

Larger variability of saccadic reaction times in schizophrenia patients

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Abstract

Slower mean reaction time (RT), known as psychomotor slowing, is well documented in patients with schizophrenia. Fewer studies have shown increased variability of RT in these patients suggesting a basic difference in the distribution of RT. In this study median RT and its variability were measured for visually guided saccades performed by 53 patients and 1089 control subjects. Then average cumulative RT distributions were derived for each group and the RT distribution for each group was modeled using a decision signal rising linearly to a threshold signaling the beginning of the visually guided saccade. There was a small increase in the median RT for patients while their RTs were much more variable from trial to trial leading to a difference in the average RT distribution of the patient group. The model application led to the conclusion that this difference in the distribution of RT for patients could be attributed to a basic difference in information processing leading to the decision to move the eyes to the visually presented target. This information-processing difference could be the result of a difference in the build-up of neuronal activity involved in the generation of visually guided saccades in the frontal cortex.

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1. Introduction

Patients suffering from schizophrenia are slower to respond than normal controls in a large variety of tasks (Nuechterlein, 1977). Although many hypotheses

(Nuechterlein, 1977) have been advanced to explain this psychomotor slowing, its neurophysiological substrate remains elusive. Furthermore psychomotor slowing has also been observed in other mental disorders suggesting that this phenomenon might not be specific for schizophrenia (Schwartz et al., 1989). Another consistent finding in RT studies in schizophrenia is the larger inter-subject and intra-subject variability of RT suggesting differences in the shape of the RT distribution (Nuechterlein, 1977) for these patients. This phenomenon per se has attracted very little attention in the relevant

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literature, and it has been considered a by-product of the increase in the mean RT, since in most studies of RT in normal individuals it has been shown that an increase in the mean RT is also followed by an increase in RT variance (Luce, 1986).

In one study it was observed that the increase in RT intra-subject variability but not RT slowing in a simple manual RT task distinguished patients with schizophrenia from other patients with psychotic symptoms (Schwartz et al., 1989). A specific increase in RT variance in schizophrenia was also observed in a manual choice RT task (Vinogradov et al., 1998). In a previous study we observed that an increase in RT variability but not mean RT in the antisaccade task identified a small group of individuals with high schizotypy within a large sample of apparently healthy army conscripts (Smyrnis et al., 2003). Taken together, these results led us to the hypothesis that an increase in RT variability might be a dissociable phenomenon in schizophrenia spectrum disorders that is not related to the well-known psychomotor slowing and a difference in the RT distribution might be present in this patient population. If such a difference in RT distribution were present, then one could gain some insight on basic information-processing differences in these patients by applying an information-processing model on the RT distribution.

In order then to test our hypothesis, we decided to use a simple RT task in which there is no obvious psychomotor slowing for patients with schizophrenia.

This single exception to the rule of psychomotor slowing is visually triggered saccades (Iacono et al., 1981; Levin et al., 1982). Gale and Holzman (2000) reviewed all studies of visually guided saccades in schizophrenia and concluded that the majority of these studies report that the mean RT in patients does not differ from that of controls. This simple stimulus–response task then offers the opportunity to study differences in the saccade RT distribution for patients with schizophrenia beyond a simple difference in the mean RT. Another advantage for the choice of this simple task is the fact that we have a good understanding of the basic neuronal circuitry underlying the programming and execution of visually guided saccades (Munoz, 2002).

In this study we compare the RTs of visually triggered saccadic eye movements in a sample of 1089 young army conscripts that participated in a study for schizophrenia proneness (Smyrnis et al., 2003) to those of a sample of 53 patients with DSM-IV schizophrenia. We used a simple method for deriving average RT distributions for the two groups (Ratcliff, 1977) and compared these RT average distributions.

