Stop! And Go? - Neuroanatomical correlates and consequences of the inhibition of ongoing responses

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Preface

This dissertation is organized in the following way: In the general introduction some current ideas and issues concerning the investigation of executive functions and inhibition will be presented. This is not done to give a full overview over these issues, which is beyond the scope of this dissertation, but as an attempt to put the studies of this dissertation into a framework of current research. In the general methods section, methods that are equal for some of the studies will be presented to avoid redundancies later in the text. After that, the dissertation is organized along three studies and an explorative analysis. For each study a separate introduction will be provided, dealing with the theoretical issues specifically concerning the question of the study, and the results for each study will also be discussed separately. In the general discussion a summary of results will be provided. Only issues emerging from a comparison across studies will be discussed there. Furthermore, some methodological limitations of the studies and implications for future research will be discussed there.

At the time this dissertation was submitted, part of the dissertation was already published (Study 3, British Journal of Psychology, 1999, 90, 509-518), and other parts (study 1 and study 2) submitted to scientific journals.

Contents

1. General introduction

1.1 Executive functions

A number of important features of the human mind are summarized under the terms “executive control” or “executive functions”. These aspects can be regarded as top down effects in contrast to bottom up effects, that only represent stimulus driven processes. Executive functions include the ability to initiate, control or discontinue action, to use information flexibly, to make reasonable inferences, to think abstractly, to respond to novel information and situations, to sequence information and to direct behavior in a goal-directed manner (e.g. Baddeley, 1996; Lezak, 1982; Logan, 1985a; Stuss & Benson, 1984). Welsh and Pennington (1988, pp. 201-202) define executive functions the following way:

> “[Executive functions are] ... the ability to maintain an appropriate problem-solving set for attainment of a future goals. This set can involve one or more of the following: (a) an intention to inhibit a response or to defer it to a later more appropriate time, (b) a strategic plan of action sequences, and (c) a mental representation of the task, including the relevant stimulus information encoded into memory and the desired future goal-state.”

The term executive function covers many abilities and, as such, is a concept for which providing a precise theoretical or operational definition is difficult. It is interesting that in order to define executive functions, authors usually refer to supposed abilities being executive functions or describe situations in which executive functions are likely to be needed (see Table 1.1). That those characterizations are necessary reveals a key aspect about executive functions. As Burgess (1997, p.84) puts it: “Neuropsychologists would hardly feel it necessary to define the circumstances under which speech production processes are likely to be needed.” The provisional and underspecified definition of executive function in both, neuropsychology and cognitive psychology, is due to several reasons.

Table 1.1. Examples of taxonomies of executive functions

Author(s), Year	**Proposed executive functions**
Baddeley, 1996	Fractionation of the central executive into four parts 1. Capacity to timeshare 2. Capacity to switch retrieval plans 3. Capacity to attend selectively 4. Capacity for temporary activation of long-term memory
Lezak, 1982	Four categories of executive capacities 1. Goal formulation 2. Planning 3. Carrying out goal-directed plans 4. Effective performance
Logan, 1985a	Executive functions 1. Choice among different strategies 2. Construction or instantiation of a chosen strategy 3. Execution and maintenance of a strategy to perform the task 4. Inhibition or disablement of a strategy in response to changes in goals or changes in the task environment
Rabbitt, 1997	Distinctions between „executive“ (EF) and „non-executive“ functions (NEF): 1. EF are necessary to deal with novel tasks 2. EF are necessary to manage the „internal information environment“ of long term memory 3. EF are necessary to initiate new and interrupt ongoing sequences of behavior 4. EF are necessary to prevent responses that are inappropriate in context 5. EF are responsible for the strategic allocation of attention and synchronization of responses 6. EF are necessary to monitor performance in order to detect and correct errors 7. EF enable attention to be sustained continuously over long periods
Stuss & Benson, 1984	Six specific prefrontal functions 1. Separation of action from knowledge 2. Ability to handle sequential behavior 3. Ability to establish or change a set 4. Ability to resist interference 5. Ability to monitor personal behavior 6. Attitudes of concern and awareness
Stuss, Shallice, Alexander & Picton, 1995	Five independent supervisory processes in attention 1. Energizing schemata 2. Inhibiting schemata 3. Adjusting contention scheduling 4. Monitoring the level of activity in schemata 5. Control of “if-then” logical processes

In comparison to other cognitive functions, executive functions are much less well understood (e.g. Burgess, 1997). Furthermore, the term executive functions is often associated with a homunculus (Pennington & Ozonoff, 1996, for homunculus conceptions see “supervisory attentional system”, SAS, Norman & Shallice, 1986; Shallice, 1988; Shallice & Burgess, 1991; or “central executive”, Baddeley, 1986). In addition, there is no clear empirical distinction between executive and non-executive function, those can rather be regarded as a continuum than as separate entities (Rabbitt, 1997).

This state of affairs is reflected in the heterogeneous picture how researchers approach the issue of executive functions. Some study specific functions (e.g. control of motor responses), other base their research on a test-oriented approach (e.g. the Wisconsin Card Sorting Test) and still other address more abstract concepts like self-awareness (see Stuss, 1991). Currently, because the term executive function has no operational definition and entails varying lists of functions, researchers have begun, rather than studying “executive functions”, to give detailed analysis of certain types of functions, for example confabulation, concept formation and response inhibition. This will also be the approach in this dissertation. The function that will be studied in the present work is the inhibition of ongoing responses.

1.2 Executive functions and the frontal lobes

The terms “executive functions” and “frontal functions” are often used interchangeably. However, the term “frontal functions” refers to a structural entity, the anterior one-third of the brain, but does not emphasize that the brain is a integrated functioning unit. The term “frontal system” reflects a more interactive approach, but again emphasizes the anatomical base (Rabbitt, 1997). Therefore the term “executive functions” is preferred. This term makes the attribution to the frontal lobes, exclusively or primarily, not necessary, it is more directly related to the psychological concept, regardless of the underlying neuroanatomy.

It is not surprising that executive functions have been associated with the frontal lobes. Patients with frontal lesions show in comparison to patients with

nonfrontal lesions a rigid behavior in sorting and categorizing tasks (Delis, et al., 1992; Milner, 1964; Nelson, 1976), are easily distracted (Knight et al., 1981; Wilkins et al., 1987) and deficits in planning and problem solving (Karnath, Wallesch & Zimmermann, 1991; Milner, 1965; Shallice & Burgess, 1991; Vilkki & Holst, 1991). The reason for attributing abilities like planning, decision making, goal-directed selection and monitoring of ongoing behavior to the frontal lobes is thus obvious: focal lesions to this cortical region often result in striking impairment of these functions (e.g. Fuster, 1989, Stuss & Benson, 1986).

It is however not always that easy to establish a relationship between executive functions and specific neuroanatomical regions or neurophysiological systems. Not everyone accepts that the major (or only) function of the frontal lobes are executive control processes (e.g. Reitan & Wolfson, 1994). There are frequent findings of frontal patients who perform perfectly well on such tests (e.g. Shallice & Burgess, 1991) and patients with non-frontal lesions who perform poorly on the supposedly frontal-specific tests (e.g. Anderson et al. 1991; Grafman et al., 1990). However, deficits in executive function are much more common after anterior damage. An additional problem is, that in some so-called “executive tests” there is a lack of evidence that poor performance is always due only to executive deficits. There are a number of potential reasons for performing poorly on such tasks, given the complexity for example of the Wisconsin Card Sorting Test (Anderson et al., 1991; Milner, 1964).

It is important to note that the prefrontal cortex has extensive reciprocal connections to many areas of the brain, including the basal ganglia, the limbic system, the thalamus and the posterior cortex. It seems plausible that executive functions, including inhibition, are sustained by a cortical and subcortical neural network, and not by a localized region such as the frontal lobes (Jahanshahi & Frith, 1998; Vilkki et al., 1996). Thus, only some disorders, which cause so-called „frontal deficits“ involve neuropathology within the prefrontal cortex, others involve brain systems outside the prefrontal cortex, but systems that are closely interconnected to it. Weinberger (1992, cited in Pennington & Ozonoff, 1996) distinguishes these two kinds of disorders as

„intrinsic“ and „extrinsic“ frontal disorders. According to this view the correlation of a deficit exists not only with a damaged region, but with the whole circuit made dysfunctional by a focal lesion.

The issue of response inhibition and its deficit should therefore be studied outside the limits of its relation with frontal lobes. It is the aim of this dissertation, not to view the frontal lobes as an isolated structure, but to take into account the interconnections to other parts of the brain. This is done in study 1, where not only patients with frontal lobes lesions, but also patients with basal ganglia lesions will be investigated (for a review of fronto-striatal circuits see Alexander, 1986).

1.3 Inhibition as an executive function

Many authors assume that a fractionation of executive processes or functions is possible (e.g. Shallice & Burgess, 1991), see Table 1.1 for some of the proposed distinct functions. Inhibition is one of the most frequently mentioned executive functions. Inhibition is important when a task is finished, when a goal is no longer relevant, when an error needs to be corrected, and when appropriate stimuli have to be selected and inappropriate rejected (Logan, 1985a).

However, recently the concept of inhibition as a distinct executive function has been challenged. Instead, it has been proposed that several quite different executive functions could more adequately be described within a single working memory framework (e.g. Kimberg et al., 1997) or as a product of controlled resources (Engle et al., 1995). Engle et al. (1995) postulate that group differences in inhibition may result from differences in controlled attentional resources, not from inefficient inhibitory mechanisms.

This proposal stems primarily (but not only) from computer simulation studies. For example Cohen and Servan-Schreiber (1992) and Kimberg and Farah (1993), who used similar architectures, modeled performance across several executive function tasks. Executive function tasks with very different surface characteristics could be modeled with a common architecture and disrupted by the same “lesion” to this architecture. Descriptively, one can say

that these “lesions” weakened the working memory representations of the current task context (Cohen & Servan-Schreiber, 1992) or the connection strengths among working memory elements (Kimberg & Farah, 1993), thereby allowing other prepotent but inaccurate response tendencies to prevail. As a result, there was increased perseverative responding across the modeled tasks. However, not all neural network models run without inhibition: for example Houghton and Tipper (1994) have put forward a neural network model where corresponding to each representation there is both an excitatory and an inhibitory node, and when there in competition, the inhibitory nodes of the rejected candidates are activated.

Does this mean that inhibition does not really exist or is a superfluous construct? It appears that the apparent confusion stems from the fact, that the same terms are used at more than one level of description (Rabbitt, 1997) and that processes are not distinguished from behavior (Burgess, 1997). It is tempting to assume that terms like “planning”, “inhibition” and “concept shifting” are not merely descriptions of different task demands, whose effects can be qualified in terms of indices that are measured in laboratory experiments, but are also labels marking qualitative distinctions between the functional processes by which these demands are met. Thus, performance indices empirically measured in laboratory tasks are often treated as being directly equivalent to the hypothetical system performance characteristics. As a results, hypothetical components such as “inhibition”, “preparation” and “planning” may have very poor construct validity, because although these demands appear logically different, they can be met by identical system architectures (Rabbitt, 1997). These terms describe what people do, but they do not enable us to define the process responsible for this behavior. Thus, a distinction between the logical status of “task performance indices” that are obtained from diagnostic tests or laboratory experiments and the “system performance characteristics” has to be made (Rabbit, 1997).

It also has to be noted that neither task performance characteristics nor models of cognitive functions can be equalized with the functional neurophysiology and neuroanatomy of the central nervous system. Those are

further different levels of description. Computational models are neither neural models nor models of neural organization (Kimberg & Farah, 1993). If several quite dissimilar deficits can be modeled in the same model, this does not mean, that the same neuronal structures take part in all those modeled functions, it simply means, that the way the brain handles different functions is similar (or might be able to do it, it is not proved that the brain does handle information the way network models in simulations do). Thus, models like those of Cohen and Servan-Schreiber (1992) and Kimberg and Farah (1993) make it probable that there are distinct areas in the brain (in this case the frontal cortex), which share the same performance characteristics, but differ in the types of elements represented. Different frontal areas may perform the same operation on different inputs. Damage to one would not be expected to impair any particular set of tasks not sharing the same representation. Thus, a large cortical area could operate according to common information processing mechanisms, but there are distinct and dissociable modules according to the content of the information represented (Kimberg & Farah, 1993, Rabbitt, 1997).

In sum, a distinction between a) the logical status of task performance indices, b) the system performance characteristics (functional models of cognitive processes), c) the functional neuroanatomy, and d) the neurophysiology of the central nervous system has to be made (Rabbitt, 1997). The studies in this dissertation will concern the observable phenomenon of response inhibition, as a task performance index – it is not the issue here, to decide whether deficits in response inhibition could be explained in computational modeling by a weakening of structures in working memory without referring to it as “inhibition”. There is no doubt that inhibition on the behavioral or cognitive level is an important observable phenomenon, regardless of the underlying system performance characteristics.

1.4 The concept of inhibition

Clark (1996) defines the term inhibition as

> “...any mechanism that reduces or dampens neuronal, mental or behavioral activity.“

He adds:

> „The danger of defining the concept so loosely may make the concept meaningless. Despite the wide range of phenomena incorporated under the general rubric of inhibition, however, the defining element in any suppression mechanism remains a diminuation of ‘activity’ relative to that which would occur without suppression, and this core element transcends conceptual levels form the molecular to the molar“ (p. 128).

Definition is as great a problem for the inhibition construct as for executive functions. Rabbitt (1997) remarks that the usage of the term “inhibition” as a component of executive behavior has tended to be somewhat promiscuous in the choice of definition of its etiology, i.e. as an observable property of single neurons, as a theoretical construct in connectionist simulations, as a property of particular information-processing modules or as a task performance index. Examples of current conceptualizations of inhibitory mechanisms and phenomena can be seen in Table 1.2

The conceptualization of Clark might be “unifying” and states an important commonality of different forms of inhibition, however, does give little help in distinguishing inhibitory mechanisms or phenomena. Noteworthy is, however, Clark’s acknowledgement, that there are different levels at which inhibitory mechanisms can be observed.

In cognitive psychology there are currently several distinct paradigms available for the investigation of inhibitory phenomena. Several theorists have proposed that inhibition may best be conceptualized as a general process operating in different domains and affecting many aspects of behavior (e.g. Clark, 1996; Dempster, 1992). Other authors propose separate processes that have different operating characteristics and that apply to different circumstances (e.g. Arbuthnott, 1995).

Arbuthnott (1995) distinguishes three kinds of relationships the targets of inhibition (e.g. information or response that is inhibited) can have to the selected targets (e.g. information or response that is activated) in several paradigms used for the investigation of inhibitory mechanisms.

Table 1.2 Examples of conceptions and typologies of inhibition

Author(s) Year	Concept
Arbuthnott, 1995	***Targets of inhibition*** in tasks can be **associative neighbors** (e.g. ambiguous words), **competitors** in the task context (e.g. negative priming, directed forgetting), produced **units themselves** (e.g. negative error priming, stop signal task). Two different ***inhibitory mechanisms*** are proposed: inhibition of either associates of an activated unit (**lateral inhibition**, e.g. suppression of irrelevant meanings of ambiguous words, some negative priming effects) or the activated unit itself (**self-inhibition**, e.g. stop signal task, some negative priming effects). The ***influence of intention*** is either **indirect** (negative priming) or **direct** (directed forgetting, stop signal task).
Clark, 1996	"unified framework for possible roles of inhibitory mechanisms" The central construct of inhibition mediates effects of causal factors that have an influence on behavior outcomes. Causal factors are for example hypoxia, aging, drugs, socialization, genetics. Effects of those factors are mediated by the **central construct of inhibition**. Effects are can be seen in areas where there is evidence of the contribution of inhibitory mechanisms, these range form elementary biological processes (e.g. measures of brain function) to basic psychological processes (e.g. perception and attention) to complex psychological domains (e.g. emotion).
Harnishfeger, 1995	A framework for the definition of ***cognitive inhibition*** 1. Cognitive inhibition has to be **distinguished from behavioral inhibition** (e.g. stop signal task). 2. Cognitive inhibition involves the control of cognitive processes, and can be **intentional** and conscious (e.g. directed forgetting, thought suppression paradigms) or **unintentional** and unavailable for conscious introspection (e.g. negative priming, stroop). 3. Cognitive inhibition has to be **distinguished from interference**. Inhibition refers to an active suppression process, interference involves a competition between multiple stimuli, processes or responses and does not necessarily involve active suppression (e.g. interference vs. negative priming condition in the stroop task).
Logan, 1994	**Reactive inhibition:** Executing a process has a side effect or leaves a residual effect that subsequent processes must overcome. The inhibitory effect on concurrent and subsequent processes is usually not intended (e.g. inhibition of return, negative priming). **Active inhibition:** inhibition as an deliberate, conscious action (e.g. stop signal inhibition).

First, the targets of inhibition can be associative neighbors, second, they can be competitors in the task context but instructionally excluded and third, they can be the produced units themselves. As underlying mechanisms for different inhibitory phenomena she proposes two distinct processes, lateral and self-inhibition. Lateral inhibition operates via preexisting inhibitory connections between nodes sharing an associative network and is probably the mechanism responsible in cases when the targets of inhibition are associative neighbors. Self-inhibition refers to the inhibition of a node immediately following its activation, and is the primary candidate mechanism, when the target of inhibition is the just produced unit (e.g. inhibition of just produced motor or speech behavior). In case the targets of suppression are competitors in the task context, but associatively unrelated distractors, Arbuthnott (1995) also assumes self-inhibition to be the underlying mechanism. In this case distractor representations are assumed to receive additional stimulation to the off-unit from a higher level match-detector process (as a results of the detection of a mismatch between distractor and the task defined target representation, e.g. negative priming with unrelated distractors). Arbuthnott (1995) furthermore points to the influence of intention on observable inhibitory phenomena. She notes that in most paradigms there is some connection between specific goals and the inhibitory effects. This influence can be either indirect (e.g. negative priming tasks) or direct (e.g. directed forgetting, stop signal task). This explicitly points to the executive component in those phenomena. She also discusses the possibility that intentional inhibition (stop signal task, directed forgetting) relies on a distinct intentional inhibitory mechanism, but she concludes that those could be modeled with a self-inhibition mechanism. In sum, Arbuthnott (1995) derives her distinction between lateral and self-inhibition from connectionist modeling and attempts to relate tasks which measure observable phenomena of inhibition to those two forms of inhibition. This attempt is quite appealing, however, it is unfortunate, that Arbuthnott (1995) does not provide any simulations of the tasks she proposes to be related to self-inhibition and lateral inhibition. As already mentioned in the previous section, it also possible

to model those phenomena in different ways (Cohen & Servan-Schreiber,1992; Kimberg & Farah, 1993).

Harnishfeger (1995) and Logan (1994) are only concerned with distinctions of observable inhibitory phenomena in different tasks, without direct reference to the system performance characteristics that might apply to them. There is a lot of evidence, that it is useful to distinguish different inhibitory phenomena according to task characteristics. Observed inhibitory phenomena dissociate in the developmental timecourse (Harnishfeger, 1995; May et al., 1995) and different regions of the brain seem to be involved in different task demands of inhibition (Connelly & Hasher, 1993; Stuss et al., 1999). Evidence for a dissociation of inhibitory phenomena comes for example from studies with brain-damaged patients. Stuss et al. (1999) investigated patients with focal lesions at different areas of the brain in an location-based ("select-what, respond-where") priming task. They found that three measures of selective attention (interference, negative priming, inhibition of return) were mediated by different brain regions.

Harnishfeger (1995) attempts to define cognitive inhibition, in doing so she suggests some broad lines of demarcation. First, she distinguishes cognitive inhibition from behavioral inhibition. Behavioral inhibition involves the control of overt behavior, such as resisting temptation, delay of gratification and motor inhibition. Cognitive inhibition involves the control of cognitive contents or processes. She also states, that although it is useful to distinguish between cognitive and behavioral inhibition, those two constructs are clearly related, e.g. cognitive inhibition can serve to facilitate behavioral inhibition (e.g. delay of gratification). This distinction of behavioral and cognitive inhibition is appealing, however, in most tasks she mentions as a measure of cognitive inhibition (e.g. negative priming), inhibition is measured by the difference of reaction times - this distinction has therefore to be treated with some caution. A second distinction Harnishfeger (1995) makes is between automatic and intentional cognitive inhibition. Automatic cognitive inhibition is important in attentional processing to gate which information will enter consciousness. Intentional cognitive inhibition is a process deliberately invoked to deal with irrelevant

stimuli, from either internal or external sources. Third, Harnishfeger (1995) distinguishes between interference and cognitive inhibition. Those two terms have often been used interchangeably in the literature, however, the constructs are not the same. Inhibition refers to an active suppression process, such as the removal of task-irrelevant information form working memory, interference refers to susceptibility to performance decrements under conditions of multiple distracting stimuli. Interference does not necessarily involve the active suppression of cognitive processes or contents. This is an important distinction, nevertheless inhibition and interference bear a certain relationship to each other, the exact nature is however still unknown (May et al., 1995).

Logan (1994) distinguishes between active and reactive inhibition. The idea behind reactive inhibition is that executing a process has a side effect that concurrent processes must overcome or leaves a residual effect that subsequent processes must overcome. The process that produces the inhibition may be engaged deliberately, but its inhibitory effect on concurrent and subsequent processes is usually not intended. Active inhibition requires a deliberate action.

The different conceptions can be related to each other, but it also becomes apparent that the authors have a different view on inhibitory phenomena. This is for example reflected in the way the role of intention is perceived. Whereas for example negative priming is viewed in the conceptions of Logan (1994) and Harnishfeger (1995) as unintended, Arbuthnott (1995) explicitly point to a role of intention, albeit indirect.

The conceptualizations given here to distinguish inhibitory phenomena are still very rough taxonomies, and should not imply that all the different inhibitory effects listed under one category are to be treated as equal. However, a rough taxonomy of inhibitory phenomena suffices for the present dissertation. Especially Logan's (1994) conception seems to be useful in this context. This dissertation is concerned with the inhibition of ongoing responses, which is conceptualized a deliberate top-down process, i.e. active inhibition. However, this dissertation is also concerned with reactive inhibition. In study 3 inhibitory

aftereffects of the inhibition of ongoing responses will be investigated, which can be conceptualized as reactive, i.e. not intended side effects.

1.5 Inhibition of ongoing responses

Complete suppression of an action is one of the most extreme forms of control, it is however required in many real life situations, where unanticipated changes in goals or in the environment suddenly make ongoing actions inappropriate. It is thus a general requirement in all kinds of cognitive control and a clear case of executive intervention (Logan, 1994). Imagine standing with your car in front of traffic lights. The light turns green and you start pressing the gas pedal. Suddenly an ambulance crosses the junction. You have to stop pressing the gas pedal immediately. Of course, in everyday actions complete inhibition of ongoing actions is only the first step towards more adaptive behavior. In the driving example, the next thing would be to change to pressing the break.

In laboratory settings, inhibition of reactions can be investigated through a comparison between conditions with and without response execution. Paradigms which are used for this aim are the stop signal task (e.g. Lappin & Eriksen, 1966; Logan, 1994; Logan & Cowan, 1984) and the go nogo task (e. g. Drewe, 1975a, b; Falkenstein et al., 1999; Konishi et al., 1998). In the go nogo task participants usually have to respond to one type of stimuli and to withhold the response to another. For example, the instruction can be to respond to a green symbol, but to withhold the response to a red one. In the stop signal paradigm the participant performs a reaction time (RT) task (usually to visual stimuli). This is occasionally interrupted by a stop signal (usually a tone) with a variable stimulus onset asynchrony (SOA) relative to the response signal (Logan, 1994). The instruction is to respond as fast as possible on all trials, but to try to stop the response if the stop signal occurs. The stop signal paradigm is regarded as an elaboration of the go nogo task, with an delay or SOA of zero in the go nogo task (Band & Boxtel, 1999).

Nevertheless, in spite of some close resemblance of these tasks, there are important differences between the stop signal task and the go nogo task. In the stop signal task, the information to inhibit the response is delivered by a second

stimulus after the usual primary task stimulus has appeared. In the go nogo task, there is no second stimulus necessary, the information, whether a response should be withheld or not is usually directly conveyed with the primary task stimulus. This is reflected in an important difference in the timing of the inhibitory process in the two tasks. In the go nogo task, it is a prepotent response which has to be inhibited, in the stop signal task, it is an ongoing response. Although ongoing responses are the continuation of prepotent responses and at early delays in the stop signal task responses might still be prepotent, the point is that in the stop signal task inhibition is usually required at a later stage of response execution. Since the stop signal task will be used in this dissertation we will refer to the construct under investigation as “inhibition of ongoing responses” rather than solely “response inhibition”.

Inhibition of a motor response is not directly observable, at least when people are successful in inhibiting. The advantage of the stop signal task is, that the time it takes to stop a reaction, i.e. the stop signal reaction times (SSRT), can be calculated. This is done by the horse race model, which basically asserts that the response production and the inhibitory process compete for the first finishing time (Logan & Cowan, 1984, the model will be presented in detail in the methods section).

Allocating inhibition of ongoing responses in the above presented concepts of inhibition, it has to be said that Arbuthnott (1995) would say the target of inhibition is the produced unit itself, that the inhibitory mechanism would be self-inhibition and that there is a direct influence of intention. Harnishfeger (1995) would describe inhibition in the stop signal task as “behavioral Inhibition” and Logan (1994) would describe it as active inhibition. We add some further remarks about inhibition in the stop signal task in contrast to so called “reactive inhibition tasks”. In reactive inhibition tasks the inhibitory processes are caused by stimuli, which have no relevance for action at the time of appearance. In contrast, all stimuli are relevant for action in the stop signal task at the time of appearance. In reactive inhibition tasks, like negative priming, there is usually a speed accuracy tradeoff, RTs and errors give information about performance. This is not the case in the stop signal task, inhibition is measured as a single

parameter, the stop signal reaction time. There is no other task which allows the measurement of the time it takes to inhibit an ongoing response.

It is also important to note, at what level the inhibition of ongoing responses in the stop signal task is usually described. The inhibitory phenomenon is explicitly allocated in the domain of observable inhibitory phenomena (Band, 1997; Logan, 1994). As Band (1997) puts it:

> "Although stop-signal inhibition as a whole works against the activation of a response, the name inhibition does not imply that a neurological model of response inhibition would consist primarily of inhibitory connections" (p. 108).

1.6 Aftereffects of inhibition

One apparent difference between several different inhibition tasks is, that in some of them inhibition is measured directly in the trial where inhibition does take place (e.g. go nogo task, stop signal task) in others inhibition is measured at a later point during the task performance, e.g. slower responding in the next trial (negative priming) or worse memory for inhibited items (directed forgetting). In the latter kind of tasks, the measures can be regarded as aftereffects of inhibition (Logan, 1994; Tipper, 1985) - inhibition in those tasks is measured as the residual effect which subsequent processes have to overcome or which impair subsequent performance.

A paradigmatic example for the measurement of inhibitory aftereffects is the negative priming (NP) task. In a typical NP task, the prime trial consists of a target stimulus, which is accompanied by interfering stimuli. If this condition is compared with conditions without distractors or equal stimuli, an interference effect becomes apparent (i.e. longer reaction times in the distraction condition). In the probe trial of a typical NP task, a previously ignored stimulus becomes the target, which results in longer reaction times compared to conditions where a new stimulus is the target. This is the negative priming effect, and it is due to the fact that the residual inhibition of the distractor must be overcome before the now relevant response can be produced. Initially, both interference and negative priming where assumed to index inhibitory distractor processing (May

et al., 1995). Interference does, however, not necessarily involve the active suppression of cognitive processes or contents (Harnishfeger, 1995, May et al., 1995). Nevertheless it is assumed that interference leads to inhibition of the distractor (otherwise no negative priming effect would be observable), although the exact point at which inhibition develops is not clear. Inhibition can develop either during selection (Neill, 1977; Neill & Westberry, 1987) or alternatively after selection, (Tipper et al., 1991; May et al., 1995), the latter alternative is more probable (May et al., 1995).

The important point here is, that inhibition in those tasks seems to have some persistence, carrying over into further trials. Inhibition may thus serve to block rejected information from immediate reactivation and function to facilitate on-line processing of target information by maintaining the distinction between distracting and goal-relevant information (May et al., 1995). Aftereffects of inhibition can thus be thought to be a general performance principle of human information processing. It seems reasonable to assume that the use of inhibitory processes leaves measurable aftereffects in other tasks apart from negative priming, where trial-to trial effects are not usually the focus of research. The procedure to calculate negative priming effects has already been applied with positive results to some tasks which were not originally designed to measure them, for example the stroop task (e.g. Neill, 1978; Lowe, 1979; see MacLeod, 1991 for a review) and the flanker task (e.g. Neill & Valdes, 1995). It seemed therefore reasonable to assume that inhibitory aftereffects might also be present after inhibition of ongoing responses in the stop signal task. This issue will be investigated in study 3 of this dissertation.

1.7 General aims of this dissertation

This dissertation is about the investigation of the inhibition of ongoing responses. One aim is to investigate the neuroanatomical correlates of this function with the anatomo-clinical-correlation method (see general methods section). The frontal lobe is a primary candidate structure for this function. Furthermore, to take into consideration that the frontal lobes do not work in isolation from other brain structures, but have extensive connections to other

parts of the brain, the possible role of other brain regions is considered and it is assumed that the basal ganglia may also play a role in the inhibition of ongoing responses (for a detailed theoretical consideration of those claims see introduction section of study 1). Therefore it will be investigated in the first study, whether patients with focal lesions to either the frontal lobes or the basal ganglia show a deficit in this function. In the second study, the inhibition of ongoing responses will be investigated in patients with traumatic brain injury, an etiology of brain-damage where frontal lesions are highly prevalent. Therefore, it might be assumed that brain-damaged patients with this etiology might also show deficits in the inhibition of ongoing responses.

The second aim of this dissertation is to analyze, whether the active inhibition of ongoing responses leaves measurable inhibitory aftereffects, i.e. the question is whether active inhibition can lead to an additional effect of reactive inhibition (see study 3 for a theoretical consideration of this hypothesis). Therefore, in the third study the question whether having to stop in one trial leaves any measurable aftereffects in the next trial will be investigated. This will be analyzed in a group of students, who performed the stop signal task. Furthermore, an exploratory analysis of the data of the patient studies regarding inhibitory aftereffects will be conducted.

2. General methods

2.1 The anatomo-clinical correlation method

According to Vallar (1999) neuropsychology has developed a main heuristic, which takes advantage of brain-damaged patients in whom mental processes are defective, treating them as experiments of nature. Two related heuristic scopes may be distinguished: First, the investigation of the neural bases of mental function, through the anatomo-clinical correlation method (neurological architecture of mental processes), and second, the investigation of mental function per se (functional architecture of mental processes). The functional architecture of mental processes may be investigated, both in healthy participants and in brain-damaged patients, without any direct reference to the structures that constitute its neural basis, investigation of the anatomical correlates of mental processes is not necessary to a research approach, which aims at expanding our knowledge as to "how the mind works". On the other hand, it is unlikely that the investigation of the neural basis of mental processes provides data relevant to our understanding of their functional architecture. A cognitive neuroscience approach, which integrates neural and behavioral data sets is therefore warranted. This dissertation is mainly concerned with the investigation of the neuroanatomical basis of the inhibition of ongoing responses. However, the issue of "how the mind works" is tapped in study 3, where aftereffects of response inhibition will be studied in healthy participants.

The chosen neuropsychological approach to the topic of response inhibition is to be viewed as an addition to approaches where healthy participants are subjected to brain imaging techniques or neurophysiological studies. In imaging studies, information about specific brain structures or events ($\hat{O}$) are regarded as a function of cognitive processes ($\emptyset$), they give information about the brain structures given the cognitive function ($P(\hat{O}/\emptyset)$. The approach of this dissertation is to obtain information about cognitive processes in dependence on a damaged brain structure ($P(\emptyset/\hat{O})$ (Sarter et al., 1996).

This neuropsychological approach to brain-behavior relationships is a necessary addition to functional imaging techniques, because those yield some

problems for interpretation Vallar (1999). One is “the ambiguity of null results”, i.e. comparatively low neuronal activity might account for negative results. Another problem of activation studies is that not only the critical or necessary areas may be activated, but also additional or incidental areas (Vallar, 1999). The anatomo-clinical-correlation method does not suffer from those problems, e.g. if the lesion of a specific cerebral region does not disrupt a given mental process, it is unlikely that the damaged area plays a substantial role. Studies on brain-damaged patients suffer, however, from other problems (e.g. the localization of naturally occurring lesions is determined by factors such as the organization of the vascular system, which may not be related to the functional architecture of interest, the effects of lesions are not selective, and the design is quasiexperimental, Vallar, 1999). Thus, approaches investigating (P(Ô/∅) and approaches investigating (P(∅/Ô) yield complementary, rather than redundant information about the relationship between brain structures (or events) and cognitive functions.

2.2 Selection of patients according to lesion criteria (study 1 and 2)

Causes of brain damage

Damage to the brain can occur for a variety of reasons, e.g. cerebrovascular disorders, intracranial tumors, traumatic brain injury, epilepsy and degenerative disorders. In this dissertation only patients with cerebrovascular disorders, intracranial tumors and traumatic brain injury will be investigated. Therefore we will refer only to those etiologies.

Cerebrovascular disorders

Cerebrovascular disorder are due to any disruption of brain function arising from some pathological condition related to the blood vessels. Vascular pathology may take many forms, however, the majority of cases are due to cerebral ischemia or hemorrhage. Symptoms depend mainly on lesion location (Walsh, 1987). For an example of a cerebrovascular lesion see figure 2.1.

