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Antisaccade performance in Korsakoff patients reveals deficits in oculomotor inhibition

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Oculomotor inhibition reflects the ability to suppress an unwanted eye movement. The goal of the present study was to assess oculomotor inhibition in patients with Korsakoff's syndrome (KS). To this end, an antisaccade task was employed in which an eye movement towards an onset stimulus has to be inhibited, and a voluntary saccade has to be executed in the opposite direction. Compared to the results of a matched control group, patients showed a higher percentage of intrusive saccades, made more antisaccade errors, and showed longer latencies on prosaccade trials. These results clearly show that oculomotor inhibition is impaired in KS. Part of these deficits in oculomotor inhibition may be explained by neuronal atrophy in the frontal areas, which is generally associated with KS.

Keywords: Korsakoff syndrome; Oculomotor inhibition; Antisaccade task.

Korsakoff's syndrome (KS) is a chronic disorder often caused by long-term excessive alcohol abuse in combination with thiamine deficiency (vitamin B_1). This disorder is characterized by severe anterograde and to a lesser extent retrograde amnesia for declarative knowledge (Fujiwara, Brand, Borsutzky, Steingass, & Markowitsch, 2008; Kopelman, 2002). Besides problems with episodic memory, deficits in executive functions have also been reported to be impaired in KS (Brand et al., 2005; Jacobsen, Acker, & Lishman, 1990). However, there is ample evidence for spared implicit memory in a variety of tasks, like implicit contextual learning (Oudman, Van der Stigchel, Wester, Kessels, & Postma, 2011), perceptual priming (d'Ywalle & Van Damme, 2007), and procedural learning (Fama, Pfefferbaum, & Sullivan, 2006).

One area that has received almost no consideration in KS is the oculomotor domain. Although fundamental oculomotor problems like nystagmus are characteristic for the acute phase generally preceding the onset of KS (Wernicke's encephalopathy; Victor, Adams, & Collins, 1971), it remains largely unknown whether any deficits in oculomotor functioning are present in the chronic phase following Wernicke's encephalopathy. It is generally assumed that following the administration of thiamine and the restoration of a nutritionally adequate diet, the confusional state associated with Wernicke's encephalopathy disappears, and the ophthalmoplegia recovers (Victor et al., 1971). To our knowledge, however, there has been only one study on oculomotor functioning in the chronic phase of KS (Kenyon, Becker, Butters, & Hermann, 1984). Results of this study showed that saccade latencies were increased, saccadic peak velocities were reduced, and saccade durations were increased compared to a control participant. Furthermore, an increased number of saccadic intrusions (i.e., unintended saccades while following a moving

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target) were recorded in two of the three tested patients.

The aim of the present study was to assess oculomotor functioning in the chronic phase of KS. As eye movements are crucial for successful navigation in our busy daily environment, this study provides a first indication of the ability of patients with KS to explore their world using eye movements. In particular, we were interested whether oculomotor inhibition—that is, the capacity to suppress an unwanted eye movement—is affected in KS. To this end, we used the antisaccade task (for a review, see Everling & Fischer, 1998; Munoz & Everling, 2004), in which participants are presented with an abrupt appearance of a visual stimulus in the periphery ("onset"), after which they have to execute an eye movement either towards the onset location ("prosaccade") or away from the onset location to its mirror opposite position ("antisaccade"). In antisaccade trials, the eye movement that is automatically evoked by the presence of the onset has to be inhibited, whereas an eye movement has to be executed to the mirror location of the onset. Because the eye movement to the mirror location of the onset has to be executed to an empty location and is fully based on task instructions, this is considered a top-down (or "voluntary") eye movement. A failure of oculomotor inhibition will then result in the execution of an erroneous eye movement toward the onset. Results in the antisaccade task with healthy individuals typically show that antisaccade trials have longer saccade latencies than prosaccade trials, and erroneous saccades to the stimulus onset in antisaccade trials are frequently made (typically around 20% of the trials; Everling & Fischer, 1998; Hutton & Ettinger, 2006; Nijboer, Vree, Dijkerman, & Van der Stigchel, 2010; Van der Stigchel, Imants, & Ridderinkhof, 2011).

The antisaccade task is a good index of oculomotor inhibition and the ability to generate a voluntary saccade. Various lines of research have revealed that these capacities are subserved by frontal brain areas that are also known to be involved in cognitive control. For instance, imaging studies have identified several frontal areas that are active during the antisaccade task such as the frontal eye fields, supplementary eye fields, and dorsolateral prefrontal cortex (Funahashi, Bruce, & Goldman-Rakic, 1993; Munoz & Everling, 2004). Lesion studies have revealed that successful inhibition in the antisaccade task relies heavily on frontal circuits, as patients with frontal lesions execute more erroneous eye movements towards a contralesional stimulus onset (Guitton, Buchtel, & Douglas, 1985; Pierrot-Deseilligny et al., 2003; Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991; Van der Stigchel, van Koningsbruggen, Nijboer, List, & Rafal, 2012). An elevated amount of directional eye movement errors in the antisaccade task is therefore generally linked to deficits associated with the frontal cortex (Everling & Munoz, 2000; Funahashi et al., 1993).