We also modeled the saccade RT distribution using the LATER model (Linear Approach to Threshold with Ergodic Rate, Carpenter and Williams, 1995; Reddi and Carpenter, 2000; Reddi et al., 2003). This model is depicted in Fig. 1a. The basic idea of the model is that the RT for making a saccade towards a visual target reflects a decision process in which a signal (decision signal) rises

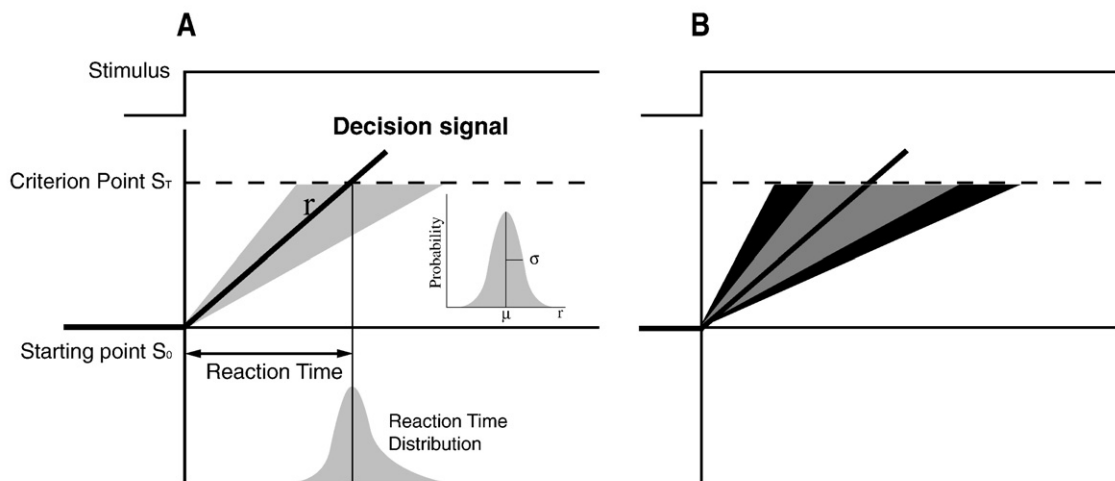


Fig. 1. A: A decision signal, depicted by the heavy black line in the figure, evolves linearly from a starting point (S_0) when the visual stimulus is where a criterion point (S_T) where a decision is made to saccade to the stimulus. The rate of this linearly increasing decision process r is thought to vary from trial to trial and this variation is modeled as a normal distribution with a mean μ and variance σ (shaded area around μ). The RT for a particular trial is equal to $(S_T - S_0)/r$. This decision process can explain the shape of the RT distribution that is skewed to the right. B: The model prediction is that the decision signal in the patient group will be more variable from trial to trial (larger σ) than the decision signal in the control group (gray area represents the σ for controls and the underlying black area represents the σ for patients).

to reach a threshold. This signal reflects the accumulation of information for deciding whether the target is indeed present in order for the saccade to be made. When this accumulation of information reaches a criterion point S_T , the saccade initiates. One can view this criterion point as the level of certainty needed to confirm the hypothesis that the target is present at the particular location in space (thus it analogues the significance criterion in statistics for hypothesis testing, Carpenter and Williams, 1995). The accumulation of information starts from a preset level of prior information S_0 that reflects prior knowledge about the presence of the target at a particular location in space (Carpenter and Williams, 1995). Finally, this accumulation of information r is considered to be linear with rate r , which varies from trial to trial. This variation of rate has a normal distribution across different trials with mean μ and variance σ (inset in Fig. 1a). The basic prediction of this model then is that the distribution of the reciprocal of RT, which is equal to r as can be seen in Fig. 1a, is normal with mean μ and variance σ . Indeed Carpenter (1981) showed that although the distribution of saccadic RTs is skewed, the distribution of the reciprocal of RT is normal. The model also makes explicit predictions on how the RT distribution will be affected by specific manipulations such as, for example, a change in prior probability for target location S_0 or the change in the criterion S_T needed for a response or the mean rate of accumulation of information μ . All these manipulations have been tested and the predictions of the model were verified experimentally (Carpenter and Williams, 1995; Reddi and Carpenter, 2000; Reddi et al., 2003).