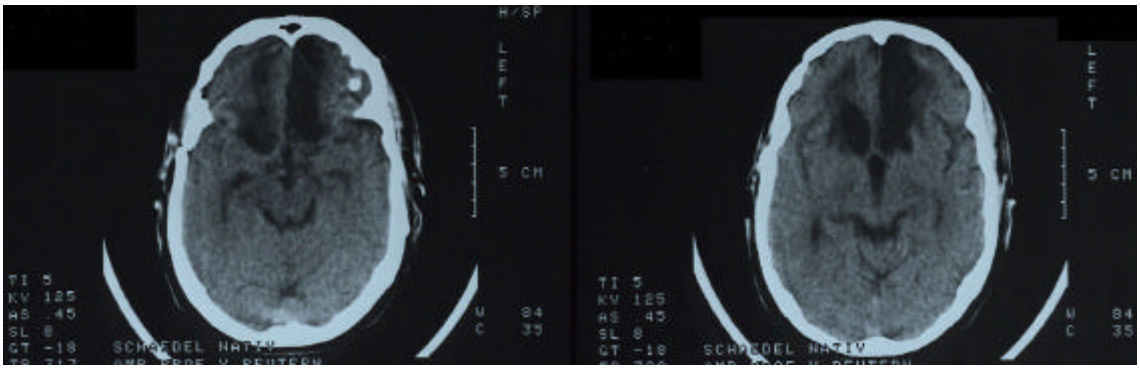

Figure 2.1. Example of a CCT scan of a cerebrovascular disorder. The scan is of a 63 year old man who had a subarachnoid hemorrhage due to an aneurysm of the arteria communicans anterior (this patient participated in study 1).

Intracranial tumors

The word tumor literally means a swelling. It usually means a neoplasm or new growth. Tumors can be distinguished according to their nature, e.g. neoplasms in the brain may be benign or malignant (the latter invade the tissue of the brain) and according to their growth rate, e.g. fast or slow growing. Tumors can produce a multitude of symptoms which depend on their location, but also on their nature and growth rate (Walsh, 1987). For an example of a tumor lesion see figure 2.1.

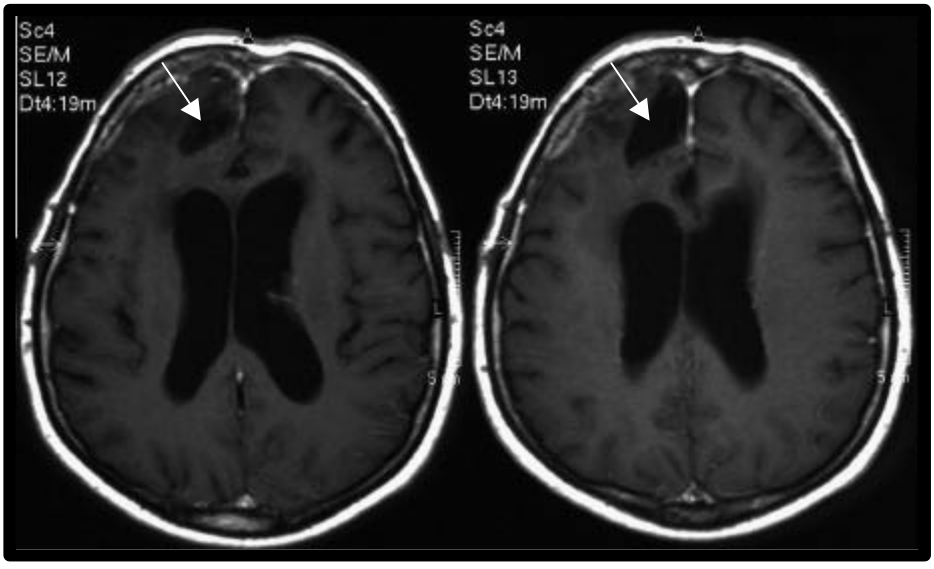

Figure 2.2. Example of a MRT scan of a tumor lesion. The scan is of a 61 year old woman who had a 7 x 6.5 x 7 cm frontal meningioma surgically removed (this patient participated in study 1).

Traumatic brain injury

Traumatic brain injury (TBI) can occur through high velocity projectiles such as bullets and shrapnel fragments and through craniocerebral injury from the rapid acceleration and deceleration of the head, for example in motor vehicle accidents. Even when the skull is not fractured, the brain may sustain a wide variety of pathological lesions. These include generalized lesions scattered throughout the brain with or without localized damage such as contusion, laceration or hemorrhage. With this complexity of pathology, clinico-anatomical correlation might seem to be an unproductive exercise. However, focal frontal lesions have a high prevalence in patients with TBI (see Mattson & Levin, 1990; Stuss & Cow, 1992 for reviews). Particularly acceleration-deceleration forces can cause the brain to be forced against bony surfaces, causing coup and contrecoup injury. The contusion, or bruising of the brain, is most likely to occur in the frontal and temporal regions, particularly in the orbital frontal and anterior temporal areas (see also Levin & Kraus, 1994). See Figure 2.3 for mechanisms of brain damage in traumatic brain injury and Figure 2.4 for the sites of cerebral contusion.

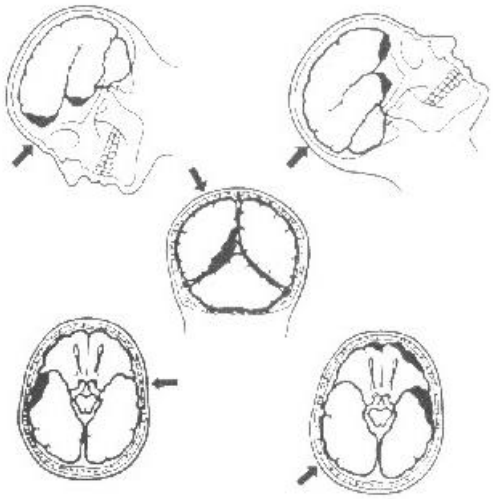

Figure 2.3. Mechanisms of cerebral contusions (adapted from Courville, 1945).

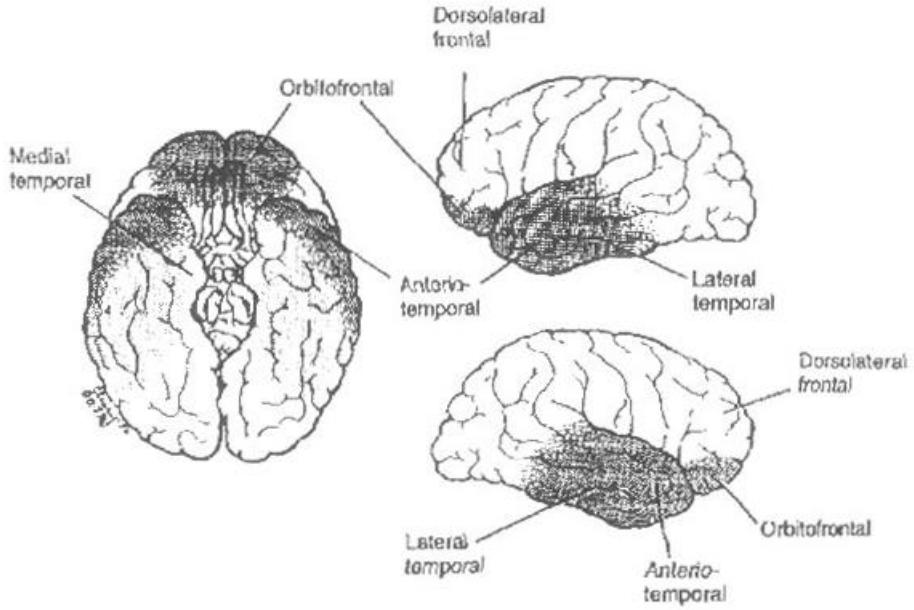

Figure 2.4. Areas predominantly affected by cerebral contusions (adapted from Courville, 1945).

The correlation between frontal dysfunction and frontal pathology in TBI may not always only be due to localized frontal damage. The primary mechanism of TBI is mechanical stretching and shearing of nerve fibers, which results in widespread diffuse damage. Diffuse axonal injury is one of the major forms of diffuse brain injury following TBI, it results in a loss of central white matter. The diffuse white matter insult may disrupt frontal connections with other cortical regions and subcortical structures. Thus, the most common neuropathological effects of significant TBI, as detected by CT and / or MRI scanning, is generalized cortical atrophy and ventricular enlargement. These neuropathological changes indicate the non-specific effects of brain injury (see Bigler, 1987). Executive deficits in TBI may therefore reflect damage to the frontal lobes and / or to pathways connecting frontal regions with other cortical and subcortical areas (Mattson & Levin, 1990; Stuss & Cow, 1992).

Selection of participants

For study 1 patients were selected according the localization of lesion. Two different etiologies of brain damage were in this group: cerebrovascular disorders and tumor resections, because both of these etiologies lead to more focal lesions. Lesions were located according to the available computer tomography (CT) or nuclear magnetic resonance tomography (MRT) scans according to Damasio and Damasio (1989) by a senior neuropsychologist. Inclusion criteria were either circumscribed cortical lesions (either inside the frontal lobes or outside) or lesions to the basal ganglia. For study 2 patients were selected according to etiology of lesion, i.e. traumatic brain injury, because of the high prevalence of frontal lesions in this etiological group.

Patients for study 1 and 2 were tested during their stay in four different rehabilitation center (Bad Berleburg, Bad Wildungen, Braunfels and Bad Salzhausen) as part of a research project which was funded by the German Research Foundation (DFG RO 529 / 12-1). Orthopedic control patients were recruited from the same rehabilitation centers as the brain-damaged patients. Patients had to be between eighteen and seventy years of age. Per institutional guidelines, all of the patients gave written informed consent. None of the patients were paid for participating in the study.

Exclusion criteria for study 1 and 2

- medical conditions not related to the brain damage which have an influence on the central nervous system
- aphasia with comprehension difficulties
- visual disorders
- neglect
- degenerative disorders
- German not as a first language
- auditory disorders
- more than one incidence of brain damage (e.g. multiple strokes)

Details of patient characteristics will be described in the methods section of the respective studies. Selection of participants for study 3 will also be described in the respective methods section.

2.3 General procedure

For study 1 and 2, suitable patients were personally informed about the study by the examiner, and asked whether they would be willing to take part. Patients were asked about demographic data at the initial interview. After that an appointment was made for the first testing session. Usually two testing sessions, each taking about one hour were necessary to do all the tasks, sometimes three sessions of shorter duration had to be conducted. In the first session the background neuropsychological assessment was started. In the second session the stop signal task was conducted and usually at least one more of the background neuropsychological tests was done.

In study 3, students who received course credit participated. Only sex and age were surveyed of the demographic variables and no background neuropsychological assessment was conducted. They were tested in one session, which lasted approximately 45 minutes.

Demographic and clinical data

The following demographic and clinical data were obtained for patient description:

- Sex
- Age
- Years of education
- Handedness premorbid
- Handedness at testing date
- Etiology of lesion (Hemorrhage / Stroke / Tumor / TBI)
- Weeks since onset of lesion
- Unconsciousness (TBI patients only, study 2)
- Edinburgh Inventory (hand preference, Oldfield, 1971)

- Functional Independence Measure (FIM, disability, Keith et al., 1987; German version: de Langen et al., 1995; Frommelt & de Langen, 1995)

Background neuropsychological assessment

The following cognitive functions were assessed for background neuropsychological data in the studies with brain damaged patients. Details will be described in the next section.

- Intellectual functioning (short form of the LPS: subtests 1+2, 4, 5, 9, 10, 12; Sturm & Wilmes, 1983)
- Verbal memory span (digit span subtest of the Wechsler Memory Scale – Revised, Wechsler, 1987)
- Verbal Memory (Auditory Verbal Learning Test, Heubrock, 1992)
- Concept formation and concept shifting (Modified Card Sorting Test, MCST, Nelson, 1976)

The inhibition of ongoing responses

To investigate the inhibition of ongoing responses, the stop signal task was conducted. The task in general, the underlying horse race model, issues concerning the design, apparatus, stimuli, and procedure will be presented below.

2.4 Background neuropsychological assessment

An analysis of intellectual functioning, memory and executive function was carried out in the patient studies. It was not possible to perform each of the neuropsychological tests with all participants. This was due to the tight time schedule in rehabilitation hospitals and due to patients leaving the hospital before assessment could be finished.

Intellectual functioning

The short form of the Leistungsprüfsystem (LPS, Sturm & Wilmes, 1983) was used. The LPS (Horn, 1962, 1983) was designed to measure intellectual functioning. For investigation of people over 50 years and older, the LPS 50+

(Sturm, et al. 1993) was developed, which is not changed in content but provides enlarged task sheets and norms for the ages from 50 to 90. The short version of the LPS which was used in this study appeared to be sensitive to brain damage (Sturm & Wilmes, 1983) and consists of the following subtests: 1+2 (verbal comprehension), 4 (reasoning), 5 (word fluency/mixed letters), 9 (space), 10 (field dependence) and 12 (closure). Raw scores were corrected for age and transformed into T-Values. One summary score (T-value) was calculated from all subtests.

Verbal memory span

The digit span subtest of the Wechsler Memory Scale – Revised (Wechsler, 1987) was used. It consists of two parts, digits forward and digits backward. Both parts consist of seven pairs of random digit chains. Within the pairs, the chains are of same length. The administrator reads the digits at a rate of one second for each digit. In the digit forward condition, the participant is supposed to repeat the digits in the same order as the administrator read them, in the digits backward condition, the participant has to reverse the order. Within a pair of digit chains, both chains are given to the participant, irrespective of whether the participant was correct in the first chain. The task is finished, when the participant is not able to reproduce any of the two chains of a pair correctly. Digits forward starts with chains of three digits, and goes up to nine in the last trial, digits backward starts with two digits and goes up to eight. For each correct digit chain the participant scores a point. A summary score of digits forward and backward was calculated.

Verbal memory

A German version (Heubrock, 1992) of the Auditory Verbal Learning Test (Lezak, 1995; Rey, 1964) was used. It serves the assessment of verbal memory under learning conditions. The task consists of two word lists, containing 15 words each. The administrator reads the words of the first list (A) in a one second rhythm. The participant has to remember as many words as possible and repeat them in random order after the list has been read. This is

repeated four more times with the same list. After that, the administrator reads once 15 words from another list (B) and the participant has to remember and repeat those. In the last part of the task, the participant is asked to recall as many words as possible from the first, several times repeated list, without hearing it again. The summary score (total score) of the five learning trials with list A was calculated for the studies here.

Concept formation and concept shifting

A computer version (Truong, 1993) of the Modified Card Sorting Test (MCST, Nelson, 1976) was used. The MCST is a modified version of the Wisconsin Card Sorting Test (Milner, 1964). At the beginning of the MCST four cards are presented on the computer screen: a red square, two green stars, three yellow crosses and four blue circles. The task is to allocate 48 stimulus cards to those target cards, according to certain rules. The participant is not told which of the three categories (color, form, number) is required, only feedback is given, whether allocation was right or wrong. In the beginning, the first category the participant chooses is reinforced. When six cards in a row are allocated correctly, he is told, that the rule for allocation has been changed. After that the second category the participant chooses is reinforced. When all three categories are done, the first chosen category is reinforced again. The task is finished, when all categories have been chosen and completed twice, or when all 48 cards are used up. The percentage of perseverative errors of all errors was used as an index in this study, since it has been frequently associated with being sensitive to executive deficits and frontal lobe lesions (Nelson, 1976 but see de Zubicaray & Ashton, 1996; Mountain & Snow, 1993, for reviews). This index is also frequently interpreted in terms of a failure of inhibition (e.g. Nelson, 1976, Milner, 1964).

2.5 Response inhibition: the stop signal task

The stop signal task

The stop signal task involves two concurrent tasks: a go task and a stop task. The go task or primary task is usually a two choice reaction time (CRT) task. The stop task usually involves the presentation of a tone (the stop signal) which signals participants to inhibit their response on that trial. The stop signal is presented at different delays between the onset of the primary task stimulus and the reaction of the participant (SOA, see below). The instruction is to respond as fast as possible on all trials, but to try to stop the response if the stop signal occurs (Logan, 1994).

The horse race model

Logan and Cowan (1984) proposed an explicit model of top-down control of response inhibition in the stop signal task. The horse race model accounts for inhibition of reactions in terms of a 'horse race' between two independent processes. One generates a response to the primary task, the other responds to the stop signal. If the primary task process finishes before the stop signal process, the response is executed. If the stop process finishes before the primary task process, the response is inhibited. Although there has been some controversy about the locus of the finish line of this race (De Jong et al., 1990; Osman et al., 1986; 1990), the general idea is that the process that finishes first determines whether a response is withheld or not. The model allows to calculate the time necessary to stop a reaction (stop signal reaction time, SSRT), which is not otherwise directly measurable. For a detailed mathematical description of the stop signal task see Logan and Cowan (1984). An illustration of the horse race model can be seen in Figure 2.5.

A necessary assumption of the horse race model is, that the stop and the go process are independent of each other. This assumption usually seems to be fulfilled (Band, 1997; Logan, 1994). Empirical data can be described quite well by the horse-race model, and the tests of the model support its validity (e.g.

Band, 1997; De Jong, et al. 1990; Logan & Cowan, 1984; Osman, Kornblum & Meyer, 1986).

The ability to inhibit actions does not seem to vary much between participants, tasks, strategies, or conditions (Logan, 1981, 1982, 1983; Logan et al., 1984). The stop signal reaction time in most situations is about 200 ms up to 250 ms.

Choice of parameters of the stop signal task

Percentage of stop signal trials

There is a tendency to delay responses as the percentage of trials with stop-signals increases (Logan, 1981; Logan & Burkell, 1986). In order not to affect the speed of the primary task, a rate of approximately 25% stop signals is recommended (Band, 1997; Logan, 1994; Logan & Burkell, 1986)

Which range of the inhibition function should be covered?

As a result of changing the delay of the stop signal, the finishing time of the inhibitory process in the race against the go-process can be moved to the latencies that are most interesting for the assessment of the inhibitory function. It is not very informative to extend measurements for the inhibition function outside the response rate range of 0.15 - 0.85 (Band 1997). If one is only interested in the stop signal reaction time and not in the inhibition function or variability of the stop signal reaction time, selection of a SOA that approximates a response rate of 0.5 is sufficient (Band, 1997).

Setting the stop signal delay(s)

There are currently several procedures to set the stop signal delay(s). First, in early studies of stopping, the SOAs were often selected as constants (e.g. Lappin & Eriksen, 1966; Logan & Burkell, 1986), ranging from 0 ms to the RT. Second, it is possible to employ adaptive procedures for the determination of SOA.

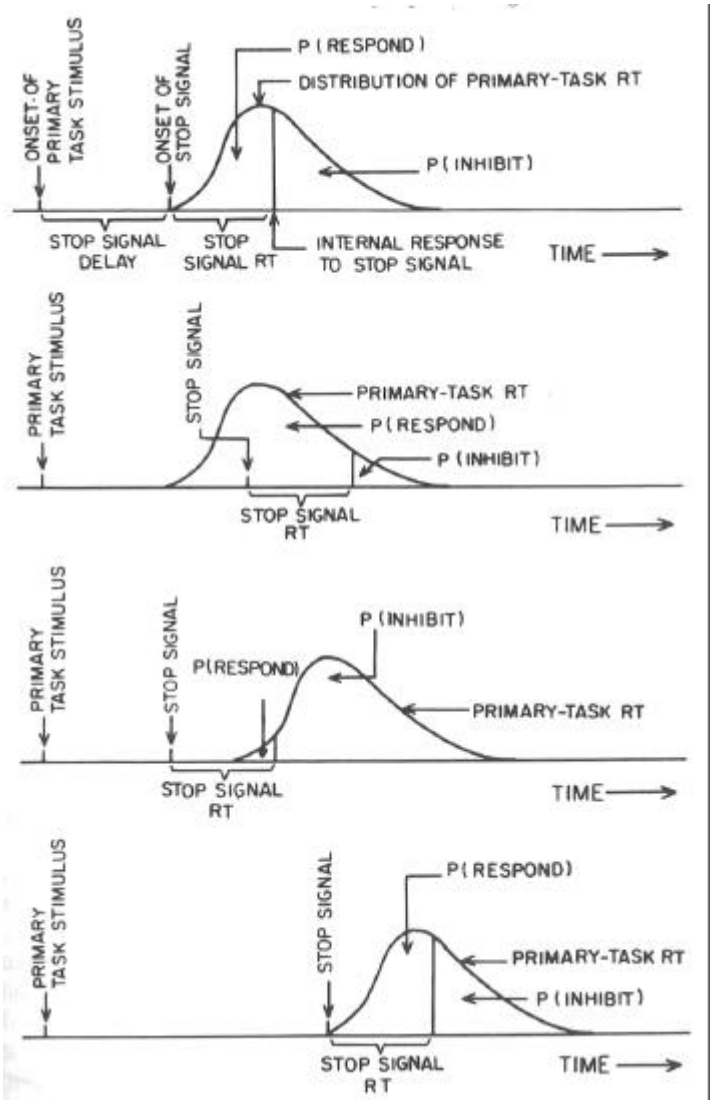

Figure 2.5. The horse race model. For simplification, the SSRT is depicted as constant. The figure illustrates how variations of the stop signal delay, primary task reaction time and stop signal reaction time affect the probability of inhibition and probability of responding. For example, if the end of the stop process (delay + SSRT) is later and the RT distribution remains the same, a larger proportion of the go-distribution falls to the left of the finishing time, and therefore more trials escape the inhibitory control. If the RT is increased, however, the same finish line is projected onto an earlier point of the RT distribution. Because then there are less responses to the left of that line, there is a higher chance of inhibition. If the variability of go-RT is high, the effect of moving the finish line is smaller than if the variability is low, because the same shift of the finish line passes a smaller part of the RT distribution. (adapted from Logan & Cowan, 1984).

In one such a procedure, SOAs are adjusted to momentaneous changes in RT, e.g. in determining the mean go-speed after each block and subsequently presenting stop-signals on SOAs of RT - 400 ms, RT - 300 ms, etc. (e.g. Logan et al., 1984; Schachar & Logan, 1990). There are several variations of this procedure to compensate for individual differences or changes in RT. The timing of the SOA can be adjusted from trial to trial or after each block. Furthermore, SOAs can be based on mean RT alone (Schachar & Logan, 1990), or on its distribution (Kramer et al., 1994; Logan et al., 1984). Third, another algorithm to set the delay is the staircase tracking algorithm (Kaernbach, 1991; Logan, Schachar & Tannock, 1997; for a mathematical description see Levitt, 1970). With the staircase tracking algorithm delays are adjusted that they yield a certain response rate (e.g. 29%, 50% and 71% probability of responding, Osman et al., 1986). Advantages and disadvantages of the different procedures to set the stop signal delay can be seen in Table 2.1.

Band (1997) tested in several simulations the advantages and disadvantage of the different procedures to set delays under different conditions. Furthermore he tested the reliability of SSRT and variability of inhibitory control. The simulations showed that it is possible to estimate the speed of stopping reliably within a test session of reasonable duration. The speed of stopping was most reliably estimated at a point in the inhibition function where the chance of inhibition was approximately 50%. He found the stop speed at this point to be robust against a variety of influences, such as the speed distribution of the stop- and response process, and SOA-dependence or primary task dependence of the stop speed. However, the simulations showed that there are presently no reliable methods to estimate the variability inhibitory control. Efficient measurements of the stop speed were possible with the staircase-tracking algorithm employing 400 trials, i.e. 100 stop-trials and 300 no-signal trials, if the staircase tracking algorithm was set to a response rate of 0.5.

Table 2.1 Advantages and disadvantages of different procedures to set stop signal delays

Advantages	Disadvantages
Fixed delays	
♦ easily to implement on computers ♦ inhibition function can be investigated	♦ Strategic effects are not compensated for ♦ frequently too narrow, too wide, too low or too high section of the inhibition function is measured ♦ cannot compensate for changes in RT ♦ response rates are not constant across groups
Adjustment to changes in RT	
♦ individual differences in RT is compensated for ♦ strategic hesitation is compensated for ♦ inhibition function can be investigated	♦ differences in variability of RT are not compensated for ♦ response rates are not constant across groups ♦ too narrow, too wide, too low or too high section of the inhibition function may be measured
Adjustment to RT and variability of RT	
♦ differences in RT and variability of RT are compensated for ♦ tendency to postpone responses is compensated for ♦ inhibition function can be investigated	♦ response rates are not constant across groups ♦ too narrow, too wide, too low or too high section of the inhibition function may be measured
Staircase tracking procedure	
♦ corrects for differences in RT distribution ♦ corrects for tendency to postpone responses ♦ response rates remain almost constant across groups, despite differences in inhibitory efficiency ♦ more data are acquired per condition (economy of design) ♦ 50% inhibition: yields the most reliable measure of SSRT ♦ 50% inhibition: a violation of the independence assumption does not affect the estimation of the stop speed	♦ inhibition function cannot be investigated

Note. Arguments for and against the different procedures are derived from Band (1997)

The only factor this procedure could not entirely compensate for, was a decreased rate of triggering the inhibition mechanism. Band (1997) concludes:

> "Given the difficulties of interpreting the slope of the inhibition function, this fast procedure for estimating the speed of stopping may be the optimal procedure for many purposes" (p. 145).

Apparatus and stimuli (all studies)

The stimuli for the choice RT task were a black square (2.5 cm side length) and a black circle (2.8 cm diameter). Participants were seated approximately 50 cm in front of a computer screen (VGA, 15''). The stop signal was a 1000 Hz tone of 500 ms duration, presented through the internal speaker to headphones. Participants responded by pressing one of two reaction buttons with the middle finger and forefinger of their preferred hand (four of the nonfrontal patients and three of the basal ganglia patients in study 1 had to use the nondominant hand because of paresis).

Design and procedure in study 1 and 2

The choice task involved discriminating the black square and the black circle, which were randomly assigned to the left and right response buttons. Each trial began with the presentation of four small squares (0.5 cm side length) which moved from the corners of the screen to the center in a fixed interval of 500 ms. This was done to capture and focus attention of the participants. Immediately thereafter one of the symbols for the choice RT task appeared. It disappeared after participants pressed one of the two response buttons. In case participants did not respond the symbol remained for 2500 ms. After an interval of 1000 ms during which the screen remained blank the next trial started. The stop signal was presented on 25% of the trials. The sequence of events within a trial can be seen in Figure 2.6.

The stop signal delay was set by a staircase tracking algorithm (Kaernbach, 1991; Levitt, 1970), which adapts to the response rate. The SOA in our study was adjusted, so that participants approximately reached a rate of 50% inhibition. This is done the following way: If in a trial with stop signal the

response was not inhibited, the SOA of the stop signal was 50 ms earlier the next time a stop-signal occurred, so that the chance of inhibition was higher, whereas correct inhibition was followed by an increase of the delay by 50 ms in the next stop-signal trial, which made it harder to inhibit the response. As a result approximately 50% of all responses are stopped (see Levitt, 1970 for a mathematical discussion of this procedure). The first stop signal was set at 200 ms. After a period of adjustment, the SOA varies around values that are most informative, and the mean SOA can subsequently be used for further calculations. This procedure inherently corrects for individual and group differences in the RT-distribution and for the tendency to postpone responses. It provides a way of measuring inhibition (SSRT) by controlling for differences in speed of responding to the go signal. This is important, because slower response execution processes are easier to stop than faster ones at equivalent delays. Because brain damage may affect the speed of the response execution process, the ability to disentangle the effects of the response execution process on the inhibition process is of importance. An additional advantage of the tracking procedure is that the response rates remain almost constant across groups, despite differences in the efficiency of inhibitory control (Band, 1997).

Participants were tested in one session, which lasted approximately 45 minutes. They performed 2 practice blocks and 10 experimental blocks. In the first practice block, which had 60 trials, participants had to perform the choice RT task alone, in the second practice block, which consisted of 40 trials, the stop signal was added. After that, participants performed 10 experimental blocks, each consisting of 40 trials (30 no-signal trials and 10 stop signal trials).

The importance of responding as fast as possible to the choice RT task was emphasized in the instructions. Participants were told to respond quickly while maintaining a high level of accuracy. They were instructed not to delay their responses in anticipation of the stop signal but to make a concerted effort to withhold the response if they detected the stop signal. It was explained to them, that they would not always be able to withhold the response and that the computer would adjust to their efficiency, yielding approximately a 50% success rate.

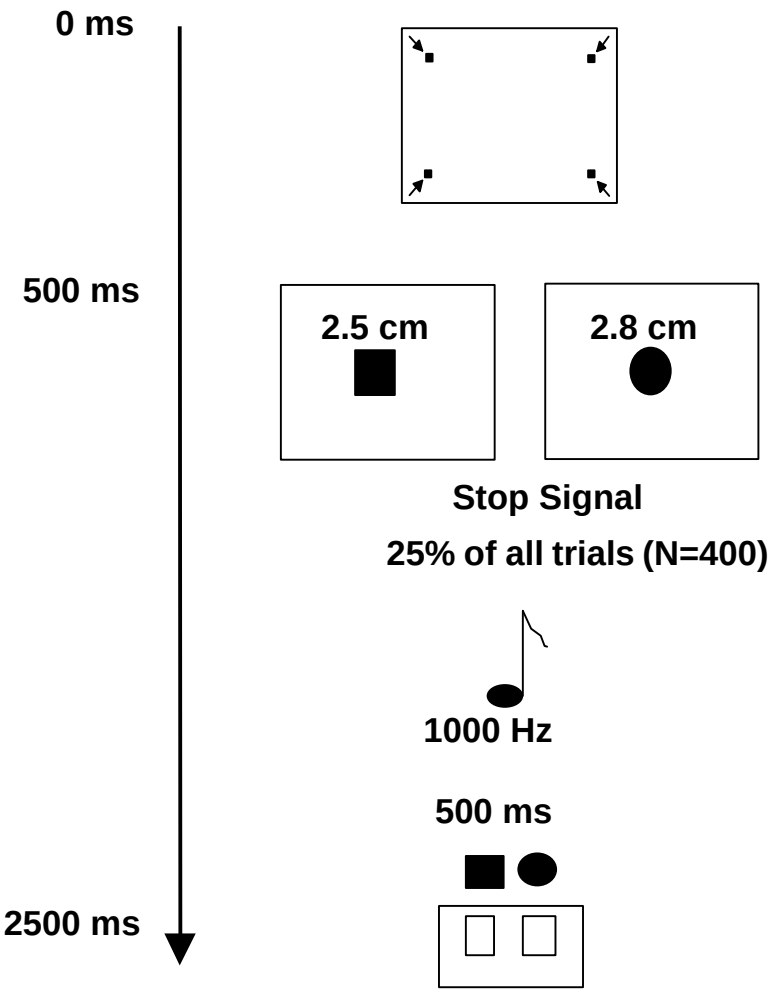

Figure 2.6. Sequence of events within a trial in the stop signal task. Each trial began with the presentation of four small squares (0.5 cm side length) which moved from the corners of the screen to the center in a fixed interval of 500 ms. Immediately thereafter one of the symbols for the choice RT task appeared. It disappeared after participants pressed one of the two response buttons. In case participants did not respond the symbol remained for 2500 ms.

The SSRT was estimated by calculating the difference between the average RT on trials without stop-signal and the average delay. Average RT on trials without stop signal, RT where the participants responded in spite of the stop signal, percentage of errors and probability of responding were further dependent variables. In addition, the last 40 trials of the first exercise block (without stop signal) were calculated as an estimation of primary task response speed, since RT in the experimental blocks might be influenced by the tendency to postpone responses (Logan, 1981; McGarry & Franks, 1997).

Procedure study 3

The procedure in study 3 differed from the procedure in study 1 and 2 in two respects: (1) the way the stop signal delay was set and (2) the number of trials. Therefore we will refer only to those aspects. This difference in procedure is due to the fact that this study with students was actually conducted before the other studies. At this time, we first thought about having several delays to be able to explore the inhibition function. Furthermore, the computer program with the staircase tracking algorithm was not available at the time the study was conducted. Results of this study were also a reason to employ the staircase tracking algorithm in the following patients studies – the response rate in the student study was on the average below 50%. As Band (1997) has shown in his simulation studies, in case several SOAs are applied, the estimated SSRT of those SOAs is overestimated when the response rate is lower than 0.5 and underestimated if the response rate is higher than 0.5 for a given SOA. Since the average probability of responding in study 3 was 39,8 %, the SSRT in this study is presumably slightly overestimated.

In study 3 the stop signal was presented at four different delays. After each experimental block the mean reaction time of the participant was calculated and the delays were set so that the stop signal occurred 100, 200, 300, and 400 ms earlier than the mean reaction time (Logan et al., 1984; Logan, 1994).

Participants were tested in one session, which lasted approximately 45 minutes. They performed 11 experimental blocks, each consisting of 60 trials. The first two blocks were for practice only; in the first block participants had to

perform the choice reaction time task alone, in the second the stop signal was added. The importance of responding as fast as possible to the choice reaction time task was emphasized in the instructions. Participants were told to respond quickly while maintaining a high level of accuracy. They were instructed not to delay their responses in anticipation of the stop signal but to make a concerted effort to withhold the response if they detected the stop signal. It was explained to them that they would not always be able to withhold the response and that the computer would adjust to their mean reaction time, so that if they respond later to the primary task, the stop signal would also be presented later.

We estimated SSRT with the following procedure: the RTs of the no-signal trials were rank ordered, and the nth reaction time was determined, where n is the number of no signal trials multiplied by the probability of responding when a stop signal occurred at a given delay. The nth reaction time estimates the time at which the stopping process finished, relative to the onset of the go signal. An estimate of the SSRT was obtained by subtracting the stop signal delay. This procedure was repeated for each delay. The SSRTs of the four delays were averaged to calculate the average SSRT (Logan & Cowan, 1984; Logan, 1994). In addition we calculated the probability of responding, the error rate and the choice reaction time (CRT) alone. The latter was done by using trials from the first exercise block. The 20 trials at the beginning of the block were dropped, thus 40 trials remained for this analysis. Details for the analysis of the inhibitory aftereffects are given in study 3.

