

Impaired response selection in schizophrenia: Evidence from the P3 wave and the lateralized readiness potential

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Abstract

Reaction times (RTs) are substantially prolonged in schizophrenia patients, but the latency of the P3 component is not. This suggests that the RT slowing arises from impairments in a late stage of processing. To test this hypothesis, 20 schizophrenia patients and 20 control subjects were tested in a visual oddball paradigm that was modified to allow measurement of the lateralized readiness potential (LRP), an index of stimulus-response translation processes. Difference waves were used to isolate the LRP and the P3 wave. Patients and control subjects exhibited virtually identical P3 difference waves, whereas the LRP difference wave was reduced in amplitude and delayed in latency in the patients. These results indicate that, at least in simple tasks, the delayed RTs observed in schizophrenia are primarily a consequence of impairments in the response selection and preparation processes that follow perception and categorization.

Descriptors: Schizophrenia, P3, Lateralized readiness potential, LRP

Although delusions and hallucinations are the most dramatic features of schizophrenia, this disorder is also accompanied by pervasive, debilitating, and treatment-resistant cognitive and psychomotor deficits (Gold, 2004). Of these, deficits in episodic memory and executive function have attracted the most interest in the research literature. However, a recent meta-analysis revealed that a deficit in processing speed, as assessed by Digit Symbol tasks, is the most robust impairment documented in the literature (Dickinson, Ramsey, & Gold, 2007). This psychometric evidence echoes the claim made by Robert Cancro more than 3 decades ago that reaction time (RT) slowing is the “closest thing to a north star in schizophrenia research” (Cancro, Sutton, Kerr, & Sugerma, 1971, p. 351). Thus, there is abundant evidence for slowed behavioral performance in schizophrenia, but the origins of this impairment remain largely obscure despite extensive behavioral studies of reaction time in the older literature (see review by Nuechterlein, 1977). That is, it is unclear if observed behavioral slowing is the result of slowing at all stages of task processing or whether slowing at a specific stage of processing is implicated. Indeed, it appears likely that the failure of this older body of research to reveal the origins of response

slowing in schizophrenia led the field to largely abandon the investigation of this robust empirical finding.

We have begun using event-related potentials (ERPs) to re-examine this issue. In our first study, we used the N2pc component to show that the allocation of visual attention occurs at the same speed in patients with schizophrenia and healthy control subjects, despite the fact that RT slowing was observed in the patients (Luck et al., 2006). The current experiment was designed to use the P3 wave and the lateralized readiness potential to determine if the categorization and response selection processes indexed by these ERP components are related to RT slowing.

P3 amplitude is reliably reduced in schizophrenia patients (see the meta-analyses of Bramon et al., 2005; Bramon, Rabe-Hesketh, Sham, Murray, & Frangou, 2004; Jeon & Polich, 2003). P3 latency is presumably more relevant than P3 amplitude for understanding the slowing of RT, but studies of the P3 in schizophrenia do not typically make a link between P3 latency and RT, and they typically use silent counting tasks in which RT cannot be measured. P3 latency is often observed to be postponed in schizophrenia patients compared to control subjects, but the size of this effect is substantially smaller than the P3 amplitude effect (Jeon & Polich, 2003). Indeed, some researchers have argued that the slowing of P3 latency arises only many years after disease onset, suggesting that it reflects secondary consequences of disease progression, or a particularly severe clinical course, rather than being a fundamental attribute of the disease (e.g., Mathalon, Ford, Rosenbloom, & Pfefferbaum, 2000). Moreover, the available meta-analyses do not compare RT and P3 latency effects, and P3 latency is not usually measured in a manner that can be directly compared with RT (see pp. 243–247

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in Luck, 2005). Thus, prior studies have not directly tested whether the slowing of RT can be explained by a slowing of the processes that lead up to the P3 wave.

P3 latency is widely considered a good measure of *stimulus evaluation time*, the time required to perceive a stimulus and determine whether it belongs to a frequent or rare category (Kutas, McCarthy, & Donchin, 1977; Luck, 2005; Magliero, Bashore, Coles, & Donchin, 1984; Polich, in press). However, P3 latency is relatively insensitive to experimental manipulations that influence the duration of response selection and execution (Magliero et al., 1984; McCarthy & Donchin, 1981). Thus, the possibility that P3 latency is relatively unimpaired in schizophrenia suggests that the slowing of RT in schizophrenia is primarily a result of post-categorization processes, at least for simple tasks. The goal of the present study was to test this hypothesis by measuring the P3 wave along with the lateralized readiness potential (LRP), which reflects the time required to determine the appropriate response for a given stimulus.

Although the present study used an oddball paradigm that is similar to those used in many previous studies of the P3 wave in schizophrenia, we took a fundamentally different analytical approach in which difference waves were used to isolate specific cognitive processes (for a detailed discussion of this approach, see chapter 2 in Luck, 2005). Subjects were required to discriminate between members of two categories (letters and digits); one of these categories was rare and the other was frequent. If a given ERP response is larger for the rare category than for the frequent category, then this ERP response must have been generated after the brain has begun to determine whether the current stimulus belonged to the rare category or to the frequent category. As a result, if the time course of the rare-minus-frequent difference wave is the same for patients and control subjects, we can unambiguously conclude that the processes up to and including categorization were not slowed in the patients. In this approach, an ERP component is used primarily to measure the processes that preceded it rather than the process that generates the component.

The present study used the same conceptual approach to examine response-related ERP activity, focusing on the LRP. The LRP is typically observed when subjects make left- versus right-hand responses for different stimulus categories. Once the subject has perceived and categorized the stimulus, the appropriate response for the category must be determined, which then leads to preparation of that response. The motor preparation leads to a negative-going potential over the motor cortex contralateral to the selected hand, and the LRP is defined as the difference in voltage between the contralateral and ipsilateral sites. Any deviation of this voltage from zero indicates that the brain must have begun to determine which response was appropriate for the current stimulus, and the LRP therefore provides a precise index of the stimulus-response translation process (also called the response selection process). It is known that the LRP, as defined in this manner, arises at least in part from primary motor cortex (Coles, 1989), and it provides a well-documented and widely used means of studying the time course of motor preparation (see review by Smulders & Miller, 2009).

Subjects in the present study responded to the rare and frequent stimulus categories with different hands, making it possible to isolate the LRP, but we counterbalanced the assignment of hands to stimulus categories across trial blocks. In addition, we included trial blocks in which the two categories were equiprobable so that we could measure the LRP in the absence of

response priming and anticipation effects. This yielded rare, frequent, and equiprobable stimulus categories, which were factorially crossed with left-hand and right-hand response categories, allowing us to isolate the LRP separately from the P3.