Pathological and radiological studies on KS patients have shown neuronal atrophy over the entire brain and in particular in the frontal lobes (Moselhy, Georgiou, & Kahn, 2001; Pfefferbaum, Sullivan, Mathalon, & Lim, 1997). Although considerable regeneration can occur (Mann & Widmann, 1995), imaging studies have revealed that perfusion loss in the orbitofrontal cortex and cingulate gyrus are persistent (Goldstein, Volkow, Wang, Fowler, & Rajaram, 2001; Volkow et al., 1997), which is in line with the results of autopsy studies (Harper, Kril, & Holloway, 1985). Therefore, given the role of frontal areas in the antisaccade task and the assumed frontal damage in KS, impaired performance on the antisaccade task (i.e., more antisaccade errors) is expected in KS patients than in a control group.

Besides directional errors, the antisaccade task provides additional measures of oculomotor inhibition that can be quantified. Before the onset is presented, the participant is required to remain fixated on the central cross. The central fixation cross indicates whether a pro- or an antisaccade is required in the present trial. Furthermore, an empty screen is presented for 250 ms between the disappearance of the fixation cross and the presentation of the target ("gap period"). A failure of oculomotor inhibition in these intervals results in the execution of an unwanted eye movement (Rommelse, Van der Stigchel, & Sergeant, 2008). In the present study, a distinction is made between "intrusive saccades" (inappropriate eye movements during the fixation period) and "anticipatory saccades" (inappropriate eye movements during the gap period in anticipation of the presentation of the onset).

It has to be noted that the unwanted eye movements during the fixation interval and antisaccade errors reflect different aspects of oculomotor inhibition. On the one hand, saccades during the fixation interval constitute of unwanted eye movement in an interval in which fixation has to be maintained. In this situation, no peripheral information is presented, and the fixation cross is the sole element present on the screen. Unwanted eye movements in this interval therefore reflect a failure of the fixation mechanism. On the other hand, antisaccade errors are observed in the situation in which a peripheral stimulus is presented, and an eye movement has to be executed in the opposite direction of the onset

stimulus. Because of the abrupt presentation of the onset, an eye movement programme to the location of the stimulus is automatically evoked. Therefore, in contrast to unwanted eye movements during the fixation interval, an unwanted eye movement in this situation is related to the failure to inhibit an actual eye movement programme evoked by a peripheral stimulus.

If deficits in oculomotor inhibition are present in KS patients, these deficits will be observed in more antisaccade (i.e., directional) errors, more intrusive saccades, or more anticipatory saccades.

Method

Participants

Thirteen KS patients participated in this study. They were all inpatients of the Korsakoff clinic of the psychiatric hospital "Vincent van Gogh", Venray, The Netherlands.

Premorbid IQ was estimated with the Dutch Adult Reading Test (Schmand, Lindeboom, & van Jarskamp, 1992), which is the Dutch version of the National Adult Reading Test (Christensen, Hazdi-Pavlovic, & Jacomb, 1991; McGurn et al., 2004). This test assesses pronunciation of words that do not follow regular grapheme–phoneme and stress rules. The score on the test is a predictor of premorbid intelligence of brain-damaged patients. This is a so-called "hold test" as pronunciation is thought to be spared, or "held", following neurological injury or decline. Moreover, performance on this test is known to be independent of verbal memory capacity. For instance, this test has been used to assess premorbid IQ in dementia in which verbal memory is known to be impaired (Christensen et al., 1991; McGurn et al., 2004).

Patients were selected such that all included patients had an estimated IQ score above 80, as a low intellectual functioning would interfere with the testing procedure. Moreover, low IQ could be related to alcohol dementia. Thirteen age-, premorbid-IQ-, and education-matched controls were included. Controls were selected such that all included control participants had an estimated IQ score between 80 and 115 (the highest IQ in the KS group). After applying the exclusion criteria explained in detail below, 11 patients (8 male) and 11 controls (4 male) were included in the analyses.

All patients fulfilled the *DSM–IV–TR* (*Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition;* American Psychiatric Association, 2000) criteria for alcohol-induced persisting amnestic disorder and the criteria for KS described by Kopelman (2002). The amnestic syndrome was confirmed by extensive neuropsychological testing. For all 11 patients assessed with the Rivermead Behavioural Memory Task (RBMT), a moderate to serious disturbance on daily memory was found (see Wilson, Cockburn, & Baddeley, 1985, Table 2). Patients were also administered the Dutch version of the California Verbal Learning Task, which measures immediate and long-term verbal memory. Except for one, all patients scored below the 15th percentile on the total number of List A words recalled in Trials 1–5 (standardized for age and gender), confirming severe verbal memory deficits. Working memory capacity was assessed using the working memory index of the Wechsler Adult Intelligence Scale (WAIS–WM; Kaufman & Lichtenberger, 2006). As can be seen in Table 1, the range of working memory capacity was broad, with 5 KS patients scoring average or above average (>28th percentile), while 6 KS patients scored below average (Uterwijk, 2000). These results are in line with the idea that working memory deficits are not consistently observed in all KS patients (Baddeley & Warrington, 1970).

