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Clinical correlates of saccadic eye movement in antipsychotic-naïve schizophrenia

Aditi Subramaniam[a,b,1,2], Vijay Danivas[a,b,1,2], Sri Mahavir Agarwal[a,b,1,2], Sunil Kalmady[a,b,1,2], Venkataram Shivakumar[a,b,1,2], Anekal C. Amaresha[a,b,1,2], Anushree Bose[a,b,1,2], Janardhanan C. Narayanaswamy[a,b,1,2], Shivarama Varambally[a,b,1,2], Samuel B. Hutton[c], Ganesan Venkatasubramanian[a,b,*,1,2], Bangalore N. Gangadhar[a,b,1,2]

[a] InSTAR Program, The Schizophrenia Clinic, Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bangalore, India
[b] Translational Psychiatry Laboratory, Neurobiology Research Centre, National Institute of Mental Health and Neurosciences, Bangalore, India
[c] University of Sussex, Brighton, United Kingdom

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ABSTRACT

Some aspects of saccadic performance have been found to be abnormal in chronic schizophrenia. The majority of this research has, however, been performed on patients treated with long-term antipsychotic medication. Very few studies have examined saccadic performance in antipsychotic-naïve/free patients. There are also very few studies describing the relationship between saccadic performance and clinical symptoms, particularly in antipsychotic free patients. In this study, we compared pro and antisaccade performance in a large sample of antipsychotic-naïve/free schizophrenia patients (N = 45) with healthy controls (N = 57). Clinical symptoms were assessed using Scale for Assessment of Positive Symptoms (SAPS) and Negative Symptoms (SANS). In the antisaccade task, patients made significantly more errors, and their correct antisaccades had smaller amplitudes in comparison to healthy controls. Higher error rates were associated with increased severity of hallucinations. In the prosaccade task, patients had less accurate final eye positions, and made saccades with slower latency and reduced amplitude compared to the healthy controls. These observations in schizophrenia patients without the potential confounds of antipsychotic treatment suggest intrinsic link between saccadic deficits and schizophrenia pathogenesis. The relationship between antisaccade errors and hallucination severity supports the potential link between hallucinations and deficits in inhibitory control.

1. Introduction

Oculomotor abnormalities such as increased antisaccade error rate and reduced smooth pursuit velocity gain have been consistently observed in schizophrenia patients (Hutton and Ettinger, 2006; O'Driscoll and Callahan, 2008), and it has been argued that the study of eye movements offers a valuable paradigm for elucidating the neurophysiological basis of schizophrenia. The neurological circuitry underlying eye movements has been well established in primates (Goldberg and Colby, 1992), and their corresponding human counterparts have also been identified using functional imaging. Importantly, the key neural circuits involved in oculomotor control share brain regions that are implicated in schizophrenia pathogenesis (O'Driscoll et al., 2000). Moreover, eye movements provide a non-invasive yet precise and accessible means of investigating psychomotor functioning as well as neural mechanisms of higher-order cognitive processes (Gooding and Basso, 2008).

Saccades are ballistic, conjugate eye movements that alter the point of fixation of the fovea. Visually guided saccades or prosaccades are generated towards a particular target in the visual field, and rely on simple sensorimotor transformations for optimal performance. Volitional saccades, such as those performed in the antisaccade task, involve higher level cognitive processes such as goal activation and spatial memory, requiring the participant to inhibit a pre-potent response of looking at a visual target, and instead generate an endogenously driven saccade to the mirror image location of the target (Hutton and Ettinger, 2006).

Many studies have shown that prosaccade performance in

* Correspondence to: Department of Psychiatry, National Institute of Mental Health And Neurosciences (NIMHANS), Bangalore 560029, India.
E-mail address: venkat.nimhans@yahoo.com (G. Venkatasubramanian).
[1] www.instar-program.org.
[2] www.transpsych-lab.org.

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schizophrenia patients is comparable with that of healthy controls, with patients showing normal latencies and accuracy (Ettinger et al., 2006; Smyrnis et al., 2004), suggesting that basic saccade circuitry may be intact in schizophrenia patients. One study reported faster prosaccade latency in severe, untreated schizophrenia that normalised after treatment with a second generation antipsychotic (Reilly et al., 2005). Medicated schizophrenia patients have also been shown to generate a higher percentage of express saccades in the gap prosaccade paradigm than healthy subjects (Winograd-Gurvich et al., 2008).

Volitional saccades (such as are required in the antisaccade task) are more cognitively complex than visually guided saccades. Numerous studies have shown that patients with schizophrenia make significantly more antisaccade errors than matched comparison subjects (Hutton et al., 1998; Radant et al., 2007; Reuter et al., 2005; Waters et al., 2009; Zanelli et al., 2005). Increased errors in the antisaccade task are generally interpreted as reflecting impaired inhibitory control mediated by dysfunctional prefrontal cortex in schizophrenia (Clementz, 1998). A number of PET and fMRI 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 (O'Driscoll et al., 1995; Sweeney et al., 1996).