We predicted that the P3 activity measured in the rare-minus-frequent difference waves would be similar for the patients and the control subjects (as previously observed by Potts, O'Donnell, Hirayasu, & McCarley, 2002), indicating that the patients are unimpaired at perceiving and categorizing simple alphanumeric characters. We further predicted that the LRP would differ between patients and control subjects, indicating that the patients are impaired at a stage that follows stimulus categorization but precedes or includes response preparation. This could take the form of a delayed LRP onset latency in patients, which would suggest that the process of stimulus-response translation is prolonged in schizophrenia. It could also take the form of a reduced LRP amplitude, which would suggest an impairment in the ability to differentially select and prepare the correct and incorrect responses.

Three recent studies have assessed the LRP in schizophrenia (Karayanidis et al., 2006; Kieffaber, O'Donnell, Shekhar, & Hetrick, 2007; Mathalon et al., 2002). Each used a task that was substantially more complex than the task used here, and each found a reduction in stimulus-locked and/or response-locked LRP amplitude in patients relative to control subjects, although this did not reach statistical significance in all cases. LRP onset was also delayed in the patients, although this was again not always significant. Together, these previous studies suggest that response selection and preparation processes may be impaired in patients. However, the complexity of the tasks in these studies makes it difficult to determine whether this was a secondary effect of impairments in earlier processes. The goal of the present study was to determine whether response selection and preparation processes are impaired in a very simple categorization task, in which the earlier stages of perception and categorization should be largely unimpaired. Indeed, we intentionally chose visual rather than auditory stimuli, because prior research indicates that the P3 wave is less impaired for visual stimuli (Jeon & Polich, 2003). By showing that LRP abnormalities can occur in the absence of P3 abnormalities, we can be more certain that the LRP abnormalities are not secondary to a deficit in perception or categorization.

Method

Participants

Twenty-three patients and 22 control subjects were tested. As detailed below, three patients and two control subjects were eliminated because of excessive artifacts, yielding a final sample of 20 subjects per group. The following subject descriptions reflect this final sample.

The patients were recruited from the outpatient clinics at the Maryland Psychiatric Research Center and were studied during a period of clinical stability. All patients met DSM-IV diagnostic criteria for schizophrenia ($N = 18$) or schizoaffective disorder ($N = 2$). Consensus diagnosis was established with a best-estimate approach based on medical records and multiple interviews. All patients were receiving antipsychotic medications. The most frequently used medication was clozapine, used alone ($N = 3$), in conjunction with risperidone ($N = 8$), or in conjunction with

Table 1. Demographic Features of the Final Patient and Control Samples (*SD* in parentheses)

	Patients with schizophrenia	Healthy volunteers
Age	47.01 (7.8)	47.44 (8.5)
Male/female	16/4	16/4
Years of education	12.45 (2.3)	14.55 (2.3)
Ethnicity (Caucasian/African American)	16/4	18/2
Wechsler Test of Adult Reading	96.85 (20.5)	109.30 (15.9)

quetiapine ($N = 1$). Of the remaining patients, four were receiving olanzapine. Risperidone, fluphenazine, ziprasidone, and quetiapine were each used by a single patient.

Control subjects were recruited through random digit dialing, word of mouth, and newspaper advertisements. All controls underwent a screening interview and denied a lifetime history of psychosis, any active Axis I disorder, and recent substance abuse (none within 6 months). All participants denied lifetime history of significant neurological conditions. As shown in Table 1, the groups were of similar age and gender, but differed in completed years of education, $t(38) = 2.8, p = .007$, and the Wechsler Test of Adult reading, $t(37) = 2.12, p = .040$ (note, however, that the patient mean of 96.8 approaches the normal population mean of 100 on this measure; note also that this measure was missing from one patient).

Stimuli and Task

The stimuli were black letters and digits, each measuring 1.6×1.6 degrees of visual angle, presented at the center of a cathode ray tube video monitor. The monitor was viewed at a distance of 110 cm and had a light gray background and a continuously visible fixation point. Each stimulus was presented for 200 ms, followed by a blank intertrial interval of 1,100–1,500 ms. Subjects pressed a button for each stimulus with the index finger of the left or right hand. During the first half of the session, subjects responded with one hand for digits and with the other hand for letters, and this was reversed for the second half. Subjects performed a brief training block prior to each half of the session. All subjects easily understood the instructions.

In each half of the session, subjects received one block in which digits appeared on 80% of trials and letters appeared on 20% of trials, one block in which this was reversed, and one block in which letters and digits were each 50% probable. The order of these three types of blocks was randomized across subjects. Each block contained 320 trials; a rest break was provided every 80 trials. Every combination of hand assignment and probability was tested in a separate block. Each subject was presented with a total of 256 rare stimuli, 1,024 frequent stimuli, and 640 equiprobable stimuli.

Recording and Analysis

The EEG was recorded from sintered Ag/AgCl electrodes at standard 10/20 locations (Fp1, Fp2, F3, F4, F7, F8, C3, C4, P3, P4, Fz, Cz, Pz) in an elastic cap. The signals were recorded using a right earlobe reference electrode and then re-referenced offline to the average of the left and right earlobes (Luck, 2005; Nunez, 1981). The horizontal electrooculogram (HEOG) was recorded between electrodes placed lateral to the external canthi. The vertical EOG was recorded from beneath the left eye, referenced to the right earlobe. The EEG and EOG were amplified and dig-

itized by a NeuroScan Synamps amplifier (Charlotte, SC) with a gain of 5,000, a bandpass of 0.05–100 Hz, and a sampling rate of 500 Hz. The baseline period was -200 to 0 ms for stimulus-locked averages and -800 to -600 ms for response-locked averages. A low-pass filter was applied prior to the latency measures (Gaussian impulse response function, half-amplitude cutoff = 5.8 Hz, full width at half maximum = 75 ms). Trials with incorrect behavioral responses or electrophysiological artifacts were excluded from the averages using our standard procedures (Woodman & Luck, 2003).

In our group's ERP studies of patients, we always exclude any subjects for whom more than 50% of trials were rejected; three patients and two control subjects were excluded for this reason. In the remaining subjects, artifacts led to the rejection of 22% of trials in the patient group and 24% of trials in the control group. Examination of the averaged HEOG waveforms after artifact rejection demonstrated that any unrejected eye movements in the direction of the responding hand were negligible, averaging less than 0.1° .

