy subjects were able to perform well in the optimised experiment assessed by the Post-Experiment Questionnaire.

Discussion

Our electrophysiological results go in line with prior research in healthy subjects in both experiments. We showed that the analyses of a selected number of visual trials with the same intensity was sufficient to show N1-ERP suppression in active conditions in the extensive experiment. In contrast to our expectations for the behavioural task, we did not find a significant difference between the two conditions for both experiments. This stands in contrast to the understanding of sensory attenuation that self-initiated actions perceived as less intense than external ones. Therefore, further changes and studies are needed to show more robust effects for the visual system whereas most of the former studies focus on the other sensory modalities. However, the development of an EEG study which is suitable for patients with schizophrenia was successful regarding the Post-Experiment Questionnaire data.

Conclusion

In conclusion, we demonstrated evidence of the neural (but not behavioural) mechanism in the visual modality. With the main aim to develop an experimental paradigm for patients to investigate dysfunctions in schizophrenia, we showed the suitability of the task assessed by the Post-Experiment Questionnaire. Further studies with a larger sample of patients are required to give more insight into the psychopathology and impaired predictive mechanisms in the visual domain in schizophrenia.

13 Zusammenfassung

Hintergrund

Vorhersagemechanismen sind für die effiziente Wahrnehmung der Umwelt und uns selbst wie auch für die Unterscheidung zwischen selbst- und fremderzeugten Situationen unerlässlich. Im Rahmen des internen Vorwärtsmodells bereitet eine Efferenzkopie des motorischen Handlungsplans die sensorischen Areale auf das reafferente Feedback vor. Bei einer Übereinstimmung zwischen dem vorhergesagten und tatsächlichen sensorischen Feedback kann die weitere Verarbeitung gedämpft werden. Dies zeigt sich sowohl in supprimierten N1-ERP-Amplituden im EEG wie auch in abgeschwächter Intensitätswahrnehmung in Verhaltensdaten. Durch diesen Mechanismus können selbsterzeugte Handlungen „dem Selbst“ korrekt zugeordnet werden, während fremderzeugte Handlungen den sensorischen Kortex nicht mit einer Efferenzkopie vorbereiten können und damit als fremd erkannt werden. Fehlfunktionen in Vorhersagemechanismen für selbsterzeugte Handlungen resultieren in einer Unstimmigkeit im internen Vorwärtsmodell, was zur Zuordnung als fremderzeugte Handlung als auch zu abnormen neurophysiologischen und Verhaltenskorrelaten führt. Dies wird als Ursache für verschiedene positive Symptome der Schizophrenie wie sensorische Halluzinationen und Passivitätsphänomene angenommen.

Hypothesen/Zielsetzung

Im ersten Teil der Studie untersuchten wir auf Efferenzkopie basierende Vorhersagen in einem umfangreichen Knopfdruckexperiment bei gesunden Probanden. Wir stellten die Hypothese auf, dass die Analyse einer ausgewählten Anzahl von visuellen Versuchen mit der gleichen Intensität ausreicht, um eine N1-ERP-Suppression unter aktiven Bedingungen zu zeigen. Wir erwarteten, dass der zweite Stimulus unter aktiven Bedingungen signifikant häufiger als intensiver wahrgenommen wird. Mit dem Hauptziel, ein optimiertes und für Patienten geeignetes Experiment zu entwickeln, stellten wir die Hypothese auf, dass nach einer Änderung des Versuchsaufbaus deutlichere N1-ERP- und Verhaltenseffekte im zweiten Teil unserer Studie auftreten, indem wir die Zeitintervalle veränderten, die Gesamtdauer verkürzten, das Präsentationsformat änderten und uns nur auf die visuelle Bedingung konzentrierten. Schließlich nahmen wir an, dass die Teilnehmer in der Lage sind, das optimierte Experiment gut zu lösen. Wir erwarteten, dass sich dies durch den Fragebogen nach dem Experiment feststellen lässt.

Material und Methoden

Die Teilnehmer drückten aktiv oder passiv eine Taste, woraufhin visuelle Reizen auf einem Computerbildschirm angezeigt wurden. Anschließend beurteilten sie, ob der erste

oder zweite Reiz heller war, indem sie eine der definierten Tasten drückten. Während der gesamten Dauer der Experimente wurde ein EEG aufgezeichnet. Die Teilnehmer wurden gebeten, einen Fragebogen über das optimierte Experiment auszufüllen, um dessen Eignung zu bewerten.

