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Saccadic eye movements as markers of schizophrenia spectrum: Exploration in at-risk mental states

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ABSTRACT

Schizophrenia is a neurodevelopmental disease with cognitive and motor impairments. Motor dysfunctions, such as eye movements or Neurological Soft Signs (NSS), are proposed as endophenotypic markers. Antisaccade (AS) and memory-guided saccades (MGS), two markers of inhibitory control mechanism, are altered in both patients with schizophrenia and their relatives, although these tools may have different sensitivities. Recently, emphasis has been put on identifying markers predictive of psychosis transition in subjects with ultra-high-risk psychosis in order to develop targeted prevention. This study investigates AS and MGS in 46 patients with schizophrenia, 23 ultra-high-risk subjects, and 39 full siblings compared to 47 healthy volunteers. NSS were assessed as a marker of abnormal neurodevelopment. The results revealed more errors in MGS in patients, ultra-high-risk subjects and siblings, than in controls, and more specifically ultra-high-risk subjects with high NSS scores. By contrast, the error rate in AS was significantly higher only in patients with schizophrenia compared to controls. These findings suggest that MGS could be more accurate to detect deficient inhibitory processes as a marker of vulnerability before the onset of schizophrenia. The use of the different paradigms (AS, MGS) revealed distinct profiles depending on the stage of the disease, indicating that some alterations could be pure endophenotypic markers of vulnerability for schizophrenia, while others could be markers of the disease progression.

1. Introduction

Schizophrenia begins in adolescence and encompasses cognitive and sensory-motor deficits (Insel, 2010). Early symptoms and dysfunctions predate the onset of the disease. These include alterations in working memory (Seidman et al., 2010) and attention (Keefe et al., 2006). Fusar-Poli et al. (2012) reported that subjects with Ultra high risk (UHR), who were prone to psychosis, showed important deficit in working memory especially in its visuo-spatial dimension. The neurodevelopmental hypothesis postulates that schizophrenia is the delayed expression of early-acquired brain abnormalities (Rappoport et al., 2005). Cognitive deficits could be considered as vulnerability markers of this disease, found in both relatives of patients and UHR. Neurological Soft Signs (NSS) are discrete sensorimotor impairments (e.g. discrete motor dyscoordination, impairment in sequencing, balance, sensory integration – see Krebs and Mouchet, 2007), associated with deviant brain development (Gay et al., 2013). Validating their status as endophenotypic markers reflecting vulnerability to schizophrenia, NSS are found in relatives of patients and within families, and follow the transmission of the genetic risk (Gourion et al., 2003, 2004). Eye movement tasks such as antisaccade (AS) or memory-guided saccades (MGS) have also been proposed as useful endophenotypes (Calkins et al., 2008) and NSS have been associated with eye movement abnormalities (Picard et al., 2009).

Eye movement paradigms are a useful tool to understand cognitive mechanisms involved in schizophrenia and their underlying neurophysiological correlates. In the antisaccade task (AS), subjects fixate a central cue, which is suddenly replaced by the onset of a peripheral target. Rather than reflexively shifting gaze to that target, subjects are instructed to look at the opposite mirror location (Hallett, 1978). In the memory-guided saccade task (MGS), subjects have to fixate on a cross in the center of a screen while a visual cue appears elsewhere; once the fixation cross disappears after a delay, they have to direct their gaze to the location where the stimulus appeared. AS and MGS involve inhibitory and working memory processes: AS requires

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disengagement of attention from a peripheral target, and working memory to make a reflexive saccade of the similar amplitude in the opposite direction (Crawford et al., 2011). MGS requires the subject to encode the spatial location of a stimulus, to manipulate visual–spatial information, maintain the representation of that location across a delay period, and finally, make a volitional response to the remembered target. Hence the subject has to refrain from making an anticipatory saccade, meaning that he/she has to wait for the extinction of the fixation point, and only at this moment, to make a saccade in a remembered location.

Correct performance of both AS and MGS requires suppression of making a saccade to the stimulus and initiation of the volitional response. However, in AS a volitional saccade has to be made immediately to the location, opposite to the peripheral target, whereas in MGS the volitional response has to be made after a delay.

Using the oculomotor delayed response task (Hikosaka and Wurtz, 1983), Luna et al. (2004) demonstrated that although basic aspects of working memory appear mature at the beginning of adolescence, the precision of corrective response still improves at the end of this period.

In schizophrenia, a large literature describes deficits in AS (Calkins et al., 2008; Nieman et al., 2000; Radant et al., 2007) and MGS (Calkins et al., 2008; McDowell and Clementz, 1996; Radant et al., 1997, Landgraf et al., 2008). These studies support a defect in the inhibitory control system and in working memory (Ross et al., 2000). Previous literature also showed that first-degree relatives of patients have altered AS (Calkins et al., 2008) and MGS (Calkins et al., 2008; Landgraf et al., 2008). Thus, inhibition errors and saccadic hypometria in MGS are cognitive endophenotypes of the disease (Landgraf et al., 2008), reflecting the vulnerability to schizophrenia. In UHR, only one study explored AS compared to patients with schizophrenia and controls, showing more errors in UHR and patients. Correlations were found between AS and spatial working memory (Nieman et al., 2007). Until now, no investigation explored MGS in UHR.

