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The antisaccade: a review of basic research and clinical studies

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Abstract—The ability to suppress reflexive responses in favor of voluntary motor acts is crucial for everyday life. Both abilities can be tested with an oculomotor task, the antisaccade task. This task requires subjects to suppress a reflexive prosaccade to a flashed visual stimulus and instead to generate a voluntary saccade to the opposite side. This article reviews what is currently known about the neural structures and processes which are involved in the performance of this task. Current data show that a variety of brain lesions, neurological diseases and psychiatric disorders result in errors, i.e. prosaccades towards the stimulus, in this task. Brain imaging studies have shown that a widely distributed cortical and subcortical network is active during the generation of antisaccades. These findings are discussed and the potential of the antisaccade task for diagnostic purposes is evaluated. © 1998 Elsevier Science Ltd. All rights reserved.

Key Words: antisaccades; saccades; eye movements; fixation.

Introduction

The analysis of eye movements has long been used as an important diagnostic tool in neurology. While optokinetic and vestibular nystagmus are widely accepted and used in the diagnosis of cerebellar and brain stem disorders, the analysis of saccadic eye movements is usually neglected. This may be partially related to the failure of early studies to detect differences in the *generation* of visually-guided saccades in neurological and psychiatric patients [23]. Only recently it has become clearer that a variety of neurological and psychiatric disorders are associated with an inability to *inhibit* saccades. The ability to suppress reflexive responses and to generate voluntary motor commands is crucial for everyday life, because it frees the organism from a stimulus-driven behavior in favor of the achievement of internal goals. It is possible to examine both abilities in one oculomotor task by presenting a visual stimulus at one side and asking the subject to look to the opposite side. A deficit in the inhibition of reflexive responses will result in a high number of saccades towards the visual stimulus (prosaccades), whereas a deficit in the generation of voluntary movements will result in a low number of saccades to the opposite side (antisaccades). This task was introduced by Peter Hallett in 1978 as a "novel task" and is now called the *antisaccade task* [57].

In the last 10 years, a large number of clinical studies have been conducted, ranging from studies with patients with discrete lesions to those with psychiatric disorders. Functional imaging techniques have been applied to discover the brain areas involved in the generation of antisaccades. Basic research has characterized the properties of antisaccades and the conditions which lead to errors in this task. Recent studies in non-human primates have started to investigate the neural processes associated with the generation of antisaccades and the suppression of reflexive saccades at the level of single neurons [116].

The findings obtained so far, suggest that the antisaccade task can—with certain restrictions—be applied as a diagnostic tool for diseases affecting cortical and/or subcortical structures. This article attempts to critically summarize the results of these studies and to characterize the neural subprocesses which underlie the control of antisaccades.

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The antisaccade task

Figure 1A shows the temporal and spatial conditions of an antisaccade task. A central fixation point (FP) is presented and the subject is instructed to fixate it. A visual stimulus is then presented in the periphery and the subject has to suppress a saccade to the stimulus (prosaccade) and generate a saccade to the mirror position (antisaccade). In the case of the task illustrated in Fig. 1, the FP point is extinguished for a constant or variable time before the stimulus is presented, which creates a temporal gap between FP disappearance and stimulus appearance (gap condition). The FP can also remain visible, which is called the overlap condition, because in this condition the stimulus and the FP overlap in time. Figure 1B shows schematically a correct antisaccade (thick line) and its reaction time (A-SRT). The thin line shows an incorrect prosaccade followed by a corrective saccade which brings the eye to the opposite side. The reaction time (P-SRT) and correction time (C-SRT) are defined accordingly. In all three cases the reaction time can be measured from stimulus appearance.

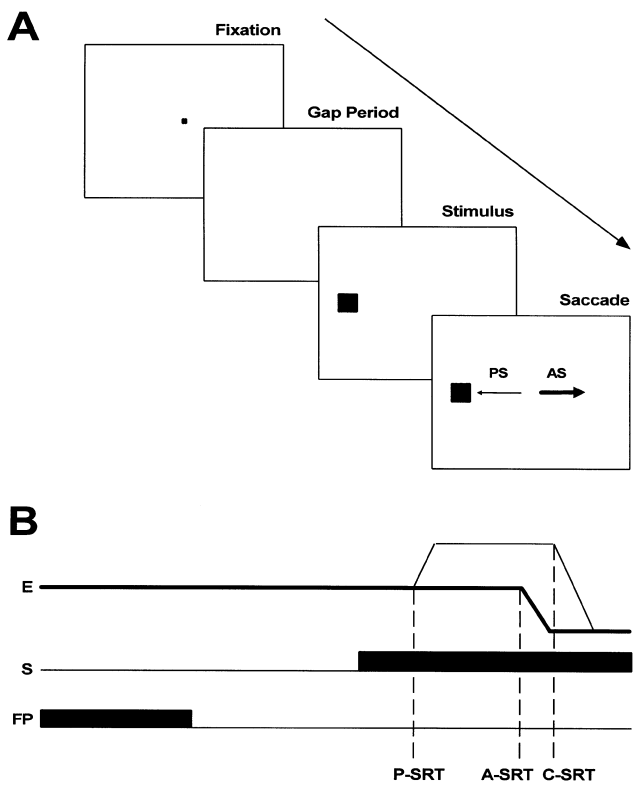

Fig. 1. Schematic representation of a gap antisaccade task. Part A shows the temporal (time flow indicated by the arrow) and spatial aspects of the task. The subject is required to fixate a central fixation point (FP) which is extinguished before a peripheral stimulus is presented. When the visual stimulus is presented, the subject is instructed to suppress a prosaccade (thin line, PS) toward the stimulus and to generate an antisaccade (thick line, AS) to the other side. Part B shows schematically the eye position traces (E) of a correct antisaccade (thick line) and an erratic prosaccade (thin line) followed by a corrective saccade in an antisaccade task. S, stimulus. P-SRT, prosaccadic reaction time. A-SRT, antisaccadic reaction time. C-SRT, correction saccadic reaction time.