Ergebnisse

In beiden Experimenten fanden wir bei gesunden Probanden signifikant kleinere N1-Spitzenwerte in aktiven als in passiven Versuchen. Der Unterschied zwischen den beiden Experimenten selbst war nicht signifikant. Die Verhaltensdaten zur Intensitäts-wahrnehmung zeigten keinen signifikanten Unterschied, weder in den einzelnen noch im Vergleich der beiden Experimente. Bei Patienten mit Schizophrenie fanden wir keine signifikanten Ergebnisse für das optimierte Experiment. Sowohl Patienten als auch gesunde Probanden waren in der Lage, das optimierte Experiment gut durchzuführen, was anhand des Fragebogens nach dem Experiment beurteilt wurde.

Diskussion

Unsere elektrophysiologischen Ergebnisse stehen im Einklang mit früheren Studien an gesunden Probanden. Wir konnten zeigen, dass die Analyse einer ausgewählten Anzahl von visuellen Versuchen mit der gleichen Intensität ausreicht, um eine N1-ERP-Suppression unter aktiven Bedingungen im umfangreichen Experiment zu zeigen. Wider Erwarten fanden wir für die Verhaltensaufgabe keinen signifikanten Unterschied zwischen den beiden Bedingungen. Dies steht im Gegensatz zu dem Verständnis der sensorischen Dämpfung, dass selbst initiierte Handlungen als weniger intensiv wahrgenommen werden als fremderzeugte Handlungen. Weitere Optimierungen und Studien sind erforderlich, um robustere Effekte für das visuelle System zu zeigen. Die Entwicklung einer EEG-Studie, die für Patienten mit Schizophrenie geeignet ist, war jedoch im Hinblick auf die Daten des Post-Experiment-Fragebogens erfolgreich.

Schlussfolgerung

Zusammenfassend konnten wir Evidenz für den elektrophysiologischen Mechanismus im visuellen System, nicht aber für die Verhaltensaufgabe zeigen. Mittels Post-Experiment-Fragebogen konnten wir die Eignung des optimierten experimentellen Versuchsaufbaus für Patienten zeigen, dessen Entwicklung unser Hauptziel war, um Funktionsstörungen bei Schizophrenie zu untersuchen. Weitere Studien mit einer größeren Patientenstichprobe sind erforderlich, um mehr Einblick in die Psychopathologie und die beeinträchtigten Vorhersagemechanismen im visuellen Bereich bei Schizophrenie zu erhalten.

14 References

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Appendix

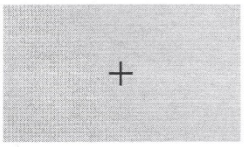
Appendix 1: Supplementary Material

Appendix 1.1: Instructions for the Optimised Experiment

Studieninstruktion

Das Experiment besteht aus drei verschiedenen Aufgabenblöcken
– einem **AKTIVEN**, einem **PASSIVEN** und einem **SCHNELLEN**.

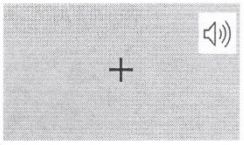
Im Folgenden wird Ihnen zunächst erklärt, wie das Experiment abläuft.



1

In jedem Durchgang sehen Sie ein Kreuz in der Mitte des Bildschirmes.

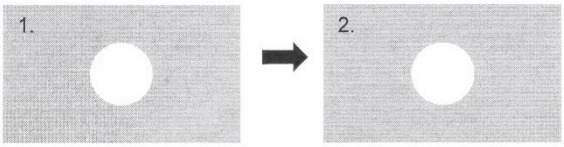
Fixieren Sie immer dieses Kreuz.



2

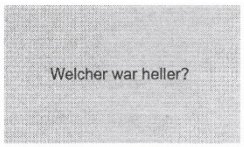
Sie hören dann einen Ton.

Auf diesen Ton hin erfolgt ein **Knopfdruck** der Apparatur auf Ihrer rechten Seite. Dieser wird Ihnen nachfolgend erklärt.



3

Nach dem Knopfdruck sehen Sie schnell aufeinander folgend **zwei Kreise**.

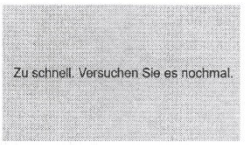


4

Sie werden gefragt, welcher der beiden Kreise heller war.

