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RESEARCH ARTICLE

Response selection in schizophrenia

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Abstract Schizophrenia patients tend to have longer and more variable latencies of response than healthy control subjects. However, the distributions of data from the two groups overlap to a large extent. Therefore, we investigated (1) whether the process of response selection in schizophrenia patients is like that of slow control subjects or has different properties, and (2) whether the intra-individual variability of schizophrenia patients is intrinsically greater than that of control subjects or reflects their longer mean latency. To answer these questions we tested schizophrenia patients and healthy control subjects in a choice reaction time (RT) task with 2-choice and 4-choice conditions. We analyzed how mean RT in the 2-choice condition predicted mean RT in the 4-choice condition and found that the relation was significantly different between the two groups. In contrast, the intra-individual variability of RT was related to mean RT in the same way for schizophrenia patients and control subjects. These results indicate that the response selection process of schizophrenia patients was not simply a slower version of the same process engaged by control subjects, but it was a selection process with different dynamic properties. In contrast, schizophrenia patients did not have a greater intrinsic variability than control subjects. Furthermore, we found that the difference Δt between RT measured in the 4-choice condition and RT predicted for the control group in the same condition could be used to discriminate effectively patients and control subjects. However, there was no significant association between Δt and clinical variables. These results suggest that Δt could reflect a trait impairment of schizophrenia independent from symptom profile. Finally, we suggest that the impairment of the process of selection of the motor response in schizophrenia reflects the alteration of the time-dependent patterns of neural activity that result from anomalies in the connectivity of the brain areas engaged for the selection of the motor response.

Keywords Schizophrenia · Decision-making · Motor planning · Information processing · Reaction time · Trait marker

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Introduction

The analysis of reaction time (RT) is an important tool for investigating how the nervous system processes information that leads to the execution of a motor response (Luce 1986). Of particular interest is the choice

RT paradigm, which requires the selection of a response among two or more alternatives. Typically, choice RT tasks are based on a one-to-one correspondence between stimulus and response. In this respect, they are well suited for investigating specifically the process of selection of a motor response independently from the judgments and strategies required by other more complex decision-making tasks (Lee 2006).

Reaction time tasks have been used also for evaluating the information processes impaired in patients with brain illnesses or injuries (Milner 1986). In regard to schizophrenia, many studies employing a vast variety of experimental tasks have shown that mean RT is typically longer for schizophrenia patients than for healthy control subjects (Nuechterlein 1977; Schatz 1998). Moreover, schizophrenia patients have also longer mean RT than other psychiatric patients, such as patients with bipolar disorder (Fleck et al. 2001) and patients with depression (Hemsley 1976). In addition to these effects on mean RT, it has been reported that the intra-individual variability of RT was greater for schizophrenia patients than for healthy control subjects (Schwartz et al. 1989; Vinogradov et al. 1998). These effects on RT reflect the disruption of information processing that plays a key role in schizophrenia (Braff 1993; Bredgaard and Glenthøj 2000; Goldberg and Gold 1995).

In the current study, we investigated the functional significance of the longer mean RT and of the greater intra-individual variability of RT in schizophrenia. In this context, it is important to point out that the differences of mean RT between schizophrenia patients and other groups of subjects, such as those mentioned above, are differences of the central tendency of the distributions. However, typically, these distributions overlap to a large extent, which means that many schizophrenia patients have RTs within the range of healthy control subjects (Gale and Holzman 2000). Therefore, the question is whether the process of response selection in schizophrenia patients functions like that of slow control subjects or whether there is evidence that it functions differently.

To answer to this question, we took advantage of the natural inter-individual variability of RT, which, even though it is considered often to be detrimental, can be used advantageously to investigate the functional properties of brain information processes (Pellizzer and Georgopoulos 1993). Furthermore, we took advantage of the fact that generally RT of a subject in one condition predicts RT of the same subject in another condition. For these reasons, we implemented a choice RT task with a 2-choice condition and a 4-choice condition. If the process of response selection of schizophrenia patients in the choice RT task functions like that of slow control subjects, then their RT in one condition should predict the same RT as slow control subjects in the other condition. On the other hand, if RT in one condition predicts a different RT in the other condition depending on the group, then it would indicate that the time course of the response selection process of the two groups has different dynamic properties. In other words, it would suggest that the time-dependent patterns of neural activity that underlies the process of response selection are modulated differently by the number of choices in the two groups.

