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Deficit of inhibition motor control in untreated patients with schizophrenia: Further support from visually guided saccade paradigms

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ABSTRACT

In addition to classical delusional, negative, and cognitive deficit, schizophrenia has consistently been associated with impairments in saccadic eye movements, e.g., an increased error rate in the antisaccade task. We hypothesized that a deficit in inhibitory control is a core defect in untreated patients with schizophrenia leading to impairment in different oculomotor paradigms. Ten drug-free or drug-naïve patients with schizophrenia were matched in age and gender to 11 healthy controls with no psychoactive substance use or abuse. They were explored using reflexive saccades with unpredictable targets with or without the gap procedure, predictive saccades and a fixation/distracter paradigm. Patients with schizophrenia displayed shorter latency in reflexive and predictive saccades. In the GAP condition, patients made more anticipatory saccades, fewer regular saccades, and had a shorter latency of express saccades than controls. In addition, patients had an increased error rate in the fixation/distracters task. Altogether, these results provide new evidence of reduced prefrontal inhibitory regulation of subcortical and brainstem systems involved in the control of saccades.

1. Introduction

Schizophrenia is a severe and disabling chronic disorder with a typical onset during adolescence or young adulthood. Schizophrenic symptoms are various and include hallucinations and delusions, as well as blunted or inappropriate affect, loss of initiative, thought and language disorders, and loss of interest. Despite extensive research, the neural basis of schizophrenia is still not well understood, although several lines of evidence suggest that a deficit in inhibitory processes could account for several schizophrenic symptoms (Lisman et al., 2008; Wobrock et al., 2008; Gonzales-Burgos and Lewis, 2008). Cognitive impairment has been recognized as one of the most prominent features characterizing schizophrenia. Oculomotor studies provide a promising approach for exploring cognitive alterations in patients with schizophrenia. Among the various anomalies in spatial attention as well as in oculomotor programming described in patients, one of the most identifiable is the deficit in inhibition (Calkins et al., 2008).

Deficiencies in inhibitory control have been reported in several types of saccadic tasks in schizophrenia, although most of the studies were carried out in medicated patients with variable disease duration, and usually explored one or two oculomotor paradigms. Impaired saccade inhibition in the antisaccade task is a consistent result in the literature (Curtis et al., 2001 also reviewed in Hutton and Ettinger, 2006) and could be associated with schizophrenia vulnerability (Calkins et al., 2008). The suppression of unwanted reflexive saccades to distracters during fixation has also been investigated in schizophrenia, with evidence of more errors in patients in some (Curtis et al., 2001; Winograd-Gurvich et al., 2008), but not all, studies (Hutton et al., 2001). Increased rates of express saccades were also described when using a "gap" paradigm (short delay between fixation point extinction and target illumination) (Currie et al., 1993; Matsue et al., 1994).

Further supporting the value of oculomotor studies to study the pathophysiology of schizophrenia, brain imaging studies have showed that there is an overlap between the regions found altered in schizophrenia and those underlying saccade generation and control. These regions include both frontal cortical areas (i.e., frontal eye field (FEF), supplementary eye field (SEF), dorsolateral pre-frontal cortex (DLPFC)) (Tsunoda et al., 2005) as well as subcortical areas (i.e., striatum and thalamus) (Buchsbaum et al., 1998; Crespo-Facorro et al. 2007; Fukumoto-Motoshima et al., 2009). More specifically, an increased rate of error in antisaccade movements in patients was found to be

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associated with reduced premotor cortex volume as a whole (Ettinger et al., 2004) and a significant lack of activation of the striatum on functional magnetic resonance imaging (fMRI) (Raemakers et al., 2002). The authors concluded that a dysfunction of the fronto-striatal thalamic loop could account for this deficit in inhibitory control.

