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ORIGINAL ARTICLE

Electrophysiological Evidence for Impaired Control of Motor Output in Schizophrenia

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Abstract

Previous research has demonstrated pervasive deficits in response-related processing in people with schizophrenia (PSZ). The present study used behavioral measures and event-related potentials (ERPs) to test the hypothesis that schizophrenia involves specific impairment in the ability to exert control over response-related processing. Twenty-two PSZ and 22 matched control participants completed a choice response task in counterbalanced testing sessions that emphasized only accuracy (the unspeeded condition) or emphasized speed and accuracy equally (the speeded condition). Control participants successfully modulated behavioral and ERP indices of response-related processing under speed pressure, as evidenced by faster and less variable reaction times (RTs) and an earlier onset and increased amplitude lateralized readiness potential (LRP). By contrast, PSZ were unable to improve RT speed or variability or to modulate the LRP under speed pressure, despite showing a decrease in accuracy. Notably, response-related deficits in PSZ emerged only in the speeded condition; behavioral and ERP measures did not differ between groups in the unspeeded condition. Together, these results indicate that impairment in the ability to exert control over response-related processing may underlie response-related deficits in schizophrenia.

Key words: control, ERPs, lateralized readiness potential, motor, response preparation, schizophrenia

Introduction

Psychomotor disturbances in people with schizophrenia (PSZ) have long been documented in both clinical and research settings. Although these deficits are less dramatic than some of the other features of schizophrenia, such as hallucinations and delusions, these deficits are a core feature of the disorder. In laboratory tasks, deficits in psychomotor functioning in PSZ are most commonly evidenced by pronounced increases in reaction time (RT) in a variety of paradigms, including both simple

and choice response tasks (Nuechterlein 1977). In addition, these deficits occur across a range of sensory input modalities (e.g., auditory and visual) and response output modalities (e.g., manual and vocal; Woodward et al. 2013).

Recently, event-related potentials (ERPs) have been combined with behavioral measures to determine the locus of psychomotor slowing in schizophrenia. Whereas behavior provides a single output measure summed across many distinct stages of processing, the millisecond-level resolution of the ERP technique allows changes in individual processing stages to be isolated and

quantified. ERP studies have shown that simple visual perception and categorization (as assessed with the P3 wave) are not slowed in PSZ compared with control participants, at least in simple task conditions. By contrast, ERP studies examining the lateralized readiness potential (LRP), an index of response-related processes, have revealed a specific impairment in PSZ in the selection and preparation of an appropriate behavioral response (Mathalon et al. 2002; Karayanidis et al. 2006; Kieffaber et al. 2007; Luck et al. 2009; Kappenman et al. 2012). The goal of the present study is to begin answering the question of why this stage of response processing is impaired in PSZ.

The LRP is typically observed in choice response tasks in which participants make a left-hand response for one stimulus and a right-hand response for another stimulus. The preparation of the response leads to a negative-going potential over the motor cortex contralateral to the responding hand (see Smulders and Miller 2012 for a review), and activity related to motor preparation is isolated from the rest of the brain's activity by taking advantage of the contralateral organization of motor cortex. That is, by subtracting the activity over the ipsilateral cortex from the activity over the contralateral cortex, the nonlateralized brain activity is subtracted out, leaving only the activity related to preparation of the response (see Smulders & Miller 2012 for a more detailed description of the isolation of the LRP). The LRP has been shown to arise at least in part from motor cortex (Coles 1989; De Jong et al. 1990) and typically begins 100-200 ms prior to the execution of the response, providing an index of preparatory processes that precede response execution.

The LRP can be measured in 2 distinct ways—time-locked to the presentation of the stimulus or time-locked to the execution of the response—each providing unique information about response-related processing. In the stimulus-locked LRP, the amount of time needed to determine which response is appropriate for the stimulus and begin preparing the response is reflected by the amount of time between the presentation of the stimulus and the onset of the LRP (the stimulus \rightarrow LRP interval). The amount of variability in the stimulus → LRP interval influences the amplitude of the stimulus-locked LRP, with greater variability leading to a broader waveform with a smaller peak amplitude in the average waveform. In the response-locked LRP, the amount of time needed to complete response execution after the response has been selected is reflected by the amount of time between the onset of the LRP and the execution of the response (the LRP \rightarrow response interval). Greater variability in the LRP \rightarrow response interval decreases the size of the average response-locked LRP. By looking at both stimulus-locked and response-locked LRP waveforms, it is possible to test specific hypotheses about how the single-trial LRP waveform varies across groups or conditions. For example, an increase in variability in the stimulus → LRP interval without any change in the LRP → response interval will lead to a reduced stimulus-locked LRP amplitude without any change in the response-locked LRP amplitude. By contrast, a reduction in the magnitude of the single-trial LRP signal will lead to reduced amplitudes in both the stimulus-locked and response-locked averages.

Previous studies of the LRP in PSZ found smaller stimuluslocked LRPs in PSZ compared with control participants across a range of tasks (Mathalon et al. 2002; Karayanidis et al. 2006; Kieffaber et al. 2007; Luck et al. 2009; Kappenman et al. 2012). A few of these studies also examined the amount of time between the presentation of the stimulus and the onset of the LRP (the stimulus → LRP interval). These studies found significant delays in the onset time of the LRP in PSZ compared with controls in a range of conditions (Karayanidis et al. 2006; Luck et al. 2009;

Kappenman et al. 2012). Indeed, the LRP was delayed by as much as 75 ms and decreased in amplitude by as much as 50% under some task conditions. These differences in the amplitude and onset latency of the LRP in PSZ were observed in tasks involving little competition between response options—for example, pressing a left button for the word "Left"—indicating that abnormalities in the LRP in PSZ are not the result of difficulty resolving conflict between response alternatives (Kappenman et al. 2012).