Furthermore, we examined the intra-subject variability of RT. Typically, subjects with longer mean RT tend to have more intra-subject variability as well (Luce 1986). Therefore, we examined whether the intra-subject variability of schizophrenia patients was intrinsically greater than that of control subjects or whether it reflected the fact that their mean RT tend to be longer than that of control subjects.

Methods

Subjects

The schizophrenia group included 21 patients who met the DSM-IV criteria for schizophrenia (14 patients: six of the undifferentiated type and eight of the paranoid type) or for schizoaffective disorder (seven patients). Diagnoses were based on the Structured Clinical Interview (First et al. 2002) administered by a trained mental health specialist. All patients were recruited from the outpatient population of the Minneapolis Veterans Affairs Medical Center (VAMC). The control group included 18 healthy subjects recruited through flyers placed at the VAMC. The control subjects did not have any diagnosis of (Axis I) mental illness. Only patients and control subjects without major medical or neurological disorder were included in the study and all gave informed consent before their participation. The experimental protocol was approved by the Institutional Review Boards of the VAMC and of the University of Minnesota.

The two groups of subjects were matched relative to age [Kolmogorov–Smirnov (K–S) $Z = 0.741$, $P = 0.642$], average parents' education (K–S $Z = 1.013$, $P = 0.256$), premorbid full scale IQ (K–S $Z = 1.087$, $P = 0.188$) estimated using the National Reading Adult Test (NART; Crawford et al. 1992; Nelson and Willison 1991), gender ratio (Fisher's exact test, $P = 0.318$) and handedness ratio (Fisher's exact test, $P = 1.000$). Although not used as a matching variable, the two groups

did not differ significantly in the amount of education either (K–S $Z = 0.791$, $P = 0.559$). The demographic data of the two groups are presented in Table 1.

The patients were evaluated also with the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962), the Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1983), and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen 1984). The scores from the SANS and SAPS subscales were used to provide ratings for negative symptoms, psychotic symptoms, and disorganized symptoms, as defined by Andreasen et al. (1995). Duration of illness and dose of antipsychotic medication at the time of testing were obtained from clinical records. The amount of medication was converted into chlorpromazine equivalent daily dosage using the conversions published by Van Kammen and Marder (1995) and Woods (2003). The scores on the clinical scales and other clinical data are indicated also in Table 1.

Task

The task consisted in pressing with a finger a button on a keypad (PST Serial Response Box, Psychology Software Tools Inc., Pittsburgh, PA, USA) as quickly as possible in response to a digit presented on a screen in front of the subject (Fig. 1). The task had two conditions presented in separate blocks: a 2-choice condition and a 4-choice condition. In the 2-choice condition, '1' or '2' was presented on the screen and the subject had to press the corresponding button on the keypad with the index finger or the middle finger, respectively. In the 4-choice condition, '1', '2', '3', or '4' was presented on the screen and the subject had to press the corresponding button on the keypad with the index finger, middle finger, ring finger, or little finger, respectively. The fingers were positioned on top of their corresponding buttons during the whole experiment. The subjects used their preferred hand to respond. In each choice condition, each stimulus was presented ten times in random order. The two conditions were presented in separate blocks of trials, the order of which was assigned randomly to each subject. The task was implemented using the software E-Prime (Psychology Software Tools Inc.).

Data analyses

We estimated the central tendency of RT of correct trials for each subject, choice condition and finger by computing the harmonic mean, which is robust to potential outliers (Ratcliff 1993). The intra-subject variability of RT was evaluated using the inter-quartile range (IQR), which is as a robust measure of the dispersion of RT (Ratcliff 1993). Statistical analyses of mean RT and IQR of RT were performed on log-transformed ($\log_{10}$) values in order to stabilize their variance (Snedecor and Cochran 1989). Only data obtained with the index and middle fingers, which were used in both choice conditions, were kept for analyses. Preliminary analyses indicated that the factor finger did not affect the results, therefore mean RT and IQR of RT for the index and middle fingers were averaged for the subsequent analyses. Statistical tests with $P < 0.05$ were considered significant. The statistical analyses were performed using SPSS 14.0 (SPSS Inc., Chicago, IL, USA). The averages of mean RT and IQR of RT are presented in Table 2 for each group and choice condition.