Moreover the model predicts that neuronal activity in areas of the brain that contribute to the generation of visually guided saccades might follow the same pattern as the decision signal. This hypothesis was tested experimentally by Hanes and Schall (1996). In that study rhesus monkeys performed saccades to visual targets while the activity of single neurons in the Frontal Eye Field was recorded. A neuron's firing rate increased linearly during the RT to reach a maximum firing rate after which the saccade was initiated. The maximum frequency did not change from trial to trial and thus could not predict differences in RT from trial to trial. In contrast the rate of the increase in the firing frequency changed from trial to trial as predicted by the model (see Fig. 1a) and this variation predicted very well the variation in RT from trial to trial. This study then showed that indeed the decision signal r of the model could be related to the firing rate of single neurons in the frontal eye field. In a recent study Connolly et al. (2005) used functional magnetic resonance imaging (fMRI) in humans and correlated the hemodynamic response during an anticipation period

before the execution of a visually guided saccade to the RT for that saccade on a trial by trial basis. They observed that the higher this preparatory activity in the contralateral frontal eye field, the shorter the RT of the subsequent saccade. This relation was significant only for the contralateral frontal eye field. Thus both in animals and in humans, the rate of rise of neuronal activity before the execution of a visually guided saccade predicts the RT of that saccade.

We used the LATER model in our analysis of the RT distributions of patients with schizophrenia and the control sample. The application of the model offered a hypothesis for the nature of the information-processing difference between patients and controls that underlies differences in the RT distributions and also offered a hypothesis for a possible neuronal substrate for this information-processing difference.

2. Methods

2.1. Participants

Fifty-three male patients (age span 18–30 years) with DSM-IV schizophrenia participated in this study. All participants provided written, informed consent, and the study protocol for the 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 Mini International Neuropsychiatric Interview (M.I.N.I., version 5.0.0., DSM-IV) (Sheehan et al., 1998). Exclusion criteria consisted of the following: neurological disorder (e.g., epilepsy and multiple sclerosis), mental retardation and drug abuse within the last year before evaluation. All patient participants were receiving antipsychotic medication (mean daily dose in chlorpromazine equivalents = 400 mg, SD = 236 mg) and were in a stable phase of the disorder during testing.

The control sample for this study was derived from the ASPIS (Athens Study for Psychosis Proneness and Incidence of Schizophrenia) data base (Evdokimidis et al., 2002; Smyrnis et al., 2002, 2003). For the purposes of the ASPIS, oculomotor task data were collected from a population of 2120 conscripts of the Greek Air Force aged 18–25 years. A randomly selected group of 200–300 conscripts was evaluated during a 6-day period every 2 months for a total of 15 months. Each conscript was tested individually in oculomotor tasks (smooth eye-pursuit, saccade, antisaccade, visual

fixation) and cognitive tasks (continuous performance test: CPT-IP, verbal and spatial working memory tests: N-back). Each individual gave written consent to participate in the study after being informed about the experimental procedures and study goals. The study protocol was approved by the Ethics Committee of the University Mental Health Research Institute. All conscripts had been examined by an army medical committee and individuals with ophthalmological problems, such as very low visual acuity (below 20–40 best corrected) or strabismus, as well as individuals with other known major medical problems, had already been excluded from the population of conscripts from which our sample originated. We did not perform an optometric evaluation of the conscripts before testing them.

The mean age of the patient group was 24 years ($SD=2.68$) while for the control sample it was 20.5 years and the difference was significant ($t_{1140}=12.9$, $P<0.01$). The two groups did not differ in the level of education (patient group mean = 12.5 years, $SD=2.23$, control group mean = 11.8 years, $SD=2.4$, $t_{1140}=1.84$, $P=0.065$).

2.2. Eye movement measurement

Oculomotor tasks were performed in a set-up that has been described in detailed in our previous studies (Evdokimidis et al., 2002; Smyrnis et al., 2002, 2003). Briefly, a PC-driven setup was used consisting of an adjustable chair for the subject and a specially designed table that had a head holder adjusted at one end and a 17-inch computer monitor mounted at the other end (1 m distance from the head holder). Eye movements were recorded from the right eye using the IRIS SCALAR® infrared device. Stimulus presentation and recording of the responses were accomplished with a program written in Turbo Pascal 7.0 for DOS. A 12-bit A/D converter was used for data acquisition (Advantech® PC-Lab Card 818L). Eye movement data were sampled at 600 Hz and stored in each PC for off-line data processing.