The main P3 measurements were taken from rare-minus-frequent difference waves, which were first collapsed across the letter and digit stimuli and across response hand. The LRP was measured from contralateral-minus-ipsilateral waveforms (relative to the responding hand for a given trial), as described by Smulders and Miller (in press). The P3 was measured at frontal (F3, Fz, F4), central (C3, Cz, C4), and parietal (P3, Pz, P4) electrode sites, and the LRP at lateral central sites (C3 and C4).

Amplitudes were measured as the mean voltage in a given measurement window (see windows in Table 2). P3 timing was quantified as midpoint latency, the time point that divided the area under the curve into two equal halves. This measure is analogous to peak latency but has a number of advantages, including greater statistical power (Kiesel, Miller, Jolicoeur, & Brisson, 2009) and the ability to make straightforward comparisons with median RTs (Luck, 2005). Because the LRP often continues well after the response, where it becomes contaminated by proprioceptive and tactile feedback activity, onset latency was used rather than midpoint latency, as is commonplace in LRP studies. Onset latency was defined as the time point at which the voltage reached 50% of the peak amplitude (this appears to be the optimal measure of onset time under many conditions—see Kiesel et al., 2008; Luck et al., 2006; Miller, Patterson, & Ulrich, 1998).

Analysis of variance (ANOVA) was used with an alpha level of .05 for all statistical tests, using the Greenhouse-Geisser epsilon correction for nonsphericity (Jennings & Wood, 1976). The analyses of behavioral data and the LRP measures included a between-subjects factor of group (patient vs. control) and a within-subjects factor of probability (rare, frequent, equiprobable). The P3 analyses included factors of group, anterior-posterior electrode position (frontal, central, parietal), and left-right electrode position (left hemisphere, midline, right hemisphere).

Table 2. Measurement Windows

Measure	Stimulus-locked		Response-locked	
	P3 (ms)	LRP (ms)	P3 (ms)	LRP (ms)
Amplitude	400–700	300–600	–200–100	–200–100
Latency	0–1,000	200–600	–600–400	–300–100

Table 3. Behavioral Results and Stimulus-locked P3 Measures Averaged Across the Parietal Electrode Sites from the Original Waveforms (standard errors in parentheses), Along with *F*, *p*, and epsilon (ϵ) Values for the Statistical Analyses

		Patients			Controls			Statistics		
Dependent variable		Freq	Rare	Equi	Freq	Rare	Equi	Group df = 1,38	Probability df = 2,76	Group \times probability df = 2,76
Stimulus-locked	Accuracy (%)	94.5 (0.5)	84.7 (1.6)	89.4 (1.2)	96.0 (0.5)	88.6 (1.5)	92.1 (1.2)	$F = 3.51$ $p = .07$	$F = 90.08$ $p = .000$ $\epsilon = .859$	$F = 1.75$ $p = .186$ $\epsilon = .859$
	Median Reaction Time (ms)	503.8 (21.64)	595.6 (19.51)	570.7 (21.09)	447.7 (11.02)	531.0 (10.16)	514.5 (11.94)	$F = 6.67$ $p = .014$	$F = 174.33$ $p = .000$ $\epsilon = .982$	$F = 0.495$ $p = .608$ $\epsilon = .982$
	Amplitude (μV)	1.82 (.329)	5.21 (.486)	2.78 (.413)	3.56 (.753)	7.12 (.926)	4.39 (.852)	$F = 3.97$ $p = .05$	$F = 127.45$ $p = .000$ $\epsilon = .683$	$F = .213$ $p = .722$ $\epsilon = .683$
	Peak Latency (ms)	446.5 (11.94)	483.1 (22.08)	450.27 (8.38)	435.10 (12.21)	492.87 (8.19)	470.97 (42.32)	$F = .162$ $p = .690$	$F = 4.44$ $p = .019$ $\epsilon = .896$	$F = .526$ $p = .574$ $\epsilon = .896$

Latency measures are typically nonlinear and tend to exhibit high levels of measurement error, and ERP studies are therefore increasingly using the jackknife approach for latency analyses (Kiesel et al., 2008; Miller et al., 1998; Ulrich & Miller, 2001). However, this approach has no effect on linear measures such as mean amplitude, and we therefore used this approach only for our latency analyses.

Correlations between RT and the key ERP measures were assessed using the Pearson *r* correlation coefficient. The jackknife approach was used for correlations involving the ERP latency measures (Stahl & Gibbons, 2004).

Results

Behavior

Mean accuracy (percent correct) and the means of the median RTs are shown in Table 3, along with a summary of the statistical analyses for these variables (*F* and *p* values will be given in the text only for tests not listed in the tables). Figure 1 shows RT probability histograms for the rare, frequent, and equiprobable stimulus categories, collapsed across the subjects in each group. Both groups were fastest for the frequent stimuli, slower for the equiprobable stimuli, and slowest for the infrequent stimuli, leading to a significant main effect of probability. Patients were slower than control subjects by approximately 60 ms at all three probability levels, leading to a significant group main effect but no group \times probability interaction. The slowing of RTs in patients was primarily due to an increase in the probability of relatively long RTs (a heavy right tail) rather than a rightward shift of the entire RT distribution.

Accuracy in both groups was highest for frequent stimuli, intermediate for equiprobable stimuli, and lowest for rare stimuli, leading to a significant main effect of probability. Although the patients were slightly less accurate than control subjects at all three probability levels, the difference was only marginally significant, and there was no interaction between group and probability.

Original ERP Waveforms

Figure 2 shows stimulus-locked ERP waveforms for the rare, frequent, and equiprobable stimulus categories. These waveforms and the following analyses of them are provided primarily

to allow comparison with prior studies, using the kinds of measures that are typically used in schizophrenia oddball studies. Specifically, we measured peak latency and mean amplitude separately from the rare, frequent, and equiprobable waveforms at the parietal electrodes using a measurement window of 400–700 ms. Table 3 summarizes the means and key statistical analyses.

P3 amplitude was clearly reduced for patients at all three probability levels, leading to a significant group main effect but no significant group \times probability interaction. Mean P3 peak latency was approximately the same for the patient and control groups. These results are broadly consistent with previous oddball studies, in which large amplitude reductions are typically observed for schizophrenia patients in the absence of large latency differences when the P3 wave is measured from the target (rare) waveforms.

The patient group also appeared to have a reduced N2 wave (ca. 250–350 ms). A statistical analysis of this effect will be presented in the next section.