2.6 Some general remarks about statistical analysis

The statistical packages used were the SAS-Program, Windows Version 6.03 (SAS Institute Inc., 1988) and the SPSS-Program Version 8.0 (SPSS Inc., 1998). All data were screened for deviation from normality, outliers and homogeneity of variance, and assumptions for statistical analysis were proved according to the recommendations of Tabachnick and Fidell (1996).

Dependent variables were submitted to analyses of variance (ANOVA) or T-test (in some nonparametric clinical variables also the Kruskal-Wallis H-Test was used). For the ANOVAs, the GLM procedure from the SAS software

package was used (this procedure is suitable for non-balanced data as in study 1).

Although we conducted several ANOVAs / T-tests in study 1 and study 2, we decided not to make an adjustment for alpha-inflation. In study 1 as well as in study 2, there was only one variable we were really interested in (i.e. the SSRT). We would have actually liked to have no significant differences in all other variables (it is however quite unlikely in research with brain damaged patients to have no differences in primary task reaction time or neuropsychological data). In some variables it was even necessary that the groups do not differ from each other (e.g. response rate in the stop signal task), to be able to interpret the results. Thus, correcting for alpha would actually have done us a favor in all variables, apart from the one we were interested in. We think that especially in this case, where significant differences are not actually wished for, the beta-risk should be taken much more seriously. After a significant ANOVA, when multiple comparisons were necessary we used the Tukey test to evaluate those (study 1, the Tukey-option in SAS also provides the Tukey-Kramer method to adjust for unequal cell sizes) or calculated contrasts (study 3).

Interpretation of results is not only based on statistical significance, but also on effect sizes, since allowing the level of significance to bear the essential responsibility for the conclusions neglects the magnitude of effect (Cohen, 1990; Zakzanis, 1998). Therefore, we will throughout the text not only state whether a result is significant or not, but provide the exact p-value and Cohen's d (Cohen, 1988) in case the effect is interesting. We will also interpret tendencies in case the facts are interesting or important for interpretation. On the other hand, even when effects are significant we will also ask the question, what an effect of the given size does mean, i.e. whether it has any practical implication. Effect sizes were calculated according to Cohen (1988). Effect sizes are not without problems themselves. The measure is expressed in terms of standard-deviation units, which means that the value of this measure does not only depend on the effect of interest but also on the selected study

population (Zakzanis, 1998). However, since there is no real alternative to this, this problem shall be stated here, but subsequently be ignored.

Correlations were estimated with the Pearson product moment correlation coefficient or the Spearman rank correlation coefficient where appropriate. We tried to be as thrifty as possible with correlations. Since correlations can differ in groups of patients with different lesion locations (Rabbitt, 1997), correlations for all participants were only calculated, when they did not significantly differ for the groups (which does however not say much with the small sample sizes used).

Further details of statistical analysis will be given for each study separately.

3. Study 1: Inhibition of ongoing responses following frontal, nonfrontal and basal ganglia lesions

3.1 Summary

Theories and research results point to the importance of circuits linking the basal ganglia and the frontal cortex in executive function and motor control (e.g. response inhibition). The aim of this study was to investigate the role of the frontal lobes and the basal ganglia in the inhibition of ongoing responses. Seventeen patients with frontal lesions (FG), 20 patients with lesions outside the frontal cortex (NFG), 8 patients with lesions to the basal ganglia (BG) and 20 orthopedic controls (OG) performed a response inhibition task (i.e. the stop-signal task). The stop signal task makes it possible to estimate the time it takes to inhibit an ongoing reaction. The FG as well as the BG showed significantly longer stop signal reaction times (SSRTs) than the OG. No significant differences in SSRT could be found between the NFG and any other group. However, effect sizes between the FG and the BG in comparison to the NFG were of medium range. Results provide some evidence for a role of the frontal lobes and the basal ganglia in the inhibition of reactions.

3.2 Introduction

Inhibition of reactions

Inhibitory control is a concept with importance for psychological theories about general principles of performance as well as theories about performance impairments in clinical groups. Complete suppression of an action is one of the most extreme forms of control, it is however required in many real life situations, where unanticipated changes in the environment suddenly make ongoing actions inappropriate.

In laboratory settings, inhibition of reactions can be investigated through a comparison between conditions with and without response execution. Paradigms which are used for this aim are the stop signal task (e.g. Lappin & Eriksen, 1966; Logan, 1994; Logan & Cowan, 1984) and the go nogo task (e. g.

Drewe, 1975a, b; Falkenstein et al., 1999; Konishi et al., 1998; Mishkin & Pribram, 1955). In the go nogo task participants usually have to respond to one type of stimuli and to withhold the response to another. For example, the instruction can be to respond to a green symbol, but to withhold the response to a red one. In the stop signal paradigm the participant performs a reaction time (RT) task (usually to visual stimuli). This is occasionally interrupted by a stop signal (usually a tone) with a variable stimulus onset asynchrony (SOA) relative to the response signal (Logan, 1994). The instruction is to respond as fast as possible on all trials, but to try to stop the response if the stop signal occurs.

Inhibition of a motor response is not directly observable, at least when people are successful in inhibiting. The advantage of the stop signal task is, that the time it takes to stop a reaction, i.e. the stop signal reaction times (SSRT), can be calculated. This is done by the horse race model, which basically asserts that the response production and the inhibitory process compete for the first finishing time (Logan & Cowan, 1984). The stop signal paradigm is regarded as an elaboration of the no/nogo task, with an delay or SOA of zero in the go nogo task (Band & Boxtel, 1999). However, in the go nogo task, the inhibition of a prepotent response is required, whereas in the stop signal task participants have to inhibit an ongoing response. Yet ongoing responses are the continuation of prepotent responses and it seems plausible that the same functional systems might take part in the inhibition of responses regardless at which stage inhibition is required.

Models of response inhibition in the stop signal task

The brain structures involved in response inhibition are of special interest. Unfortunately, there is only sparse research regarding this issue in the stop signal task.

Logan and Cowan (1984) proposed a single, global mechanism for inhibition in simple stopping tasks. This was done on the basis of findings which have shown that stopping performance proved to be similar in a wide variety of different primary tasks (Logan, 1981, 1982, 1983). However, they did not propose any brain systems which might take part in this process.

De Jong et al. (1995) proposed a two-mechanism model of response inhibition in the stop signal task. One mechanism operates at a peripheral level of the motor system (i.e. midbrain structures) and is supposed to be in work in situations where stop-all inhibition is required. The second mechanism operates centrally and is supposed to be at work when selective inhibition is required. The authors found also evidence for the operation of the central mechanism in stop-all conditions, however, they concluded that this mechanism did not play a critical role in determining actual success in withholding the response in this condition. De Jong et al. (1995) based their hypothesis on lateralized readiness potentials (LRP) and electromyographic (EMG) measures during performance in several conditions of the stop signal task (i.e. stop-all, selective-stop, stop-change). However, this position was challenged by Band and Boxtel (1999). First, Band (1997) was not able to replicate the results of De Jong et al. (1995) with a version of the go nogo task. Second, the interpretation of the data by De Jong et al. (1995) was based on the assumption of a fixed threshold for responding in LRPs, which might not be valid. Third, they criticized the logic behind inferences from response-related activity, i.e. they state that the site of inhibition is not exclusively associated with the manifestation of it. Fourth, they presented evidence, that supports cortical involvement in stop-all conditions, and fifth, they reviewed recent knowledge on neural connectivity (see Band & Boxtel, 1999, for details).

Band and Boxtel (1999) proposed that the prefrontal cortex and basal ganglia are candidate agents for response inhibition in the stop signal task. They assume that cortical and subcortical structures conjointly accomplish response inhibition and that inside this system, the prefrontal cortex is likely to be in charge, since it is supposed to be capable of modulating subcortical input to the motor cortex by gating the thalamic transmission of associated activity from the basal ganglia and cerebellum (see also Brunia, 1993). The authors argue that the integrated mechanisms of the frontal cortex, the thalamus, and the basal ganglia are responsible for stopping manual responses.

The frontal lobes and basal ganglia in response inhibition

The frontal cortex is a primary candidate structure for response inhibition. It has long been associated with inhibitory control (Fuster, 1985, 1999; Luria, 1966; Shallice, 1988). Evidence for the role of the prefrontal cortex in inhibitory mechanisms comes from a number of animal (e.g. Butters et al., 1973; Gemba & Sasaki, 1990) and human studies, using functional imaging and evoked potential techniques (e.g. Casey et al., 1997; Kiefer et al., 1998; Konishi et al., 1998, 1999) as well as brain damaged patients (e.g. Decary & Richer, 1995; Drewe, 1975 a, b; Milner, 1964; Perret, 1974, see also Andres & Van der Linden, 1998 for a review of inhibitory functions of the frontal lobes). These studies have shown that the frontal lobes play a key role in the performance of tasks that require inhibition of distracting or prepotent response tendencies or inhibition of "mental set".

The role of the basal ganglia in response inhibition has been less intensively studied. However, recent theories assume that the basal ganglia play an important role in the choice of motor programs by activating and inhibiting competing programs (Kropotov & Etlinger, 1999; Mink, 1996; Wichmann & DeLong, 1996). Mink (1996), for example, suggested that the basal ganglia act to inhibit competing motor mechanisms that could potentially interfere with the desired movement. Furthermore, the basal ganglia remove inhibition to allow a desired movement to proceed. Inability to inhibit competing motor programs results in slow movements, abnormal postures and involuntary muscle activity seen in Parkinson's disease. Further evidence for a role of the basal ganglia in inhibitory processes comes from studies with patients with Parkinson's disease, where some form of switch- or set-shifting task is used (e.g. Bowen et al., 1975; Cools et al., 1984; Flowers & Robertson, 1985; Jones et al., 1992).

Fronto-striatal circuits in motor control

The model of Band and Boxtel (1999) fits well with current research about the physiology of motor control and executive function. Most recent theories of executive function assume a coordinated communication between the frontal lobes and interconnected brain structures (e.g. Alexander et al., 1986;

Goldman-Rakic, 1987). It appears that there is an interchange of information through a number of functional loops linking frontal cortex, basal ganglia structures and motor cortex via the thalamus (Alexander et al., 1986; Groenewegen, 1997; Jahanshahi & Frith, 1998) that mediate performance on a range of tasks that tap executive function.

Alexander et al. (1986) proposed that those basal ganglia–thalamocortical circuits receive input from several separate but functionally related cortical areas, traverse specific portions of the basal ganglia and thalamus and project back upon one of the cortical areas providing input to the circuit, thus forming a partially closed loop (see Figure 3.1).

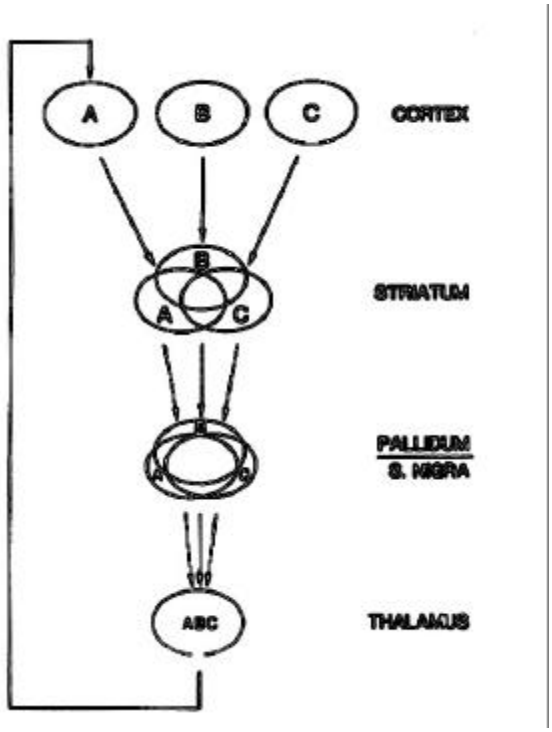

Figure 3.1 Generalized basal ganglia – thalamocortical circuit. A circuit receives output from several functionally related cortical areas (A, B, C) that send partially overlapping projections to a restricted portion of the striatum. These striatal regions send further converging projections to the globus pallidus and substantia nigra, which in turn project to a specific region of the thalamus. Each thalamic region projects back to one of the cortical areas that feed into the circuit, thereby completing the “closed loop” portion of the circuit (adapted from Alexander et al., 1986)

Multiple subsidiary circuits appear to modify and modulate the flow of information through the major basal-ganglia- thalamocortical pathways. They argue that from a functional standpoint it would seem more appropriate to attempt to rely functions to those circuits rather than to single structures of the brain.

The concept of functional loops is supported by a large basis of research on primates (see Alexander et al., 1986 for a review), but also research in humans supports this notion (see Jahanshahi & Frith, 1998). Jahanshahi and Frith (1998) reviewed studies using positron emission tomography (PET), recordings of movement related potentials and transcranial magnetic stimulation in humans. They concluded that "willed actions" are controlled by a network of frontal and subcortical areas, i.e. the basal ganglia and the thalamus. Neuropsychological studies comparing deficits in patients with Parkinson's disease, where primarily the basal ganglia are damaged, and in patients with frontal lobe lesions (e.g. Dimitrov et al., 1999; Eslinger & Grattan, 1993; Partiot et al., 1996) also point to close interconnections of these structures.

Research on the neuroanatomy of nogo performance in the go nogo task

We will now briefly review research with the go nogo task in relation to the frontal lobes and basal ganglia, since this is the most similar of available paradigms to the stop signal task and it has been used extensively in the clinical setting as well as in animal research.

The go nogo task has been employed several times with brain-damaged patients. Drewe (1975a) investigated the ability of frontal and nonfrontal patients to learn a go nogo selection. He found that even after patients with frontal lesions had reached the learning criterion, they still had some difficulty performing the task. In another study by the same author, a go nogo deficit of frontal patients, i.e. a higher number of false positives in the nogo condition, was also apparent (Drewe, 1975b). These results are supported by the study of Decary and Richer (1995), who also showed that frontal patients made more errors than either temporal lesioned patients or controls in the go nogo task.

Single case reports also point to the role of the frontal lobes in response inhibition in a go nogo task (Leimkuhler & Mesulam, 1985; Malloy et al., 1993).

Cooper et al. (1994) employed the go nogo task in patients with Parkinson's disease. Although response inhibition was not the focus of their study, the data showed that patients with Parkinson's disease made more errors in the nogo condition than controls, thus indicating a response inhibition deficit in Parkinson's disease.

The go nogo task has also been used frequently in animal studies. Watanabe (1986a, b) recorded single unit activity form the prefrontal cortex during performance of a go nogo task in three adult rhesus monkeys. He found units that showed differential activity in go nogo trials, and took this results as support of the concept that the frontal cortex is involved in response inhibition. Further evidence for the role of the frontal cortex in response inhibition was provided by Gemba and Sasaki (1990), Kalaska and Crammond (1995), Sasaki and Gemba (1986) and Sasaki et al. (1989). The study of Sasaki et al. (1989), who investigated monkeys with permanently implanted electrodes, nicely illustrates this. In the second part of their experiment they delivered brief pulses of stimulation to the implanted electrodes at the sites which were sensitive to nogo stimuli at different times after the onset of visual go stimuli. The stimulation suppressed the go movement by canceling or delaying it.

Apicella et al. (1992) investigated the neuronal activity in the striatum in a delayed go nogo task in monkeys. They found neurons that were specifically activated in the nogo condition, presumably reflecting a behavioral reaction consisting of the inhibition of movement. Thus, there is also evidence for a role of the basal ganglia in response inhibition from animal studies.

Electrophysiological studies in humans also support the notion that a no-go command is generated in the prefrontal cortex. In studies using event-related potentials (ERPs), EEG recordings have revealed a differential potential between go and nogo trials, the so-called „nogo potential", which usually shows a frontal or frontal central maximum (e.g. Gemba and Sasaki, 1989; Kok, 1986; Pfefferbaum et al., 1985). Two major ERP events, related to response inhibition, have frequently been described in go nogo tasks: The N2 and the P3

(Kiefer, 1998). Whereas early studies concentrated on the role of the P3 in response inhibition (Fallgatter et al., 1997; Karlin et al., 1970; Pfefferbaum et al., 1985; Simson et al., 1977, but see Jodo & Inoue, 1990), whose functional relation to inhibition still remains doubtful (Falkenstein et al., 1999), in later studies the role of the N2 as a reflection of response inhibition became apparent (Eimer, 1993; Falkenstein et al., 1999, Jodo & Kayama, 1992; Schröger, 1993). Since in most studies only a sparse electrode array is used, it is difficult to determine possible neural generators underlying the scalp ERPs. Therefore, Kiefer et al. (1998) recorded 64 channel EEG and conducted a source analysis. The source analysis indicated generators for the inhibition related ERP-effects in the inferior prefrontal cortex, the anterior cingulate cortex and in the left premotor cortex.

PET (Kawashima et al., 1996) and fMRI studies (Casey et al. 1997; Konishi et al., 1998; 1999) have also been employed with the go nogo task in humans. Kawashima et al. (1996) found several fields with significant activation in the go nogo task. Two of them were in the left frontal lobes, two in left nonfrontal areas, and four in the right hemisphere, solely located in the frontal lobes. Casey et al. (1997) found that activation was distributed across both dorsolateral and orbitofrontal cortex. Activity in the orbital frontal cortex and the anterior cingulate correlated with the number of false alarms. Konishi et al. (1999) found nogo activity in the posterior part of the inferior frontal sulcus of the right hemisphere, less reliably in the left hemisphere. All those studies support the involvement of frontal areas in response inhibition.

To summarize, lesion and imaging studies in humans, as well as electrophysiological studies in animals and humans point to the importance of the frontal lobes in the process of response inhibition. Furthermore, there is increasing evidence that the basal ganglia are also involved in this function.

Questions

Altogether, there is strong evidence, that the frontal lobes play an important role in the inhibition of prepotent responses, it seems likely that they are also implicated in the inhibition of ongoing responses. In addition, there is evidence,

that circuits linking the basal ganglia and the cortex may play an important role in executive function, motor control and probably response inhibition. The aim of the current study was to investigate the neuroanatomic basis of inhibition of ongoing responses in the stop signal task through the anatomo-clinical correlation method (see Vallar, 1999). Therefore, we employed the stop signal task and investigated brain damaged patients with lesions to the frontal lobes, cortical lesions other than the frontal lobes and lesions to the basal ganglia. Orthopedic patients were used as control participants. We hypothesized that only patients with lesions to the frontal lobes and to the basal ganglia would show deficits in the inhibition of ongoing responses (i.e. longer stop signal reaction times).

3.3 Methods

Participants

Brain-damaged patients with different etiologies (cerebrovascular disorders, tumor resections) were selected on the basis of lesion localization during their stay in four different rehabilitation hospitals. Lesions were located according to the available computer tomography (CT) or nuclear magnetic resonance tomography (MRT) scans. Inclusion criteria were either circumscribed cortical lesions (either inside the frontal lobe or outside) or lesions to the basal ganglia. Patients had to be between eighteen and seventy years of age. Exclusion criteria were medical conditions not related to the brain damage which have an influence on the CNS, aphasia with comprehension difficulties, visual disorders, neglect, degenerative disorders, German not as a first language and auditory disorders. Per institutional guidelines, all of the patients gave written informed consent. None of the patients were paid for participating in the study.

On the basis of our clinical and lesion criteria we assigned 17 patients with lesions anterior to the central sulcus to the frontal group (FG) and 8 patients with basal ganglia lesions to the basal ganglia group (BG). A group of 20 patients with non-frontal lesions (NFG) and 20 orthopedic control participants (OG) were selected to match the FG and BG as closely as possible in age, sex

and years of education. Using structural neuroimaging data, detailed anatomical descriptions of the lesions (Damasio & Damasio, 1989) were available for 15 patients of the FG, 18 patients of the NFG and seven patients of the BG. In 5 cases (2 FG, 2 NFG, 1 BG) there was no brain scan available, but a general reading of the scans. Tumor patients were tested postoperatively and all patients were tested in the subacute or chronic state. The Edinburgh Inventory (Oldfield, 1971) was used to asses hand preference and the Functional Independence Measure (FIM, Keith et al., 1987; German version: de Langen et al., 1995; Frommelt & de Langen, 1995) to assess disability. Demographic and clinical data of the four groups can be seen in Table 3.1, further details of the localization of lesion can be seen in the appendix.

One-way analysis of variance revealed no differences between the four groups in either age ($F(3, 61)=0.05$, $p=0.98$) or years of education ($F(3, 61)=0.09$, $p=0.96$). The three brain-damaged groups did not differ in weeks since onset of lesion (Kruskal-Wallis H-Test: $\div^2(2)=2.939$, $p=0.23$) and functional independence ($F(2, 42)=1.49$, $p=0.24$). Chi-square analysis was not performed with the nominal variables, due to low cell sizes, but it has to be noted that there are no patients with a brain tumor in the basal ganglia group.

Table 3.1 Demographic and clinical data of patients with frontal lesions (FG), patients with nonfrontal lesions (NFG), patients with basal ganglia lesions (BG), and orthopedic controls (OG).

	FG (N=17)	NFG (N=20)	BG (N=8)	OG (N=20)
Sex: (male / female)	8 / 9	10 / 10	6 / 2	10 / 10
Age (M, SD)	50 (13.6)	49.9 (8.5)	51.6 (8.5)	50.5 (11.8)
Years of education (M, SD)	10.2 (1.3)	10.4 (1.5)	10.1 (1.2)	10.3 (1.5)
Handedness premorbid (r / l / bi)[1]	16 / 1 / 0	19 / 0 / 1	8 / 0 / 0	
Handedness at testing date (r / l / bi)	16 / 1 / 0	15 / 2 / 3	5 / 3 / 0	19 / 1 / 0
Etiology (Hemorrhage / Stroke / Tumor)	10 / 1 / 6	7 / 7 / 6	6 / 2 / 0	
Weeks since onset (Median, Range)	7, 1-234	6.5, 3-416	18, 5-350	
Functional Independence Measure (M, SD)	120 (6)	114 (16)	114 (13)	

[1] r = right, l = left, bi = bilateral

[2] a higher value means higher functional independence

Background neuropsychological assessment

see general methods section

Response inhibition - the stop signal task

see general methods section

Statistical analysis

The statistical packages used were the SAS-Program, Windows Version 6.03 (SAS Institute Inc., 1988) and the SPSS-Program Version 8.0 (SPSS Inc., 1998). All data were screened for deviation from normality, outliers and homogeneity of variance, and assumptions for statistical analysis were proved according to the recommendations of Tabachnick and Fidell (1996). Dependent variables were submitted to analyses of variance (ANOVA) with one between subjects factor (GROUP: FG, NFG, BG and OG). For the ANOVAs, the GLM procedure from the SAS software package for non-balanced data was used. Post hoc comparisons were performed with the Tukey test with an alpha of 0.05. Effect sizes were calculated according to Cohen (1988). Further analyses were conducted after the results of these analyses. Those were analysis of covariance (ANCOVA) and the computation of correlations. In ANCOVA, planned comparisons were used to compare the groups. Correlations were estimated with the Pearson product moment correlation coefficient. They were only conducted for variables where group differences had emerged to estimate the relationship of those variables with SSRT. Since sample sizes are small, correlations was calculated for all participants, after proving that the correlations of each group did not significantly differ from each other.

3.4 Results

Background neuropsychology

There were no outliers, and requirements of analysis of variance were fulfilled in the neuropsychological data. Details of the results of the background neuropsychological assessment are given in Table 3.2.

Table 3.2 Neuropsychological data of patients with frontal lesions (FG), patients with nonfrontal lesions (NFG), patients with basal ganglia lesions (BG), and orthopedic controls (OG).

	FG (M, SD, N)	NFG (M, SD, N)	BG (M, SD, N)	OG (M, SD, N)
LPS (average T-value)	48 (5) 16	49 (9) 14	44 (9) 6	55 (7) 16
AVLT (total score)	36 (13) 16	42 (14) 19	34 (14) 6	51 (8) 19
Digit span (total score)	12.3 (3.3) 17	13.8 (4.1) 18	11.3 (3.5) 7	14.3 (3) 20
MCST (% perseverative errors)	25.2 (15.8) 17	20.9 (20.8) 19	20.1 (15.7) 6	18.3 (19.7) 19

Note. AVLT = Auditory Verbal Learning Test; MCST = Modified Card Sorting Test, LPS = Leistungsprüfsystem (intellectual functioning)

One-way ANOVAs showed a significant GROUP effect in intellectual functioning ($F(3,48)=4.07$, $p=0.01$) and total learning in the AVLT ($F(3,56)=5.48$, $p=0.002$). There were no GROUP effects in the total score of the digit span test ($F(3,58)=1.89$, $p=0.14$) and the percentage of perseverative errors in the MCST ($F(3,57)=0.42$, $p=0.74$). Tukey tests revealed that the BG performed significantly worse than the OG in intellectual functioning and that the FG and BG performed significantly worse than the OG in total learning of the AVLT.

Performance in the stop signal task

One participant of the FG was an univariate outlier in the primary task RT in the exercise block and in the SSRT. This participants was not considered in further analysis. In the OG one participant was an outlier in signal respond RT and another one an outlier in the percentage of errors. Since normality was threatened in percentage of errors in this group (z for skewness=4.9, z for kurtosis=8.02), this participant (outlier in error %) was deleted. To employ the

same strategy for all outliers we also deleted the other outlier (outlier in signal respond RT). Results of the stop signal task with deleted outliers are presented in Table 3.3.

Table 3.3 Results of the stop signal task of patients with frontal lesions (FG), patients with nonfrontal lesions (NFG), patients with basal ganglia lesions (BG), and orthopedic controls (OG).

	FG (M, SD)	NFG (M, SD)	BG (M, SD)	OG (M, SD)
Exercise block without stop signal				
RT (ms)	619 (88)	596 (89)	675 (190)	531 (67)
Experimental blocks				
RT, trials without stop signal (ms)	853 (273)	760 (185)	797 (176)	665 (158)
Signal respond RT (ms)	739 (226)	669 (155)	706 (149)	578 (105)
Errors %	1.4 (1.2)	1.3 (1.2)	1.6 (2.1)	1 (0.8)
Probability of responding	47.8 (3.1)	47.2 (2.4)	48 (2.8)	48.6 (1.7)
SSRT (ms)	271 (60)	249 (38)	282 (44)	228 (29)

Note. SSRT = stop signal reaction time

The probability of responding did not differ between the groups ($F(3,58)=0.88$, $p=0.46$), which shows that the staircase tracking algorithm was successfully applied to equalize response rates between groups. This is a necessary prerequisite for the interpretation of results. Furthermore, error rates did also not differ between groups ($F(3,58)=0.51$, $p=0.67$). As expected by our hypothesis, there were significant differences in the SSRTs ($F(3,58)=4.13$, $p=0.01$), the post hoc test revealed that this was due to the FG ($p=0.03$) and the BG ($p=0.03$) being significantly slower than the OG. However, results were nontransitive, the NFG did neither differ significantly form the OG nor from the FG or BG. The strength of relationship between SSRTs and group membership was $eta^2=0.18$. There were also significant differences in primary task reaction times. In the exercise block ($F(3,58)=4.31$, $p=0.008$) the post hoc test revealed a significant difference between the OG and the BG ($p=0.008$) and a tendency

between the OG and the FG (p=0.07). In the experimental blocks there were also significant differences in the primary task reaction times (trials without stop signal), here the Tukey test between the OG and the FG (p=0.045) became significant despite a nonsignificant F-value (F(3,58)=2.51, p=0.07). The signal respond reaction times (F(3,58)=2.94, p=0.04) also showed a significant difference between the OG and the FG (p=0.03). Thus, analysis of variance revealed significant differences between the controls and the frontal as well as the basal ganglia patients in the SSRT. In addition the frontal patients also showed significant slowing in primary task reaction times compared to controls, primary task reaction times for the basal ganglia patients were only significantly slower in the exercise blocks. Effects sizes for primary task RT and SSRT can be seen in Table 3.4.

Table 3.4 Effect sizes and percentage nonoverlap (Cohen, 1988) of stop signal reaction time (SSRT) and effect sizes of primary task reaction time (RT)

	FG-OG	NFG-OG	BG-OG	FG-NFG	BG-NFG	FG-BG
SSRT	0.91	0.62	1.45	0.44	0.8	0.21
% nonoverlap SSRT	51.6	38.2	68.1	27.4	47.4	14.7
RT	1.13	0.83	1.01	0.26	0.53	0.39

Note. FG-OG = frontal group in comparison to the orthopedic control group, NFG-OG = nonfrontal group in comparison to the orthopedic controls, BG-CON = basal ganglia group in comparison to the orthopedic control group, FG-NFG = frontal group in comparison to the nonfrontal group, BG-NFG = basal ganglia group in comparison to the nonfrontal group, FG-BG = frontal group in comparison to the basal ganglia group.

Differences in primary task RTs across blocks in the stop signal task

As can be seen from Table 3.2, primary task reaction times were longer in the experimental blocks than in the exercise block. A 4 (GROUP) x 2 (BLOCK: reaction times in the exercise block, reaction times in the experimental block; repeated factor) ANOVA revealed a significant main effect for GROUP (F(3,58)=3.89, p=0.01) a significant main effect for BLOCK (F(1,58)=39.74, p<0.0001) but no significant interaction of GROUP x BLOCK (F(3,58)=0.99, p=0.4). Thus, there was a strong tendency for all groups to have longer reaction times in the experimental blocks, but there was no indication, that any

group performed different in this respect. However, because of the effect of longer RTs in the experimental blocks, RTs in the exercise block will be interpreted as the general speed of responding.

Inhibition and general slowing

One might argue, that the effect of longer SSRTs might be due to an effect of general slowing in the FG and BG. Pearson product moment correlations between SSRT and primary task RT only reached significance in the control group. They were r=0.33 for the FG, r=0.06 for the NFG, r=0.47 for the BG and r=0.51, p=0.03 for the OG. Correlations did not significantly differ between the groups, the correlation for all participants of all groups was r=0.41, p=0.0009.

Two strategies were employed to investigate the effect of general slowing on inhibitory efficiency. First, an analysis of covariance (ANCOVA) was calculated with the RTs in the exercise block as a measure of general speed of responding as a covariate for SSRT. Second, we selected six participants from each group who had similar primary task reaction times in the exercise blocks for comparisons (upper limit for inclusion was the slowest control participant, lower limit was the fastest participant of the basal ganglia group).

The necessary requirements for ANCOVA were fulfilled. There were no multivariate outliers as measured by Mahalanobis distance, the slope of regression was sufficiently homogenous ($F(3, 54)=0.65$, $p=0.59$) and visual inspection of the residual plots of predicted values of SSRT against residuals did not indicate any deviation from linearity. Reliability of the covariate was tested using odd even correlations of the RTs in the exercise blocks. They were essentially the same in all subgroups, the correlation for the whole group was 0.95. After adjustment by reaction times, the SSRT did not any longer vary significantly between the groups ($F(3,57)=1.93$, $p=0.13$), although planned comparisons showed a significant effect for the OG versus the FG ($p=0.04$), and a tendency for the OG versus BG ($p=0.07$). The strength of relationship between adjusted SSRTs and group membership was partial $eta^2 = 0.092$. The adjusted marginal means are shown in Table 3.5.

Means and standard deviations of primary task RTs in the exercise block and SSRTs of the participants selected for equal primary task reaction times can be seen in Table 3.5. Effect sizes were essentially maintained (see Table 3.6). If any changes, the non-frontal group has less difference to the control group and the frontal group and basal ganglia group have larger differences to the nonfrontal group. For the following analysis alpha was set to 0.1 because of the reduced power due to the reduced sample sizes. An analysis of variance revealed a tendency for a group difference ($F(3,20)=2.67$, $p=0.07$). Planned contrasts revealed significant effect for the OG vs. the FG with $p=0.05$ and the OG vs. the BG with $p=0.03$. The strength of relationship between SSRTs and group membership was $eta^2 = 0.29$.

Table 3.5 Results of ANCOVA and selected participants in the stop signal task of patients with frontal lesions (FG), patients with nonfrontal lesions (NFG), patients with basal ganglia lesions (BG), and orthopedic controls (OG).

	FG (M, SD)	NFG (M, SD)	BG (M, SD)	OG (M, SD)
ANCOVA (primary task RT as a covariate)				
SSRT (adjusted marginal means)	268	249	271	236
Selected participants (with equivalent primary task performance)				
Primary task RT (ms)	605 (32)	605 (35)	598 (48)	604 (44)
SSRT (ms)	281 (25)	258 (27)	285 (25)	249 (27)

Note. SSRT = stop signal reaction time

Table 3.6 Effect sizes of stop signal reaction time (SSRT) for selected participants

	FG-OG	NFG-OG	BG-OG	FG-NFG	BG-NFG	FG-BG
SSRT for selected participants with equivalent primary task RT	1.23	0.33	1.38	0.88	1.04	0.16

The relationship of inhibitory efficiency and background neuropsychology

To evaluate the relationship of variables, in which differences between the groups had emerged, with inhibitory efficiency, Pearson product moment correlations of these variables with SSRT were calculated. Neither of the two neuropsychological measures in which group differences were obtained correlated significantly with SSRT. The correlations of intellectual functioning and SSRT were r=-0.12 in the FG, r=0.0 in the NFG, r=-0.17 in the BG and r=–0.23 in the OG, for all participants the correlation was r=-0.25. The correlations of total learning in the AVLT and SSRT were r=–0.08 in the FG, r=0.13 in the NFG, r=-0.46 in the BG and r=–0.15 in the OG, for all participants the correlation was r=–0.21.

3.5 Discussion

Using the stop signal task, we have shown that patients with frontal lobe and basal ganglia lesions have longer stop signal reaction times in comparison to orthopedic controls. However, results were non-transitive, brain-damaged patients with cortical lesions outside the frontal lobes differed neither significantly from controls nor from frontal or basal ganglia patients, although the effect sizes between the NFG and the FG and BG were of medium range. This issue will be discussed below. Results could not be explained by differences in other neuropsychological variables such as intellectual functioning. Thus, inhibitory efficiency seems largely independent of global cognitive impairment. Since our groups were matched on demographic variables, differences also cannot be explained by such variables. However, the speed of initiation and inhibition of reactions showed a significant relationship. This issue will also be discussed below in reference to the fronto-striatal circuits.

