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Dysfunctional Neural Processes Underlying Context processing Deficits in Schizophrenia

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Abstract

Background: People with schizophrenia (PSZ) have profound deficits in context processing, an executive process that guides adaptive behaviors according to goals and stored contextual information. Although various neural processes are involved in context processing and are affected in PSZ, the core underlying neural dysfunction is unclear.

Methods: To determine the relative importance of neural dysfunctions within prefrontal cognitive control, sensory, and motor activity to context processing deficits in PSZ, we examined event-related potentials (ERPs) in 60 PSZ and 51 normal controls (NC) during an optimal context processing task. We also analyzed the Ex-Gaussian reaction time (RT) distribution to examine abnormalities in motor control variability in PSZ.

Results: Compared to NC, PSZ had lower response accuracy and greater variability in their normal RTs during high context processing (HCP) demands. Latencies of normal and slow responses were generally increased in PSZ. HCP-related reductions in frontal ERPs were indicative of specific deficits in proactive and reactive cognitive controls in PSZ, while ERPs associated with visual and motor processes were reduced regardless of context processing demands, indicating generalized visuo-motor deficits. In contrast to previous studies, we found that diminished frontal responses reflective of proactive control to the contextual cue, rather than visual responses of cue-encoding, predicted response accuracy deficits in PSZ. Additionally, probe-related ERP components of motor preparation, prefrontal reactive control, and fronto-motor interaction predicted Ex-Gaussian indices of RT instability in PSZ.

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Conclusions: Prefrontal proactive and reactive control deficits associated with failures in using mental representation likely underlie context processing deficits in PSZ.

Keywords

schizophrenia; context processing; prefrontal dysfunction; visuo-motor deficits; ERPs; reaction time variability

INTRODUCTION

A deficit in context processing and the associated prefrontal network dysfunction has been identified as central to schizophrenia(1). Context processing involves the control of behaviors according to goals or other stored abstract representations that reflect contextual information (e.g., rules)(2), and is considered an executive function related to goal representation. Experimental studies using tasks that require updating of response rules based on previous cues (e.g.., AX-version of the continuous performance task [AX-CPT]) have demonstrated that PSZ show deficits in using contextual cue-information to guide responses(3, 4). Context processing deficits were observed from the onset of the disease(5) and predictive of the long-term outcome(6). Additionally, the deficits have been identified as a specific deficit (i.e., not attributable to generalized cognitive impairments) that is associated with genetic liability for schizophrenia(3, 4) and may therefore reflect pathology central to the disorder(5, 7, 8). Thus, it is imperative to determine the underlying abnormal neural mechanisms in PSZ. Context processing requires coordination among various neural processes including sensory encoding of context information, cognitive controls to guide sensory-motor processes, and preparation and execution of goal-relevant motor responses. Abnormalities in all of these processes have been recognized in PSZ(9-11), so the process most responsible for context processing deficits in PSZ remains controversial(12).

The control elements of context processing have be conceptualized according to the dual mechanisms of control theory which specifies two distinct prefrontal cognitive control modes with different temporal dynamics(13, 14). The proactive control mode refers to the early selection of goalrelevant information to update contextual rules or active maintenance of such information in working memory (WM) prior to a behavioral response (e.g., contextual cue processing in the AX-CPT), which in turn biases attentional and perceptual neural processes toward goal-directed behaviors. In contrast, the reactive control mode encompasses functions that are recruited for the detection and resolution of behavioral conflicts at the time a response is required (e.g., response control in Stroop task). Functional magnetic resonance imaging (fMRI) studies comparing neural responses between the AX-CPT and Stroop task(15) and those between cue- and probe-periods of the AX-CPT(16) revealed that PSZ had prefrontal cortical responses consistent with deficient proactive control but relatively intact reactive control. However, the AX-CPT also requires reactive control and the slow time-course of hemodynamic responses in fMRI provides incomplete differentiation of cue- versus probe-related neural responses. A recent EEG study using AX-CPT identified deficient midline theta oscillations associated with specific deficits in proactive control and generalized deficits in reactive control in PSZ(17). The disproportionate frequencies of AX/AY/BX/BY conditions in the task, however, might lead

to confounding effects of neural responses associated with probability in addition to those of context processing. Therefore, the use of electrophysiological measurements and an optimal task without biases toward a specific condition will improve the functional neural measurements of proactive and reactive control processes to better examine the nature of the context processing deficit in schizophrenia.