Results

Accuracy

Both control subjects and patients performed the task very accurately, which resulted in an overall rate of

Table 1 Demographic and clinical data

	Group			
	Control ($N = 18$)		Schizophrenia ($N = 21$)	
Age[a], years	47.1	(11.3)	50.1	(7.5)
Education[a], years	14.2	(1.6)	13.5	(1.4)
Average parents' education[a], years	12.8	(2.8)	11.7	(2.8)
Estimated premorbid full scale IQ (NART)[a]	108.9	(8.4)	104.3	(7.4)
Gender, male/female	15/3		20/1	
Handedness, left/right	1/17		1/20	
BPRS[a]	–	–	44.4	(9.6)
Negative symptoms[a]	–	–	7.3	(4.5)
Psychotic symptoms[a]	–	–	5.8	(2.8)
Disorganized symptoms[a]	–	–	2.1	(2.7)
Duration of illness[a], years	–	–	20.2	(10.4)
Medication[a], chlorpromazine equiv., mg/day	–	–	325	(169)
Diagnostic, schizophrenia/schizoaffective	–		14/7	

[a] Mean (standard deviation)

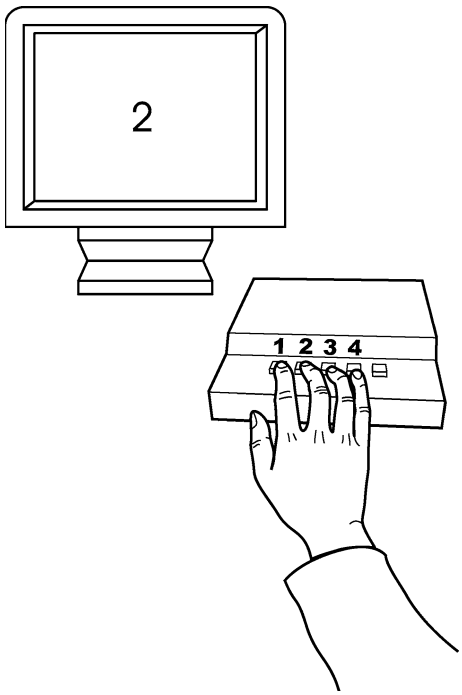

Fig. 1 Choice RT task. A digit was presented on the screen and subjects had to press as quickly as possible one of the buttons on the keypad with the corresponding finger. Two conditions were used in separate blocks of trials: a 2-choice condition and a 4-choice condition

correct trials of 98%. There was no significant difference in the rate of correct responses in the table of group × choice condition ($\chi^2(1) = 0.001$, $P = 0.969$).

Relation between mean RT in the 4-choice condition and mean RT in the 2-choice condition

We tested whether RT in the 4-choice condition (RT_4) was related to RT in the 2-choice condition (RT_2) in the same way for the schizophrenia group and the control group. In other words, is RT_4 the same for both groups when controlling for RT_2? The analysis was performed on log-transformed data in order to stabilize the variance. We analyzed the ANCOVA model:

$$Y_{ij} = \alpha_i + \beta X_{ij}, \quad (1)$$

where $Y_{ij} = \mathrm{Log}_{10}(RT_{4ij})$ and $X_{ij} = \mathrm{Log}_{10}(RT_{2ij})$ are the data from subject j of group i, α_i is the intercept for each group, and β is the slope of the relation between Y_{ij} and X_{ij}. This analysis is meaningful to perform if the distribution of the independent variable is broad enough, which was the case for both groups as can be seen in the marginal distributions plotted in Fig. 2a. In addition, the distributions of RT of schizophrenia patients and control subjects overlapped considerably which is also beneficial for this analysis. Nevertheless, despite the large overlap, the distributions were significantly different between groups in both choice conditions (2-choice: $t(37) = 2.29$, $P = 0.028$; 4-choice: $t(37) = 3.79$, $P < 0.001$).

The ANCOVA showed that Eq. 1 provided a good description of the data ($R^2 = 0.606$, $F(2,36) = 27.72$, $P < 0.001$). As expected, RT in the 2-choice condition predicted RT in the 4-choice condition with a slope β that was significantly different from 0 ($F(1,36) = 29.85$, $P < 0.001$). The estimated parameter β was 0.557 (SE 0.102). In addition, what is particularly important here is that the two groups had significantly different intercepts ($F(1,36) = 7.92$, $P = 0.008$). The estimated values of the intercepts α_i were $\alpha_{\mathrm{Control}} = 1.259$ (SE 0.272) and $\alpha_{\mathrm{Schizophrenia}} = 1.322$ (SE 0.280). The data points for each subject and the function for each group are plotted in Fig. 2a.

