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The antisaccade task as a research tool in psychopathology: A critical review

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Abstract

The antisaccade task is a measure of volitional control of behavior sensitive to fronto-striatal dysfunction. Here we outline important issues concerning antisaccade methodology, consider recent evidence of the cognitive processes and neural mechanisms involved in task performance, and review how the task has been applied to study psychopathology. We conclude that the task yields reliable and sensitive measures of the processes involved in resolving the conflict between volitional and reflexive behavioral responses, a key cognitive deficit relevant to a number of neuropsychiatric conditions. Additionally, antisaccade deficits may reflect genetic liability for schizophrenia. Finally, the ease and accuracy with which the task can be administered, combined with its sensitivity to fronto-striatal dysfunction and the availability of suitable control conditions, may make it a useful benchmark tool for studies of potential cognitive enhancers.

Descriptors: Oculomotor control, Cognition, Psychiatry, Neurology, Endophenotype, Psychopharmacology

In the antisaccade task, participants visually fixate a central stimulus that is replaced by a sudden onset target that appears at some distance to the left or right. Participants are told to refrain from looking at the peripheral target and direct their gaze instead in the opposite direction (Hallett, 1978). This deceptively simple task has a number of properties that led to its adoption as a research tool first by neurologists and more recently by psychiatrists and psychologists. Most notably, it contrasts aspects of willful behavior—a volitional saccade made in the opposite direction to a sudden-onset target—with the powerful urge to make a prepotent, or reflexive response—a prosaccade toward the target. Healthy participants typically fail to achieve this on a significant number of trials and instead make reflexive glances toward the target. Importantly, patients with lesions to the frontal lobe (Guitton, Buchtel, & Douglas, 1985) and patients with schizophrenia (Fukushima et al., 1988) make significantly more antisaccade errors than healthy individuals. Since Fukushima and colleagues' seminal report, more than 40 studies have shown increased error rates in people with schizophrenia, with no failure to replicate (Calkins, Curtis, Iacono, & Grove, 2004). Additionally, an increasing number of studies have addressed antisaccade performance in other psychiatric and neurological patient populations, such as affective disorder, attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), autism, Huntington's disease, Alzheimer's disease, and Parkinson's disease.

This review will outline how the antisaccade task has been used as a research tool in the study of normal and abnormal human brain function and will make specific recommendations for future research using this task. We will highlight areas that are considered of particular current interest to researchers in psychology, psychiatry, and neuroscience, such as the use of this task to identify specific dysfunctional cognitive and neuroanatomic systems, to identify and characterize genetic vulnerability to psychiatric disorders at a cognitive and neural level, and to provide a benchmark test for the development of pharmacological treatments of cognitive impairment. Given the large and growing body of literature on antisaccades in schizophrenia, this disorder will receive particular emphasis in our review.

Basic Research Findings

Average antisaccade error rates in healthy humans vary considerably across studies and laboratories, with some studies reporting rates as low as 5% and others as high as 25% (Reuter & Kathmann, 2004). Recent studies using large samples suggest an error rate of around 20% is typical (Ettinger et al., 2003a, 2005b; Smyrnis et al., 2002; Tatler & Hutton, 2006; see also Everling & Fischer, 1998). Error rates are not constant across the lifespan, being highest during childhood, reaching a nadir during early adulthood, and then increasing very slowly with advancing age until around 60, when the rate of increase appears to accelerate (Fischer, Biscaldi, & Gezeck, 1997; Klein & Foerster, 2001;

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Olincy, Ross, Youngd, & Freedman, 1997). The developmental profile of antisaccade errors is thus broadly consistent with the known development of the prefrontal cortex. Consequently, this task is potentially useful for researchers interested in studying the neural basis of neurodevelopmental disorders, such as schizophrenia, and psychiatric disorders that occur in predominantly pediatric or geriatric populations (Luna & Sweeney, 2001). It is important to note that a significant percentage of errors are unrecognized by participants (Mokler & Fischer, 1999). As such, the antisaccade task provides researchers with a valuable tool with which to investigate the role of conscious awareness in the monitoring, detection, and correction of errors in healthy participants and people with psychopathological disorders.

The antisaccade task yields several measures in addition to the error rate (see Figure 1) that can provide important insights into the integrity of the cognitive and neural mechanisms involved in the volitional control of behavior. These include the latencies of correct antisaccades and incorrect prosaccades, the time to correct errors (the time between an incorrect prosaccade and subsequent corrective antisaccade) and various spatial accuracy measures, including the amplitude of correct and incorrect saccades and the final eye position of correct responses. Another important measure is the percentage of errors that are corrected. Although healthy participants typically correct the vast majority of errors (Everling & Fischer, 1998), certain pathological groups fail to correct a significant proportion of their errors, suggesting a deficit not only in inhibition but also response generation (Crawford et al., 2005; Guitton et al., 1985).

Antisaccade errors typically have a mean latency that is slightly shorter than those reported for prosaccades, whereas correct antisaccades typically take around 100–150 ms longer to initiate than reflexive prosaccades (Munoz & Everling, 2004). Increased correct antisaccade latencies are generally considered to reflect the additional processing required to inhibit the reflexive prosaccade and perform the necessary spatial transformations required to provide antisaccade coordinates (Olk & Kingstone, 2003). The precise mechanisms underlying increased antisaccade latencies are, however, the topic of some debate, and may depend considerably on specific task parameters (Evdokimidis, Constantinidis, Liakopoulos, & Papageorgiou, 1996).

Correct antisaccades tend to be more strongly hypometric (i.e., undershoot the projected target location) than prosaccades (Tatler & Hutton, 2006). This increased hypometria may reflect the fact that correct antisaccades are triggered endogenously, as opposed to exogenously, in the absence of a visual target (Edelman, Valenzuela, & Barton, 2006; Mosimann, Felblinger, Colloby, & Müri, 2004). However, comparatively few studies report spatial accuracy measures, despite the fact that they may provide important information concerning the functioning of the neural systems supporting spatial working memory and sensorimotor transformations (Krappmann, Everling, & Flohr, 1998; Zhang & Barash, 2000).