Examinations of the LRP time-locked to the response have yielded mixed results. Some studies have found smaller LRPs in PSZ compared with controls (Mathalon et al. 2002; Luck et al. 2009), whereas other studies have found no decrease in the size of the response-locked LRP in PSZ (Karayanidis et al. 2006; Kieffaber et al. 2007; Kappenman et al. 2012). In other words, equating for variability in RT between groups by time-locking to the response eliminated amplitude differences in responserelated processes in PSZ, but only in some tasks and conditions. Analyses of the time between the LRP and the response have also yielded mixed results, with PSZ showing increases in the LRP → response interval compared with controls in some tasks (evidenced by an earlier onset latency of the LRP in PSZ in averages time-locked to the response; Kappenman et al. 2012, Experiment 1; Karayanidis et al. 2006), whereas other tasks found no significant difference between PSZ and controls (Kieffaber et al. 2007; Luck et al. 2009). It is unclear whether these mixed results reflect an improvement in response execution time in PSZ under some task conditions, or whether some studies lacked sufficient power on this measure to detect differences between PSZ and controls. Indeed, it is difficult to compare ERP onset latencies across conditions that differ substantially in amplitude (Luck 2014), as in many previous studies of the LRP in PSZ.

Although it is now clear that PSZ have response-related deficits that are indexed by the LRP, it is not yet known what specific impairment underlies these deficits. One possibility is that PSZ have a dysfunction in basic motor processes, resulting in difficulty activating a motor response. Indeed, PSZ exhibit a range of motor abnormalities, including impairments in facial expressions, eye movement control, dyskinesias, motor stereotypies, parkinsonism, and delayed motor development (Meehl 1989; Caligiuri et al. 1993; Jones et al. 1994; Puri et al. 1999; Walker et al. 1999; Mittal et al. 2008). Another possibility is that response-related deficits in PSZ are a consequence of deficits in exerting control over response-related processing. Previous studies demonstrated marked impairments in PSZ in a variety of control processes (Kerns et al. 2008; Luck and Gold 2008; Phillips and Silverstein 2013), which could result in a failure to appropriately set the parameters that determine the operation of motor cortex.

The goal of the present study was to distinguish between these 2 classes of explanations for impaired response-related processing in schizophrenia. To do this, we performed a simple manipulation of speed pressure. Speed pressure significantly decreases RTs in healthy individuals and has been shown to influence the LRP, shortening the LRP → response interval (Osman et al. 2000; van der Lubbe et al. 2001) or both the stimulus → LRP and LRP → response intervals (Rinkenauer et al. 2004), depending on the specific task and variant of speed pressure used. RT improvements under speed pressure are related to increased baseline BOLD activity in many areas important for motor processing, including premotor areas of frontal cortex (Forstmann et al. 2008; Ivanoff et al. 2008; Van Veen et al. 2008; van Maanen et al. 2011). If PSZ exhibit deficits in response-related processing because of impairment in the generation or implementation of control signals, then they should be selectively impaired at modulating response-related processing under speeded conditions, in which control signals are necessary to boost performance. By contrast, if the basic response activation circuitry is impaired in PSZ, then response-related deficits should be observed regardless of the need for control signals.

In the present study, we measured performance in 2 separate testing conditions: a condition that emphasized only accuracy (the unspeeded condition) and a condition that emphasized both speed and accuracy (the speeded condition). We predicted that control participants would show decreased and less variable RTs, decreased LRP → response intervals, and possibly decreased stimulus → LRP intervals under speed pressure. Given the importance of control signals in improved RTs under speed pressure (Forstmann et al. 2008; Ivanoff et al. 2008; Van Veen et al. 2008; van Maanen et al. 2011) and previous findings that PSZ exhibit impairments in control in a variety of tasks (Lesh et al. 2010; Phillips and Silverstein 2013), we predicted that PSZ would be selectively impaired at modulating the LRP and RT under speed pressure. This would indicate that at least some of the psychomotor impairments observed in this disorder reflect impairments in the generation or implementation of control signals rather than impairments in basic motor circuitry. Furthermore, by examining both stimulus-locked and response-locked LRPs, we were able to determine whether any differences between groups were related to response selection and preparation, response execution, or both processes. Given that the majority of LRP studies in PSZ have primarily found deficits in the stimulus-locked LRP, we predicted that differences between PSZ and controls would be most evident in ERPs time-locked to the stimulus, reflecting difficulty in selecting and preparing a response.

Methods

Participants

Twenty-five PSZ and 23 control participants were tested. In our group's ERP studies of psychiatric patients, we always exclude participants who exhibit EEG artifacts on >50% of trials. Three PSZ and 1 control participant were eliminated for this reason, yielding a final sample of 22 participants per group. The following descriptions reflect this final sample.

PSZ were recruited from the University of California, Davis Early Diagnosis and Preventive Treatment (EDAPT) clinic and through community flyers. PSZ were studied during a period of relative clinical stability as indicated by clinical observation and stability of pharmacological treatment, with no change in medication type or dosage for a minimum of 4 weeks prior to study. All PSZ met American Psychiatric Association (2000) diagnostic criteria for schizophrenia (N = 19) or schizoaffective disorder (N = 3). A consensus diagnosis was established with a best-estimate

approach in which information from a Structured Clinical Interview for DSM Disorders (SCID; First et al. 2002) was supplemented with information from past medical records and from clinicians who have had contact with the individual. This information is typically presented at a diagnostic meeting with clinicians and social workers involved with the EDAPT clinic. Symptom ratings for the PSZ are shown in Table 1. Eighteen PSZ were receiving atypical antipsychotic medications, 1 PSZ was receiving typical antipsychotic medication, and the remaining 3 PSZ were not receiving antipsychotic medications at the time of testing.

Control participants were recruited through a combination of word of mouth and newspaper advertisements. All controls were screened using the SCID and denied a lifetime history of psychosis, any active Axis I disorder, and recent substance abuse (within 6 months of testing). All participants denied a lifetime history of significant neurological conditions and were excluded if they reported any first-degree relatives with a psychotic disorder.

The demographic features of the groups are shown in Table 1. The groups were of similar age, race, and gender, but differed in completed years of education ($t_{(42)} = 4.10$, P < 0.001), an expected finding given that the onset of schizophrenia generally occurs in early adulthood and interferes with subsequent education. There was no significant difference between groups in parental years of education $(t_{(42)} = 0.028, P = 0.977)$.