Only a limited number of studies have been conducted in unmedicated or naïve patients. Regarding reflexive visually guided saccades, Reilly et al. (2005, 2008) have reported that naïve patients display shorter latencies compared to controls. Peak velocity was found to be similar (Reilly et al., 2005; Reilly et al., 2008), whereas Mahlberg et al. (2001) reported higher peak velocity in unmedicated patients compared to controls. Hypometric saccades were described in unmedicated patients (Mahlberg et al., 2001), while no significant differences were found in naïve patients (Reilly et al, 2005; Reilly et al., 2008). In the predictive saccade task, Harris et al. (2009) reported normal latencies and Mahlberg et al. (2001) described a higher peak velocity. In a previous independent study, we found a specific impairment in the accuracy of anticipatory saccades in antipsychotic-free or naïve patients with schizophrenia compared to controls, with no significant differences in peak velocity or latency (Krebs et al., 2001). Functional brain imaging revealed reduced activation across the dorsal neocortical oculomotor system, including bilateral FEF, SEF, intra-parietal sulcus (IPS) precuneus and cingulate cortex during smooth pursuit and visually guided saccades in naïve patients compared to controls (Keedy et al., 2006), whereas during memory guided saccades, patients displayed a reduced recruitment of the DLPFC.

We hypothesized that the deficit in inhibitory control is a core defect in patients with schizophrenia and that this deficit will be generalized across different oculomotor paradigms. To this end, we explored visually guided saccades with or without the gap paradigm, in fixation/distracters task, as well as in predictive saccades (where a prediction can be made about the target appearance) in naïve or unmedicated patients and matched controls.

2. Methods

2.1. Participants

Each participant provided written informed consent. This study was approved by the ethics committee: "Comité Consultatif de Protection des Personnes se prêtant à une Recherche Biomédicale" (CCPPRB) of the Pitié-Salpétrière Hospital (Paris).

- Ten untreated patients with schizophrenia (Patients), satisfying Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 2000) criteria according to the structured clinical interview Diagnostic Interview for Genetic Studies (DIGS 3.0; Nurnberger et al., 1994, French version Krebs et al.) were recruited from our Department at Sainte-Anne Hospital (Paris). There were eight men and two women, with a mean age ± S.D.: 27 ± 4.8 years and a mean level of education of 11.8 ± 3.3 years of education. Nine were antipsychotic naïve; one participant was treatment free for 3 months following 1 year of risperidone. The age of first psychotic episode was 22 ± 7.5 (mean ± S.D.) and the mean duration of illness was 3.3 ± 2.1 years (between first episode and time of assessment). Psychopathology was assessed with the Positive and Negative Symptoms Scale (PANSS, Kay et al., 1988): means ± S.D.: total score: 82.3 ± 8, Positive sub-score: 21.7 ± 4, Negative sub-score: 18.5 ± 7, General Psychopathology: 42.5 ± 5.
- Eleven healthy controls (Controls) (nine men and two women, mean age ± S.D.: men: 21.7 ± 2.6 years, women: 20.5 ± 0.7 years, level of education: 14.1 ± 0.7 years were screened using a Structured Clinical Interview for Non-Patients (SCID-NP) (First et al., 1995). Exclusion criteria were any personal or familial axis 1 psychiatric or neurological illnesses up to the second degree. Groups were similar for age and gender but not for level of education ($P<0.05$).
- Exclusion criteria for all subjects included organic brain pathology, head injury, electroconvulsive therapy, substance abuse or dependence, concomitant medication or current use of psychoactive substance including cannabis (checked by urinary screening the day of the test) and heavy smoking (40 cigarettes a day or more). Because it has been shown that nicotine can acutely modify saccadic parameters, in particular by decreasing the error rate in antisaccades and speeding latencies (Larrison-Faucher et al., 2004), we minimized the influence of tobacco by refraining controls and patients from smoking at the clinical research center. Ocular-motor testing occurred in the morning, 90–120 min after their arrival so that the results were not influenced by either the acute effect of tobacco or by withdrawal effect or craving.

2.2. Saccadic eye movement tasks

Participants sat on a height-adjustable chair in a darkened quiet room 150 cm in front of a light-emitting diode bar. Pre-programmed pseudo-random visual sequences were administered and sampled with a frequency of 500 Hz with data acquisition software developed in our laboratory by J. Serran and D. Vital. Horizontal eye movements were recorded using an infra-red oculography device (IRIS, Skalar) employing iris/sclera reflection (5 V, resolution of 1 min of an arc, linearity 0 ± 25°) (Reulen et al., 1986). The data acquisition was managed by our customized software (sampling frequency 500 Hz, for more details see Ramdane-Cherif et al. (2004)). Instructions were to direct the gaze toward the peripheral light as quickly and as precisely as possible, except in the fixation task. Each paradigm was presented in three blocks of 10 different trials after a practice block of 10 trials was added before the beginning of the trial procedure. The saccadic tasks were presented in the following order and there were rest breaks between all the protocols. All participants completed all tasks.

