Reduced Attentional Engagement Contributes to Deficits in Prefrontal Inhibitory Control in Schizophrenia

James L. Reilly, Margret S.H. Harris, Tin T. Khine, Matcheri S. Keshavan, and John A. Sweeney

Background: Problems with the voluntary control of behavior, such as those leading to increased antisaccade errors, are accepted as evidence of prefrontal dysfunction in schizophrenia. We previously reported that speeded prosaccade responses, i.e., shorter response latencies for automatic shifts of attention to visual targets, were associated with higher antisaccade error rates in schizophrenia. This suggests that dysregulation of automatic attentional processes may contribute to disturbances in prefrontally mediated control of voluntary behavior.

Methods: Twenty-four antipsychotic-naïve schizophrenia patients and 30 healthy individuals completed three tasks: a no-gap prosaccade task in which subjects shifted gaze toward a peripheral target that appeared coincident with the disappearance of a central fixation target and separate prosaccade and antisaccade tasks in which a temporal gap or overlap of the central target offset and peripheral target onset occurred. Sixteen patients were retested after 6 weeks of antipsychotic treatment.

Results: Patients' prosaccade latencies in the no-gap task were speeded compared with healthy individuals. While patients were not atypical in the degree to which response latencies were speeded or slowed by the gap and overlap manipulations, those patients with diminished attentional engagement on the prosaccade task (i.e., reduced overlap effect) had significantly elevated antisaccade error rates. This effect persisted in patients evaluated after antipsychotic treatment.

Conclusions: This study provides evidence that a reduced ability to engage attention may render patients more distracted by sensory inputs, thereby further compromising impaired executive control during antisaccade tasks. Thus, alterations in attentional and executive control functions can synergistically disrupt voluntary behavioral responses in schizophrenia.

Key Words: Antisaccade, attention, executive functions, prefrontal cortex, prosaccade, schizophrenia

Prefrontal cortical systems dysfunction is believed to underlie many cognitive abnormalities in schizophrenia including the regulation of attention and behavior. Cognitive neuroscience provides a useful framework for understanding mechanisms that support automatic and voluntary attention (1) and how disturbances in these processes may contribute to problems in the executive control of behavior (2). The linkage between oculomotor and attentional brain systems (3,4) makes eye movement paradigms particularly relevant for investigating mechanisms of attentional and inhibitory control deficits in schizophrenia (5).

Prosaccade paradigms measure saccadic eye movements influenced by automatic shifts of visual attention. In these tasks, subjects must disengage attention from a central location and redirect their gaze to a peripheral target when it appears. In contrast, antisaccade tasks require greater executive control of visual attention shifts because subjects must inhibit the automatic response to look toward the target and instead generate an eye movement to a mirrored location. These operations depend upon voluntary executive control processes regulated by prefrontal cortex (6–9).

Multiple studies have reported elevated antisaccade error rates in schizophrenia patients (10–12), which are believed to represent disturbances in the prefrontally mediated ability to voluntarily suppress prepotent responses (7,13). Patients followed longitudinally show a persistent elevation in antisaccade error rates over time, suggesting an enduring deficit of prefrontal functioning (14–16).

We previously reported that antipsychotic-naïve first-episode schizophrenia patients responded more quickly than healthy individuals to visual targets in a prosaccade task, suggesting an abnormality in automatic attentional regulation of sensorimotor systems by neocortical regions (17). Moreover, this speeded responding was associated with increased errors on an antisaccade task (15). These findings suggest that abnormalities in the regulation of automatic orienting and the executive control of attention may both contribute to deficits on antisaccade tasks in schizophrenia.

One approach for examining automatic attentional control is through the manipulation of visual fixation offset and peripheral target onset temporal asynchronies (Figure 1). Introduction of a temporal gap between the offset of the fixation target and peripheral cue onset reduces saccade latencies—the so-called gap effect (18,19). The offset of the central cue reduces activity in the visual fixation system, releasing the visual attention and saccade systems to more quickly respond to new stimuli (20). In contrast, overlap effects occur when the central target persists after the appearance of the peripheral cue, which prolongs activity in visual fixation systems and, in turn, increases response latencies. Gap and overlap effects thus reflect the balance between attentional systems that respond automatically to sensory input and fixation systems that maintain attention on objects

From the Center for Cognitive Medicine (JLR, MSHH, TTK, JAS), University of Illinois at Chicago, Chicago, Illinois; Department of Psychiatry and Behavorial Neurosciences (MSK), Wayne State University, Detroit, Michigan; and Department of Psychiatry (MSK, JAS), University of Pittsburgh, Pittsburgh, Pennsylvania.

Address reprint requests to James L. Reilly, Ph.D., Center for Cognitive Medicine, Department of Psychiatry, 912 South Wood Street, MC 913, University of Illinois at Chicago, Chicago, IL 60612; E-mail: jreilly@psych.uic.edu.