All patients were in the chronic, amnestic stage of the syndrome; none of the patients was in the confusional Wernicke psychosis at the moment of testing (see Table 1). Patients had an extensive history of alcoholism and nutritional depletion, notably thiamine deficiency, verified through medical charts or family reports.

For both the patients and the control group, education level was assessed using seven categories, 1 being the lowest (less than primary school) and 7 being the highest (academic degree; Verhage, 1964). Of the KS patients, 45% only finished primary school, whereas 18% of the KS group and 82% of the control group finished secondary school. A total of 36% of the KS patients and 18% of the control group finished high school. None of the participants had an academic degree. See Table 2 for a summary of the demographic and test results. A structured interview revealed that none of the control participants had a history of psychiatric and/or neurological disorder, and/or substance abuse.

The study was approved by the local ethics committee, and informed consent was obtained from each participant.

Apparatus

Participants were tested individually in a dimly lit room and were seated in front of a computer monitor from a distance of approximately 57 cm.

TABLE 1
Demographic variables and neuropsychological test results of the Korsakoff's patients

Patient	*Age (years)*	*Education*[a]	*IQ*[b]	*Time after onset*[c]	*RBMT*[d]	*WAIS–WM*[e]	*Verbal learning*[f]
1	55	6	105	1	13	9	15–50
2	68	6	112	2	1	5	5–15
3	49	2	82	6	20	2	5–15
4	62	2	97	1	6	18	<1
5	47	4	101	1	6	82	<5
6	46	6	105	1	13	37	<1
7	67	2	102	3	8	25	15
8	69	6	102	5	10	37	15
9	52	2	86	2	7	32	5–15
10	43	4	82	3	11	5	5–15
11	58	2	115	7	8	58	<1

Note. [a]Education level was assessed in 7 categories: 1, primary school, to 7, academic degree (Verhage, 1964). [b]IQ was estimated with the Dutch Adult Reading Test (Schmand et al., 1992). [c]The number of months between onset of Korsakoff's syndrome (KS) and time of testing. [d]Raw scores on RBMT (Rivermead Behavioural Memory Task): memory test for everyday memory: <10, severely impaired; 10–15, moderately impaired; 16–21, mildly impaired (Van Balen & Wimmers, 1992). [e]Percentile scores for the working memory index of the Wechsler Adult Intelligence Scale (WAIS; Uterwijk, 2000). [f]Percentile scores for the total performance on the first five learning trials, measured with the Dutch version of the California Verbal Learning Task, for measurement of long-term memory (Mulder, Dekker, & Dekker, 1996).

TABLE 2
Summary of demographic variables for all participants

Measurement	*Patients*	*Controls*	*Significance*
Age μ (*SD*)[a]	56.0 (9.43)	50.6 (6.92)	$t(20) = 1.52$, $p = .14$
Education level μ (*SD*)[b]	3.8 (1.89)	5.0 (0.63)	$U(20) = 42.0$, $p = .22$
IQ estimated mean (*SD*)[c]	99.0 (11.27)	105.1 (7.65)	$t(20) = -1.48$, $p = .15$

Note. [a]In years. Age range patients: 43–69 years; age range controls: 46–65 years. [b]Education level was assessed in 7 categories: 1, primary school, to 7, academic degree (Verhage, 1964). [c]IQ was estimated with the Dutch Adult Reading Test (Schmand et al., 1992).

The eye movements (and corresponding data) were measured with the aid of an eye tracker (Eyelink 1000 system; SR Research Ltd., Mississauga, Ontario, Canada), an infrared video-based eye tracker that has a 1,000-Hz temporal resolution and a spatial resolution of 0.01°. The Eyelink 1000 remote system corrects for head movements by measuring the distance between the camera and a small target sticker placed on the participant's forehead. The left eye was monitored.

Stimuli and procedure

Participants viewed a coloured fixation cross (1.0° × 1.0°) on a black background in the centre of the display, which was used as fixation point. The fixation cross was removed after an interval of 1,000 ms, after which a blank screen was presented for 250 ms ("gap period"). After the gap period, the onset (a grey circle with a diameter of 2.0°) appeared at a distance of 10.5° to the right or to the left of the central fixation cross. The participants were instructed to make a prosaccade or an antisaccade, depending on the colour of the fixation cross. In the antisaccade trials, the fixation cross was red, and the participant was expected to make an eye movement to the mirrored position of the onset. In the prosaccade trials, the fixation-cross was green, and the participant was expected to make an eye movement to the onset. The onset was presented for 2,000 ms. The different conditions are presented in Figure 1.