Rare-Minus-Frequent Difference Waveforms (N2 and P3 Analyses)

Stimulus-locked Waveforms. Figure 3A shows stimulus-locked ERP waveforms for the rare-minus-frequent difference waves, and Table 4 summarizes the results. The difference waves for the patient and control groups were highly similar in the P3 latency range, and the statistical analyses revealed no significant main effects or interactions involving the group factor for P3 latency or amplitude. Although it is not possible to prove the null hypothesis that there were no differences in the P3 wave as measured from the difference waves, these data show a remarkable degree of similarity and indicate that any differences between groups are minimal.

There was, however, a clear group difference in the N2 latency range, with a voltage near zero for the patient group and a substantial voltage for the control group. A similar difference between schizophrenia patients and control subjects in rare-minus-frequent difference waves has been observed previously (Potts et al., 2002). To assess the statistical significance of this effect, we measured and analyzed the N2 difference wave just as we did the P3 difference wave, but using a measurement window of 250–350 ms. Although the main effect of group was only

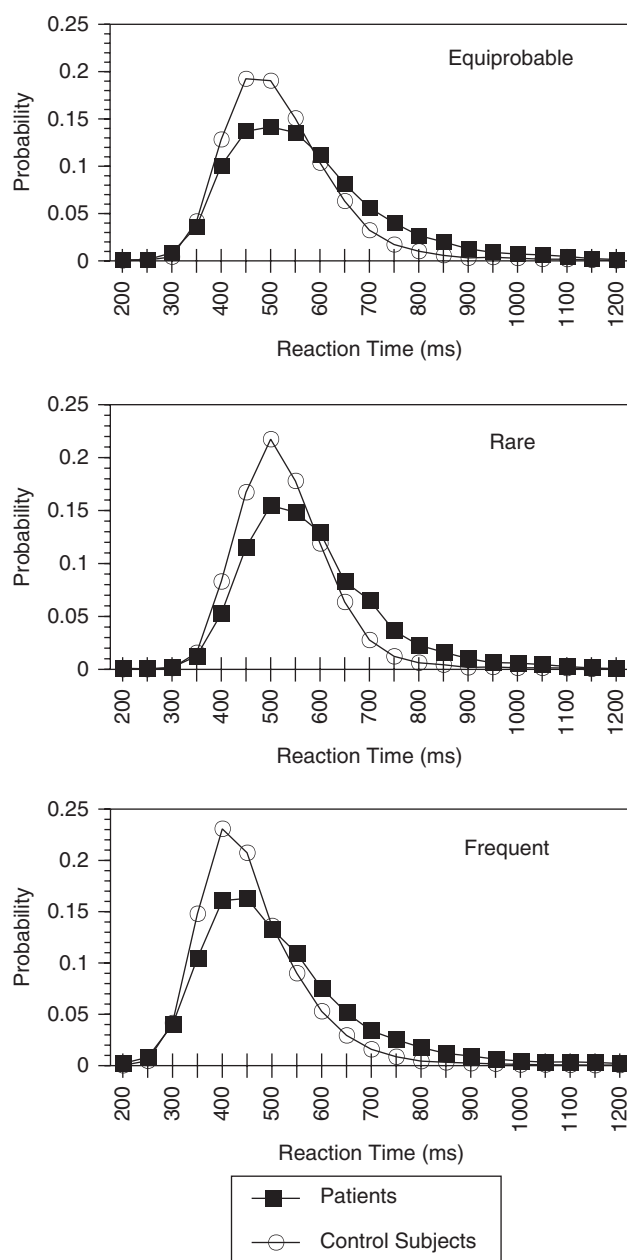


Figure 1. RT probability histograms from the patient and control groups for the rare, frequent, and equiprobable stimulus categories.

marginally significant ($F(1,38) = 3.93$, $p = .055$), the combination of a centroparietal N2 effect in the control group along with a near-zero N2 effect across sites in patients led to a significant interaction between group and anterior-posterior electrode position ($F(2,76) = 4.43$, $p = .028$). The presence of this significant N2 difference between patients and controls indicates that our lack of group differences in P3 amplitude and latency is not a result of atypical subject samples or low statistical power. The relevance of this finding will be described in the Discussion.

Response-locked Waveforms. Because the time between the stimulus and the P3 wave was the same for patients and control subjects, but patient RTs were longer than control RTs, the time between the P3 wave and the response should have been longer in patients than in control subjects. This was confirmed by the

response-locked rare-minus-frequent difference waves (see Figure 3B), in which the midpoint of the P3 wave occurred earlier relative to the response in patients than in controls. This finding demonstrates that the interval between stimulus categorization and response production is significantly slowed in patients, which directly tests the hypothesis that post-categorization response-related processes are slowed.

We observed no significant difference between patients and controls in response-locked P3 amplitude. The peak appeared to be reduced in patients, but because RT variability was substantially higher in patients than in controls (Figure 1), this difference in peak amplitude was almost certainly an artifact of greater latency variability. Our measure of mean amplitude is not impacted by the degree of latency variability (Luck, 2005), and so the lack of a patient-control difference in mean amplitude is consistent with a lack of difference in single-trial P3 amplitudes.

Contralateral-Minus-Ipsilateral Difference Waveforms (LRP Analyses)

Figure 4A shows stimulus-locked contralateral-minus-ipsilateral LRP difference waves, and Table 5 summarizes the LRP measures and statistics. For both groups, the LRP was largest for the rare stimulus category, smallest for the frequent stimulus category, and intermediate when the two categories were equiprobable, leading to a significant main effect of probability on LRP amplitude. This inverse relationship between stimulus probability and LRP amplitude may reflect different degrees of advance preparation of the responses. That is, when a given stimulus category is expected, the appropriate response can be prepared before stimulus onset, and less stimulus-triggered response activation (and hence less LRP) may be needed once the stimulus has been presented.

At all three probability levels, LRP amplitude was reduced by approximately 50% in the patient group compared to the control group, leading to a significant group main effect but no significant interaction with probability. It should be noted that this amplitude effect cannot be a consequence of greater latency variability in the patient group because the reduced patient amplitudes were observed over the entire extent of the LRP waveform. The same pattern was observed in the response-locked LRP waveforms (see Figure 4B).