Note that both the PSZ and the controls were relatively young (mean age in each group ca. 25 years of age; see Table 1), which reflects the nature of the clinic from which they were recruited. This is advantageous, because it minimizes any differences between groups that might result from extended disease duration.

Stimuli and Task

An example trial sequence is presented in Figure 1. The stimuli were black @ and \$ characters each measuring $1.6 \times 1.6^{\circ}$ of visual angle, presented at the center of a liquid crystal display video monitor. The monitor was viewed at a distance of approximately 70 cm and had a light gray background and a continuously visible fixation cross. Each stimulus was presented for 200 ms, followed by a blank interstimulus interval of 1300-1700 ms (rectangular distribution).

Participants made left-hand and right-hand button presses to the symbols using a gamepad. To avoid the build-up of automatic responding, the stimulus-response mapping switched every 20 trials. Instructions about the stimulus-response mapping were provided each time the response mapping changed. Participants completed the task in 2 separate sessions. In one session, they performed a "speeded" condition in which they were instructed to "be as fast and accurate as you can." In another session, they performed an "unspeeded" condition in which they were

Table 1 Demographic features of the final control and schizophrenia samples (SD in parentheses)

	Control participants	People with schizophrenia	
Age (years)	25.0 (5.1)	25.1 (6.0)	
Male/female	16/6	16/6	
Years of education	15.7 (2.7)	13.0 (1.4)	
Parental years of education	15.0 (2.5)	15.0 (2.8)	
Ethnicity (Caucasian/African American/Other)	16/3/3	15/3/4	
Scale for the Assessment of Negative Symptoms (SANS)	-	9.0 (2.8)	
Scale for the Assessment of Positive Symptoms (SAPS)	-	3.7 (4.1)	
Brief Psychiatric Rating Scale (BPRS)	-	40.1 (11.6)	
Global Assessment of Functioning (GAF)	-	48.0 (9.2)	

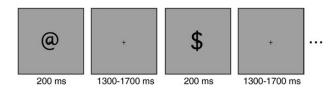


Figure 1. Example trial sequence in the task.

instructed to "be as accurate as you can." The sessions were conducted on separate days, and the order of conditions was counterbalanced across participants. Each session included a practice block of 40 trials, followed by a total of 400 experimental trials. A 30-s rest break was provided every 100 trials, and a longer (participant-determined) break was provided after 200 trials. The instructions emphasizing the speed and/or accuracy of responses were repeated at 4 separate points in each session: during the task instructions at the beginning of the session, at the beginning of the practice block, at the beginning of the experiment block, and half way through the experiment block (e.g., after 200 experimental trials).

Recording and Data Processing Procedures

The EEG was recorded from Ag/AgCl electrodes mounted in an elastic cap using a subset of the International 10/20 System sites (FP1, FP2, F3, F4, F7, F8, FC1, FC2, FC5, FC6, C3, C4, T3, T4, CP1, CP2, CP5, CP6, P3, P4, T5, T6, O1, O2, AFz, Fz, Cz, Pz, POz, and left mastoid). The signals were recorded using a right mastoid reference electrode, and the signals were re-referenced offline to the average of the left and right mastoids (Nunez 1981; Luck 2014). The horizontal electrooculogram (EOG) was recorded as the voltage between electrodes placed lateral to the external canthi and was used to measure horizontal eye movements. The vertical EOG was recorded from an electrode beneath the left eye and was used to detect blinks and vertical eye movements. Impedances were kept below 15 $k\Omega$. The EEG and EOG were amplified by a Neuroscan Synamps amplifier with a gain of 2010 and a bandpass of 0.05-100 Hz (half-amplitude cutoff, with a roll-off of $-12\,dB/octave$), and they were digitized at 500 Hz.

Signal processing and analysis were performed in Matlab using EEGLAB toolbox (Delorme and Makeig 2004) and ERPLAB toolbox (Lopez-Calderon and Luck 2014). All signal processing procedures were performed by an author who was blind to the group membership of the participants (E.S.K.). Portions of EEG containing large muscle artifacts or extreme offsets (identified by visual inspection) were removed. The average percentage of trials removed for artifacts was 8.2% for controls and 13.8% for PSZ in the unspeeded condition, and 12.1% for controls and 14.2% for PSZ in the speeded condition. Independent component analysis (ICA) was performed on the continuous data for each subject to identify and remove components associated with eyeblink activity (Jung et al. 2000). We also analyzed the data solely using artifact rejection, without any ICA correction, and the results were comparable with those presented here.

The ICA-corrected EEG data were segmented into 1000-ms epochs using a baseline of -200 to 0 ms for stimulus-locked averages and -800 to -600 ms for response-locked averages and averaged separately for each condition. Trials with incorrect behavioral responses, responses during stimulus presentation, and responses longer than 1200 ms (relative to stimulus onset) were excluded from all analyses. To isolate the LRP in each participant, we first created separate ERP waveforms for the

Table 2 Measurement windows

Measure	Stimulus-locked (ms)	Response-locked (ms)		
Mean amplitude	200 to 500	-200 to 0		
Onset latency	100 to 500	-300 to 0		

hemisphere that was contralateral to the response and the hemisphere that was ipsilateral to the response. We then created a contralateral-minus-ipsilateral difference waveform, averaged across left- and right-hand responses. This was done separately for the speeded and unspeeded conditions. LRP amplitude and latency were measured from the resulting difference waves. The LRP has a very focused scalp distribution and was therefore measured only at the lateral central sites (C3 and C4).

ERP Measurement

LRP amplitudes were measured as the mean amplitude in a given measurement window (see time windows in Table 2) relative to the baseline voltage specified above. The onset latency of the LRP was measured as the time point at which the voltage reached 50% of the peak amplitude. Because latency measures can be highly sensitive to high-frequency noise, a low-pass filter was applied prior to the latency measures (noncausal Butterworth impulse response function, half-amplitude cutoff of 15 Hz, roll-off of -12 dB/octave). All measurements were obtained from both stimulus-locked and response-locked averages. Measurement windows were chosen by visual examination of the data collapsed across conditions, participants, and groups. This procedure allows time windows to be chosen without introducing bias based on the timing of the experimental effects of interest (which are not present in the collapsed average; Luck 2014).