Each session started with a nine-point grid calibration procedure. In addition, simultaneously fixating the central fixation point and pressing the space bar checked the drift of the eye position at the start of each trial. The task consisted of 20 practice trials and 160 experimental trials. Antisaccade and prosaccade trials were randomly mixed.

After every 20 experimental trials, the task instructions, written in white, were repeated against a black background ("GREEN = GO, RED = AWAY FROM IT"). Given the known memory deficits in KS patients, the task instructions were frequently repeated to ensure that the instructions were remembered by the participant. Moreover, when the task instructions were presented on the screen, the experimenter frequently asked the participant whether the task instructions were still clear. If not, the task instructions were repeated by the experimenter.

Analyses

Intrusive saccades. These were defined as trials in which an eye movement larger than 4° was made

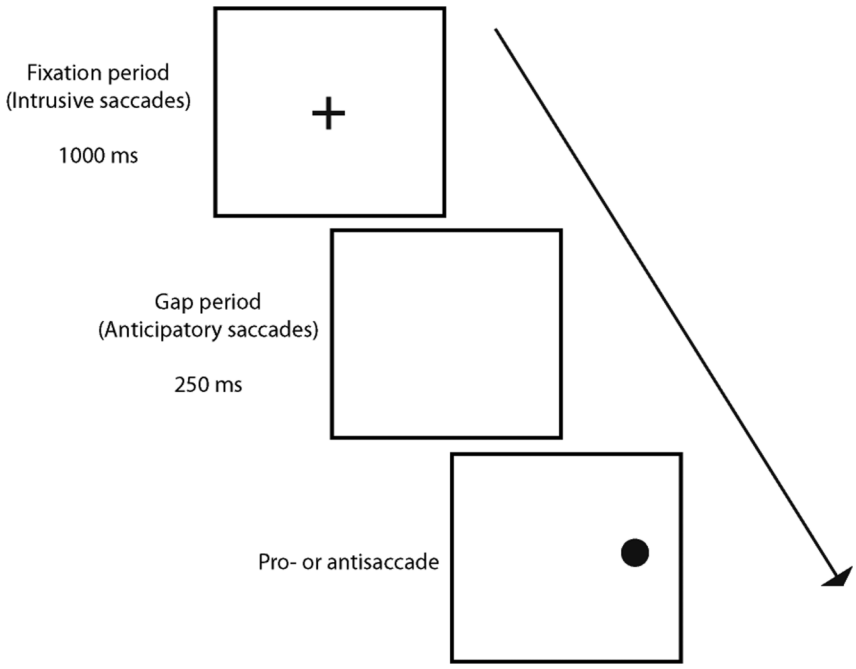

Figure 1. Sequence of the trials in the experiment. The colour of the fixation cross determined whether a pro- or an antisaccade had to be performed. When an eye movement was made in the fixation period, it was classified as an intrusive saccade. When an eye movement was made in the gap period, it was classified as an anticipatory saccade.

during the fixation period (the first 1,000 ms), irrespective of the direction of the saccade. For this measure, trials were included irrespective of performance on the antisaccade task.

Anticipatory saccades. These were defined as trials in which a saccade larger than 4° was made in the gap period, irrespective of the direction of the saccade (see Figure 1). In this interval, no stimulus is presented. A saccade in this period can therefore be seen as a prepotent (i.e., anticipatory) saccade to a location where the participant expects that he or she has to execute an eye movement towards (depending on the task). Also for this measure, trials were included irrespective of performance on the antisaccade task.

Antisaccade performance. Anti- or prosaccade latency was defined as the interval between the presentation of the onset and the initiation of a saccade. Trials were excluded when saccade latency was lower than 80 ms or higher than 1,000 ms. Trials in which no saccades were made or in which all saccades were too small (<2°) were excluded as well. These inclusion criteria are similar to those applied in studies on antisaccade performance in frontal lesion patients (e.g., Van der Stigchel et al., 2012).

When starting the analyses, it became clear that some patients were quite poor in keeping fixation before the onset was presented (>20% anticipatory and intrusive saccades in the KS group). Therefore, the chosen inclusion criteria with respect to start and endpoint of the saccade had to be more liberal than in, for instance, antisaccade studies in frontal lesion patients in order to include enough trials for a solid analysis (e.g., Van der Stigchel et al., 2012). For both anti- and prosaccades, the first saccade after the presentation of the onset needed to be initiated from a distance of 5.25° from the centre of the display (half the distance between the centre of the display and the onset location), irrespective of the location of the onset in the display. Furthermore, the endpoint of the first saccade after the presentation of the onset had to have an angular deviation of less than 90° from the centre of the onset (for prosaccades) or the mirrored onset location (for antisaccades).