2.3. Task procedure

The task was preceded by a calibration procedure, with saccades at 5° and 10° to the left and to the right of a central fixation point. During the task the subject initially fixated a target that could appear either at the center of the screen or at a peripheral position located at 8°, 6°, 4°, or 2° on an imaginary horizontal line, to the right or to the left of the screen center. After a variable period of 1–2 s a second target appeared at one of the remaining locations including the center (0) either to the

left or to the right of the first target excluding locations that were more than 10° away from the first target. The subject had 1.5 s to respond, after which the second target disappeared and the screen was black for a period of 1 s before a new target appeared. We asked the subjects to try to refrain from blinking during the execution of the eye movement and emphasized equally on both speed and accuracy. Each subject performed 90 trials (18 trials for each first target position).

2.4. Data preprocessing

An interactive PC program (created using the TestPoint® CEC) was used for detection and measurement of saccades from the eye movement record (Evdokimidis et al., 2002; Smyrnis et al., 2002, 2003). We excluded trials with artifacts (e.g. blinks) in the analysis period extending from 100 ms before the appearance of the peripheral target to the end of the first saccade as well as trials for which an eye movement occurred in the 100-ms period before the appearance of the peripheral target. In addition, we excluded trials with an RT that was not within the window of 80–600 ms (to avoid including predictive movements). On the basis of these exclusion criteria, the minimum number of trials retained for each subject was 30 and the maximum was 90.

2.5. Data analysis

The median RT and the coefficient of variation of RT were calculated for each individual. The coefficient of variation was defined as the inter-quartile range (including 50% of observations) divided by the median (Malapani et al., 2002). It is known for both humans and animals that an increase in RT mean is linearly correlated with an increase in RT variance (Gibbon et al., 1997). Thus measuring the coefficient of variation instead of the variance of RT effectively normalizes the measure of variability from this known effect of the mean RT on the RT variance. Group means of patients and controls for these measures were compared using a *t* test with different variance estimates. We also used an analysis of covariance to test for age effects on the difference between the mean RT and the RT coefficient of variation for patients and controls. The group was the independent factor (patient versus control) and the age was the covariate in this analysis.

In order to compute the average cumulative distribution for each group, the RTs for each subject were organized in ascending order and percentile values were calculated (the RT for the 5% percentile, e.g., the 10%

percentile). The percentile values were then averaged across the group to give average group percentile values that are plotted in the average cumulative distribution. Ratcliff (1977) showed that this average distribution retains the basic shape characteristics of the individual distributions. In order to test the difference between the group distributions for patients and controls, we used the Wilcoxon signed rank test.

The decision model depicted in Fig. 2a predicts that if the cumulative saccadic RT distribution is plotted using $1/RT$ instead of RT in a probit scale (a “reciprobit” plot), the RTs will fall on a straight line (Carpenter and Williams, 1995). We transformed the average cumulative distribution data of RT for the control and patient groups in a reciprobbit plot (Fig. 1b) and computed the best-fitting regression line for each group. The comparison of the two regression lines for the patient and control groups in the model analysis was performed using the homogeneity of slopes regression model analysis provided in STATISTICA 7.0 (StatSoft Inc., 1984–2004). In this analysis the dependent variable was the cumulative percentage of the RT distribution and the independent variable was the RT just as in the simple linear regression depicted in Fig. 2b, but a categorical factor was also included which was the group (patient versus control). The analysis thus tests the effect of the independent variable on the dependent variable irrespective of group (main effect of RT), the group effect that is the difference in the intercept of the regression that is due to the group factor, and finally the interaction of group and independent factor that tests if the effect of the independent factor (RT) on the dependent variable

(cumulative percentage) changes significantly between the two groups, that is, if the slope of the regression line is different between the two groups.