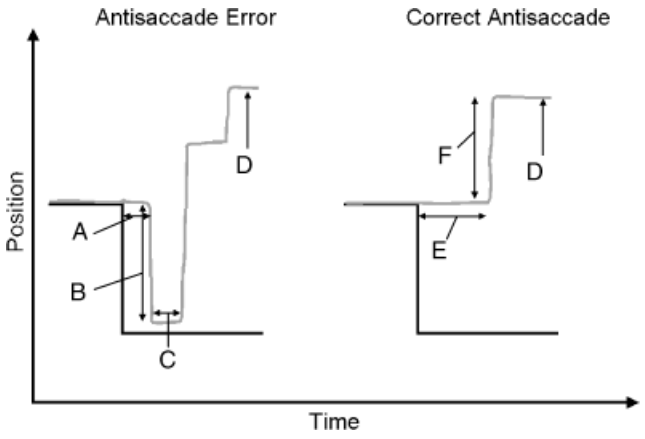

Figure 1. Antisaccade metrics. A: Error latency. B: Error amplitude. C: Time to correct. D: Final eye position. E: Correct antisaccade latency. F: Correct antisaccade amplitude.

Methodological Issues

All variants of the antisaccade task share the requirement to inhibit a reflexive saccade to a sudden onset target and initiate an alternative antisaccade, and as such they have generally been assumed in the psychiatric literature to be functionally equivalent. There are, however, several parameters on which antisaccade tasks can differ, and research in healthy participants demonstrates that these parameters can have a considerable impact on the cognitive and neural systems involved in performing the task. For example, antisaccade errors are typically more common, and correct antisaccade latencies are reduced in gap trials (in which the central fixation is extinguished shortly before the peripheral target appears) compared to step trials (in which there is no gap) and in step trials compared to overlap trials (in which central fixation and peripheral target overlap briefly; Fischer & Weber, 1997).

A parameter of critical importance to studies involving repeat testing—as, for example, in longitudinal or psychopharmacological studies—concerns the extent to which antisaccade performance varies as a function of practice. Research comparing antisaccade performance over weeks or months has found that performance is typically improved at time 2 compared to time 1 (Dyckman & McDowell, 2005; Ettinger et al., 2003a). This improvement is not typically seen in familiar oculomotor behaviors such as reflexive saccades, fixation, or smooth pursuit (Ettinger et al., 2003a) and is thus likely to reflect the learning of a previously novel response.

A further task parameter that may have profound impact on how participants perform the antisaccade task are the instructions given (Mosimann et al., 2004). Studies seldom report the instructions verbatim, and it is impossible to determine the extent to which discrepancies such as those discussed in the sections on schizophrenia endophenotypes reflect differences in task instructions that lead participants to recruit different processes in performing the task. For example, different variations on the antisaccade task employ different numbers of potential targets, and in cases where only one target in each hemifield is employed, participants are typically instructed simply to look in the opposite direction, whereas in tasks with several potential targets, participants may be asked to look at the mirror image location. The demands on the processes involved in the vector transformation are considerably greater in the latter instance.

In conducting and evaluating antisaccade research, it is important to be aware that the task yields potentially informative data in addition to the error rate, and that seemingly minor methodological changes can have significant implications for task performance and how performance deficits are interpreted. Although there have been attempts to provide solutions that allow standardization with respect to stimulus presentation,

recording, and analysis in the antisaccade task (Hartnegg & Fischer, 2002) it is inevitable that significant cross-laboratory differences will continue to exist. These must be taken into account when interpreting antisaccade data.

Models of Antisaccade Function

It is generally assumed that the sudden appearance of the target in an antisaccade task automatically triggers a motor program for a prosaccade in its direction and that errors occur when certain endogenous processes fail to inhibit or cancel this program. Recent accounts emphasize the parallel nature of motor programming in antisaccade performance and suggest that whether an error is made or not is determined by the relative strength of activation in neural systems supporting the pro- and antisaccade (Massen, 2004; Munoz & Everling, 2004; Reuter & Kathmann, 2004). These accounts argue that at stimulus onset a "competition" ensues between processes underlying the exogenously triggered prosaccade and the endogenously initiated antisaccade—the coordinates for the antisaccade being computed as soon as the stimulus location is determined. If activation in the neural systems supporting the antisaccade reaches threshold fast enough, the correct antisaccade is initiated and the reflexive saccade is canceled. Alternatively, if activation in the neural systems supporting the prosaccade reaches threshold first, an erroneous saccade toward the target is made, and the correct antisaccade follows (possibly even curtailing the erroneous saccade if it follows fast enough). As prosaccade latencies are significantly shorter than antisaccade latencies, activation in the neural systems supporting the prosaccade must be somehow reduced in order to allow activation in neural systems supporting the more complex antisaccade program time to reach threshold first.

Evidence in support of these accounts has been provided by Massen (2004), who demonstrated that manipulations that result in increased latencies for correct antisaccades also result in increased errors—if the processes underlying the correct endogenous saccade take longer to reach threshold, there is a greater probability of the process underlying the triggered saccade winning the competition. Further evidence that the erroneous prosaccade and correct antisaccade can be programmed in parallel is provided by the rapid correction times often observed in the antisaccade task—95 ms for unrecognized errors and 145 ms for recognized errors—that are considerably shorter than the average intersaccadic interval of 222 ms produced by participants intentionally generating sequences of pro- and antisaccades (Mokler & Fischer, 1999). It should be noted, however, that the extent to which the correct and incorrect responses are truly programmed in parallel is unclear. For example, errors are not always corrected quickly and are sometimes compounded by one or more further saccades toward the target before being corrected. In these instances it seems unlikely that there is much temporal overlap between the processes involved in the initial error and its eventual correction.