Participants were excluded from all analyses if fewer than 30 trials could be included in the analyses of either antisaccade or prosaccade trials. This led to the exclusion of one KS patient and one control participant. Furthermore, participants were excluded from all analyses if the rate of antisaccade errors was higher than 90%. This led to the exclusion of one KS patient and one control participant.

Differences in intrusive saccades between the two groups were analysed using a paired-sample independent *t* test. Because the task

instruction was known during the interval in which anticipatory saccades could be made, we analysed the influence of the task (antisaccade vs. prosaccade trials) for anticipatory saccades. For each dependent variable (anticipatory saccades, errors, and saccade latencies), a separate analysis of variance (ANOVA) was performed with task (antisaccade trials vs. prosaccade trials) as within-subject factor and group (KS vs. control) as between-subject factor. Saccade latencies were only analysed for correctly performed pro- and antisaccades.

Results

All means and standard deviations for the different measures are presented in Table 3.

Intrusive saccades

A paired-sample independent t test revealed that the percentage intrusive saccades was significantly higher in the KS group than in the control group, $t(20) = 2.56$, $p < .02$ (see Figure 2).

TABLE 3
Means and standard deviations for intrusive and anticipatory saccades, saccade errors, and saccade latencies for the KS and control groups

	Patients		*Controls*	
Variable	*Prosaccade*	*Antisaccade*	*Prosaccade*	*Antisaccade*
Intrusive saccades (%)	14.2 (14.6)		2.7 (2.9)	
Anticipatory saccades (%)	2.0 (1.6)	2.8 (2.7)	1.1 (1.3)	1.3 (2.0)
Saccade errors (%)	2.5 (2.8)	33.1 (21.1)	2.2 (2.5)	14.4 (0.8)
Saccade latencies (ms)	211.8 (41.7)	224.4 (58.9)	178.8 (38.5)	220.2 (48.1)

Note. KS = Korsakoff's syndrome. Standard deviations in parentheses.

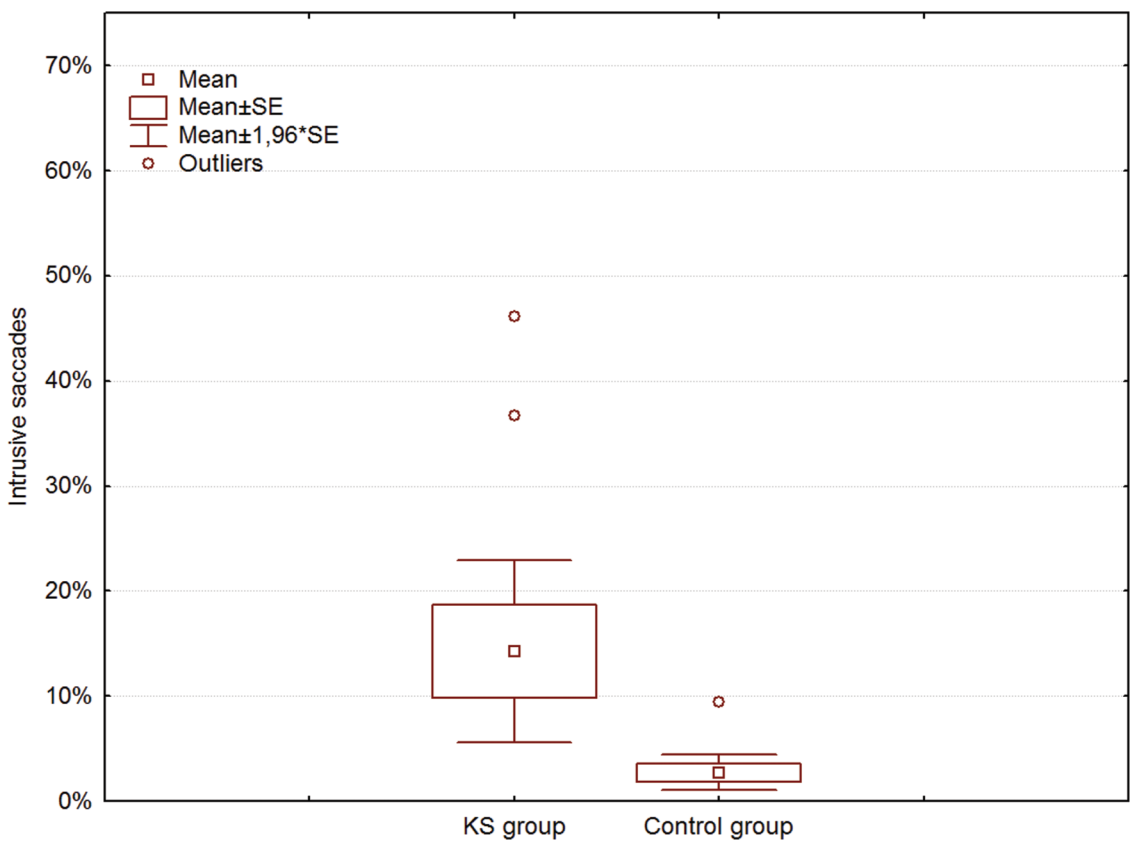

Figure 2. Box plot for the percentage of intrusive saccades. The percentage of intrusive saccades was higher in the KS (Korsakoff's syndrome) group than in the control group. The box plot furthermore shows a higher variability in the KS group than in the control group. To view a colour version of this figure, please see the online issue of the Journal.