In order to examine the value of eye movements alteration as possible markers in at-risk mental states, we compared the sensitivity of AS and MGS in subjects expressing different degrees of vulnerability to schizophrenia spectrum compared to controls. Given that maintenance is central to working memory, we decided to select a MGS paradigm sensitive to maturation through adolescence and early adulthood, with an oculomotor delayed response task including different delays of response (Luna et al., 2004, 2008; Geier et al., 2009). Patients with schizophrenia, non-psychotic siblings, ultra-high-risk subjects and controls have been assessed. Our hypothesis was that eye movements would be altered in patients, and to a lesser degree in UHR and relatives. UHR subjects were clinically assessed using the CAARMS (Comprehensive Assessment of At-Risk Mental State, McGorry et al., 2003, French version Krebs et al., 2014), a semi-structured interview. The sensitivity of each eye movement task could be different depending on the level of expression of the vulnerability to schizophrenia and on the developmental load. We thus refined the analysis, taking into account the level of NSS.

2. Method

2.1. Participants

Forty-six patients with schizophrenia (SZ) (DSM IVR APA, 2003), 23 ultra high-risk subjects (UHR), 39 full biological non psychotic siblings of patients (FS) and 47 healthy volunteers (C) were recruited in the University Department of Psychiatry of Sainte-Anne Hospital (SHU), Paris, France. Only 14 full siblings of the 46 patients participated in this study. All subjects underwent the Diagnostic interview for Genetic Studies to attest diagnosis for SZ, and to exclude any diagnosis in FS and C (Nurnberger et al., 1994).

The investigation followed the principles of the Declaration of Helsinki and was approved by the Comité de Protection des Personnes CPP, Ile de France III, Hôpital Tarnier-Cochin (2012). Oral and written informed consent was obtained from all subjects and they received 50 euros for their participation.

Concerning treatment, no treatment was permitted for C and FS. Concerning SZ and UHR no benzodiazepine was authorized, and in case of anxiety or insomnia Hydroxyzine was permitted if dosage was inferior to 50 mg. If an antidepressant treatment was delivered, the treatment had to be initiated more than three weeks prior to the study. Details of treatments for SZ and UHR are given in Table 2. Controls were matched to SZ in both age and educational level.

For all subjects, exclusion criteria were as follows: history of neurological, cerebral, ophthalmological diseases, substance abuse or dependence for a period of more than five years, intellectual deficiency, or difficulties to understand French language, Simpson-Angus score ≥ 9 (Le Seac'h et al., 2012), abnormal involuntary movement scale score > 3 (Le Seac'h et al., 2012).

2.2. Clinical assessments

SZ and UHR were clinically assessed with the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987). In UHR, the criteria were confirmed with the CAARMS (Krebs et al., 2004; Magaud et al., 2014). Neurological Soft Signs (NSS) were assessed by experienced clinicians using the standardized examination (Krebs et al., 2000), including NSS as well as an assessment of extra-pyramidal symptoms (SAS-Simpson and Angus, 1970), abnormal involuntary movements scale (AIMS-Guy, 1976) and lateralization (adapted from the Edinburgh Inventory). In a previous study examining NSS in schizophrenia, we found a cut-off score of 11 to accurately discriminate patients from controls (Ouali et al., 2006).

2.3. Ocular-motor paradigms (see Fig. 1)

Stimuli were presented on a 22-inch PC screen, the resolution was 1920 × 1080 and the refresh rate was 60 Hz. The stimulus was a white-filled square subtending a visual angle of 0.5°. The trial consisted of a target positioned at the centre of the screen for a variable delay comprised between 1500 and 2500 ms.

In the AS after this fixation period, the central target was switched off and a target on the left or right side of the screen (at 6°–12°–18° of eccentricity) simultaneously switched on for 1500 ms. Subjects were instructed to look at the central fixation point, then to trigger a saccade as soon as possible in the opposite direction and symmetrically to the lateral target. Then, the central fixation target reappeared, signaling the beginning of the next trial.

In the MGS paradigm subjects first had to fixate on the central target. After 500 ms a target appeared for 150 ms on the right or the left side of the screen at 6°–.12°–18° of eccentricity. The central target extinction occurred 1000–2000–4000–8000 ms after peripheral target presentation. Subjects were instructed to look at the fixation point at the center of the screen while a peripheral light was switched on, had to remember the location of this peripheral target, wait for the extinction of the central fixation point, and explicitly, only after the fixation point was switched off, make a saccade directed toward the remembered target location.

Each subject performed three blocks of AS and MGS tasks. The AS block contained 12 trials randomly presented: six saccades to the left and six saccades to the right side. The MGS block contained eight trials randomly presented: four saccades to the left and four saccades to the right side.

Eye movements were recorded using the Mobile EBT Tracker (SuriCog), a CE-marked medical eye-tracking device. The Mobile EBT features cameras that capture the movements of each eye independently. Recording frequency was set up to 300 Hz. The precision of this system was 0.25°. There was no obstruction of the visual field with this recording system.

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