It may be useful to note that the axes of Fig. 2a are in a logarithmic scale given that the analysis of Eq. 1 was performed on log-transformed values. However, the estimated parameters from the ANCOVA can be expressed in more familiar units (i.e., ms) in transforming Eq. 1 as:

$$10^{Y_{ij}} = 10^{\alpha_i} 10^{\beta X_{ij}}, \quad (2)$$

which gives $RT_4 = 18.2\ RT_2^{0.557}$ for the control group and $RT_4 = 21.0\ RT_2^{0.557}$ for the schizophrenia group. Therefore, the two functions plotted in Fig. 2a and representing the least-squares fit of Eq. 1 would appear as

Table 2 Average central tendency and dispersion of individual reaction time distributions for each choice condition and each group

	Central tendency of RT				Intra-individual dispersion of RT			
	2-choice		4-choice		2-choice		4-choice	
Group	Average	(SD)	Average	(SD)	Average	(SD)	Average	(SD)
Control ($N = 18$)	2.6667 (*464*)	(0.0811)	2.7438 (*554*)	(0.0745)	2.1053 (*127*)	(0.1788)	2.0283 (*107*)	(0.1676)
Schiz. ($N = 21$)	2.7438 (*554*)	(0.1218)	2.8495 (*707*)	(0.0961)	2.1889 (*154*)	(0.2274)	2.2118 (*163*)	(0.1284)

The group averages were calculated using the log-transformed ($\log_{10}$) individual mean RTs and IQR of RTs. The values in italics are the averages re-transformed in ms

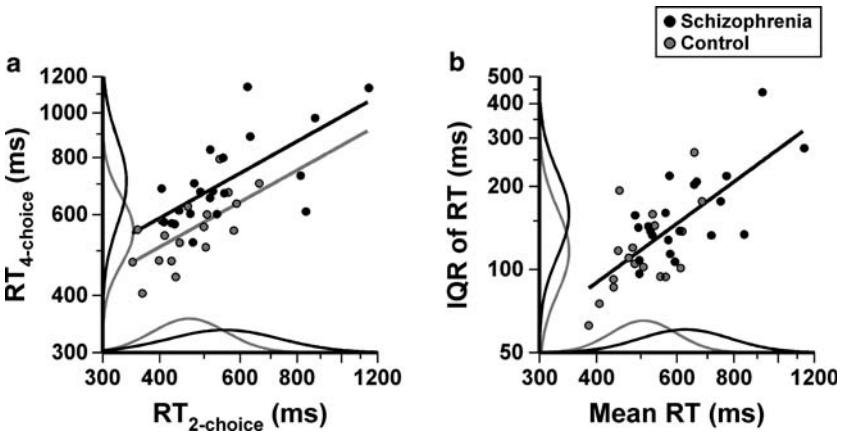

Fig. 2 **a** Scatterplot of mean RT in the 4-choice condition versus mean RT in the 2-choice condition. *Gray* data points represent data from control subjects, whereas *black* data points represent data from schizophrenia patients. The marginal Normal distributions of the data are plotted in *gray* for the control group and *black* for the schizophrenia group. The lines passing through the data points represent the least-squares fit of Eq. 1 (control group: *gray* line, schizophrenia group: *black* line). Note that the axes are in a logarithmic scale. **b** Scatterplot of inter-quartile range of RT versus mean RT. The same conventions as indicated above were used. The line passing through the data is the least-squares fit of Eq. 1 with the same α for the two groups. Note that the axes are in a logarithmic scale

two diverging curved lines if plotted using Eq. 2 in a graph with linear scale axes.

These analyses show that significantly different functions described the data for the two groups, that is to say, RT in the 4-choice condition was not the same for the two groups even after controlling for RT in the 2-choice condition. The predicted RT of schizophrenia patients in the 4-choice condition was (21.0–18.2)/ $18.2 \times 100 = 15\%$ greater than what their RT would have been if their response selection process functioned like that of control subjects.

We performed additional analyses to check whether the results were different for patients with a diagnostic of schizophrenia and those with a diagnostic of schizoaffective disorder. For this purpose we tested the ANCOVA model (Eq. 1) with the control group and the patients divided in two subgroups according to the diagnostic. We found similar results as those indicated above, that is a significant effect of the slope β ($F(1,35) = 29.22$, $P < 0.001$) and a significant difference of intercepts between groups ($F(2,35) = 4.01$, $P = 0.027$). In addition, post hoc comparisons using the Least Significant Difference indicated that the schizophrenia subgroup and the schizoaffective subgroup were both significantly different than the control group ($P = 0.033$ and 0.019, respectively), whereas the two subgroups of patients did not differ significantly from each other ($P = 0.609$).