Basic research

In his very first studies with normal subjects, Hallett [57] reported some basic observations on the performance of the antisaccade task: subjects were able to successfully look to the side opposite to the stimulus. In the beginning, however, they made quite a number of erratic saccades (30–80%) toward the stimulus before they looked to the opposite side. Later they could reduce the error rate to 5–7%. The mean reaction times of the antisaccades were prolonged as compared to prosaccades. Antisaccade amplitude was quite variable both between subjects and within subjects and antisaccade velocity profiles were altered. Secondary corrective saccades followed primary antisaccades much faster than primary prosaccades. A decrease in antisaccade peak velocity by about 30% compared with prosaccade was confirmed [122, 129]. It was also shown that skewness of the velocity profile occurs more frequently for antisaccades than for prosaccades [122].

In later studies, the longer latencies of antisaccades versus prosaccades were confirmed and it was stated that there was no significant decrease in the error rate with practice [58]. These results were later refined: when subjects were required to make antisaccades in a gap task they decreased both their error rate from an average of about 14% to11% and their average latency from about 183 ms to 171 ms within 12–15 days of everyday practice [38].

Characteristic parameters of the antisaccade

As for normal saccades the basic parameters of antisaccades are: latency, duration, velocity, size and accuracy, and correction time in the case of saccades undershooting or overshooting the required final position of the eye. In addition and specific to the antisaccade task, is the percentage of erratic prosaccades that are made in one direction or the other and the corresponding correction time. The latencies of the antisaccades depend in a way similar to those of normal saccades on retinal factors like state of adaptation and rod-cone interaction [24, 25]. Photopic stimulus luminances led to longer latencies, larger angular errors, less secondary saccades and more direction errors in antisaccades compared with prosaccades. With scotopic stimulus luminances most differences between pro- and antisaccades disappeared. This was largely the result of alterations in prosaccade performance: increased latencies, increased standard deviations of the angular errors and a decrease of the incidence of secondary saccades in prosaccades. Moreover, scotopic stimulus luminances increase the direction errors for prosaccades and antisaccades.

The role of the temporal stimulus parameters on the performance of the antisaccade task has been studied recently [41, 43]. The duration of the gap period (when present) critically altered the number of erratic prosaccades and the latency of correct antisaccades. For gap durations of 200–250 ms the mean error rate was maximal and the latency minimal as compared with either shorter or longer gap durations [41]. However, the reduction of saccadic reaction times in the gap condition (gap effect) is smaller for antisaccades than for prosaccades [43].

A dependence of antisaccade performance on the spatial stimulus parameters has also been tested [41]. It was found that the error rate increases and the latency decreases with increasing eccentricity of the stimulus from 1–12°. The size of the stimulus size, on the other hand, had little or no effect.

Randomly interleaving pro- and antisaccades in a single block was of no importance to the error rate when compared with blocks of only pro- or only antisaccades [58]. These experiments were repeated using visual cues to indicate whether pro- or antisaccades were required at any given trial [132]. It turned out that subjects made large numbers of errors even though the cue was given 100–200 ms ahead of time. The errors were of both kinds: erratic prosaccades on antisaccade trials and—more surprisingly—erratic antisaccades on prosaccade trials. The analysis revealed that subjects on many trials executed the command of the previous trial. This result clearly indicates that the generation of voluntary saccades, even when they are prosaccades, relies on non-visual functions under these particular conditions.

Single-neuron recordings in non-human primates

Single-neuron recording studies over the last 25 years have identified inhibitory control mechanisms over saccade generation at different levels. Saccadic eye movements are elicited by an activation of burst neurons (BNs) in the reticular formation which innervate the extraocular muscle motoneurons. BNs in the paramedian pontine reticular formation (PPRF) discharge a short burst of action potentials before and during horizontal saccades, and BNs in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) discharge for vertical saccades (for a review see [86]). BNs are tonically inhibited by omnipause neurons (OPNs) which are located in the nucleus raphe interpositus around the midline of the caudal pontine reticular formation [12]. OPNs discharge at a high tonic frequency between saccadic eye movements and pause before and during saccades in all directions [69, 76, 106]. Therefore, OPNs act as a gate on the saccade generating circuit (for review see [45]). It is, however, unlikely that a reduced activity of OPNs can account for reflexive prosaccades in the antisaccade task. OPNs do not alter their discharge rate when the FP is extinguished in a gap prosaccade task and they do not have different discharge rates prior to express saccades as compared with regular saccades [33]. Consequently, it seems that the activity of OPNs reflects the final decision to either hold fixation or to generate a saccade.

The saccade generator in the brain stem is innervated by frontal cortical areas [118, 121] and by the superior colliculus (SC) in the midbrain. The SC contains a topographic retinal map in its superficial layers and a saccadic motor map in its intermediate layers. Recent work has demonstrated that neurons in the rostrolateral pole in the intermediate layers of the SC are tonically active during fixation and pause before and during saccades [88, 90, 91]. The artificial inhibition of these neurons by injections of the GABA agonist muscimol resulted in an inability of monkeys to maintain fixation in a memory-guided saccade task [90, 91]. Most of these reflexive saccades had latencies in the range of express saccades. It has been proposed that fixation neurons and saccade-related neurons in the SC mutually inhibit one other [92]. Unlike OPNs in the brain stem, fixation neurons in the SC discharge action potentials at variable rates [33]. The highest discharge rate is observed in many fixation neurons immediately after a saccade, at the onset of fixation [91]. This elevation in discharge may prevent the occurrence of further saccades and help to insure visual fixation for a certain time. After the disappearance of the FP in gap prosaccade tasks, fixation neurons decrease their discharge rate [27, 33, 91]. Dorris and Munoz [27] showed that the discharges of fixation neurons in different gap intervals correlated with the mean saccadic reaction times obtained in these gap intervals.