We also tested the difference of the two average RT distributions using a non-parametric random permutation test that does not rely on specific assumptions on the shape of the data distribution (Feinstein, 1977). Different combinations of 53 control subjects were selected from the original sample of 1089, the group average cumulative RT distribution was derived, and the group median RT was calculated. Then, on the reciprobbit plot of the cumulative distribution of RT, the slope and intercept of the regression fitting line were computed for this combination. Ten thousand combinations of 53 control subjects (a subgroup of all possible combinations) were used to construct minimum–maximum intervals for the median RT, the slope and the intercept of the resulting model fitted lines of the RT distributions.

3. Results

The mean of the median RT was 186 ms (SD: 35.2) for the patients and 177 ms (SD: 21.2). This 9-ms difference was not statistically significant ($t_{53,8}=1.89$, $P=0.06$). The RT distributions for patients, though, were in many cases much broader than those for controls, indicating a larger RT variability in this group. Indeed the coefficient of variation of RT was significantly larger for patients (0.31, SD: 0.08) than for controls (0.23, SD: 0.14) ($t_{53,5}=4$, $P<10^{-3}$). Since the patients were significantly older than the controls, we retested these differences in the mean saccadic latency

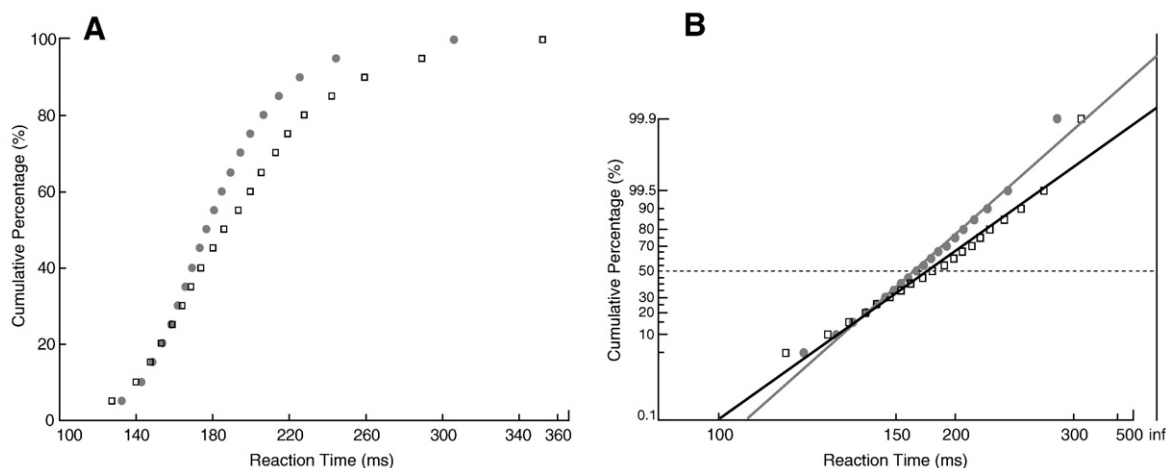


Fig. 2. A: Average cumulative distribution of RT for controls (gray filled circles) and patients (black empty squares). B: This figure presents reciprobbit plots of the average cumulative RT distributions shown in Fig. 1b. The x-axis represents $1/RT$ and it has been reversed so that RTs increase to the right. Instead of $1/RT$ units the axis is marked with the corresponding RT values. The fitted lines correspond to linear regression on the data for each distribution (gray for controls, black for patients). The lines intercept the y-axis at infinite time.

and the coefficient of variation of saccadic latency between the two groups using an analysis of covariance where age was introduced as a covariate. The mean latency difference between the two groups was significant in this analysis ($F_{1,1139}=11$, $P<10^{-2}$) and the effect of age was not significant ($F_{1,1139}=2.11$, $P=0.14$). The difference in the coefficient of variation remained highly significant ($F_{1,1139}=44.3$, $P<10^{-3}$) while the effect of age was again not significant in this analysis ($F_{1,1139}=0.65$, $P=0.4$).

