# Inhibitory deficits in schizophrenia reconsidered

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# Inhibitory deficits in schizophrenia reconsidered

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# Contents

# Chapter 1

# Introduction

## 1.1 Schizophrenia

Schizophrenia is one of the most severe psychiatric disorders. The essential features of this disorder are the presence of delusions and/or hallucinations, disturbances of the content of thought, and deterioration from a previous level of functioning. According to the criteria of the DSM-IV (American Psychiatric Association 1994), at least some of these symptoms should be present for six months to establish the diagnosis.

The incidence of schizophrenia is about 0.5/1000, with a general population prevalence of about 0.6/100 (Hare 1987). The age of onset is most common in the third decade, and is rare prior to the age of 10 or after 40. Males tend to have an earlier age of onset than females (Stromgren 1987), while both are at equal risk. Relatives of patients are at significant greater risk for developing the disorder, which suggests a genetic influence (Kendler et al. 1985).

About 25% of schizophrenic patients achieve complete remission after one or more psychotic episodes, and while the course of the illness is variable, most patients appear to function at a relatively stable level after the first few years of the disease (Ciompi 1987). Factors associated with a more favorable outcome include later age of onset, acute onset with obvious precipitating factors, good premorbid social and occupational function, and the absence of family history (Kay & Lindenmayer 1987; McGlashan 1986).

A number of attempts have been made to subtype schizophrenia. All of these rest on purely phenomenological grounds. The DSM-IV recognizes five subtypes: disorganized, catatonic, paranoid, undifferentiated, and residual. The utility of these subtypes with respect to treatment and prognosis is, however, limited. More recently, schizophrenic patients have been divided into subtypes on the basis of positive and negative symptoms (Crow 1980), although also this classification is controversial. Positive symptoms include hallucinations, delusions, and disordered thought processes, whereas negative symptoms include symptoms like apathy, flattened affect, and social withdrawal. In addition to these symptoms, schizophrenia has been associated with a variety of cognitive impairments.

## 1.2 Cognitive deficits in schizophrenia

In the first half of this century there was a trend to downplay the significance of cognitive deficits in schizophrenia. This resulted in the implicit assumption that cognitive dysfunction was secondary to disordered thought processes and impaired motivation. Many recent studies have failed, however, to confirm a substantive role for motivational factors, thought disorder, medication effects, and institutionalization, which suggested the possibility of an underlying neuropathological process that is intrinsic to the disease. This view was supported by studies that have shown that cognitive deficits appear at the time of onset of schizophrenic symptoms and remain relatively stable throughout the course of the disorder (Heaton & Drexler 1987; Hyde et al. 1994). Moreover, cognitive deficits were found to be related to social and occupational outcome (Green 1996).

Despite numerous studies that have focused on cognitive deficits in schizophrenia, the *nature* of these deficits is still unclear. Many observations have supported the general idea that schizophrenia is characterized by frontal lobe dysfunction (Goldman-Rakic 1994; Hemsley 1994), since cognitive functions that primarily rely on the frontal cortex (e.g., working memory and response inhibition) were found to be particularly compromised in patients. In contrast, other studies have reported that a substantial proportion of patients displayed *normal* cognitive performance (Bryson et al. 1993; Holthausen et al. *submitted*; Palmer et al. 1997; Silverstein & Zerwic 1985), which implicates that frontal cognitive functions are not necessarily compromised in schizophrenia. In addition, a persistent controversy in the literature concerning the cognitive deficits of patients concerns the question whether the cognitive impairments reflect a *generalized* deficit or merely *domain specific* deficits. A generalized deficit implicates that all cognitive domains are (equally) affected and that cognitive impairment reflects cognitive inefficiency, imprecision and psychomotor slowing. This view may be the holdover from the notion that cognitive deficits do not reflect real cerebral dysfunction, but are secondary to motivational deficits or disordered thought processes. In contrast, *specific* deficits have been proposed for several cognitive domains, including verbal learning, vigilance, speeded visual-motor processing (Censits et al. 1997; Saykin et al. 1991; Saykin et al. 1994) and executive functioning (Mohamed et al. 1999).

## 1.3 Methods of cognitive assessment

Cognitive studies that have been performed during the last century can be divided in two related but independent approaches with virtually independent methods and literatures: the *neuropsychological* approach and the *experimental psychological* approach. The large majority of studies addressing cognitive function in schizophrenia was based on the neuropsychological approach. Within this approach, researchers are interested in the behavioral correlates of brain disorders, which are

examined by means of tests that are specifically developed to assess the integrity of cognitive functions and associated brain regions. In contrast, the experimental psychological approach examines cognitive processes by means of information processing models. Within this approach schizophrenia is characterized as a disorder with a faulty information processing mechanism. Cognitive function is, for example, assessed by means of the skin conductance orienting response, event related brain potentials, or eye movement responses. An advantage of these experimental psychological techniques over neuropsychological tasks is that cognitive processes can be examined more selectively. In the present thesis both neuropsychological and experimental psychological methods were used to study cognitive deficits in schizophrenia. Specific emphasis was put on the potentialities of saccadic eye movement tasks.

## 1.4 Saccadic eye movement tasks

Saccades are fast eye movements that are made to fixate objects on the fovea. These eye movements can be easily implemented in simple cognitive tasks. The performance on these tasks is evaluated by the accuracy and latency of the eye movement response. In contrast to neuropsychological tasks, the performance on saccadic tasks is independent of manual and verbal capacities. Moreover, a smaller number of cognitive subprocesses is involved. These characteristics implicate that saccadic tasks target cognitive functions rather selectively. Another advantage is that the neural systems subserving saccadic tasks are well known from primate studies (Bruce & Goldberg 1985; Everling et al. 1999; Hikosaka & Wurtz 1991). Saccadic impairments can therefore be interpreted in terms of brain dysfunction, which is particularly relevant in case of a complex brain disorder like schizophrenia.

Saccadic tasks have proven to be a valuable tool in estimating cognitive abnormalities in this disease (e.g., Crawford et al. 1995; Hutton et al. 1998; Thaker et al. 1989). In particular, the antisaccade task and the memory saccade task have revealed robust abnormalities. These abnormalities typically involve a failure to suppress response tendencies towards suddenly appearing stimuli, which is usually interpreted as a failure in inhibitory brain mechanisms. These inhibitory mechanisms are presumed to be important for controlling behavior in relation to environmental influences.

## 1.5 Inhibitory deficits in schizophrenia

Since the ability to inhibit irrelevant information is thought to be an essential element of higher order cognitive functions, inhibitory deficits might render patients vulnerable to stimulus inundation, cognitive fragmentation and thought disorder.

Deficits in inhibitory function were not only established by means of saccadic tasks, also other methods of cognitive assessment have revealed an increased vulnerability

to distractors in schizophrenic patients (for reviews, see Braff 1993; Goldberg & Gold 1995). The task that is most widely used for the examination of inhibitory function is the Stroop task (Stroop 1935; for review, see MacLeod 1991). A large number of studies have demonstrated Stroop abnormalities in schizophrenic patients (e.g., Barch et al. 1999; Carter et al. 1992). Inhibitory deficits have further been demonstrated by means of the double stimulus variant of the Continuous Performance Task (DS-CPT; Rosvold et al. 1956). On this task, patients typically display low hit rates and an increased number of false alarms (for review, see Cornblatt & Keilp 1994). In addition to these frequently used neuropsychological tasks, inhibitory deficits have also been demonstrated by means of experimental psychological paradigms like the negative priming task (e.g., Beech et al. 1989; Park et al. 1996; Tipper 1985; Williams 1996).

Despite this large body of evidence for inhibitory deficits, the *nature* of these deficits is still unclear. The results from studies using different inhibition tasks are not easily interpreted in terms of a general inhibitory deficit. Inhibitory deficits as revealed by different tasks might therefore result from dysfunction of different inhibitory mechanisms. More insight on this issue is likely to be gained from studies that examine the performance of patients across a wide range of tasks that represent different inhibitory processes. Therefore, the present thesis includes a study that aimed to reveal the nature of inhibitory deficits in schizophrenia by means of various experimental psychological tasks.

### 1.6 Inhibitory deficits & antipsychotic medication

The majority of schizophrenic patients receive antipsychotic medication in order to reduce psychotic symptoms. Antipsychotics might have a beneficial effect on cognitive function (for reviews, see Meltzer & McGurk 1999; Purdon 1999). Recent studies have suggested that novel antipsychotics are superior to classical antipsychotics with respect to cognitive improvement. Moreover, this beneficial effect would be independent of symptom improvement (Purdon 1999). However, novel antipsychotics are not positively affecting all cognitive domains, and different novel drugs might have a differential effect on specific cognitive domains (Meltzer & McGurk 1999). It remains to be established whether novel antipsychotics have a positive influence on inhibitory function.

Since the majority of studies that addressed the influence of antipsychotics on cognitive function have used neuropsychological tests, interesting new knowledge might be provided by studies using saccadic paradigms. Until now, only few studies have investigated the effects of antipsychotics on saccadic performance (e.g., Hommer et al. 1991). The majority of these studies focussed only on classical antipsychotics. Moreover, the results of these studies were rather inconsistent. Therefore, the present thesis includes a study that compared the effects of two novel

antipsychotics, olanzapine and risperidone, on the cognitive processes incorporated in various saccadic tasks.

## 1.7 Antipsychotics & the saccadic system in the rat brain

Clinical studies have suggested that classical and novel antipsychotics have different effects on the saccadic brain mechanism. Despite recent developments in neuroimaging techniques (i.e., PET, fMRI), it is difficult to investigate directly the influence of antipsychotics on the generation of saccades. Interesting information can, however, be provided by studies in the rat.

An essential region of the saccadic brain system is the superior colliculus. Various influences from frontal, parietal, cerebellar and striatal regions converge to this area and provide the input that is necessary for the production of an eye movement. The superior colliculus could be considered as the final common pathway for the generation of saccadic output. Therefore, if antipsychotics have an influence on the saccadic system, this effect is likely to be reflected in the activity of the superior colliculus.

The present thesis includes a study that examined the effects of different antipsychotics on the spontaneous cell activity in the superior colliculus of the rat.

## 1.8 Outline of the thesis

*Chapter 2* presents a literature review on saccadic paradigms that have been frequently used in schizophrenia research. In this review, it is reasoned that saccadic eye movement recording provides a useful method for the assessment of cognitive functions. This review deals with 1) relevant methodological aspects related to saccadic research, 2) the brain mechanisms involved in four widely used saccadic tasks, 3) the performance of schizophrenic patients on saccadic tasks, 4) the implications of the saccadic deficits for brain dysfunction in schizophrenia.

*Chapter 3* describes a study that examined cognitive performance in first-episode schizophrenic patients by means of three saccadic tasks. This study also examined the influence of antipsychotics by comparing patients who were randomly assigned to groups treated with either olanzapine or risperidone. This study demonstrated that cognitive deficits are already present in an early phase of the disease. Patients typically failed to inhibit an inappropriate saccadic response to suddenly appearing targets. In addition, treatment with either olanzapine or risperidone had no differential effect on the saccadic performance of patients.

*Chapter 4* presents a study that compared the sensitivity of respectively saccadic and neuropsychological tasks for frontal impairment in schizophrenia. Therefore, the saccadic performance of patients with *normal* performance on frontal neuropsychological tasks (e.g., Stroop task, Trail Making Test) was compared with the performance of patients with *abnormal* performance on these tasks. This study

further examined whether frontal dysfunction was a key feature of schizophrenia, and whether the cognitive deficits in this disorder were reflecting a *generalized* deficit or merely *specific* domain deficits. The results demonstrated that the chance to detect frontal impairment was largely increased when neuropsychological tasks were combined with saccadic tasks, but that the use of one type of task was not favorable over the other in detecting frontal impairment. The data further showed that 20% of patients did not exhibit frontal deficits. Moreover, the cognitive impairments were reflecting neither a generalized deficit nor specific domain deficits.

*Chapter 5* describes a study that examined inhibitory function in first-episode schizophrenic patients by six tasks that addressed three different type of inhibitory processes (i.e., cognitive inhibition, behavioral inhibition and interference control). This study failed to reveal inhibitory deficits in first-episode patients. Comparison with the literature suggested that the unexpected negative results could probably be explained by the fact that patients exhibited symptoms that were in (nearly) full remission due to successful antipsychotic treatment. This implicates that inhibitory deficits in schizophrenia as measured by experimental psychological tasks are merely *state* than *trait* dependent.

*Chapter 6* presents an animal study that examined the influence of antipsychotics on the superior colliculus. In anaesthetized rats, changes in the spontaneous cell activity of the superior colliculus were examined upon administration of acute doses of respectively clozapine, olanzapine, risperidone, and haloperidol. The study revealed that only clozapine had a significant effect (i.e., reduction) on the firing rate of superior colliculus neurons. This finding seems in line with other studies that have demonstrated a unique action profile of clozapine.

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# Chapter 2

# Parsing cognition in schizophrenia using saccadic eye movements: a selective overview

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**Abstract**

Eye movements provide a behavioural measure of sensorimotor processing and higher cognitive functions of the brain. With the development of novel paradigms that can be used for the study of various cognitive operations, saccadic eye movements in particular, have become increasingly popular. Patients with schizophrenia have neurocognitive impairments that can be readily investigated with these paradigms. From animal, human lesion and neuroimaging studies the cerebral centres underlying saccadic eye movements have been identified. The areas of the prefrontal cortex include the dorsolateral prefrontal cortex, the frontal eye fields, the supplementary eye fields, and the anterior cingulate cortex. Pathology of saccadic eye movements, therefore, provides information on the functional status of the underlying neural circuitry in brain disorders such as schizophrenia. In this paper we evaluate: 1) methodological considerations that are central to the design and application of saccadic paradigms; 2) brain activation that is associated with saccadic paradigms; 3) recent findings in healthy subjects and schizophrenic patients; 4) saccadic abnormalities in other psychiatric and neurological disorders and in individuals at risk for developing schizophrenia.

## 1. Introduction

Neurocognitive research in schizophrenia has relied heavily on traditional psychological tests of cognition. In recent years, research on eye movement behaviour has provided an alternative index of high level cognitive functions. In schizophrenia research, abnormalities of smooth pursuit have been a primary focus of research, and are widely proposed as a potential biological marker of this disease (Clementz & Sweeney 1990; Holzman 1992; Iacono et al. 1992; Levy et al. 1994). These abnormal eye movements were first reported by Diefendorf and Dodge (Diefendorf & Dodge 1908) but only emerged as a promising biological marker for the disease in the 1970's following the demonstration of abnormalities in family and twin studies (Holzman et al. 1973, 1974). Encouragingly, smooth pursuit deficits were reliably associated with both adult and childhood forms of schizophrenia (Jacobsen et al. 1996; Ross et al. 1996). However, despite highly replicated findings there is no consensus on the neural substrates of this abnormality, nor on the underlying functional deficit (Chen et al. 1999; Levin 1984).

In recent studies, the interest of researchers has turned increasingly to saccadic eye movement paradigms. In the last 20 years novel saccadic paradigms have been developed which evaluate a variety of cognitive processes using the spatial and temporal parameters of the eye movement. In contrast to neuropsychological tests, where performance is dependent on the development of verbal and manual abilities, saccadic paradigms allow experimental manipulations that can examine behaviour in human and animal studies using an identical behavioural response, and are easily combined with functional brain imaging.

Schizophrenia is a psychotic disorder that is characterised by severe abnormalities of cognition. Assuming, that these abnormalities originate within dysfunctional cortical and subcortical neural pathways, eye movement paradigms that test cognition may provide an important and convenient technique for the exploration of these neural subsystems. Recent studies using saccadic paradigms have found evidence of selective disturbances, which correlated with cognitive measures using neuropsychological tests (Crawford et al. 1995a,b; Hutton et al. 1998; Karoumi et al. 1998; Rosse et al. 1993). Several studies have attempted to combine saccadic paradigms with the techniques of functional brain imaging to address directly the localisation of cognitive operations. Employing the precision of single unit recordings, neurophysiological studies in non-human primates have probed the characteristics of eye movement related operations at the level of the neurone.

In this selective review we consider: 1) methodological considerations that are central to the design and application of saccadic paradigms; 2) the implications of research that have attempted to unravel the underlying neural pathways using the core saccadic paradigms; 3) the implications of this research for our understanding of the pathophysiology of schizophrenia; 4) saccadic abnormalities in various other

psychiatric and neurological disorders and in individuals at risk of developing schizophrenia.

## 2. Saccadic paradigms and performance parameters

Two major types of saccadic eye movements can be distinguished: visually-guided (or reflexive) saccades and voluntary saccades. A visually-guided saccade can be defined as an automatic orienting response to a novel event in the peripheral field[1]. This requires the integration of spatial attention, visual encoding and a precisely targeted motor program, but places few demands on higher order, executive functions. In voluntary saccadic paradigms, there is an increased demand on higher order cognitive resources, which results in an increased complexity in the pattern of brain activation. Visually-guided saccades and voluntary saccades have identifiable neural pathways that relate to their corresponding cognitive operations. Studies of patients with focal brain lesions have demonstrated that deficits in one brain region can disrupt the performance in certain saccadic paradigms and spare others. By using a battery of paradigms (e.g., Crawford et al. 1995a, see Figure 1) it has been possible to dissociate key cognitive operations (Table 1) and thus identify distinctive abnormalities in the behavioural profiles of saccadic eye movements.

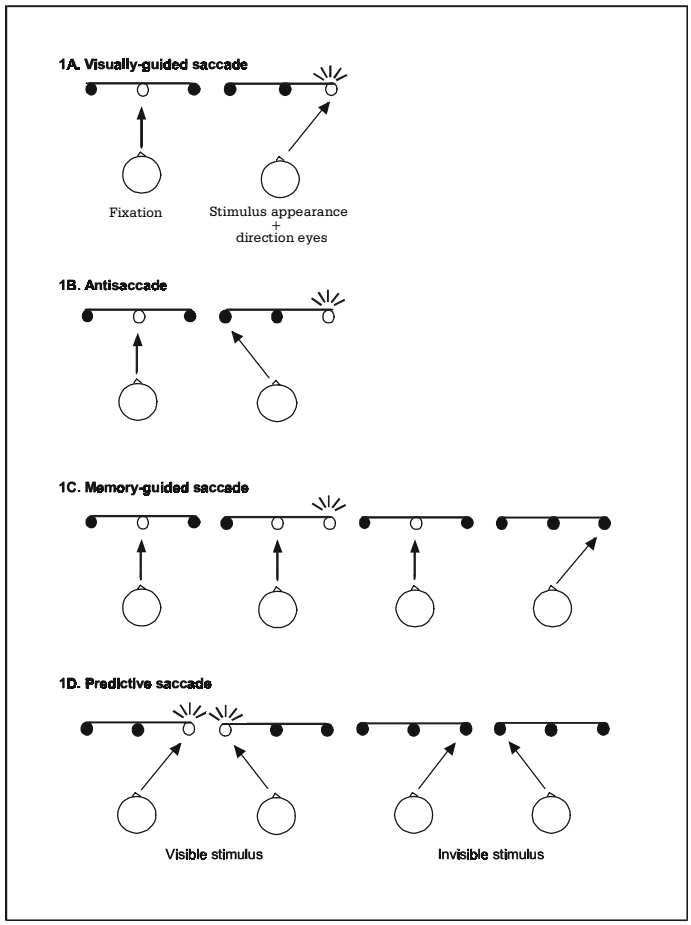


Figure 1. Saccadic paradigms

**1A:** A visual stimulus is presented in a random sequence to the left or right of a central fixation point and subjects are instructed to respond with a rapid and accurate eye movement.

**1B:** Antisaccades are directed towards a spatial position in the opposite visual field to that of the stimulus. The paradigm requires suppression of the reflexive saccade that would normally be generated in response to a novel visual target, and the generation of a volitional saccade to the opposite hemifield.

**1C:** Subjects are instructed to suppress the normal reflexive eye movement in response to a novel stimulus, and to delay the saccade until the offset of the central light. There is no visual information on the location of the previously presented target at the moment of saccadic initiation.

**1D:** A visible target steps between (two) fixed locations in a predictable temporal sequence. In some studies there is an additional phase where a series of visible targets is followed by a sequence in which target visibility is withdrawn.

Table 1
*Dissociation of two key operations in the saccadic paradigms*

| | Inhibition of prepotent responses | Spatial working memory |
|---|---|---|
| **Visually-guided saccades** | - | - |
| **Antisaccades** | + | - |
| **Memory-guided saccades** | + | + |
| **Predictive saccades *** | - | + |

* non-visible target phase (see Figure 1); **+** = cognitive operation requires high priority for correct performance;
**–** = cognitive operation requires low priority for correct performance.

A variety of cognitive operations have been explored in saccadic paradigms including: 1) spatial attention; 2) inhibition of a reflexive (i.e. prepotent) response; 3) spatial working memory; 4) predictive and anticipatory behaviour. The core paradigms include: the visually-guided saccade paradigm, the antisaccade paradigm, the memory-guided saccade paradigm, and the predictive saccade paradigm (Figure 1, Table 1). Within these paradigms many permutations are possible. This may account for a significant proportion of the variability across studies, therefore the consideration of methodological procedures is of major significance.
A number of critical judgements on the nature of the stimulus are required in the implementation of a saccadic paradigm: 1) the number of spatial locations and the eccentricity and timing of the targets; 2) presence or absence of a fixation point during target presentation; 3) timing of a temporal gap from the offset of the fixation point to the presentation of the target (gap paradigm), or duration of the fixation point while the target is presented (overlap paradigm); 4) inclusion of a target cue. The nature and specific values of these parameters can have a significant impact on performance and therefore the underlying cognitive processes. A warning cue, for example, will prepare a subject for the forthcoming stimulus, and thus supply an additional attentional component. Saccadic eye movements are highly sensitive to the characteristics of the behavioural paradigm (Crawford et al. 1995a; Hutton et al. 1998; Karoumi et al. 1998; O'Sullivan et al. 1997; Pierrot-Deseilligny et al. 1995; Rosse et al. 1993).

## 3. Visually-guided saccades

The visually-guided (‘reflexive’) saccade is the simplest and most widely studied paradigm. A visual stimulus is presented in a random sequence to the left or right of a central fixation point, and subjects are instructed to respond with a rapid and accurate eye movement. A distinction can be made between so-called express saccades, with very short latencies (85-135 ms), and regular visually-guided saccades. The rapid, express saccades accelerate the capture of visual information from the

peripheral field (Fischer & Weber 1993). Express saccades are most reliably generated when the central fixation point is absent at the time of target presentation (e.g., gap paradigm) (Fischer & Ramsperger 1984; Fischer & Weber 1993). A gap paradigm (with a gap of 200-250 ms) decreases the latency and increases the peak velocity of saccades (Pratt 1998). In contrast, a temporal *overlap* between the fixation point and the stimulus appearance leads to a latency increase (Fischer & Weber 1993). An informative (valid) visual cue to the location of the target reduces the latency, whereas an invalid cue increases the saccadic latency (Cavegn 1993). These manipulations do not affect the amplitude or the duration of saccades.

### 3.1 Visually-guided saccades in schizophrenic patients

Several recent studies showed that schizophrenics generate visually-guided saccades with normal accuracy and latency (Clementz et al. 1994; Crawford et al. 1995a,b; Fukushima et al. 1988, 1990a; Hutton et al. 1998; Karoumi et al. 1998; Maruff et al. 1998; Muller et al. 1999; Park & Holzman 1992; Straube et al. 1999). However, they have problems in the modulation of express saccades. Currie et al. (1993) reported fewer express saccades when gaps of 50-150 ms were used. In contrast, Clementz et al. (1996) reported a higher frequency of express saccades in schizophrenics compared to non-psychiatric controls. This was consistent with Matsue et al's finding (1994), who also reported a higher frequency of express saccades in patients with smooth pursuit impairment (see also Sereno & Holzman 1993). According to Clementz et al. (1996) the discrepant results of Currie et al. (1993) may be related to the relatively short fixation periods used in this study, leading to inhibition of express saccades.

### 3.2 Neural control of visually-guided saccades

Sensorimotor programming in the visually-guided paradigm can be conducted by different cortical and subcortical pathways depending on the nature of the saccadic paradigm (Fischer & Weber 1993) (Figure 2). Express saccades are generated via the lateral Geniculate Body (LGB), occipital cortex (OCC), the Superior Colliculus (SC), and brainstem premotor neurons (Figure 2, trajectory 1). The crucial involvement of the SC was demonstrated in both monkey studies (Schiller et al. 1987) and human studies (Pierrot-Deseilligny et al. 1991a), showing that SC damage reduced the ability to generate express saccades. The express saccade pathway is under inhibitory control of the frontal eye fields (FEF) and the dorsolateral prefrontal cortex (DLPFC), as was suggested by studies in patients with prefrontal lesions (Guitton et al. 1985; Pierrot-Deseilligny et al. 1991b) and primate studies (Everling & Munoz 2000). The source of this inhibitory signal is, however, unclear (Schlag et al. 1992), since the cortical projections to the SC are considered to be excitatory[2].

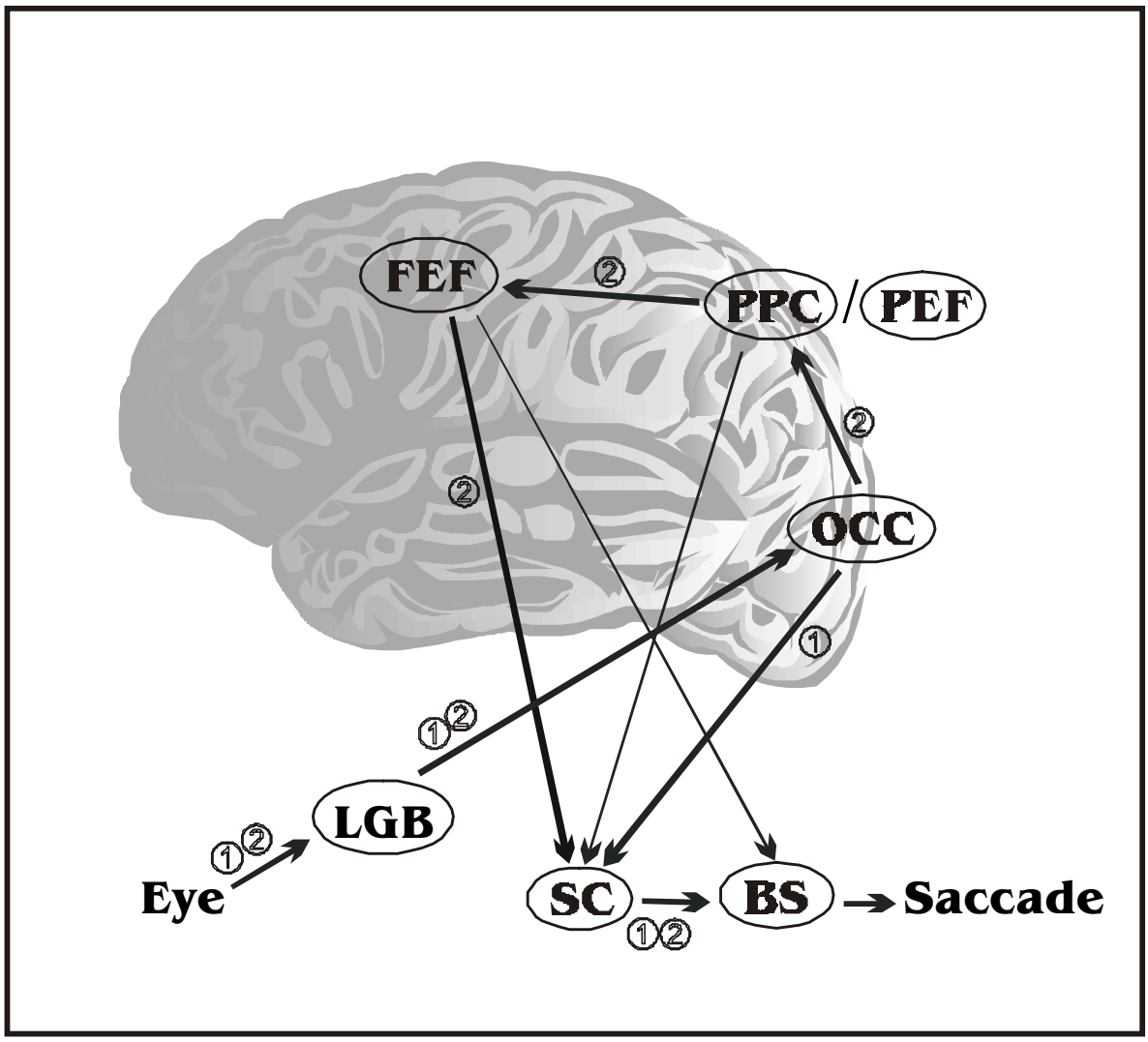


Figure 2. Neural control of visually-guided saccades
Trajectory 1, neural pathway for the generation of express saccades; Trajectory 2, neural pathway for regular visually-guided saccades; BS = brainstem; FEF = frontal eye fields; LGB = lateral geniculate body; OCC = occipital cortex; PEF = parietal eye fields; PPC = posterior parietal cortex; SC = superior colliculus.

The major inhibitory input to the SC is a GABAergic projection via the Substantia Nigra reticulata (SNr) (Grantyn et al. 1984; Hikosaka & Wurtz 1985a,b). When inhibitory subcortical signals to the SC are suppressed (resulting in disinhibition of the SC), a saccade can be triggered. In contrast to express saccades, the generation of regular visually-guided saccades involves several cortical areas (Figure 2, trajectory 2). Lesion and transcranial magnetic stimulation (TMS) studies have shown that these saccades depend on activation in the posterior parietal cortex (PPC, including the parietal eye fields, PEF) (Carter & Zee 1997; Pierrot-Deseilligny et al. 1986, 1988) and the FEF (Rivaud et al. 1994).
Functional brain imaging studies of visually-guided saccades (Table 2) agree on the activation of the FEF, the OCC, and to a lesser extent the PPC. In addition, Fox et al. (1985) also demonstrated increased activation of the supplementary motor area

Table 2

*Functional brain imaging studies of visually-guided saccades*[3]

| BRAIN AREA | Fox '85 [28] Sacc-Rest (PET) | Anderson '94 [2] Sacc-Fix (PET) | Sweeney '96 [98] Sacc-Fix (PET) | Corbetta '98 [10] Sacc-Fix (fMRI) |
|---|---|---|---|---|
| **Frontal** | | | | |
| Frontal eye fields | + | + | + | |
| Dorsolateral prefrontal cortex | | | - | |
| Precentral sulcus | | | | + |
| Middle frontal gyrus | | | | + |
| Inferolateral frontal cortex (BA 47,9,10,45,46) | | - | | |
| Supplementary motor area | + | 0 | 0 | |
| Anterior cingulate cortex (BA 24,32) | | - | | |
| **Parietal** | | | | |
| Posterior inferior parietal lobe (BA 39/40) | 0 | | | |
| Superior parietal lobe (BA 7) | | + | + | |
| Intraparietal sulcus | | | | + |
| **Temporal** | | | | |
| Posterior temporal cortex | | | + | |
| Temporal gyrus | | | - (sup)<br>- (l inf) | + (sup) |
| **Occipital** | | | | |
| Striate cortex (BA 17) | + | + | + | |
| Extrastriate cortex (BA 18,19) | 0 | + (med)<br>- (lat) | | |
| Fusiform gyrus (lateral/medial) | | | | + |
| Lingual gyrus (lateral/medial) | | | | + |
| Calcarine sulcus | | | | + |
| Basal ganglia | 0 | | | |
| Thalamus | 0 | | + (r post) | |
| Cerebellum | | | + | + (med) |

sacc = saccade; fix = fixation; BA = Broadman Area; + = increase; - = decrease; 0 = no change; r = right; l = left; lat = lateral; sup = superior; post = posterior; med = medial; inf = inferior.

(SMA), in contrast to Sweeney et al. (1996) and Anderson et al. (1994) who failed to observe this activation. Two methodological factors appear to differentiate these studies. First, Fox et al. (1985) presented targets at a single eccentricity. This absence of spatial uncertainty could have increased the activity of preparatory set cells in the SMA (Schall 1991). Second, SMA activity during visually-guided saccades may be dependent on short stimulus intervals and high re-fixation rates, since the SMA is known to be sensitive to movement rate (Jenkins et al. 1994).

These considerations suggest that parameters that can influence task difficulty are likely to have a strong influence on regional cerebral activity.

### 3.3 Implications for schizophrenia

An increased number of express saccades, as was found in two studies, might be explained by defects in the prefrontal cortex, since the pathway for generation of express saccades is under FEF and DLPFC control. However, the issue of whether abnormalities of the DLPFC or FEF are responsible for the express saccade impairments in schizophrenia is unsettled. Moreover, further studies are required to clarify the possible contribution of other cortical and subcortical areas.

Since schizophrenic patients produce regular visually-guided saccades of normal accuracy and peak velocity, the fundamental properties of the saccadic motor system (Leigh & Zee 1999) are not disrupted by the disease process. This implicates intact sensorimotor integration at the level of the OCC, PPC, SC, and brainstem premotor neurons. The FEF, however, cannot be excluded as a site of functional impairment in schizophrenia since the control of visually-guided saccades recovers shortly after a lesion of the FEF (Leigh & Zee 1999; Schiller et al. 1987).

