Chapter 3

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

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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. 2002). Estimates of this proportion vary from 19% (Holthausen et al. 2002) 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 (Hager et al. 1998), the Stroop Task (Peterson et al. 1999), the Trail Making Test (Lesnik et al. 1998), and Verbal Fluency (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 these 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 traditional 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 and 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 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 (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 obtained by each of 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 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, Skalar Medical, B.V.), and head movements were restrained by an adjustable headrest. Visual stimuli, small green squares of approximately 3 mm, were presented against the 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, this inhibition was relatively easy when compared to the antisaccade task, since the fixation point remained on during stimulus presentation, which facilitates the engagement of attention.

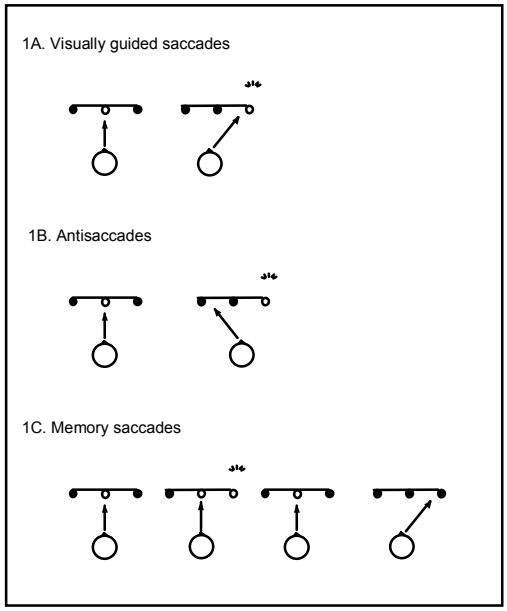

Figure 1. Saccadic paradigms
1A: A visual stimulus is presented in a random sequence to the left or right of a central fixation point and subjects are instructed to respond with a rapid and accurate eye movement
1B: Antisaccades are directed towards a spatial position in the opposite visual filed tot that of the stimulus. The paradigm requires suppression of the refexive 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

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).
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 Presence of 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.

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.

3.2 NP test performance of 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, or 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 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.

3.3 Saccadic performance of the FI, FN and control group.

The FI, FN and the control groups differed significantly for 3 of the 7 saccadic measures (Table 3): 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.

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

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 4. Presence of deficits on frontal saccadic and frontal NP measures in patients.

		Frontal *saccadic* performance**	
		normal	*impaired*
Frontal *NP* performance*	*normal*	5	9
	Impaired	3	7

* performance on CPT *d'*, Stroop interference, TMT interference, and Verbal Fluency.

** performance on antisaccade inhibition errors, memory saccade inhibition errors, and memory saccade delay errors.

3.5 Frontal saccadic measures, frontal NP measures, psychomotor speed and memory.

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 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<.00**

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 in 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, the performance of the three groups revealed a pattern similar to that of the NP tasks. 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 a larger number of cognitive processes, which provides the opportunity to compensate for problems in one task process by investing more effort in others. In combination with its slower pace, this makes the memory task is a better comparison to the NP tasks.

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 poor 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 deficit 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 respectively 79%, 67% and 67% of the 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 association 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 is 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 these areas have also been found to be active 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 two putative frontal NP measures, namely Stroop interference and TMT 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 saccade was 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 deficits in specific cognitive domains.

The use of traditional NP measures in combination with saccadic tasks appeared to increase the sensitivity to detect frontal impairment. In particular the antisaccade task appeared able to reveal frontal deficits. Frontal saccadic measures were, however, only marginally associated with frontal NP measures.

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