In the stimulus-locked averages (Figure 4A), LRP onset latency was earliest for the frequent stimulus category and longer for the equiprobable and rare stimulus categories, leading to a significant main effect of probability on LRP onset latency. Just as for the effect of probability on LRP amplitude, this latency effect probably reflects differences in the advance preparation of the two responses as a function of the probability of the responses. That is, subjects may prepare the correct response in advance on frequent trials, whereas they may prepare the incorrect response in advance on rare trials and prepare the two responses equally on equiprobable trials. Consistent with this explanation, an opposite-polarity LRP was present between approximately 200–250 ms poststimulus for the rare stimulus category in the stimulus-locked waveforms. This initial voltage reversal on rare trials indicates that subjects frequently began to prepare the frequent (incorrect) response and then switched to the infrequent (correct) response on a substantial subset of these trials (a common finding in LRP studies—see, e.g., Gratton, Coles, Sirevaag, Eriksen, & Donchin, 1988; Miller & Hackley, 1992). A t -test on the mean voltage between 200–250 ms on the rare trials indicated that this reversal was significantly different

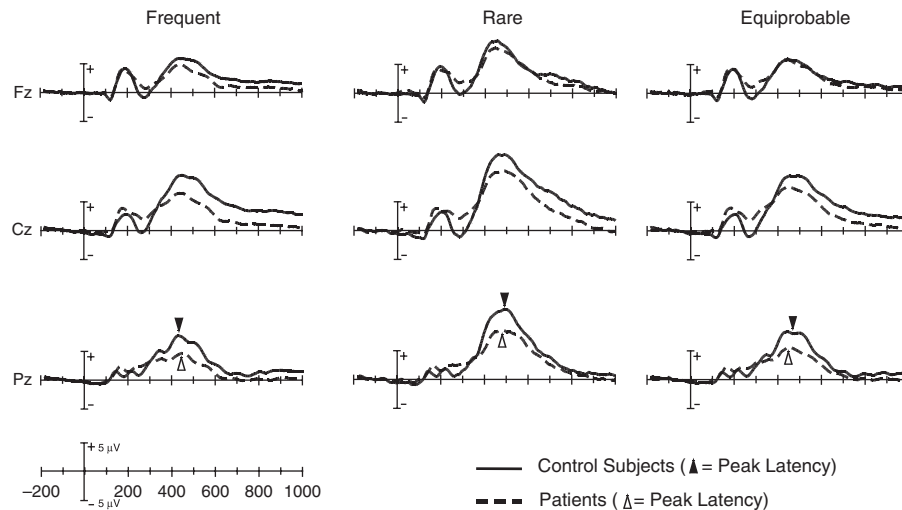


Figure 2. Stimulus-locked grand average ERP waveforms from the patient and control groups for the rare, frequent, and equiprobable stimulus categories at the frontal, central, and parietal midline electrode sites. These waveforms are comparable to those used to measure the P3 wave in most studies of schizophrenia patients. Triangles indicate mean peak latency values. A digital low-pass filter was applied offline before plotting the waveforms shown here and in the subsequent figures (Gaussian impulse response function, half-amplitude cutoff = 18.5 Hz, full width at half maximum = 23 ms).

from zero ($t(39) = 2.23, p = .032$). The size of this reversed voltage did not differ significantly between the patient and control groups ($t < 1$). However, given the small size of the voltage in both groups, this null effect should not be taken as evidence that both groups engaged in equivalent preparation of the frequent response.

LRP onset latency was significantly delayed for the patient group relative to the control group. The patient delay was largest for the frequent stimulus category ($M = 75$ ms), intermediate for the rare stimulus category ($M = 27$ ms), and smallest for the equiprobable stimulus category ($M = 12$ ms), leading to a significant group \times probability interaction. This is not the same pattern that was observed for RT, for which the patient slowing was approximately constant across probability levels. However, LRP amplitude differed considerably across probability levels, and this may have influenced the accuracy of the latency measures.

The response-locked averages shown in Figure 4B make it possible to assess the amount of time that passed between the onset of the LRP (reflecting the onset of response preparation) and the production of the button-press response. For both groups, this latency was longest for the rare stimulus category, intermediate for the equiprobable stimulus category, and shortest for the frequent stimulus category, leading to a significant main effect of probability. Although this pattern tended to be more extreme for patients, and the LRP onset tended to be earlier for patients than for controls, the main effect of group did not approach significance, nor did the group \times probability interaction. Thus, whereas the interval between stimulus onset and LRP onset was clearly delayed in patients, there was only a trend toward a delay between LRP onset and response onset. Karayanidis et al. (2006) found that this delay was significant, however, so it may be a real, although perhaps small, effect.

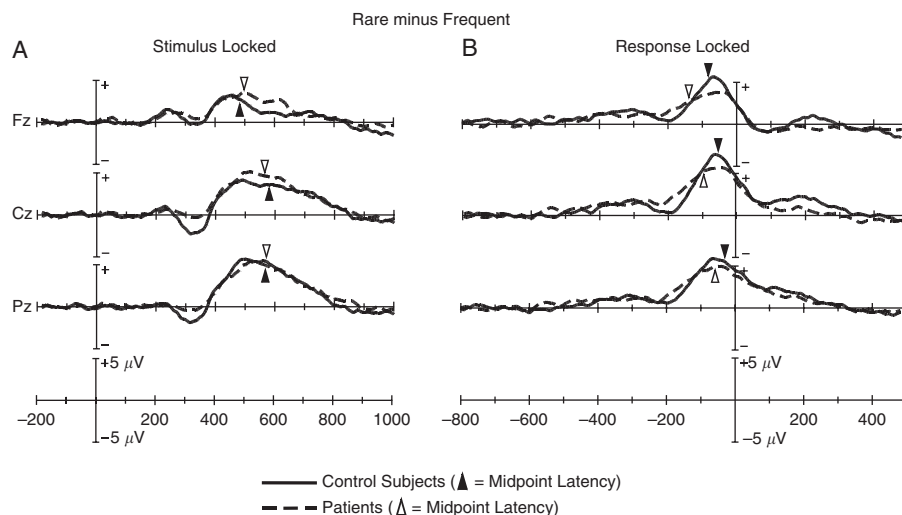


Figure 3. Stimulus-locked (A) and response-locked (B) grand average ERP difference waveforms (rare minus frequent) from the patient and control groups at the frontal, central, and parietal midline electrode sites. These waveforms isolate the brain's differential processing of the rare and frequent stimulus categories. Triangles indicate mean midpoint latency values.