## 4. Antisaccades

The antisaccade paradigm (Figure 1B) (Hallet 1978) has been used widely to explore the programming of volitional eye movements and the inhibition of inappropriate action. Antisaccades are directed towards a spatial position in the opposite visual field to that of the stimulus. The paradigm requires suppression of the reflexive saccade that would normally be generated in response to a novel visual target, and generation of a volitional saccade to the mirror position. When compared to visually-guided saccades, the mean latency of antisaccades is increased (Fukushima et al. 1988, 1990a,b; Hutton et al. 1998; Sereno & Holzman 1995; Thaker et al. 1989) and the peak velocity is reduced (Everling & Fischer 1998). Saccadic inhibition errors, resulting from a failure in the suppression of a reflexive eye movement, have latencies that are comparable to those of visually-guided saccades (Fischer & Weber 1992; Thaker et al. 1989). The frequency of inhibition errors, which varies in studies from 2% to 25% (Table 3), is dependent on properties of the paradigm. The error rate can be modulated by: 1) the eccentricity of the stimulus (Crawford et al. 1996); 2) the inclusion of a temporal gap of 200 ms between fixation and stimulus presentation (Fischer et al. 1997); 3) a paradigm in which antisaccades and visually-guided saccades are mixed (Hallet & Adams 1980); and 4) the inclusion of a valid target cue (Fischer & Weber 1992).

Table 3
*Abnormalities of antisaccades in schizophrenic patients*

| Abnormality | Study | SZ (%) | Cs (%) |
|---|---|---|---|
| **Increased number of inhibition errors** | Thaker et al. '89 [100] | 35 | 10 |
| | Thaker et al. '89 [100] | 60 [a] | 10 |
| | Fukushima et al. '90 [32] | 29 | 2 |
| | Fukushima et al. '90 [32] | 26 | 2 |
| | Clementz et al. '94 [8] | 57 | 21 |
| | Fukushima et al. '94 [30] | 34 | 4 |
| | Sereno & Holzman '95 [96] | 24 | 6 |
| | Crawford et al. '95 [11] | 52 | 21 |
| | Allen et al. '96 [1] | 36 | 13 |
| | McDowell & Clementz '97 [66] | 71 | 25 |
| | Katsanis et al. '97 [52] | 64 | 25 |
| | Hutton et al. '98 [46] | 37 | 19 |
| | Karoumi et al. '98 [50] | 52 | 19 |
| | Maruff et al. '98 [63] | 30 | 5 |
| | Crawford et al. '98 [15] | 53 | 27 |
| | Ross et al. '98 [89] | 53 | 21 |
| | McDowell et al. '99 [68] | 59 | 15 |
| | Müller et al. '99 [69] | 50 | 13 |
| **Increased latency** | Thaker et al. '89 [100]; Fukushima et al. '90 '94 [30, 32]; Tien et al. '96 [103]; McDowell & Clementz '97 [66]; Hutton et al. '98 [46]; Karoumi et al. '98 [50]; Maruff et al. '98 [63]; Crawford et al. '98 [15]; Müller et al. '99 [69] | | |
| **Decreased latency of inhibition errors** | Fukushima et al. '94 [30]; Tien et al. '96 [103] | | |
| **Decreased amplitude** | Crawford et al. '95 [12]; Hutton et al. '98 [46]; Karoumi et al. '98 [50]; Maruff et al. '98 [63]; Ross et al. '98 [89] | | |
| **Decreased peak velocity** | Fukushima et al. '90, '94[b] [30, 31]; Müller et al. '99[b] [69] | | |
| **Decreased duration** | Fukushima et al. '90 [30] | | |

SZ = schizophrenic patients; Cs = controls; TD = tardive dyskinesia; [a] = SZ with TD
[b] = SZ: AP treated.

## 4.1 Antisaccades in schizophrenia

There is a general consensus in the increased frequency of inhibition errors in schizophrenic patients (Allen et al. 1996; Crawford et al. 1995a, 1996, 1998; Fukushima et al. 1990a,b, 1994; Hutton et al. 1998; Karoumi et al. 1998; Katsanis et al. 1997; Matsue et al. 1994; McDowell et al. 1999; Muller et al. 1999; Rosse et al. 1993; Sereno & Holzman 1995; Tien et al. 1996); a consensus that is remarkable in the context of schizophrenia research. Error rates range in studies, however, from

24% to 71% (Table 3). Abnormalities of latency, amplitude, peak velocity, and duration have also been demonstrated (Table 3), although these deficits are not consistent across studies. Discrepant results may be explained partly by differences in the paradigms and factors related to population sampling in this heterogeneous disorder. For example, negative symptoms, anergia, deficit syndrome and formal thought disorder are associated with poor antisaccade performance, whereas this is not true for positive symptoms (Crawford et al. 1995b; Fukushima et al. 1994; Muller et al. 1999; Tien et al. 1996). Patients with tardive dyskinesia generate more inhibition errors than patients without tardive dyskinesia (Thaker et al. 1989). However, antipsychotic medication (Crawford et al. 1995b; Hutton et al. 1998; Muller et al. 1999) and chronicity of the disease appear to have no effect on antisaccade error rates (Crawford et al. 1995b).

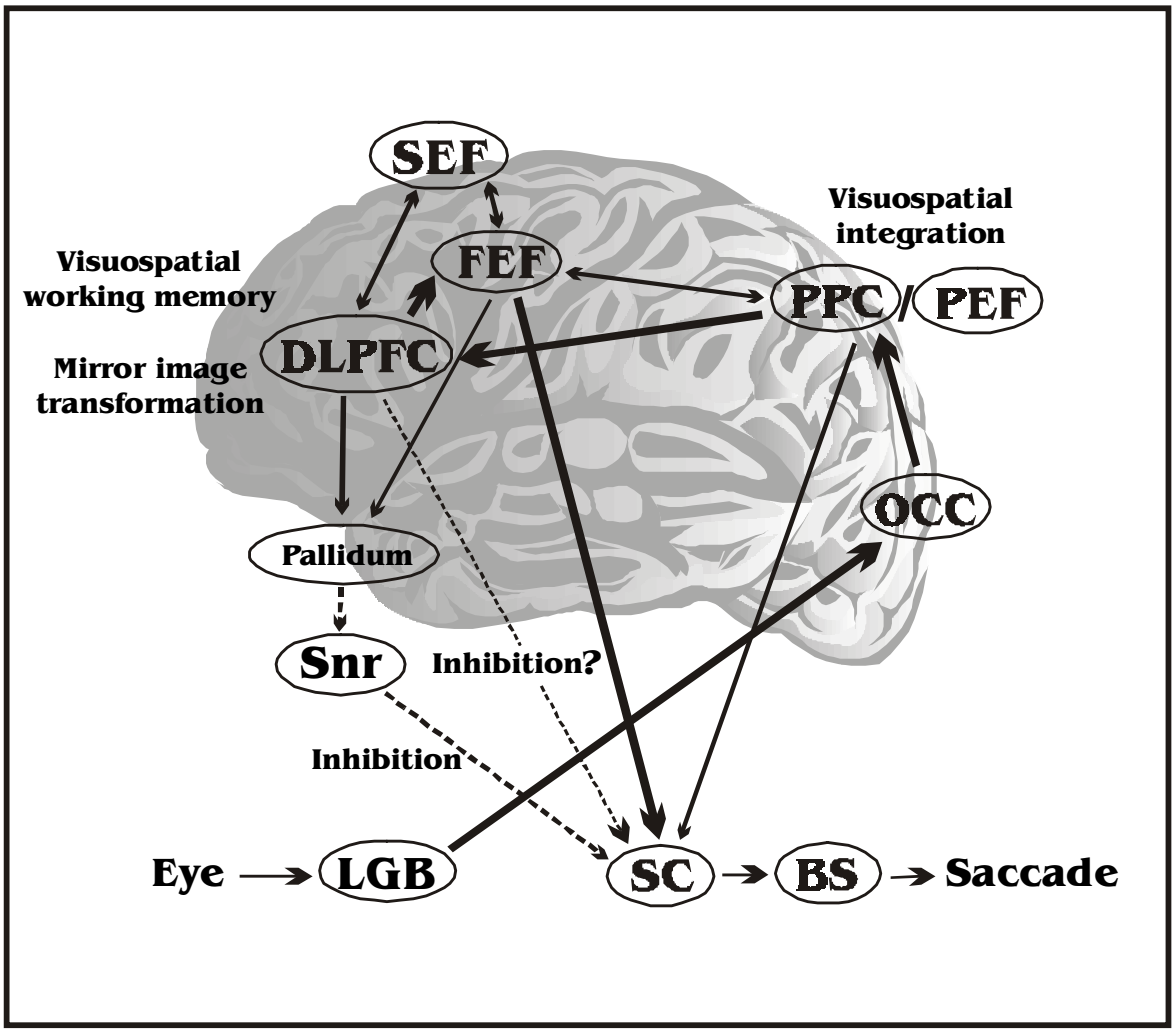


Figure 3. Neural control of antisaccades
Dotted lines represent inhibitory projections. BS = brainstem; DLPFC = dorsolateral prefrontal cortex; FEF = frontal eye fields; LGB = lateral geniculate body; OCC = occipital cortex; PEF = parietal eye fields; PPC = posterior parietal cortex; SC = superior colliculus; SEF = supplementary eye fields; SNr = substantia nigra reticulata.

### 4.2 Neural control of antisaccades

Early research (Guitton et al. 1985) lead to the view that a failure of inhibitory control in the antisaccade task was attributable to a dysfunction of the FEF. It was subsequently shown (Pierrot-Deseilligny et al. 1991b) that the critical region included the DLPFC, not the FEF (see also Rivaud et al. 1994).

Recent clinical studies suggest that the DLPFC and the FEF have distinct functions in the control of antisaccades. A lesion of the DLPFC produced a deficit in the inhibition of reflexive saccades, while a FEF lesion was associated with an increase in the latency of correct antisaccades (Pierrot-Deseilligny et al. 1991b, 1995; Rivaud et al. 1994). Single unit recordings in primates have, however, demonstrated an increased neuronal activity in the FEF during visually-guided saccades when compared to antisaccades (Everling & Munoz 2000). Besides involvement of the FEF and the DLPFC, inhibition of reflexive saccades also requires modulation of fixation units in the rostral pole of the SC, as was shown in primate studies (Everling et al. 1999); these units reduce their firing rates during antisaccades. The important role of the SC for inhibition of reflexive saccades was confirmed by a study in a patient with a SC lesion who showed an increased number of inhibition errors (Pierrot-Deseilligny et al. 1991a). For the volitional generation of a correct antisaccade and the transformation of visuospatial information to the mirror image projection, the involvement of the PPC and the DLPFC is required (Williams & Goldman-Rakic 1995) (Figure 3).

Functional imaging studies (Table 4) have provided additional support for the role of a number of brain areas in the generation of antisaccades. The study of Sweeney et al. (1996) (Table 4) demonstrated the involvement of the DLPFC. Also Muri et al. (1998) reported activation of DLPFC, but not the FEF. Both results are, however, in conflict with previous studies of O'Driscoll et al. (1995) and Paus et al. (1993), who failed to observe DLPFC activation. The inconsistent observations may partly be explained by the fact that these studies employed different manipulations of the stimulus parameters. For example, O'Driscoll et al.'s study (1995) employed a brief target flash of 100 ms, which was below the normal reaction time of a saccade. This implied that also in the baseline condition (visually-guided saccades) a spatial working memory component was involved which presumably activated the DLPFC. Sweeney et al. (1996) and Muri et al. (1998) used longer target durations (2000 ms and 700 ms, respectively).

With respect to other brain regions involved in the control of antisaccades, functional imaging studies showed increased activity for the anterior cingulate cortex (AC), supplementary eye fields (SEF) and PPC when compared to visually-guided saccades, while the OCC and the temporal cortex (TC) were found to display reduced activity.

Table 4

*Functional brain imaging studies of antisaccades*[4]

| BRAIN AREA | Paus '93 [77] Anti-Rest (PET) | Doricchi '97 [18] Anti-Fix (PET) | Paus '93 [77] Anti-Vis (PET) | O'Driscoll '95 [72] Anti-Vis (PET) | Sweeney '96 [98] Anti-Vis (PET) | Doricchi '97 [18] Anti-Vis (PET) | Müri '98 [70] Anti-Vis (fMRI) |
|---|---|---|---|---|---|---|---|
| **Frontal** | | | | | | | |
| Frontal eye fields | | + | | + | + (r) | + | 0 |
| Orbitofrontal cortex | | | | | - (l) | | |
| Dorsolateral frontal cortex | | | | 0 | + | + (8/9) | + |
| Supplementary eye fields | | | | | | | + |
| Supplementary motor area | | + (r) | | + | + (r) | + (r) | |
| Precentral sulcus (BA 6) | + (r) | | | | | | |
| Cingulate cortex (BA 24,31,32,6) | + (l 32); + (6) | + (31/32); - (24/32) | + (caud) | | - (l vntr) | + (24) | |
| **Parietal** | | | | | | | |
| Posterior parietal cortex | | | | | + | | |
| Superior parietal lobule (BA 7) | + | + | + (r) | + | | + | |
| Inferior parietal lobule (BA 39/40) | | + | | | | + | |
| **Temporal** | | | | | | | |
| BA 22/37 | + (r) | - (37) | | | | - (37) | |
| BA 21 | | - | | | | - | |
| **Occipital** | | | | | | | |
| Striate cortex (BA 17) | + (r) | | + (r) | + | | | |
| Extrastriate cortex (BA 18,19) | + (l 18); + (r 19) | - (19) | | | | - (19) | |
| **Basal ganglia** | | | | | | | |
| Caudate + putamen | | | | | + (r dors); - (l vntr) | | |
| Putamen | | | | + (r) | | | |
| Substantia Nigra reticulata | | | + (l) | | | | |
| Thalamus | | - (l) | | + (l) | + (l) | | |

anti = antisaccade; fix = fixation; vis = visually-guided saccade; BA = Broadman Area; + = increase; - = decrease; 0 = no change; r = right; l = left; vntr = ventral; dors = dorsal.

### 4.3 Implications for schizophrenia

Schizophrenics demonstrate an increased proportion of inhibition errors and increased latencies in the antisaccade task. The important neural pathways underlying the abnormality, include the OCC, PPC, DLPFC, FEF, SC and brainstem premotor neurones. In addition, imaging studies have revealed activation in a number of other regions: orbito frontal cortex (OFC), SMA, TC, AC and thalamus. The consistent pattern of results showing in patients intact visually-guided saccades (excluding express saccades), with an abnormality of antisaccades, suggests that the following regions are possible sources of the saccadic abnormalities: the DLPFC, OFC, SMA, AC, TC, and thalamus. However, the SMA can be excluded as a possible source of the abnormalities, since lesions in this area do not result in an increased number of inhibition errors (Gaymard et al. 1999); this in contrast to prefrontal lesions (Guitton et al. 1985; Pierrot-Deseilligny et al. 1991c).

## 5. Memory-guided saccades

The memory-guided saccade paradigm (Figure 1C) can be used to explore the regulation of action that is derived from an internal representation of spatial information (spatial working memory). In this paradigm, subjects are instructed to suppress the normal, reflexive eye movement in response to a novel stimulus, and to delay the saccade until the presentation of an imperative cue. There is no visual information on the location of the previously presented target at the moment of saccade initiation. This paradigm, therefore, examines respectively the inhibition of a reflexive action, the ability to generate an internal representation of space (spatial working memory), the programming of a volitional motor action, and the inhibition of the saccadic motor program during the memorisation process.

In this paradigm, the final eye position (the angle of eye rotation after corrective saccades are complete) is the most appropriate oculomotor measure of spatial working memory, though the majority of studies have been limited to the primary saccade. It is further possible to distinguish two sources of error: 1) an early impairment in the transient inhibition of the reflexive response to a prepotent stimulus, and 2) an impairment in the sustained inhibition of the response to the *internal representation* of that stimulus. When there is a failure of either process, saccades are prematurely executed and an inhibition error will be recorded, though the error may originate from distinct functional deficits. There is a wide variation in the frequency of inhibition errors reported in various studies (Table 5). The latencies of memory saccades are longer than those of visually-guided saccades (Crawford et al. 1995a; Fukushima et al. 1990b; Lueck et al. 1990) and peak velocities are decreased relative to antisaccades (Lueck et al. 1990).

Table 5
*Memory-guided saccades in schizophrenia relative to other groups*

| | Study | SZ | Cs | Notes |
|---|---|---|---|---|
| **Primary saccade undershoot (%)** | Crawford et al. '89 [13] | - | 9 | Elderly Cs vs Parkinsonians |
| | Lueck et al. '90 [62] | - | 13 | Elderly Cs vs Parkinsonians |
| | Pierrot-Deseilligny et al. '91 [81] | - | 14 | Elderly Cs |
| | Crawford et al. '95 [11] | 27 | 13 | SZ: AP free |
| | Crawford et al. '95 [12] | 38 | 38 | SZ: AP treated |
| | Müri et al. '96 [71] | - | 10 | TMS study |
| | Everling et al. '96 [21] | 32 | 19 | SZ: AP free; vertical sacc included |
| | Karoumi et al. '98 [50] | 14 | 9 | SZ: AP treated |
| | Ross et al. '98 [89] | 24[a] | 15[a] | SZ: AP treated |
| **Undershoot amplitude of final eye position** | Crawford et al. '95 [11] | 12 | 1 | SZ: AP free |
| | Crawford et al. '95 [12] | 23 | - | SZ: AP treated |
| | Müri et al. '96 [71] | - | 9 | |
| | Everling et al. '96 [21] | 18 | 16 | SZ: AP free; vertical sacc included |
| **Increased inhibition errors** | Crawford et al. '89 [13] | - | 30 | Elderly |
| | Lueck et al. '90 [62] | - | 20 | Elderly |
| | Fukushima et al. '90 [31] | 21 | 4 | SZ: AP treated |
| | Pierrot-Deseilligny et al. '91 [81] | - | 16 | Elderly |
| | Crawford et al. '95 [11] | 48 | 17 | SZ: AP free |
| | Ross et al. '98 [89] | 38 | 15 | SZ: AP treated |
| | Müller et al. '99 [69] | 66 | 15 | SZ: AP free + AP treated |
| **Increased latency** | Everling et al. '96 [21] | | | |
| | Fukushima et al. '90 [31] | | | |
| | Crawford et al. '95 [11] | | | |
| | Karoumi et al. '98 [50] | | | SZ: AP treated |
| | Müller et al. '99 [69] | | | SZ: AP free + AP treated |
| **Decreased peak velocity** | Fukushima et al. '90 [31] | | | SZ: AP treated; in large saccades |
| **Increased duration** | Fukushima et al. '90 [31] | | | SZ: AP treated; in large saccades |

SZ = schizophrenia patients; Cs = healthy controls; AP = antipsychotic; [a] = residual position error.

## 5.1 Memory-guided saccades in schizophrenia

Compared to healthy controls, schizophrenics generate memory-guided saccades with smaller amplitudes and more inhibition errors. Studies have found that saccades also differ from healthy subjects with respect to latency, peak velocity and duration (Table 5). With regard to experimental parameters, the size of the memory interval emerges as a critically important variable. Strong effects have been reported in studies that have used long intervals (2-10 seconds) (Everling et al. 1996; Park & Holzman 1992, 1993) in contrast to a study in which a short interval (500 ms) was employed and no abnormality was reported (Crawford et al. 1995a).

## 5.2 Neural control of memory-guided saccades

The PPC plays an important role in the generation of memory-guided saccades. This region is involved in early sensorimotor processing and also in the triggering of saccades via its direct projection to the SC. Projection neurones from the FEF also target the SC (both directly and indirectly via the basal ganglia). Deep layers of the SC receive a direct input from the DLPFC and indirectly via projections to the FEF. Single unit recordings in primates showed a delay-dependent change in the activity of DLPFC neurones (Funahashi et al. 1993) that was modulated via dopamine ($D_1$) receptors (Williams & Goldman-Rakic 1995). There is also good evidence from research with animal models of Parkinson's disease that memory-guided saccades are also modulated via nigro-striatal dopaminergic projections (Kato et al. 1995; Kori et al. 1995). The dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), when applied to the neostriatum, produced a selective abnormality of memory-guided saccades.

Previous research highlighted the role of the DLPFC in spatial working memory, but also in suppressing reflexive eye movements and preventing unnecessary saccades during the process of memorisation (Pierrot-Deseilligny et al. 1991b). More recently, lesions of either the DLPFC or FEF were associated with deficits of memory-guided saccades (Gaymard et al. 1999; Ploner et al. 1999). It was, however, possible to distinguish between the behavioural effects of FEF and DLPFC lesions using detailed analyses of the saccade amplitudes and distributions (Ploner et al. 1999). This demonstrated that errors of saccadic programming, even within a saccadic paradigm, might form a characteristic behavioural 'signature' with clues to the neurological origins of the abnormality. The results of brain lesion studies are consistent with functional neuroimaging evidence (Table 6) showing that both the FEF and DLPFC are involved in the generation of memory-guided saccades. Functional imaging studies also demonstrate an important contribution of the SMA, but are less consistent with respect to other areas. This might be due to the differences in the paradigms used. For example, Anderson et al. (1994) used a delay interval of 500 ms, whereas Sweeney et al. (1996) employed a delay of 2000 ms. Moreover, Sweeney et al. (1996) provided feedback.

## 5.3 Implications for schizophrenia

Neurophysiological studies suggest that the neural circuitry involved in memory-guided saccades includes the OCC, PPC, DLPFC, FEF, BG, and SC. Brain imaging studies suggest additional involvement of the OFC, TC, AC, insula, thalamus, and cerebellum. The generation of visually-guided saccades that are normal implies that some of these areas (PPC, FEF, SC, and brainstem premotor neurons) are unlikely sources of the functional brain impairment in schizophrenia. Hypometric saccades are consistent with a functional deficit in the PPC, which plays a crucial role in

spatial processing. However, the PPC is also important for the generation of visually-guided saccades, which are not impaired in schizophrenia. Therefore, it is likely that the memorisation of spatial properties, involving the DLPFC, is disrupted. Lesion studies have shown that the DLPFC is also a possible source of the inhibition errors.

## 6. Predictive saccades

Predictive saccades (Figure 1D) are generated towards an expected target location, triggered by a motor program using an internal model of target behaviour. In this paradigm, a visible target steps between (two) fixed locations in a predictable temporal sequence. In some studies, there is an additional phase where a series of visible targets is followed by a sequence in which target visibility is withdrawn (Crawford et al. 1995a; O'Sullivan et al. 1997). Using a predictive paradigm investigators have examined the programming and evolution of anticipatory behaviour. Healthy subjects are able to develop predictive behaviour within a few target presentations. This is demonstrated by a gradual reduction in the latencies towards responses that precede the target (Clementz et al. 1994; Crawford et al. 1995a,b).

Table 6

*Functional brain imaging studies of memory saccades*[5]

| BRAIN AREA | Anderson '94 [2] Mem-Fix (PET) | Anderson '94 [2] Mem-Vis (PET) | Sweeney '96 [98] Mem-Vis (PET) |
|---|---|---|---|
| **Frontal** | | | |
| Frontal eye fields | + | | + |
| Orbitofrontal cortex | | | - (l) |
| Dorsolateral prefrontal cortex | | | + |
| Supplementary motor area | + | + | + |
| Cingulate cortex, caudal (BA 24,32) | + | + | - (l ventr) |
| Cingulate cortex, rostral (BA 24,32) | - | | |
| **Parietal** | | | |
| Posterior parietal cortex | | | + |
| Superior parietal cortex (BA 7) | + (l) | | |
| Inferior parietal cortex (BA 40) | + (l) | | |
| **Temporal** | | | |
| Temporal gyrus (BA 22) | + (r sup) | | |
| Hippocampus | - | - (l) | |
| **Occipital** | | | |
| Striate cortex (BA 17) | + (ant); - (post) | - | |
| Extrastriate cortex (BA 18,19) | + | | |
| Insula | | + | |
| Thalamus | | + (med/dors) | |
| Cerebellum | + | + | |

mem = memory guided saccade; fix = fixation; vis = visually-guided saccade; BA = Broadman Area + = increase; - = decrease; 0 = no change; r = right; l = left; ant = antior; post = posterior; med = medial; ventr = ventral; dors = dorsal; sup = superior.

When the previously visible target is suddenly withdrawn, saccadic timing becomes even more pre-emptive, and curiously the amplitudes increase over a series of trials that are initiated using an auditory cue (O'Sullivan et al. 1997). Target rate has a powerful influence on saccadic latency and amplitude (Lueck et al. 1991; O'Sullivan et al. 1997), with low target rates resulting in maximal undershoot of the primary saccades and anticipatory behaviour.

### 6.1 Predictive saccades in schizophrenia

Schizophrenic patients have normal latencies of predictive saccades, irrespective of the visibility of the peripheral target (Clementz et al. 1994; Crawford et al. 1995a,b; Hommer et al. 1991), and patients are also able to develop the normal pattern of anticipatory behaviour (McDowell et al. 1996). The findings on saccadic amplitudes are less consistent across studies. Some studies have reported a large undershoot for drug-treated patients, but not for drug-free patients when compared to healthy subjects (Crawford et al. 1995a,b; Hommer et al. 1991). In the study of Clementz et al. (Clementz et al. 1994), however, no amplitude differences were reported between antipsychotic-treated schizophrenics and healthy subjects.

### 6.2 Neural control of predictive saccades

The neural circuitry involved in the generation of predictive saccades has not been extensively studied. Some clues on the important subcortical regions have emerged from studies on Parkinson's disease. Predictive saccades of these patients displayed a characteristic undershoot of the primary saccades, whereas the final eye positions were normal (Crawford et al. 1989; O'Sullivan et al. 1997). Since Parkinson's disease is characterised by a degeneration of the dopaminergic neurones in the nigrostriatal pathway, this suggested an important role of the basal ganglia in the generation of predictive saccades. The finding that medication with classical neuroleptics, which have a high affinity for dopamine receptors in the basal ganglia, were associated with hypometric predictive saccades in both bipolar disorder and schizophrenia provided some support for this hypothesis (Crawford et al. 1995b). The abnormalities of predictive saccades were most severe in psychotic patients with increased extrapyramidal symptoms. An unexpected finding was that the impairment of eye movements proved to be the most robust predictor of neuroleptic status, and was superior to conventional psychiatric and extrapyramidal rating scales[6].

Brain imaging studies of predictive saccades (Table 7) reported significant activation in the FEF and SMA. The absence of PPC and DLPFC activation suggests these areas play no major role in the generation of predictive saccades.

## 6.3 Implications for schizophrenia

The normal development of anticipatory behaviour in schizophrenics is demonstrated in the latency of predictive saccades. The amplitudes of these saccades may be reduced, although the results of studies are inconsistent. Patients on antipsychotic medication show reductions in the amplitude relative to untreated patients. The neural pathways underlying these saccades are not fully understood, although activation in the FEF and the SMA has been reported consistently in functional imaging studies. Research on Parkinson's disease suggests that the BG may also play an important role.

Table 7

*Functional brain imaging studies of predictive saccades (with visible and non-visible targets)*[7]

| BRAIN AREA | Fox '85 [28] Pred(v)-Rest (PET) | Fox '85 [28] Pred(nv)-Rest (PET) | Paus '93 [77] Pred(v)-Fix (PET) | Petit '93 [78] Pred(nv)-Rest (PET) |
|---|---|---|---|---|
| **Frontal** | | | | |
| Frontal eye fields | + | + | + | + |
| Dorsolateral prefrontal cortex | | | | |
| Supplementary motor area | + | + | + (l) | + |
| Cingulate cortex, medial (BA 24,32) | | | | + (l) |
| **Parietal** | | | | |
| Posterior parietal cortex | | | | 0 |
| Posterior inferior parietal lobule (BA 39/40) | 0 | 0 | | |
| Superior parietal cortex (BA 7) | | | + | |
| **Occipital** | | | | |
| Striate cortex (BA 17) | + | 0 | + (r) | 0 |
| Extrastriate cortex (BA 18,19) | + | + | + | + (r) |
| **Basal ganglia** | | | | |
| Caudate | 0 | 0 | | |
| Putamen | 0 | 0 | | + |
| Globus pallidus | 0 | 0 | | + |
| Insula | | | | + (r) |
| Cerebellum | | | | + |
| Thalamus | 0 | 0 | + (l) | + (r) |

Pred(v) = predictive saccades with visible targets; Pred(nv) = predictive saccades with non-visible targets; fix = fixation; BA = Broadman Area; + = increase; - = decrease; 0 = no change; r = right; l = left.

## 7. Saccadic impairments in other patient groups

The most salient saccadic abnormalities in schizophrenia are the inhibition errors and reduced spatial accuracy of volitional saccades, although neither deficit is specific to schizophrenia. Table 8 presents a selective summary of the saccadic abnormalities that have been found in other psychiatric and neurological disorders. Patients with Huntington's disease have an impairment of inhibition in the antisaccade task, in contrast to Parkinson's disease (Fukushima et al. 1994; Lueck et al. 1990) (but see Briand et al. 1999), which suggests that neural projections via the caudate are involved in the modulation of saccadic inhibition (Figure 3). An increased frequency of inhibition errors has been reported in several psychiatric disorders: e.g., bipolar disorder, depression and obsessive-compulsive disorder. In bipolar disorder, the severity of the abnormalities appears to be similar to schizophrenia, whereas for depression and obsessive compulsive disorder the abnormalities are reduced. These disorders, as in the case of schizophrenia, are associated with impaired function of the prefrontal cortex, although the specific neural mechanisms are unclear. It is not possible, therefore to extrapolate from this research to the specific pathophysiology in schizophrenia. However, there is a clear distinction in the reliability of the reported abnormality in schizophrenia research, compared to other psychiatric disorders.

## 8. Antisaccade abnormality as a biological marker in genetic research

Populations at increased risk for schizophrenia include biological relatives of patients, individuals with a schizotypal personality disorder, and individuals with high scores on psychometric measures of schizotypy. In these populations, saccadic abnormalities, in particular inhibition errors on the antisaccade paradigm, have been observed. Antisaccade errors have therefore been regarded as a behavioral marker of latent liability to the disorder. Investigation of this biological marker has attracted many researchers since it may elucidate the nature of brain abnormalities associated with the disease. The study of Clementz et al. (1994) was one of the first studies reporting that first-degree relatives of schizophrenia patients had an increased level of antisaccade errors, and that this error rate was not deviant from patients. Also Katsanis et al. (1997) and McDowell et al. (1999) demonstrated that healthy first-degree relatives of patients made more inhibition errors than healthy controls. Moreover, the error rate of relatives with multiple schizophrenic probands in their family was increased when compared to relatives with only one schizophrenic proband in their family. In addition, Crawford et al. (1998) observed an increased error rate in relatives of probands with a high error rate when compared to relatives of probands with a normal error rate. In line with these findings, Ross et al. (1998) demonstrated that parents of schizophrenia probands who had a positive family history of schizophrenia, made more inhibition errors than parents with no such

history. Either of these findings related an increase in inhibition errors to presumed increased genetic risk for schizophrenia.

An increase in the number of inhibition errors was also demonstrated in subjects with high scores on measures of schizotypy (Gooding 1999; O'Driscoll et al. 1998). O'Driscoll et al. (1998) demonstrated that the inhibition errors reflected a tendency to continue a motor set that was established in the trials immediately preceding the error. Some studies failed, however, to demonstrate a significant increase in inhibition errors in both community subjects and first-degree relatives with high scores on a measure of schizotypy (Thaker et al. 1996).

Table 8

*Saccadic abnormalities in psychiatric and neurological disorders*

| Disorder | Study | Abnormality | Studies *not* confirming the abnormalities |
|---|---|---|---|
| ***Psychiatric disorders*** | | | |
| **Bipolar disorder** | Tien et al. '96 [103]; Katsanis et al. '97 [52]; Sereno & Holzman '95 [96] | Inhib errors ↑ (20-62%) | Fukushima et al. '90 [32], Crawford et al. '95 [11], Clementz et al. '94 [8], McDowell & Clementz '97 [66] |
| **Depression** | Katsanis et al. '97 [52] | Inhib errors ↑ (45%) | |
| **Obsessive Compulsive disorder** | Tien et al. '92 [102] | Inhib errors ↑ (39%) | McDowell & Clementz '97 [66] Maruff et al. 1999 [64] |
| ***Neurological disorders*** | | | |
| **Alzheimer's disease** | Fletcher & Sharpe '86 [27] | Amplitude of pred sacc ↓<br>Latency of pred sacc ↑<br>Inhib errors ↑ (74%) | |
| **Parkinson's disease** | Kitagawa et al. '94 [53] | Inhib errors ↑ (28%)<br>(in late phase of disease) | |
| | Crawford et al. '95 [11]; Lueck et al. '90 [62] | Amplitude of mem sacc ↓ | |
| | Vermersch et al. '94 [105] | Amplitude of sequences of mem sacc ↓ | |
| | White et al. '83 [107]; Crawford et al. '89 [13]; Ventre et al. '92 [104]; Lueck et al. '92 [61] | Amplitude of pred saccs ↓ | |
| **Huntington's disease** | Lasker et al. '87 [55] | Inhib errors ↑ (60%) | |
| | Lasker et al. '88 [56] | Latency of antisacc and mem sacc ↑ | |
| | Tian et al. '91 [101] | Latency of pred sacc ↑ | |
| **Progressive Supranuclear Palsy** | Pierrot-Deseilligny et al. '89 [84]; Vidailhet et al. '94 [106] | Inhib errors ↑ (59-65%) | |

Inhib error = inhibition errors on antisaccades; antisacc = antisaccades; pred sacc = predictive saccades; mem sacc = memory saccades.