In summary, these analyses showed that RT in the 2-choice condition predicted RT in the 4-choice condition, but the prediction was different for schizophrenia patients than for healthy control subjects: RT in the 4-choice condition resulted to be greater for schizophrenia patients than for control subjects, even after controlling for RT in the 2-choice condition.

Relation between variability of RT and mean RT

We examined whether the intra-individual variability of schizophrenia patients was intrinsically greater than that of control subjects or whether it reflected the fact that their mean RT tend to be longer. For this purpose, we tested the relation between the log-transformed IQR of RT and the log-transformed mean RT across group and choice condition using an ANCOVA with group as between-subject factor and choice condition as within-subject factor. The results indicated that IQR of RT was varying significantly with mean RT ($F(1,36) = 26.30$, $P < 0.001$). In contrast, there was no significant effect of group ($F(1,36) = 0.44$, $P = 0.510$), of choice condition ($F(1,36) = 2.04$, $P = 0.162$) or of the interaction group $\times$ choice condition ($F(1,36) = 2.21$, $P = 0.146$). We checked whether the results would be different if the patients were divided between those with a diagnostic of schizophrenia and those with a diagnostic of schizoaffective disorder. We found the same statistical effects as above, that is to say, a significant relation between IQR of RT and mean RT ($F(1,35) = 24.23$, $P < 0.001$), but no significant effect of group ($F(1,35) = 0.80$, $P = 0.459$), of choice condition ($F(1,35) = 0.30$, $P = 0.585$) or of the interaction group $\times$ choice condition ($F(1,35) = 2.14$, $P = 0.133$).

Following these results, we tested the simpler model represented by Eq. 1 with $Y_{ij} = \mathrm{Log}_{10}(\mathrm{IQR}_{ij})$,

$X_{ij} = \mathrm{Log}_{10}(\mathrm{RT}_{ij})$ and with α constant. The values of Y_{ij} and X_{ij} were obtained by averaging the data from the 2- and 4-choice conditions. The marginal distributions of these variables are plotted in Fig. 2b for each group. The figure shows that these distributions overlapped to a large extent, but were nevertheless significantly different between groups (log-transformed mean RT: $t(37) = 3.24$, $P = 0.003$; log-transformed IQR of RT: $t(37) = 2.69$, $P = 0.011$). The results of the analysis indicated that the model described the data well ($R^2 = 0.510$) with a significant slope $\beta = 1.214$ (SE 0.195; $F(1,37) = 38.59$, $P < 0.001$), and an intercept $\alpha = -1.206$ (SE 0.539) that was significantly different from zero ($F(1,37) = 5.01$, $P = 0.031$). The data points for each subject and the fitted function are plotted in Fig. 2b. As indicated in the previous section, the results can be expressed in ms as $\mathrm{IQR}=0.062\ \mathrm{RT}^{1.214}$.

The results of these analyses indicate that there was a significant relation between the intra-individual variability of RT and mean RT, and that it was not significantly different between choice conditions. In addition, the results showed that the relation was not significantly different between schizophrenia patients and control subjects. Therefore, despite the fact that schizophrenia patients, as a group, had a greater variability of RT than control subjects, their variability could be accounted for by their longer mean RT.

Prediction of group membership

On the basis of the results obtained with the ANCOVAs, we investigated whether the difference between RT_4 measured experimentally and RT_4 predicted for control subjects (i.e., vertical difference between each data point and the straight gray line in Fig. 2a) could be used as a marker for differentiating schizophrenia patients from control subjects. For this purpose, we computed for each subject i the difference Δt in ms:

$$\Delta t_i = \mathrm{RT}_{4i} - 10^{\alpha_{\mathrm{Control}}}\,\mathrm{RT}_{2i}^{\beta} \tag{3}$$

using the parameter values obtained previously (i.e., $\alpha_{\mathrm{Control}} = 1.259$, $\beta = 0.557$). We used Δt to estimate the probability P of each subject i to belong to the schizophrenia group on the basis of the binary logistic regression model (Hosmer and Lemeshow 2000):

$$\mathrm{Logit}(P_i) = \alpha + \beta \Delta t_i. \tag{4}$$

Equation 4 provided a good fit of the data (Hosmer and Lemeshow-test, $\chi^2(8) = 6.56$, $P = 0.585$) with parameters $\alpha = -0.373$ (SE 0.401; Wald-test, $\chi^2(1) = 0.86$, $P = 0.353$) and $\beta = 0.011$ (SE 0.005; Wald-test, $\chi^2(1) = 5.89$, $P = 0.015$). These parameters indicate that a difference Δt of 100 ms increased the odds of being a schizophrenia patient by a factor of 3 (i.e., $e^{100\beta}$). Using the parameters estimated by the logistic regression, we computed the probability of each subject to belong to the schizophrenia group:

$$P_i = \frac{e^{\alpha+\beta\Delta t_i}}{1 + e^{\alpha+\beta\Delta t_i}}. \tag{5}$$