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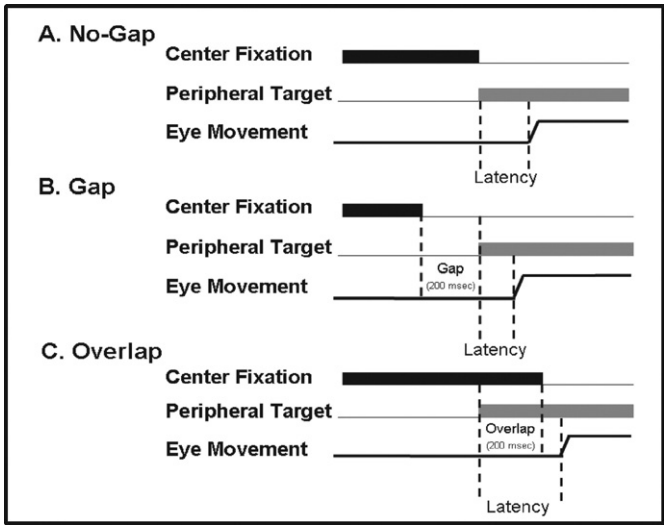

Figure 1. Manipulation of fixation at the central cue. **(A)** In no-gap trials, extinction of the central fixation target occurred simultaneous to the appearance of the peripheral target. **(B)** In gap trials, the central fixation target was extinguished 200 msec prior to the appearance of the peripheral target. Response latencies under gap conditions are speeded relative to those in no-gap or overlap conditions due to a reduction of activity in the visual fixation system that frees the visual attention and saccade systems to more quickly respond to visual inputs. **(C)** In overlap trials, the central fixation target remains illuminated for 200 msec after the appearance of the peripheral target, thus maintaining attentional engagement at the central location and prolonging response latencies.

of interest. Prior studies have reported that schizophrenia patients show the expected change in prosaccade latencies in gap and overlap conditions; however, findings are mixed as to whether the degree of change under these manipulations is atypical in schizophrenia (21–23). It is not known how the degree of release or maintenance of visual attention under these conditions is associated with antisaccade errors in schizophrenia.

The present study used three paradigms to examine the relationship of automatic attention and executive control on antisaccade task performance in schizophrenia: 1) no-gap prosaccade trials; 2) interspersed gap and overlap prosaccade trials; and 3) interspersed gap and overlap antisaccade trials. We had three aims. First, we sought to replicate in an independent sample the prior finding of speeded prosaccade latencies among untreated schizophrenia patients in a no-gap prosaccade task. Second, we aimed to determine whether any group difference in prosaccade latencies was greater in gap conditions or reduced in overlap conditions. And third, we sought to evaluate how individual differences in the extent to which visual attention was automatically released or maintained by central fixation targets were related to antisaccade error rates. This last aim sought to clarify whether our prior finding of an association of speeded orienting responses on a prosaccade task and elevated antisaccade error rates among schizophrenia patients (15) was due to a speeded release from fixation in the absence of target (increased gap effect), a less robust maintenance of visual fixation (reduced overlap effect), or a combination thereof. A subset of patients was retested after 6 weeks of treatment with antipsychotic medication to examine changes in performance after treatment and clinical stabilization.

Methods and Materials

Subjects

Twenty-four antipsychotic-naïve individuals (16 male subjects, 8 female subjects) with a DSM-IV diagnosis of schizophrenia (n = 22) or schizoaffective disorder (n = 2) according to structured clinical interviews (Structured Clinical Interview for DSM-IV [SCID]) (24) and additional clinical data reviewed at consensus diagnosis meetings participated. Thirty healthy individuals (14 male subjects, 16 female subjects) recruited from the community matched patients on age, sex, and intelligence quotient (IQ) (Table 1). Patients and healthy individuals were completely independent from those reported in prior studies (15,17). Patients first experienced psychotic symptoms 15 months on average prior to entering the study. Healthy individuals did not meet current or past criteria for any Axis I disorder according to SCID interviews, nor did they report psychotic or mood disorders among first-degree relatives. All subjects met the following criteria: 1) no systemic or neurologic disease; 2) no past head trauma with loss of consciousness; 3) no lifetime history of substance dependence and no substance abuse for at least 3 months prior to participation; 4) no benzodiazepines (for at least five half-lives) prior to testing; and 5) no coffee, tea, or cigarettes for 1 hour prior to testing. All subjects provided verbal and written informed consent. This study was approved by the University of Pittsburgh Institutional Review Board.

Procedures

Patients' baseline eye movement studies were completed prior to any lifetime antipsychotic treatment. Symptom ratings were completed by clinicians who remained blind to performance on eye movement tasks using the Brief Psychiatric Rating Scale (BPRS) (25), the Schedules for the Assessment of Positive Symptoms (SAPS) (26) and Negative Symptoms (SANS) (27), and the 24-item Hamilton Depression Rating Scale (HAM-D-24) (28) (Table 1). Sixteen patients were available for retesting after an average of 6 weeks of treatment with antipsychotic medications (13 treated with risperidone [2.6 ± 1.4 mg/day]; 3 treated with olanzapine [all 10.0 mg/day]) (Table 1). These patients did not differ on demographic or baseline clinical or eye movement performance from those available only at baseline.

Oculomotor Tasks

Subjects were tested in a darkened black room. Stimuli subtending 1° of visual angle were presented in the horizontal plane at eye level on a 20-inch monitor (Model GDM-20E21; Silicon Graphics, Sunnyvale, California) located 27 inches from the subject. A chin rest with forehead and occipital restraints minimized head movement. An examiner in an adjacent room provided instructions via intercom. Eye movements were monitored using infrared reflection sensors mounted on spectacle frames (Model 210; Applied Science Laboratories, Inc., Bedford, Massachusetts). Blinks were identified using electrodes placed above and below the left eye. Data were digitized online at 500 Hz and stored for offline analysis. Tasks were administered to all subjects in the order described below.

No-Gap Prosaccade Task. Subjects fixated a central target for a variable period (2000–3000 msec) after which the central target extinguished simultaneously with a peripheral target unpredictably appearing at 7.5° or 15.0° to the right or left of center (Figure 1A). Subjects were instructed to look to the peripheral target as soon as it appeared. The peripheral target remained illuminated for 1500 msec, after which it was extin-