Several cognitive processes have been proposed to underlie antisaccade performance. It is often argued that errors reflect a failure of frontally mediated inhibitory control (Clementz, 1998; Crawford, Bennett, Lekwuwa, Shaunak, & Deakin, 2002). More recent accounts, however, take on board the suggestion made by currently influential models of cognitive control that inhibition of erroneous information processing occurs as a direct consequence of successful activation of processing routes required to perform the correct response (Miller & Cohen, 2001). As a result recent models of antisaccade performance emphasize cognitive constructs such as working memory, goal or intention activation, and attentional focus (Mitchell, Macrae, & Gilchrist, 2002; Nieuwenhuis, Broerse, Nielen, & de Jong, 2004; Reuter & Kathmann, 2004). Although differing somewhat in terminology and detail, these accounts suggest that correct antisaccade performance depends on the ability to adequately maintain the relevant task instructions or sufficiently activate the intention to make an antisaccade. In other words, if the relevant task instructions are adequately represented, activation is increased in task-relevant neural systems (such as those involved in computing the coordinates for the correct antisaccade and in maintaining fixation when the target appears) and, as such, successful inhibition of the erroneous prosaccade emerges as a direct consequence of adequate activation of the task goal.

Various lines of evidence support these accounts. For example, increasing working memory load in healthy participants (e.g., by requiring them to perform a concurrent task that requires working memory resources) increases error rates (Mitchell et al., 2002; Roberts, Hager, & Heron, 1994). Similarly, the working memory span of individuals is associated with antisaccade performance, with low-span individuals making more erroneous reflexive saccades than individuals with high spans (Unsworth, Schrock, & Engle, 2004). Finally, as discussed below, measures of working memory function have been found to correlate with antisaccade performance in various patient populations (Gooding & Tallent, 2001; Hutton et al., 2004).

Neural Correlates of Antisaccade Performance

Early positron emission tomography and functional magnetic resonance imaging (fMRI) studies of antisaccade performance in healthy humans have contrasted indirect indices of neural activation during blocks of antisaccades and blocks of control conditions (e.g., prosaccades or fixation). These studies have shown that antisaccade performance recruits a fronto-parieto-subcortical network, primarily involving frontal eye fields (FEF), supplementary eye field, dorsolateral prefrontal cortex (DLPFC), anterior cingulate, posterior parietal cortex, thalamus, and striatum (Müri et al., 1998; O'Driscoll et al., 1995; Sweeney et al., 1996).

However, these early studies have not been able to dissociate the neural substrates of specific processes involved in task performance, such as preparation versus execution of an antisaccade. Recent methodological advances, such as event-related fMRI, enable the temporal dissection of different task components (or events) and thus allow these questions to be addressed.

For example, a number of studies have investigated changes in activation levels in frontal and parietal areas during the preparatory phase of the task, that is, in the seconds leading up to the saccadic response. Activation in the FEF (but not the intraparietal sulcus) during this preparation period is greater before antisaccades than prosaccades, suggesting additional requirements of preparatory set in antisaccade trials (Connolly, Goodale, Menon, & Munoz, 2002). FEF activation levels in the presaccade phase are also lower before reflexive errors compared to correctly performed antisaccades and prosaccades (Cornelissen et al., 2002) and presaccade activation levels in the presupplementary motor area further distinguish antisaccades

from both prosaccades and reflexive errors, with greater activation observed before antisaccades (Curtis & D'Esposito, 2003). The role of the FEF in antisaccade preparation and generation is further underscored by the observation of a relationship between *greater* preparatory FEF activity and *faster* contraversive antisaccade latencies (Connolly, Goodale, Goltz, & Munoz, 2005). Interestingly, it has also been shown that the increased activation in FEF and DLPFC following antisaccades (compared to prosaccades) is accounted for by differences in activation levels in these areas preceding the stimulus, suggesting that preparatory set-related activation might be the source of the increased signal seen in block-design studies (DeSouza, Menon, & Everling, 2003). To conclude, activation in frontal areas and their functional interactions (Miller, Sun, Curtis, & D'Esposito, 2005) may be an important determinant of the success or failure as well as the efficiency in generating a correct antisaccade.

Electroencephalographic (EEG) studies support an involvement of fronto-parietal areas in antisaccade performance. A greater increase in negative electrical activity at fronto-central and central sites, likely reflecting preparatory activity, has been observed before execution of correct antisaccades compared to prosaccades and antisaccade errors (Evdokimidis, Liakopoulos, Constantinidis, & Papageorgiou, 1996; Everling, Spantekow, Krappmann, & Flohr, 1998; Klein, Heinks, Andresen, Berg, & Moritz, 2000). A study combining EEG and magnetoencephalography (MEG) showed increased activation in medial FEF, supplementary eye fields, and DLPFC immediately preceding antisaccades compared to prosaccades (McDowell et al., 2005). Antisaccade error trials have been shown to induce error negativity (Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001), a brain wave associated with error detection in auditory or visual tasks, perhaps compatible with the observation of increased anterior cingulate activation during error trials in fMRI designs (Ford, Goltz, Brown, & Everling, 2005; Polli et al., 2005). Perceived (but to a lesser extent unperceived) errors also induced error positivity (Nieuwenhuis et al., 2001). Concerning posterior brain activity, it has been suggested that positive parietal potentials may be related to the spatial component of saccade execution (Richards, 2003), compatible with fMRI evidence of posterior parietal cortex involvement in antisaccade target coding (Medendorp, Goltz, & Vilis, 2005). Also, the above-mentioned EEG/MEG study (McDowell et al., 2005) found that cuneus activity was greater following antisaccade than prosaccade stimuli, further underscoring the additional demands on parietal sensorimotor transformations of this task (Krappmann et al., 1998; Zhang & Barash, 2000).

Research on nonhuman primates was recently reviewed in detail and will be dealt with only briefly here (Munoz & Everling, 2004). Single-neuron studies have shown that successful antisaccade performance is strongly related to fixation ability and is mediated by inhibition of saccade neurons in FEF and superior colliculus. Other brain areas, such as DLPFC or supplementary eye fields, are likely required to inhibit these neurons in order to yield successful suppression of prosaccades, whereas parietal areas may be involved in visuospatial sensorimotor transformations (Zhang & Barash, 2000). However, comparisons of animal and human studies are hampered by procedural differences, such as extensive task practicing necessary in monkeys. Effects of practice are known to operate on measures of performance (Ettinger et al., 2003a) and brain function, including an activation shift from anterior to posterior foci (Shadmehr & Holcomb, 1997).