Subjects with $P > 0.5$ were classified in the schizophrenia group and the others in the control group. The threshold $P = 0.5$ was reached at $\Delta t = 34$ ms, that is the probability of being a schizophrenia patient was greater than that of being an healthy subject when $\Delta t > 34$ ms. This procedure provided the correct classification of 77% of all the cases. The classification results per group are presented in Table 3, whereas Fig. 3 shows the histograms of Δt for the schizophrenia group and for the control group, as well as the logistic function used to classify the data.

As a comparison, the logistic regression performed using RT_4, which showed the greatest difference in mean RT between patients and control subjects, provided a correct classification of 69% of the cases. Therefore, these analyses showed that Δt was a marker that discriminated adequately patients and control subjects, and that it performed better than mean RT.

Correlations between RT-related measures and clinically related measures

Finally, we examined whether mean RT, IQR of RT and Δt were associated with the clinical measures of schizophrenia patients indicated in Table 1: Symptoms scores (i.e., BPRS; negative, psychotic, and disorganized symptoms), medication dosage and duration of illness. Eighteen rank correlation coefficients (Spearman's ρ) were computed between the two sets of variables (i.e., 3 RT-related measures × 6 clinically related measures) and their level of significance was adjusted using Bonferroni procedure (Snedecor and Cochran 1989). We found no statistically significant correlation between these variables.

Discussion

Schizophrenia patients and control subjects were tested in a choice RT task with two levels of stimulus-response uncertainty: a 2-choice condition and a 4-choice condition. Both groups performed in the task with a

Table 3 Classification results based on the logistic regression analysis

Observed group	Predicted group		Percent correct
	Control (*N*)	Schiz. (*N*)	
Control	13	5	72
Schizophrenia	4	17	81

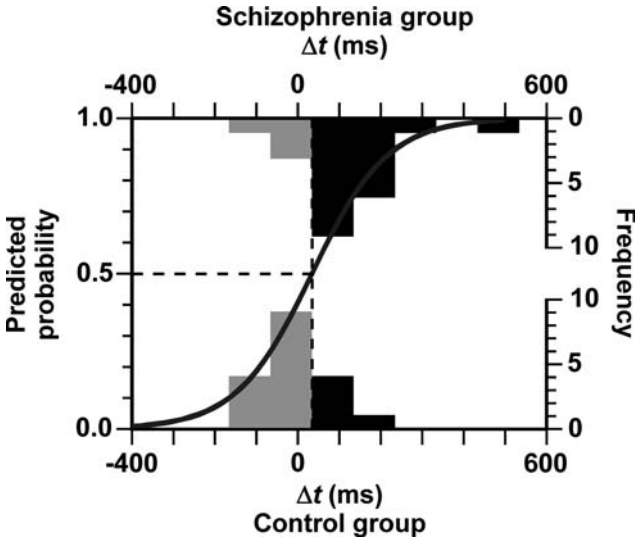

Fig. 3 Histograms of Δt for the schizophrenia group (*top*) and the control group (*bottom*). The logistic function indicates the probability to belong to the schizophrenia group as a function of Δt. The *gray bars* indicate the cases that were classified by the logistic regression as part of the control group, whereas the *black bars* indicate the data that were classified as part of the schizophrenia group

high and similar degree of accuracy, but they differed in relation to the central tendency of RT and its intra-individual dispersion. This is in agreement with findings from previous studies, as mentioned in the introduction. In this respect, these results would not add much new information to what is known already. However, the functional analyses (i.e., analyses of the functions relating variables) provided novel insights in the decision process of schizophrenia patients compared to that of healthy control subjects.