Most of the direction errors in antisaccade tasks (especially in gap antisaccade tasks) have very short latencies in the range of express saccades [36, 37, 39]. While there is currently no knowledge about the neural activity in the SC during antisaccade tasks, recent studies have started to reveal the neural processes preceding express saccades in gap prosaccade tasks. Most of the saccade-related burst neurons in the SC discharge one burst of action potentials after the appearance of a visual stimulus in their response field and a second burst prior to a saccade to this stimulus. Edelman and Keller [29] demonstrated that saccade-related burst neurons discharge only one burst prior to an express saccade. This burst occurs at the same time as the visual burst, but with a higher discharge rate. The same findings were obtained by Dorris *et al*. [28]. Furthermore, the later study could show that buildup neurons have a higher discharge rate at the end of the gap period prior to express saccades compared with regular saccades. These findings may indicate that a greater excitability of saccade-related neurons at the time of stimulus presentation can lead to an express saccade by allowing the visual burst to pass a certain threshold level which results immediately in a motor burst.

Saccade-related neurons in the SC are tonically inhibited by GABAergic neurons in the substantia nigra pars reticulata (SNpr) (for review see [64]). The injection

of the GABA antagonist bicuculline into the SC results in saccadic jerks towards the contralateral site and thereby in the inability of the monkey to hold fixation [61, 62]. The same effect is obtained by inhibiting the SNpr GABA-ergic inputs to the SC by injection of muscimol into the SNpr [63]. The SNpr is phasically inhibited by the oculomotor area in the body of the caudate nucleus [60]. The caudate nucleus in turn receives excitatory input from the frontal eye field (FEF) and supplementary eye field (SEF) [99], which are both involved in the generation of purposive saccades (for review see [59]). Fixation-related neuronal activity has been found in the frontal eye field [11], supplementary eye field [7, 72, 113, 115] and prefrontal cortex [123]. The two frontal oculomotor areas can control the initiation of saccades by the basal ganglia pathway to the SC, by projections to the SC and even directly by projection to the brain stem saccade generating circuit [118, 121]. Moreover, the SC receives projections from the parietal cortex [98] which also contains neurons with fixation-related activity [78, 112].

Despite the apparent top-down mechanism in the neural control of the initiation and inhibition of saccades described above, it should be noted that the FEF and SEF receive thalamic input from the internal medullary lamina which in turn is innervated from neurons in the brain stem, the SC and the SNpr [77]. This simple fact should prevent us from drawing any premature top-down control mechanisms in the control of saccadic eye movements and especially in the generation of antisaccades.

There are currently only two reports about single-cell activity in monkeys performing an antisaccade task. Funahashi *et al.* [50] recorded from single neurons in the dorsolateral prefrontal cortex (area 46) in monkeys during memory-guided antisaccades. In this task, the monkey had to look at a FP while a peripheral target was flashed for a short time. After a variable memory interval, the FP was extinguished and the monkey had to generate an antisaccade to the opposite side of the peripheral target flash. Funahashi *et al.* [50] found that neurons in the dorsolateral prefrontal cortex code the location of the visual stimulus during the memory interval and concluded that these neurons can either inhibit or facilitate a response. This antisaccade task differed substantially from the antisaccade tasks used in human studies, which contain no memory interval. Therefore, it is not clear whether neurons in the dorsolateral prefrontal cortex also become active during typical antisaccade tasks.

Recently, Schlag-Rey *et al.* [116] have recorded single-neuron activity in the SEF of monkeys trained on an antisaccade task which was similar to those used in human studies. The results show that the majority of neurons in the SEF have a higher saccade-related burst for antisaccades compared with prosaccades. The authors suggested that this discharge results in an inhibition of prosaccades. This is consistent with the finding that many neurons displayed a lower burst when the monkey made a prosaccade on an antisaccade trial as compared with a correct antisaccade.

Failure of fixation vs failure to produce antisaccades

The correct performance of the antisaccade task requires at least two intact subprocesses: (1) the ability to suppress a reflexive saccade towards the visual stimulus and (2) the ability to generate a voluntary saccade in the opposite direction, i.e. to a location void of any stimulus. An intact fixation system allows subjects to suppress a reflexive prosaccade towards the stimulus, giving them enough time to generate a voluntary antisaccade [56].

The importance to distinguish between these subprocesses becomes especially obvious in certain human subjects which have been called "express saccade makers" [4, 14]. These subjects have lost selectively—completely or in part—their fixation control and produce high numbers of express saccades even in the presence of a FP. Therefore it comes as no surprise that they are also impaired on the gap antisaccade task, because with a weak fixation system there is diminished inhibition of the saccade system which therefore reacts more often to visual stimuli by producing a reflex-like movement.

An experimental approach to increase the numbers of errors in normal subjects in the antisaccade task is to present the outlines of two boxes which mark the potential stimulus locations and to flash one box briefly 100 ms before the visual stimulus appears in the other box [40]. Although the flash is a valid cue for the direction of the coming antisaccade, normal subjects produce more errors in this condition than without the cues [40]. The subjects reported that they were unable to suppress the unwanted prosaccades and—even more strikingly—it turned out that on average 50% of the trials with erratic prosaccades escaped their conscious recognition [85]. Interestingly, almost all the erratic prosaccades whether recognized as errors or not were corrected immediately indicating that the subjects could generate antisaccades.

By contrast, subjects (mostly children), who also produce high error rates without the cues do not correct all of their errors [35]. They have difficulties generating saccades to the side opposite to the stimulus. An impairment to generate an antisaccade after the execution of an erratic prosaccade has also been reported for some patients with frontal lesions [56]. The lack of corrective antisaccades indicates that these two groups are impaired on the antisaccade task not only because of a lack of fixation activity, but because of a lack of ability to generate voluntary saccades. Therefore, when high error rates are observed in the antisaccade task, it is important to determine whether a subject corrects them or not. This differentiation between the components of a successful performance of the antisaccade task has been discussed in detail in the context of the significance and interpretation of the error frequency of schizophrenics and other patients [74].

