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Increased intra-subject reaction time variability in the volitional control of movement in schizophrenia

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ABSTRACT

Increased Reaction Time (RT) studies intra-subject variability is an emerging and consistent finding in RT studies of schizophrenia. A group of 23 patients suffering from DSM-IV schizophrenia and a group of 23 age-matched control subjects performed two RT tasks requiring basic sensorimotor processing and engaging two different motor systems: the Finger Lift Reaction Time task and the Voluntary Saccade Reaction Time task. The Ex-Gaussian model was applied to the RT distributions measuring the mean (mu), and standard deviation (sigma) of a Gaussian component thought to reflect sensorimotor processing and an exponential component (tau), thought to reflect an intermediate decision process. In both tasks, a significantly larger RT intra-subject variability effectively dissociated patients from controls. RT intra-subject variability in the two tasks was highly correlated only for patients. Both sigma and tau were significantly higher in the patient group with tau being the best predictor of schizophrenia. Furthermore, only in the patient group were sigma and tau highly correlated between the two tasks. The results reflect a deficit in information processing that may not be confined to decision processes related to the frontal cortex; rather, they may indicate dysfunction in distributed neural networks modulating adaptive regulation of performance.

1. Introduction

Reaction time (RT) studies demonstrate that patients suffering from schizophrenia are slower to respond than normal controls in a large variety of tasks (Nuechterlein, 1977). However, psychomotor slowing has also been observed in other mental disorders suggesting that this phenomenon might not be specific to schizophrenia (Schwartz et al., 1989). These patients also exhibit larger RT inter-subject and intra-subject variability compared to healthy controls (Shakow, 1962; Nuechterlein, 1977). Recently, several groups have suggested that RT intra-subject variability may be a specific measure of cognitive and sensorimotor processing stability rather than a by-product of increased mean RT (Rentrop et al., 2010). Neuroimaging studies have supported this proposal, showing a positive correlation between RT intra-subject variability and activation restricted primarily to frontal regions such as the dorsolateral prefrontal cortex (DLPFC) (Bellgrove et al., 2004; Yarkoni et al., 2009). Similarly, in a simple visuomotor RT task RT intra-subject variability was predicted by the rate of increase in premotor magnetoencephalographic (MEG) activity recorded from left central–frontal areas (Smyrnis et al., 2012).

A few studies have begun to unravel the connection or perhaps dissociation between mean RT and RT intra-subject variability in schizophrenia. In a simple manual response task mean RT was larger for all groups with psychotic symptoms (both schizophrenia and affective disorder) whereas RT intra-subject variability was larger specifically for the schizophrenia patients (Schwartz et al.,1989). In a later study, the increase in mean RT and RT intra-subject variability were positively related to the negative symptom load of schizophrenia patients (Schwartz et al., 1991). In a lexical decision choice RT task, mean RT and RT intra-subject variability were dissociated, the first being a specific predictor of the inability of the patients to maintain a cognitive set and the second being a specific predictor of the severity of psychotic and disorganization symptoms (Vinogradov et al., 1998). Kaiser et al., (2008) compared RT intra-subject variability in a go/no-go task among groups of patients with schizophrenia, major depression and borderline personality disorder. The RT intra-subject variability clearly dissociated schizophrenia patients from all other groups. An increase in RT intra-subject variability but not in mean RT has also been correlated with increased performance errors in patients with schizophrenia and major depression (Van den Bosch

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et al., 1996; Kaiser et al., 2008). These studies showed that RT distribution measures might provide insight into specific information processing deficits in patients with schizophrenia. In contrast to schizophrenia where RT distribution measures have not received attention these measures have been the major focus of research in Attention Deficit Hyperactivity Disorder (ADHD) (Castellanos and Tannock, 2002; Klein et al., 2006; Kuntsi and Klein, 2011). Intra-individual variability in RT was a powerful and reliable measure dissociating individuals with ADHD from normal controls independent of the particular cognitive task where RT was measured (Klein et al., 2006; Kuntsi and Klein, 2011).

RT is regularly measured in the study of saccadic eye movements, paradigms widely used in the study of psychiatric disorders and especially schizophrenia (Klein and Ettinger, 2008). Psychomotor slowing has not been observed for stimulus-elicited saccades (Iacono et al., 1981; Levin et al., 1982). In a comprehensive review of studies of visually guided saccades and schizophrenia, Gale and Holzman (2000) concluded that the mean RT in patients did not differ from that of controls. However, in a recent study of visually guided saccades, RT intra-subject variability but not mean saccadic RT was increased in patients with schizophrenia compared to healthy controls (Smyrnis et al., 2009).Volitional saccades are thought to reflect more complex processing than reflex-like stimulus-elicited saccades. Patients with schizophrenia executing volitional saccades such as antisaccades or memory saccades exhibited an increase in both mean RT and RT intra-subject variability (Crawford et al., 1998; Landgraf et al., 2008). In addition, these patients exhibited deficient performance in these volitional saccadic tasks, producing more errors in both antisaccade and memory saccade tasks (Fukushima et al., 1988; Everling et al., 1996; Boudet et al., 2005; Landgraf et al., 2008). Finally, the increase in RT intra-subject variability but not mean RT in the antisaccade task dissociated a small group of individuals with high schizotypy within a large sample of apparently healthy army conscripts (Smyrnis et al., 2003).