Patients with acquired brain lesions have been studied with a view to identifying the roles of specific cortical regions in antisaccade performance. The most consistent findings to emerge from this literature are (a) increased antisaccade latencies following FEF lesions and (b) increased error rates following DLPFC lesions (Pierrot-Deseilligny, Ploner, Müri, Gaymard, & Rivaud-Pechoux, 2002); however, see Machado and Rafal (2003) for a suggestion that contralesional inhibitory failure may follow chronic FEF damage. Importantly, error rates are increased not only following damage to DLPFC (Brodmann Area 46) but also its white matter connections with subcortical areas (Ploner, Gaymard, Rivaud-Pechoux, & Pierrot-Deseilligny, 2005). There is also evidence of increased error rates after ventral prefrontal (Walker, Husain, Hodgson, Harrison, & Kennard, 1998) and anterior cingulate (Gaymard et al., 1998) damage. On the other hand, posterior parietal cortex may be involved in the spatial programming of antisaccades (Pierrot-Deseilligny et al., 2002). However, the lesion data are not always easily reconciled with neuroimaging studies. For example, it is unclear why not all neuroimaging studies have found evidence of DLPFC activation during antisaccades, although the choice of control condition may play a role.

Neurobiological studies thus agree with cognitive models of the antisaccade as a complex, volitional behavior reliant on frontal lobe functioning and relevant subcortical connections. Antisaccade generation and reflexive saccade suppression appear to recruit brain areas typically involved in volitional, top-down behaviors, such as working memory and response inhibition, making the task intuitively appealing for studying a wide range of psychiatric disorders with deficits in these cognitive domains. Future human studies should utilize event-related fMRI to further detail the neural correlates of specific task subcomponents. For example, a "delayed antisaccade task" allows the temporal dissociation of reflexive saccade inhibition and volitional response generation (Reuter, Rakusan, & Kathmanna, 2005). Future research should investigate whether the neural correlates of these processes agree with human lesion evidence of DLPFC and FEF involvement, respectively, as outlined above (Pierrot-Deseilligny et al., 2002). Also, given evidence of *structural* as well as *functional* neural correlates of antisaccade function and dysfunction (Bagary et al., 2004; Ettinger et al., 2005a), studies combining structural and functional imaging methods are needed. Finally, it may be valuable to combine the temporal resolution of EEG with the spatial resolution of fMRI in an exploration of the neural control of antisaccades.

Antisaccade Performance in the Schizophrenia Spectrum

Of all psychiatric disorders, antisaccades have been most widely studied among people with schizophrenia. Additionally, a number of studies have investigated antisaccade performance in schizophrenia spectrum populations, such as schizotypal individuals or relatives of schizophrenia patients, to elucidate the genetic basis of this condition.

Patients with Schizophrenia

Since Fukushima and colleagues' (1988) report of increased antisaccade errors in patients with chronic schizophrenia, at least 40 other studies have replicated this finding. Error rates in patients with schizophrenia vary from around 25% up to 70%, and this range is likely to reflect differences between studies in task

parameters such as those described earlier. Importantly, abnormal performance has been observed in patients with recent onset schizophrenia and in never-medicated and unmedicated patients (Crawford, Haeger, Kennard, Reveley, & Henderson, 1995; Ettinger et al., 2004a; Hutton et al., 1998), suggesting this deficit is not due to disease chronicity or pharmacological treatment (Ettinger & Kumari, 2003). However, antisaccade performance can be influenced in specific ways by experimental pharmacological manipulations; this research is discussed in a later section.

Increased errors are generally interpreted as reflecting impaired inhibitory control mediated by dysfunctional prefrontal cortex in schizophrenia (Clementz, 1998), but although many studies have replicated the basic finding of increased errors, comparatively few have reported other potentially relevant metrics such as latency and spatial accuracy. Of those that do, the majority find increased antisaccade latencies and hypometric amplitudes relative to healthy controls (Broerse, Crawford, & den Boer, 2001).

A number of studies have employed tasks in which reflexive eye movements toward sudden onset targets need to be inhibited, but in the absence of the requirement to perform an immediate antisaccade (for a review, see Reuter & Kathmann, 2004). These studies report that schizophrenic patients make considerably fewer erroneous prosaccades in delayed antisaccade, delayed prosaccade, and no-saccade tasks compared to standard antisaccade performance, suggesting that a critical feature of antisaccade errors is that they occur in the context of the requirement to initiate a saccade at target appearance. This requirement possibly serves to increase the baseline levels of activity in the saccade-generating neurons such that the target's appearance is more likely to trigger a reflexive prosaccade in its direction.

To date no study has failed to report increased antisaccade errors in patients with schizophrenia, and several report increased correct antisaccade latencies. As argued by Reuter and Kathmann (2004), together these findings suggest that patients with schizophrenia are impaired in their ability to sufficiently activate the internal representation of the task goal—to initiate a voluntary saccade in the opposite direction to the target. This leads to an increase in the average latency of correct antisaccades and, as a consequence, an increase in the number of trials on which the erroneous prosaccade reaches its threshold first. Further support for this contention is provided by a recent study (Reuter, Herzog, & Kathmann, 2006) in which the mirror image location of the upcoming target was precued. In healthy participants such precues counterintuitively increase errors and correct antisaccade latencies. The likely explanation is that the precues are processed while participants are in "antisaccade mode"—in other words, they trigger the preparation of a saccade in the direction away from the precue, toward the location in which the target subsequently appears. If, as argued above, patients with schizophrenia are less likely to sufficiently activate the correct antisaccade task set, then the effect of the precue should be smaller in patients than in healthy participants. This is exactly what was found.