In contrast to a prefrontal cognitive control impairment in schizophrenia, recent ERP studies implied that failures in visual systems accounted for context processing(12) and WM(18) impairments in schizophrenia. In particular, Dias and colleagues(12) used the AX-CPT to show that deficient occipital responses for encoding contextual information better explained context processing impairments in PSZ than prefrontal responses. They also found that PSZ had intact top-down modulation of visual processing despite overall reductions in the visual responses, suggesting that early visual stream deficits rather than prefrontal top-down control are the primary cause of deficits in context processing and WM in schizophrenia. However, the task used in this work had much greater visual processing demands than commonly used, therefore, it is necessary to test context processing in PSZ without biases toward a specific neural process.

Context processing deficits in PSZ might also be affected by psychomotor deficits that have been clinically documented(19, 20) and demonstrated with reaction time (RT) and ERP motor components such as lateralized readiness potential (LRP)(21-23). In this regard, analysis of intra-individual variability (i.e., trial-by-trial fluctuation) in RTs may provide rich information on instability in cognitive processes probing pathophysiology in PSZ(24) unavailable to conventional mean RT analyses(25, 26). As illustrated in Figure 1C, an Ex-Gaussian distribution analysis of RT decomposes a typical positively skewed RT distribution into the parameters that estimate one's normal motor speed (μ: mean of Gaussian component), intra-individual RT variability of normal responses (σ: standard deviation [SD] of Gaussian component) that reflect trial-by-trial alterations in response processes, and finally an attentional lapse component that contributes to slow responses (τ: mean of exponential component)(25). Investigation of motor cortical activities along with the RT variability indices might further capture a problem with efficiently processing information during context processing in PSZ.

The goal of the present study was to identify behavioral features of context processing deficits and determine relative impairments in neural processes related to prefrontal cognitive controls, sensory, and motor activities, and their contributions to context processing deficits in PSZ. To identify the specific deficits in cognitive and neural processes in PSZ, we used the Stimulus Response Reversal Task (SRRT) that measures context processing without biases toward specific condition or neural processes (i.e., equivalent probabilities of conditions and sufficient stimulus duration for visual encoding). The SRRT requires both proactive controls to update response-rules and reactive controls to initiate a goal-relevant response, overriding an interference of the automatic response triggered by the probe stimulus. We also used ERP components to isolate the timing of neural responses associated with visual, cognitive control, and motor functions in context processing (see Figure 1B); 1) visual ERP components including cue and probe period visual N1 (cvN1 and pvN1) that reflect ventral occipital-temporal cortical functions of visual encoding(12, 28,

29); 2) frontal cognitive components of negative potentials including cue-locked frontal N2 (cfN2) and pre-response frontal negativity (prfN) that are known to reflect prefrontal proactive control updating contextual information(12, 30) and prefrontal reactive control activity for conflict resolution(31, 32) respectively; and 3) LRP reflecting preparatory motor processes(33). Along with a response accuracy (i.e., %Correct), we analyzed the three Ex-Gaussian RT parameters to examine various aspects of disturbances in motor control during context processing. We tested whether PSZ had differential deficits for context processing in ERP components reflecting proactive/reactive controls, visual, and motor processes. We hypothesized that ERP indices of prefrontal proactive and reactive controls rather than visual and motor processing would primarily explain performance deficits (i.e., low accuracy and high latency variability in behavioral responses) in high context processing load in PSZ.

METHODS AND MATERIALS

Participants

Sixty PSZ and 51 healthy NC subjects participated. The demographic and clinical characteristics of the participants are summarized in Supplemental Information (Table S1). Patients were recruited from hospitals, clinics, residential facilities, and community support programs for individuals with severe mental disorders in the Minneapolis-St. Paul metropolitan area. Diagnostic information was obtained by a trained interviewer completing the Structured Clinical Interview for Axis I Disorders, DSM-IV TR (SCID-I/P)(34) and the Psychosis Module of the Diagnostic Interview for Genetic Studies (DIGS)(35) with each participant. Only patients who met DSM-IV TR criteria for schizophrenia based on consensus diagnosis of two raters were included in this report. NC participants were recruited through advertising broadly in the metropolitan community. Inclusion/exclusion criteria are described extensively elsewhere(36). The Minneapolis VA Medical Center and University of Minnesota Institution Review Boards approved the protocol.