The development of fixation and voluntary saccade generation

The dual aspect of antisaccade control becomes very clear when looking at its development with age. A large number (300) of subjects, aged 8–65 years, were tested using the gap antisaccade task and the overlap prosaccade task [35]. Counting the numbers of errors obtained in the antisaccade task revealed that children below the age of 10 years are almost unable to perform the task successfully. Their mean error rate was in the order of 60% which decreased steeply until the age of 15 years and more slowly until the age of 20 years to reach a value of about 15%. The percentage number of erratic saccades that were corrected by a 1 s saccade was low (50%) for the children around the age of 10 years and increased to a mean of about 80% only at the age of 20 years. During the same period the reaction time of the correct antisaccades decreased from a mean value of 290 ms to 220 ms [35]. A dramatic improvement in the error rate in the antisaccade task between the ages 6–15 years has also been reported by Munoz *et al*. [87, 93]. After the age of 20 years, the reaction time of antisaccades increases with increasing age [35, 87, 93, 96]. Some studies also reported an increase in error rate with age ([35, 96], see however [87]).

These results suggest that the fixation system preventing reflexive saccades in the antisaccade task is developed by the age of 10 years while the voluntary component of saccade generation develops over a much longer period. In fact, it has been reported that infants as young as 4 months can learn to inhibit automatic saccades to salient stimuli indicating the effectiveness of their fixation system [67].

The generation of antisaccades

In this section we present and discuss the neuropsychological and clinical findings which have been obtained during the last decade describing the suppression of reflexive prosaccades and the generation of voluntary saccades in the antisaccade task in human subjects. These comprise studies of patients with discrete cortical or subcortical lesions or neurological diseases, positron emission tomography (PET) studies and event-related potential (ERP) studies.

Brain imaging of antisaccade generation

The results of functional neuroimaging studies have indicated that a variety of brain regions are involved in the generation of saccadic eye movements in humans. Early studies have reported an increased regional cerebral blood flow (rCBF) in the frontal and supplementary eye field [44, 82]. Later studies have provided evidence for an activation of more brain areas, including at the cortical level the cingulate gyrus and insula and at the subcortical level the globus pallidus, the striatum and thalamus [1, 95, 102, 124]. Some of these studies examined rCBF associated with the performance of antisaccades in healthy human subjects [26, 95, 100, 124]. These studies have yielded different results. Paus *et al*. [100] found a significantly larger rCBF only in the anterior cingulate cortex and the posterior parietal cortex during the performance of an antisaccade task compared to the activation during a prosaccade task. In contrast, O'Driscoll *et al*. [95] observed an increased rCBF activation in the FEF, the supplementary motor area, the thalamus, the putamen, the superior parietal lobe and area 17 during antisaccades compared to prosaccades. O'Driscoll *et al*. [95] concluded from their results that the FEF inhibit reflexive prosaccades in the antisaccade task. Sweeney *et al*. [124] demonstrated a bilateral increased rCBF in the dorsolateral prefrontal cortex, a bilateral increase in the posterior parietal cortex and an increased rCBF in the right FEF and SEF. Sweeney *et al*. [124] also observed a lower rCBF in the ventromedial prefrontal cortex, left striatum and bilateral medial-temporal cortex. The authors suggested that the lower rCBF in the ventromedial prefrontal cortex reflects the suppression of reflexive saccades. Doricchi *et al*. [26] also found an activation of a large set of cortical areas during antisaccades compared with prosaccades. These areas included the posterior parietal cortex, precentral, prefrontal cortex, cingulate cortex and supplementary motor areas.

These PET studies although not yet coherent have shown that many cortical and subcortical areas have an altered rCBF during the performance of an antisaccade task compared with a prosaccade task. This indicates that the correct performance of antisaccades relies on an activation of a widely distributed neural network which includes virtually all known oculomotor areas.

The disadvantage of PET is the low temporal resolution, because this technique requires an integration of the positron emitting tracer over a time window of 40–120 s. This makes it impossible to differentiate between areas which are active during the inhibition of the reflexive prosaccade and those which are involved in the programming of the antisaccade. Therefore, these studies do not necessarily support the hypothesis that the frontal cortex is involved in the inhibition of reflexive prosaccades in the antisaccade task. In fact, the only area which has shown consistently to have an increased rCBF in all four studies is the parietal cortex.

Human electrophysiology of antisaccade generation

Cortical ERPs have a temporal resolution in the timescale of milliseconds which can help to distinguish between activation preceding and accompanying saccades. The clear disadvantage of this technique is the low spatial resolution and the restriction to the analysis of cortical processes. Saccadic eye movements are preceded

by two distinct cortical potentials, a presaccadic negativity (similar to a readiness potential before finger movements) and a presaccadic positivity (similar to a premotor positivity prior to finger movements) [2]. Brickett *et al.* [8] found a lower presaccadic positivity prior to antisaccades compared with prosaccades at an electrode over the central parietal cortex. A lower presaccadic positivity in the last 100 ms prior to saccade onset has been confirmed [30, 32]. It has been hypothesized that this reduction reflects a frontal mechanism of inhibiting reflexive saccades [30]. Moreover, an increased presaccadic negativity over central and frontal recording sites has been observed prior to antisaccades compared with prosaccades [32]. The analysis of stimulus-locked event-related potentials has demonstrated that correct antisaccades are preceded by a negative potential with the greatest amplitude over the parietal cortex contralateral to the stimulus, which then shifts to the side ipsilateral to the stimulus, i.e. contralateral to the instructed movement [34]. This finding was interpreted as the neural correlate of the shift of the representation of the stimulus from the contralateral to the ipsilateral hemisphere.