Statistical Analysis Procedures

Repeated-measures analysis of variance (ANOVA) and t tests were used with a 2-tailed alpha level of .05 for all statistical tests, and probability values were adjusted when appropriate with the Greenhouse-Geisser epsilon correction for nonsphericity (Jennings and Wood 1976). The repeated-measures analyses of behavioral data and LRP measures included a betweensubjects factor of group (PSZ vs. controls) and a within-subjects factor of condition (speeded vs. unspeeded).

Results

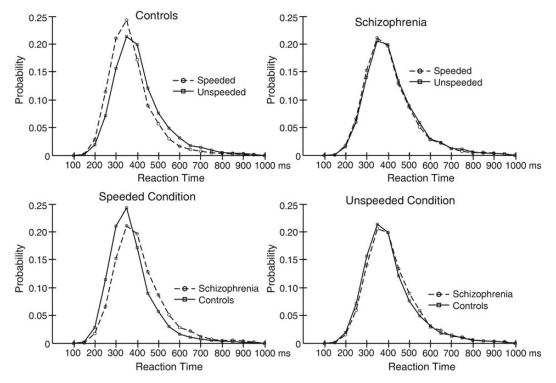
Behavior

Behavioral performance was quantified as median RT on correct trials, RT variability (standard deviation of RT) on correct trials, and percent correct. Group means for these variables are shown in Table 3, along with a summary of the statistical analyses (values will be given in the text only for tests not listed in the tables).

Figure 2 shows RT probability distributions aggregated across the participants in each group. Data from the speeded and unspeeded conditions are overlaid separately for each group in the top panel of Figure 2. The speed instructions had a strong impact on the distribution of RTs in control participants, with an increased proportion of early RTs and reduced variance in the speeded condition compared with the unspeeded condition. By contrast, the speed instructions had no visible impact on the RT distributions in PSZ. The same data are shown in the bottom

Table 3 Behavioral results and stimulus- and response-locked LRP measures at C3/4 (standard errors in parentheses), along with F, P, and partial eta-squared (η_p^2) values for the statistical analyses

Dependent variable	Control participants		People with schizophrenia		Statistics		
	Speeded	Unspeeded	Speeded	Unspeeded	Group df = 1,42	Condition df = 1,42	Group × condition $df = 1,42$
Median RT (ms) 381.0 (8.91) 4	381.0 (8.91)	412.4 (10.36)	416.1 (9.94)	417.4 (9.21)	F = 2.39	F = 16.15	F = 13.81
				P = 0.130	P < 0.001	P = 0.001	
					$\eta_{\rm p}^2 = 0.054$	$\eta_{\rm p}^2 = 0.278$	$\eta_{\rm p}^2 = 0.247$
RT variability (ms) 97.14 (5.16) 108.65 (5.4	108.65 (5.67)	108.11 (5.55)	109.30 (4.83)	F = 0.680	F = 5.85	F = 3.87	
				P = 0.414	P = 0.020	P = 0.056	
				$\eta_{\rm p}^2 = 0.016$	$\eta_{\rm p}^2 = 0.122$	$\eta_{\rm p}^2 = 0.084$	
Accuracy (%) 93.1 (.010) 94.2 (.010)	94.2 (.010)	89.8 (.014)	93.0 (.010)	F = 2.92	F = 7.96	F = 2.02	
				P = 0.095	P = 0.007	P = 0.162	
				$\eta_{\rm p}^2 = 0.065$	$\eta_{\rm p}^2 = 0.159$	$\eta_{\rm p}^2 = 0.046$	
Stimulus-locked LRP							
Amplitude (μ V) -1.1 (.180) -0.89 (.172)	-0.89 (.172)	-0.70 (.179) -0.84 (.174)	-0.84 (.174)	F = 0.827	F = 0.115	F = 4.23	
				P = 0.368	P = 0.736	P = 0.046	
				$\eta_{\rm p}^2 = 0.019$	$\eta_{\rm p}^2 = 0.003$	$\eta_{\rm p}^2 = 0.091$	
Onset latency (ms) 237.7 (8.40) 268.5 (9.32)	268.5 (9.32)	292.1 (11.46)	273.8 (12.85)	F = 4.94	F = 0.827	F = 12.85	
				P = 0.032	P = 0.368	P = 0.001	
				$\eta_{\rm p}^2 = 0.105$	$\eta_{\rm p}^2 = 0.019$	$\eta_{\rm p}^2 = 0.234$	
Response-locked LRP							
Amplitude (μ V)	-1.42 (.217)	-0.98 (.209)	-1.17 (.202)	F = 1.74	F = 0.913	F = 1.53	
				P = 0.194	P = 0.345	P = 0.223	
				$\eta_{\rm p}^2 = 0.040$	$\eta_{\rm p}^2 = 0.021$	$\eta_{\rm p}^2 = 0.035$	
Onset latency (ms) -120.3 (9.46) -132.4 (7.19)	-132.4 (7.15)	-124.2 (9.15)	-134.7 (7.58)	F = 0.080	F = 7.20	F = 0.037	
				P = 0.778	P = 0.010	P = 0.848	
					$\eta_{\rm p}^2 = 0.002$	$\eta_{\rm p}^2 = 0.146$	$\eta_{\rm p}^2 = 0.001$



 $\textbf{Figure 2}. \ RT\ probability\ histograms\ for\ the\ speeded\ and\ unspeeded\ conditions\ for\ people\ with\ schizophrenia\ and\ controls. The\ top\ panel\ shows\ data\ from\ the\ speeded\ and\ unspeeded\ conditions\ for\ people\ with\ schizophrenia\ and\ controls. The\ top\ panel\ shows\ data\ from\ the\ speeded\ and\ unspeeded\ conditions\ for\ people\ with\ schizophrenia\ and\ controls.$ unspeeded conditions overlaid, separately for controls (left) and people with schizophrenia (right). The bottom panel shows data from people with schizophrenia and controls overlaid separately for the speeded (left) and unspeeded (right) conditions.

panel of Figure 2, but with PSZ and control participants overlaid separately for each condition. In the unspeeded condition, the distributions were highly similar for PSZ and control participants.