Neuropsychological and Clinical Correlates

A critical endeavor in psychopathological research is to explain the clinical features of different disorders in terms of impairments to fundamental cognitive processes. These processes also impact on neuropsychological test performance, and as such, it is important to consider the neuropsychological and clinical correlates of antisaccade performance. As outlined in the previous section, it is generally assumed that increased antisaccade errors in patients with schizophrenia reflect an underlying abnormality in prefrontal function. On the assumption that the same prefrontal dysfunction underlies both increased antisaccade errors and impaired executive function, several studies have sought to identify whether a relationship exists between the two. The majority of studies do indeed observe significant correlations, although there are exceptions (for a review, see Hutton et al., 2004). Most of these studies used the Wisconsin Card Sorting Test (WCST) as an index of executive function. A key cognitive process embedded in the WCST is the inhibition of a previously learned response and the shifting of cognitive set to facilitate a different response. As such the correlations are often interpreted as reflecting a common underlying deficit in inhibitory processes. However, the WCST is a procedurally complex task that requires the operation of a number of cognitive processes simultaneously, including the ability to maintain the current sorting rule in mind. Recent studies suggest that in schizophrenia the working memory component of the WCST may be paramount to performance (Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997).

In a study of 109 recent-onset patients, the only neuropsychological measures that correlated significantly with antisaccade error rate were three measures of spatial working memory (Hutton et al., 2004). Two other studies that specifically examined the relationship between antisaccade and working memory performance also observed significant correlations (Gooding & Tallent, 2001; Nieman et al., 2000). In the Gooding and Tallent study, a mediation analysis was performed that demonstrated that performance on working memory tasks is an important contributor to antisaccade deficits in schizophrenic patients. It should be noted that despite the significant associations found in these studies, measures of working memory function accounted for comparatively small amounts of variance in antisaccade performance—for example, the R^2 value for the strongest correlation in the study by Hutton and co-workers (2004) was 0.124.

A small number of studies also investigated the relationship between various measures of psychopathology and antisaccade performance in schizophrenia. The results of these studies are somewhat inconsistent, but in general suggest that antisaccade errors are increased in patients with high levels of negative symptoms (Crawford et al., 1995; Ettinger et al., 2004a, 2006; Nkam et al., 2001; Tien, Ross, Pearlson, & Strauss, 1996; but see Hutton et al., 2004). This is compatible with converging evidence that negative symptoms are associated with more severe prefrontal cortex dysfunction (Ho et al., 2003). However, given the finding that increased antisaccade errors are also observed in patients in clinical remission (Curtis, Calkins, Grove, Feil, & Iacono, 2001) who had very low levels of negative symptoms, the overall contribution of symptoms to antisaccade performance is likely to be small. This contention is supported by a longitudinal study (Gooding, Mohapatra, & Shea, 2004) that found that antisaccade performance remained relatively stable, despite significant changes in clinical state.

Taken together, these studies support the hypothesis that antisaccade dysfunction in schizophrenia involves working memory processes mediated by the prefrontal cortex. Future studies aimed at determining the relationship between antisaccade performance and symptoms over a longer time course are needed given the fluctuating nature of symptoms in

schizophrenia. It is worth noting that, in most studies, psychopathological rating scales are administered to patients, but only a minority of papers report correlational analyses between these measures and antisaccade performance. The few studies that do report correlations tend to report significant ones, which may reflect a publication bias toward positive results. In the future it will be important that researchers test for clinical correlates of antisaccade performance, if their data permit, and report both positive and negative results.

Neural Correlates of the Antisaccade Deficit in Schizophrenia

Functional neuroimaging studies suggest that reduced fronto-striatal activation underlies the antisaccade deficit in people with schizophrenia. An early single photon emission tomography study found that patients with high error rates had decreased activation in anterior cingulate, insula, putamen, and globus pallidus, when compared to patients with good performance (Crawford et al., 1996). This study had the advantage of circumventing disease-related confounds in the group comparison. A more recent block-design fMRI study demonstrated that schizophrenic patients did not display increased activation in DLPFC during antisaccades compared to prosaccades, as was seen in healthy controls (McDowell et al., 2002). Prosaccade performance was normal in the patient group and was associated with normal fronto-parietal activation levels. An event-related fMRI study of saccadic disinhibition, combining antisaccades with the less demanding fixation-with-distractors task, showed reduced activation in caudate and putamen in patients relative to healthy controls (Raemaekers et al., 2002).

Structural neuroimaging studies further support the hypothesis of fronto-striatal neural substrates of antisaccade abnormalities in schizophrenia. An early computed tomography study showed that increased error rates were associated with structural frontal lobe atrophy (Fukushima et al., 1988), whereas a recent volumetric MRI study of first-episode psychosis patients using the regions-of-interest (ROI) approach found gain and latency to be associated with caudate volumes, indicating that larger caudate volumes were associated with hypometric gain and longer latencies (Ettinger et al., 2004a). Using voxel-wise analysis of structural MRI data, Bagary and colleagues (2004) observed that in first-episode psychosis patients greater error rates were correlated with reduced gray matter volume in the right medial superior frontal cortex.

The contingent negative variation (CNV) is an event-related brain wave observed in EEG studies; it is thought to reflect delay-related and preparatory prefrontal activity. Schizophrenic patients show reduced CNV before antisaccades compared to healthy subjects and fail to show increased CNV during antisaccades compared to prosaccades (Klein, Heinks, et al., 2000). It was also found in one patient that the CNV was smaller before error trials than correct antisaccade trials.

These studies suggest that antisaccade deficits in schizophrenia patients are an expression of abnormal fronto-striatal circuitry. However, only a surprisingly small number of studies so far have addressed this issue, warranting independent replication. Detailed studies of the neural correlates of specific task components, as outlined above, are needed.

Do Antisaccade Deficits Mark Genetic Liability for Schizophrenia?

Given the inconsistent findings of genetic studies using the schizophrenic disease phenotype, a number of researchers have focused the search for schizophrenia genes on endophenotypes, or intermediate markers of genetic vulnerability. An endophenotype is a biological or behavioral marker thought to be a more proximal reflection of one or several causative polymorphisms than the clinical phenotype (Cannon, 2005; Gottesman & Gould, 2003). Given that an endophenotype is assumed to have a simpler genetic and phenotypic architecture than the illness phenotype, it may be preferentially used in molecular genetic designs such as association or linkage studies. This section will consider whether antisaccade deficits may represent a potential endophenotype for schizophrenia.