Müri *et al.* [94] applied single transcranial magnetic pulsed stimuli over the right frontal eye field in healthy human subjects. Magnetic stimulation did neither interrupt visual fixation nor alter the amplitudes of visually guided saccades. However, when a magnetic stimulus was applied 50–90 ms after the appearance of the visual stimulus, latencies of rightward antisaccades were significantly increased by an average of about 70 ms. This prolongation was only observed when the magnetic stimulus was given within a certain period, which varied between subjects.

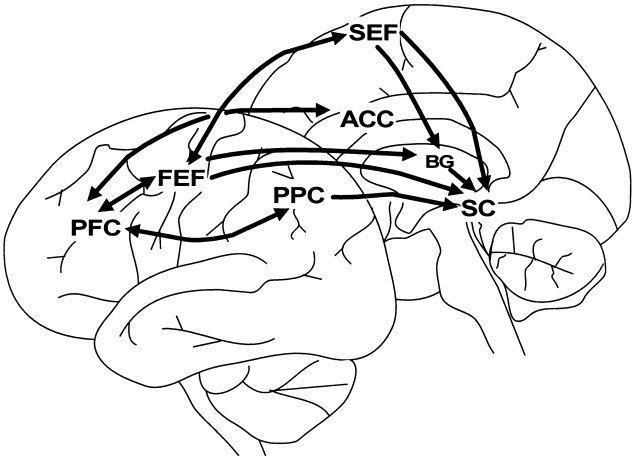

Fig. 2. Structures believed to be involved in the antisaccade generation. The figure shows the cortical and subcortical structures which are involved in the correct performance of the antisaccade task in humans and it illustrates a simplified schematic of their connectivity. See text THE GENERATION OF ANTISACCADES for details. ACC, anterior cingulate cortex. BG, basal ganglia. FEF, frontal eye field. PFC, prefrontal cortex. PPC, posterior parietal cortex. SC, superior colliculus. SEF, supplementary eye field.

Clinical studies

A variety of studies have tested patients with different cortical and subcortical lesions and patients with neurological and psychiatric disorders in the antisaccade task. Based on studies with brain lesion patients and patients with neurological diseases, we will discuss in the first part of this section the involvement of different cortical and subcortical areas in the correct performance of the antisaccade task (Fig. 2). In the second part we will present studies involving patients with psychiatric disorders, mainly schizophrenia and discuss the sensitivity of the antisaccade task as a diagnostic tool for these disorders. A quick overview and additional data can be found in Table 1 which summarizes the results of these studies concerning the error rates in the antisaccade task.

Superior colliculus

Pierrot-Deseilligny *et al.* [105] tested a human subject with a lesion affecting the right SC due to a small haematoma. In the first examination 17 days after the lesion, they found a high percentage of reflexive saccades toward the right side in a fixation task. This finding can be interpreted as an overactivation of the left SC due to the loss of inhibitory input from the right SC or due to destruction of efferent fibers from the SNpr. Interestingly, the subject elicited reflexive saccades in an antisaccade task not only to the right but also to the left side. This finding is currently difficult to interpret and suggests that an increased error rate in the antisaccade task is not necessarily identical to a failure in visual fixation. Pierrot-Deseilligny *et al.* [105] could also show in their study that the failure to suppress reflexive saccades after SC lesions can be compensated. The authors found lower error rates at the second examination 80 days after the lesion.

Basal ganglia

Studies of patients suffering from discrete lesions or neurological diseases affecting the basal ganglia (BG) have yielded controversial results about the role of the BG in the antisaccade task. Vidailhet *et al.* [131] have shown that neither patients with corticobasal degenerations nor patients with striatonigral degenerations made more errors in the antisaccade task than control subjects. It has also been demonstrated that lesions of the globus pallidus and putamen do not result in an impairment in the antisaccade task [130]. However, Huntington's disease (HD), which is characterized by degenerations in the caudate and SNpr, leads to deficits in the initiation of saccades without a target [73], in the generation of antisaccades and in the suppression of reflexive prosaccades in the antisaccade task [71, 110]. An involvement of the

Table 1. List of studies of the antisaccade task in different diseases. The number of control and test subjects and their age range is given. The results are listed in the right columns