By contrast, control participants showed an increase in shortlatency RTs and less RT variability than PSZ in the speeded condition.

It is complicated to statistically compare RT distributions, so our statistical analyses of RT focused on median RT and RT variability. For median RT, the pattern of results shown in the RT distributions led to a significant group × condition interaction, along with a significant main effect of condition. Planned follow-up t-tests indicated that controls were significantly faster in the speeded condition than in the unspeeded condition ($t_{(21)} = 5.04$, P < 0.001, Cohen's d = 1.075), whereas RTs for PSZ were nearly identical in the speeded and unspeeded conditions ($t_{(21)} = 0.237$, P = 0.816, Cohen's d = 0.051). In addition, PSZ were significantly slowed compared with controls in the speeded condition ($t_{(42)} = 2.63$, P = 0.012, Cohen's d = 0.813) but not in the unspeeded condition ($t_{(42)} = 0.360$, P = 0.721, Cohen's d = 0.111). Thus, PSZ were unable to decrease their RTs under speed pressure, whereas controls exhibited a 31-ms reduction in RT in the speeded condition.

Like median RT, RT variability was decreased in the speeded condition compared with the unspeeded condition in controls but not in PSZ, although the group × condition interaction was only marginally significant (P=0.056; see Table 3). In addition, the overall difference between the speeded and unspeeded conditions was significant. Planned follow-up t-tests indicated that RTs were significantly less variable in the speeded condition compared with the unspeeded condition in controls ($t_{(21)}=9.84$, P=0.005, Cohen's d=2.098) but not in PSZ ($t_{(21)}=0.100$, P=0.755, Cohen's d=0.021). There were no significant differences in RT variability between PSZ and controls for either the speeded ($t_{(42)}=1.45$, P=0.155, Cohen's d=0.446) or the unspeeded condition ($t_{(42)}=0.087$, P=0.931, Cohen's d=0.027).

Response accuracy was high in both groups (see Table 3). Both PSZ and controls exhibited a small reduction in accuracy in the speeded condition compared with the unspeeded condition, leading to a significant main effect of condition. This is exactly what would be expected from a speed-accuracy tradeoff. The difference in accuracy between the speeded and unspeeded conditions was numerically larger in PSZ (a 3.2% reduction) than in controls (a 1.1% reduction), but the group × condition interaction did not reach significance. Planned follow-up t-tests indicated that the reduction in accuracy in the speeded compared with the unspeeded condition was significant for PSZ ($t_{(21)} = 2.66$, P = 0.015, Cohen's d = 0.567) but not for controls $(t_{(21)} = 1.16,$ P = 0.260, Cohen's d = 0.247). The finding of a significant reduction in accuracy in the speeded compared with the unspeeded condition in PSZ provides important evidence that PSZ made an effort to modulate performance in response to task instructions. Thus, the lack of a difference in RT between the speeded and unspeeded conditions in PSZ cannot be explained by a lack of understanding or motivation to follow the speed instructions. Additional pairwise tests showed that accuracy in the speeded condition was marginally significantly lower in PSZ compared with controls ($t_{(42)} = 2.00$, P = 0.053, Cohen's d = 0.616), with no significant difference between groups in the unspeeded condition ($t_{(42)} = 0.874$, P = 0.387, Cohen's d = 0.270).

ERP Waveforms

Contralateral-minus-ipsilateral grand average difference waves are shown in Figure 3 (stimulus-locked) and Figure 4 (response-locked). The top panel of each figure shows the speeded and unspeeded conditions overlaid separately for controls and PSZ to facilitate evaluation of the effect of speed pressure in each group. The same data are depicted in the bottom panel, with PSZ and control waveforms overlaid separately for each condition to facilitate the comparison between groups. LRP measures and statistics are summarized in Table 3.

Stimulus-locked LRP

Figure 3 shows that the LRP was larger in the speeded condition than in the unspeeded condition in control participants, especially during the early portion of the LRP time range. However, there was no hint of this in PSZ; indeed, the unspeeded LRP was slightly larger than the speeded LRP in PSZ. Similarly, Figure 3 shows that the stimulus-locked LRP was larger in the controls than in PSZ in the speeded condition, especially in the early portion of the LRP time range, with little or no difference between groups in the unspeeded condition. These observations were supported by a significant group x condition interaction in an analysis of LRP amplitude. Planned follow-up t tests showed that LRP amplitude was significantly increased in the speeded condition compared with the unspeeded condition in control participants ($t_{(21)} = 2.42$, P = 0.025, Cohen's d = 0.516), but not in PSZ ($t_{(21)} = 0.989$, P = 0.334, Cohen's d = 0.211). Although the mean LRP amplitude was numerically larger in controls than in PSZ in the speeded condition, pairwise t-tests did not yield a significant difference in either the speeded condition ($t_{(42)} = 1.48$, P = 0.146, Cohen's d = 0.457) or the unspeeded condition ($t_{(42)} = 0.221$, P = 0.826, Cohen's d = 0.068). Thus, the clear finding here was that controls exhibited a larger effect of speed pressure than PSZ.

As shown in Figure 3, the LRP voltage increased more rapidly following stimulus onset for the speeded condition than for the unspeeded condition in control participants but not in PSZ.

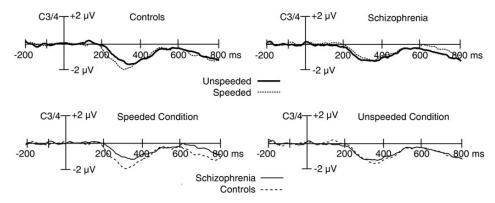


Figure 3. Stimulus-locked grand average ERP difference waveforms (contralateral-minus-ipsilateral) collapsed across the C3 and C4 electrode sites. The top panel shows data from the speeded and unspeeded conditions overlaid separately for controls (left) and people with schizophrenia (right). The bottom panel shows data from people with schizophrenia and controls overlaid separately for the speeded (left) and unspeeded (right) conditions. A digital low-pass filter was applied offline before plotting the waveforms shown here and in the subsequent figures (Butterworth impulse response function, half-amplitude cutoff = 30.0 Hz, 12 dB/oct roll-off).