The frontal lobes and basal ganglia in response inhibition

The longer stop signal reaction times in patients with frontal lobe and basal ganglia lesions in comparison to orthopedic controls seem to confirm the role of those structures in response inhibition. The proposition of Band and Boxtel

(1999), that the prefrontal cortex and the basal ganglia are candidate agents for response inhibition in the stop signal task has therefore proved to be a valid assumption. The results highlight the role of frontostriatal circuits in response inhibition. A lesion to any point in such a circuit should lead to the same deficits in performance, regardless of the location of the lesion within the circuit. Therefore, the deficits of patients with frontal and with basal ganglia lesions should be comparable, which they were in our study. This is also in accordance with other studies, which showed comparable deficits in patients with frontal and basal ganglia lesions (e.g. Dimitrov et al.,1999; Eslinger & Grattan, 1993; Partiot et al., 1996).

Our results also correspond to and extend the results of studies using the go nogo task. Those studies have already provided evidence for the role of the frontal cortex in response inhibition (e.g. Casey et al., 1997; Decary & Richer, 1995; 1997; Drewe, 1975a, b; Kiefer et al., 1998; Konishi et al., 1999; Watanabe, 1986a, b). In contrast to earlier studies, however, we employed the first time a task which measured the internal reaction time to a stop signal and not just the presence or absence of a response. Furthermore, response inhibition in the stop signal task, which was used in our study, is required at a later step in the response execution process than in the go nogo task used in the previous studies.

The issue of the role of the basal ganglia in response inhibition has seldom been directly addressed before, although there are some studies on the role of the basal ganglia on change or switching performance (e.g. Bowen et al., 1975; Cools et al., 1984; Flowers & Robertson, 1985; Jones et al., 1992). Our study corresponds with the results of Apicella et al. (1992) who found neurons in the striatum in monkeys, which were specifically activated in the nogo condition, presumably reflecting the inhibition of movement. The results also indicate that it may be worthwhile to have a closer look at the role of the basal ganglia in response inhibition.

Response inhibition as a diagnostic marker

Although effect sizes were of medium range between basal ganglia or frontal patients in comparison to nonfrontal patients, those effects did not reach significance. Some impairment in response inhibition is also to be expected in patients with damage outside the crucial areas mentioned, since those frontostriatal circuits do not work in isolation of the rest from the brain. The frontostriatal loops do not function in a fully segregated manner, instead each circuit seems to have both closed-loop and open-loop elements (Jahanshahi & Frith, 1998; Alexander, 1986). For example, relevant sensory information from posterior brain regions must be utilized. With respect to response inhibition Kawashima et al. (1996) found several areas with significant activation in the go nogo task in comparison to response selection only, six of those areas were located in the frontal cortex, but also two nonfrontal cortical areas were activated.

Although results point to a role of frontostriatal circuits in response inhibition, prolonged SSRTs in the stop signal task can by no means be used as a diagnostic marker for a deficit in those structures. As Zakzanis (1998) argues, a diagnostic marker should be capable of discriminating approximately all patients form all normal healthy controls on the dependent variable of interest. When the mean effect size is not able to discriminate all patients from controls, i.e. an effect size of more than 3.0, which would mean that there is approximately a 5% overlap of the groups, it is hard to argue in favor of a specific impairment as being a reliable characteristic of the lesion. An effect of this size is, however, rarely given in any neuropsychological measure. If one looks at the studies who employed the go nogo task (Decary & Richer, 1995; Drewe, 1975a, b) effect sizes are on the average in the range of 1.0.

Looking at the patients individually there were 4 patients in the frontal group (23,5%, including the outlier), no patient in the nonfrontal group and two patients in the basal ganglia group (25%) whose performance was three standard deviations below the mean of the control group. Using the more liberal criterion of two standard deviations below the mean of the control group, eight patients of the frontal group (47%), three patients of the nonfrontal group

(15%) and four patients of the basal ganglia group (50%) were below that criterion. Thus, although deficits in response inhibition cannot be said to be a reliable characteristic of the lesion, significant impairment in response inhibition can be found in quite a lot of patients with those lesions.

Inhibition and initiation of reactions

Inhibition and initiation of reactions showed a significant relationship in the current study (r=0.41 for the whole group) and differences between the groups diminished (but did not totally disappear) after analysis of covariance. However, when participants with essentially the same primary task reaction times were selected, the differences between the groups remained. These results may seem contradictory, but can be explained by methodological differences. Analysis of covariance can lead to overadjustment when groups differ on the covariate, it is however an accepted procedure to use ANCOVA in this case in a quasi-experimental design (Tabachnick & Fidell, 1996). On the other hand, matching participants ex post facto on a "nuisance" variable results in "systematic unmatching" of participants (Tupper and Rosenblood, 1984).

What follows from the relationship of primary task RT and SSRT? It seems likely that at least in part the same neuronal structures are involved in the inhibition and initiation of reactions. We derived our hypothesis about the structures which could possibly be involved in response inhibition from studies on structures taking part in inhibitory processes as well as from general concepts about motor control, which entail the initiation of movements. Jahanshahi and Frith (1998) state that willed actions are controlled by a network of frontal and subcortical areas, which are activated with self-generated actions involving nonroutine decision making, regardless of whether the nature of the decision making is related to "what to do" or "when to do" or "whether or not to act" (p. 494). Likewise, Mink (1996) proposed that it is the role of the basal ganglia to activate and inhibit competing motor programs. In addition to deficits in response inhibition, there is also empirical evidence that the process of motor preparation appears to be impaired in patients with prefrontal lesions (Alivisatos & Milner, 1989; Verfaellie & Heilman, 1987). The role of the frontal cortex in

response activation is also supported in the studies of Watanabe (1986b) and Casey et al. (1997) who employed the go nogo task. Therefore, it seems likely that damage to the crucial structures may result in impairment in response initiation as well as response execution.

Alternatively, it could be argued, that brain structures involved in response inhibition and response initiation are close to each other, but since lesions are not isolated on small spots but usually involve several structures those lesions affect both systems. On a more fine-grained level, the same structures may take part in both processes, but different neuronal units are responsible for different aspects. Watanabe (1986b) found that of 512 units in the prefrontal cortex, 253 showed differential activation in go and nogo trials. However, it remains unclear, how far the activity of the remaining neurons reflects that they take part in both response initiation and response inhibition or reflect further mental processes in the task, e.g. stimulus processing.

Even if there is some overlap in the neuronal structures for response inhibition and response initiation, this overlap does not necessarily have to be perfect. As our comparisons of patients with similar primary task RTs has shown, general motor slowing seems to explain part of the results, but not all of them. Even though effects were smaller when controlling for primary task response speed, they did not disappear, indicating, that the structures responsible for initiation and inhibition are at least partly separable from the other. This is also in accordance with a recent study of Williams et al. (1999), who investigated the development of inhibitory control over life span with the stop signal task. He found that age-related changes in inhibitory control could not be explained by general speeding or slowing of responses, although a significant amount of variance was accounted for SSRT by go signal reaction time in adults.

Executive impairment in our patient samples

Unexpected was the fact, that the perseverative errors of the MCST did not differentiate between our groups, especially frontal patients and controls. This negative result might be due to three different reasons: a) the MCST is not a

sensitive measure of frontal lobe damage, b) our patients did not have executive deficits, and c) the controls performed worse than expected.

The result, that the MCST did not discriminate between nonfrontal and frontal patients is not an isolated finding. De Zubicaray and Ashton (1996) reviewed studies investigating the MCST's differential sensitivity to frontal lobe dysfunction. They found that evidence regarding the sensitivity to frontal lobe dysfunction is weak. More surprising is however, that the orthopedic controls did not perform significantly better than the patients. The effect size for the difference between controls and frontal patients in our study was 0.39, which shows that there is some effect, but not a very big one. Few studies have investigated the differential performance of normals and those with frontal dysfunction on either the MCST or the WCST. There are some reports of patients with frontal lobe damage who did not show deficits in the WCST (Eslinger & Damasio, 1985; Heck & Bryer, 1986, for reviews see de Zubicaray & Ashton, 1996; Mountain & Snow, 1993). This is however an exception to the rule, most studies find differences in comparison to healthy controls (e.g. Grafmann et al.,1990). Looking at the values of our patients, it seems that our control group performed slightly worse than in some, but not all, studies (see de Zubicaray & Ashton, 1996 for control group data of several studies using the MCST). It might be, that our selection of the control group was conservative, since we employed orthopedic controls and not healthy persons. However, this approach seems sensible, since it corrects for general effects of being ill and having to stay in hospitals and taking various medications.

Do our frontal patients perform better than in other studies? Nelson (1976) recommended a cutoff of 50% perseverative errors or greater for detecting frontal lobe dysfunction. This score correctly classified 38% of her patients with frontal lobe lesions (8 of 21). Taking into account that she had discarded 4 frontal patients who had no difficulties in the MCST and had made few errors, this cutoff classified at least 32% of her patients correctly (8 of 25, the % perseverative errors score for those patients cannot be derived from the presented data). In our study only two of 17 frontal patients (i.e. 12%) had a score that high. On the average Nelson's (1976) patients had a mean score of

42% perseverative errors (however, this value excludes the four patients without difficulties). In comparison, our sample of frontal patients showed an average value of 25% perseverative errors. It cannot be ruled out, that our effects would have been greater in a patient sample with more executive deficits. However, selectively including patients who show executive disturbance in studies produces a bias, and this is not the case in our study; our patient sample represents patients selected for specific lesions, irrespective of behavioral disturbances.

The tendency to wait in the experimental block

Primary task reaction times in the experimental blocks were significantly longer than in the exercise block for all groups. Longer reaction times in the experimental blocks could be due to two reasons: a) effects of fatigue, and b) a tendency to wait for stop signals in spite of instructions. It cannot be ruled out, that fatigue has some influence on this effect. However, this effect should be much less pronounced than the obtained prolongation of RTs. An interpretation of the data as a tendency to wait is in accordance with other studies (Logan, 1981; McGarry & Franks, 1997), although the prolongation of RTs was less pronounced in those studies. This might be due to the fact, that it is much easier to persuade students not to employ any waiting strategy than patients.

It might have been expected that when a strategy is employed, frontal patients differ from the other patients in either being more impulsive or more conservative (Shallice & Evans, 1978; Vilkki & Holst, 1991). However, the interaction between group and block was not significant, which indicates, that the tendency to prolong RTs was independent of group membership. The strategic behavior happened, even though patients were explained that they would not profit from waiting for the stop signal. They were also reminded several times during the task breaks to respond as fast as possible.

However, the tendency to wait has no implication for the validity of our results. This tendency is unlikely to influence SSRT, since the tracking procedure is able to compensate for group as well as individual differences in primary task RT (Band, 1997). Furthermore, the probability of responding was

not different between the groups and close to 50%. If there is any systematic error, all groups should be affected.

Conclusion

This study provides support for a role of fronto-striatal circuits in the inhibition of reactions. The results also provide evidence, that it is useful to rely functions such as response inhibition to functional circuits or networks of interconnected brain structures, rather than isolated brain regions. The obtained effects are, however, too small for SSRT to serve as an diagnostic marker of those brain regions. The neuronal structures for response inhibition and response initiation seem to be at least in part overlapping. Further studies comparing more participants with lesions in different frontal regions, basal ganglia regions and also posterior regions have to determine a more detailed anatomical assignment of this function.

4. Study 2: Inhibition of ongoing responses in patients with traumatic brain injury

4.1 Summary

In addition to slowness of information processing, it is often assumed that high level control processes are deficient in traumatic brain injury (TBI). The aim of this study was to investigate a specific executive function, the inhibition of ongoing responses in TBI. 27 patients with TBI (TBI) and 27 orthopedic patients (OC) performed the stop signal task, which makes it possible to estimate the time it takes to inhibit an ongoing reaction. Contrary to expectations, patients with TBI did not show deficits in the inhibition of ongoing reactions. None of the clinical, demographic or neuropsychological data showed a significant relationship to speed of inhibition, apart from age, which showed a significant relationship only in the TBI. It seems likely, that deficits in the complete inhibition of responses are not very common after TBI.

4.2 Introduction

Disruption of executive functions involving mood, behavior, and aspects of cognition is frequently reported in patients with traumatic brain injury (Leon et al., 1998; Levin & Kraus, 1994; Mattson & Levin, 1990; Umilta & Stablum, 1998). Clinical descriptions of patients with TBI often include features that are associated with frontal lobe injury or executive function deficits, such as poor impulse control, decreased flexibility, impaired attention, perseveration, and diminished divergent thinking. Although slowness of information processing appears to account for many of the deficits after TBI (Ponsford & Kinsella, 1992; Schmidt et al., 1996; Veltman, 1996; Whyte et al., 1997), some authors assume that in addition to slowness, the degree of controlled processing (Cicerone et al., 1996; Park et al., 1999) or supervisory strategy (Azouvi et al., 1996, Spikman et al., 1996; Stablum et al., 1994) required to perform a task is another important factor.

The broad term “executive functions” usually refers to a long list of abilities, such as planning, anticipation, action sequencing, cognitive flexibility or

monitoring (for reviews see Fuster, 1999; Lezak, 1982; Stuss & Benson, 1986). One frequently mentioned ability in the context of executive function is inhibition (Fuster, 1985, 1999).

Most of the studies in TBI measured inhibition as interference (i.e. being more distractible than controls points to a deficit in the inhibition of irrelevant stimuli) (Veltman et al., 1996) or used complex tasks such as the Wisconsin Card Sorting Test (Gansler et al., 1996). Gansler et al. (1996) showed that response inhibition involved in establishing and maintaining response set is apparently impaired in patients with TBI. Vakil et al. (1995) demonstrated impaired negative priming in the Stroop task in patients. Spikman et al. (1996) also found that patients were impaired in all conditions of the Stroop-task in comparison to controls. However, no specific deficits remained, when general slowing was controlled for. Veltman et al. (1996) measured inhibition on the basis of the differences between a distraction condition and a condition without distraction. Controlling for slowness in the basic condition, they found no interaction effect between patients and controls, both needed more time for the distraction task. Although the increase in time needed in the distraction condition was slightly larger in the patients, the proportional increase in time needed for the distraction task was almost the same in both groups. The findings of their study thus point to the conclusion that there are no specific deficits in inhibition and interference.

Inhibition is not a unitary concept, but several forms of inhibition can be distinguished (Arbuthnott, 1995; Harnishfeger, 1995). Arbuthnott (1995) distinguishes between the targets of inhibition in several tasks. Targets of inhibition can be associative neighbors (e.g. in tasks with ambiguous words), competitors in the task context (e.g. distracting stimuli) or the produced units themselves (e.g. when a particular response has to be inhibited). She further states that the influence of intention on inhibition can be either indirect (e.g. distracting stimuli are inhibited) or direct (e.g. a particular response has to be inhibited). In the above mentioned studies, which are mainly concerned with the inhibition of distracting stimuli, the target of inhibition is mainly a competitor in the task context and the influence of intention is indirect. Contrary to this, the

focus of this study will be on another form of inhibition, where the target of inhibition is the produced unit itself and inhibition is fully intentional. This is measured as a deliberate and complete suppression of an ongoing motor response. Complete response suppression is one of the most extreme forms of control, it is however required in many real life situations, where unanticipated changes in the environment suddenly make ongoing actions inappropriate.

To our knowledge there are only few studies specifically addressed to the issue of response inhibition in patients with TBI. Braun et al. (1989) found that paradigms designed to elicit commission errors (a go nogo paradigm and a paradigm with prestimulus warning) were the most sensitive, particularly the error rate measures for these tasks, to distinguish patients with TBI and controls. Using discriminant function analysis, they showed that the go nogo paradigm classified participants better than complex choice reaction time (CRT) paradigms. Collins and Long (1996) compared simple and choice RT (the CRT task was actually a go nogo task) in patients with TBI. Both tasks were able to discriminate between TBI and control participants, but the CRT task yielded the best classification rate (however not statistically significant). Unfortunately, the authors did not analyze error rates. Cremona-Meteyard and Geffen (1994) studied event-related potentials (ERPs) in patients with TBI in a task which included a nogo condition. They found that patients did not show the normal attenuated contingent negative variation (CNV) following nogo cues. They interpreted this finding as perseverative behavior. However, usually the major ERP events related to response inhibition in go nogo tasks are the N2 and the P3 (Kiefer et al., 1998), which were, apart from being delayed in patients as were all components in the study, essentially normal.

In sum, studies investigating different forms of inhibition have brought mixed results so far. The purpose of this study was to investigate one particularly important executive function, the complete and active inhibition of an ongoing action. Therefore, we compared a group of patients with TBI with a group of orthopedic controls in their ability to inhibit an ongoing motor response. Since inhibition of a motor response is usually not directly observable, at least when people are successful in inhibiting, we used the stop signal task, which allows to

calculate the time it takes to stop a reaction, i.e. the stop signal reaction time (SSRT). We assumed that patients with TBI would show less inhibitory efficiency than controls in the stop signal task, since studies using the go nogo tasks have provided some evidence for a response inhibition deficit in TBI (Braun et al., 1989; Collins & Long, 1996). In addition, the relation of clinical characteristics, demographic variables and neuropsychological data to response inhibition was evaluated.

4.3 Methods

Participants

Two groups of patients participated in the present study. A group of patients who had sustained traumatic brain injury (TBI, N=27) and an orthopedic control group (OC, N=27).

Ages in the TBI ranged from 17 to 68 years, in the OC ages ranged from 21 to 69 years. In both groups schooling ranged from 9 to 13 years. T-tests revealed no differences between the two groups in either age ($T(52)=0.55$, $p=0.58$) or years of education ($T(52)=0.09$, $p=0.93$). All participants were right-handed and the patients in the TBI were all able to perform the task with their preferred hand. The time since trauma in the TBI ranged from 3 weeks to 10 years, the median was 8 weeks. All patients were tested in the subacute or chronic state. Severity of head injury ranged from mild to severe. Because the Glasgow Coma Scale was not available for the majority of TBI patients a detailed neuropsychological assessment was carried out to provide an estimate of the cognitive impairment and disabilities.

Exclusion criteria were medical conditions not related to brain damage which could have an influence on the central nervous system, aphasia with comprehension difficulties, visual disorders, neglect, degenerative disorders, German not as a first language and auditory disorders. Participants were recruited from four different rehabilitation hospitals. Per institutional guidelines, all patients gave informed consent. None of the patients were paid for participating in the study.

The Edinburgh Inventory (Oldfield, 1971) was used to asses hand preference and the Functional Independence Measure (FIM, Keith et al., 1987; German version: Frommelt & de Langen, 1995; de Langen et al., 1995) to assess disability. Demographic and clinical data of two groups are presented in Table 4.1.

Table 4.1. Demographic and clinical data of TBI patients and orthopedic controls

	TBI	OC
Sex (male / female)	21 / 6	21 / 6
Age (M, SD)	40.6 (14.5)	42.7 (13.7)
Years of education (M, SD)	10.6 (1.5)	10.6 (1.6)
Handedness premorbid (r / l / bi[1)]	27 / 0 / 0	27 / 0 / 0
Handedness now: (r / l / bi)	27 / 0 / 0	
Functional Independence Measure[2]	120.9 (4.1)	
Unconsciousness: none / less than a day / more than a day	9 / 5 / 13	
Weeks since onset of lesion (Median, Range)	8, 3-696	

[1] r = right, l = left, bi = bilateral

[2] a higher value means higher functional independence

Background neuropsychological assessment

see general methods section

Response inhibition - the stop signal task

see general methods section

Statistical analysis

The statistical package used was the SAS-Program, Windows Version 6.03 (SAS Institute Inc., 1988). All data were screened for deviation from normality, outliers and homogeneity of variance, and assumptions for statistical analysis were proved according to the recommendations of Tabachnick and Fidell (1996). Group differences were evaluated using T-tests. Effect sizes were calculated according to Cohen (1988). Where appropriate, correlations were

estimated with Pearson product moment correlations and Spearman rank correlations.

4.4 Results

Results of the neuropsychological assessment

There were no outliers and data were sufficiently normal distributed. Details of the results of the background neuropsychological assessment are given in Table 4.2.

Table 4.2. Neuropsychological data of TBI patients and orthopedic controls

	TBI	OC
	M (SD) N	M (SD) N
Intellectual functioning (LPS, T-score)	49 (7) 25	58 (6) 26
AVLT – total learning (total score)	45 (14) 27	55 (10) 24
Digit span (total score)	15.2 (4) 26	15.1 (3.5) 27
MCST: % perseverative errors of all errors	15 (18) 24	10 (13) 25

T-tests showed that the TBI performed significantly worse than the OC in intellectual functioning ($T(49)=4.6$, $p>0.0001$) and total learning in the AVLT ($T(49)=3.08$, $p=0.003$). There were no significant differences in the total score of the digit span test ($T(51)=0.08$, $p=0.94$) and the percentage of perseverative errors in the MCST ($T(47)=1.18$, $p=0.24$).

Performance in the stop signal task

In each group one participant was deleted from analysis of the stop signal task, because of outliers (one participant in the TBI had outliers in three variables: RT in the exercise block, SSRT and error %, one participant in the OC had one outlier in error %). Therefore, results of the stop signal task are presented for the remaining 26 participants of each group. Results of the stop signal task are presented in Table 4.3.

Table 4.3. Results of the stop signal task

	TBI M (SD)	OC M (SD)
Exercise block without stop signal		
Reaction times	534 (88)	504 (65)
Experimental blocks		
RTs, trials without stop signal	753 (216)	729 (236)
Signal respond RTs	674 (188)	647 (205)
Errors %	0.6 (0.6)	0.7 (0.7)
Probability of responding	48.1 (2.3)	47.7 (2.7)
SSRT	238 (45)	232 (39)

The probability of responding did not differ between the groups (T(50)=0.58, p=0.56), which shows that the staircase tracking algorithm was successfully applied to equalize response rates between groups. This is a necessary prerequisite for the interpretation of results. Furthermore, error rates did also not differ between groups (T(50)=-0.17, p=0.86). Contrary to our hypothesis there were no significant differences in the SSRTs (T(50)=0.53, p=0.6, effect size 0.14). There were also no significant differences in the primary task RT in the exercise block (T(50)=1.41, p=0.16, effect size 0.39) as well as in the experimental blocks in the trials without (T(50)=0.39, p=0.7) and with stop signal (T(50)=0.51, p=0.61).

Differences in exercise block and experimental block of the stop signal task

As can be seen in Table 4.3, primary task reaction times were longer in the experimental blocks than in the exercise block. A 2 (GROUP: TBI, OC) x 2 (BLOCK: reaction times in the exercise block, reaction times in the experimental block) ANOVA revealed a significant main effect for BLOCK (F(1,50)=61.67, p=0.0001) but no significant interaction of GROUP x BLOCK (F(1,50)=0.01, p=0.92). Thus, there was a strong tendency for both groups to have longer reaction times in the experimental blocks, but there was no indication, that any

group behaved different in this respect. Because of the effect of longer RTs in the experimental blocks, RTs in the exercise block will be interpreted as an indicator of the general speed of responding.

Inhibition and clinical characteristics, demographic characteristics and neuropsychological data

In TBI participants, SSRT showed no relationship to functional independence in the FIM (r=-0.04). Spearman rank correlations between SSRT and days of unconsciousness (r=0.26) and time since lesion (r=0.07) were also both low and not significant.

Years of education did not show a significant relationship to SSRT in either group (TBI: r= -0.24, OC: -0.1). Age correlated significant in the TBI with SSRT (r=0.39, $p < 0.05$), but not in the OC (r=-0.05). However, those correlations were not significantly different from each other (Fisher's Z-Test: z=1.567, p=0.12).

The correlations of SSRT with the background neuropsychological variables can be seen in Table 4.4. None of those correlations was significant.

Table 4.4. Correlations of SSRT and background neuropsychology

	Intellectual functioning (LPS, T-value)	AVLT – total learning (total score)	Digit span (total score)	MCST: % perseverative errors of all errors
TBI	-0.23	-0.28	-0.36[a]	-0.07
OC	-0.08	-0.06	-0.17	0.04

Note. [a] p=0.07

4.5 Discussion

The present study found no evidence of a deficit in the inhibition of ongoing responses in patients with TBI in comparison to orthopedic controls. This result does not seem to be due to insufficient power, because the sample size was reasonably large and the effect size between the TBI and OC for SSRT was 0.14, which it quite small. In addition, clinical characteristics of the TBI and background neuropsychological variables did not show any significant

relationship to the ability to inhibit reactions. Of the demographic variables, only age showed a significant relationship to SSRT, and this only in the TBI. However, correlations of TBI and OC did not differ significantly from each other. Both groups of participants showed a tendency to wait in the experimental blocks.

The failure to detect inhibitory deficits

One might argue, that patients were not impaired enough, and therefore the failure to detect deficits in response inhibition might be due to this. However, half of our TBI (N=13) was reportedly unconscious for at least 24 hours, and can therefore be considered to have suffered severe head injuries. Furthermore, TBI patients showed significant impairment in intellectual functioning and memory.

In addition to no difference in inhibitory efficiency between the two groups, there was also no significant difference in the RTs in the exercise block between the groups, although overall general slowing is one of the most consistently reported effects of TBI. However, the RT difference had an effect size of 0.39 in our study. Other authors have also reported that the effect of general slowing frequently does not reach significance (Stuss et al., 1989). It might be, that our selection of the control group was conservative, since we employed orthopedic controls and not healthy participants. However, this approach seems appropriate, since it corrects for general effects of being ill, having to stay in hospitals and taking various medications.

Impaired executive functions after TBI are not always demonstrated (e.g. Ponsford & Kinsella, 1992; Veltman et al., 1996). Our study adds to this and indicates, that one specific executive function, the inhibition of ongoing responses, seems to be preserved in the majority of TBI patients. In fact, only three of 27 participants the TBI had an SSRT below two standard deviations of the OC (11%, including the outlier).

The results of our study seem to be in line with the results of Robertson et al. (1997). Robertson et al. (1997) investigated patients with TBI with the sustained attention to response task (SART). This task involves the withholding

of key presses to rare (1 in 9) targets. They presented empirical evidence that the SART is sensitive to sustained attention and not an impaired ability to inhibit a response, although it consists of a go nogo task. In their view errors were not seen as failures in withholding a response but as the consequence of a failure in maintaining an optimum approach to the task over time. It could be, that we obtained no deficits in response inhibition because the stop signal task made it possible to maintain an optimal task approach over time, even though it took participants approximately 45 minutes to complete the task. The acoustic stop signal might have served as an alerting element. It could also be, that in the study of Braun et al. (1989), who found that commission errors in go nogo tasks were particularly sensitive in discriminating head injured patients from controls, those errors were more indicative of a nonoptimum task approach, rather than inhibitory difficulties.

Executive impairment in the TBI patients

Unexpected was the fact, that the perseverative errors of the MCST did not differentiate between the TBI and OC patients. This negative result might be due to three different reasons: a) the MCST is not a sensitive measure in patients with TBI, b) the controls performed worse than expected, and c) our patients did not have executive deficits.

The effect size for the difference between controls and TBI patients in our study was 0.32, which is small. To our knowledge no studies have investigated the sensitivity of the MCST in patients with TBI. Some studies, however, found significant differences between patients with TBI and controls in the Wisconsin Card Sorting Test (Cockburn, 1995; Axelrod et al., 1994). Of course, although the use of the MCST is frequently advocated as an alternative to the WCST and measures are thought to be comparable (e.g**.** Greve & Smith, 1991), there is evidence that the equivalence of the two tests is doubtful (e.g. de Zubicaray & Ashton, 1996). However, the score we used, the percentage of perseverative errors, is one in which both tests seem to be comparable (van Gorp et al., 1997). Thus, it could have been expected, that patients with TBI perform worse than controls in the MCST.

Looking at the values of our patients, it seems that our control group did not perform worse than control participants in other studies (see de Zubicaray & Ashton, 1996 for control group data of several studies using the MCST). It seems thus likely, that our patients have less executive deficits than patients in some other studies. It cannot be ruled out, that our effects for SSRT would have been greater in a patient sample with more executive deficits. However, selectively including patients who show executive disturbance in studies produces a bias, and this is not the case in our study; our patient sample represents TBI patients selected irrespective of behavioral disturbances. Furthermore, SSRT and MSCT performance did not show a significant relationship with each other, which is in accordance with other studies showing no or only low correlations between executive function tests (Duncan, 1997). Duncan (1997) found that the median correlation between several measures of "perseveration" was 0.1, and the median correlation between measures of "disinhibition" was –0.01 in patients with TBI. Thus, even if we had had patients who show executive impairment in the MCST, it remains doubtful that they would also have shown impairment in SSRT.

The relationship of clinical and demographic characteristics and inhibitory efficiency

Inhibitory efficiency showed no relationship to clinical measures of the TBI. This is in accordance with other studies, who demonstrate that traditional severity measures are probably not very valid and interesting or useful for functional evaluation (Braun et al., 1989).

Age correlated significant with SSRT in the TBI, but not in the OC, those correlations were, however, not significantly different from each other. Our results for the OC is in accordance with a study of Williams et al. (1999) who found only limited evidence of slowing of the SSRT across adulthood, young adults were in their study approximately 20 ms faster than the oldest group (over 60 years). Some investigators proposed that older people are more affected by head injury than younger people, because they may have less available reserves to cope with the insult (Stablum et al., 1996). This might be

the reason for the correlation of age with SSRT in the TBI group. However, the issue of the effects of TBI and age on SSRT cannot be clearly resolved in this study, further investigations would be necessary.

The tendency to wait in the experimental block

Primary task reaction times in the experimental blocks were significantly longer than in the exercise block for all groups. Longer reaction times in the experimental blocks could be due to two reasons: (a) effects of fatigue and (b) a tendency to wait for stop signals in spite of instructions. It cannot be ruled out, that fatigue has some influence on this effect. However, this effect should be much less pronounced than the obtained prolongation of RTs. An interpretation of the data as a tendency to wait is in accordance with other studies (Logan, 1981; McGarry & Franks, 1997), although the prolongation of RTs was less pronounced in those studies. This might be due to the fact, that it is much easier to persuade students not to employ any waiting strategy than patients.

However, the tendency to wait has no implication for the validity of our results. The interaction between group and strategy was not significant, which indicates, that the tendency to prolong RTs was independent of group membership. This tendency is also unlikely to influence SSRT, since the tracking procedure is able to compensate for group as well as individual differences in primary task RT (Band, 1997). Furthermore, the probability of responding was not different between the groups and close to 50%. If there is any systematic error, both groups should be equally affected.

Conclusion

The present study found no evidence of difficulties in inhibiting ongoing responses in patients with TBI. It seems likely, that difficulties in the complete suppression of responses is not a very common deficit after TBI.

5. Study 3: Inhibitory aftereffects in the stop-signal paradigm

5.1 Summary

The inhibition of responses to interfering stimuli in a trial results in longer reaction times in the following trial in which to-be-ignored stimuli become targets. This is due to the fact that the residual inhibition of the distractor must be overcome before the now relevant response can be produced. Such negative priming effects are well-known inhibitory aftereffects and the focus of intensive research. However, it seems reasonable to assume that the use of inhibitory processes leaves measurable aftereffects in a variety of other tasks and situations. Therefore, the aim of the present study was to investigate whether the aftereffects of inhibition could be obtained in a task measuring motor inhibition (i.e., the stop signal task). Our results indicate that inhibitory aftereffects were present in the stop signal task whether or not participants were successful in inhibiting their reactions. They were greater after unsuccessful than after successful inhibition. Moreover, inhibitory aftereffects were greater when both trials consisted of the same primary task properties. Strategic effects might explain part of the results, but there is evidence that a specific inhibition of either the stimulus, or the response to that stimulus, or both plays a role in the constitution of the aftereffects.

5.2 Introduction

In many psychological tasks performance in one trial is influenced by the properties of the preceding trial or trials. This has been reported for simple two choice reaction time tasks (Green et al., 1983; Kirby, 1980; Kornblum, 1973; Laming, 1968; Remington, 1969; Soetens et al., 1984; Soetens et al., 1985) and for reaction times (RTs) following errors (Laming 1979; Rabbitt, 1966a; Rabbitt 1966b; Rabbitt & Rogers, 1977). Trial order effects can be inhibitory or facilitatory (Soetens et al., 1984).

A special case of trial order effects occurs in tasks where stimuli interfere with each other (Eriksen & Eriksen, 1974; Tipper, 1985; Houghton & Tipper, 1996; Neill et al., 1995). Inhibition of interfering stimuli results in longer reaction

times (RTs) in the next trial when to-be-ignored stimuli become targets. This is due to the fact that the residual inhibition of the distractor must be overcome before the now relevant response can be produced (e.g., Tipper, 1985; Houghton & Tipper, 1996; Neill et al. 1995). Such negative priming effects are well-known inhibitory aftereffects (Logan, 1994) and the focus of intensive research. Although the exact relationship between the primary task interference and the negative priming effect is still unresolved, in general, variables that increase interference also increase negative priming (Neill et al., 1995).

It seems reasonable to assume that the use of inhibitory processes leaves measurable aftereffects in other tasks, where trial-to trial effects are not usually the focus of research. The procedure to calculate negative priming effects has already been applied with positive results to some tasks which were not originally designed to measure them, for example the stroop task (e.g. Neill, 1978; Lowe, 1979; see MacLeod, 1991 for a review) and the flanker task (e.g. Neill & Valdes, 1995). Inhibition in these tasks is usually referred to as 'cognitive inhibition' (Harnishfeger, 1995).