Reference	Number of controls	Age (years)	Errors [%]	Number of subjects	Age (years)	Errors [%]	Diff.?	Task/exp
ADHD								
Rothlind *et al.* [111]	20	10	30	21	11	40	no	antigap
Affective disorders								
Fukushima *et al.* [49]	36	18–42	2±4	13	14–38	4±4	no	anti
Alzheimer								
Currie *et al.* [21]	332	15–89	9±7	30	49–89	10–100	yes	Fingert
Flechtner and Sharpe [42]				6	57–76	74		anti
HIV								
Johnston *et al.* [68]	9	34±6	18	12	39±8	67	yes	anti
Merrill *et al.* [83]	25	22–48	4	47	22–61	70	yes	antigap
Huntington								
Currie *et al.* [21]	332	18–89	9±7	5	18–64	40	yes	Fingert.
Lasker *et al.* [71]	22	13–69	17±10	20	17–65	60±20	yes	anti
Genetic marker for Huntington								
Rothlind *et al.* [110]	56	20–43	29±14	20	20–43	30±21	no	anti
Lateral sclerosis								
Shaunak *et al.* [120]	11	27–69	10±10	17	28–69	32	yes	antigap 0
Obsessive compulsive disorder								
Tien *et al.* [127]	14	22–56	11	11	27–54	39	yes	anti
Pseudodementia								
Currie *et al.* [21]	332	18–89	9±7	12	35–84	–	no	Fingert.
Progressive supranuclear palsy								
Pierrot-Deseilligny *et al.* [104]	40	64±10	15±3	40	51–80	59	yes	antigap
Vidailhet *et al.* [131]	12	64±8	11	10	63±5	65–82	yes	antigap
Parkinson								
Fukushima *et al.* [47]	20	45–72	15±11	22	40–70	25±9	no	anti
Kitagawa *et al.* [70]	20	57±9	15±11	32	45–70	28±19	yes	antigap
Lueck *et al.* [75]	10	64–84	31±13	10	54–72	39±12	no	anti
Vidailhet *et al.* [131]	12	64±8	11	14	62±7	13	no	anti
Schizophrenia								
Clementz *et al.* [16]	27	35±14	22±16	30	35±10	58±22	yes	anti
Fukushima *et al.* [46]	10	20–39	0	12	19–41	0–60	yes	anti
Fukushima *et al.* [48]	36	18–42	2±3	32	17–41	2±22	yes	anti
Fukushima *et al.* [49]	24	18–42	4±2	24	17–41	26±22	yes	anti
Fukushima *et al.* [47]	9	19–39	4±5	18	16–43	34±21	yes	anti
Rosse *et al.* [109]	12	38±12	29±13	27	39±7	39±9	yes	antigap
Sereno and Holman [119]	14	32	6	17	33	24	yes	antigap
Thaker *et al.* [126]	8	25–35	10±8	18 TD	27–48	60±25	yes	anti
Schizophrenia first degree relatives								
Clementz *et al.* [16]	27	35±14	22±16	32	49±17	32±23	yes	anti
Schizophrenia spectrum personality diagnoses								
Thaker *et al.* [125]	51	29±7	24±22	32	30±8	24±13	no	anti
Lesions								
Fukushima *et al.* [47]	20	45–72	15±11	10 frontal	26–72	41±32	yes	anti
Gaymard *et al.* [52]	20	44±16	13	2 SEM	34–48	5–6	no	antigap
Guitton *et al.* [56]	9	y. adult	20±5	26 frontal	y. adult	59±9	yes	antigap
Guitton *et al.* [56]	9	y. adult	20±5	7 temp.oral	y. adult	19±5	no	antigap
Pierrot-Deseilligny *et al.* [103]	20	70±9	13	1 sup coll	70	51	yes	antigap
Pierrot-Deseilligny *et al.* [103]	20	59±9	13	16 PFC	58±14	59–81	yes	antigap
Pierrot-Deseilligny *et al.* [103]	20	59±9	13	10 FEF	58±14	7–31	no	antigap
Pierrot-Deseilligny *et al.* [103]	20	59±9	13	10 PPC	58±14	17–34	no	antigap
Pierrot-Deseilligny *et al.* [103]	20	59±9	13	9 SMA	58±14	4–16	no	antigap
Rivaud *et al.* [107]	12	52±13	6±33	3 FEF	55±13	14	no	antigap

Table 1.—*continued*

Reference	Number of controls	Age (years)	Errors [%]	Number of subjects	Age (years)	Errors [%]	Diff.?	Task/exp
Lesions—*continued*								
Vertmesch *et al*. [130]	12	47±10	11	9 putamen/ globus pallidus	44+11	15	no	antigap
Vidailhet *et al*. [131]	12	64±8	11	10 Cort-Basal	65±6	22–52	yes	antigap
Vidailhet *et al*. [131]	12	64±8	11	14 Striangr	62+9	7–14	no	antigap

caudate nucleus and the SNpr in the antisaccade task is supported by the finding that patients with progressive supranuclear palsy (PSP) have increased error rates [6, 104]. This neurodegenerative disease with a largely unknown pathophysiology leads to degenerations of the caudate, SNpr and SC. However, brain lesions in this disease also widely affect the cholinergic system, including the nucleus basalis of Meynert. Recently, it has been reported that the administration of physostigmine, an acetylcholinesterase inhibitor, led to an increased regional cerebral blood flow and a reduction of direction errors in the antisaccade task [6]. This finding indicates that the increased errors of PSP patients are at least partly the result of the described frontal syndrome in this disease. The diffuse neural degenerations in PSP make it difficult, however, to draw any strong conclusions based on these findings. Subjects with Parkinson's disease (PD) which is characterized mainly by degenerations of neurons in the substantia nigra pars compacta (SNpc) have no increased error rate in the antisaccade task [47, 75, 131]. Only severely impaired patients generate more reflexive saccades and have longer latencies in this task [70]. Kitagawa *et al*. [70] interpreted the longer latencies of antisaccades in these patients as a sign of a frontal lobe disorder in late PD. The authors also showed that PD patients who took anticholinergics had higher error rates than PD patients who did not take anticholinergics.

Taken together, these studies only provide evidence for participation of the caudate nucleus and the SNpr in the suppression of reflexive saccades, whereas the putamen and the globus pallidus seem not to be crucial for the correct performance of the task. This finding is consistent with the described results from primate studies concerning the specific oculomotor function of parts of the caudate and the SNpr.

Cortex

Traditionally, the prefrontal cortex is considered to be involved in suppressing a reflexive in favor of a deliberate behavior (for review see [51, 54]). Therefore, Guitton *et al*. [56] hypothesized that the frontal cortex imposes a high level control on reflexive saccades. Indeed, the authors found that patients with unilateral lesions in the frontal lobe either could rarely inhibit a reflexive saccade toward the visual stimulus or had difficulties to initiate the antisaccade. They suggested that the FEF and/or the SEF were the critical structures for the correct performance of the antisaccade task. Later lesion studies, however, did not confirm this assumption. Neither lesions of the SEF [52, 103] nor lesions of the FEF [107] resulted in an increased error rate in an antisaccade task. Instead, an increased number of reflexive saccades has been reported after lesions of the dorsolateral prefrontal cortex [47, 103]. Recently, it has also been demonstrated that lesions of the anterior cingulate cortex results in a high number of reflexive saccades in the antisaccade task [53]. Lesions in the parietal lobe [103] and lesions in the temporal lobe [56] have been reported not to affect the performance in the antisaccade task. However, the negative results of an involvement of the SEF, FEF, parietal cortex, and temporal cortex should be interpreted very cautiously. The PET studies discussed above have shown that the SEF [26, 95, 124], FEF [26, 95, 124], posterior parietal cortex [26, 95, 100, 124] and temporal cortex [124] alter their activity during the performance of an antisaccade task compared with a prosaccade task. Moreover, the results from the recent single-cells recordings in monkeys [116] have indicated an involvement of the SEF in the inhibition of reflexive saccades and in the generation of antisaccades. These discrepancies may be the result of compensatory processes after brain lesions which help to restore the initial functions. These compensatory processes can be very efficient in the case of saccades, as primate studies have shown. The temporarily inactivation of neurons in the FEF by muscimol injections completely inhibits visually-guided saccades [22], whereas the effects of permanent lesions of the FEF on visually-guided saccades are compensated within a few weeks [114].