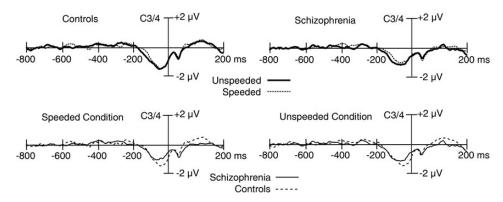


Figure 4. Response-locked grand average ERP difference waveforms (contralateral-minus-ipsilateral) collapsed across the C3 and C4 electrode sites. The top panel shows data from the speeded and unspeeded conditions overlaid separately for controls (left) and people with schizophrenia (right). The bottom panel shows data from people with schizophrenia and controls overlaid separately for the speeded (left) and unspeeded (right) conditions.

This led to a significant group × condition interaction for stimulus-locked LRP onset latency (which reflects the stimulus → LRP interval). The main effect of group was also significant, but this was driven almost entirely by group differences in the speeded condition (see Table 3). Planned follow-up t-tests showed that LRP onset latency decreased in the speeded condition compared with the unspeeded condition in controls ($t_{(21)} = 3.82$, P = 0.001, Cohen's d = 0.814), but not in PSZ ($t_{(21)} = 1.65$, P = 0.113, Cohen's d= 0.352). Similarly, LRP onset latency was delayed in PSZ relative to controls in the speeded condition ($t_{(42)} = 3.83$, P < 0.001, Cohen's d = 1.181) but not in the unspeeded condition ($t_{(42)} = 0.331$, P = 0.742, Cohen's d = 0.102).

These differences in the stimulus-locked LRP indicate that controls were able to use the task instructions to modulate the speed at which they selected and prepared a response following a stimulus, whereas PSZ were not.

Response-Locked LRP

Although the response-locked LRP amplitude was slightly reduced in PSZ compared with controls in both the speeded and unspeeded conditions (see Fig. 4), there were no significant main effects or interactions (see Table 3). Planned follow-up analyses showed no difference between PSZ and controls in the speeded ($t_{(42)} = 1.673$, P = 0.102, Cohen's d = 0.516) or unspeeded condition ($t_{(42)} = 0.866$, P = 0.391, Cohen's d = 0.267). In addition, the amplitude of the response-locked LRP was not modulated by speed pressure in the controls ($t_{(21)} = 0.282$, P = 0.781, Cohen's d = 0.060) or in PSZ ($t_{(21)} = 1.27$, P = 0.219, Cohen's d = 0.271).

The amount of time between the onset of the LRP and the execution of the response (the LRP → response interval) was decreased in the speeded condition compared with the unspeeded condition in both groups, leading to a significant main effect of condition. Planned follow-up t-tests indicated that the reduction in the LRP → response interval in the speeded condition compared with the unspeeded condition was significant in controls $(t_{(21)} = 2.14, P = 0.044, Cohen's d = 0.456)$ but did not reach significance in PSZ ($t_{(21)} = 1.68$, P = 0.107, Cohen's d = 0.358). However, the effect was approximately 12 ms for both groups, so the fact that the P-value was below 0.05 for controls and above 0.05 for PSZ should not be taken as evidence that the effect was larger for controls than for PSZ. In addition, pairwise comparisons of PSZ and controls yielded no significant difference in the LRP \rightarrow response interval for either the speeded condition $(t_{(42)} = 0.301, P = 0.765, Cohen's d = 0.093)$ or the unspeeded condition ($t_{(42)} = 0.224$, P = 0.824, Cohen's d = 0.069).

The lack of group differences in the response-locked LRP waveforms suggests that the single-trial LRP was not reduced in PSZ and, additionally, that PSZ were not impaired at executing a response once the LRP had been generated. This further supports the hypothesis that the group differences observed in the stimulus-locked data from the speeded condition reflect an inability of PSZ to modulate the speed at which a response is selected and prepared.

ERP-RT Correlations

Correlations between RT and the LRP were computed separately for PSZ and controls to determine within-group relationships. Note that only stimulus-locked LRP measures were used, because ERP measures and RT are necessarily related in averages that are time-locked to the response. For controls, median RT was significantly positively correlated with the onset latency of the LRP in the unspeeded condition (r(22) = 0.678, P = 0.001). However, this correlation was weaker and nonsignificant in the speeded condition (r(22) = 0.213, P = 0.341), which may reflect a compression of range in the speeded condition. For PSZ, median RT was positively correlated with the onset latency of the LRP in both the unspeeded condition (r(22) = 0.456, P = 0.033) and the speeded condition (r(22) = 0.726, P < 0.001), illustrating that longer LRP onset latencies were associated with longer RTs in both conditions. None of the correlations between LRP amplitude and median RT reached significance for either group.

Discussion

The present study examined behavioral and ERP indices of response-related processing in PSZ and matched control participants in separate testing sessions that emphasized the accuracy of responses (the unspeeded condition) or emphasized both the speed and accuracy of responses (the speeded condition). If basic motor processes are impaired in schizophrenia, then PSZ should exhibit slowed RTs and impaired LRPs independent of speed pressure. Alternatively, if schizophrenia involves impaired generation or implementation of control signals, then PSZ should be specifically impaired at modulating response-related processes according to task demands.

Consistent with the latter hypothesis, we found that PSZ were unable to modulate RTs or LRP measures in the speeded condition relative to the unspeeded condition. By contrast, controls exhibited faster RTs, reduced RT variability, increased stimulus-locked LRP amplitudes, and decreased stimulus \rightarrow LRP latencies in the speeded condition compared with the unspeeded condition. Significant group × condition interactions were found for all of these variables. Moreover, there was no hint of substantial RT or LRP differences between PSZ and controls in the unspeeded condition, but several significant group differences were observed in the speeded condition. These results provide strong evidence of an impairment in control rather than an impairment in intrinsic motor processing. A broadly analogous pattern of results was obtained in a recent study, in which control participants but not PSZ exhibited an increase in LRP amplitude when the response was associated with auditory feedback (Ford et al. 2014).