## 9. General conclusions

In recent years there has been a growing interest in the eye movement abnormalities in schizophrenia, demonstrated by dozens of publications and large scale funding of major research projects in Europe and North America. Saccadic paradigms now supplement the more traditional methods of cognitive research. Research strategies that examine a profile of saccade performance across a range of saccadic eye movement tests can target different neuropsychological operations. The antisaccade and the memory-guided saccade paradigm, in particular, are increasingly used to probe selective neurocognitive operations. Current developments suggest that research programs incorporating a battery of saccadic paradigms combined with neuroimaging, clinical and psychopathological observations are likely to become more characteristic of future developments, and will provide an important tool in unravelling the pathophysiology of this mysterious disorder.

[1] A definition that distinguishes parsimoniously between different categories of saccades is problematic. The term visually-guided saccade refers equally to an automatic visual orienting response to a novel target, and to a sequence of saccades in a visual search. For the purposes of this review, we have adopted an operational definition of visually-guided saccades that is widely applicable to the published papers.

[2] Neurophysiological evidence showed that activation of the FEF excited SC cells that encode saccades with the same vector but inhibited other cells (e.g. Schlag et al. 1992). It was suggested that this inhibition could be generated via direct topographical projections to the SC. Alternatively an inhibitory signal could be generated by disinhibition via the Substantia Nigra reticulata (SNr) or within the SC itself (Grantyn et al. 1984).

[3] Numbers in brackets refer to the number of the study in the reference list.

In the study of Fox et al. (1985) brain activation during visually-guided saccades was compared with a condition of rest. In the studies of Anderson et al. (1994) and Sweeney et al. (1996) visually-guided saccades were compared with a fixation condition.

[4] In the study of Paus et al. (1993) the brain activation during antisaccades was compared with a condition of rest. In the study of Doricchi et al. (1997) antisaccades were compared with a fixation condition. In the other studies antisaccades were compared with the brain activation during visually-guided saccades.

[5] Anderson et al. (1994) compared brain activation during memory-guided saccades with visual fixation. In the same study they also compared memory-guided saccades with visually-guided saccades, as did Sweeney et al. (1996).

[6] However, patients with first episode SZ show a deficit that is independent of neuroleptic status (Hutton et al, in press), showing that patient chronicity should not be overlooked.

[7] Fox et al. (1985) compared brain activation during predictive saccades (vision (v) and no-vision (nv)) with the rest condition. Paus et al. (1993) compared a visible predictive saccade paradigm with a condition of rest. Petit et al. (1993) compared predictive saccades with no target with rest.

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# Chapter 3

## Differential effects of olanzapine and risperidone on cognition in schizophrenia? A saccadic eye movement study

In press

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**Abstract**

Recent studies suggested that novel antipsychotics have positive effects on certain cognitive functions in schizophrenia. The present study investigated this claim by means of saccadic paradigms, which provide a selective index of cognitive function. First-episode schizophrenics were randomly assigned to either olanzapine or risperidone treatment and compared to healthy controls for three saccadic paradigms. Also the influence of symptom profile, extrapyramidal symptoms, age, education, gender, hospitalization, and medication dose on cognitive performance was investigated.

Both patient groups showed substantial problems in inhibitory control of saccades. A high level of education appeared to be protective for this impairment.

## 1. Introduction

Cognitive dysfunctions are considered to be among the core deficits of schizophrenia, since they contribute to disease chronicity, prognosis and social functioning (Andreasen 1997; Goldman-Rakic 1994; Green 1996; Hemsley 1994). Treatments that ameliorate cognitive dysfunctions, therefore, have important implications for prognosis and long-term outcome. There is increasing interest in the influence of antispychotic medication on cognition, in particular, the effects of novel antipsychotics (APs) have been the focus of many recent studies (for reviews, see Meltzer & McGurk 1999; Purdon 1999). There is a consensus that novel APs are superior to classical APs with regard to improvement of cognitive function that is independent of improvement in psychopathology. However, novel APs do not have positive effects on all cognitive functions, and some novel APs (in particular clozapine, olanzapine and risperidone) appeared to have variable effects on cognitive processes (Meltzer & McGurk 1999). Further clarification of the effects of these drugs on cognition will have important implications for clinical and scientific progress by facilitating patient management and providing new insights into the pharmacological modulation of neuropsychological function.

With the precise recording of various spatial and temporal parameters of a rapid eye movement, saccadic eye movement paradigms provide a selective index of cognitive function. Cognitive processes that are commonly incorporated in saccadic tasks include visuospatial attention, spatial working memory, and response inhibition (Broerse et al. 2001). A large number of studies have shown saccadic impairments in schizophrenic patients (e.g., Crawford et al. 1995a,b; Hutton et al. 1998; Thaker et al. 1989). In order to understand these impairments, it is useful to make a distinction between visually-guided (externally driven) saccades and voluntary saccades (internally driven; antisaccades, memory-guided saccades, and predictive saccades). The generation of visually-guided (or reflexive) saccades primarily requires the resources of spatial attention and a precise motor program, whereas voluntary saccades require additional involvement of higher order, executive functions, such as working memory. A large number of studies have shown that schizophrenic patients perform accurately on the former category of saccades (Crawford et al. 1995a; Hutton et al. 1998; Karoumi et al. 1998), while they have severe problems with voluntary saccades, especially when they have to suppress (inhibit) response tendencies towards novel targets (Crawford et al. 1995a; Hutton et al. 1998; Karoumi et al. 1998; McDowell & Clementz 1997).

Only few studies have investigated the influence of APs on saccadic tasks (Hommer et al. 1991), focusing primarily on the effects of classical APs. These APs mainly target the dopaminergic nigrostriatal structures that are involved in the generation of saccades. Crawford et al. (1995b) and Hommer et al. (1991) showed that administration of classical APs resulted in a reduced accuracy of internally driven

saccades (in this case predictive saccades). Crawford et al. (1995b) also found a trend towards more antisaccade inhibition errors. Hutton et al. (1998) reported reduced amplitudes for antisaccades, while the latency and the number of inhibition errors were decreased. In one of the few studies to examine the effects of novel APs, Burke et al. (1998) showed that risperidone improved antisaccade performance by reducing the number of inhibition errors. This improvement was predicted by treatment duration. In contrast, Sweeney et al. (1997) found a detrimental effect of risperidone on visually-guided saccades that was manifested in reduced amplitudes, later onset, and changes in peak velocity.

In the present explorative study we investigated the performance of first-episode schizophrenic patients and healthy controls on three saccadic tasks: visually-guided saccades, antisaccades, and memory-guided saccades. Although several studies have reported robust saccadic abnormalities for chronic schizophrenic patients, only one study has reported abnormalities in first-episode psychotic patients (Hutton et al. 1998). It is important to confirm this finding, since this would support the controversial notion of cognitive impairment immediately after disease onset. Using saccadic tasks which measured psychomotor function, selective attention, visuospatial working memory, and executive functioning, we investigated whether symptom profile, extrapyramidal symptoms, age, education, gender, hospitalization, and medication dose had an influence on performance.

We hypothesized that patients would perform worse than controls on the antisaccade and memory-guided saccade task, but not on the visually-guided saccade task. In addition, we examined whether two novel APs, olanzapine and risperidone, had differential effects on saccades. In studies that reviewed recent research, Meltzer & McGurk (1999) and Purdon (1999) concluded that risperidone had positive effects on (selective) attention, alertness, visuomotor tracking, working memory, motor function, and executive functioning (set shifting), whereas olanzapine had positive effects on attention (reaction time), motor function, visuospatial, and executive skills. However, risperidone was examined more frequently, and thus the reported beneficial effects on more cognitive domains may be over reported in comparison to the effects of olanzapine. As yet, risperidone appears to be superior to olanzapine with respect to spatial working memory. There is, however, a need for studies conducting a direct comparison between the two drugs. Based on the work of Meltzer & McGurk (1999) and Purdon (1999), we hypothesized that patients treated with risperidone would perform better than patients treated with olanzapine on saccadic measures of (visuospatial) working memory.

## 2. Methods and Materials

### 2.1 Subjects

The study included 33 patients (24 males, 9 females) who had recently experienced their first psychotic episode according to DSM-IV criteria (American Psychiatric Association 1994) and received a diagnosis within the schizophrenia spectrum (schizophrenia, schizophreniform disorder, schizoaffective disorder). All patients were in a relatively stable phase of their illness and received either olanzapine or risperidone for at least 7 weeks. Mean age was 28.8 (SD 8.3) years and average education was at high school level. The presence of symptoms was assessed with the Positive and Negative Symptom Scale (PANSS), and severity of extrapyramidal symptoms was judged by the Extrapyramidal Symptom Rating Scale (ESRS). Exclusion criteria were: 1) age under 17 or above 60 years; 2) systemic or neurological illness; 3) severe mental retardation; 4) history of alcohol or drug abuse; 5) use of medication other than olanzapine or risperidone; 6) tardive dyskinesia or severe extrapyramidal symptoms; 7) impaired vision or hearing loss.
Patients were randomly assigned to either olanzapine or risperidone treatment. The olanzapine group consisted of 21 patients and the risperidone group of 12 patients. Characteristics of these groups are described in Table 1. The relatively small size of the risperidone group was due to exclusion of patients who were on combined drug therapy.
A control group of 23 healthy volunteers (15 males, 8 females), recruited from the local community, was included to evaluate the saccadic performance of patients. These subjects had no history of psychiatric or neurological illness. Moreover, they had no first-degree relatives with a schizophrenia spectrum disorder. Mean age was 22.1 (SD 2.8) years and average education was at high school level. Informed consent was obtained for all subjects.

### 2.2 Eye movement measurement

Subjects were seated 90 cm from a big television screen while their heads were stabilized in a chin rest. Targets (green squares subtending 0.25° of visual angle) were displayed on the screen on four locations at 7.5° and 15° on either side of a fixation point. In each saccadic task the total number of trials was 48. The experiments were conducted in the dark and eye movements were recorded using an infrared limbus reflection device (IRIS, Skalar Medical BV, The Netherlands).

Table 1

*Group characteristics*

| | Olanzapine (n=21) | Risperidone (n=12) | Controls (n=23) | Sign |
|---|---|---|---|---|
| **Age** (range) | 28.81 (17-56) | 28.67 (19-44) | 22.09 (17-26) | .002 |
| **Male/female ratio** | 14/7 | 10/2 | 15/8 | ns |
| **Education** (range)* | 3.93 (1-7) | 3.18 (1-7) | 5.13 (3-7) | ns |
| **Inpatients/outpatients** | 11/10 | 5/7 | - | ns |
| **Median duration of illness in weeks** (range) ** | 52 (8-520) | 30 (12-260) | - | ns |
| **Median duration of treatment in weeks** (range) ** | 15 (7-52) | 12 (7-32) | - | ns |
| **Mean medication dose in mg/day** (range) | 9.05 (5-15) | 3.63 (2-6) | - | - |
| **Negative symptoms** (range) | 10.75 (7-21) | 11.13 (7-20) | - | ns |
| **Positive symptoms** (range) | 10.44 (7-23) | 9.75 (7-17) | - | ns |
| **General psychopathology** (range) | 22.81 (17-33) | 21.38 (16-27) | - | ns |

* According to a continuous scale ranging from low education (1) to university grade (7).
** The median was chosen in order to minimize the influence of extremes.

## 2.3 Saccadic tasks

*Visually guided saccade task*. After 800 ms of central fixation, a peripheral target was randomly presented for 1000 ms to either the left or right (Figure 1A). Simultaneous with target presentation a buzzer signal was initiated for 200 ms. Subjects were asked to move their eyes as quickly and accurately as possible to the target location, and afterwards return to central fixation. Inter-trial interval was 1000 ms and trial duration was 2800 ms.

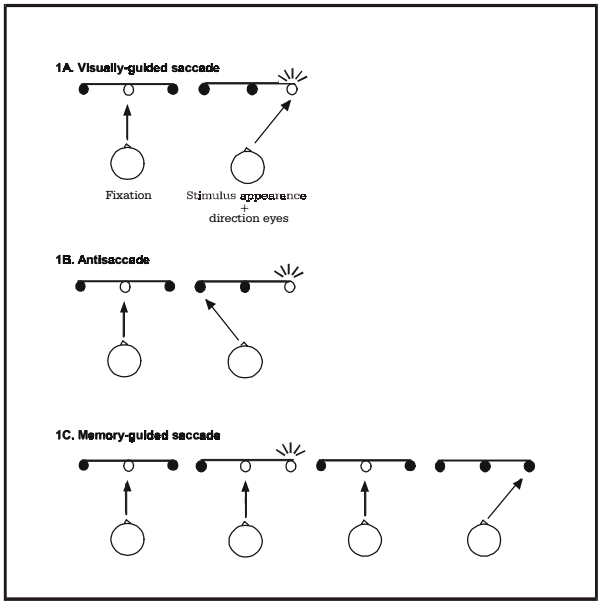


Figure 1. Saccadic paradigms

**1A:** A visual stimulus is presented in a random sequence to the left or right of a central fixation point and subjects are instructed to respond with a rapid and accurate eye movement.
**1B:** Antisaccades are directed towards a spatial position in the opposite visual field to that of the stimulus. The paradigm requires suppression of the reflexive saccade that would normally be generated in response to a novel visual target, and the generation of a volitional saccade to the opposite hemifield.
**1C:** Subjects are instructed to suppress the normal reflexive eye movement in response to a novel stimulus, and to delay the saccade until the offset of the central light. There is no visual information on the location of the previously presented target at the moment of saccadic initiation.

*Antisaccade task*. After 800 ms of central fixation, a peripheral target was randomly presented for 2000 ms to either the left or right side (Figure 1B). Simultaneous with target presentation a buzzer signal was initiated for 200 ms. Subjects were asked to move their eyes to the mirror image location. Trial duration was 2800 ms.
*Memory-guided saccade task*. After 800 ms of central fixation, a peripheral target was randomly presented for 200 ms to either the left or right (Figure 1C). The fixation point remained on, and subjects were asked to delay the saccade until the fixation point extinguished (after 500 ms). At the moment of saccade initiation no information on the previous target location was available. Simultaneous with fixation point offset, a buzzer signal was initiated for 200 ms. Inter-trial interval was 3000 ms and trial duration was 4500 ms.

### 2.4 Data analysis

Saccadic analysis was conducted off-line using interactive propriety software (developed at the University of Maastricht, The Netherlands). In the visually-guided saccade paradigm, the latency of the primary saccades was analyzed. This measure was presumed to reflect psychomotor functioning (Table 2), since processing of visuospatial information and transformation of this information into an oculomotor program was involved. We also measured the number of false anticipations, which implicated saccades that were made in advance of the target presentation due to false predictions of alternation between the left and right side (despite the instruction of randomization). The number of false anticipations was thought to reflect executive functioning, since preventing oneself from making erroneous alternating saccades involves the maintenance of task instructions in working memory.
In the antisaccade paradigm, we analyzed latency and percentage of inhibition errors. An inhibition error was scored when the participant moved the eyes reflexively to the peripheral target rather than to the opposite site. Inhibition errors resulted from a failure to suppress the prepotent reflexive saccade to the target. We presumed that latency and inhibition errors were both measures of executive functioning and perhaps also of selective attention, since the task requires the participant to ignore a visual distractor and to maintain in working memory the task instructions in order to inhibit the reflexive response to the target. In addition, the latency of inhibition errors was analyzed.
In the memory-guided saccade paradigm, we analyzed the accuracy of both the primary saccades and the final eye positions (eye positions after corrective saccades were made). Final eye position was presumed to be an index of spatial working memory (Crawford et al. 1989). We also measured the percentage of inhibition errors and the percentage of errors in delaying the saccade. Delay errors were interpreted as a measure of executive functioning, since the oculomotor program for the saccade, which is prepared immediately after stimulus presentation, should be

controlled (inhibited) during the delay period. As a criterion for differentiating between delay errors and inhibition errors we used the individual mean latency of inhibition errors on the antisaccade task. Saccades exceeding this mean latency plus one SD were categorized as delay errors.

In order to examine whether first-episode patients performed worse than healthy controls on each of the eleven saccadic measures, the data were analyzed by means of two-tailed *t* tests or Mann-Whitney *U* tests. Differences between patients using olanzapine or risperidone and healthy controls were examined by one-way analysis of variance (ANOVA), followed by post hoc testing (Tukey HSD, two-tailed tests with $\alpha$=.05). When variables did not resemble the normal distribution, non-parametric Kruskal-Wallis one-way analysis of variance was performed, followed by Mann-Whitney *U* tests for multiple comparisons. The relation between various saccadic measures was examined by means of parametric and nonparametric correlation analyses for the patient and control group separately.

Table 2
*Saccadic paradigms, performance parameters and cognitive functions*

| Saccadic paradigm | Parameter | Cognitive function |
|---|---|---|
| Visually-guided saccades | Latency | Psychomotor function |
| | False anticipations | Executive function |
| Antisaccades | Latency | Executive function / Selective attention |
| | Inhibition errors | Executive function / Selective Attention |
| Memory-guided saccades | Amplitude | Visuospatial Working Memory |
| | Inhibition errors | Executive function / Selective Attention |
| | Delay errors | Executive function |

## 3. Results

### 3.1 First-episode patients versus healthy controls

The patient and control group did not differ significantly for gender and level of education, whereas there was a difference for age ($z$=-3.60, $p$=.000). Since age was found to have an influence on some measures of saccadic performance (Fischer et al. 1997), correlation analysis was performed in order to reveal significant effects of age on each of the saccadic measures. However, no significant correlations were obtained. Compared to controls, patients made significantly more inhibition errors on the antisaccade task ($t$=4.50, $df$=46.98, $p$<0.001; Table 4) and the memory-guided saccade task ($z$=-2.64, $p$=.008; Table 5). On the memory-guided saccade task, patients also differed significantly from controls for the number of delay errors ($z$=-

2.02, $p$=.043), the final eye position to small target eccentricities ($t$=2.50, $df$=50, $p$=.016), and the amplitude of primary saccades to large target eccentricities ($t$=-3.29, $df$=50, $p$=.002).

### 3.2 Correlations between saccadic measures

Because of multiple comparisons in the correlation analysis, only two-tailed $p$-values smaller than 0.01 were considered significant for correlation coefficients. Within the patient group we found significant correlations between the following saccadic measures: 1) latency of visually-guided saccades and latency of incorrect antisaccades ($r$=0.48, $p$=.005); 2) latency of correct and incorrect antisaccades ($r$=0.73, $p$<.001); 3) antisaccade inhibition errors and final eye position to small target eccentricities ($r$=0.52, $p$=.003); 4) amplitudes to small and large target eccentricities ($p$-values ranging from .002 to .004).

Within the control group the following saccadic measures were significantly correlated: 1) latency of visually-guided saccades and latency of correct antisaccades ($r$=0.70, $p$<.001); 2) latency of visually-guided saccades and latency of incorrect antisaccades ($r$=0.63, $p$=.002); 3) amplitudes to small and large target eccentricities ($p$-values ranging from .000 to .003).

### 3.3 Correlations between saccadic performance and disease-related factors

Within the patient group, age, symptom profile (PANSS subscales), extrapyramidal symptoms, duration of illness, medication dose, and duration of medication treatment were not correlated with saccadic performance. However, a significant negative correlation was found between the level of education and the latency of both correct ($r$=-0.62, $p$=.001) and incorrect ($r$=-0.50, $p$=.009) antisaccades. Inpatients and outpatients showed equal performance, and also female and male patients did not differ on the tasks.

### 3.4 Olanzapine group versus risperidone group versus healthy controls

The olanzapine, risperidone, and control group did not differ for gender and level of education, whereas there was a difference for age ($\chi^2$=12.95, $df$=2, $p$=.002). The olanzapine and risperidone group were significantly older than the control group ($p$=.000 and $p$=.006 respectively). The medication groups were similar for inpatient/outpatient ratio, duration of illness, duration of medication treatment, and severity of positive symptoms, negative symptoms, and general symptoms. For none of the saccadic variables significant differences were found between the two medication groups (Table 3, 4 and 5). The olanzapine and risperidone group differed, however, significantly from controls for antisaccade inhibition errors ($p$=.007 and $p$=.002 respectively) and the amplitudes of primary saccades to large target eccentricities ($p$=.045 and $p$=.006 respectively). The olanzapine group, in

contrast to the risperidone group, differed significantly from controls for inhibition errors on the memory-guided task ($p$=.002) and the final eye position to small target eccentricities in this task ($p$=.048). The risperidone group differed significantly from controls for the latency of correct antisaccades ($p$=.032).

Table 3
*Visually-guided saccades*

| | **Patients (all) (n=33)** Mean (SD) | **Controls (n=23)** Mean (SD) | **Sign** | **Olanzapine (n=21)** Mean (SD) | **Risperidone (n=12)** Mean (SD) |
|---|---|---|---|---|---|
| **Latency correct saccades** | 200.91 (30.24) | 199.88 (31.85) | ns | 201.36 (33.68) | 200.12 (24.43) |
| **Number of false anticipations** | 5.58 (5.79) | 2.59 (2.28) | ns | 5.71 (5.33) | 5.33 (6.76) |

Table 4
*Antisaccades*

| | **Patients (all) (n=33)** Mean (SD) | **Controls (n=23)** Mean (SD) | **Sign** | **Olanzapine (n=21)** Mean (SD) | **Risperidone (n=12)** Mean (SD) |
|---|---|---|---|---|---|
| **Latency correct antisaccades** | 368.68 (75.08) | 334.47 (65.97) | ns | 349.65 (70.50) | 398.82 (74.99)[a] |
| **Latency inhibition errors** | 242.74 (54.67) | 230.78 (50.47) | ns | 239.10 | 249.11 (55.08) |
| **Percentage inhibition errors** | 26.49 (17.02) | 11.43 (7.49) | .000 | 24.84 (15.81)[b] | 29.36 (19.33)[a] |

[a] significantly different from controls, but not different from olanzapine group.
[b] significantly different from controls, but not different from risperidone group.

## 4. Discussion

We examined saccadic eye movements in three saccade tasks in first-episode psychotic patients and healthy controls. Our patient group performed worse than controls on the antisaccade and memory-guided saccade task. Impairment was most pronounced for the number of inhibition errors, which is in accordance with previous studies (e.g., Crawford et al. 1995b; Schultz & Andreasen 1999). Inhibition errors reflect a failure in the control of response tendencies and have been attributed to dorsolateral prefrontal dysfunction (Pierrot-Deseilligny et al. 1991).

Table 5
*Memory-guided saccades*

| | Patients (all) (n=33) Mean (SD) | Controls (n=23) Mean (SD) | Sign | Olanzapine (n=21) Mean (SD) | Risperidone (n=12) Mean (SD) |
|---|---|---|---|---|---|
| **Percentage inhibition errors** | 8.07 (9.34) | 2.40 (3.95)* | .008 | 10.46 (10.55)[a] | 3.50 (5.57) |
| **Percentage delay errors** | 16.12 (13.54) | 7.80 (5.30) | .043 | 16.43 (12.43) | 15.59 (15.79) |
| **Ampl prim saccs 7.5° targets** | 5.78 (1.02) | 6.00 (1.31) | ns | 5.72 (1.11) | 5.85 (0.88) |
| **Ampl f.e.p. 7.5° targets** | 7.18 (0.77) | 6.67 (0.65) | .016 | 7.22 (0.88)[a] | 7.10 (0.51) |
| **Ampl prim saccs 15° targets** | 10.50 (1.81) | 12.06 (1.52) | .002 | 10.76 (2.03)[a] | 10.05 (1.32)[b] |
| **Ampl f.e.p. 15° targets** | 13.17 (0.92) | 13.76 (1.17) | ns | 13.21 (0.87) | 13.08 (1.04) |

f.e.p.= final eye position after corrective saccades; prim saccs = primary saccades.
[a] significantly different from controls, but not different from risperidone group.
[b] significantly different from controls, but not different from olanzapine group.

In addition, patients showed more delay errors in the memory-guided task. These errors reflect a failure in delaying an already prepared saccadic motor program, which could be interpreted as a failure in executive control. For the memory-guided task, patients also showed significantly reduced amplitudes on targets with large eccentricity, whereas amplitudes on targets with small eccentricity were more accurate than those of controls. These findings are difficult to interpret and should first be confirmed by studies using a larger sample.

Within the patient group we found a number of correlations between the various saccadic measures. First, a positive correlation between antisaccade inhibition errors and final eye position of small saccades was obtained. It is possible that both measures depend on a common cognitive process; in this respect, (visuospatial) working memory is the most likely candidate. Second, whereas none of the demographic and disease-related factors was significantly correlated with saccadic performance, we found a negative correlation between the latency of both correct and incorrect antisaccades and the level of education. Higher educated patients performed better than lower educated patients. Perhaps intelligence protects patients from poor performance on measures of executive function and attention. This would be in line with the findings of (Holthausen et al. *submitted*), who demonstrated that patients with normal performance on neuropsychological tasks scored higher on intelligence tests than patients with impaired performance. However, the present negative correlation needs to be confirmed in future studies in which IQ and level of education are established more extensively.

With respect to differential effects of risperidone and olanzapine, no significant group differences on any of the saccadic measures were found. This was surprising and counter to our hypothesis. We predicted superior beneficial effects for risperidone on measures of spatial working memory. In fact, the risperidone group performed even slightly worse on these measures, as was indicated by a reduced accuracy in the amplitudes of memory-guided saccades. Since previous studies reported reduced accuracy on the memory-guided task after treatment with classical APs (Crawford et al. 1995b; Hommer et al. 1991), there is a possibility that our findings were related to medication dose, because risperidone in a high dose has an action profile which resembles that of classical APs. However, our dose range was low and similar to the doses used in other studies (2 to 6 mg/day), thus it seems unlikely that this could explain the discrepancy between our results and the results from previous studies reporting fairly beneficial effects of risperidone on neuropsychological measures of visuospatial working memory. It seems plausible that olanzapine and risperidone have no differential effects on the cognitive functions targeted in this study. However, future studies in which these drugs are directly compared in a design with baseline measurements are warranted. Additional clues about the influence of novel APs on saccades might also be provided by studies investigating smooth pursuit eye movements, since during these eye movements the saccadic system is also active. Moreover, important information might be revealed by studies investigating the effects of single doses of APs in healthy controls, since this provides knowledge on direct effects of APs without interference from disease related factors. Currently neither type of studies has been conducted with novel APs.

A comparison of these saccadic data with patients on risperidone and olanzapine, and those of other studies with classical APs in similar experimental paradigms (Crawford et al. 1995b; Hutton et al. 1998), is consistent with a beneficial effect of some novel drugs on cognition. However, confirmation of this possibility will have to await direct head-to-head studies comparing the effects of classical and novel APs.

An important factor that might explain the failure to find significant differences between the olanzapine and risperidone group might be the small size of the groups. It seems, however, unlikely that larger groups would have resulted in significant effects, since power analysis revealed that significant results could be obtained with our group sizes. Moreover, many studies have shown that with similar or even smaller group sizes significant differential drug effects could be obtained.

The omission of baseline measurements might also have prohibited us from finding differential effects, since with our design we could not establish individual improvement after treatment duration. Nevertheless, we think that the random group

assignment in combination with close matching provided a good opportunity to find significant group differences.

In sum, the present study replicates the previous finding that not only chronic schizophrenic patients, but also first-episode patients have substantial problems with cognitive processes incorporated in saccadic tasks. Apparently cognitive abnormalities are already present in an early phase of the disease. Schizophrenic patients are particularly impaired in the inhibitory control of reflexive saccades, though a high level of education appears to be an important protective factor. We also have demonstrated that random assignment to either treatment with risperidone or olanzapine did not result in differential saccadic performance between the groups.

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# Chapter 4

# Does frontal normality exist in schizophrenia? A saccadic eye movement study

Published

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**Abstract**

Many observations have supported the general idea of impaired frontal function in schizophrenia. In particular neuropsychological studies have shown severe frontal deficits. However, other studies found normal cognitive function in a proportion of patients. Since saccadic tasks also provide an index of frontal function, we examined the presence of frontal deficits in patients by means of both neuropsychological and saccadic tasks, and compared the sensitivity of both approaches for frontal impairment. In addition, we examined the relationship between saccadic and neuropsychological measures.

Twenty-four schizophrenic patients and twenty healthy controls completed an extensive neuropsychological battery and three saccadic tasks. Based on the neuropsychological battery alone, 42% of the patients showed frontal deficits, whereas combined use of neuropsychological and saccadic tasks resulted in 79% with frontal deficits. The antisaccade task appeared able to detect frontal deficits in patients who were without frontal impairment on the neuropsychological battery. Saccadic deficits were, however, not necessarily accompanied by deficits on frontal neuropsychological measures. This suggests that the saccadic and neuropsychological tasks used in the present study targeted different frontal functions. This view was supported by the lack of correlations between saccadic and frontal neuropsychological measures.

## 1. Introduction

Many observations have supported the general idea of impaired frontal function in schizophrenia. In particular, studies addressing frontal functions by means of neuropsychological (NP) tests have demonstrated severe cognitive deficits. It has, therefore, been proposed that frontal cognitive deficits are among the core deficits of schizophrenia (Goldman-Rakic 1994; Hemsley 1994). However, this assumption is not in accordance with studies that found a substantial proportion of patients with normal NP performance, including performance on frontal tasks (Silverstein & Zerwic 1985; Bryson et al. 1993; Palmer et al. 1997; Holthausen et al. *submitted*). Estimates of this proportion vary from 19% (Holthausen et al. *submitted*) to 73% (Bryson et al. 1993).

In order to determine if frontal impairment is a core deficit of schizophrenia, it seems worth the effort to evaluate frontal functions by means of an alternative method, namely the recording of saccadic eye movements. Saccades are fast eye movements, which are made to fixate objects on the fovea. These eye movements can be easily implemented in various cognitive tasks. An advantage of such tasks is that the neural systems subserving these tasks are well known from primate studies (Bruce & Goldberg 1985; Hikosaka & Wurtz 1991; Everling et al. 1999) and performance is not dependent on manual and verbal capacities. In addition, a smaller number of cognitive subprocesses are involved, since the visual stimuli are very simple and do not require complex integrative processing (in contrast to pictures, words, etc), and the eye movement response does not require cross-modal integration. Due to these characteristics, we presume that saccadic tasks target frontal functions rather specifically.

Saccadic tasks have proven to be a valuable tool in estimating functional impairment in certain psychiatric patient groups (Everling & Fischer 1998). In particular, in schizophrenic patients saccadic abnormalities were found (Thaker et al. 1989; Crawford et al. 1995; Hutton et al. 1998). With respect to these abnormalities, it is useful to make a distinction between visually guided (or externally driven) saccades and voluntary saccades, which are usually generated in (simple) cognitive paradigms (Tusa et al. 1986). Visually guided saccades require mainly spatial attention and the generation of a precise motor program, whereas voluntary saccades require intact higher order, executive functions. A large number of studies have shown that schizophrenic patients perform accurately on visually guided saccades (Crawford et al. 1995; Hutton et al. 1998; Karoumi et al. 1998), whereas they have severe problems with voluntary saccades, as measured in, for example, the antisaccade and memory saccade task. On these tasks, patients show typical failures in suppressing response tendencies towards suddenly appearing stimuli (Crawford et al. 1995; McDowell & Clementz 1997).

Saccadic tasks and NP tasks have both been used to assess frontal functions. It is, therefore, not surprising that several studies have looked at the relationship between these tasks in psychiatric patient groups (Rosse et al. 1993; Crawford et al. 1995; Schreiber et al. 1995; Tien et al. 1996; Radant et al. 1997; Karoumi et al. 1998; Snitz et al. 1999; Nieman et al. 2000; Gooding & Tallent 2001). The majority of these studies, however, used only few NP tests. Moreover, the results were inconsistent, except for a positive association between antisaccade inhibition failures and performance on the Wisconsin Card Sorting Test (WCST; perseveration errors) (Rosse et al. 1993; Crawford et al. 1995; Tien et al. 1996; Radant et al. 1997; Karoumi et al. 1998) and a spatial working memory task (Gooding & Tallent 2001). These positive associations have been attributed to a common dependency on the (dorsolateral) prefrontal cortex (DLPFC), which has been reported to be crucially involved in each of these tasks (Berman et al. 1986; Goldman-Rakic 1994; O'Driscoll et al. 1995; Sweeney et al. 1996; Doricchi et al. 1997). Since neuroimaging studies have shown that various other NP tasks, like the Continuous Performance Task (e.g., Hager et al. 1998), the Stroop Task (e.g., Peterson et al. 1999), the Trail Making Test (e.g., Lesnik et al. 1998), and Verbal Fluency (e.g., Hugdahl et al. 1999), are also dependent on the (pre)frontal cortex, it remains to be elucidated why previous studies failed to find consistent associations between these tasks and saccadic tasks. The extent of DLPFC involvement in the NP tasks might determine whether significant relations are obtained.