Therefore, despite the negative findings of the cited lesion studies, it is still possible and likely that a distributed network of cortical and subcortical areas is involved in the performance of the antisaccade task in healthy humans. This assumption is supported by the clinical findings that a variety of diffuse cortical disease processes such as Alzheimer's disease [21, 42], amyo-

trophic lateral sclerosis [120] or the acquired immunodefiecincy syndrome (AIDS) dementia complex [20, 68, 83] also cause difficulties in suppressing reflexive saccades in the antisaccade task.

The antisaccade task as a diagnostic tool

In the last 10 years, a great effort has been made to evaluate the validity of the antisaccade task as a diagnostic tool for disorders which are known or suspected to involve the frontal cortex and/or the basal ganglia.

Basal ganglia diseases

Based on the finding of increased error rates in patients with HD [71], Rothlind *et al.* [110] tested whether error rates in the antisaccade task can be used as a biological marker for HD. It was found, however, that only affected subjects, but not young adults with the genetic marker for HD, had increased error rates. Vidailhet *et al.* [131] tested whether the antisaccade task can be used to differentiate between different parkinsonian syndromes, including striatonigral degeneration (SND), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP) and PD. The authors found that only patients with PSP had an increased percentage of errors in the antisaccade task and concluded that the antisaccade task may be valuable in the early differential diagnosis between SND, CBD and PSP. The results, however, also showed that the antisaccade task cannot be used to differentiate between SBD, CBD and PD.

Schizophrenia

The largest group of patients which have been tested in the antisaccade task so far are schizophrenics. A vast number of neurochemical, neuroanatomical and neuropsychological studies have implicated the frontal cortex in the genesis of schizophrenia (for reviews see [74, 133]). Therefore, it is not surprising that the finding of a poor performance of patients with frontal lesions [56] led to many studies with patients with schizophrenia. All studies conducted so far reported that many schizophrenics had higher error rates in the antisaccade task than normal control subjects (Table 1). This research can be divided into at least two streams: (a) studies which evaluated the relationship between the performance in the antisaccade task and frontal lobe syndromes in schizophrenia, and (b) studies which evaluated the performance in the antisaccade task as a biological marker for schizophrenia.

Before we review these results, it is important to see why schizophrenics make more errors in the antisaccade task. Is the high number of reflexive saccades specific for the antisaccade task or do schizophrenics create reflexive saccades already in fixation tasks? Unfortunately, the studies which investigated this question have yielded controversial results. Fukushima *et al.* [48] tested schizophrenics in a fixation task (subjects were required to maintain fixation and to inhibit saccades to flashed visual targets), in a memory-guided saccade task (subjects were required to suppress a saccade to a flashed target and execute a remembered saccade after the disappearance of the FP) and an antisaccade task. Many patients generated a high percentage of reflexive saccades in the fixation task and the memory-guided saccade task. Clementz *et al.* [16] who tested schizophrenic patients in a fixation task and an antisaccade task did not find differences in the percentage of reflexive saccades between patients and normal control subjects in the fixation task, but did in the antisaccade task. Further studies have confirmed an increased percentage of reflexive saccades of schizophrenic patients in memory-guided saccade tasks [31, 81]. Based on these few controversial studies, it is hard to decide whether schizophrenic patients really have a general deficit to inhibit reflexive saccades to distracting stimuli. The commonality of the memory-guided saccade task and the antisaccade task is that both tasks require subjects to suppress a saccade to a stimulus and at the same time require subjects either to remember its spatial location or to use it for a spatial transformation process. The increased error rates in schizophrenics may be the result of a failure to cope with these dual task demands.

Several studies have evaluated the correlation of the error rate in the antisaccades with the performance on the Wisconsin Card Sorting-test (WCST) [109], which is an established test for the diagnosis of a frontal lobe disorder [84]. A significant correlation between the error rates in the antisaccade task and the error rates in the WCST has been reported consistently in schizophrenics [18, 19, 109, 128]. These findings favor the assumption that the poor performance of schizophrenics in the antisaccade task is indeed related to a dysfunction in frontal cortex. Further, 73% of patients with an increased rate of reflexive saccades in the antisaccade task showed an atrophy of the frontal cortex in a CT-scan, whereas no abnormalities were found in any patient with normal performance [48]. Crawford *et al.* [19] used single-photon emission tomography to identify the areas in schizophrenic patients which are related to a poor performance in the antisaccade task. The authors found that schizophrenic patients with greater error rates had a significantly decreased rCBF bilaterally in the anterior cingulate, insula, and in the left striatum compared with schizophrenics with normal error rates.

Schizophrenic patients with tardive dyskinesia (TD) have higher error rates than schizophrenics without TD [126]. TD is thought to involve a GABAergic dysfunction of the basal ganglia. Therefore, Thaker *et al.* [13, 126] have proposed that the basal ganglia participate in the suppression of reflexive saccades in the antisaccade task. This hypothesis is consistent with the high error rates in patients with HD [71]. Taken together, the results obtained so far suggest that a dysfunction in the frontal

cortex or in the BG may be responsible for the increased percentage of reflexive prosaccades in schizophrenia.