Anticipatory saccades

No main effect of group, $F(1, 20) = 2.66$, $p = .12$, or task, $F(1, 20) = 1.52$, $p = .23$, was observed. The interaction between group and task was also not significant ($F < 1$).

Antisaccade performance

The exclusion criteria explained above led to an exclusion of 17.9% of the trials in the patient group and 6.5% of the trials in the control group. The majority of these trials were excluded because the saccade was not initiated from a location near the centre of the screen.

The analyses on the saccade errors were performed on the remaining trials. For this measure, a main effect of group was observed, $F(1, 20) = 7.47$, $p < .02$. The patient group made more errors than the control group. Furthermore, a main effect of task, $F(1, 20) = 38.93$, $p < .0001$, revealed that more errors were made on antisaccade trials than on prosaccade trials.

The significant interaction between group and task, $F(1, 20) = 7.29$, $p < .02$, can be explained by the finding that the difference between the groups was only observed for antisaccade trials, $t(20) = 2.75$, $p < .02$, and not for prosaccade trials ($t < 1$). See Figure 3.

Interestingly, although the inclusion criteria were chosen quite liberal, the analyses still revealed a clear difference in antisaccade performance between the two groups. These criteria were necessary because of the poor fixation in the patient group. Although choosing liberal inclusion criteria introduces noise to the data, the effect was apparently quite robust.

When analysing saccade latencies in the pro- and antisaccade task, one patient was excluded because he executed fewer than 10 correct antisaccades (all other participants had more than 15 correct antisaccades). No main effect of group was observed ($F < 1$). A main effect of task was observed, $F(1, 19) = 19.27$, $p < .001$, indicating that saccade latencies in the antisaccade trials were longer than latencies in the prosaccade trials. Furthermore, a