A useful schizophrenia endophenotype must meet a number of validity criteria (e.g., Gottesman & Gould, 2003). First, it should be observed in the patient group under study. Second, it should be a trait, not state, marker. Third, it should be heritable. Fourth, given its assumed reflection of a genetic predisposition to schizophrenia, it should be observed in clinically unaffected populations at increased genetic risk for the illness. The two most widely studied such populations are (a) schizotypal individuals and (b) unaffected biological relatives of schizophrenia patients. Both populations are thought to be at increased risk for developing schizophrenia and display behavioral and biological abnormalities similar to people with schizophrenia. The five endophenotype criteria will be addressed in the following paragraphs.

First, the occurrence of antisaccade deficits in the patient group has been established (see above). Second, antisaccade performance has been shown to be temporally stable in healthy volunteers (Ettinger et al., 2003a), in people with schizophrenia and their relatives (Calkins, Iacono, & Curtis, 2003; Gooding et al., 2004), and in people with high levels of schizotypal traits (Gooding, Shea, & Matts, 2005). Trait nature is an important criterion of any putative endophenotype. Third, heritability of antisaccade performance was demonstrated in healthy monozygotic and dizygotic twins, with effects of additive genes estimated to account for more than half of the variance in antisaccade errors (Malone & Iacono, 2002).

Concerning the observation of antisaccade deficits in populations at increased genetic risk for schizophrenia, numerous studies link elevated levels of schizotypal traits to increased antisaccade error rates on step antisaccade tasks in nonclinical samples (Ettinger et al., 2005b; Gooding, 1999; Holahan & O'Driscoll, 2005; Larrison, Ferrante, Briand, & Sereno, 2000; O'Driscoll, Lenzenweger, & Holzman, 1998; Smyrnis et al., 2003; but see Holahan & O'Driscoll, 2005,and Klein, Brügner, Foerster, Müller, & Schweickhardt, 2000, for a failure to replicate this relationship using gap and overlap tasks). This deficit may be related more closely to positive than negative schizotypal symptoms (Ettinger et al., 2005b; Holahan & O'Driscoll, 2005) and is not due to increased levels of general psychopathology or neuroticism (Ettinger et al., 2005b; Smyrnis et al., 2003). Longitudinal research has shown that performance deficits in schizotypals are consistent over time periods of up to 5 years (Gooding et al., 2005). Increased error rates also occur in some people with a clinical diagnosis of schizotypal personality disorder (Brenner, McDowell, Cadenhead, & Clementz, 2001; Cadenhead, Light, Geyer, McDowell, & Braff, 2002).

There is also evidence of increased error rates among biological first-degree relatives of schizophrenia patients (Clementz, McDowell, & Zisook, 1994; Curtis et al., 2001; Ettinger et al., 2004b; Karoumi et al., 2001; Katsanis, Kortenkamp, Iacono, & Grove, 1997; McDowell & Clementz,

1997; McDowell, Myles-Worsley, Coon, Byerley, & Clementz, 1999). However, other studies have failed to find significant differences between relatives and controls (Brownstein et al., 2003; Crawford et al., 1998; Louchart-de la Chapelle et al., 2005). The reasons for this inconsistency are unclear. A recent meta-analysis suggested that antisaccade performance in relatives may be significantly heterogeneous and related to the presence of schizophrenia spectrum symptoms in relatives (Levy et al., 2004). However, an explicit test of this hypothesis showed that relatives display increased error rates in the absence of psychiatric symptoms (Calkins et al., 2004), suggesting that psychiatric symptoms are not a necessary condition for the existence of increased error rates in relatives. Interestingly, two studies reported impairments in relatives compared to controls when both groups have schizophrenia spectrum symptoms but no differences when neither group displayed such symptoms (Thaker et al., 2000; Thaker, Cassady, Adami, Moran, & Ross, 1996), suggesting interactive effects of symptoms and antisaccade deficits in the relatives.

There is additional support of the endophenotype candidacy of increased antisaccade error rates. First, relatives from multiply affected schizophrenia families display higher error rates than relatives from singly affected schizophrenia families (McDowell et al., 1999) and first-degree relatives appear to differ from controls with larger effect sizes than second-degree relatives (McDowell et al., 1999), suggesting an effect of genetic loading. Second, one study showed increased errors in schizophrenia patients' parents *with* a family history of schizophrenia (so-called likely gene carriers) but not in parents *without* a family history (so-called less likely gene carriers; Ross et al., 1998). Third, there is evidence of linkage of a combined impairment of antisaccade errors and P50 suppression to a locus on chromosome 22q11–12 (Myles-Worsley et al., 1999), and a recent study observed a trend-level association of antisaccade errors with the Val158Met polymorphism of the catechol-O-methyltransferase gene (Stefanis et al., 2004), located in chromosome 22q11.

In addition to findings concerning reflexive errors, there is also evidence of reduced spatial accuracy (Ettinger et al., 2004b; Karoumi et al., 2001; Ross et al., 1998) and increased latency (Thaker et al., 1996, 2000) among relatives and co-twins (Ettinger et al., 2006) of schizophrenia patients, suggesting that multiple performance indices may have to be considered as endophenotypes. Interestingly, however, latency (Brenner et al., 2001; Ettinger et al., 2005b; Gooding, 1999; O'Driscoll et al., 1998) and spatial accuracy (Brenner et al., 2001; Ettinger et al., 2005b) appear unaffected among schizotypal individuals, suggesting that these two high-risk groups display only partially overlapping genetic vulnerabilities, at least with regards to antisaccade function.