The aim of the present study was to investigate whether or not aftereffects of inhibition could also be obtained in a task measuring motor or behavioral inhibition (Dempster, 1993; Harnishfeger, 1995). Therefore, it seemed appropriate to use the stop signal task (Lappin & Eriksen, 1966; Logan & Cowan, 1984; Logan et al., 1984; Osman et al., 1986). In this task inhibition of simple motor reactions takes place in stop signal trials and is measured by the stop signal reaction time, i.e. the time it takes to inhibit a reaction.

It seemed reasonable to assume that behavioral inhibition, like cognitive inhibition, has effects that last longer than the immediate effect of being successful or not. The question arises, whether or not inhibiting or trying to inhibit reactions on one trial leaves an aftereffect in the next trial. Kramer et al. (1992, cited by Logan, 1994) found that go signal RTs were slower on trials following successful inhibition than on control trials. They compared young and old adults and found that this effect was stronger for older participants than for younger ones (50 ms vs. 21 ms, respectively). Apart from this report, there are no further studies investigating inhibitory aftereffects in the stop signal task.

Therefore, the aim of our study was to replicate the results of Kramer et al. (1992, cited by Logan 1994). In addition we asked whether an inhibitory aftereffect is also observable when inhibition is not successful in the first trial. Furthermore, we wanted to see if the degree of similarity between the properties of trial n and trial n-1 (i.e., the primary task symbols and the corresponding response) has any influence on the size of inhibitory aftereffects. We assumed, that an inhibitory aftereffect would always be observable after a stop-signal occurred, and that this effect would be more pronounced when the properties of the trial n were the same as those of trial n-1. This would reflect the results obtained with negative priming tasks: not all responses are slowed, only those that bear a specific distractor-to-target relationship (Tipper, 1985; Houghton & Tipper, 1996; Neill et al., 1995; May et. al., 1995).

5.3 Methods

Participants

Participants were 37 undergraduate students (24 female, 13 male), receiving course credit for participating. Three of the participants (2 female, 1 male) were excluded from analysis because contrary to instructions, they started waiting for the stop signal, which resulted in mean RTs over 1000 ms and late stop signals. The remaining 34 participants had a mean age of 24 years (minimum 20, maximum 35 years).

The stop signal task

see general methods section

Data analysis

Data were analyzed with the SAS-Program, Windows Version 6.03 (SAS Institute Inc., 1988). To evaluate whether our results were comparable to the findings reported in the literature we estimated SSRT with the following procedure: the RTs of the no-signal trials were rank ordered, and the nth reaction time was determined, where n is the number of no signal trials multiplied by the probability of responding when a stop signal occurred at a given delay. The nth reaction time estimates the time at which the stopping process finished, relative to the onset of the go signal. An estimate of the SSRT was obtained by subtracting the stop signal delay. This procedure was repeated for each delay. The SSRTs of the four delays were averaged to calculate the average SSRT (Logan & Cowan, 1984; Logan, 1994). In addition we calculated the probability of responding, the error rate and the choice reaction time (CRT). The latter was done by using trials from the first exercise block. The 20 trials at the beginning of the block were dropped, thus 40 trials remained for this analysis.

In analyzing our results we first calculated the RTs of no signal trials, depending upon the properties of trial n-1. Trials n-1 were classified as follows: (a) no signal trials, (b) stop signal trials with successful inhibition and (c) stop signal trials without successful inhibition. The factor ‘properties of trial n-1’ was called EVENT.

As a further step, these RTs were further split into trials where trial n and trial n-1 consisted of the same primary task stimulus and trials where trial n and trial n-1 consisted of different primary task stimuli. This factor was called SYMBOL.

5.4 Results

The probability of responding to the stop signal was 39.8% (SD=6), the error rate was 2.3%, and the SSRT was 239 ms (SD=28). The CRT in the exercise block (M=485, SD=48) was significantly faster than the CRT in the experimental block (no-signal RTs) ($T=3.12$, $p<0.004$), as calculated by a T-test for dependent samples. Results closely resemble those reported in other studies (e.g. Logan, 1981; Logan et al., 1984; Logan & Cowan, 1984; De Jong et al., 1995).

In the next step we evaluated whether there were any differences in trials following successful or unsuccessful inhibition compared to control trials. Table 5.1 presents the RTs of no signal trials, depending upon the properties of trial n-1.

Table 5.1 Reaction times of no signal trials for correct responses only, depending upon the properties of trial n-1 for all trials

	RT in ms	Number of trials per participant
Trial n-1	M (SD)	M (SD)
no signal	507 (57)	281 (19)
stop-signal, successful inhibition	536 (72)	60 (8)
stop-signal, no inhibition	550 (79)	38 (6)

A repeated-measures analysis of variance revealed a significant effect of EVENT ($F(2,66)=31.7$, $p<0.0001$). Contrasts between the first (no signal in trial n-1) and the second (successful inhibition in trial n-1) condition ($F(1,33)=42.8$, $p<0.0001$, M=29 ms, SD=26 ms, effect size for dependent samples=1.2) and between the first and the third (no inhibition in trial n-1) condition ($F(1,33)=51.72$, $p<0.0001$, M=43 ms, SD=35 ms, effect size for dependent samples=1.2) were both significant. Also the contrast between the two

conditions where trial n-1 was a stop signal was significant ($F(1,33)=5.78$, $p<0.02$, $M=14.5$ ms, $SD=35$ ms, effect size for dependent samples=0.4). These results confirm that it took participants longer to respond in trials following a stop signal whether or not inhibition was successful, than on control trials. Furthermore reactions were significantly longer after unsuccessful than after successful inhibition.

As a further step, trial couples were separated into those where the primary task consisted of the same symbol in both trials and those where the symbols were different. Table 5.2 presents the RTs of no signal trials, depending upon the properties of trial n-1 and separated for same and different symbols in both trials.

Table 5.2 Reaction times of no signal trials for correct responses only, depending upon the properties of trial n-1 for trials with same symbols and for trials with different symbols.

	RT in ms	Number of trials per participant
Trial n-1	M (SD)	M (SD)
same symbols		
no signal	506 (53)	143 (11)
stop-signal, successful inhibition	541 (71)	29 (4)
stop-signal, no inhibition	559 (87)	19 (3)
different symbols		
no signal	507 (64)	138 (8)
stop-signal, successful inhibition	530 (76)	31 (5)
stop-signal, no inhibition	536 (70)	19 (4)

A repeated measures analysis of variance again revealed a significant effect of EVENT ($F(2,66)=27.95$, $p<0.0001$), as well as a significant effect of SYMBOLS ($F(1,33)=8.46$, $p<0.006$). The interaction between these two factors was also significant ($F(2,66)=5.18$, $p<0.008$), indicating that it took participants longer to respond on trials when trial n-1 was a stop-signal trial with the same primary task properties than when trial n-1 was a stop-trial with different primary task properties, but that there was no such effect in trials which were not preceded by a stop signal (see Figure 5.1).

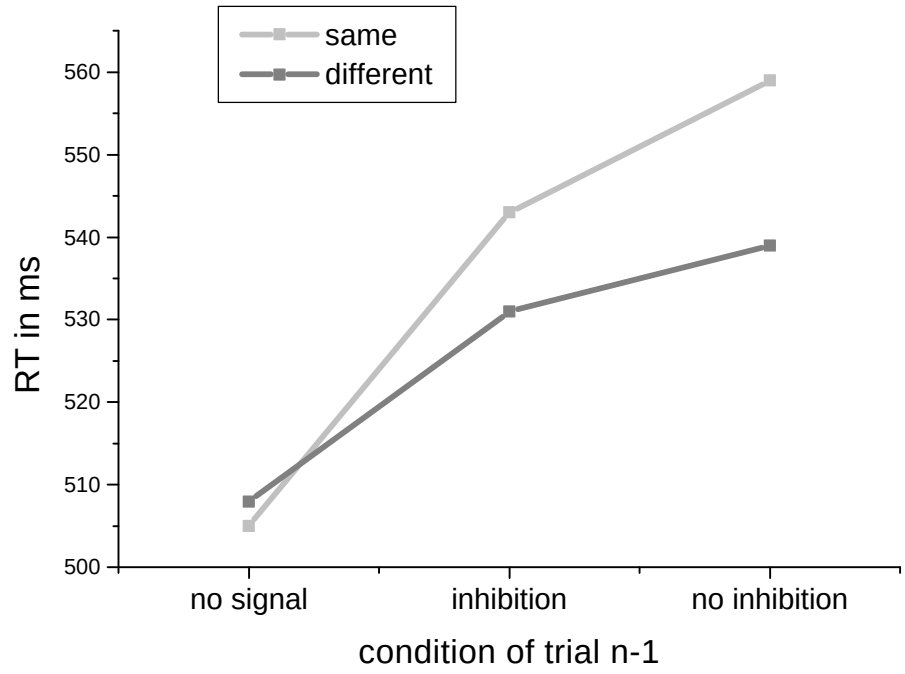

Figure 5.1 Reaction times of no signal trials for correct responses only, depending upon the properties of trial n-1 for trials with same symbols and for trials with different symbols.

5.5 Discussion

Our results provide evidence that inhibitory aftereffects occur after motor inhibition in the stop signal task. Inhibitory aftereffects in this task occur whether or not the participant is successful in inhibiting the reaction in the previous trial. We obtained a 29 ms difference between trials following successful inhibition and control trials, which is similar to the 21 ms obtained by Kramer et al. (1992, cited by Logan, 1994). There was also a significant difference between trials following successful and unsuccessful inhibition, it took participants longer to respond in the latter case. Furthermore, our results show that inhibitory aftereffects were greater when both trials consisted of the same primary task properties and when inhibition was not successful.

The aftereffects cannot be explained by the horse-race model, because the model only explains performance on a single trial, without reference to the serial position of that trial. The model treats the trials as independent from each other. Several mechanisms might be responsible for the obtained aftereffects, which we can only speculate about at this point.

Strategic effects

CRT was significantly longer during the experimental blocks where the stop signal was presented than in the exercise block with the choice task alone. This effect is in accordance with results from other studies (Logan, 1981; McGarry & Franks, 1997). One could argue that participants increase their decision criterion after a stop signal occurs in terms of a variable criterion model (Grice et al., 1982; Jacobs, 1993) and thus deliberately prolong their reaction. Although participants were explicitly told not to start waiting for stop-signals and although the probability of a stop-signal occurring was always ¼, such strategic criterion-shift effects cannot be ruled out with the current design.

The effect that unsuccessful inhibition resulted in longer aftereffects fits well into a strategic account, since it seems more logical to change strategies in unsuccessful trials than in successful. However, another explanation seems also plausible here: it might be that a failure in inhibiting the response is equivalent to making an error for the participants. It is known that reaction

times following errors are slower than reactions following correct responses (Laming, 1979; Rabbitt & Rogers, 1977), and thus this effect may account for the difference between successful and unsuccessful inhibition.

It can be ruled out that strategic effects account for the whole pattern of results. The influence of same and different symbols in both trials warrants another explanation. We assume that a response strategy such as deliberately prolonging responses needs some time to build up and that participants might use the intertrial interval for this process. However, they have no way of predicting which trial will be the next, so the way they set their response criterion at this stage will equally influence all following trials. Thus, strategic effects might only account for a general slowing after stop signal trials but not for this specific effect.

Specific mechanisms

It seems more likely that some specific mechanism, perhaps similar to the mechanisms responsible for negative priming is in operation here. Unfortunately, until now, no single mechanism has been able to explain the negative priming effect. Different mechanisms seem to work together and depend on the experimental context (for an overview see May et al., 1995; Neill et al., 1995; Neill & Valdes, 1995; Tipper & Milliken, 1995). There are two main ways to explain the negative priming effect, which can also be applied to the aftereffects of motor inhibition: one inhibitory and one mnestic (May et al., 1995).

The inhibition model (Neill, 1977; Tipper, 1985) assumes that something is inhibited on the prime trial, or shortly thereafter, and that this inhibition carries over to affect processing on the probe trial. One version of the inhibition model can be regarded as the cognitive blocking hypothesis (Tipper & Cranston, 1985). The authors posit that if detected, a familiar distractor stimulus activates its internal memory representations. An inhibitory mechanism then functions to decouple the activated representation of distractors from response output. Inhibition on the prime trial impedes responding on the next. Thus, inhibition operates in a forward direction. Applied to the stop signal paradigm, the

inhibition that has built up in stop signal trials would decouple the representation of the stimulus from the response output and thus result in a delayed response on the subsequent trial. In addition to the cognitive blocking hypothesis there are several other views about the exact locus of inhibition in the negative priming task (Neill et al., 1995): One deals with the inhibition / suppression of response (e.g. Dalrymple-Alford & Budayr, 1966; see however Tipper et al., 1988), another with the inhibition of irrelevant cognitive representations (e.g. Neill, 1979; but see Lowe, 1979).

An alternative explanation to inhibitory accounts is the episodic retrieval theory (Neill & Valdes, 1992), based on Logan's (1988) instance theory of automatization. According to this view, the presentation of a stimulus automatically evokes the most recent episode involving that stimulus. The retrieved episode contains information (or tags) about the stimulus, including the response or nonresponse that was associated with it. However, this theory only seems to account for some instances of negative priming and fails to account for others (May et al., 1995). For example, it cannot explain instances where negative priming reverses to positive priming (e.g. Lowe, 1979; Neill, 1979; Neill & Westberry, 1987; Neumann & De-Schepper, 1991). Furthermore, episodic retrieval theory predicts that participants should be impeded in making a response in a target-to-distractor condition. However, participants typically show facilitation in this condition (Kane et al., 1994; Neill, 1978). Applied to the stop signal paradigm, the theory would account for the obtained aftereffects in the following way: If, in one trial, a square appears as the primary task symbol and then a stop signal occurs, this episode is encoded in memory. If the next trial consists again of a square, a 'do-not-respond' tag is automatically retrieved. This tag necessarily conflicts with the current response requirement.

We do not know enough about the aftereffects of motor inhibition to decide between inhibition-based accounts or episodic retrieval accounts. However, the task requires that inhibition of the response takes place in the first trial. To adopt an episodic retrieval account one would have to argue that this inhibition does not last, but instead leaves a trace in memory, which is then reactivated in the next trial.

Future studies should evaluate the exact nature of the aftereffect of motor inhibition and conditions and contexts that influence them. For example, studies with different stimulus response mappings (e.g. 2:1) will allow us to differentiate between different hypothesis concerning the effect of the properties of trial n-1. Varying the intertrial intervals will make it possible to evaluate strategic effects. It could be argued that a strategy needs some time to build up, whereas a true inhibitory effect should decrease with time.

Conclusion

Our study provides evidence that the inhibition of reactions leaves measurable inhibitory aftereffects. It does not seem likely that the pattern of results can be explained solely by strategic effects. Instead we assume that specific mechanisms are at work here, which might resemble mechanisms explaining the negative priming effect. Clearly, further studies are necessary to describe and explain the phenomenon.

6. An explorative analysis of inhibitory aftereffects in brain-damaged patients

6.1 Summary

For the current investigation data of studies 1 and 2 were analyzed in respect to inhibitory aftereffects. Inhibitory aftereffects were obtained after successful as well as after unsuccessful inhibition, this was the case in all groups. Aftereffects were, however, not significantly larger after successful than after unsuccessful inhibition. Furthermore, aftereffects were also not significantly larger when both trials consisted of the same symbol than when they consisted of different symbols. There were also no differences in regard to the aftereffects between the patients and controls. Results of this analysis must, however, remain inconclusive, since specific effects might have been obscured by the tendency of participants to wait in the experimental blocks during the performance of the stop signal task.

6.2 Introduction

The results of study 3 provide evidence that inhibitory aftereffects occur after inhibition trials in the stop signal task. Inhibitory aftereffects occurred when the participant was successful inhibiting the reaction as well as when the participant was not successful inhibiting the reaction on the previous trial. There was a significant difference between trials following successful and unsuccessful inhibition, indicating that it took participants longer to respond after unsuccessful inhibition. Furthermore, our results showed that inhibitory aftereffects were greater when both trials consisted of the same primary task properties. Strategic effects might explain part of the results, e.g. participants might adopt a more conservative response criterion after a stop signal, especially after unsuccessful inhibition. An alternative explanation might be that unsuccessful inhibition is perceived as an error by participants and some form of post-error slowing takes place. There was, however, evidence, that a specific form inhibition of either the stimulus, or the response to that stimulus, or both plays a

role in the constitution of the aftereffects, possibly comparable to the negative priming effect.

The aim of this analysis was to reanalyze the data of study 1 and study 2 to see, whether we could also find inhibitory aftereffects. We want to emphasize here, that any results obtained in this analysis have to be regarded with extreme caution. This is due to mainly two reasons. First, participants started to prolong their RTs during the experimental blocks. This however poses a serious problem for the analysis of inhibitory aftereffects. Especially in conditions, for which only few RT measurements are available, these might not be very reliable. Furthermore, this gross strategic behavior might cover more subtle effects that consist of a few milliseconds. Therefore, any results of this analysis should be regarded rather as a help for hypothesis generation for future studies, than as definitive research results. Second, the study design was planned for the investigation of SSRT and not for the study of inhibitory aftereffects.

6.3 Method

Data from studies 1 and 2 were used for analysis of inhibitory aftereffects. Data were analyzed with the SAS-Program, Windows Version 6.03 (SAS Institute Inc., 1988). To answer the questions of the analysis, the RTs of no signal trials were calculated, depending upon the properties of trial n-1. Trials n-1 were classified as follows: (a) no signal trials, (b) stop signal trials, successful inhibition, and (c) stop signal trials, unsuccessful inhibition. The factor ‘properties of trial n-1’ was called STOP. These RTs were further split into trials where trial n and trial n-1 consisted of the same primary task stimulus (repetitions) and trials where trial n and trial n-1 consisted of different primary task stimuli (alternations). This factor was called SYMBOL. Means and standard deviations of RTs for the groups were calculated from the median RTs of the individual participants. RTs were subjected to analysis of variance, for study 1 this was done in a 4 (GROUP) x 3 (STOP) x 2 (SYMBOL) design, for study 2 this was done in a 2 (GROUP) x 3 (STOP) x 2 (SYMBOL) design.

6.4 Results

Patients with focal lesions

The upper part of Table 6.1 presents the reaction times of trial order effects for the different conditions for all groups.

Table 6.1. Reaction times of no signal trials for correct responses only, depending upon the properties of trial n-1, once separately for same and different symbols and once irrespective of symbols, for patients with focal lesions and their orthopedic controls

		FG	NFG	BG	OG
		N=16	N=20	N=8	N=18
	Number of trials per Participant	RT in ms	RT in ms	RT in ms	RT in ms
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
same symbols					
same, no signal	107 (6)	830 (275)	739 (191)	786 (183)	635 (165)
stop-signal, successful inhibition	18 (2)	907 (342)	803 (190)	844 (171)	681 (169)
stop-signal, no inhibition	17 (2)	871 (266)	799 (167)	891 (207)	675 (157)
different symbols					
different, no signal	106 (6)	860 (270)	759 (189)	777 (161)	653 (155)
stop-signal, successful inhibition	20 (2)	934 (331)	790 (220)	808 (192)	660 (175)
stop-signal, no inhibition	17 (3)	894 (273)	808 (205)	869 (242)	679 (135)
all trials					
no signal	213 (12)	843 (268)	749 (187)	786 (174)	645 (160)
stop-signal, successful inhibition	38 (3)	909 (320)	793 (199)	824 (177)	671 (166)
stop-signal, no inhibition	34 (4)	877 (249)	801 (189)	879 (215)	675 (144)

Note. The number of trials does not amount to the total number of trials, since there were ¼ of stop-signal trials followed by another stop signal and stop signal trials at the end of blocks.

A 4 x 3 x 2 analysis of variance with one between participant factor (GROUP: FG, NFG, BG, OG) and two within participant factors (STOP: no signal in trial n-1, stop signal with successful inhibition in trial n-1, stop signal with unsuccessful inhibition in trial n-1; SYMBOL: same symbol in both trials, different symbols in both trials) was conducted. There was a significant main effect for group

(F(3,58)=3.3, p=0.03), Tukey tests revealed that this effect reflects the longer RTs of the FG in comparison to the OG in all conditions. The effect of SYMBOL was not significant (F(1,58)=0.15, p=0.7), but the effect of STOP (F(2,116)=17.62, p=0.0001) was. Of the two-way interactions GROUP x SYMBOL was not significant (F(3,58)=1.82, p=0.15) and also not the interaction SYMBOL x STOP (F(2,116)=1.98, p=0.14), but the interaction GROUP x STOP showed a tendency (F(6,116)=1.86, p=0.09). The three way interaction of GROUP x SYMBOL x STOP was not significant (F(6,116)=0.27, p=0.95).

To evaluate the STOP-effect and the tendency for an interaction of STOP x GROUP, we looked at the contrasts between the STOP conditions. The RTs for those conditions, regardless of the SYMBOL-effect can be seen in the lower part of Table 6.1 and in Figure 6.1. The contrast between no signal in trial n-1 and stop signal, successful inhibition in trial n-1 was significant (F(1,58)=20.41, p=0.0001, but showed no GROUP-effect (F(3,58)=1.1, p=0.36), and so was the contrast between no signal in trial n-1 and stop signal unsuccessful inhibition (F(1,58)=36.3, p=0.0001), which also showed no group effect (F(3,58)=1.9, p=0.14), thus indicating that inhibitory aftereffects were obtained after successful as well as after unsuccessful inhibition. The contrast between successful and unsuccessful inhibition was not significant (F(1,58)=0.48, p=0.49), but here the GROUP effect showed a tendency (F3,58)=2.61, p=0.06). A Tukey test for the difference between successful and unsuccessful inhibition for the four groups revealed a tendency for the BG vs. the FG (p=0.06). However, there was no significant difference or tendency between any of the focal lesion groups in comparison to orthopedic controls.

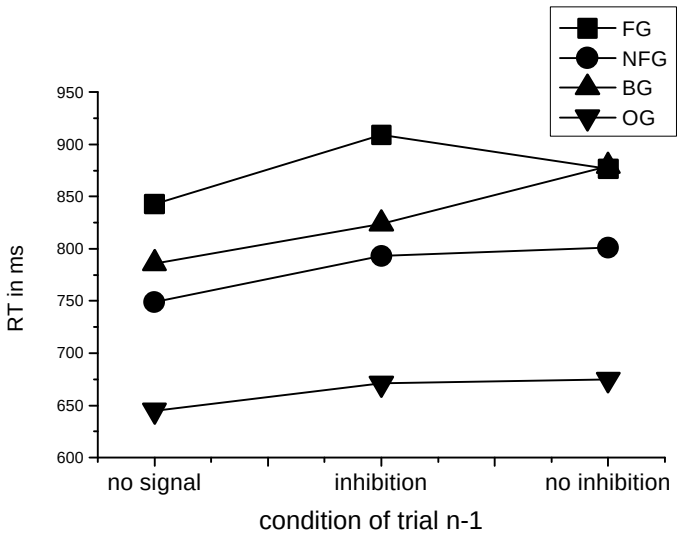

Figure 6.1. RTs after no signal trials and after trials with successful or unsuccessful inhibition, irrespective of the symbol in trial n-1 for patients with focal lesions and their orthopedic controls

Patients with TBI

The upper part of Table 6.2 presents the reaction times for the different conditions for the two groups.

Table 6.2. Reaction times of no signal trials for correct responses only, depending upon the properties of trial n-1, once separately for same and different symbols and once irrespective of symbols for TBI patients and orthopedic controls

		TBI N=26	OC N=26
	Number of trials per participant M (SD)	RT in ms M (SD)	RT in ms M (SD)
same symbols			
same, no signal	109 (8)	740 (222)	717 (243)
stop-signal, successful inhibition	19 (3)	785 (217)	737 (222)
stop-signal, no inhibition	17 (2)	793 (223)	755 (247)
different symbols			
different, no signal	107 (7)	749 (204)	711 (237)
stop-signal, successful inhibition	20 (3)	778 (244)	743 (272)
stop-signal, no inhibition	18 (3)	787 (225)	747 (251)
all trials			
no signal	215 (15)	743 (211)	714 (238)
stop-signal, successful inhibition	38 (3)	783 (229)	735 (233)
stop-signal, no inhibition	34 (3)	786 (221)	743 (243)

Note. The number of trials does not amount to the total number of trials, since there were ¼ of stop-signal trials followed by another stop signal and stop signal trials at the end of blocks.

A 2 x 3 x 2 analysis of variance with one between factor (GROUP: TBI, OC) and two within factors (STOP: no signal in trial n-1, stop signal with successful inhibition in trial n-1, stop signal with unsuccessful inhibition in trial n-1; SYMBOL: same symbol in both trials, different symbols in both trials) was conducted. There was no significant main effect for group ($F(1,50)=0.34$, $p=0.56$). The effect of SYMBOL was also not significant ($F(1,50)=0.08$, $p=0.78$), but the effect of stop was ($F(2,100)=16.27$, $p=0.0001$). None of the

interactions were significant (GROUP x SYMBOL: F(1,50)=0.01, p=0.93; GROUP x STOP: F(2,100)=0.27, p=0.77; SYMBOL x STOP: F(2,100)=0.2, p=0.82; GROUP x SYMBOL x STOP: F(2,100)=0.48, p=0.62).

To evaluate the STOP-effect, we looked at the contrasts between the STOP conditions. The RTs for those conditions, regardless of the SYMBOL-effect can also be seen in the lower part of Table 6.2 and Figure 6.2. The contrast between no signal in trial n-1 and stop signal, successful inhibition in trial n-1 was significant (F(1,50)=16.19, p=0.0002), and so was the contrast between no signal in trial n-1 and stop signal unsuccessful inhibition in trial n-1 (F(1,50)=28.36, p=0.0001), thus showing that inhibitory aftereffects were obtained after successful as well as after unsuccessful inhibition. The contrast between successful and unsuccessful inhibition in trial n-1 was not significant (F(1,50)=2.02, p=0.16).

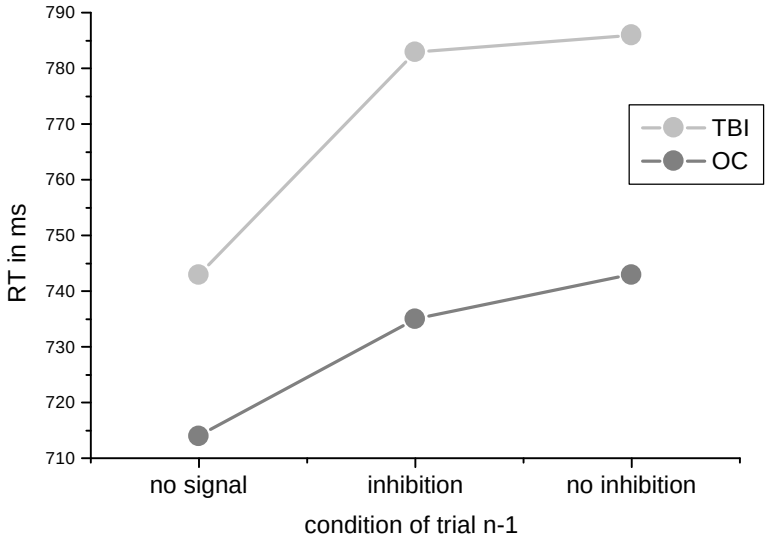

Figure 6.2. RTs after no signal trials and trials after successful or unsuccessful inhibition, irrespective of the symbol in trial n-1 for TBI patients and orthopedic controls

6.5 Discussion

The results of the analysis were basically the same for the study of patients with more focal lesions and for the study of patients with more diffuse lesions, therefore they will be discussed together. Inhibitory aftereffects were obtained after successful as well as after unsuccessful inhibition in all groups. These aftereffects were not significantly greater after unsuccessful than after successful inhibition. Furthermore, we found that aftereffects were not significantly greater when both trials consisted of the same symbol than when they consisted of different symbols. In addition, there was also no significant difference between any patient group and control participants.

Why did we not find any specific effects in the inhibitory aftereffects?

As already mentioned, participants started to prolong their RTs during the experimental blocks. This provides a serious methodological problem for the inhibitory aftereffects. It could be argued, that this general strategic behavior was so strong, that it superimposed any specific effects. Therefore, effects between successful and unsuccessful inhibition and effects between same and different symbols in both trials were diminished. There are, however, some further differences in comparison to our previous study in addition to the grossly strategic behavior, which have to be discussed.

The populations studied are different. However, since those negative results were not only obtained for brain-damaged patients, but also for orthopedic controls it seems unlikely that this factor contributes much to the negative results. Our selection of the controls is conservative, they presumably show more variance than healthy controls and show general effects of being ill and having to stay in hospitals and taking various medications. These factors should however not have so much influence to make general performance principles disappear.

Another difference to the previous study was the way the stop signal delay was set. In the student-study the delay was set with the MRT minus delay procedure, in the patient studies the staircase tracking algorithm was used. However, although it might be possible that inhibitory aftereffects vary with the

size of the delay, an issue which is not yet investigated, there is no obvious reason, why they should be influenced by the way the delay is set.

The behavior of participants differed in one further aspect: The RTs after no signal trials were on the average the same in the student study regardless whether those were trials followed by the same or different symbol. This was not the case in our patient groups. Furthermore, some of the groups seem to be more variable in this respect (see Table 6.3).

Table 6.3. RTs when trial n-1 was a no signal trial, having the same or the different symbol as trial n

	Students	FG	NFG	BG	OG	TBI	OC
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
RT same	506 (53)	830 (275)	739 (191)	786 (183)	635 (165)	740 (222)	717 (243)
RT different	507 (64)	860 (270)	759 (189)	777 (161)	653 (155)	749 (204)	711 (237)
Difference	-1 (23)	-30 (64)	-20 (50)	9 (40)	-18 (32)	-8 (50)	6 (29)

It seems that there exist differences between participants, whether they respond faster after same symbol or after different symbol trials. In studies of simple two choice reaction time both repetition (trial is the same as the preceding trial) and alternation (trial is different from the preceding trial) effects have been found (for a review see Luce, 1986). The magnitude and direction of the sequential effects depends upon the relative frequency with which signals are presented and upon the tendency for the signals to be repeated in the presentation schedule. Those factors were both 50:50 for each signal in our study. Another variable is the response stimulus interval (RSI) or the interstimulus interval (ITI) . Kirby (1980) states that repetition effects are usually found for RSIs of less than approximately half a second, and alternation effects with RSIs of greater than half a second. However, although studies are fairly consistent about repetition effects in short RSIs, the results concerning long RSIs are not unequivocal, some studies also find repetition effects at long RSIs (e.g. Laming, 1968, Bertelson & Renkin, 1966). In addition, Kirby (1976) was able to produce either repetition or alternation effects at long RSIs by instructing participants to attend to those. Two kinds of explanations have been offered for sequential

affects: automatic facilitation and subjective expectancy (e.g. Kirby, 1976; Soetens, 1998; for a review see Luce, 1986). Automatic facilitation of the repeated signal is likely to have a brief temporal span and is stimulus determined. This effect seems to account for the repetition effect at short RSIs or ITIs. Subjective expectancy usually has stronger influence at longer RSIs or ITIs. Depending upon the expectation of the participant both, repetition or alternation effects can occur. The ITI in our study was 1000 ms. Thus, repetition or alternation effects can both appear in our data and it is likely, that these effects are based on subjective expectancy in the individual participants.

How could expectation of a certain symbol influence the inhibitory aftereffects? It could be, that the stop signal slows reaction time because it interposes an extra trial between stimulus and response and the benefit from expectation is lost. From this, no slowing would be predicted, if the trials were unexpected, but significant slowing, if trials are expected (loss of expectancy effect). It seems not probable that this effect alone could account for the inhibitory aftereffects, but it might play a contributing role. The hypothesis would be, that the expected symbol would provide greater inhibitory aftereffects than the unexpected symbol.

We thought about building extreme groups of participants showing either a alternation or a repetition effect from our orthopedic and brain damaged patients. However, as we already mentioned, the quality of our data is not very good for the investigation of inhibitory aftereffects. Furthermore, selecting extreme groups cannot replace an experimental design, which manipulates expectations about repetitions and alternations (e.g. in manipulating the ratios of repetitions and alternations in the following pattern: 70:30, 50:50 and 30:70). Therefore we decided to refrain from this and leave this issue for future experimentation.

No specific explanation regarding the negative results between successful and unsuccessful inhibition can be offered. We previously argued that this significant effect in our student study might be due to strategic behavior or post error slowing. One could argue, that the patients did not adopt this strategy or

did not show post error slowing. However, it seems likely that the gross strategic behavior of the patients diminished more subtle effects.

Speculations about brain areas involved in the inhibitory aftereffects

Why did we not find differences between patients and controls? First, it might again be argued, that the gross strategic behavior has obscured any subtle effects. Second, an important factor is, that group selection was not conducted for the investigation of inhibitory aftereffects. Which anatomo-clinical correlations could be expected for the inhibitory aftereffects depends on the underlying mechanisms of them, which have not been investigated in detail yet. However, some speculations can be mentioned here. The speculations we will put forward will be based on studies on negative priming, the use of strategies in brain-damaged patients and the brain regions involved in error detection and compensation, since those phenomena were considered to play a role in the constitution of the aftereffects.

Regarding negative priming, there is to our knowledge only one study investigating this effect in patients with focal lesions (Stuss et al., 1999). They found that patients with right, left or bilateral prefrontal damage showed diminished negative priming in a spatial location task, which was in some patient groups dependent on task complexity. Patients with right posterior lesions showed similar diminished negative priming deficits as the right frontal patients. However, the authors used a location based negative priming task, in which participants select the target stimulus on the basis of a physical attribute and respond to the object's location. In case the inhibitory aftereffects in the stop signal task are comparable to negative priming effects, they would be comparable with identity based negative priming tasks. Negative priming of identity and negative priming of location have been associated with two separate inhibitory systems (Connelly & Hasher, 1993) in reference to the two visual pathways that send information to the frontal cortex, proposed by Ungerleider and Mishkin (1982). One pathway, the ventral or occipitotemporal pathway, which passes through the inferior temporal lobe, might be associated with identity negative priming, whereas the other pathway, the dorsal or

occipitoparietal pathway, which passes through the posterior parietal area, might play a role in location negative priming. Both of the proposed pathways involve the frontal cortex. An dissociation between these two forms of negative priming can occur, this has especially been shown in studies with older adults (Connelly & Hasher, 1993; see Fox, 1995; May et al., 1995 for reviews). Older adults show an impairment in identity negative priming, but preserved location negative priming. If inhibitory aftereffects in the stop signal task resemble identity negative priming, this might entail the ventral pathway, which passes through the inferior temporal lobe.