The main goal of the present study was to evaluate the assumption that frontal impairment is a core deficit of schizophrenia, an assumption which implies that *all* patients show frontal deficits. Since the use of NP tests has revealed inconsistent results, frontal function was examined by means of NP tasks as well as saccadic tasks, which were presumed to target frontal function more specifically. We examined whether adding saccadic tasks to a NP test battery would increase the sensitivity to detect frontal impairment, and whether specific saccadic measures were more sensitive to frontal deficits than NP tasks. Therefore, we first established the number of patients with frontal deficits based on the NP tasks alone, and compared this with the number of patients obtained when NP tasks were combined with saccadic tasks. Second, we compared the performance on specific saccadic measures in patients *with* and *without* frontal impairment on the NP test battery. We also examined the number of patients showing deficits in two other, non-frontal domains, namely psychomotor speed and memory. Finally, we were interested in the relationship between saccadic measures which were presumed to target frontal function and frontal NP measures, since the literature provides inconsistent results on these correlations.

## 2. Methods

### 2.1 Subjects

The study included 24 patients (18 males and 6 females) who had recently experienced a first or a second psychotic episode according to DSM-IV (American Psychiatric Association 1994) and received a diagnosis within the schizophrenia spectrum (schizophrenia, n=12; schizophreniform disorder, n=11; schizoaffective disorder, n=1). The diagnosis was based on a structured interview (SCAN; Wing et al. 1990). Exclusion criteria were severe mental retardation, systemic or neurologic illness, severely impaired vision, medication other than antipsychotics, and severe tardive dyskinesia. The mean age was 26.54 (SD 8.47) years and average education was at high school level. Eighteen patients used atypical antipsychotic medication (olanzapine or risperidone), five patients used classic antipsychotic medication, and one patient was drug-free.

A control group of 20 healthy volunteers (15 males and 5 females), recruited from the local community, was included to evaluate the saccadic performance of patients. The mean age of this group was 20.95 (SD 2.80) years and average education was at high school level.

The patient and control groups were matched for gender and level of education, whereas there was a difference for age ($p$=.007). The factor age is known to have an influence on both cognitive (Elias et al. 1990) and saccadic performance (Fischer et al. 1997), however, the age difference between our groups was too small (5.6 years) to have a significant influence on performance.

### 2.2 Neuropsychological measures

An extensive NP test battery was completed. Tests included a double stimulus Continuous Performance Task (CPT; Van den Bosch et al. 1996), a computerized Stroop task (developed at our own laboratory; partly based on the traditional version of Stroop 1935), the Trail Making Test (TMT; Vink & Jolles 1985), a Finger Tapping test, the Dutch translation of the California Verbal Learning Test (CVLT; Delis et al. 1987), the Rey Complex Figure (RCF; Rey 1964), and Verbal Fluency (VF). Table 2 shows the 15 measures that were obtained by these tests. The following four measures were considered to reflect frontal functioning: CPT *d'*, Stroop interference, TMT interference, and VF items in category. The raw test scores of the control group were converted into $z$ scores, and patients showing a $z$ score below –2 on one of the four frontal measures were characterized as 'frontally impaired' (FI), whereas the other patients were characterized as 'frontally normal' (FN). This criterion for group assignment was chosen, because of its frequent use in clinical settings. A similar procedure was used to determine the presence of deficits in two non-frontal domains, psychomotor speed and memory. The following five

measures were considered to reflect psychomotor speed: CPT reaction time, Stroop word reading and color naming, TMT trail A, and Finger Tapping, whereas memory function was presumed to be reflected in: CVLT encoding, consolidation, retrieval, total intrusions, and RCF percentage recall.
In order to examine the relationship between saccadic measures and NP performance in the frontal, psychomotor speed, and memory domains, we calculated three composite scores for each of these domains. These were based on the mean *z* scores of the NP measures described above.

### 2.3 Saccadic eye movement recording

Subjects were comfortably seated 90 cm in front of a color monitor in a darkened room. Eye movements were recorded using an infrared limbus reflection device (IRIS, Skalar Medical BV, The Netherlands), and head movements were restrained by an adjustable headrest. Visual stimuli, small green squares of approximately 3 mm, were presented against a darkened color monitor. Before presentation of the tasks, subjects were presented with calibration stimuli and a series of 20 practice trials. Saccades were identified using interactive software (developed at the University Maastricht, The Netherlands) which enabled the rejection of artifacts due to, for example, eye blinks. Saccade detection was based on a velocity criterion of 30°/s in addition to an acceleration across three consecutive samples. Since the minimum latency of a visually guided saccade is approximately 100 ms (Fischer & Ramsperger 1984), the first saccade of at least 3° made 100 ms after target onset was scored as the response.

### 2.4 Saccadic measures

Three saccadic tasks were completed: a visually guided saccade task, an antisaccade task and a memory saccade task (Figure 1).
*Visually-guided saccade task.* After central fixation (800 ms), a stimulus was randomly presented 7.5° or 15° to the left or right for 1000 ms. Subjects were expected to respond with a rapid and accurate eye movement. Intertrial interval was 1000 ms, and 48 trials were completed. This task required the integration of spatial attention, visual perception, and a precisely targeted motor program, but placed few demands on higher order, executive functions. The performance was evaluated for latency of saccadic onset and the number of too early anticipations on stimulus behavior.
*Antisaccade task.* After central fixation (800 ms), a stimulus was randomly presented 7.5° or 15° to the left or right for 2000 ms. Subjects were required to direct a saccade towards the spatial position in the visual field opposite to that of the stimulus. There was no intertrial interval, and 48 trials were completed. The task required both the suppression of the reflexive saccade that would normally be generated in response to

a novel visual target and the generation of a volitional saccade to the opposite hemifield. The performance was evaluated for the number of inhibition errors (reflecting a failure in the ability to suppress a response tendency), the latency of appropriate saccades, and the latency of the inhibition errors.

*Memory saccade task.* After central fixation (800 ms), a stimulus was randomly presented 7.5° or 15° to the left or right for 200 ms. Subjects were required to suppress the reflexive saccade to the stimulus and delay the saccade for 700 ms (until fixation point offset). There was no information on the location of the previously presented stimulus at the moment of saccade initiation. Intertrial interval was 3000 ms, and 48 trials were accomplished. This task examined the ability to generate an internal representation of space as well as the programming of a volitional motor action and the ability to delay (inhibit) the saccadic motor program during the memorization period. The task also examined the inhibition of an immediate saccadic reflex to the stimulus. However, inhibition of this reflex was relatively easy as compared to the antisaccade task, since the fixation point remained on during stimulus presentation, which facilitates the engagement of attention. Performance on this task was evaluated for two parameters. First, the number of immediate inhibition errors (reflecting a failure in the ability to suppress a response tendency), which occur in the early phase of the delay period (0 to 250 ms), and second, the number of delay errors (reflecting a defect or weakness in inhibition mechanisms which normally prevent an already prepared saccadic motor program from being directly initiated), which occur in the late phase of the delay period (250 to 700 ms).

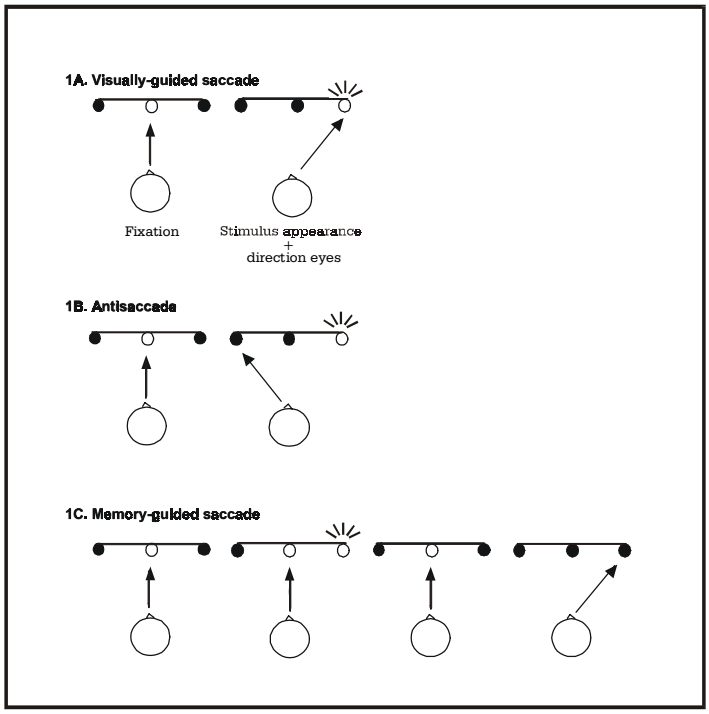


Figure 1. Saccadic paradigms

**1A:** A visual stimulus is presented in a random sequence to the left or right of a central fixation point and subjects are instructed to respond with a rapid and accurate eye movement.

**1B:** Antisaccades are directed towards a spatial position in the opposite visual field to that of the stimulus. The paradigm requires suppression of the reflexive saccade that would normally be generated in response to a novel visual target, and the generation of a volitional saccade to the opposite hemifield.

**1C:** Subjects are instructed to suppress the normal reflexive eye movement in response to a novel stimulus, and to delay the saccade until the offset of the central light. There is no visual information on the location of the previously presented target at the moment of saccadic initiation.

Based on animal studies (Funahashi et al. 1993; Everling & Munoz 2000) and studies in patients with brain lesions (Pierrot-Deseilligny et al. 1991a,b), the following measures from the antisaccade and memory saccade task were considered to reflect frontal function: antisaccade inhibition errors, memory saccade inhibition errors, and memory saccade delay errors. The raw test scores on these measures were converted into *z* scores, and patients showing a *z* score below –2 on at least one of these measures were regarded as showing frontal saccadic impairment.

### 2.5 Statistical analyses

Differences between the FI and FN group on major demographic variables (age, gender, and level of education) were examined by means of *t* tests or chi-square analyses. Differences between the FI, FN and control groups on saccadic and NP measures were examined by one-way analysis of variance (ANOVA) followed by post hoc testing (Fishers' protected *T* tests, $\alpha$=.05). When variables did not resemble the normal distribution, non-parametric Kruskal-Wallis tests followed by Mann-Whitney *U* tests were performed. The relationships between saccadic and NP performance were examined in the total sample with Pearson correlation coefficients.

## 3. Results

### 3.1 Frontal, psychomotor speed, and memory deficits in patients

Table 1 shows how deficits in the frontal, psychomotor speed, and memory domains were distributed within the patient sample when the NP test battery was considered alone and when the NP tasks were combined with the three putatively frontal saccadic measures. Based on the NP tasks alone, 10 patients (42%) showed frontal impairment, whereas combined use of NP and saccadic tasks revealed 19 patients (79%) with frontal deficits. Combined use of NP and saccadic tasks also revealed that none of our patients were without cognitive deficits.

### 3.2 Neuropsychological performance in the FI, FN, and control groups

Based on the NP test battery, 10 patients were characterized as 'frontally impaired' (FI group), while 14 patients were characterized as 'frontally normal' (FN group). No significant differences were found in age, gender, and level of education between the FI, FN, and control groups. Table 2 shows the performance of these groups on all NP measures included in the test battery.

Table 1

*Cognitive deficits in the frontal, psychomotor speed, and memory domain in patients*

| **Defective cognitive domain** | **Number of patients** | |
|---|---|---|
| | *NP tasks alone* | *NP + saccadic tasks* |
| None | 1 | 0 |
| Frontal [a] | 1 | 2 |
| Speed [a,b] | 5 | 2 |
| Memory [a] | 5 | 2 |
| Frontal + Speed | 1 | 4 |
| Frontal + Memory | 1 | 4 |
| Speed + Memory | 3 | 1 |
| Frontal + Speed + Memory | 7 | 9 |
| *Overall frontal* (either with or without deficits in other domains) | 10 | 19 |
| *Overall speed* (either with or without deficits in other domains) | 16 | 16 |
| *Overall memory* (either with or without deficits in other domains) | 16 | 16 |

[a] no deficits in the other two domains; [b] speed = psychomotor speed.

### 3.3 Saccadic performance in the FI, FN and control groups

The FI, FN and the control groups differed significantly for 3 of the 7 saccadic measures (Table 3), namely the number of inhibition errors on the antisaccade task ($F$=7.87, $p$=.001), the number of inhibition errors on the memory task ($\chi^2$=6.85, $p$=.033), and the number of delay errors on the memory task ($F$=3.79, $p$=.032).

Both the FI and FN group showed significantly more inhibition errors on the antisaccade task than controls ($p$ values of .016 and .003 respectively). With respect to the memory task, the FI group showed significantly more inhibition errors ($p$=.022) and delay errors ($p$=.025) than the control group, whereas differences between the FI and FN group and the FN and control group were not significant.

### 3.4 Presence of deficits on *frontal* saccadic and *frontal* NP measures in patients

Table 4 shows that patients with impaired performance on frontal NP measures did not necessarily perform poorly on frontal saccadic measures, and vise versa. Three patients with normal saccadic performance showed impaired performance on NP measures, while nine patients with impaired saccadic performance showed normal NP performance.

Table 2

*Neuropsychological performance in the FI, FN, and control group*

| | FI patients (n=10) Mean (SD) | FN patients (n=14) Mean (SD) | Controls (n=20) Mean (SD) | Sign | Post hoc |
|---|---|---|---|---|---|
| **CPT** | | | | | |
| *d'* | 2.74 (1.04) | 3.86 (.35) | 4.25 (.51) | .000 | FI<FN+CS |
| RT (ms) | 546.6 (116.19) | 495.14 (73.69) | 441.85 (65.94) | .007 | FI>CS |
| **Stroop** | | | | | |
| Word reading (s) | 43.8 (7.72) | 40.62 (5.57) | 37.03 (4.39) | .011 | FI>CS |
| Color naming (s) | 45.71 (7.60) | 37.50 (5.96) | 34.41 (5.12) | .000 | FI>FN=CS |
| Interference (s) | 10.45 (5.82) | 6.95 (3.35) | 8.58 (5.97) | .284 | |
| **Trail Making** | | | | | |
| Trail A (s) | 46.00 (22.36) | 35.57 (10.50) | 25.05 (6.66) | .000 | FI>CS |
| Interference | 70.58 (57.96) | 37.10 (25.00) | 45.71 (22.65) | .065 | |
| **Verbal Fluency** | | | | | |
| Category words | 16.25 (2.63) | 17.92 (3.36) | 22.05 (6.38) | .008 | FI<CS |
| **Finger tapping** | | | | | |
| Number of taps | 52.1 (10.18) | 56.16 (13.41) | 64.54 (11.40) | .020 | FI<CS |
| **CVLT** | | | | | |
| Encoding (trial 1-5) | 38.80 (8.64) | 48.64 (7.39) | 55.20 (6.26) | .000 | FI<FN<CS |
| Consolidation | 1.80 (2.04) | 1.64 (2.02) | 2.40 (1.60) | .462 | |
| Retrieval | 5.40 (2.95) | 5.57 (1.87) | 5.15 (1.84) | .849 | |
| Total intrusions | 6.20 (5.94) | 4.36 (5.26) | 1.16 (1.20) | .007 | FI>CS |
| **RCF** | | | | | |
| Copy | 30.22 (4.63) | 32.36 (4.14) | 32.98 (2.2) | .155 | |
| Percentage recall | 45.43 (23.91) | 62.17 (24.0) | 70.39 (16.92) | .018 | FI<CS |

FI=frontally impaired; FN=frontally normal; CS=controls.

### 3.5 Correlations between measures

The signs of the raw data were adjusted so that a lower value on any measure represented poorer performance. Using a Bonferroni correction, only two-tailed *p* values smaller than .003 were considered significant for correlation coefficients. As shown in Table 5, antisaccade inhibition errors were significantly correlated with CPT *d'* ($r$=.45, $p$=.002) and with the composite score for psychomotor speed ($r$=.49, $p$=.001), while inhibition errors on the memory saccade task were significantly correlated with the composite score for memory ($r$=.47, $p$=.001).

Table 3

*Saccadic performance in the FI, FN, and control group*

| | FI patients (n=10) Mean (SD) | FN patients (n=14) Mean (SD) | Controls (n=20) Mean (SD) | Sign | Post hoc |
|---|---|---|---|---|---|
| **Visually guided task** | | | | | |
| Latency | 197.32 (30.11) | 199.13 (35.05) | 196.04 (25.10) | .958 | |
| Early anticipations | 7.8 (8.69) | 5.71 (5.37) | 2.75 (2.31) | .376 | |
| **Antisaccade task** | | | | | |
| Latency | 387.63 (78.17) | 369.22 (62.37) | 330.55 (58.79) | .064 | |
| Inhibition errors | 28.89 (15.56) | 31.04 (20.82) | 12.59 (7.35) | **.001** | FI=FN>CS |
| Latency Inhibition errors | 247.19 (58.15) | 237.29 (41.20) | 221.00 (40.56) | .331 | |
| **Memory task** | | | | | |
| Inhibition errors | 8.67 (5.81) | 9.28 (11.49) | 3.40 (4.89) | **.033** | FI>CS |
| Delay errors | 21.25 (19.63) | 14.22 (9.24) | 8.31 (5.40) | **.032** | FI>CS |

FI=frontally impaired; FN=frontally normal; CS=contols.

Table 4

*Presence of deficits on frontal saccadic and frontal NP measures in patients*

| | | Frontal *saccadic* performance[b] | |
|---|---|---|---|
| | | *normal* | *impaired* |
| **Frontal *NP* performance**[a] | *normal* | 5 | 9 |
| | *impaired* | 3 | 7 |

[a] performance on CPT *d'*, Stroop interference, TMT interference, and VF items in category.
[b] performance on antisaccade inhibition errors, memory saccade inhibition errors, and memory saccade delay errors.

## 4. Discussion

In order to examine whether frontal impairment is a core deficit of schizophrenia, we examined frontal function with two different approaches. In addition, we examined whether combined use of traditional NP and saccadic tasks would increase the sensitivity to detect frontal impairment. Based on the NP tasks alone, 42% of our patients demonstrated frontal deficits, whereas combined use of NP and saccadic tasks revealed frontal impairment in 79% of our patients. This suggests that addition of saccadic tasks to the NP measures used in the present study significantly increased the sensitivity to detect frontal impairment.

The question whether the saccadic measures were more sensitive to frontal impairment than NP tasks, was addressed by comparing the performance on saccadic measures

Table 5

*Correlations between frontal saccadic measures and NP measures*

| | Antisaccade *Inhibition errors* | Memory saccade *Inhibition errors* | Memory saccade *Delay errors* |
|---|---|---|---|
| **Frontal** (composite score) | .32 | .24 | -.03 |
| **CPT** *d'* | **.45 *** | .22 | .28 |
| **Stroop** interference | .14 | .33 | -.14 |
| **TMT** interference | -.04 | .10 | -.21 |
| **VF** items in category | .11 | .17 | .003 |
| **Psychomotor speed** (composite score) | **.49 **** | .33 | .40 |
| **Memory** (composite score) | .35 | **.47 *** | .41 |

* = $p<.002$; ** = $p<.001$

of patients *with* and *without* frontal impairment on a NP battery. A high level of antisaccade inhibition errors was obtained in FN patients, who were presumed to have intact frontal function. Apparently, the antisaccade task was able to reveal frontal deficits which were not detected by the frontal NP tasks used in the present study. This might be due to a strong stimulus-response compatibility (Gale & Holzman 2000) and the absence of verbal and manual task components. These characteristics might imply a relatively short and restricted pathway in the brain, which probably reduces the impact of (inhibitory) control mechanisms. With respect to the memory saccade task, only the FI group performed significantly worse than controls. This suggests that the memory task is less sensitive to frontal impairment than the antisaccade task, which might be due to the fact that, although both tasks address inhibitory functions, the memory task addresses them in a less stringent way. In the memory task, visual targets are presented while the fixation point remains on, which implies that the orienting system is not fully prepared for immediate action. In the antisaccade task, however, fixation point offset results in disengagement of attention, which renders subjects more vulnerable to an immediate response to novel targets. The memory task also requires an extra cognitive process (i.e., working memory) and has a slower pace, which increases the opportunity to compensate for problems in one task process by investing more effort in others. In this respect, the memory task is a better comparison to the NP tasks than the antisaccade task.

Although the high antisaccade error rate in the FN group suggests that this task is more sensitive to frontal impairment than the NP tasks, a closer look at the presence of *frontal saccadic* and *frontal NP* deficits in individual patients revealed that patients with impaired performance on frontal saccadic measures not necessarily performed poorly on frontal NP measures, and vise versa. These findings suggest

that the frontal saccadic and NP tasks address, at least to some extent, different frontal functions. This was interpreted as evidence for the notion that combined use of NP and saccadic tasks is the most favorable method to assess frontal function. Future studies using, for example, functional brain imaging techniques should provide evidence for the idea that our frontal saccadic and NP measures indeed target different frontal functions.

The finding that 21% of our patients did *not* show frontal impairment on either the NP or the saccadic tasks, contradicts the notion of frontal deficits as a core deficit of schizophrenia. On the other hand, all our patients suffered from deficits in either the frontal, speed, or memory domain, which strongly suggests that *cognitive* deficits (instead of *frontal* deficits) are a core feature of the disease.

A related issue, is the ongoing debate as to whether the cognitive deficits in schizophrenia should be characterized as a *generalized* cognitive deficit or as deficits in *specific* cognitive domains. The common view is that schizophrenic patients suffer from specific deficits against a background of generalized cognitive dysfunction, with specific impairment in verbal learning, vigilance, speeded visual-motor processing (Saykin et al. 1991, 1994; Censits et al. 1997) and executive functioning (Mohamed et al. 1999). The present study did not support the idea of cognitive deficits being a generalized deficit, since only nine patients showed deficits in all three domains. We also failed to find evidence for the existence of specific deficits in either the frontal, psychomotor speed, or memory domain, since deficits in these three domains were present in 79%, 67% and 67% of the patients, respectively. Thus, although frontal dysfunction, but also memory and psychomotor speed impairment, is likely to be found in schizophrenia, impairment in either of these domains is not necessarily present in this psychiatric syndrome. At this point, it should, however, be noted that the present study included first-episode patients with relatively few symptoms. This implicates that the cognitive deficits might have been more severe in chronically ill patients.

With respect to the relationship between saccadic performance and NP performance within the frontal, psychomotor speed, and memory domain, our main finding was a remarkable lack of significant associations between frontal saccadic measures and the composite score for frontal NP function. With respect to individual frontal NP measures, however, we found a strong correlation between antisaccade inhibition errors and CPT *d'*. Apparently, antisaccade performance and the sensitivity to detect targets in a memory-load CPT depend on a common function, and thus probably on common brain regions. This idea was supported by neuroimaging studies reporting that the CPT is associated with brain activation in the right DLPFC and the mesial frontal cortex (Hager et al. 1998), while bilateral activation of these areas has also been found during the antisaccade task (Sweeney et al. 1996; Doricchi et al. 1997).

For the other frontal NP measures, we found, however, no significant association with saccadic measures, which suggests a lack of overlap in the frontal functions addressed by both type of measures. This is also suggested by our finding that deficits on frontal saccadic measures were not necessarily accompanied by deficits on frontal NP measures. It should be noted here, that our patients showed a remarkable accurate performance on a putative frontal NP measure, namely Stroop interference. Other studies have also failed to observe an association between frontal saccadic measures and frontal NP measures, except for the WCST and a working memory task. We hypothesize that, compared to NP tests, voluntary saccades depend on a relatively limited set of brain regions, with crucial involvement of the DLPFC. The probably limited DLPFC dependence of our NP tasks might have resulted in only marginal associations with the saccadic measures, as compared to NP tasks with large DLPFC involvement, like the WCST and tests of spatial working memory.

Another intriguing finding was that psychomotor speed abilities were significantly associated with antisaccade inhibition errors. This was unlikely to be caused by an underlying defect in basic oculomotor processes, since the performance on visually-guided saccades was accurate. It appeared that all psychomotor speed measures were significant contributors to the association, except for Finger Tapping. This suggests that a general slowness in information processing was underlying the association rather than a deficit in motor abilities. Slow processing of incoming information, and probably also slow rehearsal of task instructions, might have resulted in greater problems to overcome response tendencies.

With respect to the significant correlation between memory saccade delay errors and performance in the memory domain, it appeared that encoding deficits were mainly responsible for the significance of the association. This may be because of the relatively slow pace of the memory saccade task (trial duration of 4.5 s, as compared to 2.8 s in the antisaccade task), which required active rehearsal of the task instruction *not* to initiate the saccade before fixation point offset. However, the oculomotor program for the saccadic eye movement was already prepared immediately after stimulus presentation. Poor encoding of the task instruction might, therefore, have rendered patients vulnerable to early initiation of saccades.

In sum, the present study does not support the view that frontal impairment is a core deficit of schizophrenia, but our results do support the notion that *cognitive* deficits are a core feature of the disease. We did not found evidence for the existence of either a generalized deficit or specific domain deficits. The use of NP measures in combination with saccadic tasks appeared to increase the sensitivity to detect frontal impairment. In particular the antisaccade task was able to reveal frontal deficits. Frontal saccadic measures were, however, only marginally associated with frontal NP measures.

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# Chapter 5

## Inhibition deficits in schizophrenia? A cognitive study

Submitted

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**Abstract**

Numerous studies using a variety of experimental tasks have demonstrated inhibition deficits in schizophrenia. Although these deficits seem rather diffuse and task-related, it is not unlikely that they result from one underlying deficit. Therefore we examined the performance of first-episode patients and healthy controls on a range of inhibition tasks that were assumed to measure interference control (Stroop task, Simon task), cognitive inhibition (Negative Priming task, Cross-modal Matching task), and behavioral inhibition (Continuous Performance task, Go/nogo task). The study revealed unexpected negative results, suggesting that first-episode patients do not exhibit inhibition deficits. The fact that patients were relatively free of symptoms and successfully treated with antipsychotics probably explained the normal inhibitory performance. Apparently, inhibitory deficits are merely state than trait dependent. The finding that inpatients performed somewhat worse than outpatients, supported this view. In addition, correlation analyses supported the use of a classification for different inhibitory processes.

## 1. Introduction

A large number of experimental studies have indicated that selective attention is impaired in schizophrenia. These selective attention deficits have also been characterized as inhibition deficits, since patients exhibit an increased vulnerability to distractors (for reviews, see Braff 1993; Goldberg & Gold 1995). The ability to inhibit irrelevant information in order to select information that is relevant for goal-directed behavior is an essential element of higher order cognitive function. Deficits in inhibitory function might render patients vulnerable to stimulus inundation and cognitive fragmentation, and might explain the disordered thought processes and distractibility in complex social situations.

Inhibition deficits have been studied by a variety of experimental tasks, among which the Stroop task is the most widely used (Stroop 1935; for review, see MacLeod 1991). In this task, words printed in certain colors are presented, and subjects have to ignore the word, while naming the color. When the word meaning and its color are incongruent (e.g., the word BLUE is printed in red), responses are relatively slow. This increase in reaction time (RT) is referred to as Stroop interference. Recent work in experimental psychology has employed a single-trial version of the Stroop task. In this version, incongruent (conflict) and congruent color-words are intermixed with neutral stimuli (e.g., rows of colored X's or neutral words) and sequentially presented. Comparison of RTs to incongruent and neutral stimuli will reveal interference effects, while comparison of RTs to neutral and congruent stimuli might reveal facilitation. Interference results from the fast obligatory process of reading that interferes with the intentional process of color naming. Interference and facilitation are suggested to be distinct and dissociable operations, with interference being subject to cognitive control and facilitation reflecting a more automatic process. A large number of studies have examined Stroop performance in schizophrenic patients. The most common observation of recent studies seems a normal interference effect in combination with large facilitation and a high error rate (Barch et al. 1999a,b; Carter et al. 1992; Chen et al. 2001; Perlstein et al. 1998; Phillips et al. 1996; Taylor et al. 1996). Increased facilitation and high error rates were thought to reflect an abnormality in the automatic component of information processing (i.e., enhanced spreading activation) (Carter et al. 1992).

Inhibitory deficits in schizophrenic patients have also been examined by means of the Continuous Performance Task (CPT; Rosvold et al. 1956). In this task, subjects have to detect a target among a sequence of briefly presented stimuli, and avoid responding to distractors. Some studies have defined targets by a single item (e.g., the letter X), while others used a particular sequence of items (e.g., 3 followed by 7). Regardless of the task variant, schizophrenic patients were found to show impaired performance (for a review, see Cornblatt & Keilp 1994). Patients typically displayed

lower hit rates and more false alarms, which is usually interpreted as reflecting a reduced ability to differentiate targets from non-targets and a failure to inhibit responses to distractors.

In addition to the Stroop and the CPT, which both have a large tradition in clinical research, inhibitory function has also been examined by more experimental psychological paradigms, like the negative priming (NP) task (Tipper 1985). In a standard NP task, two stimuli (referred to as prime and probe) are successively presented. Both stimuli contain a target and a distractor, and subjects have to respond to the target and ignore the distractor. Reaction times are typically increased when the probe target is identical or semantically related to the prime distractor. This slowing is referred to as the NP effect. According to Tipper (1985), distractive information of the prime is semantically processed but blocked away from the effectors. Thus, the prime distractor is inhibited in order to prevent response competition. This inhibitory process reduces the availability of distractor information for subsequent selection (for reviews, see Fox 1995; May et al. 1995). Various studies have reported impaired NP performance in schizophrenic patients (e.g., Beech et al. 1989a; Park et al. 1996; Williams 1996). The most common observation seems a reduced (or even reversed) NP effect, indicating that inhibition of distractors was not successfully completed.

Despite this large body of evidence for inhibitory deficits in schizophrenic patients, the *nature* of these deficits is still unclear. Stroop results are somewhat inconsistent, but have suggested a difficulty in suppressing the influence of automatically processed distractors that trigger a strong response tendency. Negative priming studies have suggested a difficulty in suppressing the influence of distractors that *not* necessarily trigger a strong response tendency. Results from the CPT have suggested a failure in suppressing responses to stimuli that slightly differed from targets in occasions where a strong response bias was created.

These three conclusions are not easily interpreted in terms of a uniform inhibition deficit[1]. Nevertheless, it is not unlikely that inhibitory deficits in patients result from *one* underlying deficit. In order to investigate this possibility, we examined inhibitory function across a range of inhibition tasks. These tasks were chosen according to a workable taxonomy of inhibition processes which was based on the classifications proposed by Nigg (2000), Harnishfeger (1995), and Rafal & Henik (1994). Voluntary (effortful) inhibitory processes were divided into: a) processes of interference control, b) cognitive inhibition, and c) behavioral inhibition (Table 1). Interference control was examined by the Stroop task and the Simon task (Simon & Rudell 1967). Both tasks require the maintenance of response performance in the presence of competing, distracting, or interfering stimuli that evoke a competing motor response. In a typical Simon task, subjects have to press a left- or right-hand key, depending on a previously defined stimulus dimension (e.g., color). Stimuli are

presented to the left or right side of a screen, which provides an irrelevant directional cue that interferes with processing the relevant stimulus dimension. Reaction times are reduced when the stimulus location does not correspond to the response key. This slowing is referred to as the Simon effect (for a review, see Lu & Proctor 1995). The Simon effect has been attributed to an automatic activation of the response that corresponds to the stimulus location. Based on the similarities with the Stroop task, we hypothesized that schizophrenic patients would display a larger Simon effect and more errors than healthy controls. *Cognitive inhibition* was examined by a NP task and a Cross-modal matching task (CMM task). These tasks required the suppression of mental contents (i.e., figures, words, pictures). Although CMM tasks have been used in many variants, they typically contain stimuli from different modalities (e.g., visual and auditory, or pictures and words). For the present purposes we used a task in which pictures and words were combined in a context display, and subjects had to ignore one modality. Subsequently, a test display had to be judged for its association with the relevant modality of the context display. Gernsbacher & Faust (1991) demonstrated that a short interval between the context and test display is usually accompanied by relatively large interference effects. However, when this interval is long, the immediate interference effects disappear. This condition allows the examination of the ability to suppress the influence of the distractor modality, which could be done by manipulating the relationships between the distractor and the test stimulus. With respect to schizophrenic patients, we expected to find significant interference effects on long interval trials. *Behavioral inhibition* was examined by a double stimulus CPT and a Go/nogo task. Both tasks required the suppression of a response tendency which was automatically established by frequent target occurrence. Go/nogo tasks have been used in many

Table 1
*Classification of inhibition processes*

| Inhibition process | Description | Tasks |
|---|---|---|
| **Interference control** | Maintenance of response performance in the presence of competing, distracting, or interfering stimuli that evoke a competing motor response. | Stroop task<br>Simon task |
| **Cognitive inhibition** | Suppression of mental contents. | Negative priming task<br>Cross-modal matching task |
| **Behavioral inhibition** | Suppression of a prepotent automatic or intentional response such as a key press. | DS-CPT*<br>Go/nogo task |

*Double stimulus CPT (e.g., the 3-7 CPT).

variants, but they typically require a simple response to frequently occurring targets, while this response must be suppressed to infrequently occurring non-targets. We hypothesized that schizophrenic patients would display an increased number of responses to non-targets.

These six inhibition tasks were examined in first-episode patients and healthy controls. Within the patient sample, inpatients and outpatients were analyzed separately, since previous studies have suggested that current symptomatology was determining task performance. Inclusion of healthy volunteers was relevant for comparison reasons, but also for validating the classification of inhibition tasks into the three categories of inhibitory processes.