Taken together, there is evidence that antisaccade performance deficits might mark genetic liability for schizophrenia. Schizotypal individuals have subtly but reliably increased error rates. Findings from relatives suggest overall impairments of medium effect size with some heterogeneity in this population (Calkins et al., 2004; Levy et al., 2004). Reasons for the observed inconsistencies between family studies are unclear but are likely to involve factors accounting for inconsistencies and heterogeneity among other psychiatric (endo-)phenotypes, such as the absence of large effect sizes, genetic stratification, or the existence of phenocopies (Gardner et al., 2006; Klein & Stewart, 2004). There are also methodological features that have not been examined in relation to deficits among relatives, such as temporal characteristics of antisaccade trials or the role of task instructions.

Directions for future research include the question of whether a neurobiologically more proximal antisaccade endophenotype, for example, derived from measures of brain activation underlying task performance, could be profitably employed in the identification and characterization of susceptibility genes (Raemaekers, Ramsey, Vink, van den Heuvel, & Kahn, 2005). Additionally, the extent to which other antisaccade performance parameters, such as spatial accuracy or latency, constitute schizophrenia endophenotypes should be investigated further. Another important question concerns the nosological specificity of these findings, that is, whether relatives of nonschizophrenic patient groups with antisaccade deficits also show these deficits. For example, preliminary evidence from presymptomatic Huntington gene carriers suggests nonsignificant impairments of small to large effect size (Blekher et al., 2004) on error rate, latency, and velocity in this population (however, see Rothlind, Brandt, Zee, Codori, & Folstein, 1993). Given the genetic and clinical overlap of schizophrenia with other psychiatric disorders and previous observations of shared endophenotypes for schizophrenia and, for example, bipolar disorder (Kathmann, Hochrein, Uwer, & Bondy, 2003; McDonald et al., 2004), diagnostic specificity need not constitute a necessary endophenotype validity criterion.

Antisaccades in Other Neuropsychiatric Disorders

Compared to the considerable body of research on patients with schizophrenia, comparatively few studies have explored antisaccade performance in other psychiatric disorders. Studies that have compared antisaccade performance in patients with schizophrenia to patients with affective disorder have produced inconsistent results. Several studies have found increased antisaccade errors in groups of patients diagnosed with bipolar disorder (Gooding & Tallent, 2001; Katsanis et al., 1997; Tien et al., 1996), but not all do (Crawford et al., 1995). However, a recent study showed that antisaccade performance is not temporally stable in bipolar disorder (whereas schizophrenia patients in the same study showed reliable performance), suggesting that this deficit may be a state not trait marker of bipolar disorder (Gooding et al., 2004).

In addition, one study (Curtis et al., 2001) found increased errors in a mixed group of patients with either major depression with psychotic features or bipolar disorder with psychotic features. Together these findings suggest that increased antisaccade errors may be associated with disorders in which psychosis is a feature. Given observations of shared genetic vulnerability between bipolar disorder and schizophrenia (McDonald et al., 2004; Möller, 2003), it remains to be tested whether antisaccade deficits reflect vulnerability to either or both of these diseases, although the low temporal stability in the bipolar group would argue against this (Gooding et al., 2004). The possibility that increased errors may be even less specific is raised by the finding that antisaccade errors were also increased in a group ($N = 29$) of patients with unipolar depression, of whom only 11 were diagnosed as having psychotic features (Sweeney, Strojwas, Mann, & Thase, 1998).

The results of studies examining antisaccade performance in patients with OCD are somewhat more consistent. Two studies have found that patients with OCD have increased antisaccade latencies, but not error rates compared to controls (Maruff, Purcell, Tyler, Pantelis, & Currie, 1999; McDowell & Clementz,

1997). Two early studies reported increased antisaccade error rates in patients with OCD compared to controls (Rosenberg, Dick, O'Hearn, & Sweeney, 1997; Tien, Pearlson, Machlin, Bylsma, & Hoehn-Saric, 1992); however, both of these studies had small *N*s and a small number of trials. Also, patients in the Rosenberg study displayed increased error rates only at one target position. As Tourette's syndrome can co-occur with OCD, and antisaccade errors have been shown to be increased in patients with this disorder (Dursun, Burke, & Reveley, 2000; Farber, Swerdlow, & Clementz, 1999; Mostofsky, Lasker, Singer, Denckla, & Zee, 2001), it will be important for future studies to ensure that such patients are excluded, or at least treated separately in any analyses.

Very few studies have explored antisaccade errors in other psychiatric patient populations, although increased error rates have been documented in ADHD (for a recent review, see O'Driscoll et al., 2005). This deficit may be more pronounced in the combined (inattentive and hyperactive/impulsive) subtype of ADHD than in the inattentive subtype and is most likely an expression of fronto-striatal pathology (O'Driscoll et al., 2005). Antisaccade abnormalities have also been demonstrated in autism (Minshew, Luna, & Sweeney, 1999) and dyslexia (Biscaldi, Fischer, & Hartnegg, 2000).

Increased antisaccade errors are also found in a number of neurological patient groups, including Alzheimer's disease (Shafiq-Antonacci, Maruff, Masters, & Currie, 2003), Huntington's disease (Lasker & Zee, 1997), Lewy body dementia (Mosimann et al., 2005), and progressive supranuclear palsy (Vidailhet et al., 1994). Reports of antisaccade errors in Parkinson's disease are inconsistent (Mosimann et al., 2005; Vidailhet et al., 1994), although the finding that a diagnosis of dementia is associated with impairments in this population suggests that deficits may only be observed when the disease has progressed to the extent that prefrontal cortex deterioration is likely (Vidailhet et al., 1994). An important difference between many neurological and psychiatric disorders, such as schizophrenia, is that prosaccades appear more impaired in the former than the latter conditions, suggesting a more widespread degeneration of brain areas involved in oculomotor control (Lasker & Zee, 1997; Mosimann et al., 2005; Shafiq-Antonacci et al., 2003).