RT and task complexity

We found that RT in the 2-choice condition predicted well RT in the 4-choice condition for both groups, because subjects tended to perform consistently slow or fast across tasks. As expected, RT in the 4-choice condition was longer than in the 2-choice condition, which indicates that additional time-consuming processing was required when the number of choices increased (Luce 1986). However, RT in the 4-choice condition increased by a greater amount for schizophrenia patients than for healthy control subjects. This effect occurred even for patients who had similar RTs than control subjects in the 2-choice condition. Larger increases of RT in schizophrenia patients compared to control subjects when the task complexity increased have been documented in various contexts, such as in relation to an increase in attentional demand (Fuller et al. 2006; Seidman et al. 1998), an increase in working memory load (Krieger et al. 2005) or an increase in complexity of the rule associating stimulus and response (Posada and Franck 2002).

In the current task, however, there is no indication that the increase in number of choices was associated with an increase in attentional demand, memory load or a more complex stimulus-response rule. In fact, in both choice conditions, visual attention was required to be oriented toward the center of the display where the stimulus was presented without any difference in attentional demand between conditions. In addition, although the task required that subjects kept in memory the instructions, it did not require that the response be found through a search among a memorized list of items. Finally, the rule of the task, which was to press the button corresponding to the digit presented on the display, remained constant across conditions.

In contrast, the increase in number of choices in the RT task was associated with an increase of uncertainty about the upcoming stimulus-response. Several studies have shown that the degree of uncertainty affects the amount of planning of the upcoming response; the greater the uncertainty, the less the motor response can be prepared before it needs to be executed (Basso and Wurtz 1997; Pellizzer and Hedges 2003, 2004). The consequence of less motor planning is that when the stimulus is presented more processing is needed to select the appropriate response, which lengthens RT. Therefore, it can be concluded that the effect on RT of schizophrenia patients in the current choice RT task was related to the process of planning and selection of the motor response and not to other aspects such as attention, memory or use of a rule.

Response selection in schizophrenia

The functional analysis of the relation between RT in the 4-choice condition and RT in the 2-choice condition rejected the null hypothesis that, regardless of processing speed, the response selection process of schizophrenia patients was like that of control subjects. On the other hand, the analysis of the relation between

intra-individual variability of RT and mean RT showed that there was no significant difference between the two groups. Therefore, there is no indication that the intra-individual variability of schizophrenia patients was functionally different from the intra-individual variability of control subjects.

These results indicate that the response selection process of schizophrenia patients cannot be considered as functioning like that of control subjects. It is not, even, like the selection process engaged by slow control subjects, but it is a process with different dynamic properties. In other words, the time-varying pattern of activation of the neural network engaged during motor planning and response selection was affected differently by the number of choices in the two groups. In addition, the results suggest that even though the time course of neural activity might be have been altered in schizophrenia patients, there was no extra-variability in this process. In conclusion, provided that the interactions between elements of a neural network are a key factor determining its dynamic properties (Erlhagen and Schöner 2002), these results suggests that the connectivity within the network engaged for response selection is affected in schizophrenia patients.

RT and brain connectivity

The response selection process in the choice RT task engaged necessarily an ensemble of different brain areas. In particular, it has been shown that choice RT tasks activate primarily parietal and frontal cortical areas (Cavina-Pratesi et al. 2006; Dassonville et al. 2001; Schumacher et al. 2003). The pathways connecting these brain areas play a key role in determining the latency of response. In fact, individual differences in RT have been found to be associated with individual differences in the structural properties of cerebral white matter, as measured using diffusion tensor imaging (Madden et al. 2004; Tuch et al. 2005). These results imply that if these pathways were dysfunctional, then RT would be affected. These considerations are interesting in relation with the hypothesis of disconnection within brain networks in schizophrenia patients (Friston 1998). The disconnection hypothesis implies that schizophrenia patients have difficulty with processing, coordinating and responding to information (Andreasen et al. 1998).

Studies in which diffusion tensor imaging has been used to investigate the white matter of schizophrenia patients have found abnormalities of the connectivity across different regions of their brain (Kanaan et al. 2005; Kubicki et al. 2007). These studies support the hypothesis that the dysfunction of pathways in the brain plays a key role in schizophrenia. However, the results have been inconsistent regarding the pathways that show abnormalities (Kanaan et al. 2005). These inconsistencies might be related to methodological limitations that need to be addressed in the future (Kubicki et al. 2007). In any case, these studies are consistent with the hypothesis that abnormalities in the brain connectivity of schizophrenia patients alters the dynamics of neural activation during response selection, which has the consequence of changing the relation between RT and number of choices.