Table 4. *P3 Rare-Minus-Frequent Difference Wave Measures (within-subjects standard errors in parentheses), Along with F, p, and epsilon (ϵ) Values for the Statistical Analyses*

	Dependent variable	Patients			Controls			Statistics		
		Frontal	Central	Parietal	Frontal	Central	Parietal	Group df = 1,38	Anterior-posterior df = 2,76	Anterior-posterior \times group df = 2,76
Stimulus-locked	Amplitude (μ V)	2.15 (.388)	3.45 (.476)	3.39 (.409)	1.76 (.485)	2.92 (.524)	3.56 (.424)	$F = .214$ $p = .646$	$F = 20.73$ $p = .000$ $\epsilon = .735$	$F = 1.09$ $p = .328$ $\epsilon = .735$
	Midpoint Latency (ms)	498.43 (22.77)	566.99 (17.07)	572.72 (12.01)	483.65 (32.21)	581.98 (22.86)	567.67 (15.06)	$F = 0.004$ $p = .950$	$F = 18.42$ $p = .00003$ $\epsilon = .608$	$F = .480$ $p = .528$ $\epsilon = .608$
Response-locked	Amplitude (μ V)	1.81 (.477)	3.09 (.475)	2.82 (.313)	2.19 (.431)	3.12 (.505)	2.84 (.373)	$F = .073$ $p = .789$	$F = 13.99$ $p = .000$ $\epsilon = .855$	$F = .451$ $p = .609$ $\epsilon = .855$
	Midpoint Latency (ms)	-140.55 (21.43)	-94.08 (15.50)	-50.74 (13.16)	-82.51 (16.16)	-49.97 (14.79)	-29.09 (18.45)	$F = 4.17$ $p = .048$	$F = 30.28$ $p = .000$ $\epsilon = .682$	$F = 1.98$ $p = .161$ $\epsilon = .682$

ERP-RT Correlations

Correlations between RT ERP measures were computed separately for the patient and control groups to determine within-group relationships.¹ To avoid inflating the experimentwise Type 1 error rate, only the most theoretically relevant correlations were examined. For the P3 wave, we focused on the rare-minus-frequent waveforms, and we correlated mean amplitude and midpoint latency with median RT from rare trials.² For the LRP, we focused on the contralateral-minus-ipsilateral difference waves, and the ERP measures were averaged across stimulus probability levels and then correlated with median RT, which was also averaged across stimulus probability levels. Only stimulus-locked ERP measures were used, because response-locking necessarily distorts the relationship between ERP measures and RT.

We found that longer RTs were associated with smaller P3 amplitudes and longer P3 latencies in both patients and control subjects (see Table 6). These correlations reached significance only for the amplitude and onset latency analyses in control subjects, but the general pattern was consistent across groups and measures. These findings indicate that, for both patients and

controls, a portion of the subject-to-subject variance in RT can be explained by individual differences in stimulus evaluation time.

Longer LRP onset latencies were associated with longer RTs in both control subjects and patients, but this correlation reached significance only for the control subjects (perhaps because the lower LRP amplitude in patients added noise to the latency measurements). The correlation between LRP amplitude and RT was near zero for control subjects, but the patients showed a significant correlation between LRP amplitude and RT, with smaller (less negative) LRP amplitudes associated with longer RTs. Thus, not only did the patient group exhibit lower LRP amplitudes than the control group, individuals in the patient group with lower LRP amplitudes exhibited longer RTs. This finding is consistent with the possibility that the factors that produce a smaller LRP in patients overall play a key role in the longer RTs typically exhibited by patients in simple choice RT tasks.

Discussion

This study used difference waves to isolate and measure the processes involved in perceiving and categorizing an alphanumeric stimulus and then selecting, preparing, and executing a behavioral response to this stimulus. When conventional measures were used instead of difference-wave measures, the results were very much like those of previous oddball studies in schizophrenia patients. That is, amplitude in the P3 latency range was reduced in patients, but there was no significant difference in latency. In addition, patient RTs were slowed by approximately 60 ms compared to control RTs. Thus, the basic paradigm and subject populations used in this study appear to yield findings consistent with the larger literature on schizophrenia.

P3 Difference-wave Findings

Additional information was provided by the difference-wave analyses. First, the rare-minus-frequent difference waves—which correspond to the brain's differential response to the rare and frequent stimulus categories—were nearly identical for the patients and control subjects in the P3 latency range. The absence of a latency difference indicates that the schizophrenia patients were able to perceive the stimuli and then categorize them as

¹We also examined correlations between the ERP measures and measures of symptom severity in the patient group. Symptom severity showed no clear relationship with the ERP measures: in particular, none of the correlations with the psychotic symptom factor from the Brief Psychiatric Rating Scale (i.e., the sum of the hallucination, unusual thought content, and suspiciousness items—Overall & Gorham, 1962) or with total negative symptom score from the Scale for the Assessment of Negative Symptoms (Andreasen, 1983) approached significance.

²We chose to correlate P3 latency from the rare-minus-frequent difference waves with the RT from rare trials for the following reasons. First, the rare-minus-frequent difference waves were the focus of our other P3 analyses. Second, these difference waves help to isolate the P3 wave from other overlapping components. Third, the difference between the rare and frequent ERPs in the P3 latency range primarily reflects the addition of the P3 wave on rare trials and thus provides a good measure of the detection of the rare stimulus, making it appropriate to compare this latency with the RT from rare trials. Finally, it would not be appropriate to correlate the P3 from the rare-minus-frequent difference wave with the difference in RT between rare and frequent trials because the latency of the peak of the rare-minus-frequent difference is not the same as the difference between the peaks of the rare and frequent trials.