Regarding errors (the term errors is used here to refer to "slips" and not "mistakes", see Reason, 1990), areas of the frontal lobes have been implicated in the detection and compensation of them, especially the anterior cingulate cortex (ACC). Studies using event related potentials point to the existence of a brain system for error detection and compensation, whose activity is reflected in the error related negativity (ERN), which is characterized by a negative peak about 100 ms following the onset of electromyographic activity when the participant makes an error on that trial (e.g. Gehring et al., 1993; Dehaene et al., 1994). Studies suggest that the ERN may be generated in the anterior cingulate cortex (Coles, 1998; Miltner et al., 1997; Dehaene et al., 1994). The exact role of the ERN and the ACC are still a subject of dispute. Scheffers et al. (1996) for example proposed that the ERN plays a role in error detection, whereas Carter et al. (1998) suggested that the ACC is active in conditions in which errors are likely to occur, but not error detection itself. It has also been proposed, that the activity of the error detection system is related to the degree to which responses are slowed after errors (Coles et al., 1995).

Regarding the use and application of strategies, there are a lot of reports describing the behavior of frontal patients as "bizarre" (e.g. Burgess & Shallice, 1996), being either more impulsive or more conservative than other participants (Shallice & Evans, 1978; Vilkki & Holst, 1991). Executive deficits and deficits in strategy application are also found in patients with posterior lesions, however, they are much less prevalent than in patients with frontal lesions (e.g. Channon & Crawford, 1999). There is also evidence, for a role of the basal ganglia in

executive deficits in association with frontal-striatal circuits (e.g. Dimitrov et al., 1999; Eslinger & Grattan, 1993; Partiot et al., 1996), however, those deficits do not necessarily include the application of strategies, but more likely shifting deficits. For example Day et al. (1984) found that patients with Parkinson's disease are able to employ a predictive motor strategy. Patients with Parkinson's disease seem, however, to have difficulties to shift or refocus attention to an dimension which has previously been irrelevant (i.e. 'learned irrelevance', Owen et al., 1993).

In sum, it might be worthwhile to include again a frontal group in any systematic investigation of inhibitory aftereffects in future studies. However, it would seem advisable to have different "nonfrontal" groups, e.g. having a separate temporal lesioned group.

Conclusion

Aftereffects in this analysis were again obtained after successful as well as after unsuccessful inhibition. However, no specific effects emerged. Most of the negative results can probably be explained by the low quality of the patient data for the investigation of the inhibitory aftereffects. The negative result of the SYMBOL effect might furthermore be due to variable expectations of alternations and repetitions within the groups.

7. General discussion

7.1 Summary of results

The preceding studies had two general aims. The first aim was to investigate neuroanatomical correlates of the inhibition of ongoing responses, the second aim was to investigate the consequences of inhibiting an ongoing response for the next trial in the stop signal task (i.e. inhibitory aftereffects).

In the first study we investigated the role of the frontal lobes and the basal ganglia in the inhibition of ongoing responses. Patients with frontal lesions as well as patients with basal ganglia lesions showed significantly longer stop signal reaction (SSRTs) than orthopedic patients. No significant differences in SSRT could be found between the nonfrontal patients and any other group, although effect sizes of the frontal group and the basal ganglia group in comparison to the nonfrontal group were of medium range. Results provided support for a role of fronto-striatal circuits in the inhibition of reactions, and also support for the notion, that it is useful to rely cognitive functions to functional circuits or networks of interconnected brain structures, rather than isolated brain regions. The obtained effects were, however, too small for SSRT to serve as an diagnostic marker of those brain regions (Zakzanis, 1998). SSRT and primary task RT showed a significant relationship, thus indicating that the neuronal structures for response inhibition and response initiation seem to be at least in part overlapping.

In the second study, we investigated the inhibition of ongoing responses in patients with traumatic brain injury. Contrary to expectations, patients with TBI did not show significantly longer SSRTs. It seems therefore likely, that deficits in the complete suppression of responses are not very common after TBI.

In the third study, we investigated, whether the inhibition of ongoing responses leaves measurable inhibitory aftereffects. The data of a student sample, who had performed the stop signal task were analyzed for inhibitory aftereffects. The results indicated that inhibitory aftereffects were present in the stop signal task whether or not participants were successful in inhibiting their reactions. Moreover, inhibitory aftereffects were greater when both trials consisted of the same primary task properties. Strategic effects might explain

part of the results of this study, but there was evidence that a specific inhibition of either the stimulus, or the response to that stimulus, or both play a role in the constitution of the aftereffects.

In an explorative investigation the data of study 1 and study 2 were analyzed in respect to inhibitory aftereffects. Inhibitory aftereffects were again obtained after successful as well as after unsuccessful inhibition, this was the case in all groups. However, no specific effects were significant. Furthermore, no significant differences between the brain-damaged patient groups and control groups emerged. Results of this analysis must, however, remain inconclusive, since specific effects might have been obscured by the tendency of participants to wait in the experimental blocks during the performance of the stop signal task.

In the following sections, we will compare results across studies and discuss major conclusions. Furthermore, we will discuss some general methodological limitations of the studies and sketch perspectives for future research. We will not discuss single studies in detail, since this has already been done in the discussion section of each study.

7.2 Neuroanatomy of response inhibition

The involvement of the frontal lobes in the inhibition of ongoing responses

The results of study 1 support a role for the frontal lobes in the inhibition of ongoing responses. Even though the difference between basal ganglia and frontal patients in comparison to nonfrontal patients was not significant, the effect size was of medium range. Study 2 did, however, not add further support to the notion of the role of the frontal lobes in response inhibition.

Of course, in study 1 the patient selection criterion was a different one – those patients were selected according to lesion criteria, in study 2 patients were selected according to the etiology of brain damage. However, frontal lobe lesions are highly prevalent in this group, some patients showed evidence of focal frontal lesions in their brain scans, and presumably others had diffuse

frontal lesions. Although this negative result is in accordance with many studies in the literature (e.g. Spikman et al, 1996; Veltman et al., 1996), where executive deficits are much less reliably found in TBI than in patients with focal lesions, it still remains an issue of discussion.

Apart from etiology, in what respect did the patients differ from each other? The TBI patients were on the average nine years younger than the patients with frontal lesions in study 1, both groups were, however, compared with orthopedic controls of their age. It has been suggested, that within patients with TBI that older people are more affected by head injury than younger people, because they may have less available reserves to cope with the insult (e.g. Stablum et al., 1996), and that younger people can often cope quite well. However, TBI patients performed significantly worse than the OC in two of the neuropsychological measures, the total score of the AVLT and intellectual functioning. The FG performed only significantly worse than the OG in total score in the AVLT, the difference in intellectual functioning did not reach significance, although there was an effect. Thus, impairment in the TBI was evident and it does not seem likely that a better ability to cope with brain injury can account for the results.

It seems most likely that frontal lesions in patients with TBI may differ from those patients with focal lesions, i.e. it might be that in the TBI group the crucial frontal areas were not affected in the majority of patients. The issue of different lesion locations as an explanation for the differences in results has to remain an issue of further investigation. An alternative explanation would be, that diffuse damage, which is prevalent in TBI, does not per se suffice to produce deficits in the inhibition of ongoing responses, specific systems have to be damaged to produce those deficits.

Since it is presumably not the whole frontal lobe which takes part in response inhibition, future studies should compare patients with focal right, left and bilateral frontal lesions, to investigate whether any performance differences emerge. Furthermore, a more detailed anatomical assignment with groups of participants with lesions to different areas of the frontal lobes (e.g. basal-medial, mesial, dorsolateral, orbital) should be conducted (see Stuss & Benson, 1984).

The same is true for the investigation of patients with basal ganglia lesion. Those should also be divided into groups according to laterality and the precise lesion location (striatum, pallidum, substantia nigra). This could yield a more detailed neuroanatomical assignment of the inhibition of ongoing responses.

The neuroanatomy of motor control

In study 1 we argued, in line with Band and Boxtel (1999), that the available neuropsychological and neurophysiological data support a role of the prefrontal cortex and the basal ganglia as a candidate structures for the inhibition of motor responses. Because cortical and subcortical structures form a loop, it was proposed that those structures conjointly accomplish response inhibition. The data of study 1 indicated, that lesions to those structures can indeed lead to deficits in the inhibition of ongoing responses.

Of course, the frontal cortex and the basal ganglia are not the whole story concerning motor control. Response-generating processes pass through a number of processing phases. Most of this processing seems to happen in parallel, only few studies point to serial processing (Dettmers, 1997). Goldberg (1985, 1987) proposed a “dual premotor system hypothesis”, on which also the model of Band and Boxtel (1999) for response inhibition is based. Goldberg (1985, 1987) assumes the existence of two loops, a medial and a lateral loop, that lead along cortical as well as subcortical motor structures (see Figure 7.1). In the medial loop, virtually all regions of the cerebral cortex project via the basal ganglia and motor nuclei of the thalamus back to restricted regions of the cerebral cortex, most notably the supplementary motor area (SMA). This loop is thought to operate in a feed-forward mode and to function as an integrated system for the selection of responses. According to Goldberg (1987) it is primarily this medial system that is responsible for volitional control over behavior and the capacity for acting autonomously, because the system has the capacity to act selectively on external information for behavioral cueing. Response inhibition is thought to be related to the medial loop (Band & Boxtel, 1997).

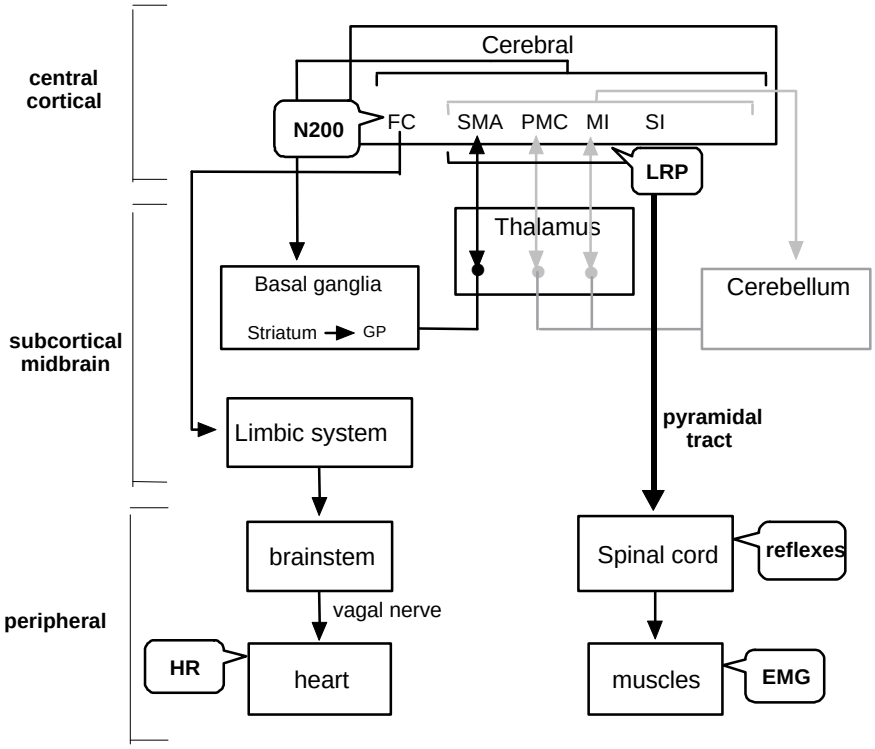

Figure 7.1. Schematized diagram containing the most important anatomical structures involved in response activation and inhibition. In the medial loop (depicted in black) widespread regions of the cortex project through the basal ganglia and thalamus to the SMA. In the lateral loop (depicted in grey), the motor, somatosensory and parietal cortices project via the cerebellum and the thalamus back to premotor and primary motor areas. The major output from the motor cortex to the spinal cord and muscles is formed by the pyramidal tract. The callouts contain the psychophysiological measures reflecting the activity of the structures to which they point. FC: frontal cortex; GP: globus pallidus, MI: primary motor cortex; PC: parietal cortex; PMC: premotor cortex; SI: somatosensory cortex; SMA: supplementary motor area (adapted from Band & Boxtel, 1999)

In the other, the lateral loop, activity from more restricted areas of the cortex, most notably somatosensory and posterior association areas is focused back through the cerebellum and specific motor nuclei of the thalamus to the primary motor cortex. The function of this feedback-dependent loop is thought to be the context-dependent adjustment of the parameters of the first loop by translating sensory information into immediate adjustments of motor activity to improve the timing and smoothness of actions (Goldberg, 1985).

It becomes apparent from the graph, that it may be worthwhile to investigate a variety of other brain areas in relation to response inhibition. Especially the thalamus, which has been proposed to have a critical role in the information transmission (Goldberg, 1985) or to have a gating function (Brunia, 1993) would seem worthwhile an investigation. Furthermore, Goldberg (1985) assumes that the lateral loop functions to perform context-dependent adjustment of the parameters of the movement strategy selected by the operation of the medial loop. Thus, those two loops do not work in isolation, and it might be of interest to investigate the role of parts of the lateral loop, for example the cerebellum, in the context of response inhibition. In addition, although there is insufficient evidence to support the notion that the SMA is an inhibitory agent (Band & Boxtel, 1999), the possibility certainly deserves further investigation.

Speculations: How is response inhibition accomplished by the brain?

A deficit after a lesion to a certain brain area does not tell anything about the way how brain structures work together. Several authors have suggested a hierarchical organization of response control with a higher-level role for the prefrontal cortex (e.g. Fuster, 1989; Norman & Shallice, 1986). Between the leading activity of the prefrontal cortex and the final commands from the primary motor cortex, there are some preparatory processes of the premotor area and supplementary motor area (Goldberg, 1985). The primary motor cortex is the last cortical level where motor activity can be modulated. The frontal lobes are thus thought to cooperate with subcortical structures, but seem to play the leading role in the control of responses. The prefrontal cortex is likely to be in charge, since it is capable of modulating subcortical input to the motor cortex by

gating the thalamic transmission of associated activity from the basal ganglia and the cerebellum (Band & Boxtel, 1999; Goldberg, 1985, 1987).

Most models are not very explicit about the mechanism by which the prefrontal cortex exerts inhibition. One explicit model was proposed by Brunia (1993). Brunia (1993) hypothesized, that selection for action takes place in an interaction between the prefrontal cortex and subcortical motor structures. He furthermore proposed that the site of response selection is in the thalamus. Cerebellum and basal ganglia outputs are sent to the motor cortex via interconnection in the reticular nucleus of the thalamus. Important is, that the transfer in the thalamus takes place under selective control of the prefrontal cortex, which is responsible for opening and closing the "thalamic gate". Brunia (1993) referred to this mechanism as „gating". He argued: „For a go command to be followed, the thalamic motor gate has to be open, whereas a no-go command implies an active closing of that gate. There is supporting evidence for the notion that a no-go command is generated in the (pre)frontal cortex" (Brunia, 1993, p.336). The gating model can also explain results of studies showing that response inhibition is associated with heart rate deceleration (Collet et al., 1999; Jennings et al., 1992). Brunia assumes that the frontal areas that are involved in the gating mechanism also influence heart rate changes related to attention and response intention. It is thus possible to view cardiac deceleration in association with inhibition as a correlate of central inhibition originating from the same areas in the frontal cortex (Band & Boxtel, 1999).

Of course, this theory about how response inhibition could be accomplished by the brain cannot be proved or rejected with the present research. It is, however, an interesting issue to speculate about those mechanisms. It might furthermore be interesting to investigate in future studies heart rate changes and other autonomic responses, like respiration or electrodermal activity, which have also been shown to be sensitive to response inhibition (Collet et al., 1999), in patients who show decreased inhibitory efficiency.

7.3 Inhibitory aftereffects

Persistence of inhibition

Inhibition in the stop signal task seems to have some persistence, carrying over into further trials. It has been shown, that inhibitory processes leave measurable aftereffects in a variety of tasks, for in the example negative priming tasks of location and identity (for reviews see Fox, 1995; May et al., 1995), the stroop task (e.g. Neill, 1978; Lowe, 1979; see MacLeod, 1991 for a review) and the flanker task (e.g. Neill & Valdes, 1995). Aftereffects of inhibition can thus be thought to be a general performance principle of human information processing.

Although inhibitory aftereffects in experimental paradigms are operationalized as an impairment in performance (slower RT), in real life the mechanisms responsible for those effects do actually serve to facilitate efficient performance. For example, if distracting information captures someone's attention this can be dangerous or irritating. It has therefore been hypothesized that inhibition in negative priming tasks may serve to block rejected information from immediate reactivation and function to facilitate on-line processing of target information by maintaining the distinction between distracting and goal-relevant information (May et al., 1995). The aftereffects of response inhibition may reflect a similar function. A just rejected motor program, which has become inappropriate is blocked from immediate reactivation to facilitate the distinction between goal-relevant and irrelevant responses.

Inhibitory aftereffects in existing frameworks of inhibition and speculations about common underlying processes

In the general introduction, we tried to allocate the inhibition of ongoing responses into different frameworks of inhibition. Harnishfeger (1995) would describe the inhibition of ongoing responses as "behavioral inhibition", Logan (1994) would describe it as active inhibition, and Arbuthnott (1995) would say that the target of inhibition is the produced unit itself, that the inhibitory mechanism would be self-inhibition and that there is a direct influence of intention. How can we relate the inhibitory aftereffects to the conceptualizations

mentioned in the introduction? Harnishfeger (1995) would describe them as "unintentional cognitive inhibition" and Logan would describe them as "reactive inhibition". It is not clear how Arbuthnott (1995) would describe the target of inhibition – it might be the produced unit itself or competitors in the task context (this issue might resolve itself when further investigation of the aftereffects will be undertaken). She would say that the influence of intention is indirect (if we assume the ideal case that participants do not start waiting for the stop signal), and that the inhibitory mechanims is self-inhibition. See Table 7.1 for those characterizations.

Table 7.1 Inhibition of ongoing responses and inhibitory aftereffects in existing frameworks of inhibition

Stop-signal inhibition	**Inhibitory aftereffects**
Harnishfeger 1995	
behavioral inhibition	cognitive inhibition, unintended
Logan, 1994	
active inhibition	reactive inhibition
Arbuthnott, 1995	
Target of inhibition:	
produced unit itself	produced unit itself?
	competitors in the task context?
Inhibitory mechanims	
self-inhibition	self-inhibition
Intention	
direct	indirect

In Arbuthnott's (1995) framework it is interesting to note, that self-inhibition may be the same underlying process in both forms of inhibition. This points to a possible way the inhibition of ongoing responses could be related to the inhibitory aftereffects and how both inhibitory phenomena in this task might be modeled within an common framework. However, both phenomena might as well be modeled by some other model, which describes those phenomena in terms of associations in working memory (Kimberg & Farah, 1993). The possible underlying processes of inhibition of ongoing responses and inhibitory aftereffects are an interesting issue, and should be investigated in future

simulation studies. Any model of the underlying processes should be able to explain both phenomena in one framework.

Common brain structures for the inhibition of ongoing responses and inhibitory aftereffects? - Speculations

The inhibitory aftereffects are clearly related to the inhibitory process in the previous trial. Does this imply, that the same brain structures play a role in both phenomena? Assuming that a common mechanism is responsible for both phenomena may seem to imply that this would be the case. However, we have also argued, that the inhibitory aftereffects might resemble identity negative priming, which might imply a role for the temporal lobes, which were not considered as a candidate structure for the inhibition of ongoing responses.

Inhibiting an ongoing response seems to be one process, carrying something of this inhibition over into the next trial is presumably caused by this process, but might require another process, and to overcome this residual effect in the next trial probably still another. Thus, we think that brain structures related to the two phenomena should be at least partly overlapping, but that this overlap does not necessarily have to be total. One speculation might be, that the frontal cortex could be a key structure which plays a role in both phenomena, but that other brain areas may differ.

7.4 Limitations and methodological problems

The design of the stop signal task

A problem in the design of the stop signal task in our patient studies was, that it was not possible to prevent patients from employing a waiting strategy. This behavior is presumably responsible for the partly negative results of the explorative analysis of inhibitory aftereffects in brain damaged patients. One possibility to prevent this in future studies would be to set a smaller response window and to give feedback about primary task RT and to set goals for responding fast. The response window was set to 2500 ms in the current study, because we wanted to assess patients who were markedly slowed.

However, only few patients had RTs longer than 1000 ms in the exercise block of the stop signal task. Thus, it seems that a response window of 1000 ms would suffice for most patients. It should be taken into consideration, to set the response window individually for each patient in accordance with his or her RT in the exercise block. Adjusting the response window individually might not be suitable for the investigation of inhibitory aftereffects (they might differ with trial length), but should be considered in the investigation of SSRT in future studies.

One general issue also has to be said about the interpretation of SSRT. The SSRT can be influenced by the triggering rate of the inhibitory process. Failures to trigger the inhibitory mechanism result in longer SSRT. Longer SSRTs in that case could be interpreted as either longer RTs to stop signals or as failures in triggering the stop mechanism. The conclusion would still be an inhibitory deficit in some patients, however of a different quality. In the simulation studies of Band (1997) a failure to trigger the inhibitory mechanims was the only factor the tracking procedure could not compensate for (none of the other procedures to set the delay could either). If a deficiency in triggering the inhibitory process is suspected in a given data set, there is no way to correct the estimation of the stop-process duration (Band, 1997). It is easier to evaluate, whether failures to trigger the inhibitory mechanims happened in datasets with fixed delay procedures, than in data, where the staircase tracking algorithm is used, like in our patient studies (a participant who is not always able to trigger the inhibitory process would never be able to reach the asymptotic no-response level, even when stop-signals are presented well in advance of the primary task stimulus; Band, 1997). That failures in triggering the inhibitory mechanims influenced our data is, however, quite unlikely. Frequent failures to trigger the inhibitory mechanism should show up in a higher probability of responding and a short delay of the stop signal. Occasional failures of triggering the response mechanism should not have much influence on the probability of responding, because the delay after a failure will be shorter, and the probability of responding higher if the mechanism is triggered in the next stop signal trial. However, a slight increase in the probability of responding might still be observed. Furthermore, participants were under close

observation throughout the testing session by the examiner and no behavioral indication of failures in triggering the inhibitory mechanism were observed. Instead, effort to inhibit responses was visible, even when inhibition was not successful. In addition, aftereffects of inhibition were found after successful as well as after unsuccessful inhibition in all groups. The stop signal was a clearly audible tone and difficult to ignore, it might even have had an alerting function. There were also no failures to trigger the response mechanism in our data (i.e. there were no omission errors in the trials without stop signal). The correlations between primary task RT and SSRT across groups also make it likely, that speed was the important factor. Thus, although it can not totally be ruled out that failures to trigger the inhibitory mechanism happened, this seems quite unlikely.

Selection of participants

In study 1, patients with cerebrovascular disorders and tumor patients were investigated. Patients with intracranial tumors or stroke are the most frequent participants for neuropsychological research. Although those two etiologies are frequently combined in neuropsychological research, this approach suffers from some problems (Anderson et al., 1990). The dysfunction caused by stroke depends largely on direct and radical destruction of neurons. In contrast, tumors begin by displacing neuronal structures, and may not actually cause neuronal destruction for relatively long periods. The first systematic comparison of the cognitive impairments between patients with tumor and patients with stroke based on modern neuropsychological and neuroanatomical procedures has been undertaken by Anderson et al. (1990). They tried to match the location and size of cerebrovascular lesion to the location and size of the tumor lesions on an a case-by-case basis. However, tumor growth does not respect vascular boundaries, it was therefore not possible to match all participants. Furthermore, tumor participants were somewhat younger than their stroke counterparts (the age differences in the groups were consistent with age-of-onset factors in these two pathology types). Anderson et al. (1990) found differences in the neuropsychological impairments of the two groups.

Impairments caused by tumors were generally milder as compared to those caused be stroke, and there was greater variability in the degree of cognitive impairment within the tumor group. Those results are in agreement with the pathophysiological properties of tumor growth and cerebrovascular disorders. It was not possible to select participants with only one etiology for study 1 if we wanted reasonable group sizes. There was, however, no indication of differences between cerebrovascular patients and tumor patients in study 1 of this dissertation. This issue remains, however, something to be concerned about and to be investigated in future studies.

A further methodological limitation of the selection of our patients concerns the matching procedure. Although we were able to match the groups on important demographic variables like age, sex and years of education, this was done on group basis and not on a case by case basis. As Tupper and Rosenblood (1984) argue, it is preferable to do the matching on individual participants rather than on groups. A case by case match is, however, quite difficult to accomplish when several patient groups are investigated.

One further issue concerning the patient selection in study 1 was that not all participants were right handed and some of them had to perform the stop signal task with their nondominant hand. That not all participants were right handed is probably not a great problem, since participants could perform the task with their preferred hand and we did not compare right vs. left sided lesions. However, having to perform a task with the nondominant hand might be a problem. There is no study which investigates, whether participants are better in stopping reactions with their preferred hand than the other, so it is uncertain, what the effect of having to perform the task with the nondominant hand might be. This problem is, however, nearly unavoidable in neuropsychology. Four patients of the NFG (whole group of twenty) and three patients of the BG (whole group of eight) had to use the nondominant hand because of paresis. Of the three patients of the BG, who had to use the nondominant hand, none was three standard deviations below the mean of the OG (two of the other BG patients were), two were two standard deviations below the OG mean. Thus, it

is unlikely that the effect of the BG is due to performing the task with the nondominant hand.

One implicit assumption of the anatomo-clinical correlation method ins constancy (Vallar, 1999). Constancy refers to the notion that investigation of the organization of the normal mind through brain damaged patients is possible only if after a cerebral lesion mental processes do not undergo a functional reorganization that involves the generation of new components or new connections. If this is the case, the mental processes of a brain-damaged patient would be qualitatively different, in terms of functional architecture, from those of a normal participant. After damage to a specific component, patients may develop specific strategies, which are not typically used by normal participants. In this case the constancy assumption, however, remains valid, provided that such strategies are part of the behavioral repertoire of the normal participant, i.e. they are based on the components of the normal system spared by the lesion. The postulate that, at least in adult participants, the reorganization of the system after a brain lesion does not include qualitative changes, such as novel components or connections cannot be easily verified. Data indicate, that some degree of plasticity is a feature of the central nervous system, in order to cope, at least in part, with the damage produced by a lesion. This ability does not necessarily imply, however, that the post-lesional organization is qualitatively different from the normal system. The constancy assumption has to be treated with great caution. Thus, a problem in our patient selection concerns the inclusion of patients after varying intervals of brain damage in our studies (most patients were postacute, but some where also chronic). This remains an issue for further studies.

Another problem in the patient studies might be, that for some patients CT scans, for other MRT scans were available for the localization of lesion. MRT scans usually provide a better image of the brain structures, and thus lesions are more easily detected (Hadley & Teasdale, 1988). It is, however, quite unlikely that we overlooked lesions in patients in study 1 were only a CT scan was available, since cerebrovascular and tumor lesions are usually focal and relatively easy to detect. The different quality of scans was, however, the

reason, why we did not build subgroups of TBI, selecting those with frontal lesions and diffuse damage. Especially for the evaluation of diffuse damage, the scans might have been misleading.

One last remark to our selection criteria: we excluded participants with speech comprehension difficulties to make sure, that task instructions would be understood. However, such a procedure can lead to selectively excluding patients with severe left sided lesions. This is a general problem in neuropsychological research, since a prerequisite for the performance of most tasks is that patients are able to comprehend verbally given instructions. There was, however, no indication in our sample that we had more patients with right sided lesions, most of the frontal patients had bilateral lesions and in the other groups lesions seemed equally distributed. There was also no indication in our data that patients with left-sided lesions were less impaired than patients with right sided lesions.

Statistical analysis

There are some methodological issues concerning the evaluation of the correlation of primary task RT and SSRT. In study 1 we had conducted an ANCOVA and a comparison of subgroups with similar primary task RTs. Both however, are problematic from the methodological perspective.

In ANCOVA, one of the major requirements is the independence of the independent variable and the covariate. In practice, this requires random assignment of participants. In a study with attribute variables as independent variables (in our case lesion location) it is very unlikely to have independence of the treatment and the covariate (Tupper & Rosenblood, 1984). This is also true for study 1 – the longer primary task RTs are an effect of brain damage and thus related to our independent variable. Most authors, however, accept the use of ANOCA in quasiexperimental research in cases like ours (Huitema et al., 1980; Tabachnick & Fidell, 1996).

With respect to the comparison of subgroups with similar primary task RTs it has to be said that Tupper and Rosenblood (1984) argue against matching participants ex post facto. They state that “systematic unmatching” occurs when

participants are equated on a “nuisance” variable. By holding identified nuisance variables constant, the result will generally be to systematically unmatch the pairs with regard to some other (unidentified) nuisance variable(s). Furthermore, the selected subpopulations are not representative, the matching procedure identifies a sample from the population that differs systematically from the population of interest. Any inferences can only be made to the sample that has been collected by matching, not to the population. An additional problem is that the employed procedure automatically results in the selection of extreme groups (“fast” brain-damaged and “slow” orthopedic participants), regression effects are thus likely to apply to those subsamples.

7.5 Perspectives

Some perspectives for future research have already been pointed out in the sections above and in the discussion sections of the single studies, some more might, however, be added. Of course, first of all a cross-validation of the results has to be done, i.e. the observed effects should be replicated in new samples (Cohen, 1994).

Perspectives for the investigation of inhibition of ongoing responses in brain damaged patients

Further interesting studies in the inhibition of responses might be to compare the performance of brain damaged patients across different inhibition tasks (e.g. like Kramer et al., 1994 have done it in elderly participants). A comparison of the performance in the stop signal task and a go nogo task might for example be interesting, to evaluate, whether patients with difficulties in one task show also difficulties in the other. Also a comparison of the inhibition of ongoing responses in the stop signal task with inhibitory phenomena in other tasks might be a worthwhile endeavor. Associations and dissociations of different inhibitory phenomena might be investigated this way.

The stop signal task was used in its basic form in the present investigation. However, stopping an action or response is only the first step towards a new goal in a changing environment, a general requirement in all kinds of cognitive

control. Stopping an action does at least in some cases also imply switching to another, alternative action (Logan, 1994). Further investigations could be directed at the next step after stopping, i.e. a change to another reaction. This is something, which can be measured with the stop-change paradigm (e.g. Logan & Burkell, 1986). Another interesting investigation in the context of stopping performance in brain-damaged patients could also be selective stopping, which resembles situations in which the stop signal is not always a signal to stop (e.g. a pedestrian walks consciously over the crosswalk, in spite of the red traffic lights, because he or she is sure that no cars are approaching) or not everything must be stopped (e.g. one has to stop driving at a junction if one does not have the right of way, but not if one has). The former can be experimentally studied in stopping tasks where two different tones are presented in the same fashion as stop signals, but only one of the tones signals the participants to stop the reaction (Riegler, 1986, cited in Logan, 1994). The latter can be studied in tasks where participants are asked to selectively inhibit one response but not another, e.g. only the response assigned to the right index finder (e.g. DeJong et al., 1995). Stopping is an extreme form of control. Many changes in goals in the environment are more subtle, requiring only to do something a little bit different. More subtle forms of inhibition are required for adaptation, rather than cancellation of ongoing behavior (Logan, 1994). Thus, it could also be of interest to investigate response inhibition in some kind of tracking task, where the direction of tracking changes, but tracking has not to be stopped.

For our hypothesis in study 1 we have frequently referred to patients with Parkinson's disease as a model for basal ganglia lesions, since research on patients with focal basal ganglia lesions is sparse. However, in Parkinson's disease, it is primarily the dopaminergic pathway which is damaged. Furthermore, connections of the frontal lobes and the basal ganglia are primarily dopaminergic (e.g. Robbins et al., 1993). Thus, one might speculate that dopamine plays a role in the inhibition of ongoing responses. It could therefore be interesting to evaluate the inhibition of ongoing responses under neuropharmacological aspects in brain damaged patients.

Perspectives for the investigation of inhibitory aftereffects

It still remains an issue to investigate the inhibitory aftereffects produced by the stop signal task in brain damaged patients with a design suited for this purpose. However, before this should be done, it would be useful to find out more about the aftereffects themselves, about the conditions under which they occur, which factors influence them, to what phenomena they can be related and how they could be best explained.

For a more detailed evaluation of the factors influencing the inhibitory aftereffects, it might be worth to vary experimentally the probability of two stop signals following each other. In study 3, the probability of two stop signals following each other was 25% (like the overall probability of a stop signal). Without changing the overall probability of the stop signal, the probability of two stop signals after each other could be manipulated, e.g. to 0%, 10%, 20% and 30%. It would be especially interesting to see whether in the 0% condition inhibitory aftereffects could also be obtained. It is known from negative priming experiments that the expectation of a conflict in the probe trial is sometimes a necessary condition for the appearance of the negative priming effect (Tipper & Cranston, 1985, Tipper et al., 1990; for an overview see May et al., 1995). It might therefore be that no inhibitory aftereffects could be obtained in a 0% condition. However, if stable inhibitory aftereffects can be obtained in a 0% condition, the trials could be used more efficiently for the investigation of the aftereffects in further experiments.

A further aspect that might have an influence on the aftereffects is the stop signal delay. However, if any effect could be found for the different delays, this might be confounded by the fact that at earlier delays successful inhibition is more probable. Therefore, such an experiment should be conducted with a large number of trials, and with delays not too far at the ends of the inhibition function, to be able to compare aftereffects after successful and after unsuccessful inhibition separately over different delays of the stop signal.