## 2. Methods

### 2.1 Subjects

The study included 21 patients (17 males and 4 females) who had recently experienced a first or second psychotic episode according to DSM-IV criteria (American Psychiatric Association 1994) and received a diagnosis within the schizophrenia spectrum (schizophrenia: n=13; schizophreniform disorder: n=7; schizoaffective disorder: n=1) (SCAN; Wing et al. 1990). The patient group consisted of 13 inpatients and eight outpatients who were seen at the hospital once or twice a month. Inpatients were tested within the first two months of admission, while acute positive symptoms were in almost complete remission. The presence of current positive and negative symptoms was assessed by the Positive and Negative Symptom Scale (PANSS; Kay et al. 1987). The mean score of positive symptoms was 9.96 (range 7-13), while for negative symptoms this was 9.95 (range 7-14). Outpatients were no longer than two years ill and their acute positive symptoms were in full remission. For this group, no PANSS scores were obtained. All patients were treated with stable doses of atypical antipsychotics for at least 6 weeks (12 patients received olanzapine and 9 risperidone). Exclusion criteria were age under 17 or above 35 years, severe mental retardation, systemic or neurologic illness, medication other than antipsychotics, history of alcohol or drug abuse, severe tardive dyskinesia, and severe extrapyramidal symptoms. The mean age was 25.95 (SD 5.26) years and average education was at high school level.

The control group consisted of 21 healthy volunteers (12 males and 9 females) recruited from the local community. These participants were free of lifetime diagnoses of affective or psychotic disorder and had no first-degree relatives with these disorders. The mean age was 23.67 (SD 2.83) years and average education was at high school level.

## 2.2 Measures

The six tasks were programmed on an IBM-compatible computer using Micro Experimental Laboratory (MEL, version 2.0) and were administered in a standardized order within one test session. Subjects were given instructions which discouraged a speed-accuracy tradeoff in that they were told to respond as quickly as they could while making as few errors as possible. Tasks were separated by short pauses, and the total test duration was about 2 hours. Short practice periods preceded the tasks to ensure that participants understood the instructions and were performing the tasks appropriately.

### 2.2.1 Stroop task

On a black computer screen a series of the words RED, BLUE, YELLOW, and GREEN (upper case letters of 1.5 cm) was presented in either the congruent or incongruent color. These color-words were intermixed with neutral stimuli consisting of four or five X's printed in one of the four colors. Congruent, incongruent, and neutral stimuli were randomly presented in an equal number, and subjects had to respond by pressing a color-labeled button that corresponded to the stimulus color. Stimuli were displayed for 700 ms, with an inter stimulus interval of 3300 ms. A total number of 160 stimuli were presented in 8 blocks of 20 stimuli. After each block subjects received feedback (number of errors in preceding block). Performance was evaluated for the interference effect ($RT_{incongruent}$ - $RT_{neutral}$), the facilitation effect ($RT_{neutral}$ - $RT_{congruent}$), and number of errors.

### 2.2.2 Simon task

The letters L and R (upper case, 2.0 x 2.0 cm) were randomly presented to the left or right of the screen (Figure 1A). Subjects had to respond with their left or right index finger according to the lexical meaning of the letter and ignore the stimulus location. In 50% of the trials the meaning and location conflicted. Stimuli were presented for 600 ms on a gray background, followed by a blank screen for 900 ms. A central fixation cross remained on screen throughout the task. Subjects were administered a total number of 250 trials, divided into 10 blocks of 25 trials. After each block, subjects received feedback (number of errors in preceding block). Performance was evaluated for the Simon effect ($RT_{incongruent}$ - $RT_{congruent}$) and number of errors.

### 2.2.3 NP task

Based on the task used by DeSchepper & Treisman (1996), subjects were presented with two overlapping nonsense shapes (green and red) and had to decide whether the green shape matched a white shape presented on the right side of the screen (Figure 1B). If the green and white shape matched, they had to press a key labeled *same*, and if not, they had to press a key labeled *different*. Each trial started with a fixation

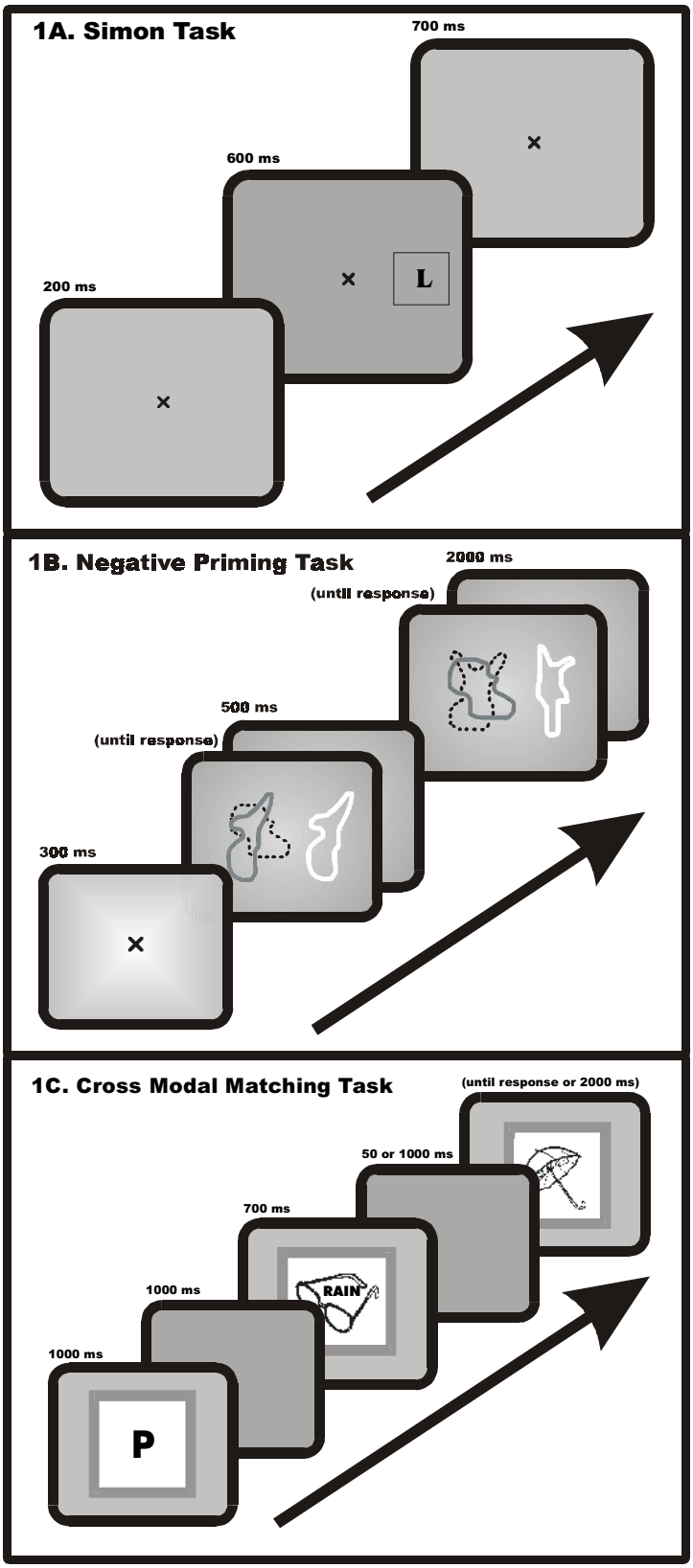



Figure 1. Task displays

1A: Simon task, 1B: Negative Priming task, 1C: Cross Modal Matching task. Dotted lines in 1B represent the red figure that should be ignored, grey lines represent the green figure that should be attended to, and white lines represent the white comparison figure.

cross displayed for 300 ms, followed by the first pair of overlapping shapes (referred to as prime). The prime was terminated by the subjects' response or after 5 sec if no response had been given. After 500 ms the following pair (referred to as probe) was presented. Also for the probe a same-different judgement had to be made, and the display was terminated by the subjects' response or after 5 sec. The screen was cleared for 2 sec until the next pair of trials was initiated. A set of 16 unfamiliar closed shapes (drawn by hand) was used to create all displays, and the paired shapes were presented on a black background. In 33 % of the trials, the unattended red shape in one pair became the attended green shape in the next pair (NP trials). Subjects were administered 200 trials, presented in 10 blocks of 20 trials. No feedback was given. Performance was evaluated for the NP effect ($RT_{NP\ probe}$ - $RT_{neutral\ probe}$) and number of errors.

### 2.2.4 CMM task

Based on the task used by Gernsbacher & Faust (1991), subjects were presented a context display, which contained a line drawn picture and a superimposed word (Figure 1C), followed by a test display, which contained either another picture or another word[2]. Half the time the test display contained another picture (picture trial), and half the time the test display contained another word (word trial). Subjects had to verify if the picture [word] of the test display was related to the picture [word] of the context display. On half the trials, the test display was related to what the subjects were to focus on in the context display, while in the other trials there was no relationship. For examination of interference control, only the *un*related trials were used. On half of these unrelated trials, the test display was related to what the subjects were supposed to ignore (experimental trials; Figure 1C), while on the other half there was no relationship (control trials). The test displays were presented at two intervals: immediately (50 ms) and 1 sec after the context display. Each trial began with a warning signal, which was either a P or a W (randomly chosen). This signal remained on screen for 1 sec and indicated whether the trial was a picture or word trial. One second after the warning signal had disappeared, the context display was presented for 700 ms, followed by the test display, which was presented with a delay of 50 ms or 1 sec. The test display remained on screen until the subjects responded or 2 sec had elapsed. Subjects responded by pressing either a key labeled *same* or a key labeled *different*. After each trial subjects received feedback (RT for correct responses, and 'error' for false responses). Subjects were presented six blocks of 24 trials. Half of the blocks consisted of context and test displays separated by a delay of 50 ms, and half of the blocks consisted of trials with a 1-sec delay. These blocks were alternated. Performance was evaluated for the interference effect on the two delays ($RT_{experimental}$ - $RT_{control}$) and number of errors.

### 2.2.5 CPT

The 3-7 variant of the classical CPT was used. A series of digits (2.0 x 2.0 cm) ranging from 0 to 9 was presented in the center of a black computer screen and had to be monitored for a specific target which was defined as the digit 7 in case it was preceded by 3. Subjects had to respond to targets by pressing the spacebar. A total number of 360 stimuli was presented in 12 blocks of 30 stimuli. In each block, the combination 3-7 occurred 6 times, while the combinations of X-7 and 3-$X^3$ occurred 3 times each. Stimulus presentation rate was varied over the blocks in order to determine if response patterns would change when the possibility was reduced that stimulus appearance served as a motivational cue to maintain task performance. In blocks 1-4, presentation rate was moderate: stimulus presentation time was 400 ms and inter stimulus interval was 1600 ms. In blocks 5-8, presentation rate was fast: presentation time was 400 ms and interval was 600 ms. In blocks 9-12, stimulus presentation time was slow: presentation time was 400 ms and interval was 2600 ms. Performance was evaluated for mean RT, number of omissions (failure to respond to the combination 3-7), and number of false alarms (including responses to 3, responses to digits following 3, and responses to 7 not following 3).

### 2.2.6 Go/nogo test

On a black computer screen, a series of green and red squares (1.5 x 1.5 cm) was randomly presented on six possible locations to the left or right of a center fixation point. Subjects had to respond to green squares (go trials) by pressing as fast as possible with the index finger of either the left or right hand according to the site of stimulus appearance. Seventy-five percent of the stimuli consisted of green squares and 25 % of red squares (nogo trials). A total number of 200 stimuli was presented in 5 blocks of 40 trials. After each block subjects received feedback (number of errors in the preceding block). Stimuli were presented for 700 ms with an interval of 300 ms. Fourteen healthy controls and 13 patients were administered three additional blocks in which the interval was prolonged to 2300 ms. This was done in order to determine if response patterns would change when the possibility was reduced that stimulus appearance had served as a motivational cue to maintain performance. Performance was evaluated for the number of responses to nogo-stimuli and mean RT to go-stimuli.

## 2.3 Data analysis

Individual data were first trimmed for outliers according to a procedure in which RTs that were two S.D.'s above or below the mean were discarded. The number of trials discarded in each task was less than 1%. For some of the tasks (i.e., Stroop task, NP task, CMM task, CPT) the RT data of correct trials were transformed by means of squareroot transformations to produce approximately normal distributions.

The performance of patients and controls was compared by submitting the RT data to repeated measures analyses of variance (ANOVAs) with the appropriate designs (described in the Results section). Planned comparisons were conducted to follow-up on significant main effects and interactions. In addition, group differences were evaluated by means of independent samples *t*-tests in which the difference scores (Stroop interference, Stroop facilitation, Simon effect, NP effect, and CMM interference) were used as dependent variables. In order to account for 'general slowness' in patients, difference scores were also calculated as ratio scores [(RT experimental trials - RT control trials) / RT control trials]. With respect to the error scores, data on the Stroop, Simon, NP, CMM task were transformed by squareroot transformations. Similar to the RT data, error data were submitted to repeated measures ANOVAs or Mann-Whitney's *U* tests (CPT and Go/nogo task) in order to examine differences between patients and controls. Differences between inpatients, outpatients, and controls were examined by means of repeated measures ANOVAs or Kruskall-Wallis' tests (followed by Mann-Whitney's *U* tests). Correlation analyses were carried out to determine the relationships among different measures of each of the three inhibitory processes. Correlation analyses were also conducted to determine relationships between measures of inhibition and demographic variables.

## 3. Results

There were no significant differences between patients and controls for age [$U$=177, $p$>0.1], gender [$\chi 2$=2.79, $p$=0.1], and level of education [$U$=150, $p$>0.05].

### 3.1 Stroop task

For both RT and error data (Table 2), a 3 x 2 analysis of variance (ANOVA) with condition (congruent, incongruent, neutral) as a within-subjects factor and group (patients vs. controls) as a between-subjects factor was conducted. Subsequently, ANOVAs were conducted to examine differences between inpatients, outpatients, and controls.

*RT.* The ANOVA on the transformed RT data revealed a significant main effect of group, i.e. patients were slower than controls [$F$(1,39)=5.57, $p$<0.05], and a significant main effect of condition [$F$(2,78)=65.15, $p$<0.000]. Planned comparisons revealed that RTs were slower for incongruent than neutral stimuli (interference effect) [$F$(1,39)=67.68, $p$<0.000], but not faster for congruent as compared to neutral stimuli (facilitation effect), although the significance reached trend level [$F$(1,39)=3.72, $p$=0.06]. Patients and controls did not differ for the amount of interference [patients: 44.23 ms vs. controls: 38.65 ms; $F$(1,39)=0.06, $p$>0.5; Figure 2] and facilitation [patients: 3.76 ms vs. controls: 11.41 ms; $F$(1,39)=0.71, $p$>0.1; Figure 2]. Independent samples *t*-tests with interference and facilitation effects as dependent variables also failed to reveal significant group differences [interference:

$t(39)=-0.53$, $p>0.5$; facilitation: $t(39)=1.64$, $p>0.5$], as did the analysis of the ratio interference and facilitation scores [interference: $t(39)=0.08$, $p>0.5$; facilitation: $t(39)=0.77$, $p>0.5$].

*Errors.* The ANOVA on the transformed error data failed to reveal significant effects. Correlation analysis revealed for the patient group significant negative correlations between RT and errors in each of the three conditions [$p$-values ranging from 0.003 to 0.01]. This implicates that a speed-accuracy tradeoff was determining task performance.

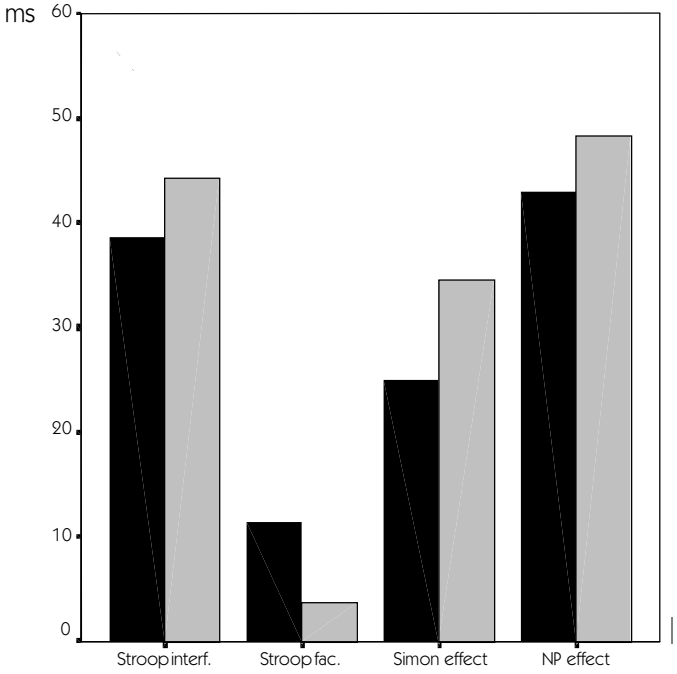
Table 2

*Means and standard deviations for RTs and errors in each of the three conditions of the Stroop task*

| | **Patients** | **Controls** |
|---|---|---|
| | **n=21** | **n=21** |
| ***Incongruent*** | | |
| **RT** (ms) | 854.4 ± 137.5 | 762.6 ± 120.4 |
| **Errors** (%) | 3.5 ± 4.8 | 4.9 ± 6.2 |
| ***Congruent*** | | |
| **RT** (ms) | 806.4 ± 135.7 | 712.5 ± 107.0 |
| **Errors** (%) | 3.5 ± 5.2 | 3.2 ± 3.4 |
| ***Neutral*** | | |
| **RT** (ms) | 810.1 ± 126.7 | 723.9 ± 117.6 |
| **Errors** (%) | 3.1 ± 4.1 | 3.5 ± 3.0 |

Figure 2

*Stroop interference and facilitation, Simon effect and Negative Priming effect for patients (grey) and controls (black)*




### 3.2 Simon task

For both RT and error data (Table 3), a 2 x 2 analysis of variance (ANOVA) with condition (congruent vs. incongruent) as a within-subjects factor and group as a between-subjects factor was conducted.

*RT.* The ANOVA revealed a significant main effect of group, i.e. patients were slower than controls [$F(1,38)=11.60$, $p<0.005$]. There was also a significant main effect of condition, i.e. RTs were slower for incongruent trials [$F(1,38)=129.44$, $p<0.000$]. The interaction between group and condition was not significant, indicating that the groups did not differ in the magnitude of the Simon effect [patients: 34.49 ms vs. controls: 25.05 ms; $F(1,38)=3.25$, $p=0.08$; Figure 2]. An independent samples $t$-test with the Simon effect as the dependent variable also

failed to reveal significant group differences [$t(38)=-1.80$, $p>0.05$], as did the analysis of the ratio Simon effect [$t(38)=-1.17$, $p>0.1$]. However, the ANOVA and *t*-test results were significant at trend level, indicating that patients displayed a larger Simon effect.

*Errors.* The ANOVA on the transformed error data did not reveal significant differences between patients and controls [$F(1,38)=0.97$, $p>0.1$]. There was, however, a significant main effect of condition, i.e. more errors were made on incongruent trials [$F(1,38)=114.74$, $p<0.000$].

Correlation analysis failed to reveal significant correlations between RT and errors in both groups, indicating the absence of a speed-accuracy tradeoff.

Table 3

*Means and standard deviations for RTs and errors in the two conditions of the Simon task for patients and controls*

| | **Patients** n=21 | **Controls** n=21 |
|---|---|---|
| ***Incongruent*** | | |
| **RT** (ms) | 550.5 ± 50.4 | 498.5 ± 40.0 |
| **Errors** (%) | 15.1 ± 7.7 | 12.0 ± 7.4 |
| ***Congruent*** | | |
| **RT** (ms) | 516.0 ± 43.9 | 473.5 ± 43.9 |
| **Errors** (%) | 7.5 ± 5.7 | 6.3 ± 4.4 |

### 3.3 NP task

For both RT and error data (Table 4), a 2 x 2 x 2 analysis of variance (ANOVA) with condition (neutral vs. NP) and response (same vs. different) as within-subjects factors and group as a between-subjects factor was conducted.

*RT.* The ANOVA on the transformed RT data did not reveal differences between patients and controls [$F(1,40)=1.99$, $p>0.1$]. However, there was a significant main effect of condition, i.e. RTs were slower in the NP condition [$F(1,40)=64.35$, $p<0.000$]. There was also a significant main effect of response, i.e. RTs were faster for 'same trials' than for 'different trials' [$F(1,40)=7.00$, $p<0.05$]. The interaction between group and condition was not significant, indicating that the NP effect was not different between patients and controls [patients: 48.24 ms; controls: 43.01 ms;

Table 4

*Means and standard deviations for RTs and errors in each of the conditions of the NP task for patients and controls*

| | | | Patients | Controls |
|---|---|---|---|---|
| | | | n=21 | n=21 |
| ***Prime*** | | | | |
| | **Same** | **RT** (ms) | 856.0 ± 146.0 | 833.2 ± 163.8 |
| | | **Errors** (%) | 4.8 ± 3.8 | 4.5 ± 4.4 |
| | **Different** | **RT** (ms) | 805.5 ± 108.7 | 789.5 ± 143.4 |
| | | **Errors** (%) | 3.1 ± 2.7 | 3.1 ± 2.1 |
| ***Probe*** | | | | |
| **Negative priming** | | | | |
| | **Same** | **RT** (ms) | 855.5 ± 114.3 | 811.6 ± 163.9 |
| | | **Errors** (%) | 8.0 ± 8.2 | 6.5 ± 8.4 |
| | **Different** | **RT** (ms) | 899.1 ± 131.9 | 827.2 ± 140.9 |
| | | **Errors** (%) | 15.3 ± 7.5 | 14.7 ± 11.3 |
| **Neutral** | | | | |
| | **Same** | **RT** (ms) | 816.2 ± 106.3 | 771.9 ± 168.5 |
| | | **Errors** (%) | 5.5 ± 5.4 | 4.7 ± 5.0 |
| | **Different** | **RT** (ms) | 841.9 ± 129.5 | 780.8 ± 144.1 |
| | | **Errors** (%) | 4.5 ± 6.4 | 4.0 ± 4.1 |

$F(1,40)=0.06$, $p>0.5$; Figure 2]. An independent samples *t*-test with the NP effect as the dependent variable also failed to reveal significant group differences [$t(39)=0.12$, $p>0.5$], as did an analysis of the ratio NP score [$t(39)=0.54$, $p>0.5$]. An independent samples *t*-test with the NP effect as the dependent variable also failed to reveal significant group differences [$t(39)=0.12$, $p>0.5$], as did an analysis of the ratio NP score [$t(39)=0.54$, $p>0.5$].

*Errors.* The ANOVA on the transformed error data did not reveal differences between patients and controls [$F(1,40)=0.56$, $p>0.1$]. However, there was a significant main effect of condition, i.e. more errors were made in the NP condition [$F(1,40)=31.18$, $p<0.000$]. There was also a significant main effect of response, indicating that more errors were made for the 'different condition' [$F(1,40)=18.74$, $p<0.005$]. In addition, the interaction between condition and response was significant [$F(1,40)=37.88$, $p<0.000$].

Correlation analysis was performed on the combined data of same and different trials. This analysis revealed significant negative correlations between RT and error rate in both groups. These negative correlations were obtained for the neutral as well as the NP condition. This finding implicates that a speed-accuracy tradeoff was a significant determinant of task performance.

### 3.4 CMM task

For both RT and error data (Table 5), a 2 x 2 x 2 x 2 analysis of variance (ANOVA) was conducted with group as a between-subjects factor and condition (experimental vs. control), stimulus type (word vs. pictures), and interval (short vs. long) as within-subjects factors.

*RT.* The ANOVA on the transformed RT data revealed a significant main effect of group, i.e. patients made overall slower responses [$F(1,37)=7.66$, $p<0.01$]. A significant interaction between group and condition indicated that patients displayed more interference [$F(1,37)=4.39$, $p<0.05$; Figure 3]. A significant main effect of stimulus type indicated that responses were slower to word trials [$F(1,37)=8.70$, $p=0.005$]. A significant interaction between stimulus type and group showed that patients made slower responses to word trials [$F(1,37)=5.2$, $p<0.05$]. A significant main effect of interval indicated that responses were slower on short interval trials [$F(1,37)=16.43$, $p<0.000$]. The four-way interaction was significant [$F(1,37)=5.79$, $p<0.05$], indicating that patients displayed more interference on short interval word trials. Independent samples *t*-tests with the interference effects in the four conditions (defined by stimulus type and interval) as the dependent variables, confirmed that significant group differences were only existent for short interval word trials [$t(38)=-2.14$, $p<0.05$; Figure 3]. This was also found for the ratio interference scores [$t(38)=-2.26$, $p<0.05$]. Additional paired-samples *t*-tests demonstrated that this effect was resulting from significant facilitation in the control group [$t(18)=-2.52$, $p<0.05$]. Further, patients displayed a marginally significant interference effect on long interval picture trials [$t(19)=2.0$, $p=0.06$].

*Errors.* The ANOVA on the transformed error data revealed a significant main effect of group, i.e. patients made more errors than controls [$F(1,37)=14.63$, $p<0.000$]. There were also significant main effects of condition and interval, respectively, i.e. more errors were made in the experimental condition [$F(1,37)=11.72$, $p<0.005$] and in the short interval condition [$F(1,37)=14.38$, $p=0.001$]. A significant interaction between stimulus type and interval indicated that more errors were made on word trials with a short interval [$F(1,37)=4.13$, $p<0.05$].

Correlation analysis was performed on the combined data of word and picture trials. Amongst patients, significant positive correlations were found between RT and errors in the four conditions (defined by stimulus type and interval), which indicated that task performance was not determined by a speed-accuracy tradeoff.

Table 5

*Means and standard deviations for RTs and errors in the CMM task*

| | | | | Patients n=21 | Controls n=21 |
|---|---|---|---|---|---|
| ***Pictures*** | | | | | |
| | **Short interval** | **Experimental** | | | |
| | | | *RT (ms)* | 904.0 ± 224.9 | 755.3 ± 161.8 |
| | | | *Errors (%)* | 23.3 ± 20.4 | 7.6 ± 8.3 |
| | | **Control** | | | |
| | | | *RT (ms)* | 909.5 ± 216.3 | 752.0 ± 141.7 |
| | | | *Errors (%)* | 15.6 ± 19.9 | 7.6 ± 10.5 |
| | **Long interval** | **Experimental** | | | |
| | | | *RT (ms)* | 875.5 ± 213.0 | 724.3 ± 152.5 |
| | | | *Errors (%)* | 20.6 ± 19.2 | 5.3 ± 7.7 |
| | | **Control** | | | |
| | | | *RT (ms)* | 826.2 ± 203.8 | 727.9 ± 166.0 |
| | | | *Errors (%)* | 11.7 ± 11.1 | 3.5 ± 6.5 |
| ***Words*** | | | | | |
| | **Short interval** | **Experimental** | | | |
| | | | *RT (ms)* | 962.0 ± 266.4 | 746.5 ± 149.8 |
| | | | *Errors (%)* | 21.7 ± 21.8 | 12.3 ± 13.3 |
| | | **Control** | | | |
| | | | *RT (ms)* | 919.9 ± 205.8 | 783.8 ± 150.4 |
| | | | *Errors (%)* | 15.0 ± 13.1 | 5.3 ± 7.7 |
| | **Long interval** | **Experimental** | | | |
| | | | *RT (ms)* | 937.7 ± 257.6 | 730.0 ± 142.6 |
| | | | *Errors (%)* | 14.4 ± 14.5 | 2.9 ± 6.2 |
| | | **Control** | | | |
| | | | *RT (ms)* | 909.3 ± 236.1 | 718.6 ± 132.2 |
| | | | *Errors (%)* | 7.2 ± 9.7 | 2.3 ± 4.7 |

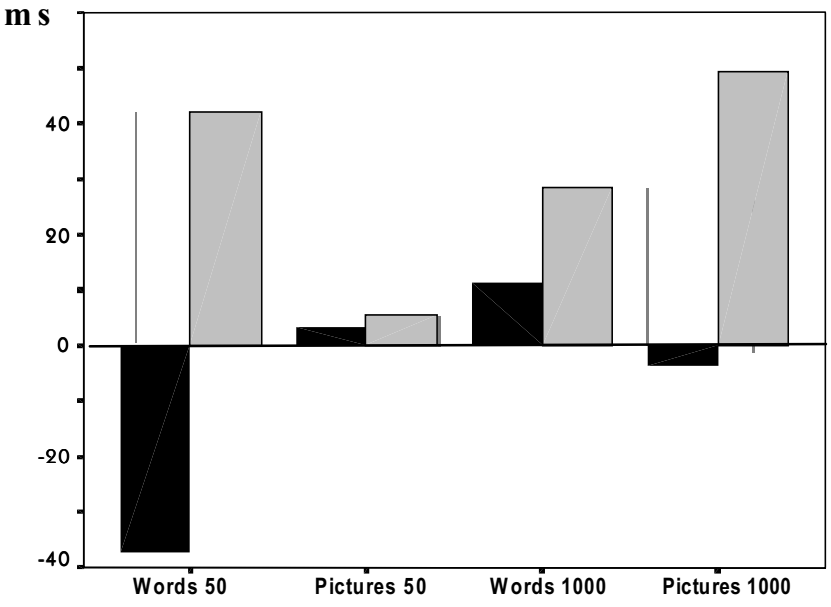



Figure 3

*Interference effects in the Cross Modal Matching Task for patients (grey) and controls (black)*

### 3.5 CPT

*RT.* The transformed data (Table 6) were submitted to a 3 x 2 analysis of variance (ANOVA) with presentation rate (fast, moderate, slow) as a within-subjects factor and group as a between-subjects factor. A significant main effect of group was found, i.e. patients responded slower than controls [$F(1,40)=11.88$, $p=0.001$]. There was also a significant main effect of condition, indicating that RTs were fastest when stimulus presentation rate was fast [$F(2,80)=37.51$, $p<0.000$].

Planned comparisons revealed slower responses for patients in all three conditions and a significant interaction between group and condition, indicating a disproportionate slowing for patients when stimulus presentation rate was slow [$F(1,40)=4.35$, $p<0.05$].

*Errors.* False alarms and omissions were combined across the three conditions and submitted to Mann-Whitney's *U* tests. This revealed that patients displayed more omissions than controls [$U=120.0$, $p=0.005$].

Correlation analysis failed to reveal a significant relationship between RT and errors, indicating that a speed-accuracy tradeoff was absent.

Table 6

*Means and standard deviations for RTs and errors in each of the three conditions of the CPT*

| | | Patients n=21 | Controls n=21 |
|---|---|---|---|
| ***Fast*** | **RT** (ms) | 413.5 ± 61.2 | 344.5 ± 29.9 |
| ***Moderate*** | **RT** (ms) | 439.2 ± 100.9 | 380.0 ± 41.6 |
| ***Slow*** | **RT** (ms) | 489.5 ± 123.6 | 401.5 ± 42.6 |
| **Overall false alarms** (%) | | 0.7 ± 0.8 | 0.6 ± 0.7 |
| **Overall omissions** (%) | | 2.1 ± 3.0 | 0.3 ± 0.6 |

### 3.6 Go/nogo task

*RT.* For block 1-5 (performed by all participants; Table 7), data were analyzed using a Mann-Whitney's *U* test. This revealed that patients were significantly slower than controls [$U=71.00$, $p<0.000$].

For those participants who had performed block 1-8, RT data were submitted to a 2 x 2 analysis of variance (ANOVA) with stimulus presentation rate (fast vs. slow) as a within-subjects factor and group as a between-subjects factor. This ANOVA revealed a significant main effect of group, indicating that patients were significantly slower than controls [$F(1,25)=12.21$, $p<0.005$]. There was also a

significant main effect of condition, i.e. RTs were faster when stimulus presentation rate was fast [$F(1,25)=5.27$, $p<0.05$].

*Errors.* For block 1-5, a Mann-Whitney's *U* test did not reveal differences between patients and controls [$U=166.50$, $p>0.1$]. For block 1-8, the ANOVA also failed to reveal significant group differences [$F(1,25)=0.83$, $p>0.1$]. There was, however, a significant main effect of condition, indicating that more errors were made when stimulus presentation rate was fast [$F(1,25)=5.98$, $p<0.05$].

Correlation analysis performed on the combined data of block 1-8 failed to reveal a significant relationship between RT and errors. Thus, there was no speed-accuracy tradeoff.

Table 7

*Means and standard deviations for RTs and errors in each of the two conditions of the Go/nogo task for patients and controls*

| | | | Patients n=21 | Controls n=21 |
|---|---|---|---|---|
| ***Fast*** | | | | |
| | **Go trials** | **RT** (ms) | 405.2 ± 34.6 | 353.8 ± 19.5 |
| | **Nogo trials** | **Errors** (%) | 4.3 ±3.5 | 6.9 ± 6.4 |
| ***Slow*** | | | | |
| | **Go trials** | **RT** (ms) | 418.4 ± 47.2 | 372.0 ± 23.7 |
| | **Nogo trials** | **Errors** (%) | 2.6 ± 3.1 | 2.7 ± 2.9 |

### 3.7 Inpatients vs. outpatients vs. controls

*Stroop*. For both RT and errors, the ANOVAs failed to reveal differences between the groups, although for the RT data the main group effect reached trend level [$p<0.06$], indicating that inpatients were responding more slowly than controls [$p<0.05$].