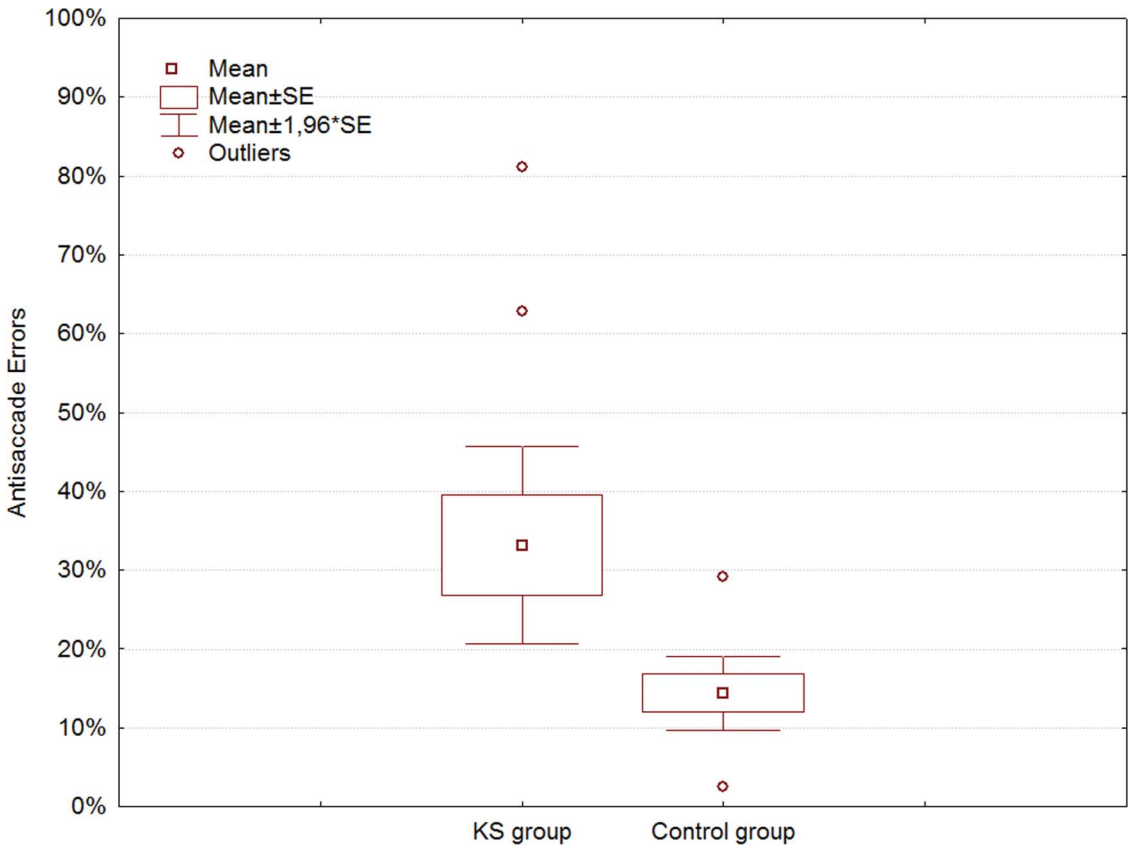

Figure 3. Box plot for the percentage of antisaccade errors. The percentage of antisaccade errors was higher in the KS (Korsakoff's syndrome) group than in the control group. The box plot furthermore shows a higher variability in the KS group than in the control group. For both the KS group and the control group, there was one participant who was an outlier for both the percentage of intrusive saccades and the percentage of antisaccade errors. To view a colour version of this figure, please see the online issue of the Journal.

significant interaction between task and group was observed, $F(1, 19) = 5.44$, $p < .05$. This interaction can be explained by the finding that saccade latencies of the patient group were longer than those of the control group on prosaccade trials—albeit at a trend level; $t(19) = 1.88$, $p = .08$—but not on antisaccade trials ($t < 1$).

Correlations between test results

As described, we observed two important deficits in the patient group: more intrusive saccades and more antisaccade errors. To further investigate the nature of these deficits, we performed additional correlations on the various test results for the patient group. Both these measures did not correlate with IQ, working memory capacity as indexed by the WAIS, verbal immediate and long-term memory as indexed by the California Verbal Learning Task, and daily memory capacity as indexed by the RBMT (ps $> .20$).

We also investigated whether the time after the onset of KS correlated with our measures (intrusive saccades, antisaccade errors, prosaccade latency). These correlations were not significant (ps > 33). It has to be noted that the relatively small sample size is likely to contribute to the lack of significant correlations.

Discussion

The aim of the current study was to assess the ability to suppress an unwanted eye movement (i.e., oculomotor inhibition) in KS. Compared to the results of the matched control group, KS patients showed a higher percentage of intrusive saccades during the fixation period and made more antisaccade errors. These errors reflect different aspects of oculomotor inhibition: Intrusive saccades are constituted of unwanted eye movement in an interval in which fixation has to be maintained (a failure of the fixation mechanism), whereas antisaccade errors are related to the failure to inhibit an actual eye movement programme evoked by a peripheral stimulus. These results clearly show that oculomotor inhibition is impaired at multiple levels in KS. No correlations of aspects of oculomotor inhibition with IQ, working memory, daily memory, and verbal immediate and long-term memory were observed, but this might be explained by the relatively small sample ($n = 11$).

Results showed no difference between the patient and the control group for the percentage of anticipatory saccades during the gap period. Although this type of error has been linked to failures in oculomotor inhibition (Mostofsky, Lasker, Cutting, Denckla, & Zee, 2001; Rommelse, Van der Stigchel, Witlox, et al., 2008), these findings have been observed in a different task from the one current employed—namely, the memory-guided saccade task. In this task, the participant is not allowed to make a saccade towards the target but has to remember the location of the target. After a certain delay, the participant then has to execute a saccade to the memorized location. In this task, the interval is longer than the interval in the present study (250 ms vs. 3,000 ms; e.g., Rommelse, Van der Stigchel, Witlox, et al., 2008). It is therefore possible that the use of a longer interval might have resulted in a difference between the patient and the control group.

One might argue that the higher number of antisaccade errors and intrusive saccades are due to memory deficits in KS. We consider this unlikely for two reasons. First, directional errors were exclusive to the antisaccade condition. A general failure to remember the task instruction would have resulted in more directional errors in both the pro- and the antisaccade conditions. Second, we frequently repeated the task instruction during the experiment to make sure the task instructions were present in working memory. In half of the patients, no deficits in working memory were present, in line with the idea that working memory deficits are not observed in all KS patients (Baddeley & Warrington, 1970). Therefore, we argue that the observed deficits in oculomotor behaviour are independent of the memory deficits in KS.

The results also showed that saccade latencies were increased in the patient group compared to the control group. This result is in line with the one other study on oculomotor functioning in KS in which the three tested KS patients showed longer latencies while tracking a moving stimulus (Kenyon et al., 1984). Interestingly, the longer latencies in the current study were only observed in prosaccade trials, and not in antisaccade trials. This seems to indicate that the slowing in saccade initiation in KS is only observed for the more reflex-like prosaccades and not for the more voluntary antisaccades. This dissociation between eye movements with a more reflexive and more voluntary component might be a residual effect of the fundamental oculomotor problems associated with the confusional Wernicke psychosis, which might only be observed for the more reflexive prosaccades (all patients were tested within seven months after the onset of KS). To investigate whether the prolonged prosaccades were driving the error patterns in antisaccades, we performed a correlation for the KS group between prosaccade latencies and

antisaccade errors. This correlation was not significant ($r = -.37$, $p > .05$). Although speculative, this seems to indicate that these deficits can be disentangled.