In the present study, significant differences in the LRP between PSZ and controls were found only in the stimulus-locked averages, indicating that response selection and preparation processes (and not response execution processes) were selectively impacted by failure to exert control in PSZ in the present study. This included both delayed onset of response selection and preparation (as evidenced by an increased stimulus → LRP interval) and increased variability in the timing of response selection and preparation (as evidenced by decreased stimulus-locked LRP amplitude in the absence of decreased response-locked LRP amplitude).

It is important to ask whether the failure of PSZ to improve response processing in the speeded condition in the present study might reflect a lack of motivation to improve speed or a failure to understand the instructions. This is unlikely, because PSZ were significantly less accurate in the speeded condition than in the unspeeded condition. Decreased accuracy is a common side effect of speed pressure (the well-known speed-accuracy tradeoff), and decreased accuracy in the speeded condition in PSZ provides direct evidence that PSZ made an effort to modulate performance along the speed-accuracy curve in response to speed pressure in the present study. This effect was statistically indistinguishable in PSZ and controls (and was numerically larger in PSZ than in controls). Thus, although PSZ were unable to improve RT or modulate LRP measures under speed pressure, the decreased accuracy in the speeded condition indicated both an understanding of the task demands and a motivation to improve performance in accordance with task instructions.

A number of studies have investigated the neural basis of improved response processing under speed pressure (Forstmann et al. 2008; Ivanoff et al. 2008; Van Veen et al. 2008; van Maanen et al. 2011; Heitz and Schall 2012). In general, these studies indicate that speeded responding is related to an overall increase in baseline activity, in contrast to a change in the threshold for making a response. fMRI studies have identified a frontostriatal network associated with speeded responding, including modulation of activity in pre-supplementary motor area (pre-SMA). In addition, these modulations in baseline activity have been related to top-down signals from prefrontal cortex (Van Veen et al. 2008), indicating that prefrontal control may underlie improvements under speed pressure. Together, these results suggest that the impairments in response-related processing observed in the present study are a consequence of dysfunctional control. Although the present study cannot address the precise source of impaired control, dysfunction in control mechanisms -including maintaining the context for responding, required for speeded performance in the present study—have been implicated widely as a source of impaired performance across multiple domains in schizophrenia, including a deficit in top-down cognitive control (Lesh et al. 2010) and a deficit in context-sensitive gain control (Phillips and Silverstein 2013). These deficits have

been linked to reduced engagement of dorsolateral prefrontal cortex and associated functional connectivity in task-related networks in fMRI studies (Yoon et al. 2008; Minzenberg et al. 2009; Fornito et al. 2013).

Although the results of the present study indicate that deficits in control may underlie response-related impairments in PSZ in some contexts, they do not rule out the possibility that basic motor processes are also dysfunctional. Indeed, RT slowing in schizophrenia has been documented in a range of tasks and modalities across decades of research, and a unitary deficit in control may not be able to explain all of these findings. It is also important to note that the present study involved a somewhat modest amount of speed pressure, and it is possible that a stronger incentive to exert control might yield a different pattern of results. Nonetheless, the present results provide clear evidence of an impairment in the generation or implementation of control signals, at least under some conditions.

In studies of schizophrenia, it is always necessary to ask whether the use of antipsychotic medications may be driving the results. Although it is impossible to conclusively exclude the influence of medication without studying medication-naïve individuals, the results of the present study seem unlikely to be caused by medication use. Specifically, PSZ performed as well as controls in the unspeeded condition, indicating that the influence of medication on the dopamine system did not cause a general degradation in response-related (or other) processes in the present sample. Moreover, although dopamine has been hypothesized to play a role in modulating response thresholds in speed-accuracy tradeoffs (Lo and Wang 2006), direct administration of bromocriptine (a dopamine receptor agonist) has been shown to have no effect on performance under speed or accuracy emphasis (Winkel et al. 2012). In addition, the PSZ in the present study were relatively young (mean age ca. 25 years of age), and were therefore less progressed in disease duration and medication use compared with many samples of PSZ studied in the literature. However, it is important for future research to examine unmedicated, first-episode, and prodromal patients to fully determine whether medication or disease duration influence the relationship between response-related deficits and control.

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References

American Psychiatric Association. 2000. Diagnostic and statistical manual of mental disorders, 4th ed. Washington (DC): American Psychiatric Association.

Caligiuri MP, Lohr JB, Jeste DV. 1993. Parkinsonism in neurolepticnaive schizophrenic patients. Am J Psychiatry. 150:1343-1348. Coles MG. 1989. Modern mind-brain reading: psychophysiology, physiology, and cognition. Psychophysiology. 26:251-269.