Clementz *et al.* [16] compared the performance of non-schizophrenic psychiatric controls, non-psychiatric controls and first degree relatives of schizophrenic patients with schizophrenics in the antisaccade task. They found higher error rates in schizophrenics and their first degree relatives than in both control groups. Another study reported significant longer latencies of antisaccades in relatives of schizophrenic patients with and without schizophrenia spectrum personality disorders [125]. These observations extended the known finding of a deficit in smooth pursuit eye movements of schizophrenics and their first degree relatives [15, 16, 55], which has been discussed as a biological marker for schizophrenia [65, 66]. The same may be the case for increased errors in the antisaccade task. Indeed, several studies reported a correlation between disturbed smooth pursuit eye movements in schizophrenics and the performance in the antisaccade task [79, 80,117, 119].

Despite the clear differences in the error rate between many (not all) schizophrenic patients and normal control subjects, it is unclear whether the antisaccade task can actually differentiate between subjects with schizophrenia and subjects with other psychiatric diseases, since a number of these also show increased error rates. Tien *et al.* [128] compared the error rates of schizophrenic patients with patients with bipolar disorder. While both groups had significantly higher error rates than normal control subjects, the error rates between both groups did not differ. Sereno and Holzman [119] compared the performance of schizophrenic patients, non-schizophrenic psychiatric patients, and normal controls. Both schizophrenics and psychiatric control subjects had greater error rates and longer latencies of antisaccades than normal control subjects. Increased error rates in the antisaccade task have also been reported for patients with obsessive compulsive disorders [127].

However there are some psychiatric disorders that may be distinguished from schizophrenia based on the antisaccade task. Fukushima *et al.* [49] reported that patients with affective disorders do not have increased error rates. Moreover, patients with pseudodementia do not vary in the error rates from control subjects [21].

Attention deficit hyperactivity disorder

Ross *et al.* [108] tested children with attention deficit hyperactivity disorder (ADHD) in a delayed saccade task. Results of this study showed that the ADHD children had difficulties in suppressing saccades toward the stimuli during the delay period. Rothlind *et al.* [110] studied children with ADHD in the antisaccade task, and found that ADHD made more reflexive prosaccades than control children in this task. These differences, however, were not significant. However, the antisaccade task in this study comprised only 10 trials which may have accounted for the lack of significant differences. Munoz *et al.* [89] could confirm higher error rates in the antisaccade task relative to age-matched controls in a portion of children with ADHD. The authors concluded that this may indicate multiple subtypes within the ADHD diagnosis, only some of which are impaired on the antisaccade task.

Dyslexia

The involvement of oculomotor deficits in dyslexia has generated controversy ([97, 101] see however [8, 9]). Obviously, the motor part of saccade generation seems to be intact. A preponderance of express saccades in the overlap prosaccade task was also observed in the subjects with a selective impairment involving only reading and writing, called D2-subjects [3, 5]. D1-dyslexic subjects with additional problems such as concentration or auditive discrimination difficulties or deficits in short-term memory showed scattered reaction time distributions. Using the gap antisaccade task it was found that especially male dyslexics, D1 and D2, produce excessive numbers of errors in comparison with age-matched normally reading subjects [5]. D2-subjects produced their errors as express saccades, whereas D1 subjects had rather long latencies of their erratic prosaccades. A detailed analysis will have to show whether they have a weak fixation system or a weak voluntary control by looking at the corrections of the errors.

Conclusion

In this section, we will attempt to evaluate the validity of the antisaccade task as a diagnostic tool in neurology and psychiatry. A complicating factor is the lack of certainty as to which brain structures are involved in the performance of antisaccades. If we combine the data from all brain imaging studies and lesions studies conducted so far, we end up with a long list of possibly involved brain areas: dorsolateral prefrontal cortex, FEF, SEF, anterior cingulate, posterior parietal cortex, area 17, insula, thalamus, putamen, caudate, SNpr and SC. The ERP studies have shown that antisaccades are preceded by a higher negativity over fronto-central areas than prosaccades. Moreover, ERP data suggest a function of the parietal cortex in the shift of the neural representation of the visual stimulus. Our knowledge about the neural processes underlying the generation of antisaccades has been substantially elaborated by data from single-cell recordings in the SEF in monkeys, which demonstrated that neurons in the SEF discharge at a higher rate prior to antisaccades, than prior to incorrect prosaccades in the antisaccade task. Further experimental work with non-human primates will certainly greatly improve our knowledge of the specific functions of the areas involved in the antisaccade task.

In the light of the large number of structures involved, it is not surprising that the error rate in the antisaccade task can be high and above normal in different clinical conditions. This suggests that despite a high sensitivity of the antisaccade task, its specificity for a disease or the location of the involved brain structure may be low. While many authors tend to interpret failures in the antisaccade task as indications for frontal or prefrontal deficits; review of the different components that must be intact for a successful performance of the antisaccade task shows that such a conclusion may be premature or even wrong. The correct performance of the antisaccade task depends on at least two intact subprocesses: an intact fixation system and the ability to generate a voluntary saccade to the opposite side. As described, the fixation system comprises omnipause neurons in the brain stem, fixation neurons in the rostral SC, parts of the caudate and SNPr, and neurons in the SEF, FEF and area 46. Diseases in any of these areas may lead to deficits in the suppression of reflexive saccades in the antisaccade task.

Currently, we know practically nothing about the neural structures and processes involved in the generation of voluntary saccades. It is usually neglected in clinical studies that the antisaccade task can be used to probe both subprocesses. A high error rate, especially if the incorrect prosaccades have latencies in the range of express saccades, indicates that subjects have an inability to inhibit reflexive saccades. If subjects correct these direction errors, then it is clear that they do not have difficulties in generating voluntary saccades. Clinical studies in the next few years will have to focus on this differentiation. This extra information together with the latencies of the incorrect prosaccades, and the latency of correction saccades may help to increase the value of the antisaccade task as a diagnostic tool.

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