*Simon.* For the RT data, the main effect of group was significant [$F(2,37)=3.58$, $p<0.05$]. Post hoc comparisons indicated that inpatients responded slower than controls [$p=0.01$], while outpatients were slower at trend level [$p=0.06$]. The interaction between condition and group was also significant [$F(2,37)=3.58$, $p<0.05$]. Planned comparisons revealed that the Simon effect was larger for inpatients as compared to controls [$F(1,31)=8.55$, $p<0.01$]. For the error data, the ANOVA did not reveal significant group differences.

*NP*. For both RT and errors, no significant group differences were obtained.

*CMM*. For the RT data, there was a significant main effect of group [$F(2,36)=7.07$, $p<0.01$]. Post hoc comparisons revealed that outpatients were slower than inpatients

[$p$=0.01] and controls [$p$<0.005]. In addition, the interaction between group and condition was significant [$F$(2,36)=6.00, $p$<0.01]. Planned comparisons revealed that outpatients displayed more interference than controls [$F$(1,25)=12.78, $p$=0.001]. For the error data, there was a significant main effect of group [$F$(2,36)=6.06, $p$=0.005]. Post hoc comparisons showed that outpatients made more errors than controls [$p$<0.01].

*CPT.* For the error data, the main effect of group was significant [$F$(2,39)=6.17, $p$=0.005]. Post hoc comparisons indicated that inpatients and outpatients were slower than controls [$p$=0.01 and $p$<0.05, respectively]. For the error data, significant differences between the groups were found for the number of omissions [Kruskall-Wallis: $\chi^2$=8.30, $p$<0.05]. Post hoc comparisons revealed that both patient groups displayed more omissions than controls [inpatients vs. controls: Mann-Whitney's $U$=88.00, p=0.05; outpatients vs. controls: $U$=32.00, $p$=0.01].

*Go/nogo.* For the RT data, a significant difference between the groups was found for block 1-5 [Kruskall-Wallis: $\chi^2$=14.15, $p$=0.001]. Both inpatients and outpatients were slower than controls [$p$=0.001 and $p$<0.01, respectively]. The ANOVA performed on block 1-8 revealed a significant main effect of group [$F$(2,24)=6.48, $p$<0.01]. Post hoc comparisons indicated that inpatients were slower than controls [$p$=0.005]. There was also a significant interaction between group and condition [$F$(2,24)=6.29, $p$<0.01]. Planned comparisons revealed that inpatients and controls showed an increase in RTs in the slow condition, while outpatients displayed a decrease. Therefore, the interaction was significant when outpatients were compared with inpatients [$F$(1,11)=6.61, $p$<0.05] and with controls [$F$(1,16)=12.95, $p$<0.005]. It should, however, be noted that the group of outpatients consisted of only four subjects. For the error data, no significant group differences were found.

### 3.8 Correlation analyses

Correlation analyses for task measures belonging to the same category of inhibitory processes were first carried out for the total sample (n=42). This analysis failed to reveal significant correlations between the Stroop and the Simon task (*interference control*), although the inhibition errors on both tasks correlated at trend level [$p$=0.06]. For the NP task and the CMM task (*cognitive inhibition*), no significant correlations were found, except for a modest negative correlation between NP errors and short interval CMM interference [$r_s$=-0.32, $p$<0.05]. For the CPT and the Go/nogo task (*behavioral inhibition*), a significant correlation was found between RTs on both tasks [$r_s$=0.57, $p$<0.000], and between CPT omissions and RT on the Go/nogo task [$r_s$=0.29, $p$<0.05].

When the same analyses were carried out for patients and controls separately, the patient group revealed a significant negative correlation between NP errors and short interval CMM interference [$r_s$=-0.64, $p$<0.005]. For controls, a significant positive

correlation was found for errors on the Stroop and errors on the Simon task [$r_s$=0.55, $p$=0.01], and a significant negative correlation was observed for Stroop facilitation and errors on the Simon task [$r_s$=-0.54, $p$=0.01]. Further, the NP effect appeared to be inversely related to short interval CMM interference [$r_s$=-0.46, $p$<0.05].
Correlation analysis for inhibition measures and the demographic variables age, level of education, and medication, failed to reveal significant correlations.

## 4. Discussion

The present study clearly demonstrates that first-episode schizophrenic patients do not exhibit inhibitory deficits, since none of the tasks showed abnormal inhibitory function. Although this finding was unexpected, a closer look at the extensive literature learns that the reported deficits are less robust than generally assumed, and that performance might be critically dependent on disease-related factors and task properties.

### 4.1 Stroop task

Patients displayed an overall increase in RT, but normal interference and error rates. Further, they displayed a lack of facilitation, which was similar to controls. Normal interference in first-episode patients was also found by Chen et al. (2001) and in a number of studies that included chronic patients (Barch et al. 1999a,b; Boucart et al. 1999; Carter et al. 1992; Cohen et al. 1999; Perlstein et al. 1998; Phillips et al. 1996; Salo et al. 1996, 1997; Taylor et al. 1996). However, Hepp et al. (1996) reported a disproportionate interference effect in first-episode patients, as did the majority of studies that used the card version of the task (e.g., Wysocki & Sweet 1985). Our failure to observe significant facilitation in both patients and controls is consistent with the results of Hepp et al. (1996) and several studies including chronic patients (Boucart et al. 1999; Salo et al. 1997). However, Chen et al. (2001) found significant (but not increased) facilitation, while the majority of studies in chronic patients reported increased facilitation (Barch et al. 1999a,b; Carter et al. 1992; Cohen et al. 1999; Perlstein et al. 1998; Taylor et al. 1996). The error rate of our patients was relatively low and comparable to controls. This is consistent with the study of Chen et al. (2001), but contrasts with other studies that have demonstrated an increased error interference[4] (Barch et al. 1999a,b; Perlstein et al. 1998). Since increased error interference (as well as increased facilitation) was observed in the absence of RT interference, Barch et al. (1999a) have suggested that interference effects were reflected in errors, rather than in RTs. Our results failed, however, to support this view. Unfortunately, our data were characterized by a speed-accuracy tradeoff. It is, however, not likely that this tradeoff has obscured inhibition deficits, since the groups displayed similar RT and error scores.

The absence of deficits in our patient group might be related to sample characteristics and task properties. Hepp et al. (1996) found larger interference in acute and schizoaffective patients as compared to patients with a recurrent episode. This suggests that the phase of the illness determined task performance. However, we found similar performance for inpatients and outpatients, despite a longer duration of illness and (intuitively) less severe symptoms in outpatients. In the study of Carter et al. (1993), increased interference was limited to paranoid patients, while increased facilitation was limited to patients of the undifferentiated subtype. Phillips et al. (1996) failed, however, to find an effect of illness subtype. The use of antipsychotics might also have normalized attentional impairment (e.g., Spohn & Strauss 1989). However, this could not be confirmed by others (Carter et al. 1993; Chen et al. 2001; Hepp et al. 1996; Salo et al. 1996; Schooler et al. 1997)[5]. With respect to task parameters, the choice of the neutral condition seems important. More 'wordlike' neutral stimuli were associated with smaller interference and larger facilitation (Barch et al. 1999a). This factor could, however, not fully account for the discrepant findings among studies. It remains to be determined to what extent the use of a self-paced task (Hepp et al. 1996) and manual instead of a vocal responding might have affected performance.

### 4.2 Simon task

Patients displayed normal performance despite an overall increase in RTs. However, when inpatients and outpatients were analyzed separately, inpatients displayed a significantly larger Simon effect than controls. This finding suggests that performance was determined by the phase of the illness and probably also by current symptomatology. In contrast to the Stroop task, the Simon task has not been extensively studied in schizophrenia. Therefore, we will consider the results in light of our Stroop findings. Both tasks were presumed to measure interference control, an assumption that was supported by significant correlations between the tasks. It should, however, be noted that such correlations were only found within the control group, which suggests that the performance of patients was determined by other (random) factors. In contrast to the Stroop task, the Simon task revealed a significant increase in interference for inpatients, which suggests that the Simon task is more sensitive to deficits in interference control than the Stroop task. Probably it was particularly difficult for these patients to overrule responses that are elicited by the spatial location of stimuli. This seems in line with numerous studies that have demonstrated an increased vulnerability to distractive spatial cues in schizophrenia (see, for example, the literature on the antisaccade task; Broerse et al. 2001a).

### 4.3 NP task

Patients displayed normal performance on the NP task. Even the commonly observed increase in RTs was absent. Normal NP was also found by others (Baving et al. 2001; Laplante et al. 1992; Moritz et al. 2001; Salo et al. 1997)[6], although the majority of studies have reported reduced NP (Beech et al. 1989a; Jones et al. 2001; McDowd et al. 1993; Moritz et al. 2000; Park et al. 1996; Peters et al. 2000; Williams 1996). Interestingly, some of these studies demonstrated that reduced NP was related to current symptomatology (Jones et al. 2001; Park et al. 1996; Peters et al. 2000; Williams 1996)[7]. This might explain why we found normal NP in relatively asymptomatic patients. Probably, NP deficits are merely *state* than *trait* dependent, which was also suggested by studies reporting normal NP in healthy first-degree relatives (Claridge & Beech 1996) and reduced NP in high schizotypes (in particular those with positive symptoms) (e.g., Beech et al. 1989b). The normal error rate observed in the present study, was frequently observed by others (e.g., Beech et al. 1989a; Moritz et al. 2001), although also increased error rates were found (Peters et al. 2000; Salo et al. 1997). Unfortunately our data were characterized by a speed-accuracy tradeoff. It is, however, not likely that this tradeoff has obscured NP deficits, since our groups displayed similar RT and error scores. The use of antipsychotics might have normalized NP deficits, since Salo et al. (1997) found reduced NP in unmedicated patients as compared to medicated patients. These authors also found reduced NP within the same patients when tested off medication as compared to testing on medication. However, Williams (1996) and Peters et al. (2000) failed to observe a significant relationship between the use of medication and the NP effect. Also task characteristics might have influenced NP performance. Moritz et al. (2001) demonstrated, for example, that the use of a mask as well as very short stimulus durations should be avoided, since these result in performance that is reflecting deficits in backward masking and critical stimulus duration rather than NP deficits. Further study should determine to what extent the choice of stimulus material[8] and manual instead of vocal responding (Park et al. 1996) had affected performance.

### 4.4 CM task

Patients displayed an overall increase in RT and errors, and tended to display the expected interference on long interval trials (see Figure 3). In contrast, on short interval trials the interference effects were smaller than expected, while the control group displayed an unexpected facilitation for word trials. Our findings on long interval trials are in line with the results of Gernsbacher & Faust (1991) and could be interpreted as modest evidence for a less efficient inhibition mechanism in patients. With respect to short interval trials, however, our results are different, since we failed to observe the interference that Gernsbacher & Faust (1991) reported for both

pictures and words. Although further study is needed to explain these differences, the observed facilitation can be explained by the fact that pictures achieve semantic processing more rapidly than words (e.g., Smith & Magee 1980). Short interval trials presumably provided not enough time for full semantic word processing, while automatic processing of distractive pictures was fully completed. Picture information was therefore dominating consciousness, implicating that it was relatively easy to decide whether the distractive picture was related to the test word. In case of a relationship (experimental trials), subjects might have deduced that the target word was probably *not* related to the test word. If the distractive picture was, however, *unrelated* to the test word (control trials), this deduction strategy was useless, and matching probably had to be based on incomplete word processing. This might have resulted in increased RTs. Support for such a mechanism came from several subjects reporting that the distractive information had actually helped them. With respect to the performance of patients, the absence of facilitation could be explained by two different mechanisms. First, reduced semantic processing might have resulted in incomplete processing of both pictures and words, implicating that distractive picture information was less dominant. Deduction strategies were, therefore, useless, which implicates that patients were not able to avoid distractor interference on experimental trials. Alternatively, *increased* semantic processing might have resulted in picture information being highly dominant. Inefficient use of deduction strategies might, however, also have resulted in an inability to avoid distractor interference on experimental trials. Verbal fluency tasks have demonstrated impaired semantic processing in patients (for review, see Heinrichs & Zakzanis 1998). However, it remains to be determined to what extent semantic picture processing is impaired. Further study is also needed to determine if task switching costs might have affected the performance of patients. Moreover, future studies with larger samples should determine whether the present findings for inpatients and outpatients are reliable.

With respect to the classification of the CMM task as a *cognitive inhibition* task, the significant association between the CMM and NP task suggests that both tasks were indeed measuring common cognitive components. However, significant correlations were only found for the control group, which implicates that the performance of patients was determined by other (random) factors.

### 4.5 CPT

Patients displayed an overall increase in RT and disproportionate slowing when stimulus presentation rate was decreased. In addition, patients displayed an increased number of omissions, while the number of false alarms was comparable to controls. This pattern was found for both inpatients and outpatients. General slowness and an increased number of omissions have been reported by many other

studies (e.g., Cornblatt et al. 1989; Earle-Boyer et al. 1991; Elvevag et al. 2000). On the other hand, disproportionate slowing was not found by Elvevag et al. (2000). Nevertheless, this slowing seems in line with the work of Cohen & Servan-Schreiber (1992), who have proposed that long delays require the use of an internal representation of context, which might be impaired in patients. This assumption was confirmed by an increased number of omissions and false alarms (Cohen et al. 1996; Servan-Schreiber et al. 1996). With respect to false alarms, the normal performance of our patients was in line with the studies of Cornblatt et al. (1989) and Jones et al. (2001). However, Earle-Boyer et al. (1991) and Elvevag et al. (2000) have reported increased false alarm rates. Unfortunately, many authors did not provide information on false alarms, since they evaluated performance by means of a measure which combined hits and false alarms into one index of target sensitivity (*d'*).
Several factors might be related to the normal false alarm rate of our patients. First, some studies have suggested that CPT deficits were related to the negative syndrome (Neuchterlein et al. 1986) and positive formal thought disorder (Neuchterlein et al. 1986; Pandurangi et al. 1994). Other studies failed, however, to confirm a relationship between current symptoms and CPT deficits (e.g., Asarnow & MacCrimmon 1978; Orzack & Kornetsky 1966). Since previous studies mainly focussed on *d'* and the number of omissions, further study is needed to determine whether false alarms are associated with current symptomatology. Second, several studies have shown that CPT deficits can be normalized by antipsychotics (Earle-Boyer et al. 1991; Orzack et al. 1967; Spohn et al. 1977) Other studies failed, however, to demonstrate differences between patients who were tested on and off medication (Cannon et al. 1994; Pandurangi et al. 1994), and between medicated and non-medicated patients (Cornblatt et al. 1988, 1989; Harvey et al. 1990). Further study is needed to determine whether antipsychotics have a specific influence on false alarms. Finally, the task might have been too easy. However, Elvevag et al. (2000) demonstrated that an increase in task difficulty (due to manipulation stimulus-response mapping, target probability, or the delay), did not result in a differential performance of patients.

### 4.6 Go/nogo task

Patients responded significantly slower than controls, but displayed normal performance with respect to errors. In contrast to the CPT, slow stimulus presentation did not induce disproportionate slowing. Probably the spatial dimension of Go/nogo stimuli has served as a stronger motivational cue to maintain fast responding than the centrally presented CPT stimuli. This would be in line with our findings on the Simon task that have suggested that the spatial location of stimuli elicits a relatively strong response tendency (an thus interference effect). Similar to the CPT, the normal performance of our patients might be related to the fact that

symptoms were in nearly full remission or the successful treatment with antipsychotics. Moreover, task characteristics might have played a role. Further study should confirm the relevance of each of these factors.
Since the Go/nogo task and the CPT were both presumed to measure behavioral inhibition, it was interesting that, except for a positive correlation between the RTs of both tasks, no significant correlations were found. Apparently, the tasks did not measure a common construct.

### 4.7 Conclusions

Our study produced unexpected negative results, suggesting that first-episode patients do not exhibit deficits in either interference control, cognitive inhibition, or behavioral inhibition. Despite numerous studies that have reported inhibitory impairment, we are not unique in reporting normal performance. Comparison with the literature learned that the crucial factors for finding normal inhibitory function were probably the nearly full remission of symptoms and the successful treatment with antipsychotics. This implicates that inhibitory deficits are merely state than trait dependent. The fact that inpatients performed somewhat worse than outpatients supports this view. Further support would be provided by studies demonstrating normal inhibitory function in healthy first-degree relatives and impaired inhibitory function in high schizotypes. Noteworthy, it is unclear to what extent task characteristics have obscured deficits. Previous studies have shown, however, that the effects in the Stroop task, the NP task, and the CPT are relatively independent of task parameters. Our data seem to suggest that stimuli with a spatial dimension (Simon task and Go/nogo task) elicit a particularly strong response tendency in patients. This is in line with the robust deficits generally observed on the antisaccade task. Further exploration of spatial inhibitory functions in schizophrenic patients would therefore be worthwhile.
It should be noted that, despite the absence of inhibitory deficits, our patients performed by no means normally. A remarkable slowness was found for the majority of tasks. It is still unclear what processes are underlying this slowness. Therefore, explanation of these processes remains a huge challenge for future research. Since many studies have demonstrated that basic motor and oculomotor systems are intact in schizophrenia (e.g., Broerse et al. *in press*), general slowness is assumed to result from abnormalities in higher order processes. In the present study, slowness was most evident for the CPT, followed by the Go/nogo task. The NP task did, however, not produce general slowness. This might be related to the fact that NP stimuli did not directly trigger a specific response. Moreover, the NP task required relatively less working memory resources, since the same/different judgement could be made in the presence of the comparison figure and there was no need to overrule a response bias. In contrast, the CPT and the Go/nogo task required

that subjects remained prepared to overrule a response tendency. This mental preparation required much effort, which is probably lacking in patients. Therefore, RTs might have been increased.

The Stroop and the Simon task appeared to measure a common cognitive construct, as did the NP and the CMM task. In contrast, the CPT and the Go/nogo task did not share common cognitive components. Although these results tentatively suggest that dividing inhibitory function into separate inhibitory processes is meaningful, the choice of the inhibition taxonomy, as well as the choice of tasks remains a matter of discussion. Therefore we emphasize that the present study focussed on central rather than peripheral inhibition, which implicates that inhibition in the early stages of sensation and perception, as well as inhibition of motor responses, was not addressed. Interestingly, Nigg (2000) included a fourth category of inhibition processes, namely oculomotor inhibition. First-episode patients with symptoms in nearly full remission were found to display severe oculomotor inhibition deficits (Broerse et al. 2001b). These deficits were, however, not associated with Stroop performance, which suggests that deficits are merely task-dependent than resulting from one general inhibition deficit. Future studies should examine whether chronically ill patients and first-episode patients with acute symptoms display inhibitory deficits on the presently used tasks. If this is indeed the case, more knowledge might be provided about the underlying mechanism of inhibitory deficits. In addition, it would be interesting to examine whether the normal performance of symptom-free patients was also reflected in normal brain activity. Brain imaging studies might also be helpful for validation of the inhibitory taxonomy used in the present study.

[1] There is still discussion about the exact processes underlying Stroop interference and NP effects (for reviews, see Fox 1995; MacLeod 1991; May et al. 1995), which complicates the interpretation of deficits in patients.

[2] Stimulus material was selected from the set of pictures published by Snodgrass & Vanderwart (1980). This set of 260 pictures was designed to achieve a relative homogeneity of visual appearance and the objects were chosen to avoid equivocation. Moreover, data on inter individual naming consistency were given. Although the name-consistency data applied to the English language, naming of these common objects appears to be relatively unequivocal in other (related) languages as well.

[3] The X's could be any number, except the 3 and 7.

[4] Error interference was calculated by ($errors_{incongruent} - errors_{neutral}$).

[5] Schooler et al. (1997) failed to observe differences between patients in a medicated state, as compared to an unmedicated state. Chen et al. (2001) found an increased facilitation in medicated patients as compared to unmedicated patients. Hepp et al. (1996) observed abnormalities in medicated patients. Carter et al. (1993) and Salo et al. (1996) observed normal performance in inpatients withdrawn from medication.

[6] It should be noted that in the study of Laplante et al. (1992) the interaction was non-significant and in the study of Moritz et al. (2001) normal NP was found when no mask was used and the prime was presented for 250 ms.

[7] Peters et al. (2000) found reduced NP in patients with positive symptoms, while asymptomatic patients did not differ from controls. Jones et al. (2001) reported reduced NP in patients with positive and patients with negative symptoms, in contrast to asymptomatic patients. Williams (1996) observed reduced NP in patients with reality distortion and disorganization, but not in patients with psychomotor poverty. Park et al. (1996) observed a lack of NP in patients with acute symptoms as compared to chronic patients.

[8] The majority of studies have used Stroop stimuli, although other verbal material (e.g., Williams 1996) and spatial material (e.g., McDowd et al. 1993; Park et al. 1996) were also used.

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# Chapter 6

## Antipsychotics and single cell activity in the rat superior colliculus

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**Abstract**

Schizophrenic patients have problems with saccadic eye movements that can be characterized as a loss of control over the saccadic system. Preliminary clinical results suggest that antipsychotics can either disrupt or improve saccadic performance. The brain mechanism through which antipsychotics affect the saccadic system is subject of study. The Superior Colliculus (SC) is crucially involved in the generation of saccades. Previous experimental studies showed that the Substantia Nigra reticulata (SNr), a structure with profound inhibitory influence on the SC, is differentially affected by classical and atypical antipsychotics.

The present study addressed the potential effects of atypical antipsychotics (clozapine, olanzapine and risperidone) and a classical antipsychotic (haloperidol) on the firing rate of SC cells in the rat. In anaesthetized animals we performed extracellular recordings on spontaneous active neurons in the intermediate and deep layers of the SC. After subcutaneous injection of the antipsychotics, changes in firing rate were compared with responses upon saline injection. Olanzapine (1.0 mg/kg), risperidone (0.3 and 1.0 mg/kg), and haloperidol (0.5 mg/kg) did not significantly alter cell activity, but clozapine (10.0 mg/kg) induced a short lasting but significant decrease. Except for clozapine, the effects of antipsychotics on the SC were nonsignificant and therefore independent of the effects in the SNr. Our results support the notion that clozapine has an action profile that is different from the other atypical antipsychotics.

## 1. Introduction

Schizophrenic patients often have problems with saccadic and smooth pursuit eye movements. Both problems are related to a loss of control over the saccadic system, which shows an increased vulnerability for distracting visual input. The eye movement deficits have therefore been characterized as saccadic inhibition failures. Since the oculomotor system itself is not affected, the inhibition problems are probably due to dysfunction(s) of cortical association areas.

Schizophrenic patients are usually treated with antipsychotics. Although not frequently examined, some studies have suggested that these drugs have an influence on saccadic performance and therefore contribute to the saccadic problems of patients. Hommer et al. (1991) have shown that treatment with classical antipsychotics results in impaired performance (reduced length, prolonged onset times, and distractibility) of saccades incorporated in cognitive paradigms (henceforth complex saccades). Also in healthy controls, single doses of classical antipsychotics were found to disturb saccadic performance (King et al. 1990, 1991; King & Bell 1990). With respect to atypical antipsychotics, the performance of complex saccades was found to improve after risperidone treatment (Burke et al. 1998). However, Sweeney et al. (1997) reported adverse effects of risperidone, but not haloperidol, on simple saccades (length and onset).

These preliminary results suggest that classical and atypical antipsychotics have differential effects on saccades, which is probably due to differential effects on the saccadic brain mechanism. An important brain region for the generation of saccades is the Superior Colliculus (SC). This structure receives input from frontal (Illing & Graybiel 1985), parietal (Lynch et al. 1985), cerebellar (Westby et al. 1994), and striatal regions (Hikosaka & Wurtz 1991). Because of this convergent input, we hypothesized that potential effects of antipsychotics on the saccadic brain mechanism might eventually affect the SC (either directly or indirectly).

Despite recent developments in neuroimaging techniques, it is difficult to examine directly the influence of antipsychotics in the human brain during the generation of saccades. However, clues can be provided by studies in the rat. Although the saccadic system in rats is organized somewhat differently from that in humans, essentially the same brain areas are involved (Hikosaka & Wurtz 1991). The SC is strongly influenced by the Substantia Nigra reticulata (SNr), the major output structure of the basal ganglia. This area plays an important role in motor behavior. The SNr is via gamma-aminobutyric acid (GABA) inhibitory neurons connected with the intermediate and deep layers of the SC, which are involved in the generation of saccades (Chevalier et al. 1981, 1984; Deniau & Chevalier 1992; Hikosaka & Wurtz 1983; Redgrave et al. 1992; Vincent et al. 1978; Westby et al. 1994). Also in the SNr, saccade-related neurons tend to be located in a restricted, lateral region (Deniau & Chevalier 1992; Redgrave et al. 1992). The inhibitory influence of the

SNr on the SC is tonic and only absent when SNr neurons temporarily stop discharging. This results in a burst of SC activity, which allows the generation of saccades. However, suppression of the tonic influence of the SNr does not directly increase SC activity; it rather releases SC cells from inhibition, and allows excitatory influences to control SC output (Westby et al. 1994). In monkeys, both disruption of the SNr-SC connection and reduction of inhibitory influences resulted in poor fixation and irrepressible saccades (Hikosaka & Wurtz 1983, 1985a,b, 1991). In contrast, increasing the inhibitory input resulted in problems with the initiation of saccades (Munoz & Wurtz 1991).
Neurons in the SNr of rats were found to be differentially influenced by classical and atypical antipsychotics (Bruggeman et al. 1997; Timmerman et al. 1999). Administration of the atypical drugs clozapine, olanzapine, and risperidone induced a significant decrease in the spontaneous firing rate, while the classical drug haloperidol resulted in a non-significant increase. In the present study we examined the effects of antipsychotics on spontaneously active neurons in the intermediate and deep layers of the SC. In anaesthetized rats, extracellular recordings were made upon injections of respectively clozapine, olanzapine, risperidone, and haloperidol. Although the study was explorative, we hypothesized that the atypical antipsychotics would result in an increased firing rate, whereas haloperidol would show either no effect or a slightly reduced firing rate.

## 2. Methods

### 2.1 Animals

For the experiments, male Wistar rats (270-320 g; CDL Groningen, The Netherlands) were used. The rats were kept on a 12-h light/dark cycle with lights on at 6 a.m. and had free access to food and water. All experiments were conducted in accordance with guidelines published in the National Institute of Health guide for the care and use of laboratory animals (National Institute of Health 1996) and all protocols were approved by the Groningen University Institute Animal Care and Use Committee.

### 2.2 Drugs

The drugs used for the experiments were clozapine (RBI, Natick, MA, USA), olanzapine (kindly donated by Eli Lilly, Indianapolis, USA), risperidone (kindly donated by Janssen Pharmaceuticals, Beerse Belgium), and haloperidol (Sigma, St. Louis, MO, USA).

### 2.3 Experimental procedure

Rats were anaesthetized with chloral hydrate (400 mg/kg intraperitoneal administration, (i.p.)), which was maintained during the whole experimental procedure

by additional i.p. injections every 30 min. Rats were placed in a stereotaxic frame (Kopf). Body temperature was maintained at 37° C by means of a heating pad. For subcutaneous (s.c.) injection of the antipsychotics, a polyethylene tubing was placed in the neck. A hole was drilled above the SC at the coordinates AP -7.0 and ML +2.1 from the Bregma (Paxinos & Watson 1982). A stainless-steel microwire electrode (California Fine Wire, Grover City, CA, USA) was soldered into a microtech (Boothwyn, PA, USA) miniature connector strip (GF-4). The diameter of the wire was 50 μm at the tip with no insulation and 100 μm with insulation. The electrode was slowly lowered until 4.2 mm below the dura by means of a microdrive. From this point tonically firing cells with a typical activity pattern of 5-20 Hz (biphasic action potentials) and no response to visual and auditory stimuli were expected to be found over a distance of 1.2 mm (the intermediate and deep layers of the SC). These cells were chosen for our experiments, because of their connection to the SNr (Westby et al. 1993). This connection allowed us to extrapolate from our previous findings in the SNr. Noteworthy, in the intermediate and deep layers of the SC we also found light sensitive cells with a typical activity pattern of repetitive bursts. Despite the fact that the generation of saccades has been associated with bursts of SC activity (resulting from the release of tonic SNr firing), we did not chose these cells for our experiments, since a pilot study demonstrated that these cells were not connected to the SNr. Moreover, the presence of repetitive bursts is difficult to interpret in anesthetized rats (which were not able to make eye movements).

Although the study was aimed to record single-unit activity, it cannot be excluded that occasionally multi-unit activity was recorded. The amplified and band-pass filtered electrophysiological signals (300 Hz to 20 kH; AM Systems Inc, Everett, USA) were continuously monitored on an oscilloscope and audiospeaker. Computerized data acquisition (Spike2 CED, Cambridge, UK) served for on-line template identification. The data were recorded both as individual events and as number of events per 10 sec.

Upon finding a single cell, the spontaneous firing rate was monitored for at least 60 min in order to check whether the cell showed stable firing over time. Moreover, we monitored the effects of anesthesia wearing off. All cells showed increases in firing rate due to anesthesia effects. In case of stable firing and a gradual anesthesia-related increase, a new and last injection of the anesthetic was given 10 min before the start of actual data recording. The actual data acquisition started with establishing a 5 min baseline firing rate ($t_{-5}$-$t_0$), which was followed by an injection (s.c.) of either saline, clozapine, olanzapine, risperidone, or haloperidol. Total recording time after drug injection was 30 min ($t_0$-$t_{30}$). For all experiments the means of the 10 sec count data were calculated for 5 min intervals throughout the experiment. These data were subsequently converted to % of baseline activity.

Each rat received only one drug injection throughout the experiments. For studying

the effects of the four antipsychotics, the following numbers of rats were used: clozapine n=9, olanzapine n=5, risperidone n=12, and haloperidol n=6. The drugs were dissolved in a 0.9% saline solution (pH 5), and administered in a volume of 0.5 ml in the following doses: clozapine 10.0 mg/kg, olanzapine 1.0 mg/kg, risperidone 1.0 mg/kg and 0.3 mg/kg, and haloperidol 0.5 mg/kg. Drug effects were compared to saline injections (pH=5; 0.5 ml; volume identical to that of the drugs; n=6).
Upon completion of the experiments, the rats were deeply anesthetized with chloral hydrate and the recording site of the recording electrode was marked by passing current through the electrode (50 μA for 10 sec). The rats were subsequently perfused with a lethal 4% formaldehyde solution. The brain was removed and stored in a 5% potassium ferrocyanide-4% formaldehyde solution. The stored brain was frozen and slices of 16 μm were taken throughout the SC to verify electrode placement. Data were only included if the electrode was located in the intermediate and deeper layers.

### 2.4 Statistical analysis

The data were analyzed by repeated measurement ANOVA with the type of antispychotic drugs as a between subject factor and the 5 min interval data as within subject factors. Oneway ANOVA analyses with a priori contrasts were used to detect significant differences ($p<0.05$) between the four antipsychotics and the saline injections.