Drücken Sie **V**, wenn Sie glauben, dass der erste Kreis heller war.
Drücken Sie **N**, wenn Sie glauben, dass der zweite Kreis heller war.

Die Aufgabenblöcke unterscheiden sich darin, wie der **Knopfdruck** erfolgt.



I

Bei den **AKTIVEN** Blöcken drücken Sie den Knopf **kurz nach** dem Ton.

Wenn Sie den Knopf zu schnell drücken, erhalten Sie den Hinweis, dass Sie es erneut versuchen sollen.

II

Bei den **PASSIVEN** Blöcken bewegt sich der Knopf von selbst und Sie lassen Ihren Finger **entspannt**.

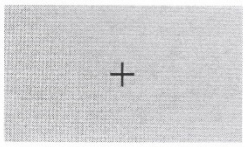
III

Bei den **SCHNELLEN** Blöcken drücken Sie den Knopf **so schnell wie möglich** nach dem Ton.

Sie werden nun zunächst einige Übungsdurchgänge machen, um mit der Aufgabe vertraut zu werden. Bei Fragen melden Sie sich bei der Versuchsleitung.

Studieninstruktion - Kontrollblock

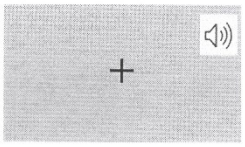
Der Kontrollblock besteht wieder aus drei verschiedenen Aufgabenblöcken
– einem **AKTIVEN**, einem **PASSIVEN** und einem **SCHNELLEN**.



1

In jedem Durchgang sehen Sie ein Kreuz in der Mitte des Bildschirmes.

Fixieren Sie immer dieses Kreuz.

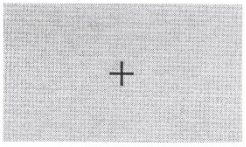


2

Sie hören dann einen Ton.

Auf diesen Ton hin erfolgt ein **Knopfdruck** der Apparatur auf Ihrer rechten Seite.

Der Knopfdruck unterscheidet sich wieder zwischen den **AKTIVEN**, **PASSIVEN** und **SCHNELLEN** Aufgabenblöcken.



3

Fixieren Sie nach dem Ton weiterhin das Kreuz.

Am Ende von jedem Durchgang verschwindet das Kreuz kurz.

Wenn es wieder auftaucht, beginnt der nächste Durchgang.

Appendix 1.2: Post-Experiment Questionnaire

Questionnaire

Dysfunctional prediction mechanisms in Schizophrenia
Translational Neuroimaging Marburg
Department of Psychiatry and Psychotherapy
Philipps-University Marburg, UKGM GmbH
Rudolf-Bultmann-Straße 8
35039 Marburg

To be completed by the investigator
Subject number: Group: please mark with a cross ◦ Student ◦ Patient Investigator: Date:

Thank you for your participation in the study. In order for us to gain the most accurate results, please answer the questions as honestly as possible. Thank you for your cooperation!

	Totally agree	**Agree**	**Neutral**	**Disagree**	**Totally disagree**
I was able to concentrate well for the entire duration of the experiment.					
The experiment was too long.					
There were enough breaks.					
The tasks were well explained to me.					
The tasks between the breaks were too long.					
I always understood what was required of me.					
The experiment was too complicated for me.					
The instructions were very clear and I understood what I had to do.					
I could easily remember which key had which meaning.					
There were too many different keys I had to operate.					
I was able to sit comfortably during the experiment.					
I couldn't tell the difference between brightness of the circles.					
I often pressed the wrong button by mistake.					
Not all circles were equally bright.					
I often had to guess at the answers because I wasn't paying attention.					

I was often unsure of the answers.					
In the end, I couldn't concentrate as well.					

Questions for measurements in which we recorded an EEG					
	Totally agree	**Agree**	**Neutral**	**Disagree**	**Totally disagree**
It took too much time to apply the EEG electrodes.					
The preparation took too long.					
The EEG electrodes distracted me from the task at hand.					
I did not mind having the EEG electrodes applied.					
The preparation made me tired.					
The EEG cap bothered me during the investigation.					
The EEG cap was uncomfortable.					
I would participate in another experiment.					