An interesting question would be the timecourse of the inhibitory aftereffects. In negative priming studies manipulations of the intertrial interval (ITI) within

blocks often led to a diminuation of the effect with larger ITIs, whereas manipulation of the ITI between the blocks or between groups often yielded a relatively constant negative priming effect, regardless of the ITI (Neill et al. 1992; for an overview see May et al., 1995). It would therefore be of interest to manipulate the ITI in the stop signal task between and within blocks and / or groups.

As already mentioned in the explorative analysis, there might be an effect of the expectation of repetitions or alternations of the primary task symbol on the inhibitory aftereffects. In manipulating the probability of repetitions and alternations (e.g. 30:70, 50:50 and 70: 30) this issue could be investigated.

A further worthwhile investigation would be to allocate two stimuli to each of the two response buttons. This would clarify the effects of stronger inhibitory aftereffects after repetition trials in study 3 further and the issue, whether the reaction to a specific stimuli or a specific response is inhibited.

It was not possible in study 3 to look at all possible trial order effects, e.g. to look at two stop signals following each other, or to investigate the effect of the trial before the stop signal on the stop signal trial, since any effects we would have obtained would be modified by the four different stop signal delays we had in this study, which would not have left enough trials (see appendix). In one previous study Osman et al. (1986) showed that stimulus-response repetition showed a greater probability of responding in stop signal trials for a given delay following repetition than alternation trials. This effect might, however, not be specific and simply explained by the horse race model, because faster responses are less easily to stop than slower at a given delay (reaction times in their study was faster for repetitions than for alternations). The study of further trial order effects in the stop signal task might be an issue worth of further investigation.

7.6 Conclusion

The studies of this dissertation revealed some interesting results about neuroanatomical correlates of the inhibition of ongoing responses and about inhibitory aftereffects in the stop signal task. There was some support for the notion that the frontal lobes and the basal ganglia play a crucial role in the inhibition of ongoing responses. In addition, results showed that inhibitory aftereffects are present in the stop signal task. Necessarily, since this was the first time inhibition of ongoing responses was investigated with the stop signal task in brain-damaged patients, and since this was also the first investigation of inhibitory aftereffects in the stop signal task, this research raises a lot of questions for future studies.

8. Summaries

8.1 English summary

The term “inhibition” refers to mechanisms that reduce or dampen neuronal, mental or behavioral activity. On the behavioral and cognitive level inhibition is important when a task is finished, when a goal is no longer relevant, when an error needs to be corrected and when appropriate stimuli have to be selected and inappropriate rejected. Inhibition is however, not a unitary concept, several distinct forms of inhibition can be distinguished.

In this dissertation inhibitory phenomena were investigated in brain-damaged patients and healthy persons with the use of the stop signal task (Logan & Cowan, 1984). This task has the advantage that the time it takes to stop an ongoing reaction can be measured (stop signal reaction time, SSRT). The first aim of this dissertation was to investigate neuroanatomical correlates of the inhibition of ongoing responses with the anatomo-clinical-correlation method (study 1 and 2). The second aim was to investigate the consequences of the inhibition of ongoing responses for the next trial in the stop signal task (study 3).

Theories and research results point to the importance of circuits linking the basal ganglia and the frontal cortex in executive function and motor control (e.g. response inhibition). Therefore in study 1, the role of the frontal lobes and the basal ganglia in the inhibition of ongoing responses was investigated. Seventeen patients with frontal lesions (FG), 20 patients with cortical lesions outside the frontal cortex (NFG), 8 patients with lesions to the basal ganglia (BG) and 20 orthopedic controls (OG) performed the stop-signal task. The FG as well as the BG showed significantly longer SSRTs than the OG. No significant differences in SSRT could be found between the NFG and any other group. However, effect sizes between the FG and the BG in comparison to the NFG were of medium range. Results provide some evidence for a role of the frontal lobes and the basal ganglia in the inhibition of ongoing reactions.

In study 2, the inhibition of ongoing responses was investigated in patients with traumatic brain injury (TBI), an etiology of brain-damage where frontal lesions are highly prevalent. Therefore, it might be assumed that brain-

damaged patients with this etiology also show deficits in the inhibition of ongoing responses. A group of 27 patients with TBI (TBI) and a group of 27 orthopedic control patients (OC) performed the stop signal task. Contrary to expectations, patients with TBI as a group did not show significantly longer SSRTs. It seems therefore likely, that deficits in the complete suppression of responses are not very common after TBI.

In the third study it was investigated, whether the inhibition of ongoing responses leaves measurable inhibitory aftereffects. Aftereffects of inhibition like the negative priming effect are well-known and focus of intensive research. It seemed reasonable to assume that the use of inhibitory processes leaves measurable aftereffects in a variety of other tasks and situations. The data of 34 students, who had performed the stop signal task were analyzed for inhibitory aftereffects. The results indicated that inhibitory aftereffects were present in the stop signal task whether or not participants were successful in inhibiting their reactions. They were greater after unsuccessful than after successful inhibition. Moreover, inhibitory aftereffects were greater when both trials consisted of the same primary task symbols. Strategic effects might explain part of the results of this study, but there was evidence that specific inhibition of either the stimulus, or the response to that stimulus, or both play a role in the constitution of the aftereffects.

In an explorative investigation the data of study 1 and study 2 were analyzed in respect to inhibitory aftereffects. Inhibitory aftereffects were again obtained after successful as well as after unsuccessful inhibition, this was the case in all groups. However, none of the specific effects became significant and no significant group differences emerged. Results of this analysis must, however, remain inconclusive, since specific effects might have been obscured by the tendency of participants to wait in the experimental blocks during the performance of the stop signal task.

The studies of this dissertation reveal some interesting results about neuroanatomical correlates of the inhibition of ongoing responses and about inhibitory aftereffects in the stop signal task. Necessarily, since this was the first time the inhibition of ongoing responses was investigated with the stop

signal task in brain-damaged patients, and since this was also the first investigation of inhibitory aftereffects in the stop signal task, the current research raises a lot of questions for future studies.

8.2 Deutsche Zusammenfassung

Der Begriff „Inhibition“ bezieht sich auf Mechanismen, die neuronale, kognitive oder Verhaltensaktivität reduzieren. Inhibition ist wichtig, wenn eine Aufgabe beendet ist, wenn ein Ziel nicht länger relevant ist, wenn ein Fehler korrigiert werden muß oder wenn geeignete Stimuli ausgewählt und nicht geeignete zurückgewiesen werden müssen. Inhibition ist kein einheitliches Konzept, mehrere unterschiedliche Formen der Inhibition können unterschieden werden.

In der vorliegenden Dissertation wurden Inhibitionsprozesse unter Verwendung der Stop Signal Aufgabe bei hirngeschädigten und bei gesunden Personen untersucht. Die Stop Signal Aufgabe ermöglicht es die Zeit zu schätzen, die benötigt wird, um eine bereits initiierte Reaktion zu hemmen (Stop Signal Reaktionszeit, SSRT). Das erste Ziel dieser Arbeit war es, die neuroanatomischen Korrelate der Inhibition bereits initiierter Reaktionen mit der anatomisch-klinischen Korrelationsmethode zu untersuchen (Studie 1 und 2). Das zweite Ziel war die Untersuchung der Konsequenzen der Hemmung bereits initiierter Reaktionen für das nächste Trial in der Stop Signal Aufgabe (Studie 3).

In der ersten Studie wurden die Rolle der Frontallappen und der Basalganglien bei der Inhibition bereits initiierter Reaktionen untersucht. Hierzu führten siebzehn Patienten mit Läsionen im frontalen Kortex (FG), 20 Patienten mit kortikalen Läsionen außerhalb des frontalen Kortex (NFG), 8 Patienten mit Läsionen an den Basalganglien (BG) und 20 orthopädische Kontrollpersonen (OG) die Stop Signal Aufgabe durch. Die FG und die BG zeigten signifikant längere SSRTs als die OG. Es wurden keine signifikanten Unterschiede zwischen der NFG und den anderen Gruppen in der SSRT gefunden. Die Effektstärken zwischen der FG und der BG im Vergleich zur NFG lagen jedoch im mittleren Bereich. Die Ergebnisse deuten darauf hin, daß die Frontallappen und die Basalganglien an der Inhibition bereits initiierter Reaktionen beteiligt sind.

In der zweiten Studie wurde der Frage nachgegangen, ob Inhibitionsdefizite nach traumatischen Hirnschädigungen auftreten. Hierzu wurden eine Gruppe von 27 Patienten mit einem Schädelhirntrauma (SHT) und eine Gruppe von 27

orthopädischen Patienten mit der Stop Signal Aufgabe untersucht. Patienten mit einem SHT zeigten als Gruppe keine signifikant längeren SSRTs als orthopädische Kontrollpersonen. Dies kann als Hinweis darauf gewertet werden, daß Defizite in der Hemmung bereits initiierter Reaktionen nach einen SHT nicht sehr häufig sind.

In der dritten Studie wurde untersucht, ob die Inhibition bereits initiierter Reaktionen meßbare Auswirkungen auf nachfolgende Durchgänge hat. Die Daten von 34 gesunden Versuchspersonen, die die Stop Signal Aufgabe durchgeführt hatten, wurden hierzu analysiert. Nacheffekte traten sowohl nach erfolgreicher als auch nach nicht erfolgreicher Inhibition auf. Die Nacheffekte waren nach nicht erfolgreicher Inhibition größer als nach erfolgreicher Inhibition. Auch waren die Nacheffekte bei identischen Stimuli in der Primäraufgabe größer als bei nicht-identischen Stimuli. Auch wenn strategische Effekte die Ergebnisse teilweise erklären können, ergaben sich Hinweise darauf, daß ein spezifischer Inhibitionsmechanismus bei der Entstehung der Nacheffekte eine Rolle spielt.

In einer explorativen Analyse wurden die Daten der Studien 1 und 2 in Hinblick auf inhibitorische Nacheffekte ausgewertet. Nacheffekte traten wiederum sowohl nach erfolgreicher als auch nach nicht erfolgreicher Inhibition auf. Spezifische Effekte wurden jedoch nicht signifikant. Die Ergebnisse dieser Analyse lassen jedoch keine endgültigen Schlußfolgerungen zu, da die Daten nur bedingt zur Untersuchung der inhibitorischen Nacheffekte geeignet waren.

Die Studien dieser Dissertation beinhalten einige interessante Ergebnisse über neuroanatomische Korrelate der Inhibition bereits initiierter Reaktionen und über inhibitorische Nacheffekte in der Stop Signal Aufgabe. Da dies die erste Untersuchung der Inhibition bereits initiierter Reaktionen mit der Stop Signal Aufgabe bei hirngeschädigten Patienten ist und auch die erste Untersuchung über inhibitorische Nacheffekte in der Stop Signal Aufgabe, werfen die Ergebnisse viele weitere spannende Fragen für die zukünftige Forschung auf.

9. References

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience, 9*, 357-381.

Alivisatos, B., & Milner, B. (1989). Effects of frontal or temporal lobectomy on the use of advance information in a choice reaction time task. *Neuropsychologia, 27*(4), 495-503.

Anderson, S. W., Damasio, H., Jones, R. D., & Tranel, D. (1991). Wisconsin Card Sorting Test performance as a measure of frontal lobe damage. *Journal of Clinical and Experimental Neuropsychology, 13*(6), 909-922.

Anderson, S. W., Damasio, H., & Tranel, D. (1990). Neuropsychological impairments associated with lesions caused by tumor or stroke. *Archives of Neurology, 47*(4), 397-405.

Andres, P., & Vanderlinden, M. (1998). Inhibition capacity: A "frontal" function? *European Review of Applied Psychology, 48*(1), 33-39.

Apicella, P., Scarnati, E., Ljungberg, T., & Schultz, W. (1992). Neuronal activity in monkey striatum related to the expectation of predictable environmental events. *Journal of Neurophysiology, 68*(3), 945-960.

Arbuthnott, K. D. (1995). Inhibitory mechanisms in cognition: Phenomena and models. *Current Psychology of Cognition, 14*(1), 3-45.

Axelrod, B. N., Goldman, R. S., Tompkins, L. M., & Jiron, C. C. (1994). Poor differential performance on the Wisconsin Card Sorting Test in schizophrenia, mood disorder, and traumatic brain injury. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 7*(1), 20-24.

Azouvi, P., Jokic, C., Van der Linden, M., Marlier, N., & Bussel, B. (1996). Working memory and supervisory control after severe closed-head injury: A study of dual task performance and random generation. *Journal of Clinical and Experimental Neuropsychology, 18*(3), 317-337.

Baddeley, A. (1996). Exploring the central executive. *Quarterly Journal of Experimental Psychology: Human Experimental Psychology, 49a*(1), 5-28.

Baddeley, A. D. (1986). *Working memory*. Oxford: Clarendon Press.

Band, G. P. H. (1997). *Preparation, adjustment, and inhibition of responses.*

Unpublished PhD thesis. Amsterdam: Universiteit van Amsterdam.

Band, G. P. H., & van Boxtel, G. J. M. (1999). Inhibitory motor control in stop paradigms: review and reinterpretation of neural mechanisms. *Acta Psychologica, 101*, 179-211.

Bertelson, P., & Renkin, A. (1966). Reaction times to new versus repeated signals in a serial task as a function of response-signal time interval. *Acta Psychologica, Amsterdam, 25*(2), 132-136.

Bigler, E. D. (1987). The clinical significance of cerebral atrophy in traumatic brain injury. *Archives of Clinical Neuropsychology, 2*, 293-304.

Bowen, F. P., Kamienny, R. S., Burns, M. M., & Yahr, M. D. (1975). Parkinsonism: Effects of levodopa treatment on concept formation. *Neurology, 25*(8), 701-704.

Braun, C. M. J., Daigneault, S., & Champagne, D. (1989). Information processing deficits as indexed by reaction time parameters in severe closed head injury. *The International Journal of Clinical Neuropsychology, 11*(4), 167-176.

Brunia, C. H. M. (1993). Waiting in readiness: Gating in attention and motor preparation. *Psychophysiology, 30*, 327-339.

Burgess, P. W. (1997). Theory and methodology in executive function research. In P. Rabbitt (Ed.), *Methodology of frontal and executive function* (pp. 81-116). Hove: Psychology Press.

Burgess, P. W., & Shallice, T. (1996). Bizarre responses, rule detection and frontal lobe lesions. *Cortex, 32*(2), 241-259.

Butters, N., Butter, C., Rosen, J., & Stein, D. (1973). Behavioral effects of sequential and one-stage ablations of orbital prefrontal cortex in the monkey. *Experimental Neurology, 39*(2), 204-214.

Carter, C. S., Braver, T. S., Barch, D. M., Botvinick, M. M., Noll, D., & Cohen, J. D. (1998). Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science, 280*, 747-749.

Casey, B. J., Trainor, R. J., Orendi, J. L., Schubert, A. B., Nystrom, L. E., Giedd, J. N., Castellanos, F. X., Haxby, J. V., Noll, D. C., Cohen, J. D., Forman, S. D., Dahl, R. E., & Rapoport, J. L. (1997). A developmental functional MRI

study of prefrontal activation during performance of a Go-No-Go task. *Journal of Cognitive Neuroscience, 9*(6), 835-847.

Channon, S., & Crawford, S. (1999). Problem-solving in real-life-type situations: the effects of anterior and posterior lesions on performance. *Neuropsychologia, 37*(7), 757-770.

Cicerone, K. D. (1996). Attention deficits and dual task demands after mild traumatic brain injury. *Brain Injury, 10*(2), 79-89.

Clark, J. M. (1996). Contributions of inhibitory mechanisms to unified theory in neuroscience and psychology. *Brain and Cognition, 30*(1), 127-152.

Cockburn, J. (1995). Performance on the Tower of London test after severe head injury. *Journal of the International Neuropsychological Society, 1*(6), 537-544.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences*. (2nd ed.). Hillsdale, New Jersey: Lawrence Erlbaum.

Cohen, J. (1990). Things I have learned (so far). *American Psychologist, 45*(12), 1304-1312.

Cohen, J. (1994). The earth is round (p< .05). *American Psychologist, 49*(12), 997-1003.

Cohen, J. D., & Servan-Schreiber, D. (1992). Context, cortex, and dopamine: a connectionist approach to behaviour and biology in schizophrenia. *Psychological Review, 99*, 45-77.

Coles, M. G. H. (1998). Preparation, sensory-motor interaction, response evaluation, and event-related brain potentials. *Current Psychology of Cognition, 17*, 737-748.

Coles, M. G. H., Scheffers, M. K., & Fournier, L. (1995). Where did you go wrong? Errors, partial errors, and the nature of human information processing. *Acta Psychologica, 90,* 129-144.

Collet, C., Dittmar, A., & Vernet Maury, E. (1999). Programming or inhibiting action: Evidence for differential autonomic nervous system response patterns. *International Journal of Psychophysiology, 32*(3), 261-276.

Collins, L. F., & Long, C. J. (1996). Visual reaction time and its relationship to neuropsychological test performance. *Archives of Clinical Neuropsychology*

11(7), 613-629.

Connelly, S. L., & Hasher, L. (1993). Aging and the inhibition of spatial location. *Journal of Experimental Psychology: Human Perception and Performance, 19*(6), 1238-1250.

Cools, A. R., van den Bercken. J. H., Horstink, M. W., van Spaendonck K. P. & Berger H. J. (1984). Cognitive and motor shifting aptitude disorder in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry, 47*(5), 443-453.

Cooper, J. A., Sagar, H. J., Tidswell, P., & Jordan, N. (1994). Slowed central processing in simple and go/no-go reaction time tasks in Parkinson's disease. *Brain, 117*(3), 517-529.

Courville, C. B. (1945). *Pathology of the nervous system*. Montainview: Calif: Pacific Press.

Cremona Meteyard, S. L., & Geffen, G. M. (1994). Event-related potential indices of visual attention following moderate to severe closed head injury. *Brain Injury, 8*(6), 541-558.

Dalrymple Alford, E. C., & Budayr, B. (1966). Examination of some aspects of the stroop color-word test. *Perceptual and Motor Skills, 23*(3), 1211-1214.

Damasio, H., & Damasio, A. R. (1989). *Lesion analysis in neuropsychology.* New York: Oxford University Press.

Day, B. L., Dick, J. P., & Marsden, C. D. (1984). Patients with Parkinson's disease can employ a predictive motor strategy. *Journal of Neurology, Neurosurgery and Psychiatry, 47*(12), 1299-1306.

De Jong, R., Coles, M. G., Logan, G. D., & Gratton, G. (1990). In search of the point of no return: The control of response processes. *Journal of Experimental Psychology Human Perception and Performance, 16*(1), 164-182.

De Jong, R., Coles, M. G. H., & Logan, G. D. (1995). Strategies and mechanisms in nonselective and selective inhibitory motor control. *Journal of Experimental Psychology: Human Perception and Performance, 21*(3), 498-511.

de Langen, E. G., Frommelt, P., Wiedmann, K. D., & Amann, J. (1995).

Messung der funktionalen Selbständigkeit in der Rehabilitation mit dem Funktionalen Selbstandigkeitsindex (FIM). *Rehabilitation, 34*(1), 4-11.

de Zubicaray, G., & Ashton, R. (1996). Nelson's (1976) Modified Card Sorting Test: A review. *Clinical Neuropsychologist, 10*(3), 245-254.

Decary, A., & Richer, F. (1995). Response selection deficits in frontal excisions. *Neuropsychologia, 33*(10), 1243-1253.

Dehaene, S., Posner, M. I., & Tucker, D. M. (1994). Localization of a neural system for error detection and compensation. *Psychological Science, 5*(5), 303-305.

Delis, D. C., Squire, L. R., Bihrle, A., & Massman, P. J. (1992). Componential analysis of problem-solving ability: Performance of patients with frontal lobe damage and amnesic patients on a new sorting test. *Neuropsychologia, 30*(8), 683-697.

Dempster, F. N. (1992). The rise and fall of the inhibitory mechanism: Toward a unified theory of cognitive development and aging. *Developmental Review, 12*(1), 45-75.

Dempster, F. N. (1993). Resistance to interference: Developmental changes in a basic processing mechanism. In M. L. Howe & R. Pasnak (Eds.), *Emerging themes in cognitive development: Vol. 1. Foundations.* (pp. 3-27). New York: Springer.

Dettmers, C., Fink, G. R., Rijntjes, M., Stephan, K. M., & Weiller, C. (1997). Kortikale Kontrolle der Willkuermotorik: Funktionelle Bildgebung der motorischen Exekutive des ZNS. *Neurologie & Rehabilitation, 3*(1), 15-27.

Dimitrov, M., Grafman, J., Soares, A. H. R., & Clark, K. (1999). Concept formation and concept shifting in frontal lesion and Parkinson's disease patients assessed with the California Card Sorting Test. *Neuropsychology, 13*(1), 135-143.

Drewe, E. A. (1975a). Go-no go learning after frontal lobe lesions in humans. *Cortex, 11*(1), 8-16.

Drewe, E. A. (1975b). An experimental investigation of Luria's theory on the effects of frontal lobe lesions in man. *Neuropsychologia, 13*(4), 421-429.

Duncan, J., Johnson, R., Swales, M., & Freer, C. (1997). Frontal lobe deficits

after head injury: unity and diversity of function. *Cognitive Neuropsychology, 14*(5), 713–741.

Eimer, M. (1993). Effects of attention and stimulus probability on ERPs in a Go/Nogo task. *Biological Psychology, 35*(2), 123-138.

Engle, R. W., Conway, A. R. A., Tuholski, S. W., & Shisler, R. J. (1995). A resource account of inhibition. *Psychological Science, 6*(2), 122-125.

Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception and Psychophysics, 16*(1), 143-149.

Eslinger, P. J., & Damasio, A. R. (1985). Severe disturbance of higher cognition after bilateral frontal lobe ablation: Patient EVR. *Neurology, 35*(12), 1731-1741.

Eslinger, P. J., & Grattan, L. M. (1993). Frontal lobe and frontal-striatal substrates for different forms of human cognitive flexibility. *Neuropsychologia, 31*(1), 17-28.

Falkenstein, M., Hoormann, J., & Hohnsbein, J. (1999). ERP components in Go Nogo tasks and their relation to inhibition. *Acta Psychologica, 101*(2-3), 267-291.

Fallgatter, A. J., Brandeis, D., & Strik, W. K. (1997). A robust assessment of the NoGo-anteriorisation of P300 microstates in a cued continuous performance test. *Brain Topography, 9*(4), 295-302.

Flowers, K. A., & Robertson, C. (1985). The effect of Parkinson's disease on the ability to maintain a mental set. *Journal of Neurology, Neurosurgery and Psychiatry, 48*(6), 517-529.

Fox, E. (1995). Negative priming from ignored distractors in visual selection: A review. *Psychonomic Bulletin and Review, 2*(2), 145-173.

Frommelt, P., & de Langen, E. G. (1995). ICIDH und Funktionaler Selbstaendigkeitsindex (FIM). In R.-G. Matthesius, K.-A. Jochheim, G. S. Barolin, & C. Heinz (Eds.), *ICIDH. International Classification of Impairments, Disabilities, and Handicaps.* (pp. 125-142). Berlin / Wiesbaden: Ullstein Mosby.

Fuster, J. M. (1985). The prefrontal cortex, mediator of cross-temporal

contingencies. *Human Neurobiology, 4*(3), 169-79.

Fuster, J. M. (1989). *The prefrontal cortex: Anatomy, Physiology, and Neuropsychology of the Frontal Lobe*. (2nd ed.). New York: Raven Press.

Fuster, J. M. (1999). Synopsis of function and dysfunction of the frontal lobe. *Acta Psychiatrica Scandinavica, 99*(Suppl. 395), 51-57.

Gansler, D. A., Covall, S., McGrath, N., & Oscar Berman, M. (1996). Measures of prefrontal dysfunction after closed head injury. *Brain and Cognition, 30*(2), 194-204.

Gehring, W. J., Goss, B., Coles, M. G., Meyer, D. E., & Donchin, E. (1993). A neural system for error detection and compensation. *Psychological Science, 4*(6), 385-390.

Gemba, H., & Sasaki, K. (1989). Potential related to no-go reaction of go/no-go hand movement task with color discrimination in human. *Neuroscience Letters, 101*(3), 263-8.

Gemba, H., & Sasaki, K. (1990). Potential related to no-go reaction in go/no-go hand movement with discrimination between tone stimuli of different frequencies in the monkey. *Brain Research, 537*, 340-344.

Goldberg, G. (1985). Supplementary motor area structure and function: Review and hypotheses. *Behavioral and Brain Sciences, 8*, 567-616.

Goldberg, G. (1987). From intent to action: Evolution and function of the premotor systems of the frontal lobe. In E. Perecman (Ed.), *The frontal lobes revisited* (pp. 273-306). New York: The IRBN Press.

Goldman-Rakic, P. S. (1987). Circuit basis of a cognitive function in non-human primates. In S. M. Stahl, S. D. Iversen, & G. EC (Eds.), *Cognitive neurochemistry* (pp. 90-110). Oxford: Oxford University Press.

Grafman, J., Jonas, B., & Salazar, A. (1990). Wisconsin Card Sorting Test performance based on location and size of neuroanatomical lesion in Vietnam veterans with penetrating head injury. *Perceptual and Motor Skills, 71*(3), 1120-1122.

Green, D. M., Smith, A. F., & von Gierke, S. M. (1983). Choice reaction time with a random foreperiod. *Perception and Psychophysics, 34*(3), 195-208.

Greve, K. W., & Smith, M. C. (1991). A comparison of the Wisconsin Card

Sorting Test with the Modified Card Sorting Test for use with older adults. *Gerontology and Geriatrics Education, 11*(4), 57-65.

Grice, G. R., Nullmeyer, R., & Spiker, V. A. (1982). Human reaction time: Toward a general theory. *Journal of Experimental Psychology: General, 111*(1), 135-153.

Groenewegen, H. J. (1997). Cortical-subcortical relationships and the limbic forebrain. In M. R. Trimble & J. L. Cummings (Eds.), *Contemporary behavioral* neurology (Vol. 16, pp. 29-48). Boston, MA: Butterworth-Heinemann.

Hadley, D. M., & Teasdale, G. M. (1988). Magnetic resonance imaging of the brain and spine. *Journal of Neurology, 235*, 193-206.

Harnishfeger, K. K. (1995). The Development of Cognitive Inhibition. In F. N. Dempster & C. J. Brainerd (Eds.), *Interference and Inhibition in Cognition* (pp. 175-204). San Diego: Academic Press.

Heck, E. T., & Bryer, J. B. (1986). Superior sorting and categorizing ability in a case of bilateral frontal atrophy: An exception to the rule. *Journal of Clinical and Experimental Neuropsychology, 8*(3), 313-316.

Heubrock, D. (1992). Der Auditiv-Verbale Lerntest (AVLT) in der klinischen und experimentellen Neuropsychologie. Durchführung, Auswertung und Forschungsergebnisse. *Zeitschrift für Differentielle und Diagnostische Psychologie, 13*(3), 161-174.

Horn, W. (1962). Leistungsprüfsystem LPS [Testmappe]. Göttingen: Hogrefe.

Horn, W. (1983). Leistungsprüfsystem LPS [Testmappe]. Göttingen: Hogrefe.

Houghton, G., & Tipper, S. P. (1994). A model of inhibitory mechanisms in selective attention. In D. Dagenbach & T. H. Carr (Eds.), *Inhibitory Processes in attention, memory and language* (pp. 53-112). San Diego: Academic Press.

Houghton, G., & Tipper, S. P. (1996). Inhibitory mechanisms of neural and cognitive control: Applications to selective attention and sequential action. *Brain and Cognition, 30*(1), 20-43.

Huitema, B. E. (1980). *The Analysis of Covariance and Alternatives*. New York: John Wiley & Sons.

Jacobs, A. M. (1993). Modeling the effects of visual factors on saccade latency. In G. d'Ydewalle & J. Van Rensbergen (Eds.), *Perception and Cognition* (pp. 349-361). Amsterdam: Elsevier Science Publishers B.V.

Jahanshahi, M., & Frith, C. D. (1998). Willed action and its impairments. *Cognitive Neuropsychology, 15*(6-8), 483-533.

Jennings, J. R., Van der Molen, M. W., Brock, K., & Somson, R. J. M. (1992). On the synchrony of stopping motor responses and delaying heartbeats. *Journal of Experimental Psychology: Human Perception and Performance, 18*(2), 422-436.

Jodo, E., & Inoue, K. (1990). Effects of practice on the P300 in a Go/NoGo task. *Electroencephalography and Clinical Neurophysiology, 76*(3), 249-257.

Jodo, E., & Kayama, Y. (1992). Relation of a negative ERP component to response inhibition in a Go/No-go task. *Electroencephalography and Clinical Neurophysiology, 82*(6), 477-482.

Jones, D. L., Phillips, J. G., Bradshaw, J. L., Iansek, R., & Bradshaw, J. A. (1992). Impairment in bilateral alternating movements in Parkinson's disease? *Journal of Neurology, Neurosurgery and Psychiatry, 55*(6), 503-6.

Kaernbach, C. (1991). Simple adaptive testing with the weighted up-down method. *Perception and Psychophysics, 49*(3), 227-229.

Kalaska, J. F., & Crammond, D. J. (1995). Deciding not to go: Neuronal correlates of response selection in a go/nogo task in primate premotor and parietal cortex. *Cerebral Cortex, 5*(5), 410-428.

Kane, M. J., Hasher, L., Stoltzfus, E. R., Zacks, R. T., & Conelly, S. L. (1994). Inhibitory attentional mechanisms and aging. *Psychology and Aging, 9*(1), 103-112.

Karlin, L., Martz, M. J., & Mordkoff, A. M. (1970). Motor performance and sensory-evoked potentials. *Electroencephalography and Clinical Neurophysiology, 28*(3), 307-313.

Karnath, H. O., Wallesch, C. W., & Zimmermann, P. (1991). Mental planning and anticipatory processes with acute and chronic frontal lobe lesions: A comparison of maze performance in routine and non-routine situations. *Neuropsychologia, 29*(4), 271-290.

Kawashima, R., Satoh, K., Itoh, H., Ono, S., Furumoto, S., Gotoh, R., Koyama, M., Yoshioka, S., Takahashi, T., Takahashi, K., Yanagisawa, T., & Fukuda, H. (1996). Functional anatomy of GO/NO-GO discrimination and response selection - a PET study in man. *Brain Research, 728*(1), 79-89.

Keith, R. A., Granger, C. V., Hamilton, B. B., & Sherwin, F. S. (1987). The functional independence measure: a new tool for rehabilitation. In M. G. Eisenberg & R. C. Grzesiak (Eds.), *Advances in clinical rehabilitation* (Vol. 1, pp. 6-18). New York: Springer Verlag.

Kiefer, M., Marzinzik, F., Weisbrod, M., Scherg, M., & Spitzer, M. (1998). The time course of brain activations during response inhibition: Evidence from event-related potentials in a go/no go task. *Neuroreport, 9*(4), 765-770.

Kimberg, D. Y., Desposito, M., & Farah, M. J. (1997). Cognitive functions in the prefrontal cortex - Working memory and executive control. *Current Directions in Psychological Science, 6*(6), 185-192.

Kimberg, D. Y., & Farah, M. J. (1993). A unified account of cognitive impairments following frontal lobe damage: The role of working memory in complex, organized behavior. *Journal of Experimental Psychology: General, 122*(4), 411-428.

Kirby, N. (1980). Sequential effects in choice reaction time. In A. T. Welford (Ed.), *Reaction times* (pp. 129-172). London: Academic Press.

Kirby, N. H. (1976). Sequential effects in choice reaction time: automatic facilitation or subjective expectancy? *Journal of Experimental Psychology: Human Perception and Performance, 2*, 567-577.

Knight, R. T., Hillyard, S. A., Woods, D. L., & Neville, H. J. (1981). The effects of frontal cortex lesions on event-related potentials during auditory selective attention. *Electroencephalography and Clinical Neurophysiology, 52*(6), 571-582.

Kok, A. (1986). Effects of degradation of visual stimuli on components of the event-related potential (ERP) in go/nogo reaction tasks. *Biological Psychology, 23*(1), 21-38.

Konishi, S., Nakajima, K., Uchida, I., Kikyo, H., Kameyama, M., & Miyashita, Y. (1999). Common inhibitory mechanism in human inferior prefrontal cortex

revealed by event-related functional MRI. *Brain, 122*, 981-991.

Konishi, S., Nakajima, K., Uchida, I., Sekihara, K., & Miyashita, Y. (1998). No-go domninant brain activity in human inferior prefrontal cortex revealed by functional magnetic resonance imaging. *European Journal of Neuroscience, 10*, 1209-1213.

Kornblum, S. (1973). *Sequential effects in choice reaction time . A tutorial review.* New York: Academic Press.

Kramer, A. F., Humphrey, D. G., Larish, J., Logan, G. D., & Strayer, D. L. (1992, March). *Aging and Inhibition.* Paper presented at the Paper presented at the Conference on Cognition and Aging, Atlanta, GA.

Kramer, A. F., Humphrey, D. G., Larish, J. F., & Logan, G. D. (1994). Aging and inhibition: Beyond a unitary view of inhibitory processing in attention. *Psychology and Aging, 9*(4), 491-512.

Kropotov, J. D., & Etlinger, S. C. (1999). Selection of actions in the basal ganglia-thalamocortical circuits: review and model. *International Journal of Psychophysiology, 31*, 197-217.

Laming, D. R. J. (1968). *Information theory of choice reaction times*. London: Academic Press.

Lappin, J. S., & Erikson, C. W. (1966). Use of a delayed signal to stop a visual reaction-time response. *Journal of Experimental Psychology, 72*(6), 805-811.