## 3. Results

Figure 1 presents the mean firing rate of SC cells during the 30 min recording period upon each of the five antipsychotic injections. Each curve is depicted against the saline curve. Upon saline injection, the spontaneous SC activity gradually increased to 164% of baseline within the 30 min recording time. This increase was presumed to reflect the level of anesthesia.
As Figure 1A shows, clozapine in a dose of 10 mg/kg i.p. decreased the spontaneous firing rate. Activity change was significant at 5 to 15 min after injection (implicating significant differences for two five min periods; $t_5$-$t_{10}$: $t$=-2.32, $df$=32, $p$=0.027 and $t_{10}$-$t_{15}$: $t$=-2.53, $df$=32, $p$=0.016). At 15 min the firing rate was decreased to 95% of baseline, whereas the saline curve showed an increase to 133%. Also olanzapine in a dose of 1.0 mg/kg i.p. showed a decrease in spontaneous cell activity, however, the response did not differ significantly from saline and was delayed as compared to clozapine (Figure 1B). With respect to risperidone, a dose of 1.0 mg/kg i.p., was found to have no effect on SC firing rate (Figure 1C). However, this dose might have

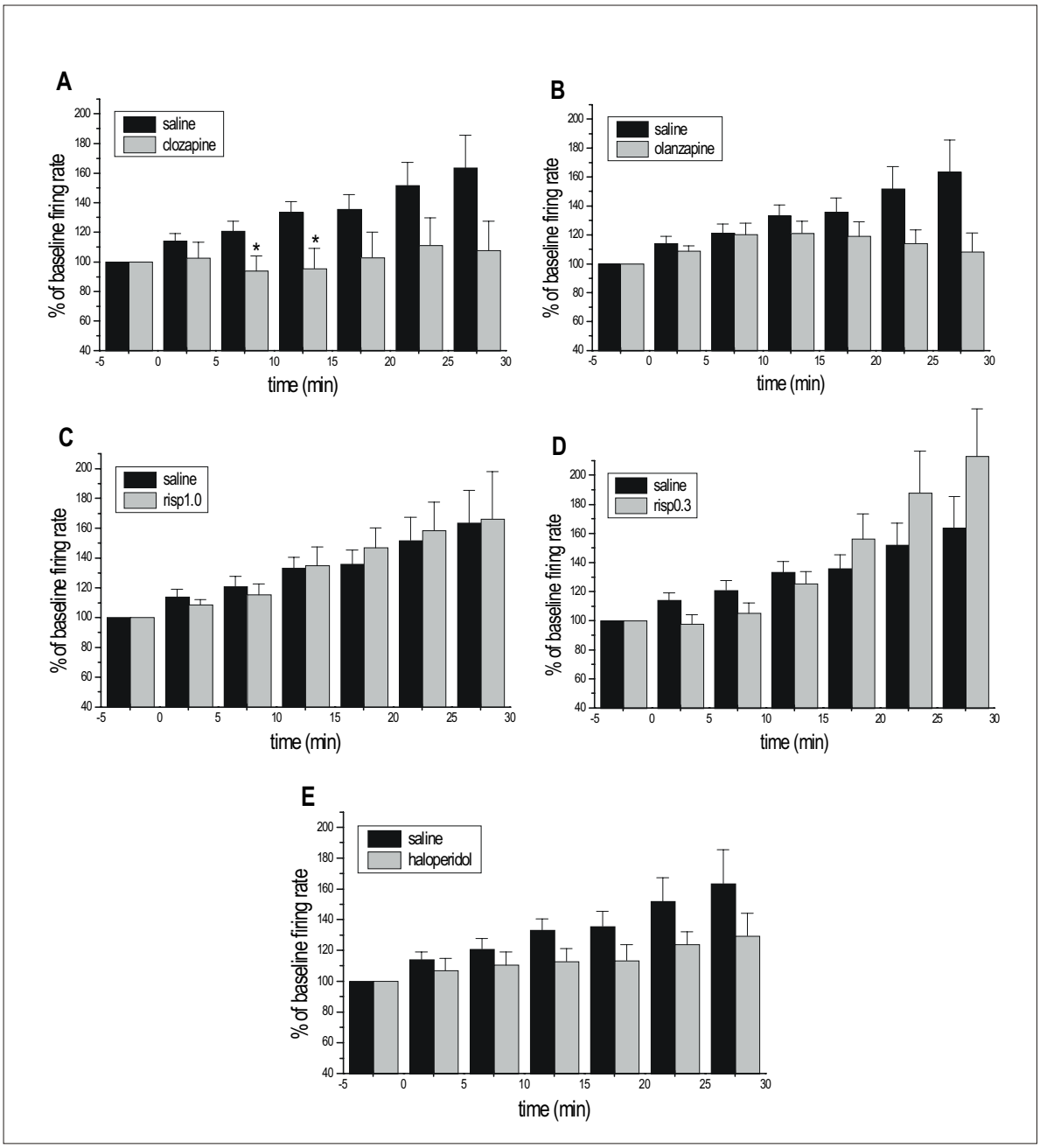


Figure 1

Effects of s.c. administration of antipsychotics on SC cell firing rate compared to saline (n=6).

**A** clozapine 10 mg/kg (n=9), **B** olanzapine 1.0 mg/kg (n=5), **C** risperidone 1.0 mg/kg (n=6), **D** risperidone 0.3 mg/kg (n=6), and **E** haloperidol 0.5 mg/kg (n=6). Data are expressed as percentages of baseline activity, determined from the average of successive 10 sec bin counts obtained over a 5 min interval shown in the first column. The other columns represent the average activity over 5 min intervals. All values are means ± S.E.M.

* $p<0.05$

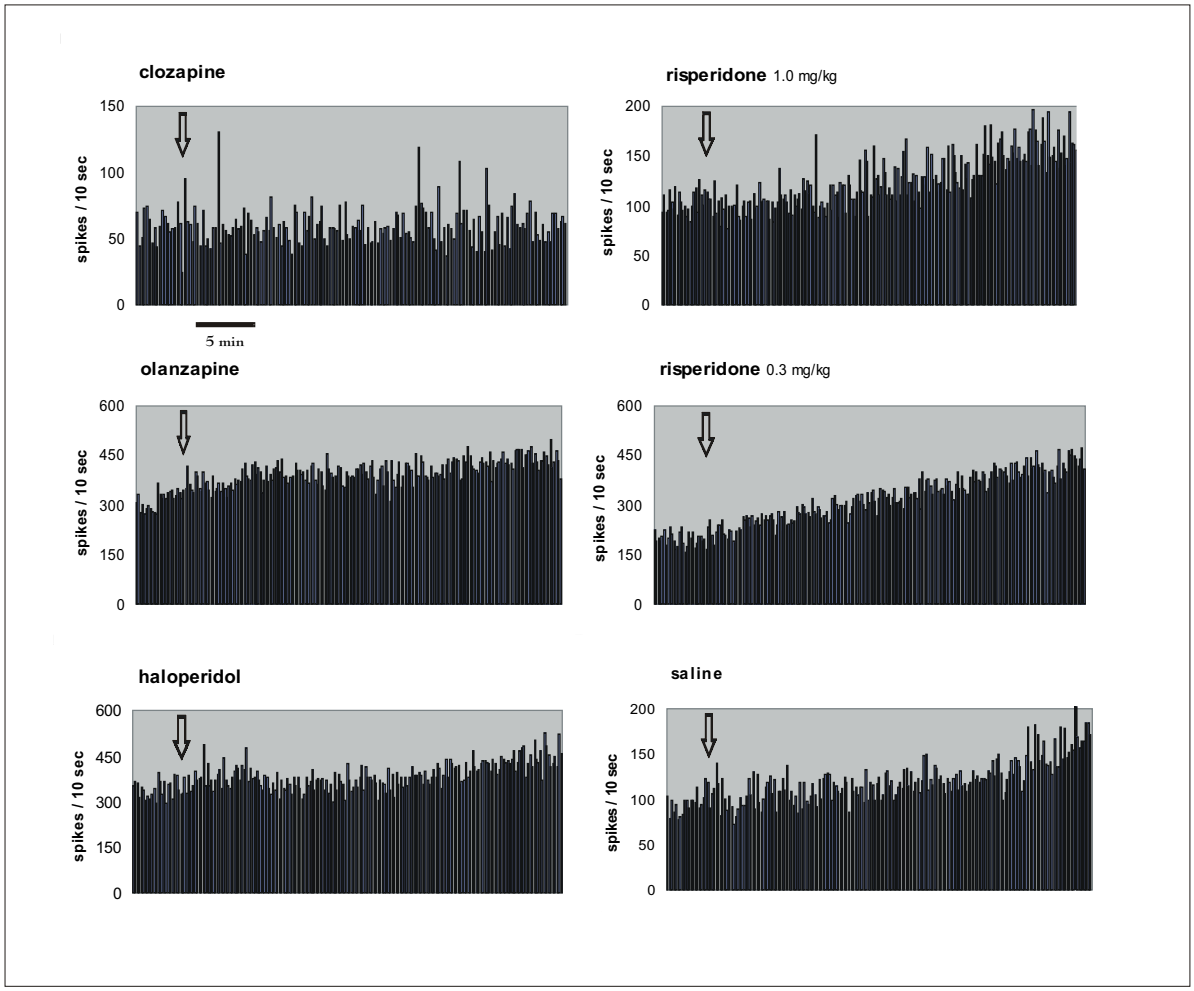


Figure 2
Rate meter traces of six SC cells upon administration of antipsychotics and saline. The traces represent spikes per 10 s over a recording period ranging from $t_{-5}$ to $t_{30}$.

been relatively high and possibly within the classical antipsychotic range (Hoffman & Donovan 1995; Leysen et al. 1993). Therefore the effects of risperidone were also studied in a dose of 0.3 mg/kg i.p. This dose also showed no significant effects, although there was a tendency towards an increased firing rate at 15 min after injection (Figure 1D). Haloperidol in a dose of 1.0 mg/kg i.p. did not change SC activity, although the firing rate was somewhat decreased compared to saline (Figure 1E). Figure 2 shows the rate meter traces of six SC cells upon injection of antipsychotics and saline.

## 4. Discussion

We investigated the influence of clozapine, olanzapine, risperidone and haloperidol on the spontaneous firing rate of neurons in the intermediate and deep layers of the SC. Only clozapine was found to have a small but significant effect, i.e. a decrease in the firing rate.

This finding was counter to our hypothesis, since we presumed a close inhibitory connection between the SNr and the SC, and this would predict effects opposite to those found in our previous SNr studies, i.e. a decrease in the firing rate for atypical antipsychotics, but not for haloperidol (Bruggeman et al. 1997; Timmerman et al. 1999). The present findings suggest that classical and atypical antipsychotics do not have a differential effect on the spontaneous firing rate of SC cells.
With respect to olanzapine, the 30 min curve suggests that the activity might have decreased when the recording period was prolonged. However, other studies using the same dose have reported effects *within* 30 min. Stockton & Rasmussen (1996) showed, for example, complete reversal of d-amphetamine-induced inhibition of A10 DA cell activity within 5 min after olanzapine injection (0.18 mg/kg i.v.), and Gleason & Shannon (1997) reported a decrease in locomotor activation within 40 min after drug administration.
The drug doses used in the present study were within the range commonly used in other studies. Many studies have demonstrated significant effects for clozapine and haloperidol administered in doses of respectively 10.0 mg/kg s.c. and 0.5 mg/kg s.c. (Arnt & Skarsfeldt 1998; Ashby & Wang 1996). With respect to olanzapine, Gleason & Shannon (1997) have shown that a dose of 1.0 mg/kg s.c. was effective in reversing locomotor activation, while even lower doses (0.03-0.1 mg/kg s.c.) were able to reverse phencyclidine-induced hyperlocomotion. In our previous SNr studies we observed significant effects for olanzapine in a dose range of 50-1600 μg/kg i.v. (Timmerman et al. 1999). Since 4.0 mg/kg s.c. is the lowest dose reported to induce catalepsy (an experimental measure for EPS) (Hoffman & Donovan 1995), our dose of 1.0 mg/kg s.c. was considered to display an atypical action profile. With respect to risperidone, catalepsy was associated with a dose of 2.0 mg/kg s.c. (Hoffman & Donovan 1995; Leysen et al. 1993). Thus, by using a dose of 1.0 mg/kg we might have studied risperidone in a more classical than atypical antipsychotic profile. Therefore, we also examined risperidone in a dose of 0.3 mg/kg s.c. In our previous SNr studies a dose of 100-3200 μg/kg i.v. was effective (Bruggeman et al. 1997).

### 4.1 An explanation for the lack of significant changes in SC activity

The lack of significant increases in SC firing rate upon administration of atypical antipsychotics might be related to the finding of Westby and colleagues (Westby et al. 1993, 1994) that suppression of the SNr input to the SC enhances the sensitivity of the SC for the input from other regions. This implicates that suppression of the SNr by atypical antipsychotics does not necessarily leads to an increase in SC firing rate. If antipsychotics reduce the excitatory input from cortical areas, the activity of this region might decrease. With respect to the saccadic brain mechanism, an important frontal input to the SC comes from the FEF (Hikosaka & Wurtz 1991). The activity in this region might be altered by atypical antipsychotics, since these

drugs specifically target the 5-$HT_2$ receptors of this region (Ashby & Wang 1990). In the present study, clozapine might have affected this frontal region more than the other atypical antipsychotics. This would support the notion that clozapine is different from other atypical antipsychotics, as was suggested by animal studies showing no extrapyramidal side effects (EPS) after clozapine treatment, while both olanzapine and risperidone induced EPS upon high doses (Hoffman & Donovan 1995; Kalkman et al. 1997). However, the effect of clozapine and the trend of olanzapine to reduce SC activity might also be explained by other characteristics of the typical receptor profiles of these drugs, e.g., clozapine and olanzapine have a more pronounced action on $D_1$ and muscarine receptors than risperidone and haloperidol (Jackson et al. 1998).

### 4.2 Anesthesia

The influence of anesthesia on the spontaneous cell activity was rather large. Within 30 min the firing rate increased to 164%, which implicates that the anesthetic might have interfered with the effects of the antipsychotics. Chloral hydrate could, for example, potentially have reduced the excitatory cortical input to the SC, resulting in a decrease in the spontaneous cell activity.

Ideally, the experimental setup allows to control for the possible effects of anesthesia. In the present study, there are, however, several reasons why it is unlikely that the drug effects were completely cancelled out by chloral hydrate. First, the results of previous SNr studies showed that significant differential drug effects could be obtained despite an increase in SNr activity to 120%. Second, chloral hydrate is generally presumed to have a rather *a-specific* effect on the brain (it is an alcohol), which implicates no gross *differential* effects on the four antispychotic drugs. Third, several studies failed to demonstrate a change in the sensitivity to various psychoactive drugs in chloral hydrate anesthetized rats as compared to awake animals (see Claassen 1994). It should, however, be noted that other studies did report a sensitivity change, and that this change was probably dependent on the level of anesthesia (Melis et al. 1998). In some of these studies the changes implicated, however, a decrease in the sensitivity, whereas in other studies an increase was reported. Because of these inconsistent findings, it is unclear whether in the present study chloral hydrate might have had severe and differential effects on each of the drugs. Future studies in which the level of anesthesia is kept constant (by means of chloral hydrate *infusion* instead of i.p. bolus injections), should confirm the drug effects obtained in both the present en previous SNr studies. Moreover, future studies in awake animals are necessary to confirm the present findings.

### 4.3 Connection between the SNr and SC

Although we based our hypotheses on previous studies examining the effects of antipsychotics in the SNr, these studies did not identify the target areas of the SNr neurons. However, we assumed that there were nigrocollicular cells among them, since the SNr in rats has a lamellar organization (Deniau & Chevalier 1992) and cells were chosen from a broad medial area.

To ensure that our SC cells were connected with the SNr, we selected cells which were characterized by others as such (Chevalier et al. 1981; Westby et al. 1993, 1994). Chevalier et al. (1981) demonstrated that 80% of the SC cells displayed a decrease in the firing rate after SNr stimulation, whereas 20% showed an increase. The majority of the inhibited cells was located within the caudal two thirds of the intermediate and deep SC layers, while the excited cells were widely distributed throughout all layers. Excitation appeared to be the result of fibers passing through and in the vicinity of the SNr. Likewise, Westby et al. (1994) demonstrated for 88% of the SC cells in the intermediate and deep layers an increased firing rate after GABA injection in the SNr, whereas 11% showed a decrease. For this latter group no site specificity in either the SC or SNr could be found. The authors concluded that the reverse effects were probably due to an intrinsic circuitry within the SNr or SC.

After completing the study, Niemi-Junkola & Westby (1998) demonstrated, however, a large heterogeneity in the responses of SC cells upon SNr inhibition. In their study only 54% of the SC cells appeared to be under inhibitory tone of the SNr, whereas previous studies have reported an inhibitory SNr-SC connection for 80 to 88% of the SC cells (Chevalier et al. 1981; Westby et al. 1994). In addition, 28% of the neurons was excited by the SNr, while 18% showed no response upon SNr manipulation. Unlike previous reports that could not relate the paradoxical responses to specific locations within the SC (Chevalier et al. 1981; Westby et al. 1994), this study showed that the majority of cells in the intermediate layers received an inhibitory input, whereas the majority of cells in the deep layers received an excitatory input. Since we based our study upon the assumption that the majority of SC cells in both layers was under inhibitory influence, we might have combined cells under different SNr influences within each of the four experimental groups. This would explain our large within-group variety. Although the results of Niemi-Junkola & Westby (1998) need to be confirmed by others, their findings have shown that it is of crucial importance to establish the connection between the SNr and SC before carrying out other manipulations.

## 5. Conclusion

Significant changes in spontaneous cell activity in the intermediate and deep layers of the SC were found only upon clozapine injection, whereas olanzapine, risperidone and haloperidol did not show significant effects. These findings support the notion that clozapine is different from the other atypical antipsychotics. However, these results were also unpredicted, since previous studies demonstrated significant effects upon administration of atypical antipsychotics in the SNr. The present findings suggest that despite a strong inhibitory SNr-SC connection, the influence of antipsychotics on the SC is not necessarily dependent on changes in the SNr. Since atypical antipsychotics exert a profound influence on frontal areas, and these areas also project to the SC, a combination of changes in frontal regions and the SNr might have contributed to our findings. On the other hand, future studies should examine the potential influence of the anesthetic on the four antispychotics. With respect to human studies, it would be interesting to confirm the unique influence of clozapine on both the saccadic brain mechanism and the performance of saccadic eye movements.

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# Chapter 7

## Summary and general discussion

Numerous studies have demonstrated abnormalities in the cognitive abilities of schizophrenic patients. Some researchers have proposed that the abnormalities are characterized by deficits in *specific* cognitive domains, whereas others have suggested that *all* cognitive domains are compromised (generalized deficit). Cognitive deficits have further been interpreted in terms of abnormal functioning of the frontal lobes. Despite these different ideas about the *nature* of cognitive deficits, researchers seem to agree on an important characteristic of these deficits, namely the inability to inhibit more or less automatic, but irrelevant responses. An inability to inhibit irrelevant information might render patients vulnerable to stimulus inundation, which would explain the cognitive fragmentation and distractibility in complex social situations.

The fast majority of studies that examined cognitive function in schizophrenia was based on traditional neuropsychological tasks. Therefore, evidence of inhibitory impairment was mainly provided by neuropsychological studies. The results of these studies are, however, inconsistent and failed to elucidate the nature of inhibitory deficits. These limitations are probably related to the fact that neuropsychological inhibition tasks often measure, besides inhibitory function, also other cognitive operations, which hinders the interpretation of the results. This problem can be circumvented by the use of experimental psychological paradigms, since experimental psychologists have been very inventive in developing promising new paradigms that can selectively target inhibitory operations. The diversity of inhibition tasks that have been described in the literature, raises, however, the question whether these tasks measure one general inhibitory function or merely different type of inhibitory processes. With respect to schizophrenia, experimental psychological studies using different paradigms have reported inhibitory impairment.

Inhibitory processes have also been examined by means of more biologically oriented methods (e.g., the skin conductance orienting response, prepulse inhibition, P50). In this respect, the use of saccadic eye movements seems a valuable technique. Saccadic paradigms can evaluate cognitive processes using the spatial and temporal parameters of the eye movement. Particularly useful for the study of inhibitory

function, is the antisaccade task. Studies that have used this task in schizophrenic patients, reported consistent and robust failures to inhibit prepotent responses.
Despite numerous studies that have demonstrated inhibitory deficits in schizophrenia, the *nature* of these deficits is still unclear. Clarification of the processes underlying these deficits might, however, reveal interesting knowledge about the pathophysiology of schizophrenia. In this respect, cognitive studies that combine different research strategies (e.g., neuropsychological tasks, experimental psychological tasks and biologically oriented indices) might be particularly informative.
Based on these considerations, the aim of the present thesis was: 1) To describe inhibitory function in schizophrenia, 2) To characterize the nature of inhibitory deficits, and 3) To evaluate different methods of cognitive assessment. In order to achieve these goals, inhibitory function as well as other cognitive functions were examined by means of saccadic, experimental psychological and neuropsychological paradigms. To characterize the nature of the inhibitory deficits, the following questions were addressed: 1) Are inhibitory deficits in different tasks due to one underlying cause? 2) Are inhibitory deficits related to demographic and disease-related factors? 3) Are inhibitory deficits influenced by antipsychotic treatment? 4) Are inhibitory deficits state or trait dependent? and 5) Does the literature about inhibitory brain mechanisms provides clues about the pathophysiology of schizophrenia?

### 7.1 Evidence and interpretation of inhibitory deficits in schizophrenia

The studies presented in the chapters 3, 4 and 5 have revealed interesting knowledge about inhibitory function in first-episode schizophrenic patients. The neuropsychological test battery yielded inconsistent results, since the Continuous Performance Test (CPT) and the Trail Making Test (TMT) revealed deficits, whereas the Stroop task failed to do so. Apparently, these three neuropsychological tasks measure different inhibitory processes (which was confirmed by the absence of correlations between the tasks). The CPT revealed an inhibitory deficit that was related to sustained attention, whereas the TMT revealed modest inhibitory impairment that was related to task switching abilities. However, the interpretation of these abnormalities is difficult, because the CPT as well as the TMT tap, besides inhibitory function, also other cognitive operations. The interference index of the Trail Making Test reflects, for example, also working memory capacity and task switching abilities. Poor performance is therefore not necessarily resulting from a failure in inhibitory control. In addition, performance deficits might result from poor orchestration of the different cognitive operations required by the task. Further, normal performance on these measures cannot be unequivocally interpreted in terms of adequate inhibitory control, since the multiple cognitive operations provide an opportunity to

compensate, implicating that poor inhibitory control might be obscured by the investment of extra effort in other cognitive operations.

Such interpretation problems are reduced when experimental psychological tasks are used, since these tasks generally target inhibitory processes very selectively (i.e., through the use of proper control conditions and minimal involvement of other cognitive operations). Chapter 5 described six experimental psychological tasks that were presumed to represent three distinct classes of inhibitory processes. The results of this study showed that first-episode patients exhibit normal inhibitory function. In light of this finding, one might conclude that the inhibitory problems observed in the CPT and the TMT must be explained by deficits in cognitive operations other than inhibitory function or by poor orchestration of these operations.

This conclusion seems, however, preliminary, since the highly specific saccadic paradigms also revealed robust inhibitory impairment in patients. This impairment reflected a failure in respectively the control of response tendencies (antisaccade task) and the control of an already prepared oculomotor program (memory saccade task). Patients had particular problems in situations that required the suppression of an immediate visual response (reflex) towards suddenly appearing stimuli. Noteworthy, the *sudden onset* of the stimuli as well as the *simplicity* (single dimension) of the stimuli and the requirement of an *immediate response*, could not be considered as crucial factors for eliciting the inhibitory deficits in patients, since these characteristics were also present in the experimental tasks. In contrast, the requirement of an eye movement response (instead of a vocal or manual response) might have crucially distinguished the experimental tasks from the saccadic tasks. Responding by means of an eye movement implicates a strong stimulus-response compatibility and a relatively short and restricted pathway in the brain. This reduces the impact of inhibitory control mechanisms, and thus requires critical tuning of inhibitory action. In schizophrenic patients, this tuning might be defective. Further study is needed to explore the possibility that in schizophrenia inhibitory mechanisms are not disrupted, but merely characterized by poor timing.

With respect to the saccadic inhibition problems of patients, it was interesting to find in patients a particularly strong response tendency in experimental psychological tasks that employed *spatial* stimuli (i.e., Simon task, go/nogo task). This finding tentatively suggests that also in the antisaccade task, the spatial dimension of stimuli might have played a role in the inappropriate application of inhibitory action. Further study should, however, explore the role of spatial stimulus characteristics in inhibitory control in patients. Further study should also explore whether inhibitory function is deficient in other situations that implicate strong stimulus-response compatibility, and thus critical tuning of inhibitory mechanisms.

Interestingly, the results of Chapter 4 demonstrated that the saccadic measures of inhibitory function were not related to neuropsychological measures of inhibitory

function. Apparently, these measures did not address a common inhibitory process. Moreover, patients who performed poorly on saccadic tasks, did not necessarily perform poorly on neuropsychological tasks, and vice versa. This supports the notion that not only different inhibitory processes are measured, but also that these processes might be independently from each other disturbed in schizophrenia.

## 7.2 Towards a taxonomy of inhibitory processes

The results of the chapters 3, 4 and 5 suggest that neuropsychological, experimental psychological and saccadic paradigms measure different inhibitory processes. Therefore, the use of a classification of inhibitory processes is warranted. Chapter 5 presented a workable taxonomy of inhibitory processes that has obvious face value and distinguishes processes of cognitive inhibition, behavioral inhibition, and interference control. Classification of inhibitory processes provides a useful framework for the interpretation of inhibitory performance in subjects. Particularly clinical studies might benefit from such a framework, since these studies often have to communicate the *meaning* of deficits.

To validate an inhibition taxonomy, one could perform correlation analyses on the tasks that are presumed to represent the different categories of inhibitory processes. The results of Chapter 5 provided some evidence for the idea that the Negative Priming task and the Cross Modal Matching task measured a common construct (cognitive inhibition). Similarly, there was modest evidence for the notion that the Stroop task and the Simon task measured a common construct (interference control). The data failed, however, to reveal a common inhibitory component for the CPT and the go/nogo task. Noteworthy, correlations between the tasks representing different categories of inhibitory function were nonsignificant, indicating that the proposed distinction was, at least to some extent, meaningful. Nevertheless, the choice of the taxonomy as well as the choice of the tasks that represent the different categories within a taxonomy remains a matter of discussion. Further study is needed to determine how saccadic inhibition and neuropsychological inhibitory processes (e.g., TMT interference) relate to this taxonomy. The absence of correlations between the saccadic tasks and the neuropsychological tasks (i.e., Stroop task, CPT) suggests that saccadic inhibition should be considered as a separate category of inhibitory processes.

## 7.3 Selection of paradigms

Only few studies have presented a clear rationale for selecting one paradigm over another. Studies that aim to obtain an *overall* picture of cognitive function often have used neuropsychological tasks, since these tasks can cover a large number of cognitive domains. Experimental tasks can also be used for these purposes, however, the specificity of these tasks implicates that a large number of tasks will be

necessary. Moreover, the administration of individual tasks usually takes long, implicating that total testing duration would become unacceptably long and performance is likely to be negatively influenced by factors like fatigue and poor motivation. Saccadic tasks could *not* be used for the assessment of overall cognitive function, since these tasks allow the investigation of only a small set of cognitive operations. However, an advantage of these tasks is that the performance is independent of verbal and manual abilities, which minimizes the risk that problems in the vocal or motor system will interfere with the outcome.

From a *treatment perspective* it seems most relevant to obtain information about the cognitive abilities within a particular *context*. Obviously, neuropsychological tests contain stimulus material that is more compatible with daily life situations than experimental and saccadic paradigms. The neuropsychological approach is therefore particularly useful for revealing cognitive *limitations* in patients. However, when such limitations are established, some fine tuning by means of experimental psychological or saccadic paradigms is warranted in order to reveal the underlying defective processes. Only when the underlying mechanisms are clearly defined, one could consider cognitive training. In light of these considerations, it will further be interesting to investigate whether patients will report *subjective* inhibitory problems in case of abnormal performance on experimental psychological or saccadic tasks.

### 7.4 Inhibitory function & demographic and disease-related factors

The studies described in this thesis demonstrated that the performance on neuropsychological, experimental, and saccadic measures of inhibition was *not* correlated with age, gender, and level of education, except for a significant association between saccadic performance and level of education. Higher educated patients were found to make faster antisaccades, which suggests that a high level of education (and thus perhaps intelligence) protects patients from poor inhibitory control.

Hospitalization was not a factor of major importance, although some experimental paradigms demonstrated that outpatients performed slightly better than inpatients. With respect to symptom profile, the present data failed to reveal a significant association between symptoms and inhibitory control. However, this might have been due to the fact that symptoms were in (nearly) full remission. The literature on experimental paradigms suggests that symptom profile is an important determinant of inhibitory function. Therefore, further study on this issue is warranted (see also 7.6).

## 7.5 The influence of antipsychotics

The studies described in this thesis included patients who were all successfully treated with novel antipsychotics. Recent studies have suggested that antipsychotics have an effect on cognitive function. It has further been suggested that novel antipsychotics are superior to classical antipsychotics with respect to cognitive improvement, although they may not have a positive effect on *all* cognitive domains. Moreover, different types of novel antipsychotics might have differential effects on cognition. However, the results of Chapter 3 contradict this notion, since two novel antipsychotics, olanzapine and risperidone, appeared to have similar effects on visuospatial integration, visuospatial working memory and inhibitory function. Comparison of these results with data from previous studies using classical antipsychotics, is consistent with a beneficial effect of novel drugs. However, confirmation of this possibility has to await further studies that directly compare medication-free patients with patients using novel and classical antipsychotics.

If saccadic paradigms are used for the study of drug effects on cognition, it is important to exclude the possibility that the antipsychotics are affecting the saccadic system itself rather than the cognitive operations incorporated in the saccadic paradigms. Therefore, the present thesis included an animal study that directly investigated the effects of antipsychotics on the saccadic brain mechanism. In anaesthetized rats, extracellular recordings were performed on spontaneous active neurons in the superior colliculus upon single injections of novel antipsychotics (clozapine, olanzapine and risperidone) and a classical antipsychotic (haloperidol). Since the superior colliculus is crucially involved in saccade generation, potential effects of antipsychotics were presumed to be observable in this region. The results of this study showed that only clozapine had a small but significant effect on the spontaneous cell activity. Clozapine reduced the firing rate. This finding is in line with previous studies that have demonstrated unique qualities for this drug (e.g., minimal extrapyramidal side effects, superior effects in symptom treatment). Overall, the effects of antipsychotics on the superior colliculus were, however, marginal. Nevertheless, previous studies have reported a significant effect of antipsychotics on an important input structure of the superior colliculus, the substantia nigra reticulata. In the present study, the effects on nigrocollicular input were probably cancelled out by changes in other input structures as well (presumably the prefrontal cortex). Further study should, however, confirm this possibility. Further study should also confirm these findings in chronically treated and *awake* animals. Moreover, clinical studies should examine whether the unique influence of clozapine on the superior colliculus is reflected in the saccadic performance of patients. It could be hypothesized that the reduction of spontaneous activity in the superior colliculus leads to a situation in which reflexive saccades are less easily triggered. This would probably improve inhibitory control.

## 7.6 Are inhibitory deficits state or trait dependent?

Within schizophrenia research, there is an ongoing debate on the importance and meaning of cognitive deficits. Older theoretical accounts have proposed that deficits are *secondary* to the disease process. This notion implicates that cognitive impairment will gradually develop during the course of the illness. Moreover, chronically ill patients would display deficits in *all* cognitive domains, whereas recent onset patients would show normal performance or minor impairment in (some) cognitive domains. More recent authors have, however, proposed that the cognitive deficits are *inherent* to the disorder. This implicates that the deficits are already present in an early phase of the disease. An interesting but unsettled issue is, however, whether cognitive deficits are *state* or *trait* dependent. If they are trait dependent, impairment would be present even before the first symptoms appear. Moreover, deficits would be present in populations at risk for schizophrenia (i.e., first-degree relatives and high schizotypes). On the other hand, if cognitive deficits are *state* dependent, impairment would be confined to patients who are actually ill. Thus, cognitive impairment would be associated with the presence of symptoms.

The chapters 3, 4 and 5 have provided interesting knowledge on this issue, since the studies described in these chapters included first-episode schizophrenic patients with symptoms that were in (nearly) full remission. The results on the neuropsychological and saccadic tasks have demonstrated that inhibitory deficits were already present in an early phase of the disease. Moreover, these deficits were not dependent on the presence of acute symptoms. These findings suggest that inhibitory deficits are inherent to the disease and probably trait dependent. Trait dependency was also suggested by studies in first-degree relatives and high schizotypes. These studies have proposed that in particular the antisaccade task is a *behavioral marker* of latent liability to the disorder. Studies in chronically ill patients have further revealed that deficits were relatively severe as compared to first-episode patients, whereas the deficits in populations at risk for schizophrenia were less severe. These findings suggest that inhibitory deficits are trait dependent, but also deteriorate during the course of the disorder.

In contrast, the experimental psychological tasks (Chapter 5) have suggested that inhibitory deficits in schizophrenia are *state* dependent, since normal performance was found for first-episode patients, while the literature has described clear abnormalities for chronically ill patients. Chapter 5 further revealed that inpatients performed somewhat worse than outpatients (who were less ill), which is in line with studies that have demonstrated an influence of symptom profile. Further study in first-degree relatives and high schizotypes is needed to provide additional information on this issue. As yet, it seems that the different (and independent) inhibitory mechanisms as measured by the neuropsychological, experimental psychological and saccadic tasks differentially relate to the disease process.

## 7.7 Inhibitory deficits and brain dysfunction

One of the most intriguing issues with respect to the inhibitory problems in schizophrenia, is the interpretation in terms of brain dysfunction. In the present studies, inhibitory deficits were most profound for the saccadic paradigms. Detailed knowledge about the saccadic brain mechanism is therefore supposed to be useful for elucidating the pathological brain processes underlying schizophrenia. Animal studies and studies in patients with brain lesions have demonstrated that saccades are generated via a pathway that mainly involves the visual cortex, the parietal cortex (parietal eye fields), the frontal cortex (frontal eye fields) and the superior colliculus. If (reflexive) saccades should be suppressed, additional involvement of the dorsolateral prefrontal cortex is necessary. This region is able to suppress the activity of the superior colliculus, and thus the saccadic output. Interestingly, the various saccadic abnormalities that have been observed in schizophrenic patients (i.e., an increased number of express saccades, antisaccade errors, memory saccade errors, and inaccurate memory saccades) are all consistent with a functional deficit in the dorsolateral prefrontal cortex. This region has also been associated with two other tasks that often have demonstrated gross abnormalities in schizophrenia: the Wisconsin Card Sorting Test and (spatial) working memory tasks. Apparently, the dorsolateral prefrontal cortex plays an important role in the pathophysiology of schizophrenia.

In line with this notion, the majority of studies have implicitly or explicitly presumed that schizophrenia is above all a disease of abnormal frontal lobe functioning. In order to validate this presumption, a study was performed that examined the presence of frontal impairment by means of various neuropsychological and saccadic paradigms (Chapter 4). If frontal dysfunction is indeed a core feature of the disease, the fast majority of patients should perform poorly on these measures. The neuropsychological test battery demonstrated, however, that only 42% of patients exhibited frontal deficits. This percentage increased to 80% when the neuropsychological tasks were combined with saccadic tasks. Interestingly, saccadic and neuropsychological impairment failed to show large overlap in individual subjects. These findings suggest that frontal functions are not necessarily compromised in schizophrenia, and that schizophrenia is merely characterized by variable frontal deficits. Noteworthy, the present study was based on a small subset of frontal tasks and a selective group of patients first-episode patients with relatively few acute symptoms). Future studies using a more extensive set of frontal measures should, therefore, confirm the present findings in chronically ill as well as first-episode patients.