The greater variability of RTs for patients implies a shape difference in the RT distribution for this group. This difference was studied by deriving an average cumulative RT distribution for each group using the method proposed by Ratcliff (1977). Fig. 2a illustrates the two average cumulative RT distributions of patients and controls. It can be observed that the two cumulative distributions differ in shape and this difference was significant (Wilcoxon test, $Z=3.285$, $P=0.01$).

We then addressed the question of how this difference in RT distribution might be related to a difference in information processing in patients with schizophrenia. We used the LATER model applied to the RT distribution for visually triggered saccades as described in the introduction and illustrated in Fig. 1a.

Fig. 2b presents the model fit to the two group distributions of patients and controls. The model fit for each group was excellent (linear regression R^2 was 0.96 for the patient group and 0.98 for the control group). The two-group-model-fitted lines differed significantly, both in intercept ($F=18.65$, $P<10^{-3}$) and in slope ($F=13.47$, $P<10^{-3}$, see Section 2). We also performed a non-parametric permutation test to construct minimum–maximum intervals for the median RT, the slope and the intercept of the fitted line in the reciprobbit plot for 10,000 randomly selected groups of 53 control subjects selected among the 1089. As shown in Table 1, the patient group median was well within the control minimum–maximum interval, while the slope and the intercept of the patient RT distribution were outside the corresponding control intervals. Thus no random combination of 53 control subjects could produce the

particular model slope and intercept observed for the group of 53 patients.

In the description of the LATER model, the slope of the fitted line in the reciprobbit plot is equal to $(S_T - S_0)/\sigma$ while the intercept is equal to $\mu/(\sigma \cdot \sqrt{2})$ (Fig. 1a). A decrease in slope and intercept that was observed in the schizophrenia patient group corresponds to an increase in the model σ as shown in Fig. 1b. This figure shows the model prediction that the decision signal in the patient group is more variable from trial to trial than the decision signal in the control group.

4. Discussion

The results of this study provide evidence in favor of the hypothesis that a specific difference in patients with schizophrenia is in the RT distribution, and this difference is present in a simple task in which there is no large psychomotor slowing. There was an increase in the mean saccadic RT for patients with schizophrenia that was significant after controlling for age differences between controls and patients. This increase, though, was very small (5% of the mean for the control group) and did not survive the rigorous non-parametric permutation test where the confidence intervals for the mean patient RT included the mean of the controls (see Table 1). In contrast to this small increase in mean RT, there was a highly significant increase in the variability of RT in the patient group that was confirmed in the significantly larger coefficient of variation for this group (an increase of 35% compared with the coefficient of variation for controls). This difference suggested a difference in RT distribution between these patients and the controls that was confirmed by using the LATER model for RT distribution. The model parameters were significantly different for patients than for controls (Table 1).

Previous studies have examined RT of visually triggered saccades in patients with schizophrenia, and most of these studies have reported that the mean RT of patients is not different from that of controls (Iacono et al., 1981; Levin et al., 1982; Gale and Holzman, 2000). In a recent study Reilly et al. (2005) reported that RT in visually triggered saccades were faster for patients with schizophrenia that were drug naïve and this difference then disappeared when these patients were treated with antipsychotics. Examination of their data do not reveal differences in the variability of RT between patients and controls that were especially present for large target eccentricities even at baseline. In this study all patients were receiving medication and were in a stable condition when they were tested. It would be

Table 1
Results of the permutation test comparing the RT distributions of patients and controls.

	Patient group mean	Control group mean	Minimum permutation value	Maximum permutation value
Median RT	186 ms	177 ms	167 ms	191 ms
Slope	854	1064	929	1216
Intercept	4.7	6.1	5.2	7.0

interesting to extend this study to a patient group of never medicated patients and test the dispersion of the RT distribution in this group. According to our prediction, the variability of RT in this group would be larger than for controls when normalizing for the mean RT.