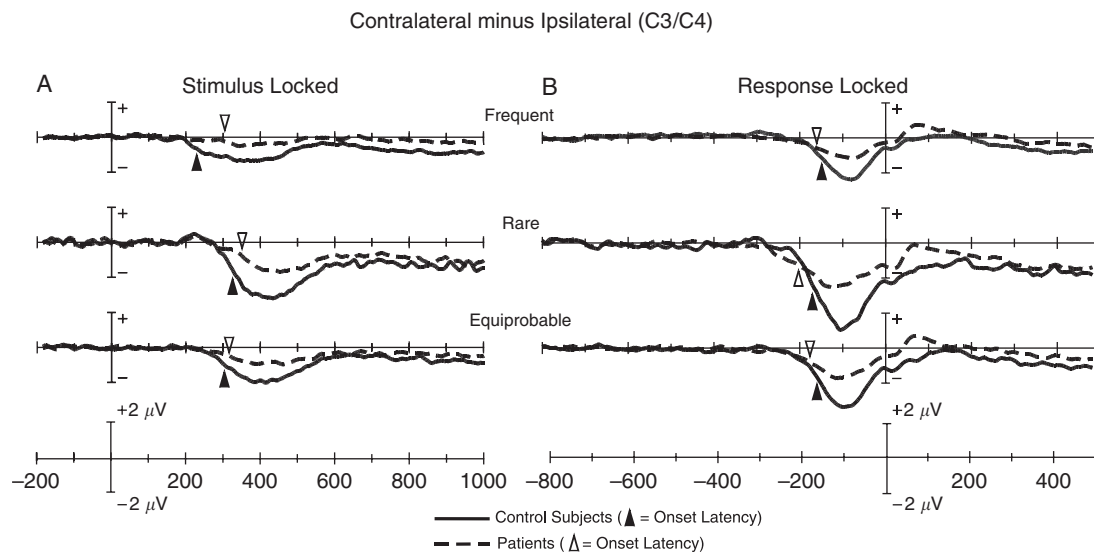


Figure 4. Stimulus-locked (A) and response-locked (B) grand average ERP difference waveforms (contralateral minus ipsilateral) from the patient and control groups for the rare, frequent, and equiprobable stimulus categories, averaged over the C3 and C4 electrode sites. These waveforms isolate the lateralized readiness potential, which reflects the outcome of the processes that determine which motor response is appropriate for a given stimulus category. Triangles indicate mean onset latency values.

members of the rare or frequent category just as quickly as were the control subjects. In addition, because stimulus-locked P3 latency was not delayed, but RT was delayed, the interval between the P3 and the response was significantly delayed in the response-locked averages. Thus, we found no evidence of a delay in the processes leading up to the P3, but we found a significant delay in the P3-RT interval. This pattern is exactly what would be expected if patients are not slowed at perceiving and categorizing simple stimuli but are slowed at selecting, preparing, or executing the appropriate response. To our knowledge, no previous studies of the P3 wave in schizophrenia have provided this sort of complete and direct assessment of the relationship between P3 latency and RT. It should be noted, however, that this pattern of results may be limited to simple visual discriminations; patients tend to exhibit larger P3 amplitude reductions for auditory stimuli than for visual stimuli (Ford, 1999; Jeon & Polich, 2003), and patients exhibit significant impairment in more complex visual discrim-

ination tasks (e.g., Doniger, Foxe, Murray, Higgins, & Javitt, 2002; Fuller et al., 2006).

One plausible explanation is that the patients were impaired at activating the P3-generating neural machinery for all stimulus categories and not just for the rare category. Alternatively, it is possible that the P3 generator itself is intact in patients but the inputs to this generator operate abnormally. It is also possible that the amplitude reduction in the P3 range reflects a change in some other component that is not probability sensitive but overlaps the P3 wave, and that the prototypical probability-sensitive P3b component is not actually impaired in schizophrenia. However, this seems unlikely given previous evidence that the P3b component itself is impaired in schizophrenia (O'Donnell et al., 1999). Unfortunately, these possibilities cannot easily be addressed on the basis of prior studies of the P3 in schizophrenia, because so few studies actually report the data necessary to determine whether the rare-minus-frequent difference is reduced in patients.

Table 5. LRP Difference Wave Measures (within-subjects standard errors in parentheses), Along with *F*, *p*, and epsilon (ϵ) Values for the Statistical Analyses

	Dependent variable	Patients			Controls			Statistics		
		Freq	Rare	Equi	Freq	Rare	Equi	Group df = 1,38	Probability df = 2,76	Group \times Probability df = 2,76
Stimulus-locked	Amplitude (μ V)	-.264 (.131)	-1.170 (.259)	-.695 (.128)	-.914 (.209)	-2.315 (.273)	-1.411 (.227)	$F = 10.346$ $p = .003$	$F = 39.888$ $p = .000$ $\epsilon = .830$	$F = 2.136$ $p = .135$ $\epsilon = .830$
	Onset Latency (ms)	304.78 (14.60)	353.72 (10.95)	315.86 (12.00)	230.15 (8.26)	326.38 (6.84)	304.31 (8.13)	$F = 10.77$ $p = .0002$	$F = 41.00$ $p = .000$ $\epsilon = .963$	$F = 8.30$ $p = .0007$ $\epsilon = .963$
Response-locked	Amplitude (μ V)	-.397 (.138)	-1.53 (.285)	-.723 (.137)	-1.010 (.195)	-2.84 (.310)	-1.75 (.249)	$F = 12.488$ $p = .001$	$F = 54.667$ $p = .000$ $\epsilon = .785$	$F = 2.983$ $p = .070$ $\epsilon = .785$
	Onset Latency (ms)	-160.41 (11.00)	-203.46 (22.03)	-175.06 (10.07)	-147.54 (7.29)	-168.74 (7.60)	-159.53 (5.51)	$F = 2.21$ $p = .145$	$F = 8.38$ $p = .002$ $\epsilon = .718$	$F = 1.14$ $p = .312$ $\epsilon = .718$

Table 6. *Pearson r and Associated p Values for the Correlations Between Median Reaction Time and the Major P3 and Lateralized Readiness Potential (LRP) Measures*

Variable	Patients		Control subjects	
	r	p	r	p
Stimulus-locked P3				
Amplitude (μ V)	-.349	.132	-.485	.030
Midpoint latency (ms)	.305	.192	.366	.112
Stimulus-locked LRP				
Amplitude (μ V)	.471	.036	.060	.800
Onset latency (ms)	.358	.121	.473	.035

N2 Findings

Although patients exhibited normal activity in the P3 latency range in the rare-minus-frequent difference waves, they showed a substantially reduced amplitude in the N2 latency range. A similar finding was obtained by Potts et al. (2002), who examined difference waves in a task that combined an oddball procedure with manipulations of visual selective attention, and it can also be seen in the original waveforms in the present study and in previous studies of schizophrenia (Bruder et al., 1998; Ford et al., 1994). How can we explain a reduction in one component but no reduction in a later component? It seems likely that these components are not serial stages but instead independently operate on the outputs of perception and categorization processes. This independence makes it possible to have impairments in the P3 but not the N2. Potts et al. (2002) proposed that the N2 component reflects a high-level object recognition process that is impaired in schizophrenia patients but is not needed for discriminating among relatively simple stimuli, such as those used in the present study.