The idea that different frontal functions could be independently from each other compromised in schizophrenia, suggests that besides the dorsolateral prefrontal cortex also other frontal regions (e.g., the anterior cingulate cortex) play a role in the

pathophysiology of the disease. This possibility can be explored by means of functional neuroimaging techniques like PET and fMRI. It would be interesting to use these methods to examine whether the inhibitory deficits as revealed by respectively the saccadic and neuropsychological measures reflect different abnormalities in the brain. The results of the present studies predict that the antisaccade task will reveal abnormal brain activity in the dorsolateral prefrontal cortex, while the neuropsychological tasks might show abnormal activity in other (probably more widespread) frontal regions. Functional neuroimaging studies might further explain why the experimental tasks, despite their presumed selectivity, failed to reveal inhibitory deficits. In addition, neuroimaging techniques provide the opportunity to validate the classification of inhibitory processes into cognitive inhibition, behavioral inhibition, and interference control. Tasks belonging to each of these categories should reveal a unique activation network. If neuroimaging studies indeed reveal different brain mechanisms, this would strongly support the notion that terms like *inhibition* and *inhibitory function* are too global and should be replaced by more precise definitions. Validation of different inhibitory processes by means of neuroimaging studies, also provides the opportunity to compare directly the brain activity patterns of patients and controls for each of the inhibitory processes. Moreover, it would be interesting to examine whether such neuroimaging data would support the behavioral data of this thesis.

# Hoofdstuk 8

## Samenvatting

Talloze studies hebben laten zien dat schizofrenie gepaard gaat met cognitieve stoornissen. Volgens sommige onderzoekers worden deze stoornissen gekenmerkt door defecten in *specifieke* cognitieve domeinen, terwijl andere onderzoekers veronderstellen dat *alle* cognitieve domeinen gestoord zijn (algemeen defect). Daarnaast worden de cognitieve stoornissen bij schizofrenie vaak toegeschreven aan een disfunctie van de frontale cortex. Ondanks deze verschillende opvattingen over de *aard* van de cognitieve stoornissen, lijkt men het eens over de problemen die patiënten hebben bij het onderdrukken van min of meer automatische doch irrelevante reacties op omgevingsprikkels (inhibitiestoornissen). Een onvermogen om irrelevante informatie te filteren, impliceert dat een enorme hoeveelheid aan indrukken moet worden verwerkt. Dit zou kunnen verklaren waarom patiënten last hebben van een gefragmenteerd denkpatroon en verhoogd afleidbaar zijn in complexe sociale situaties.

Veruit de meeste studies naar het cognitieve functioneren van schizofreniepatiënten zijn gebaseerd op methoden uit de traditionele neuropsychologie. Aanwijzingen voor inhibitiestoornissen zijn dan ook voor een belangrijk deel afkomstig van neuropsychologische studies. De resultaten van deze studies zijn echter inconsistent en nauwelijks informatief ten aanzien van de *aard* van de stoornissen. Dit is vooral te wijten aan de geringe selectiviteit waarmee neuropsychologische taken de verschillende cognitieve functies in kaart brengen. Dit probleem kan echter worden beperkt door het gebruik van paradigma's uit de experimentele psychologie. Binnen deze stroming zijn een groot aantal selectieve inhibitieparadigma's ontwikkeld, waarvan sommigen zijn toegepast in schizofrenieonderzoek. Deze paradigma's bevestigden het bestaan van inhibitiestoornissen. Echter, de variatie in de taken werpt de vraag op of de stoornissen het gevolg zijn van één algemeen inhibitiedefect, of dat er sprake is van stoornissen in verschillende inhibitieprocessen.

Inhibitieprocessen kunnen daarnaast ook worden bestudeerd aan de hand van meer biologisch-georiënteerde methoden (zoals bijvoorbeeld het meten van de huidgeleidingsrespons of 'event related potentials'). In dit opzicht is de registratie van saccadische oogbewegingen een interessante techniek. Kenmerkend voor saccade paradigma's is dat cognitieve processen worden bestudeerd aan de hand van

de spatiële en temporele parameters van de oogbewegingsrespons. Ten aanzien van inhibitieprocessen is met name de antisaccade taak een zeer bruikbaar instrument. Deze taak heeft bij schizofreniepatiënten zeer consistente en robuuste afwijkingen laten zien.
Ondanks het feit dat via verschillende methoden inhibitiestoornissen bij schizofrenie zijn aangetoond, is de *aard* van deze stoornissen nog steeds onduidelijk. Omdat een beter inzicht in deze stoornissen wellicht interessante informatie oplevert over de pathofysiologie van schizofrenie, is het interessant om inhibitieprocessen nader te bestuderen aan de hand van onderzoek waarin verschillende onderzoeksmethoden worden gecombineerd.
Deze overwegingen vormden het uitgangspunt voor de studies in dit proefschrift. De volgende onderzoeksdoelen stonden daarbij centraal: 1) Het *beschrijven* van inhibitieprocessen bij schizofrenie; 2) Het karakteriseren van de *aard* van inhibitiestoornissen, en 3) De evaluatie van verschillende onderzoeksmethoden. Om deze onderzoeksdoelen te verwezenlijken, werden bij schizofreniepatiënten en gezonde vrijwilligers zowel inhibitieprocessen als andere cognitieve processen bestudeerd aan de hand van saccade taken, experimenteel psychologische taken, en neuropsychologische taken. De aard van de inhibitiestoornissen werd vervolgens onderzocht aan de hand van de volgende onderzoeksvragen: 1) Kunnen de stoornissen op verschillende inhibitietaken worden toegeschreven aan één onderliggend pathofysiologisch proces? 2) Zijn demografische en ziekte-gerelateerde factoren van invloed op inhibitiestoornissen? 3) Is de behandeling met antipsychotica van invloed op inhibitieprocessen? 4) Zijn inhibitiestoornissen 'state dependent' of 'trait dependent'? en 5) Biedt de literatuur over inhibitiemechanismen in het brein aanknopingspunten voor een beter inzicht in de pathofysiologie van schizofrenie?

## 8.1 Resultaten en interpretatie van inhibitieonderzoek bij schizofrenie

De hoofdstukken 3, 4 en 5 hebben interessante informatie opgeleverd ten aanzien van de inhibitiestoornissen bij eerste-episode schizofreniepatienten. De resultaten op de neuropsychologische testbatterij waren inconsistent, aangezien patiënten slecht presteerden op de Continuous Performance Task (CPT) en de Trail Making Test (TMT), maar een normale prestatie leverden op de Stroop taak. Blijkbaar doen deze drie taken een beroep op verschillende inhibitieprocessen. Dit werd bevestigd door de afwezigheid van significante correlaties tussen de verschillende taken. De CPT onthulde inhibitiestoornissen die samenhingen met volgehouden aandacht, terwijl de inhibitiedefecten op de TMT samenhingen met de flexibiliteit in het cognitieve handelen. De interpretatie van deze inhibitiestoornissen is echter lastig, omdat beide neuropsychologische taken naast inhibitie ook andere cognitieve handelingen meten. De interferentiemaat van de TMT weerspiegelt bijvoorbeeld zowel inhibitoire

functies als de capaciteit van het werkgeheugen en het vermogen om te switchen tussen taken. Een slechte prestatie is daarom niet automatisch het gevolg van een inhibitieprobleem. Bovendien kan een slechte prestatie voortkomen uit een onjuiste afstemming (regulatie) van de verschillende cognitieve handelingen, waardoor de timing van inhibitieprocessen in het geding komt. Daarnaast bieden de verschillende cognitieve handelingen binnen één taak de mogelijkheid tot compensatie, waardoor inhibitiestoornissen gecompenseerd zouden kunnen worden door het investeren van extra energie in andere cognitieve handelingen.

Dergelijke interpretatieproblemen zijn minder evident bij experimenteel psychologische taken, omdat deze taken in de regel selectiever zijn (bijvoorbeeld door een zorgvuldig gekozen controleconditie). Hoofdstuk 5 beschreef zes experimenteel psychologische taken die verondersteld worden een beroep te doen op drie verschillende inhibitieprocessen. De resultaten van deze studie lieten zien dat eerste-episode schizofreniepatiënten op alle drie de inhibitieprocessen normaal presteerden. In het licht van deze bevinding, kan geconcludeerd worden dat de inhibitieproblemen zoals die gevonden werden op de CPT en de TMT, het gevolg moeten zijn van disregulatie en/of stoornissen in *andere* cognitieve handelingen dan de inhibitoire functies.

Deze conclusie is echter voorbarig wanneer eveneens de saccade taken in het verhaal worden betrokken. De saccade paradigma's onthulden namelijk zeer robuuste inhibitiedefecten wanneer gevraagd werd een onmiddellijke visuele respons (reflex) naar een plotseling verschijnende visuele stimulus te onderdrukken (antisaccade taak). Deze inhibitieafwijkingen kunnen niet worden toegeschreven aan het *plotselinge verschijnen* van de stimuli, de *eenduidigheid* van de stimuli, of het feit dat een *onmiddellijke* respons gegeven diende te worden. Deze kenmerken waren immers ook aanwezig bij de experimenteel psychologische taken. Waarschijnlijk was het feit dat gereageerd moest worden in de vorm van een oogbewegingsrespons (in plaats van een manuele of vocale respons) de cruciale factor voor het uitlokken van inhibitiedefecten. Het genereren van een oogbewegingsrespons impliceert een sterke compatibiliteit tussen stimulus en respons, en een relatief kort traject in het brein. Hierdoor is de impact van inhibitoire controlemechanismen beperkt, waardoor een goede timing van deze mechanismen essentieel wordt. Hierin schuilt mogelijk het probleem bij schizofreniepatiënten. Toekomstig onderzoek moet echter uitwijzen in hoeverre inderdaad sprake is van inhibitoire mechanismen die niet zozeer defect, maar eerder slecht getimed zijn.

In dit verband is het interessant dat patiënten een extra sterke neiging tot reageren vertoonden op experimenteel psychologische taken waarbij gebruik werd gemaakt van *spatiële* stimuli (zoals bijvoorbeeld de Simon taak of de Go/nogo taak). Wellicht speelt daarom ook in de antisaccade taak het spatiële karakter van de stimuli een belangrijke rol in het uitlokken van de inhibitiefouten. Toekomstig onderzoek moet

uitwijzen in hoeverre spatieel stimulusmateriaal inderdaad een belangrijke rol speelt bij de inhibitiestoornissen van schizofreniepatiënten. Daarnaast moet onderzocht worden in hoeverre inhibitiedefecten optreden in andere situaties waarbij de stimulus-respons compatibiliteit groot is.
De resultaten van Hoofdstuk 4 lieten zien dat inhibitieprocessen zoals die gemeten werden aan de hand van saccade taken niet correleerden met neuropsychologische inhibitietaken. Blijkbaar doen beide type taken een beroep op verschillende inhibitiemechanismen. Bovendien bleek dat patiënten met een slechte saccadeprestatie niet per definitie slecht presteerden op neuropsychologische taken, en vice versa. Indien de afwijkingen op de neuropsychologische inhibitietaken inderdaad het gevolg zijn van inhibitiedefecten, kunnen er bij schizofrenie dus verschillende inhibitieprocessen onafhankelijk van elkaar gestoord verlopen.

## 8.2 Naar een taxonomie van inhibitieprocessen

De resultaten van de hoofdstukken 3, 4 en 5 suggereren dat neuropsychologische, experimenteel psychologische en saccade taken een beroep doen op verschillende inhibitieprocessen. Om die redenen is het verhelderend om een classificatie van inhibitieprocessen te gebruiken. In Hoofdstuk 5 werd een classificatie gepresenteerd waarbij een opdeling werd gemaakt in *cognitieve inhibitie*, *respons inhibitie* en *interferentiecontrole*. Classificatie van inhibitieprocessen lijkt van belang voor de interpretatie van onderzoeksresultaten, aangezien hierdoor eventuele stoornissen meer betekenis krijgen. Met name klinische studies, waarin relatief vaak afwijkingen gevonden worden, zouden hiervan kunnen profiteren.
Voor de validatie van inhibitieclassificaties, kan men gebruik maken van correlatie analyse. Taken die verondersteld worden één bepaalde categorie te representeren, dienen onderling hoog te correleren, terwijl taken uit *verschillende* categorieën niet gecorreleerd mogen zijn. Hoofdstuk 5 liet zien dat de Negatieve Priming taak en de Cross Modal Matching taak een gemeenschappelijk component hebben (cognitieve inhibitie). Ook de Stroop taak en de Simon taak doen een beroep op een gemeenschappelijk construct (interferentiecontrole). De CPT en de go/nogo taak bleken, daarentegen, niet gerelateerd. Verder bestonden er geen significante correlaties tussen de taken uit de verschillende categorieën, wat impliceert dat de classificatie voor een belangrijk deel betekenisvol is. Niettemin blijft zowel de keuze voor een bepaalde classificatie als de keuze van taken die de verschillende categorieën representeren onderwerp van discussie. Toekomstig onderzoek moet daarnaast uitwijzen hoe saccadische inhibitie en inhibitie tijdens neuropsychologische taken (bijvoorbeeld de TMT) binnen deze classificatie passen. De afwezigheid van correlaties tussen de saccade taken en de neuropsychologische taken (Stroop taak, CPT) doet vermoeden dat saccadische inhibitie een aparte categorie van inhibitieprocessen vormt.

## 8.3 De selectie van inhibitieparadigma's

Slechts zelden wordt in klinische studies verantwoording afgelegd voor de keuze van bepaalde inhibitietaken. Over het algemeen hangt deze keuze samen met het uiteindelijke onderzoeks*doel*. Onderzoekers die geïnteresseerd zijn in het *algehele* cognitieve functioneren, kiezen veelal voor neuropsychologische taken, aangezien deze taken het hele terrein van cognitieve functies lijken te dekken. Experimenteel psychologische taken hebben de potentie om een nauwkeuriger beeld op te leveren, echter, het nadeel van dit type taken is dat een zeer groot aantal taken moet worden afgenomen om een compleet beeld te krijgen. Bovendien hebben deze taken in de regel een lange afnameduur, waardoor de kans op vermoeidheid en verveling groot is. Het lijkt dus verstandig om experimenteel psychologische taken uitsluitend te gebruiken in situaties waarin de bestudering van specifieke cognitieve functies gewenst is, of in situaties waarin neuropsychologische taken specifieke functiestoornissen hebben aangetoond. Saccade taken lenen zich eveneens voor dit soort 'fine-tuning', maar deze taken niet geschikt zijn voor de bestudering van alle cognitieve domeinen. Saccade taken zijn met name bruikbaar voor onderzoek naar visuospatiële functies (integratie van visuospatieel materiaal, visuospatieel werkgeheugen), anticipatoir gedrag en inhibitieprocessen. Een groot voordeel van saccade taken is dat de prestatie onafhankelijk is van het verbale en motorische vermogen, waardoor motorische problemen bijvoorbeeld nooit zullen interfereren met de taakprestatie.

Vanuit een *behandelperspectief* is het zinvol om te kijken naar het cognitieve functioneren *binnen een bepaalde context*. Met name de neuropsychologische taken bevatten testmateriaal dat grote overeenkomsten vertoont met situaties uit het dagelijks leven. Deze taken zijn daarom zeer bruikbaar voor het vaststellen van de cognitieve *beperkingen* bij patiënten. Wanneer echter in een bepaald domein beperkingen worden gevonden, verdient het aanbeveling om de onderliggende mechanismen aan de hand van experimenteel psychologische en/of saccade taken nader te onderzoeken. Alleen wanneer deze onderliggende mechanismen precies bekend zijn, heeft het zin om de mogelijkheid van cognitieve training te overwegen. In dit verband is het eveneens relevant dat toekomstig onderzoek zich richt op de vraag in hoeverre bepaalde inhibitiestoornissen gepaard gaan met *subjectieve* problemen ten aanzien van het eigen cognitieve functioneren.

## 8.4 De invloed van demografische en ziekte-gerelateerde variabelen

De studies in dit proefschrift lieten zien dat de prestatie op neuropsychologische en experimenteel psychologische taken niet correleert met leeftijd, geslacht en opleidingsniveau. Dit gold eveneens voor de saccade taken, met uitzondering van de positieve correlatie tussen de antisaccade taak en het opleidingsniveau. Hoger opgeleide patiënten reageerden sneller op deze taak dan lager opgeleiden. Wellicht

is een hoog opleidingsniveau (en dus misschien intelligentie) een beschermende factor voor een slechte prestatie.
Voor wat betreft de saccade taken, was er geen verschil tussen patiënten die poliklinisch werden behandeld en patiënten die waren opgenomen. Daarentegen werd voor sommige experimenteel psychologische en neuropsychologische taken een iets betere prestatie voor gevonden poliklinische patiënten.
Verder was er geen relatie tussen de aanwezigheid van symptomen en de prestatie op inhibitietaken. Dit is echter waarschijnlijk het gevolg van het feit dat de patiënten relatief weinig last hadden van symptomen. De literatuur suggereert namelijk dat het symptoomprofiel een belangrijke determinant is van de prestatie op experimenteel psychologische inhibitietaken. Deze kwestie verdient verder onderzoek (zie paragraaf 8.6).

## 8.5 De invloed van antipsychotica

Het onderzoek in dit proefschrift is gebaseerd op een patiëntenpopulatie die succesvol werd behandeld met antipsychotica. Recente studies hebben aangetoond dat antipsychotica van invloed zijn op cognitie. Daarbij lijken nieuwere typen antipsychotica, de zogenaamde atypische antipsychotica, een gunstiger effect te sorteren dan klassieke antipsychotica. Daarnaast blijkt uit de literatuur dat niet *alle* cognitieve functies gunstig beïnvloed worden door antipsychotica. Bovendien lijken niet alle atypische antipsychotica hetzelfde effect te sorteren.
Hoofdstuk 3 liet zien dat twee atypische antipsychotica, olanzapine en risperidone, geen differentieel effect hebben op bepaalde cognitieve functies (waaronder inhibitie). Een vergelijking met eerdere studies naar het effect van klassieke antipsychotica is consistent met het idee dat atypische antipsychotica een gunstiger effect hebben dan klassieke antipsychotica. Echter, dit moet geverifieerd worden in studies waarin een directe vergelijking wordt gemaakt tussen medicatievrije patiënten en patiënten die respectievelijk atypische en klassieke antipsychotica gebruiken.
Wanneer het effect van antipsychotica op cognitie wordt bestudeerd aan de hand van saccade paradigma's (Hoofdstuk 3), is het van belang uit te sluiten dat de resultaten het gevolg zijn van effecten op het saccademechanisme an sich. Het gaat immers om de effecten op de *cognitieve* processen binnen de saccade paradigma's. Daarom is in dit proefschrift een dierstudie opgenomen waarin gekeken werd naar de invloed van antipsychotica op het saccade mechanisme in het brein. In geanaestheseerde ratten, werd de spontane celactiviteit in de colliculus superior bestudeerd na toediening van acute doseringen van zowel atypische antipsychotica (olanzapine, clozapine en risperidone) als een klassiek antipsychoticum (haloperidol). Omdat de colliculus superior een cruciale rol speelt in het saccademechanisme, werd verondersteld dat eventuele effecten van antipsychotica meetbaar moesten zijn in dit hersengebied. De

resultaten van deze studie lieten zien dat alleen clozapine een klein, maar significant effect had op de vuurfrequentie (afname). Deze bevinding bevestigt het unieke karakter van clozapine zoals dat reeds eerder werd gesuggereerd in studies die een minimum aan extrapiramidale effecten en superieure therapeutische effecten in therapie-resistente patiënten aantoonden. Over het geheel genomen waren de effecten van antipsychotica op de colliculus superior echter marginaal.
Eerdere studies lieten zien dat antipsychotica van invloed zijn op een structuur met belangrijke afferente projecties naar de colliculus superior, de substantia nigra reticulata. In de huidige studie is het effect via de substantia nigra reticulata wellicht opgeheven door effecten in andere structuren met afferente projecties naar de colliculus superior. De prefrontale cortex lijkt in dit verband een plausibele kandidaat. Toekomstig onderzoek moet echter uitwijzen of dit inderdaad het geval is. Toekomstig onderzoek moet eveneens uitwijzen of chronische toediening van antipsychotica van invloed is op de colliculus superior activiteit. Daarnaast lijkt het relevant om de huidige bevindingen te repliceren in *wakkere* dieren, en dient te worden onderzocht in hoeverre de unieke invloed van clozapine weerspiegeld wordt in de saccadeprestatie van patiënten. Het lijkt niet onlogisch om te speculeren dat een clozapine-geïnduceerde afname in de activiteit van de colliculus superior gepaard gaat met een toestand waarin reflexieve saccades minder makkelijk getriggerd worden. Dit zou kunnen betekenen dat het eenvoudiger wordt om deze saccades te onderdrukken. Clozapine zou dus bij patiënten een verbetering in saccadische inhibitieprocessen kunnen bewerkstelligen.

## 8.6 Zijn inhibitiedefecten *state dependent* of *trait dependent*?

Onderzoekers zijn het niet eens over de *betekenis* van cognitieve stoornissen voor het ziektebeeld schizofrenie. Theoretische verhandelingen uit het verleden veronderstelden dat cognitieve stoornissen secundair zijn aan het ziekteproces. Dit standpunt impliceert dat cognitieve afwijkingen ernstiger worden naarmate de ziekte zich ontwikkelt. In chronisch zieke patiënten zouden derhalve *alle* cognitieve domeinen gestoord moeten zijn, terwijl in eerste-episode patiënten hooguit enkele domeinen afwijkingen laten zien. Recentere studies veronderstellen echter dat cognitieve defecten inherent zijn aan het ziekteproces. Deze visie impliceert dat de afwijkingen reeds in een vroeg stadium van de ziekte aanwezig zijn. Een interessante vraag is dan in hoeverre de cognitieve defecten *state* of *trait dependent* zijn. In geval van *trait dependency*, zouden de stoornissen al waarneembaar moeten zijn voordat de eerste symptomen zich aandienen. Daarnaast zouden ze ook aanwezig moeten zijn in populaties die een risico lopen op het ontwikkelen van schizofrenie (zoals eerstegraads verwanten en personen met schizotypische persoonlijkheidskenmerken). Indien de cognitieve defecten daarentegen *state*

*dependent* zijn, zouden ze alleen gevonden moeten worden in patiënten die op het moment van testen ziekteverschijnselen (symptomen) vertonen.
De hoofdstukken 3, 4 en 5 hebben op dit punt interessante informatie opgeleverd, aangezien deze studies patiënten includeerden die een eerste psychotische episode meemaakten waarvan de acute symptomen grotendeels in remissie waren. De neuropsychologische en saccade taken wezen uit dat inhibitiedefecten reeds in een vroeg stadium van de ziekte aanwezig zijn. Bovendien bleek dat deze defecten onafhankelijk zijn van het symptoombeeld. Deze bevindingen suggereren dat inhibitiedefecten inherent zijn aan het ziektebeeld en dat er mogelijk sprake is van *trait dependency*. Dit is in overeenstemming met de bevindingen van studies in risico-populaties. Sommige van deze studies hebben zelfs gesuggereerd dat de prestatie op de antisaccade taak gezien een *gedragsmarker* is voor de kwetsbaarheid voor schizofrenie. Verder kan uit studies bij chronisch zieke patiënten geconcludeerd worden dat de stoornissen bij deze groep patiënten relatief ernstig zijn in vergelijking tot eerste-episode patiënten. Daarentegen lijken de stoornissen in risicopopulaties minder ernstig. Deze bevindingen suggereren dat inhibitiedefecten, ondanks het feit dat ze *trait dependent* zijn, eveneens verergeren in de loop van het ziekteproces.
De resultaten op de experimenteel psychologische taken (Hoofdstuk 5) suggereerden op ondubbelzinnige wijze dat inhibitiestoornissen bij schizofrenie *state dependent* zijn, aangezien er geen afwijkingen werden gevonden bij eerste-episode patiënten, terwijl de literatuur afwijkingen rapporteert voor chronisch zieke patiënten. Bovendien bleek dat poliklinisch behandelde patiënten op sommige taken beter presteerden dan patiënten die waren opgenomen (en dus ernstiger ziek waren), wat impliceert dat de aanwezigheid van symptomen van invloed is op de inhibitieprestatie. Toekomstig onderzoek bij risico-populaties (eerstegraads verwanten en mensen met schizotypische persoonlijkheidskenmerken), kan op dit punt wellicht meer informatie opleveren. Vooralsnog lijken neuropsychologische, experimenteel psychologische en saccade taken een beroep te doen op verschillende inhibitiemechanismen die ieder op eigen wijze verband houden met de ziekte.

## 8.7 Inhibitiedefecten en pathologie van het brein

Een van de meest intrigerende kwesties aangaande de inhibitieproblemen van schizofreniepatiënten is de interpretatie van deze problemen in termen van hersendisfuncties. In de huidige studies werden de meest robuuste inhibitiedefecten gevonden voor de saccade paradigma's. Daarom werd verondersteld dat via het saccademechanisme belangrijke informatie verkregen kan worden over de pathofysiologie van schizofrenie. Dierstudies en studies in patiënten met hersenlaesies hebben aangetoond dat saccades worden gegenereerd via achtereenvolgens de visuele cortex, de parietale cortex (het parietale blikveld), de frontale cortex (het frontale

blikveld), en de colliculus superior. Indien (reflexieve) saccades onderdrukt moeten worden, komt eveneens de dorsolaterale prefrontale cortex in beeld. Dit gebied is in staat om de activiteit in de colliculus superior te onderdrukken, en kan derhalve de productie van een oogbeweging voorkomen. Alle saccade-afwijkingen die bij schizofreniepatiënten zijn gevonden (een verhoogd aantal express saccades, antisaccade inhibitiefouten, geheugensaccade inhibitiefouten en onnauwkeurigheden in de geheugensaccades) zijn consistent zijn met een functioneel defect in de dorsolaterale prefrontale cortex. Dit gebied wordt eveneens geassocieerd met twee andere taken waarop patiënten forse afwijkingen vertonen, namelijk de Wisconsin Card Sorting Test en (spatiële) werkgeheugen taken. De dorsolaterale prefrontale cortex lijkt dus een belangrijke rol te spelen in de pathofysiologie van schizofrenie.
In overeenstemming met dit idee, wordt in de meerderheid van de studies impliciet of expliciet verondersteld dat er bij schizofrenie sprake is van afwijkingen in de frontale cortex. Om deze veronderstelling te valideren, werd in dit proefschrift onderzocht in hoeverre frontale stoornissen inderdaad bij patiënten aanwezig waren (Hoofdstuk 4). Dit werd gedaan aan de hand van zowel neuropsychologische taken als saccade taken De resultaten op de neuropsychologische testbatterij demonstreerden slechts voor 42% van de patiënten frontale afwijkingen. Dit percentage steeg naar 79% wanneer eveneens saccade taken werden gebruikt. Verder bleek dat op individueel niveau weinig overlap bestond tussen stoornissen op de saccade taken en stoornissen op de neuropsychologische taken. Kennelijk doen beide type taken een beroep op verschillende frontale functies die onafhankelijk van elkaar defect kunnen zijn. Deze bevindingen impliceren dat schizofrenie niet per definitie gepaard gaat met frontale stoornissen. In dit verband is het echter belangrijk om op te merken dat de huidige studie gebaseerd is op een beperkte set van frontale taken en een specifieke patiëntenpopulatie (eerste-episode patiënten met relatief weinig symptomen). Toekomstig onderzoek moet daarom uitwijzen of dezelfde bevindingen worden verkregen wanneer een uitgebreidere set frontaaltaken wordt toegepast bij zowel eerste-episode als chronisch zieke patiënten.
Indien bij schizofrenie inderdaad *verschillende* frontale functies onafhankelijk van elkaar zijn aangedaan, kan verondersteld worden dat naast de dorsolaterale prefrontale cortex, ook andere frontale gebieden (bijvoorbeeld de anterieure cingulate cortex) een rol spelen in de pathofysiologie van de ziekte. Deze mogelijkheid kan worden onderzocht aan de hand van neuroimaging technieken zoals PET en fMRI. Neuroimaging studies moeten uitwijzen in hoeverre de inhibitiedefecten zoals die gevonden werden op respectievelijk de saccade taken en de neuropsychologische taken, gepaard gaan met een abnormale activiteit in verschillende hersengebieden. De bevindingen uit dit proefschrift doen vermoeden dat een hoog percentage antisaccadefouten gepaard gaat met een abnormale (verminderde) activiteit in de dorsolaterale prefrontale cortex, terwijl stoornissen op

de neuropsychologische taken gepaard gaan met een abnormale activiteit in andere (misschien meer diffuse) frontale gebieden. Neuroimaging studies kunnen mogelijk ook verklaren waarom de experimenteel psychologische taken, ondanks hun vermeende specificiteit, geen afwijkingen lieten zien. Daarnaast bieden neuroimaging technieken de mogelijkheid om de hypothetische opdeling van inhibitieprocessen in respectievelijk cognitieve inhibitie, respons inhibitie, en interferentiecontrole te valideren. Taken die behoren tot ieder van deze categorieën zouden een uniek activiteitspatroon moeten genereren. Indien dit inderdaad het geval is, wordt daarmee onderschreven dat termen als *inhibitie* en *inhibitoire functies* te globaal zijn en vervangen dienen te worden door meer specifieke omschrijvingen. De validatie van verschillende inhibitieprocessen op basis van activiteitspatronen in het brein biedt tevens de mogelijkheid om voor ieder type inhibitieproces een directe vergelijking te maken tussen de hersenactiviteit van patiënten en die van gezonde vrijwilligers. Het is bijzonder interessant om te kijken in hoeverre dergelijke neuroimagingdata de gedragsdata uit dit proefschrift zullen ondersteunen.

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# Publications

1. Broerse, A., Crawford, T.J. & den Boer, J.A. (2001). Parsing cognition in schizophrenia using saccadic eye movements: a selective review. *Neuropsychologia*, 39(7), 742-756.
2. Broerse, A. Crawford, T.J., & den Boer, J.A. (2001). Saccade paradigma's en cognitie: een overzicht. *Nederlands Tijdschrift voor Psychiatrie*, 43(4), 233-244.
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5. Broerse, A., Timmerman, W., Westerink, B.H.C. & den Boer, J.A. (2002). Antipsychotics & single cell activity in the rat Superior Colliculus. *Progress in Neuro-Psychiatry and Clinical Neurosciences*, 26, 1-7.
6. Broerse, A., Crawford, T.J. & den Boer, J.A. Differential effects of olanzapine and risperidone on cognition in schizophrenia? A saccadic eye movement study. *Journal of Neuropsychiatry and Clinical Neurosciences*, *(in press)*.
7. Broerse, A., Cornelissen, F.W. & den Boer, J.A. (2000). fMRI of inhibition. *Schizophrenia Research*, 41(1), A249 pp 136.
8. Broerse, A., Holthausen, E.A.E., van den Bosch, R.J. & den Boer, J.A. (2001). Saccadic performance of neuropsychologically normal schizophrenic patients. *Schizophrenia Research*, 49(1-2) Supplement pp 212.
9. Broerse, A. & den Boer, J.A. Inhibition deficits in schizophrenia? A cognitive study. *Journal of Abnormal Psychology, (submitted)*
10. Crawford, T.J., Broerse, A. & den Boer, J.A. (1999). Dopamine and impairment at the executive level. *Behavioral and Brain Sciences*, 22, 678-679.
11. Crawford, T.J. & Broerse, A. (2001). Recent Saccadic eye movement research uncovers patterns of cognitive dysfunction in schizophrenia? *Journal of Advances in Schizophrenia and Brain Research,* 3, 48-52.
12. Nieuwenhuis, S., Broerse, A., Nielen, M.M.A. & de Jong, R. A goal activation approach to the study of executive control: Application to antisaccade tasks? *Cognitive Psychology (submitted)*

# Curriculum Vitae

Annelies Broerse werd op 14 november 1970 geboren te Enschede en groeide op in Rijsenhout. In 1989 slaagde zij voor haar VWO diploma aan het Haarlemmermeerlyceum te Hoofddorp. In september van datzelfde jaar begon zij aan de studie Beweginswetenschappen aan de Vrije Universiteit te Amsterdam, en in 1996 werd het doctoraal diploma in de hoofdrichting Bewegingsagogiek en de nevenrichting Gezondheidkunde behaald. In 1993 begon zij eveneens aan de Vrije Universiteit met de studie Psychologie. Binnen deze studie werd gekozen voor de hoofdrichting Psychonomie, en na een afstudeerstage (Vrije Universiteit) waarin onderzoek werd gedaan naar afwijkingen in het EEG en hartritmevariabiliteit bij migrainepatiënten, behaalde zij in 1997 het doctoraal diploma. Vanaf maart 1997 is zij verbonden aan de afdeling Psychiatrie van de Rijksuniversiteit Groningen, waar zij als Assistent in Opleiding onderzoek verrichtte naar het cognitieve functioneren van patiënten met schizofrenie.