Additional comments:

Umfrage zum Experiment

EEG-Korrelate dysfunktionaler Vorhersagemechanismen bei Schizophrenie
Translational Neuroimaging Marburg
Klinik für Psychiatrie und Psychotherapie
Universitätsklinikum Gießen und Marburg GmbH
Rudolf-Bultmann-Straße 8
35039 Marburg

Vom Versuchsleitenden auszufüllen
Probandennummer: Gruppe: bitte ankreuzen ◦ Student ◦ Patient Versuchsleiter/in: Datum:

Wir danken Ihnen für Ihre Teilnahme an der Studie. Damit wir möglichst genaue Ergebnisse erzielen können, beantworten Sie die Fragen bitte so ehrlich wie möglich. Herzlichen Dank für Ihre Mithilfe!

	Stimme völlig zu	**Stimme zu**	**Neutral**	**Lehne ab**	**Lehne völlig ab**
Ich konnte mich über die gesamte Dauer des Experiments gut konzentrieren.					
Das Experiment war zu lang.					
Es gab genug Pausen.					
Die Aufgaben wurden mir gut erklärt.					
Die Aufgabenteile zwischen den Pausen waren zu lang.					
Ich habe immer verstanden, was von mir verlangt wird.					
Das Experiment war mir zu kompliziert.					
Die Aufgabenstellung war sehr klar und ich habe verstanden, was zu tun ist.					
Ich konnte mir gut merken, welche Taste welche Bedeutung hatte.					
Es waren zu viele verschiedene Tasten, die ich bedienen musste.					
Ich konnte während der Untersuchung gemütlich sitzen.					
Ich konnte keinen Unterschied in der Helligkeit der Kreise erkennen.					
Ich habe oft versehentlich falsch gedrückt.					
Es waren nicht alle Kreise gleich hell.					
Ich musste bei den Antworten oft raten, da ich nicht aufgepasst habe.					

Ich war mir oft unsicher bei den Antworten.					
Am Ende konnte ich mich nicht mehr so gut konzentrieren.					

Fragen für Messungen, in denen wir ein EEG aufzeichneten					
	Stimme völlig zu	**Stimme zu**	**Neutral**	**Lehne ab**	**Lehne völlig ab**
Das Anbringen der EEG-Elektroden hat zu viel Zeit gebraucht.					
Die Vorbereitungen dauerten zu lange.					
Die EEG-Elektroden haben mich von der Aufgabe abgelenkt.					
Es hat mich nicht gestört, die EEG-Elektroden anbringen zu lassen.					
Die Vorbereitungen haben mich müde gemacht.					
Die EEG-Haube hat mich während der Untersuchung gestört.					
Die EEG-Haube war unangenehm.					
Ich würde noch einmal an einer Untersuchung teilnehmen.					

Zusätzliche Kommentare:

Appendix 2: Results of the Post-Experiment Questionnaire of Healthy Subjects

Question No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Healthy Subject																									
1	3	2	4	5	2	5	2	5	4	2	2	4	2	4	2	4	4	2	2	2	5	2	1	1	3
2	4	2	2	4	2	4	2	4	5	2	3	3	2	4	2	2	2	2	2	2	4	2	2	2	5
3	5	2	5	5	2	5	1	5	5	1	3	3	2	5	1	3	2	1	2	1	5	1	1	1	4
4	2	3	4		2		1	5	5	1	4	2	3	4	2	4	5	1	1	1	2	1	1	1	4
5	3	2	5	5	1	5	1	5	5	1	4	2	1	5	2	4	4	1	1	1	5	1	1	1	5
6	4	2	4	5	2	5	1	5	4	1	4	3	2	5	3	4	4	2	2	1	5	3	2	2	4
7	4	3	5	5	2	5	1	4	5	1	4	3	2	3	2	3	4	2	2	1	5	2	2	2	5
8	4	2	4	5	1	5	1	5	5	1	4	2	2	4	2	3	3	1	2	1	5	1	2	2	4
9	4	3	5	5	3	4	2	5	5	3	5	3	4	5	3	4	5	3	2	1	5	2	1	2	4
10	2	3	4	5	2	4	1	5	5	1	4	4	3	4	4	5	4	3	3	1	5	1	1	2	5
11	4	3	5	5	2	5	1	5	5	1	4	4	3	4	2	3	4	2	2	1	5	2	1	1	5
12	5	2	5	5	2	5	1	5	5	1	5	2	1	4	2	4	1	2	2	2	2	2	2	2	4
13	2	3	5	5	3	5	1	5	5	1	5	3	1	5	1	4	5	1	1	1	5	1	1	1	5
14	5	1	5	5	1	5	1	5	5	1	5	3	1	5	2	3	2	1	1	1	5	1	1	1	5
15	4	2	5	5	2	5	1	5	5	1	4	3	2	3	2	4	3	2	1	1	5	1	1	1	5
16	3	3	4	4	3	4	2	3	4	2	4	2	3	5	3	4	4	3	2	1	4	2	1	1	4
17	4	2	5	5	1	5	1	5	5	1	5	2	1	5	2	4	1	1	1	1	1	1	1	1	5
18	5	2	4	4	2	4	2	4	5	1	4	3	2	4	2	2	2	2	2	2	4	2	2	3	5
19	3	2	3	5	2	5	2	5	4	2	3	2	2	4	2	4	5	2	2	2	2	2	2	2	4
20	5	2	5	5	2	5	1	5	5	1	5	2	1	5	1	4	2	3	2	1	1	1	1	1	5
21	5	1	5	5	1	5	1	5	5	1	4	3	1	4	1	2	2	1	1	1	1	1	1	1	4
22	2	3	5	5	2	5	1	5	5	1	4	3	3	5	1	4	4	2	1	1	1	1	1	1	5
23	4	1	5	5	2	5	1	5	5	1	4	3	2	5	2	4	4	1	1	1	1	1	1	1	5
24	5	3	4	4	2	5	2	5	4	4	4	4	3	3	3		3	4	3	3	3	4	3	4	4
MODE	4	2	5	5	2	5	1	5	5	1	4	3	2	5	2	4	4	2	2	1	5	1	1	1	5
MAX	5	3	5	5	3	5	2	5	5	4	5	4	4	5	4	5	5	4	3	3	5	4	3	4	5
MIN	2	1	2	4	1	4	1	3	4	1	2	2	1	3	1	2	1	1	1	1	1	1	1	1	3
RANGE	3	2	3	1	2	1	1	2	1	3	3	2	3	2	3	3	4	3	2	2	4	3	2	3	2

Score (Point) I totally agree (5), I agree (4), Neutral (3), I disagree (2), I totally disagree (1), No Answer (empty)

Appendix 3: List of Academic Teachers

My academic teachers in Marburg were:

Aigner, Adelmeyer, Albers, Baranovski, Bartsch, Bauer (Stefan), Bauer (Uta-Maria), Becker (Annette), Becker (Katja), Bertoune, Besgen, Bette, Bien, Bliemel, Bogdan, Bonaterra, Bösner, Cabanel, Carl, Cetin, Cordes, Czubayko, Damm, de Cruppé, Decher, del Ray, Denkert, Denzer, Donner-Banzhoff, Eberhart, Falkenberg, Felgentreff, Feuser, Frink, Fuest, Geisel, Geks, Geraedts, Gesche, Göbel, Görg, Gremke, Gress, Grgic, Grote, Günther, Haberhausen, Häuser, Hertl, Hildebrandt, Hoch, Hoffmann, Holzer, Hoyer, Jansen (Andreas), Jansen (Malin), Josephs, Kalder, Kann, Kanngießer, Karatolios, Keber, Keil, Kinscherf, Kircher, Kirschbaum, Kleinholdermann, Kluge, Knorrenschild, Köhler, Kruse, Kühnert, Lill, Lohoff, Lüsebrink, Mahnken, Maier (Rolf), Markus, Meissner, Michielis-Corsten, Milani, Mirow, Moll, Muigai, Müller (Hans-Helge), Nenadić, Neubauer, Neumüller, Nimsky, Oberwinkler, Oliver, Opitz, Pagenstecher, Paul, Pedrosa, Peterlein, Pfützner, Plant, Pöttgen, Preisig-Müller, Rastan, Reese, Renigunta, Renke, Renz, Rinné, Rost, Ruchholtz, Rust, Sahmland, Saß, Schäfer, Schieffer, Schu, Schulze, Schütz, Schwabe, Seitz, Sekundo, Sevinc, Simon, Sommer, Stahl, Stathopoulus, Steiniger, Straube, Stuck, Swaid, Tackenberg, Thieme, Timmermann, Tsalouchidou, Vahdad, Visser, Vogelmaier, Vogt, Vorwerk, Wagner (Uwe), Weber, Weihe, Westermann, Wilhelm, Wilhelmi, Wrocklage, Wulf, Ziller.

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