Based on the similarity of RT results of schizophrenia patients performing manual and saccadic tasks, we hypothesized that RT distribution characteristics could provide a robust dissociation of patients with schizophrenia from healthy controls in both types of sensorimotor processing. More specifically we hypothesized that the increase in RT variability in schizophrenia would be the same for the oculomotor and the hand motor system thus reflecting a common underlying mechanism producing increased variability in different brain systems. Tasks were designed to elicit a purely volitional movement (finger lift or saccade) in response to a visual stimulus. We then applied the Ex-Gaussian model to the RT distributions of both patients and healthy controls. The model is a Probability Density Function (PDF) formed by the combination of a Gaussian component and an exponential 'tail'. The model provides three basic parameters: mu and sigma correspond to the mean and SD of the Gaussian component while tau corresponds to the slope of the exponential component (Luce, 1986). The Ex-Gaussian model has been proposed to capture more accurately the RT distribution which is skewed to the right and thus cannot be described by a normal distribution (Luce, 1986). The Ex-Gaussian model exponential tau has also been shown to be most sensitive measure dissociating normal controls from schizophrenia patients in the study of Rentrop et al. (2010). The Ex-Gaussian model has also been used for the analysis of RT distribution differences between ADHD patients and controls (Leth-Steensen et al., 2000; Hervey et al., 2006; Vaurio et al., 2009; Buzy et al., 2009; Kollins et al., 2009). Our hypothesis was that specific differences in these RT distribution measures between schizophrenia patients and healthy controls would be observed that would be independent of the motor system involved.

2. Methods

2.1. Participants

The study sample consisted of 23 male patients suffering from DSM-IV schizophrenia and 23 healthy male controls. All participants provided written, informed consent and the study protocol for participation of patients was approved by the ethics committee of Eginition University Hospital. Patients were evaluated in the Psychosis Unit of the Psychiatry Department of the National and Kapodistrian University of Athens at Eginition Hospital and the diagnosis of schizophrenia confirmed by a trained psychiatrist with the use of the DIP-DM diagnostic module (McGuffin et al., 1991). The diagnostic module is designed around the Operational Criteria Checklist for Psychosis (OPCRIT) algorithm and is capable of generating diagnoses under DSM-IV. Criteria for exclusion were organic cerebral illness, mental retardation, benzodiazepine use, any oculomotor dysfunction and drug abuse within the year prior to evaluation. All patient participants were being treated with antipsychotic medication (mean daily dose in chloropromazine equivalents=858 mg, S.D.=753.90 mg) and were in a stable phase of the disorder during testing (Kroken et al., 2009).

The mean age of both groups was 30 years (S.D.=7.46 for patients and S.D.=6.46 for the control group) and did not differ significantly between the two groups ($t_{44}=-0.14$, $P<0.88$). The mean education level was 14 years for patients (S.D.=3.26) and 17 years for the control group (S.D.=2). This statistically significant difference ($t_{44}=3.59$, $P<0.01$) was included as a parameter in ANOVA analyses (see Section 2.6) and produced no significant effects on RT.

Given that all motor responses were recorded form the right hand or eye, we administered a self-report questionnaire of lateral preference to all our subjects (Coren et al., 1979). This test provides score between +12 (complete right-side preference) and −12 (complete left-side preference). There was no significant difference between the two groups ($t_{44}=-0.71$, $P<0.47$).

2.2. Visual stimulus presentation

The visual stimulus for both the finger lift and the voluntary saccade reaction time tasks consisted of a black plastic box fitted with two white, high-luminance Light Emitting Diodes (LEDs) on its front surface, the central target and the peripheral target. The box was located in front of the subject at a distance of 60 cm. Subjects sat on a height-adjusted chair and their heads were fixed with a head retention mechanism to directly face the central target with the LEDs at eye level. The peripheral target was 9 cm to the right of the central target such that a saccade from central to peripheral traversed a 10° angle. Both tasks were carried out in low-luminance ambient conditions.

2.3. Finger lift reaction time task

The apparatus to record the finger-lift response was custom-made and consisted of a wooden surface on which a hand retention glove was mounted to maintain a constant hand and finger position during each trial. It was placed in front of the subject at the height of the resting position of the right hand. With the arm in the glove, only the subject's fingers were uncovered and free to move. The subject was instructed to rest his index finger on a small conductive metal surface which was placed in front of the retention glove at the resting position of the index finger. The metal surface was connected to the anode of a 9 V battery. The cathode was connected to the subject's arm via an antistatic wrist wrap. When the subject's index finger was in contact with the metal surface, the circuit was closed producing an output voltage detected by a Digital-to-Analog Converter (DAC, Advantech USB-4716A) connected to a PC. This voltage was always much higher than the threshold we have set for the detection of the movement. Therefore possible changes in conductance in patients due to antipsychotic medication could not interfere with the process of movement detection

At the start of the finger lift task, both targets emitted 50% of their total luminance (controlled by the Advantech USB-4716 A DAC). The subject was instructed to touch the metal surface with his index finger to initiate a trial. After a random intertrial interval (ITI) of 1–2 s, the central target changed to 75% of its total luminance. The subject was instructed to lift his index finger as quickly as possible in response, opening the circuit and producing a voltage difference detected by the DAC converter. RT was defined as the time between central target brightening to detection of the voltage change recorded to the PC. After the finger lift, the central target returned to 50% luminance indicating the end of the trial. Software to control the finger lift task procedure was written in the DELPHI programming language.

2.4. Voluntary saccade reaction time task

Eye movements in the voluntary saccade task were recorded from the right eye using the IRIS SCALAR infrared eye movement recording device. The device was