As mentioned in the introduction, an elevated number of antisaccade errors have been linked to deficits in frontal areas (Guitton et al., 1985; Pierrot-Deseilligny et al., 2003; Pierrot-Deseilligny et al., 1991; Van der Stigchel et al., 2012). Various frontal areas, like the dorsolateral prefrontal cortex and the frontal eye fields, project to the superior colliculus, a motor map in the midbrain in which the competition between possible saccade goals is assumed to be resolved (Munoz, 2002). These areas are responsible for lowering the activity evoked by the onset stimulus in the motor map of the superior colliculus, while activating the location of the motor map towards which the saccade has to be executed. Any failure in this process will result in an antisaccade error. Antisaccade errors in the patient group were also elevated when compared to those in previous studies on healthy individuals (33% errors in the current study and around 20% in previous studies; Everling & Fischer, 1998; Hutton & Ettinger, 2006; Nijboer et al., 2010; Van der Stigchel et al., 2011). Although the lesion profile of KS involves the entire cortex (Moselhy et al., 2001), we hypothesize on the basis of the knowledge about the neural basis of this aspect of oculomotor inhibition that the increased antisaccade errors can be explained by the neuronal atrophy in the frontal areas that are generally associated with KS (Moselhy et al., 2001; Pfefferbaum et al., 1997).

Finding no correlation between antisaccade errors and working memory capacity might be considered inconsistent with the idea that successful performance in the antisaccade task is subserved by frontal areas. As noted, however, oculomotor inhibition has been associated with various areas in the frontal cortex, like the dorsolateral prefrontal cortex (Pierrot-Deseilligny et al., 1991), the frontal eye fields (Van der Stigchel et al., 2012), and the ventrolateral frontal cortex (Walker, Husain, Hodgons, Harrison, & Kennard, 1998). This indicates that various aspects of oculomotor inhibition may be distributed throughout the frontal cortex (Hodgon et al., 2007). The areas responsible for the observed deficits in oculomotor inhibition might therefore be different from the areas involved in working memory.

With respect to the inability to remain fixated during the fixation period, the superior colliculus might play an important role in this deficit. To maintain fixation, the superior colliculus contains fixation neurons that fire during fixations but cease firing just before and during saccades (Munoz & Wurtz, 1993). Compared to the knowledge about the neural regions modulating directional antisaccade errors, less is known about the cortical areas that project to the superior colliculus and modulate oculomotor control during the fixation period. Interestingly, one of the frontal areas that have been proposed to modulate the fixation neurons in the superior colliculus is the dorsolateral prefrontal cortex (Meeter, Van der Stigchel, & Theeuwes, 2010). Indeed, the dorsolateral prefrontal cortex projects densely to the intermediate and deep layers of the superior colliculus (Johnson & Everling, 2006). It has to be noted, however, that no correlation was observed between the antisaccade errors and intrusive saccades in the current study. Although speculative, this might indicate that these errors reflect two separate processes. Given that KS patients show neural damage in both cortical and subcortical areas (Reed et al., 2003), it is therefore difficult to pinpoint specific regions that might be responsible for the increased percentage of intrusive saccades observed in the current task.

Eye movements are one of the most thoroughly studied domains in the field of cognitive neuroscience. Numerous ingenious paradigms have been developed to unravel their underlying neurological and cognitive substrates. This, in turn, has prompted researchers to assess eye movements in various psychiatric disorders and has facilitated the understanding of the complex underlying neuropathophysiology of these disorders (Rommelse, Van der Stigchel, & Sergeant, 2008). In particular, the antisaccade task has been commonly used in various psychiatric disorders and is frequently proposed as a diagnosis tool in this domain (Everling & Fischer, 1998; Hutton & Ettinger, 2006). The present study provides a first insight in the oculomotor functioning of KS patients in an antisaccade task.

Although the study included only a limited number of patients, and the criteria for trial inclusion were quite liberal in order to include a sufficient number of trials, it provides the first clear evidence that oculomotor inhibition is impaired in KS patients. Although the memory deficits are the primary deficits in the chronic phase of KS, and oculomotor deficits are not present on first sight, the current experimental evidence suggests that failures in oculomotor functioning constitute a secondary area in which KS patients are impaired. Eye movements are crucial for successful navigation in our daily busy environment, and future studies could correlate the present measures to the functioning of these patients in daily life in order to quantify the value of these measures in the treatment and diagnosis of KS.

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