LRP Findings

As in previous studies (Karayanidis et al., 2006; Kieffaber et al., 2007; Mathalon et al., 2002), LRP amplitude was dramatically reduced in patients compared to control subjects. The average reduction was 50%, and it was observed at all three probability levels. In addition, the degree of LRP amplitude reduction among patients was significantly correlated with the degree of RT slowing. In previous studies, more complex tasks were used, and the reduction in LRP amplitude was accompanied by other abnormalities in the target-elicited waveforms, making it difficult to know whether the LRP reduction was a secondary consequence of impairments in earlier processes. In the present study, however, the task was very simple, and patients exhibited no impairment in the rare-minus-frequent P3 wave. Thus, it is now possible to attribute the reduction in LRP amplitude to processes that follow perception and categorization.

The most obvious abnormality in the patient LRP waveforms was the reduction in amplitude, which was equally large in the stimulus-locked and response-locked averages. The onset of the LRP relative to stimulus onset was delayed by only 12 ms in patients relative to control subjects for the equiprobable stimuli, which was much less than the 60-ms RT delay. Because the LRP cannot be elicited until the brain has begun to determine which response is appropriate for the current stimulus, the small size of the LRP onset latency effect might seem to suggest that the slowing of RT cannot be explained by a slowing of the response selection process. However, one must be cautious in relating the size of an ERP latency effect to the size of an RT effect, because they may reflect different portions of the distribution of

single-trial latencies (see pp. 243–247 in Luck, 2005). Our measure of P3 midpoint latency is closely related to the median of the distribution of single-trial latencies, and can therefore be directly compared with median RT, but our measure of LRP onset latency is more closely related to the first quartile of the distribution of single-trial latencies and cannot be directly compared to median RT. In the RT distributions shown in Figure 1, patient RTs differ from control RTs primarily in the right tail of the distribution of RTs, with relatively little difference along the rising edge of the distribution. Thus, we would not expect the slowing of LRP onset latency to be as great as the slowing of median RT.

The response-locked averages provide useful information about the relationship between the slowing of LRP onset and the slowing of RT. If a portion of the slowing of RT in patients was caused by a slowing of processes that follow LRP onset, then this should have caused an increase in the time between LRP onset and the response in the response-locked averages (just as we observed an increase in the time between the P3 and the response). Although LRP onset was somewhat earlier for patients than for controls in the response-locked averages, this effect did not approach significance. Thus, we observed a highly significant delay in LRP onset latency for patients in the stimulus-locked averages but no significant change for patients in the response-locked averages. This suggests that most or all of the delay in patient RTs can be explained by an increase in the amount of time required to determine the appropriate response for the current stimulus rather than an increase in the amount of time required to execute the response once the response has been selected. This conclusion must be considered tentative, however, because it relies on differences in statistical significance that could reflect differences in sensitivity rather than true differences in the underlying brain activity. Additional research is necessary to determine whether patients also exhibit slowing of response preparation and execution processes.

The overall pattern of P3 and LRP latency results nicely mirrors the results of pharmacologic manipulations of the dopamine (DA) system. Specifically, DA manipulations do not change P3 latencies, consistent with a role of DA in processes that follow stimulus evaluation (Naylor, Halliday, & Callaway, 1985). However, DA manipulations influence the amount of time between stimulus onset and LRP onset, without affecting the time between LRP onset and the response (Rammsayer & Stahl, 2006). Together, these results suggest that DA plays a specific role in the response selection process, which is consistent with the present conclusion that schizophrenia—which clearly involves DA dysregulation—leads to impairments in response selection. However, DA manipulation has not yet been shown to influence LRP amplitude, so the details of the relationships among DA, schizophrenia, and the LRP remain to be elucidated.

Possible Explanations of the LRP Amplitude Reduction

What might account for the reduced LRP amplitude observed in patients? Because the LRP is defined as a difference between the electrodes contralateral and ipsilateral to the response hand, reduced amplitude could be a consequence of: 1) a selective reduction of activity over the contralateral hemisphere (reduced activation of the correct hand), and/or 2) increased activation over the ipsilateral cortex (increased activation of the incorrect hand). Evidence of increased ipsilateral motor activation in schizophrenia patients has been observed in a neuroimaging study (Mattay et al., 1997), but we cannot be certain that this is

the cause of the LRP effect observed here. The following are some potential explanations of the observed LRP reduction.

First, the neural circuit that generates the LRP might be impaired in schizophrenia patients, which would lead directly to a reduction in the voltage produced during preparation of the correct response. This is plausible given that motor cortex—where the LRP is largely generated—operates through a dopamine-mediated loop with the basal ganglia. Dysfunction of this loop might directly reduce the ability of motor cortex to generate the LRP.

Second, the cognitive processes responsible for determining the appropriate response code for the current stimulus might be impaired, leading to a weakened input to the motor cortex contralateral to the appropriate response hand. In this scenario, motor activation would accumulate at a slower rate, requiring more time to reach the threshold for initiating a response, which would explain the combination of reduced LRP amplitude and delayed RTs.

Third, patients may produce a subthreshold activation of the incorrect response, increasing the voltage over the hemisphere ipsilateral to the correct response. This could arise from a failure of prefrontal control systems to suppress the inappropriate S-R mapping rule (as in the Stroop task—see Cohen, Barch, Carter, & Servan-Schreiber, 1999). Alternatively, activation of one response might ordinarily lead to lateral inhibition of competing responses, and a reduction in this inhibition could lead to increased activation of the incorrect response (and an increase in

the voltage over the hemisphere ipsilateral to the correct response). This would be consistent with the growing evidence of abnormalities in the function of inhibitory inter-neurons in patients with schizophrenia, especially in the motor system (Fitzgerald et al., 2004; Hashimoto et al., 2008; Oxley et al., 2004).

Although we cannot distinguish between these potential explanations (which are not mutually exclusive), the present results are important because they indicate that RT slowing—a “north star” of schizophrenia research—is associated with a specific stage of processing that lies between stimulus evaluation and response initiation. This will help to focus future research on a relatively narrow range of underlying mechanisms.

Medication Effects

It is conceivable that the LRP abnormalities were a consequence of the use of antipsychotic medications. However, this seems unlikely given the extensive evidence that antipsychotic medications are not responsible for RT slowing in schizophrenia (Medalia, Gold, & Merriam, 1988; Zahn, Pickar, & Haier, 1994). Given the close association between the LRP and RT in general and the correlation observed between patient LRP amplitude and RT in the present study, it would be extremely difficult to explain how medications could influence the LRP without also influencing RTs. Nonetheless, it will be important for future research to examine the LRP in unmedicated, first-episode, and prodromal patients.

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