There is sparse literature on the relationship between antisaccade error rates and specific measures of psychopathology in schizophrenia. It is also worth noting that, in most antisaccade studies, psychopathological rating scales are administered to patients, but only a minority of papers report correlational analyses between these measures and antisaccade performance (Hutton and Ettinger, 2006). An earlier study examining schizophrenia patients reported that the internally guided and externally triggered saccades showed abnormally long latencies, slightly smaller gains, and an increased rate of suppression errors regardless of the medication status (Muller et al., 1999); nonetheless, the saccadic velocity did not differ significantly between patients and controls (Straube et al., 1999). Yet another study reported elevated antisaccade error rate in schizophrenia patients (Harris et al., 2009). The results of some of the other studies are 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., 2004, 2006). In a recent report, it was reported that antipsychotic-naïve first-episode schizophrenia patients demonstrated intact performance on a predictive saccade task; however, after treatment with antipsychotic medications, the patients showed a selective deficit in the accuracy of anticipatory responses (Keedy et al., 2014). In addition, previous studies have shown that antipsychotic medication can impair antisaccade task performance; for example risperidone (Schmechtig et al., 2013) as well as haloperidol (Babin et al., 2011) were shown to result in deficient task performance. These inconsistent observations might potentially be due to differences in the size and type of study sample, variations in the methodology and confounds of antipsychotic treatment. Thus, there is a need to further examine the saccadic performance and its relationship with symptom profile in antipsychotic naïve/free patients.

Our study aimed to overcome some of the limitations of the previous studies by studying a relatively large sample of antipsychotic-naïve/free schizophrenia patients. We used a standard gap saccade paradigm for both the prosaccade and antisaccade tasks. In addition, we examined for potential correlations between eye movement parameters and clinical symptom scores. Impaired intentional inhibitory control has been associated with the genesis of hallucinations (Waters et al., 2003). Since performance in antisaccade task reflects the ability for intentional inhibition, we hypothesized that there will be a significant correlation between antisaccade performance deficits and hallucinations score.

2. Methods

Patients attending the out-patient clinical services of the National Institute of Mental Health & Neurosciences (India), who fulfilled DSM-IV criteria for schizophrenia (N = 45; age = 31.2 ± 7.2 years; 31 men) were examined in this study. The patients were either antipsychotic-naïve (N = 37; never treated with any psychotropic medications including antipsychotics) or antipsychotic-free (N = 8; not having received any psychotropic medication including antipsychotics atleast for the past six weeks). The diagnosis of schizophrenia was established using Mini International Neuropsychiatric Interview Plus (Sheehan et al., 1998), which was confirmed by another psychiatrist through an independent clinical interview. The details related to illness onset and antipsychotic-naïve/free status was carefully ascertained by reliable information obtained from at least one reliable adult relative. Clinical symptoms were assessed using Scale for Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1983). The sub-scale scores of clinical symptoms represent sum of relevant items that have been shown to be valid (Andreasen and Olsen, 1982).

Healthy controls (N = 57; age = 26.8 ± 3.2 years; 35 men), who volunteered for study, were screened to rule out any psychiatric diagnosis using the MINI Plus (Sheehan et al., 1998) as well as a comprehensive mental status examination. None of the controls had family history of psychiatric disorder in first-degree relatives.

Only those subjects that were right-handed [as ascertained by Edinburgh Handedness Inventory (Oldfield, 1971)], were examined in this study. None of the participants had clinically significant ophthalmological problems or uncorrected refractory errors. Patients and controls did not have features suggestive of alcohol abuse / dependence. None used stimulant or opiate drug. None had history or clinical feature suggestive of neurological/medical disorder. None had abnormal movements as assessed by Abnormal Involuntary Movements Scale. Clinical assessments and eye tracking experiments were performed on the same day before starting antipsychotics. After complete description of study to the subjects, written informed consent was obtained. The research protocol was reviewed and approved by the National Institute of Mental Health and Neurosciences (NIMHANS) ethics committee.

2.1. Eye tracking methodology

Eye movement recordings were conducted in a room with controlled illuminance. Before the eye tracking experiments, the ocular dominance was assessed using the hole-in-the-card-test (Dolman method) (Cheng et al., 2004). In this test, the participant was instructed to hold a piece of cardboard with a central circular hole through which they had to view a target at about 6 m away with both eyes open. Subsequently, each eye was occluded in turn. The target would not be seen through the hole when the dominant eye was covered; on the contrary, the target persisted to be seen when the non-dominant eye was covered since the dominant eye would continue to fix the target. In this forced-choice test of dominance, there was only one result for dominance (left or right). The eye movement data of the subject was recorded using the dominant eye to avoid potential confounding effect of differential dominance on eye tracking measures (Vergilino-Perez et al., 2012).

Stimuli were displayed on a 22-in. flat screen monitor (FuzHion, Viewsonic, 120 Hz) placed 74.3 cm in front of the subject. Eye tracking data were collected using an EyeLink 1000 eye tracker (SR Research, Canada) sampling at 1000 Hz. Head movements were constrained using chin rest and forehead abutments. The saccadic task was based on the principles and procedures as described earlier (Taylor and Hutton, 2009). All subjects were explained about the task in detail and it was ensured that they understood the task.

Each participant performed a total of 24 prosaccade trials in one block followed by 48 antisaccade trials in the subsequent block. We chose to have lesser number of prosaccade trials since they were relatively easier for the patients to learn and perform; since we examined schizophrenia patients that were antipsychotic-naïve, lesser number of prosaccade trials ensured that the total duration of the eye tracking