Leimkuhler, M. E., & Mesulam, M. M. (1985). Reversible go-no go deficits in a case of frontal lobe tumor. *Annals of Neurology, 18*(5), 617-9.

Leon Carrion, J., Alarcon, J. C., Revuelta, M., Murillo Cabezas, F., Dominguez Roldan, J. M., Dominguez Morales, M. R., Machuca Murga, F., & Forastero, P. (1998). Executive functioning as outcome in patients after traumatic brain injury. *International Journal of Neuroscience, 94*(1-2), 75-83.

Levin, H., & Kraus, M. F. (1994). The frontal lobes and traumatic brain injury. *Journal of Neuropsychiatry and Clinical Neurosciences, 6*(4), 443-454.

Levitt, H. (1970). Transformed up-down methods in psychoacoustics. *The Journal of the Acoustical Society of America, 49*(2), 467-477.

Lezak, M. D. (1982). The problem of assessing executive functions. *International Journal of Psychology, 17*, 281-297.

Lezak, M. D. (1995). *Neuropsychological assessment*. (3rd ed.). New York: Oxford University Press.

Logan, G. D. (1981). Attention, automaticity, and the ability to stop a speeded choice response. In J. Long & A. Baddeley (Eds.), *Attention and Performance* (Vol. 11, pp. 205-222). Hillsdale: Erlbaum.

Logan, G. D. (1982). On the ability to inhibit complex movements: A stop-signal study of typewriting. *Journal of Experimental Psychology Human Perception and Performance, 8*(6), 778-792.

Logan, G. D. (1983). On the ability to inhibit simple thoughts and actions: I. Stop-signal studies of decision and memory. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 9*(4), 585-606.

Logan, G. D. (1985). Executive control of thought and action. *Acta Psychologica, 60*, 193-210.

Logan, G. D. (1985a). Executive control of thought and action. Special Issue: Action, attention and automaticity. *Acta Psychologica, 60*(2-3), 193-210.

Logan, G. D. (1985b). On the ability to inhibit simple thoughts and actions: II. Stop-signal studies of repetition priming. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 11*(1-4), 675-691.

Logan, G. D. (1988). Toward an instance theory of automatization. *Psychological Review, 95*(4), 492-527.

Logan, G. D. (1994). On the ability to inhibit thought and action: A users' guide to the stop signal paradigm. In D. Dagenbach & T. H. Carr (Eds.), *Inhibitory Processes in Attention, Memory and Language* (pp. 189-239). San Diego: Academic Press.

Logan, G. D., & Barber, C. Y. (1985). On the ability to inhibit complex thoughts: A stop-signal study of arithmetic. *Bulletin of the Psychonomic Society, 23*(5), 371-373.

Logan, G. D., & Burkell, J. (1986). Dependence and independence in responding to double stimulation: A comparison of stop, change, and dual-task paradigms. *Journal of Experimental Psychology: Human Perception and Performance, 12*(4), 549-563.

Logan, G. D., & Cowan, W. B. (1984). On the ability to inhibit thought and

action: A theory of an act of control. *Psychological Review, 91*(3), 295-327.

Logan, G. D., Cowan, W. B., & Davis, K. A. (1984). On the ability to inhibit simple and choice reaction time responses: A model and a method. *Journal of Experimental Psychology: Human Perception and Performance, 10*(2), 276-291.

Logan, G. D., Schachar, R. J., & Tannock, R. (1997). Impulsivity and inhibitory control. *Psychological Science, 8*(1), 60-64.

Lowe, D. G. (1979). Strategies, context, and the mechanism of response inhibition. *Memory and Cognition, 7*(5), 382-389.

Luce, R. D. (1986). *Response times: their role in inferring elementary mental organization*. New York: Oxford University Press.

Luria, A. R. (1966). *Higher cortical functions in man*. New York: Basic Books.

Mac Leod, C. M. (1991). Half a century of research on the stroop effect: an integrative review. *Psychological Bulletin, 109*, 163-203.

Malloy, P., Bihrle, A., Duffy, J., & Cimino, C. (1993). The orbitomedial frontal syndrome. *Archives of Clinical Neuropsychology, 8*(3), 185-201.

Mattson, A. J., & Levin, H. S. (1990). Frontal lobe dysfunction following closed head injury. *Journal of Nervous and Mental Disease, 178*(5), 282-291.

May, C. P., Kane, M. J., & Hasher, L. (1995). Determinants of negative priming. *Psychological Bulletin, 118*(1), 35-54.

McGarry, T., & Franks, I. M. (1997). A horse race between independent processes: evidence for a phantom point of no return in the preparation of a speeded motor response. *Journal of Experimental Psychology: Human Perception and Performance, 23*, 1533-1542.

Milner, B. (1964). Some effects of frontal lobectomy in man. In J. M. Warren & K. Akert (Eds.), *The frontal granular cortex and behavior* (pp. 313-334). New York: McGraw-Hill.

Milner, B. (1965). Visually-guided maze learning in man: effects of bilateral hippocampal, bilateral frontal, and unilateral cerebral lesions. *Neuropsychologia, 3*, 317-338.

Miltner, W. H. R., Braun, C. H., & Coles, M. G. H. (1997). Event-related brain potentials following incorrect feedback in a time-estimation task: Evidence for

a "generic" neural system for error detection. *Journal of Cognitive Neuroscience, 9*(6), 788-798.

Mink, J. W. (1996). The basal ganglia: focused selection and inhibition of competing motor programs. *Progress in Neurobiology, 50*(4), 381-425.

Mishkin, M., & Pribram, K. H. (1955). Analysis of the effects of frontal lesions in monkeys: I. Variations of delayed alternations. *Journal of Comparative and Physiological Psychology, 48*, 492-495.

Mountain, M. A., & Snow, W. G. (1993). Wisconsin Card Sorting Test as a measure of frontal pathology: A review. *Clinical Neuropsychologist, 7*(1), 108-118.

Neill, W. T. (1977). Inhibitory and facilitatory processes in selective attention. *Journal of Experimental Psychology: Human Perception and Performance, 3*, 444-450.

Neill, W. T. (1978). Decision processes in selective attention: Response priming in the Stroop Color-Word task. *Perception and Psychophysics, 23*(1), 80-84.

Neill, W. T. (1979). Switching attention within and between categories: Evidence for intracategory inhibition. *Memory and Cognition, 7*(4), 283-290.

Neill, W. T., & Valdes, L. A. (1992). Persistence of negative priming: Steady state or decay? *Journal of Experimental Psychology: Learning, Memory, and Cognition, 18*(3), 565-576.

Neill, W. T., & Valdes, L. A. (1995). Faciliatory and Inhibitory Aspects of Attention. In A. F. Kramer, M. G. H. Coles, & G. D. Logan (Eds.), *Converging Operations in the Study of Visual Selective Attenttion* (pp. 77-106). Washington, DC: American Psychological Association.

Neill, W. T., Valdes, L. A., & Terry, K. M. (1995). Selective attention and the inhibitory control of cognition. In F. N. Dempster & C. J. Brainerd (Eds.), *Interference and Inhibition in Cognition* (pp. 207-263). San Diego: Academic Press.

Neill, W. T., Valdes, L. A., Terry, K. M., & Gorfein, D. S. (1992). Persistence of negative priming: II. Evidence for episodic trace retrieval. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 18*(5), 993-1000.

Neill, W. T., & Westberry, R. L. (1987). Selective attention and the suppression of cognitive noise. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 13*(2), 327-334.

Nelson, H. E. (1976). A modified card sorting test sensitive to frontal lobe defects. *Cortex, 12*(4), 313-324.

Neumann, E., & DeSchepper, B. G. (1991). Costs and benefits of target activation and distractor inhibition in selective attention. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 17*(6), 1136-1145.

Norman, D. A., & Shallice, T. (1986). Attention to action: willed and automatic control of behaviour. In R. J. Davidson, G. E. Schwartz, & D. Shapiro (Eds.), *Consciousness and self-regulation: advances in research and theory* (pp. 1-18). New York: Plenum.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 9*(1), 97-113.

Osman, A., Kornblum, S., & Meyer, D. E. (1986). The point of no return in choice reaction time: Controlled and ballistic stages of response preparation. *Journal of Experimental Psychology: Human Perception and Performance, 12*(3), 243-258.

Osman, A., Kornblum, S., & Meyer, D. E. (1990). Does motor programming necessitate response execution? *Journal of Experimental Psychology: Human Perception and Performance, 16*(1), 183-298.

Owen, A. M., Roberts, A. C., Hodges, J. R., Summers, B. A., Polkey, C. E., & Robbins, T. W. (1993). Contrasting mechanisms of impaired attentional set-shifting in patients with frontal lobe damage or Parkinson's disease. *Brain, 116*, 1159-75.

Park, N. W., Moscovitch, M., & Robertson, I. H. (1999). Divided attention impairments after traumatic brain injury. *Neuropsychologia, 37*(10), 1119-1133.

Partiot, A., Verin, M., Pillon, B., C., T. F., Agid Y, & B, D. (1996). Delayed response tasks in basal ganglia lesions in man: Further evidence for a striato-frontal cooperation in behavioural adaptation. *Neuropsychologia,*

34(7), 709-721.

Pennington, B. F., & Ozonoff, S. (1996). Executive functions and developmental psychopathology. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 37*(1), 51-87.

Perret, E. (1974). The left frontal lobe of man and the suppression of habitual responses in verbal categorical behaviour. *Neuropsychologia, 12*(3), 323-330.

Pfefferbaum, A., Ford, J. M., Weller, B. J., & Kopell, B. S. (1985). ERPs to response production and inhibition. *Electroencephalography and Clinical Neurophysiology, 60*(5), 423-434.

Ponsford, J., & Kinsella, G. (1992). Attentional deficits following closed-head injury. *Journal of Clinical and Experimental Neuropsychology, 14*(5), 822-838.

Rabbitt, P. (1997). Introduction: Methodologies and models in the study of executive function. In P. Rabbitt (Ed.), *Methodology of frontal and executive function* (pp. 1-38). Hove: Psychology Press.

Rabbitt, P. M. (1966). Error correction time without external error signals. *Nature, 212*, 438.

Rabbitt, P. M. (1966). Errors and error correction in choice-response tasks. *Journal of Experimental Psychology, 71*(2), 264-272.

Rabbitt, P. M., & Rogers, B. (1977). What does a man do after he makes an error. An analysis of response programming. *Quarterly Journal of Experimental Psychology, 29*, 727-743.

Reason, J. (1990). *Human error*. Cambridge, MA: Cambridge University Press.

Reitan, R. M., & Wolfson, D. (1994). A selective and critical review of neuropsychological deficits and the frontal lobes. *Neuropsychology Review, 4*(3), 161-198.

Remington, R. J. (1969). Analysis of sequential effects on choice reaction times. *Journal of Experimental Psychology, 82*(2), 250-257.

Rey, A. (1964). L'examen clinique en psychologie. *Presses Universitäire en France*.

Riegler, G. L. (1986). *Are stop and go processes independent in the stop signal*

paradigm? Unpublished thesis. West Lafayette: Purdue University.

Robbins, T. W., Roberts, A. C., Owen, A. M., Sahakian, b. J., Everitt, B. J., Wilkinson, L., Muir, J., De Salvia, M., & Tovée, M. (1994). Monoaminergic-dependent cognitive functions of the prefrontal cortex in monkey and man. In A. M. Thierry, J. Glowinsky, P. S. goldman-Rakic, & Y. Christen (Eds.), *Motor and cognitive functions of the prefrontal cortex* (pp. 93-111). New York: Springer.

Robertson, I. H., Manly, T., Andrade, J., Baddeley, B. T., & Yiend, J. (1997). "Oops!": Performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. *Neuropsychologia, 35*(6), 747-758.

Sarter, M., Bernston, G. G., & Cacioppo, J. T. (1996). Brain imaging and cognitive neuroscience: toward strong inference in attributing function to structure. *American Psychologist, 51*(1), 13-21.

SAS. (1988). SAS System for Windows (Version 6.03). Cary, NC: SAS Institute Inc.

Sasaki, K., & Gemba, H. (1986). Electrical activity in the prefrontal cortex specific to no-go reaction of conditioned hand movement with colour discrimination in the monkey. *Experimental Brain Research, 64*(3), 603-6.

Sasaki, K., Gemba, H., & Tsujimoto, T. (1989). Suppression of visually initiated hand movement by stimulation of the prefrontal cortex in the monkey. *Brain Research, 495*(1), 100-107.

Schachar, R., & Logan, G. D. (1990). Impulsivity and inhibitory control in normal development and childhood psychopathology. *Developmental Psychology, 26*(5), 710-720.

Scheffers, M. K., Coles, M. G. H., Bernstein, P., Gehring, W. J., & Donchin, E. (1996). Event-related brain potentials and error-related processing: An analysis of incorrect responses to go and no-go stimuli. *Psychophysiology, 33*(1), 42-53.

Schmidt, I. W., Brouwer, W. H., Vanier, M., & Kemp, F. (1996). Flexible adaptation to changing task demands in severe closed head injury patients: A driving simulator study. *Applied Neuropsychology, 3*, 155-165.

Schroeger, E. (1993). Event-related potentials to auditory stimuli following

transient shifts of spatial attention in a Go/Nogo task. *Biological Psychology, 36*(3), 183-207.

Shallice, T. (1988). *From neuropsychology to mental structure*. Cambridge: Cambridge University Press.

Shallice, T., & Burgess, P. (1991). Higher-order cognitive impairments and frontal lobe lesions in man. In H. S. Levin, H. M. Eisenberg, & A. L. Benton (Eds.), *Frontal lobe function and dysfunction.* (pp. 125-138). New York: Oxford University Press.

Shallice, T., & Burgess, P. W. (1991). Deficits in strategy application following frontal lobe damage in man. *Brain, 114*, 727-741.

Shallice, T., & Evans, M. E. (1978). The involvement of the frontal lobes in cognitive estimation. *Cortex, 14*(2), 294-303.

Simson, R., Vaughan, H. G., & Ritter, W. (1977). The scalp topography potentials in auditory and visual Go/NoGo tasks. *Electroencephalography and Clinical Neurophysiology, 43*(6), 864-875.

Soetens, E. (1998). Localizing sequential effects in serial choice reaction time with the information reduction procedure. *Journal of Experimental Psychology: Human Perception and Performance, 24*(2), 547-568.

Soetens, E., Boer, L. C., & Hueting, J. E. (1985). Expectancy or automatic facilitation? Separating sequential effects in two-choice reaction time. *Journal of Experimental Psychology: Human Perception and Performance, 11*(5), 598-616.

Soetens, E., Deboeck, M., & Hueting, J. (1984). Automatic aftereffects in two-choice reaction time: A mathematical representation of some concepts. *Journal of Experimental Psychology: Human Perception and Performance, 10*(4), 581-598.

Spikman, J. M., van Zomeran, A. H., & Deelman, B. G. (1996). Deficits of attention after closed-head injury: Slowness only? *Journal of Clinical and Experimental Neuropsychology, 18*(5), 755-767.

SPSS. (1998). SPSS 8.0. Chicago: SPSS Inc.

Stablum, F., Leonardi, G., Mazzoldi, M., Umilta, C., & Morra, S. (1994). Attention and control deficits following closed head injury. *Cortex, 30*(4), 603-618.

Stablum, F., Mogentale, C., & Umilta, C. (1996). Executive functioning following mild closed head injury. *Cortex, 32*(2), 261-278.

Sturm, W., & Willmes, K. (1983). LPS-K - eine LPS-Kurzform für Hirngeschädigte Patienten; mit Anleitungen zur psychometrischen Einzelfalldiagnostik. *Diagnostica, 29*, 346-358.

Sturm, W., Willmes, K., & Horn, W. (1993). Leistungsprüfsystem für 50-90jährige (LPS 50+) [Testmappe]. Göttingen: Hogrefe.

Stuss, D. T. (1991). Self, awareness, and the frontal lobes: a neuropsychological perspective. In J. Strauss & Goethals (Eds.), *The self: interdisciplinary approaches* (pp. 255-278). New York: Springer Verlag.

Stuss, D. T., & Benson, D. F. (1984). Neuropsychological studies of the frontal lobes. *Psychological Bulletin, 95*, 3-28.

Stuss, D. T., & Benson, D. F. (1986). *The frontal lobes*. New York: Raven Press.

Stuss, D. T., & Gow, C. A. (1992). "Frontal dysfunction" after traumatic brain injury. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 5*(4), 272-282.

Stuss, D. T., Shallice, T., Alexander, M. P., & Picton, T. W. (1995). A multidisciplinary approach to anterior attentional functions. *Annals of the New York Academy of Sciences, 769*, 191-212.

Stuss, D. T., Stethem, L. L., Hugenholtz, H., Picton, T., Pivik, J. & Richard, M.T. (1989). Reaction time after head injury: Fatigue, divided and focused attention, and consistency of performance. *Journal of Neurology, Neurosurgery and Psychiatry, 52*(6), 742-748.

Stuss, D. T., Toth, J. P., Franchi, D., Alexander, M. P., Tipperd, S., & Craik, F. I. M. (1999). Dissociation of attentional processes in patients with focal frontal and posterior lesions. *Neuropsychologia, 37*(9), 1005-1027.

Tabachnick, B. G., & Fidell, L. S. (1996). *Using multivariate statistics*. (3rd ed.). New York: Harper Collins College Publishers.

Tipper, S. P. (1985). The negative priming effect: Inhibitory priming by ignored objects. *Quarterly Journal of Experimental Psychology: Human Experimental Psychology, 37a*(4), 571-590.

Tipper, S. P., Brehaut, J. C., & Driver, J. (1990). Selection of moving and static objects for the control of spatially directed action. *Journal of Experimental Psychology: Human Perception and Performance, 16*(3), 492-504.

Tipper, S. P., & Cranston, M. (1985). Selective attention and priming: Inhibitory and facilitatory effects of ignored primes. *Quarterly Journal of Experimental Psychology: Human Experimental Psychology, 4*, 591-611.

Tipper, S. P., MacQueen, G. M., & Brehaut, J. C. (1988). Negative priming between response modalities: Evidence for the central locus of inhibition in selective attention. *Perception and Psychophysics, 43*(1), 45-52.

Tipper, S. P., & Milliken, B. (1995). Distinguishing between inhibition-based and episodic retrieval-based accounts of negative priming. In A. F. Kramer, M. G. H. Coles, & G. D. Logan (Eds.), *Converging Operations in the Study of Visual Selective Attention.* (pp. 337-363). Washington, DC: American Psychological Association.

Tipper, S. P., Weaver, B., Cameron, S., Brehaut, J. C., & Bastado, J. (1991). Inhibitory mechanisms of attention in identification tasks: time-course and disruption. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 17*, 681-692.

Truong, M. K. (1993). Short Wisconsin Card Sorting Test nach Nelson 1976 (Version 1.1). Wuppertal: Universität-GHS Wuppertal, Klinische Psychologie.

Tupper, D. E., & Rosenblood, L. K. (1984). Methodological consideration in the use of attribute variables in neuropsycholgical research. *Journal of Clinical Psychology, 6*(4), 441-453.

Umilta, C., & Stablum, F. (1998). Control processes explored by the study of closed-head-injury patients. In G. Mazzoni & T. O. Nelson (Eds.), *Metacognition and cognitive neuropsychology: Monitoring and control processes* (pp. 37-52). Mahwah, NJ: Lawrence Erlbaum Associates.

Ungerleider, L. G., & Mishkin, M. (1982). Two cortical visual systems. In D. J. Ingle, M. A. Goodale, & R. J. W. Mansfield (Eds.), *Analysis of visual behavior* (pp. 549-586). Cambridge, MA: MIT Press.

Vakil, E., Weisz, H., Jedwab, L., Groswasser, Z., & Aberbuch, S. (1995). Stroop color-word task as a measure of selective attention: Efficiency in closed-

head-injured patients. *Journal of Clinical and Experimental Neuropsychology, 17*(3), 335-342.

Vallar, G. (1999). The methodological foundations of neuropsychology. In G. Denes & L. Pizzamiglio (Eds.), *Handbook of clinical and experimental neuropsychology* (pp. 95-131). Hove: Psychology Press.

van Gorp, W. G., Kalechstein, A. D., Moore, L. H., Hinkin, C. H., Mahler, M. E. Foti, D, & Mendez, M. (1997). A clinical comparison of two forms of the Card Sorting Test. *Clinical Neuropsychologist, 11*(2), 155-160.

Veltman, J. C., Brouwer, W. H., van Zomeren, A. H., & van Wolffelaar, P. C. (1996). Central executive aspects of attention in subacute severe and very severe closed head injury patients: Planning, inhibition, flexibility, and divided attention. *Neuropsychology, 10*(3), 357-367.

Verfaellie, M., & Heilman, K. M. (1987). Response preparation and response inhibition after lesions of the medial frontal lobe. *Archives of Neurology, 44*(12), 1265-1271.

Vilkki, J., & Holst, P. (1991). Mental programming after frontal lobe lesions: Results on digit symbol performance with self-selected goals. *Cortex, 27*(2), 203-211.

Vilkki, J., Virtanen, S., Surma Aho, O., & Servo, A. (1996). Dual task performance after focal cerebral lesions and closed head injuries. *Neuropsychologia, 34*(11), 1051-1056.

Walsh, K. (1987). *Neuropsychology*. Edinburgh: Churchill Livingstone.

Watanabe, M. (1986a). Prefrontal unit activity during delayed conditional Go/No-go discrimination in the monkey: I. Relation to the stimulus. *Brain Research, 382*(1), 1-14.

Watanabe, M. (1986b). Prefrontal unit activity during delayed conditional Go/No-go discrimination in the monkey: II. Relation to Go and No-go responses. *Brain Research, 382*(1), 15-27.

Wechsler, D. (1987). WMS-R: Wechsler Memory Scale - Revised. San Antonio: The Psychological Corporation Harcourt Brace Jovanovich Inc.

Weinberger, D. E. (1992). *A neural system approach to the frontal lobes.* Paper presented at the Presented at the American Academy of Neurology, San

Diego.

Welsh, M. C., & Pennington, B. F. (1988). Assessing frontal lobe functioning in children: views from developmental psychology. *Developmental Neuropsychology, 4*, 199-230.

Whyte, J., Fleming, M., Polansky, M., Cavallucci, C., & Coslett, H. B. (1997). Phasic arousal in response to auditory warnings after traumatic brain injury. *Neuropsychologia, 35*(3), 313-324.

Wichmann, T., & DeLong, M. R. (1996). Functional and pathophysiological models of the basal ganglia. *Current Opinion in Neurobiology, 6*, 751-758.

Wilkins, A. J., Shallice, T., & McCarthy, R. (1987). Frontal lesions and sustained attention. *Neuropsychologia, 25*(2), 359-365.

Williams, B. R., Ponesse, J. S., Schachar, R. J., Logan, G. D., & Tannock, R. (1999). Development of inhibitory control across the life span. *Developmental Psychology, 35*(1), 205-213.

Zakzanis, K. K. (1998). Brain is related to behavior ($p < .05$). *Journal of Clinical and Experimental Neuropsychology, 20*(3), 419-427.

10. Appendix

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Study 1: Localization of lesions in the frontal group

Etiology / Diagnosis	Frontal lesion			
	Basal – medial	Dorso-lateral	Mesial	Orbital
Infarct basal of the anterior horns	3	0	0	0
SAB A. carotis interna	0	2	0	0
SAB, A. communicans anterior	1	0	1	0
Tumor	0	3	3	0
Astrozytoma	0	2	0	0
SAB, AV-malformation	2	0	0	0
SAB A. communicans anterior	3	0	3	0
Olfactoriusmeningioma	3	0	3	3
SAB A. communicans anterior	0	1	0	0
Convexity meningioma	0	2	0	0
SAB A. carotis interna	0	2	0	0
SAB A. pericallosa	3	0	3	0
Meningioma fronto-basal	3	3	3	3
SAB, A. communicans anterior	2	0	3	0
Meningioma	3	0	3	0
SAB Ramus A. communicans anterior	0	3	0	0
SAB, A. communicans anterior	0	3	3	0

1= right 2= left, 3 bilateral; SAB = subarachnoid hemorrhage; A. = arteria

Study 1: Localization of lesions in the non-frontal group

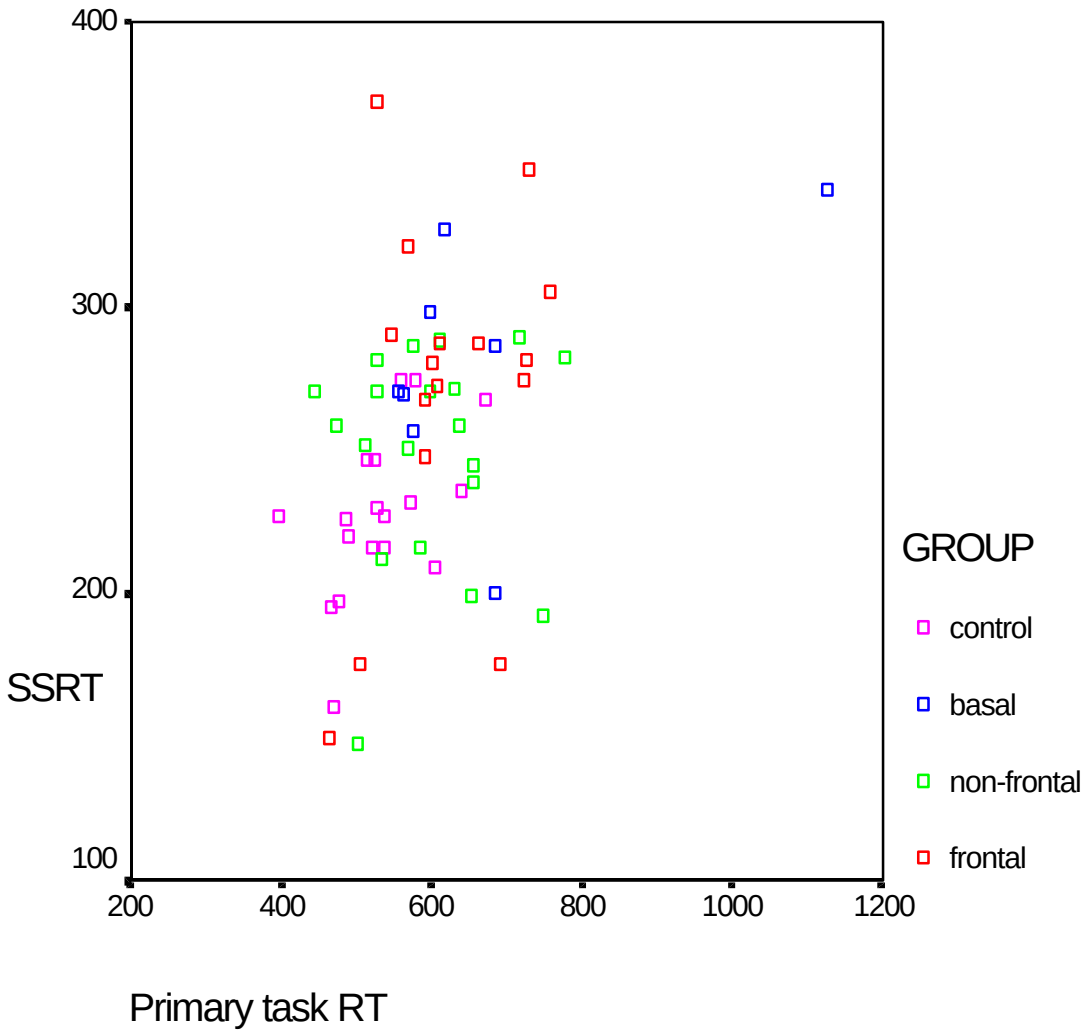
	Non-frontal lesion		
Etiology / Diagnosis	**Temporal**	**Parietal**	**Occipital**
Infarct, Stenosis A. carotis interna, origin	0	2	0
SAB, A. cerebri media	2	0	0
SAB A. basilaris	1	1	0
Infarct	1	0	0
Tumor	0	2	0
Infarct	0	2	2
SAB A. cerebri media	2	2	0
Infarct	2	2	0
Glioblastom corpus collosum			
Tumor	0	2	2
Infarct periventricular medulla	1	0	0
Glioblastoma	0	2	2
Infarct A. cerebri media	2	2	0
SAB	0	1	0
SAB, Pica-Aneurysma	1	0	0
Parenchymatous hemorrhage	1	1	0
Infarct A. communicans media	1	1	0
Meningioma medial sphenoid bone	0	0	0
SAB	0	2	0
Meningioma medial sphenoid bone	2	0	0

1= right 2= left, 3 bilateral; SAB = subarachnoid hemorrhage; A. = arteria

Study 1: The go nogo task in patients with focal lesions

Author(s), Year	**Participants**	**Method**	**Results**
Decary & Richer, 1995	- 8 frontal (6r, 2l) - 8 temporal (4r, 4l) - 8 controls (resection for relieve of epilepsy!, at least one year after surgery)	- 3 go nogo (equiprobable, 15:85; 85:15) - several other RT tasks	go nogo Response times: no group effect Error Rates: F more errors
Drewe, 1975	12 LF 12 RF 12 R NF 12 L NF	- go nogo - several other RT tasks	go nogo - F more errors than NFs - NFs improved over blocks Fs not - LFs did not differ from RFs
Drewe, 1975	12 LF 12 RF 12 R NF 12 L NF	go - no go learning:	* no difference LF + RF * F were impaired in - number of patients reaching criterion - trials to criterion - errors - more false positive errors => even after reaching criterion F patients had some difficulty
Leimkuhler & Mesulam, 1985	50-year-old woman large meningioma in the falx involving the medial aspects of the frontal lobes bilaterally		many errors of commission in the go-no go test. Following surgical excision of the tumor, her go-no go performance became normal.
Malloy et al., 1993	32 yr., orbitomedial frontal lesion		go nogo deficits

Study1: Correlation SSRT and primary task RT



Study 2: The go nogo task in patients with TBI

Author(s), Year	**Participants**	**Method**	**Results**
Cremona-Meteyard & Geffen, 1994	11 CHI 8 CON	go nogo ERPs	TBI did not show the normal CNV after no go cues (interpretation as perseverative behavior)
Braun et al., 1989	22 CHI 22 Controls	several RT tasks.	paradigms designed to elicit commission errors (a go/no-go paradigm, and a paradigm with prestimulus warning on a random interstimulus interval) were the most sensitive, particularly error rate measures for these tasks.
Collins & Long, 1996	47 impaired TBI 47 nonimpaired TBI 48 controls (students!).	simple and choice reaction time (RT**)** (go nogo!) Impairment Index	Median RT scores were better able to discriminate between impaired TBI patients and normal controls; go nogo yielded a better classification rate (not statistically significant) intraindividual variability of RT scores was better able to discriminate between nonimpaired TBI patients and normal controls.

Delays, Reaction times and probability of responding for stop-signal trials, depending upon the properties of trial n-1 for all trials and separated for same and different symbols in both trials (trial n as a stop signal trial).

	Trial n: stop signal trial							
	successful inhibition		no inhibition		All Stop Signal Trials			
Trial n-1	Average delay M (SD)	Number of trials per participant M (SD)	Average delay M (SD)	Number of trials per participant M (SD)	RT in ms M (SD)	Number of trials per participant M (SD)	Average delay M (SD)	P(respond) M (SD)
all trials								
no signal	130 (67)	62 (7)	348 (74)	39 (6)	482 (53)	102 (5)	215 (64)	39 (6)
stop signal, successful inhibition	215 (69)	8 (3)	369 (65)	8 (2)	492 (59)	17 (3)	292 (59)	50 (14)
stop signal, no inhibition	189 (66)	8 (2)	299 (108)	2 (2)	483 (105)	11 (2)	211 (68)	19 (14)
same symbols								
no signal	117 (67)	28 (4)	350 (71)	17 (3)	485 (54)	45 (2)	203 (64)	37 (7)
stop signal, successful inhibition	249 (78)	3 (1)	403 (58)	5 (1)	514 (75)	8 (1)	345 (60)	62 (15)
stop signal, no inhibition N=29	233 (68)	1 (1)	378 (112)	1 (1)	490 (70)	2 (1)	318 (110)	55 (40)
different symbols								
no signal	141 (67)	34 (5)	349 (78)	23 (4)	481 (58)	57 (4)	224 (64)	40 (7)
stop signal, successful inhibition	196 (71)	6 (2)	310 (69)	3 (2)	464 (63)	9 (2)	244 (59)	39 (17)
stop signal, no inhibition	183 (66)	8 (2)	231 (91)	1 (1)	477 (157)	9 (1)	192 (66)	14 (14)

Note: The data of all 34 participants were not available for all conditions.

It would be an interesting issue to analyze all possible trial combinations for aftereffects. The current data set does however not make such an analysis sensible. The table shows the values for aftereffects where the second trial is a stop signal. The probability of responding varies in the different conditions. ($F(2, 66)=104.36$, $p>0.0001$) all contrasts were significant. However, the same analysis for average delay as a dependent variable also yielded a significant effect ($F(2,66)=255$, $p>0.0001$). This is due to the fact, that during the experiment, after a late delay, where it is more difficult to inhibit a reaction, it was more probable to have an early delay and vice versa. Thus, it is not possible to differentiate between effects of the previous trial and the effects of stop signal delay. Furthermore, there is another problem: trial numbers are quite low and for the separation between symbols there were not even for all participants data available.

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Erklärung

Ich versichere, daß ich meine Dissertation

Stop! And Go? - Neuroanatomical correlates and consequences of the inhibition of ongoing responses

selbständig, ohne unerlaubte Hilfe angefertigt und mich dabei keiner anderen als der von mir ausdrücklich bezeichneten Quellen und Hilfen bedient habe.

Die Dissertation wurde in der jetzigen oder in einer ähnlichen Form noch bei keiner anderen Hochschule eingereicht und hat noch keinen sonstigen Prüfungswecken gedient.

Marburg, den 03.04.2000 Martina Rieger