RT and schizophrenia symptoms

The difference Δt between RT measured in the 4-choice condition and RT predicted for control subjects in the same condition discriminated well schizophrenia patients from control subjects. This measure could reflect the degree of severity of the underlying pathology. However, there was no association between Δt, mean RT or intra-individual variability of RT and clinical variables. Similarly, other studies have reported no relation between RT and schizophrenia symptoms (Fleck et al. 2001; Gale and Holzman 2000), whereas some have found significant correlations (Cadenhead et al. 1997; Malla et al. 1995; Ngan and Liddle 2000; Schwartz et al. 1989, 1991). However, even in the latter cases, the results have been inconsistent. Indeed, mean RT has been associated, depending on the study, with the score for psychotic symptoms (Schwartz et al. 1989), or for negative symptoms (Cadenhead et al. 1997; Schwartz et al. 1991) or for disorganized symptoms (Malla et al. 1995; Ngan and Liddle 2000). Furthermore, RT variability has been found to be associated with negative symptoms in one study (Schwartz et al. 1991) and with positive, disorganization and tension/hostility symptoms in another (Vinogradov et al. 1998).

There are several possible reasons for these inconsistencies. First, the differences in methods for scoring symptoms and the part of subjectivity associated with them are likely to produce variations in the results. Second, schizophrenia patients are heterogeneous which could lead to samples of patients with different characteristics across studies. Third, the symptoms and their degree of severity fluctuate with time, which affects evidently the assessment of the relation between these symptoms and other variables. Finally, often correlation analyses have been performed without consideration for the number of correlation coefficients computed, which is a procedure vulnerable to spurious findings (Snedecor and Cochran 1989).

In spite of these problems, it is remarkable that finding a deficit of RT in schizophrenia patients is a robust result across studies, whereas finding a relation between this deficit and symptoms is not. This suggests that deficits of RT are common in schizophrenia patients and that they are present across the variety of symptom profiles expressed by the illness. In addition, deficits of RT have been shown to be more pronounced in schizophrenia patients than in other psychiatric patients (Fleck et al. 2001; Hemsley 1976). Therefore, it is not entirely surprising that deficits in choice RT have been found to be a marker of genetic vulnerability for schizophrenia (Bredgaard and Glenthøj 2000; Cannon et al. 2000).

In the current experiment, we showed that mean RT cannot be a good indicator of impairment because of the large overlap between the distributions of RT of schizophrenia patients and control subjects. In contrast, Δt provided a better marker that discriminated well schizophrenia patients from control subjects. However, as discussed above, Δt was not related to the severity of symptoms. This indicates that Δt could reflect a trait impairment of schizophrenia independent from the fluctuation of symptoms observed during the course of the illness. In this case, the magnitude of Δt could indicate the severity of the trait impairment.

Are RT deficits related to medication or illness?

Finally, it is legitimate to question whether the deficits of RT in schizophrenia are related to medication effects or to the illness. In our view, even though longer RTs could be related to medication, it is unlikely that medication could produce a different effect depending on choice condition as found in the current study (Fig. 2a). In addition, we found no significant correlation between the amount of medication and any RT-related measures. Furthermore, there are several lines of evidence that the origin of these deficits is not related to the drug treatment. For one thing, deficits of RT in schizophrenia have been documented before the introduction of neuroleptics (Shakow 1963). Second, first-episode, drug-naïve schizophrenia patients have also longer RTs than control subjects (Krieger et al. 2005). Third, RTs from healthy first-degree relatives of schizophrenia patients tends to be longer than RTs from control subjects (Laurent et al. 2000; Schreiber et al. 1992; Walker and Shaye 1982). These results suggest that the neural deficits revealed by RT tasks predate the administration of antipsychotic medication in patients and, more generally, that deficits in RT tasks indicate a genetic liability to schizophrenia (Bredgaard and Glenthøj 2000; Cannon et al. 2000). In summary, these studies indicate that the deficits of RT in schizophrenia are associated, at least in part, with the disease process.

Conclusions

In summary, we found that the functional properties of the response selection process of schizophrenia patients was not simply a slower version of the same process engaged by control subjects, but it was a selection process with different dynamic properties. In contrast, the intra-individual variability of schizophrenia patients was not functionally different from the intra-individual variability of control subjects. Additional analyses suggested that a simple RT-related measure, Δt, which is less likely to be affected by medication than mean RT, could reflect a trait impairment of schizophrenia independent from the fluctuation of symptoms. We suggest that deficits of RT in schizophrenia result from anomalies of the connectivity between brain areas engaged for the selection of the motor response.

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