2.2.1. Reflexive saccades

Peripheral targets appeared for a duration of 800 ms with a pseudo-random eccentricity (±4–12°) and timing (duration of fixation between targets: 1500–2500 ms), simultaneous to a central fixation offset (SIMPLE) or 200 ms after the fixation offset (GAP) (Fig. 1).

2.2.2. Predictive saccade tasks (PREDICTIVE)

In all predictive paradigms, the targets were illuminated at a fixed frequency of 0.7 Hz. Depending on the block, targets were predictive both in timing and space (PREDICTIVE_B, PREDICTIVE_L and PREDICTIVE_R) or in timing but not in location (PREDICTIVE_T). In PREDICTIVE_B, the target appeared alternatively at ± 5° across the midline (i.e., 5° of eccentricity on left and right, similarly to Krebs et al., 2001). In order to detect a specific impairment due to the midline crossing, we tested two similar tasks, differing only in that the target remained in the left hemi-field (PREDICTIVE_L, alternating position from −5° to 0°) or in the right hemi-field (PREDICTIVE_R, 0° to +5°). In PREDICTIVE_T, the locations of the targets were pseudo-randomly distributed between ± 4 and 12°, thus the subject could anticipate when a target would appear but not where (Fig. 1). In predictive saccades, the instruction was the same as for simple saccades, but due to the regular rhythm imposed by the task, after a short delay (between two and five saccades) participants anticipate the appearance of the target, with a preplanned response based on the memory of the target location in the predictive tasks B, L and R but only based on "expectation" of target in task T.

2.2.3. Fixation/distracters (FIXATION)

The central light remained illuminated for 30 s. The distracters, namely peripheral targets, appeared randomly on 10 occasions with a pseudo-eccentricity (±4–12°), and for a fixed duration of 800 ms, while the central fixation remained illuminated. There was an equal number of left and right distracters and the instruction was to keep the gaze on the central light.

2.2.4. Saccade analyses

Two raters, blind to the clinical status and medication of the participants, analyzed the tracks, using our interactive software (computerized calibration and semi-automatic detection of saccades (Ramdane-Cherif et al., 2004). (1) *latency* (ms): delay between the target and primary saccade, (2) *rate* of anticipatory (latency<80 ms),

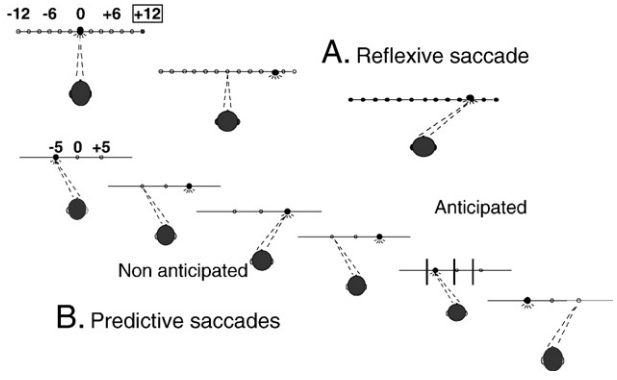

Fig. 1. A—The visual stimulus is presented in a random sequence to the left or right of a central fixation point and subjects are instructed to direct their gaze to the peripheral target with a rapid and accurate eye movement. The target is illuminated simultaneously to the offset of the fixation point (SIMPLE) or 200 ms after the offset (GAP). B—The visual target steps between two fixed locations (−5 and +5, PREDICTIVE_B; −5 and 0, PREDICTIVE_L; 0 and +5, PREDICTIVE_R) or appears in a pseudo-random location (PREDICTIVE_T) in a predictive temporal sequence. After a few saccades, the subject anticipates the target and direct his gaze toward the predicted location, when the target is still invisible.