A previous study showed that the increase in RT variance was correlated with deterioration of performance of patients with schizophrenia in a selective attention task (van den Bosch et al., 1996). Also in a previous study we observed that the increase in RT variability of the antisaccades was highly correlated with deterioration in antisaccade performance in a high schizotypy group (Smyrnis et al., 2003). Thus this difference in the shape of the RT distribution in schizophrenia might be a core difference that might be linked to performance deficits in these patients. We are currently testing this prediction by correlating the dispersion of the RT distribution with measures of performance in tasks such as the antisaccade and the cognitive tasks that were used in our battery. This will be the focus of a future report. In this study we emphasize the observation that the RT-distribution difference is present for patients in a very simple voluntary movement task such as the visually triggered saccades. This implies a very basic difference in decision making between patients and controls in a very simple decision process such as the decision to move the eyes to a visual target. If such a basic decision process is different in these patients, this might have implications for all decision processes that are more complicated such as those involved in complex cognitive tasks. These results then are in our view of importance in the study of cognition in schizophrenia.

The application of the LATER model (Carpenter and Williams, 1995) to our data showed that patients with schizophrenia have larger variability in the rate of rise of the decision signal from trial to trial, while the threshold and the mean of that signal do not differ from those of controls. Many models of RT distributions have been employed in the relevant literature (for a review, see Luce, 1986). The best known alternative model to the LATER model for simple RT tasks is the diffusion model (Ratcliff, 1978; Smith, 2000; Diederich and Busemeyer, 2003). In the form of this model that can be applied to simple RT tasks (Smith, 2000), a decision signal rises to a threshold and this reflects the time of the RT in the same fashion as in the LATER model. The major difference between the two models is that the rise of the decision signal in the diffusion model obeys a stochastic process that represents the accumulation of information available to the decision mechanism at any

given time while the process in the LATER model is a deterministic one that obeys a simple linear process with a mean rate (Fig. 1a). We chose to model our data using the LATER model. The first reason for this choice is the simplicity of the LATER model compared with the more complicated diffusion model that still captures all the characteristics of the saccadic RT distribution. Another reason is the fact that the LATER model was proved to be superior to diffusion models when simulating the decision process for generating a saccade to a supra-threshold stimulus that is very easily and unambiguously detected while diffusion models might dominate the process of decision when stimuli are hard to detect (Carpenter, 2005). Finally, the LATER model has already been tested neurophysiologically in a simple saccade RT task and it was found that the activity of frontal eye field neurons of the monkey closely followed the predictions for the decision signal of the model (Hanes and Schall, 1996). Similarly in humans the prediction of the model that the rate of rise of the neuronal activity during the preparatory period before the execution of a visually guided saccade would predict the RT of that saccade was confirmed for the contralateral frontal eye field using fMRI in humans (Connolly et al., 2005). These results then can lead to the prediction that the rate of increase but not the maximum level of neural activity in the contralateral frontal eye field of patients with schizophrenia might vary from trial to trial and this variation might be the neurophysiological substrate of the information-processing difference for these patients in the task. We recently applied the LATER model in a neural network simulation that tried to capture the basic RT distribution characteristics of voluntary saccades (Cutsuridis et al., 2007). The neural network consisted of a layer of frontal eye field neurons driving the activity of a layer of superior colliculus neurons. We showed in that simulation that variability in the rate of rise of frontal eye field neurons driving collicular neurons led to more variable RTs. Moreover, the increased neuronal variability was the result of increased variability in ionic I_{NaP} and synaptic I_{AMPA} and I_{NMDA} conductances. If indeed a greater trial by trial variation in neuronal activity were confirmed in patients with schizophrenia, it would be of interest to further explore this difference with a series of testable hypotheses concerning its biological basis at the level of ionic channels and maybe the level of the genes controlling the expression of these channels.

This study demonstrated a basic RT distribution difference in patients with schizophrenia. It remains to be tested whether this difference is specific for schizophrenia patients and also whether it is present in relatives of

patients, suggesting a genetic predisposition of this effect. Finally, the observation that the average RT distribution of patients is different from the average distribution of controls suggests that at least for some patients the individual RT distributions might differ from those of controls so a subject by subject analysis is warranted. Our data for each subject were not enough for a subject by subject analysis of the characteristics of the RT distribution. The fact that this is a very simple task that patients can easily perform suggests the promise of exploring saccadic RT distributions in single patients.

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