Compared to the remarkable consistency found in the schizophrenia literature, the extent and nature of antisaccade deficits in other psychiatric populations thus remains unclear. In general, the findings are consistent with the hypothesis that antisaccade errors are increased in neuropsychiatric disorders that implicate frontal lobe dysfunction. However, no studies to date have used neuroimaging techniques to explore the neural correlates of antisaccade performance in nonschizophrenic patient populations. Well-powered studies that explore antisaccade performance simultaneously in multiple psychiatric populations are needed to determine the extent to which any measures of antisaccade performance are specific to schizophrenia (or psychosis more generally), whether different psychiatric disorders are associated with different patterns of antisaccade abnormalities, and whether these abnormalities reflect state as opposed to trait characteristics.

Pharmacological Modulation of Antisaccade Performance

A number of pharmacological compounds affect antisaccade performance in psychiatric and healthy humans in a manner consistent with cognitive and neurobiological research outlined above, suggesting that the task may serve as a useful tool in drug research.

The neurotransmitter acetylcholine plays an important role in cognition. Nicotine, a cholinergic agonist, reduces error rates in healthy and schizophrenic smokers without affecting antisaccade latencies or prosaccades performance (Dépatie et al., 2002; Powell, Dawkins, & Davis, 2002). On the other hand, procyclidine, an anticholinergic compound, may impair performance in schizophrenia patients (Ettinger et al., 2003b). These findings are compatible with antisaccade impairments in Alzheimer's disease, a condition with known cholinergic neuron degeneration (Shafiq-Antonacci et al., 2003), and with the role of cholinergic agonists as cognitive enhancers in neuropsychiatric disorders (Levin, 1992).

Methylphenidate is a cognitive enhancer that blocks reuptake of both dopamine and noradrenaline by inhibiting the dopamine transporter. Two experimentally controlled studies of boys with ADHD showed that methylphenidate treatment is associated with accelerated antisaccade and prosaccade latency as well as reduced antisaccade error rate (Klein, Fischer, Fischer, & Hartnegg, 2002; O'Driscoll et al., 2005).

Antagonists at the 5-hydroxytryptamine (5HT)-2 receptor, such as risperidone or cyproheptadine, improve error rates in people with schizophrenia (Burke & Reveley, 2002; Chaudhry, Soni, Hellewell, & Deakin, 2002;however, see Harris, Reilly, Keshavan, & Sweeney, 2006). Risperidone also prolongs prosaccade latencies of step (Reilly, Harris, Keshavan, & Sweeney, 2005) but not gap tasks (Burke & Reveley, 2002), suggesting that the beneficial effects on antisaccade errors may reflect a gain secondary to this prosaccade impairment. These pharmacological effects are consistent with parallel processing models of competition between antisaccade and prosaccade generation and suggest that 5HT-2 antagonists may slow prosaccades, resulting in the antisaccade program being completed first (Massen, 2004).

Benzodiazepines, on the other hand, do not consistently affect prosaccade latencies but increase antisaccade latencies and error rates (Green & King, 1998; Green, King, & Trimble, 2000). These compounds thus affect voluntary antisaccade generation to a greater extent than the reflexive component.

The sensitivity of antisaccade performance to manipulation of neurotransmitter systems implicated in the pathophysiology and treatment of a number of neuropsychiatric conditions suggests that this task may serve as a benchmark test in developing drugs aimed at improving neurocognitive deficits. The task may allow the study of dissociable pharmacological influences on reflexive and volitional responses, as illustrated in parallel processing accounts of the task (Massen, 2004). Of additional advantage in this context are the excellent reliability of performance measurement, the ease of task administration, the clarity of instructions (making failures to comprehend unlikely), the existence of suitable oculomotor control conditions (e.g., the prosaccade and fixation tasks), and the well-known neural correlates of the oculomotor system. One example for such an application is the ketamine model of psychosis, which is known to induce the positive, negative, and cognitive symptoms (Krystal et al., 1994) of psychosis and has been shown to induce antisaccade deficits in monkeys (Condy, Wattiez, Rivaud-Pechoux, & Gaymard, 2005) and, nonsignificantly, in humans (Radant, Bowdle, Cowley, Kharasch, & Roy-Byrne, 1998). Of further relevance to schizophrenia research is the putative link of antisaccade deficits with schizophrenia candidate polymorphisms discussed earlier,

which suggests that this task may be a useful target (endo-) phenotype in *pharmacogenetic* studies of cognitive enhancers.

Conclusions

Research summarized in this review points to significant impairments on the antisaccade task in patient groups involving fronto-striatal pathology, in particular schizophrenia. These impairments are broadly compatible with a "competition" model of antisaccade performance, which suggests that antisaccade errors are a function of the ability to adequately activate an internal representation of the task goal within prefrontally mediated working memory.

However, if the antisaccade task is to provide psychiatric researchers with further insights, a number of fundamental issues remain to be resolved. In particular, it will be important to establish whether antisaccade abnormalities in various psychiatric disorders reflect the same underlying neuropathological abnormalities. The limited research to date has found that impairments in nonschizophrenic patient populations are generally not as severe as in schizophrenia, suggesting only partially overlapping neuropathology. Future studies utilizing a more complete set of antisaccade performance measures, including latency and spatial accuracy, may be instructive in addressing issues of nosological and neuropathological specificity.

As Reuter and Kathmann (2004) point out, another crucial task for future research is to develop a more comprehensive cognitive model of antisaccade performance and further clarify the relationship between antisaccade performance and constructs such as inhibition, working memory, and goal activation. Recent antisaccade research in nonpsychiatric populations might provide a good basis on which to proceed and to interpret findings in psychiatric patients. In particular, research that experimentally varies antisaccade task conditions, both in terms of the stimulus properties and instructions given, will allow more concrete conclusions to be drawn concerning the cognitive and neural processes underlying antisaccade performance in healthy and neuropsychiatric populations. One potentially useful future direction would be to employ contingency analysis, as this approach can address important issues concerning deficits associated with ongoing monitoring and control of behavior in patients with psychiatric disorders.

As outlined above, there is evidence that antisaccade deficits may mark genetic liability for schizophrenia. For this research program to progress, large-scale molecular genetic studies of antisaccade performance, such as linkage or candidate gene designs, are required. These studies should take the above recommendations concerning various performance parameters into consideration by investigating genetic effects on latency and spatial accuracy as well as reflexive errors.

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