- De Jong R, Coles MG, Logan GD, Gratton G. 1990. In search of the point of no return: the control of response processes. J Exp Psychol Hum Percept Perform. 16:164-182.
- Delorme A, Makeig S. 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods. 134:9-21.
- First MB, Spitzer RL, Miriam G, Williams JBW. 2002. Structured clinical interview for DSM-IV-TR axis I disorders, research version, patient edition with psychotic screen. New York (NY): Biometrics Research, New York State Psychiatric Institute.
- Ford JM, Palzes VA, Roach BJ, Mathalon DH. 2014. Did i do that? Abnormal predictive processes in schizophrenia when button pressing to deliver a tone. Schizophr Bull. 40:804-812.
- Fornito A, Zalesky A, Breakspear M. 2013. Graph analysis of the human connectome: promise, progress, and pitfalls. Neuroimage. 80:426-444.
- Forstmann BU, Dutilh G, Brown S, Neumann J, Cramon Von DY, Ridderinkhof KR, Wagenmakers E-J. 2008. Striatum and pre-SMA facilitate decision-making under time pressure. Proc Natl Acad Sci USA. 105:17538-17542.
- Heitz RP, Schall JD. 2012. Neural mechanisms of speed-accuracy tradeoff. Neuron. 76:616-628.
- Ivanoff J, Branning P, Marois R. 2008. fMRI evidence for a dual process account of the speed-accuracy tradeoff in decision-making. PLoS One. 3:e2635.
- Jennings JR, Wood CC. 1976. The e-adjustment procedure for repeated-measures analyses of variance. Psychophysiology.
- Jones P, Murray R, Jones P, Rodgers B, Marmot M. 1994. Child developmental risk factors for adult schizophrenia in the British 1946 birth cohort. Lancet. 344:1398-1402.
- Jung TP, Makeig S, Humphries C, Lee TW, Mckeown MJ, Iragui V, Sejnowski TJ. 2000. Removing electroencephalographic artifacts by blind source separation. Psychophysiology. 37:163-178.
- Kappenman ES, Kaiser ST, Robinson BM, Morris SE, Hahn B, Beck VM, Leonard CJ, Gold JM, Luck SJ. 2012. Response activation impairments in schizophrenia: evidence from the lateralized readiness potential. Psychophysiology. 49:73-84.
- Karayanidis F, Nicholson R, Schall U, Meem L, Fulham R, Michie P. 2006. Switching between univalent task-sets in schizophrenia: ERP evidence of an anticipatory task-set reconfiguration deficit. Clin Neurophysiol. 117:2172-2190.
- Kerns JG, Nuechterlein KH, Braver TS, Barch DM. 2008. Executive functioning component mechanisms and schizophrenia. Biol Psychiatry. 64:26-33.
- Kieffaber P, O'Donnell B, Shekhar A, Hetrick W. 2007. Event related brain potential evidence for preserved attentional set switching in schizophrenia. Schizophr Res. 93:355-365.
- Lesh TA, Niendam TA, Minzenberg MJ, Carter CS. 2010. Cognitive control deficits in Schizophrenia: mechanisms and meaning. Neuropsychopharmacology. 36:316-338.
- Lo C-C, Wang X-J. 2006. Cortico-basal ganglia circuit mechanism for a decision threshold in reaction time tasks. Nat Neurosci.
- Lopez-Calderon J, Luck SJ. 2014. ERPLAB: an open-source toolbox for the analysis of event-related potentials. Front Hum Neurosci. 8(Article 213):1-14.
- Luck SJ. 2014. An introduction to the event-related potential technique, 2nd ed. Cambridge: MIT Press.
- Luck SJ, Gold JM. 2008. The construct of attention in schizophrenia. Biol Psychiatry. 64:34-39.
- Luck SJ, Kappenman ES, Fuller RL, Robinson B, Summerfelt A, Gold JM. 2009. Impaired response selection in schizophrenia:

- evidence from the P3 wave and the lateralized readiness potential. Psychophysiology. 46:776-786.
- Mathalon DH, Fedor M, Faustman WO, Gray M, Askari N, Ford JM. 2002. Response-monitoring dysfunction in schizophrenia: an event-related brain potential study. J Abnorm Psychol. 111:22-41.
- Meehl PE. 1989. Schizotaxia revisited. Arch Gen Psychiatry. 46:935.
- Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC. 2009. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. Arch Gen Psychiatry.
- Mittal VA, Neumann C, Saczawa M, Walker EF. 2008. Longitudinal progression of movement abnormalities in relation to psychotic symptoms in adolescents at high risk of schizophrenia. Arch Gen Psychiatry. 65:165-171.
- Nuechterlein KH. 1977. Reaction time and attention in schizophrenia: a critical evaluation of the data and theories. Schizophr Bull. 3:373-428.
- Nunez PL. 1981. Electric fields of the brain. New York, NY: Oxford University Press
- Osman A, Lou L, Müller-Gethmann H, Rinkenauer G, Mattes S, Ulrich R. 2000. Mechanisms of speed-accuracy tradeoff: evidence from covert motor processes. Biol Psychol. 51:173-199.
- Phillips WA, Silverstein SM. 2013. The coherent organization of mental life depends on mechanisms for context-sensitive gain-control that are impaired in schizophrenia. Front Psychol. 4(Article 307):1-15.
- Puri BK, Barnes TR, Chapman MJ, Hutton SB, Joyce EM. 1999. Spontaneous dyskinesia in first episode schizophrenia. J Neurol Neurosurg Psychiatry. 66:76–78.
- Rinkenauer G, Osman A, Ulrich R, Müller-Gethmann H, Mattes S. 2004. On the locus of speed-accuracy trade-off in reaction time: inferences from the lateralized readiness potential. J Exp Psychol Gen. 133:261-282.
- Smulders FTY, Miller JO. 2012. The lateralized readiness potential. In: Luck SJ, Kappenman ES editors. The Oxford handbook of event-related potential components. Oxford University Press. p. 209–229.
- van der Lubbe RH, Jaśkowski P, Wauschkuhn B, Verleger R. 2001. Influence of time pressure in a simple response task, a choiceby-location task, and the Simon task. J Psychophysiol. 15:241.
- van Maanen L, Brown SD, Eichele T, Wagenmakers E-J, Ho T, Serences J, Forstmann BU. 2011. Neural correlates of trial-to-trial fluctuations in response caution. J Neurosci. 31:17488-17495.
- Van Veen V, Krug MK, Carter CS. 2008. The neural and computational basis of controlled speed-accuracy tradeoff during task performance. J Cogn Neurosci. 20:1952-1965
- Walker E, Lewis N, Loewy R, Palyo S. 1999. Motor dysfunction and risk for schizophrenia. Dev Psychopathol. 11:509-523.
- Winkel J, van Maanen L, Ratcliff R, van der Schaaf ME, van Schouwenburg MR, Cools R, Forstmann BU. 2012. Bromocriptine does not alter speed-accuracy tradeoff. Front Neurosci. 6 (Article 126):1-6.
- Woodward ND, Duffy B, Karbasforoushan H. 2013. Schizophrenia research. Schizophr Res. 152:446-449.
- Yoon J, Minzenberg M, Ursu S, Walters R, Wendelken C, Ragland J, Carter C. 2008. Association of dorsolateral prefrontal cortex dysfunction with disrupted coordinated brain activity in schizophrenia: relationship with impaired cognition, behavioral disorganization, and global function. Am J Psychiatry. 165:1006-1014.