Stimulus Response Reversal Task (SRRT) and Evaluation of Task Performances

In SRRT, subjects were asked to select responses to a directional probe word (“Left” or “Right”) according to a contextual cue (a red or green rectangle) presented prior to the probe. In low context processing (LCP: green cue) condition, subjects had to respond with the thumb of the hand indicated by a probe. In high context processing (HCP: red cue) condition, they had to respond with the thumb of the opposite hand. The HCP and LCP conditions were intermixed with the equivalent frequency in a block, which consisted of 71 test trials. Subjects completed three blocks of SRRT trials (see Figure 1A for details of a trial sequence and the timings of SRRT). We computed %Correct index of response accuracy, and estimated μ, σ, and τ parameters of an Ex-Gaussian distribution for central tendency and variability of RT during context processing using only correct trials (see Figure 1C for details). To this end, we used *retimes* R package (https://cran.r-project.org/web/packages/retimes/) that utilizes methods described by Heathcote(37).

Electroencephalography (EEG) Recordings and Processes

EEG was collected at a sampling rate of 1024 Hz using a 64 or 128 channel BioSemi ActiveTwo EEG system (http://www.biosemi.com/) while participants performed SRRT. All

EEG processing was conducted using Matlab (The Mathworks, Inc., Natick, MA), including low-pass filtering (256 Hz cut-off frequency), high-pass filtering (.5 Hz cut-off frequency), down-sampling to 256 Hz using anti-aliasing resample function, and referencing to linked earlobe signal. Noisy electrode signals were identified via visual inspection and excluded from processing. EEG was segmented to three types of epochs: time-locked to cue-onsets (−500–2000 ms), probe-onsets (−500–1500 ms), and response-onsets (−1100–100 ms). Atypical noisy time-segments, physiological and electrode-specific artifacts were removed using a custom Matlab-based pipeline using independent component analysis (ICA; see Supplemental Information for details). After ICA-denoising, excluded bad electrode signals were interpolated using the spherical spline method(38) with optimal interpolation parameters(39). Finally, all scalp EEG signals were referenced to the average signal to produce an unbiased topographical distribution of EEG signals, then 64 and 128 channel EEG data were converted to an 81-channel 10-10 EEG standard montage using BESA (https://www.besa.de) to produce topographical distributions of ERP components with the same montage.

ERP Analyses

Cue-, probe-, and response-locked ERPs were computed by averaging corresponding EEG epochs filtered at 30-Hz low-pass for trials with correct responses. Baseline correction was conducted by subtracting mean amplitudes of 100 ms pre-stimulus time-window (i.e., pre-cue 100 ms for cue-locked ERPs and pre-probe 100 ms for probe- and response-locked ERPs). Spatiotemporal windows for ERP quantification and analyses were determined based on previous studies with minor modification to account for ERP differences due to differences in the stimuli and temporal structure of the tasks. Visual ERP components (cvN1 and pvN1) were quantified at bilateral occipito-temporal sites(11, 28; see Figure 3). Frontal cognitive components of cfN2(12, 30) and prfN(31) were quantified at Fz and FCz respectively along with bilateral frontal sites (F3 and F4; see Figure 4) where their HCP-LCP amplitude differences were maximal (see Figure 4). We included the bilateral occipital and frontal electrodes to test if PSZ had lateralized deficits in the neural processes as reported in neuroimaging studies(5, 40). Finally, the LRP being typically most obvious around 100 ms prior to a response in bilateral central electrodes (C3 and C4) was quantified using the formula isolating interhemispheric differences in motor potentials(33). The onset latency of the LRP was determined as the time point at which the amplitude reached 50% of its peak amplitude(22). To minimize high-frequency signals causing measurement error in the LRP onset-latency, we applied an 8-Hz low-pass filter to the LRP. The details of ERP component measurements were summarized in Figure 3, 4, and 5 legends. See additional details of ERP analyses in Supplemental Information.

Statistical Analyses

For behavioral performance and ERP components, repeated-measures ANOVAs with a between-group factor of diagnostic group (PSZ and NC) and a within-group factor of cue condition (HCP and LCP) were conducted for dependent variables of behavioral indices and each ERP component. Any significant interaction effect was further analyzed with ANOVA and t-tests. Effect sizes were estimated using η^2 and Cohen's d formulae. To identify neural processes predictive of context processing abilities, we conducted multiple regression

analyses with predictors being amplitudes of the ERP component amplitudes and the dependent variable being one of the four task performance indices (i.e., %Correct, μ, σ, τ). To control problems due to multicollinearity among the predictors(41, 42), we conducted ridge regression analyses using the *ridge* R package (https://cran.r-proiect.org/web/packages/ridge/index.html) that automatically determines an optimal ridge regularization parameter and provides significance tests of predictors(43, 44; see Supplemental Information for details). To test if the cognitive and neural processes during SRRT predict schizophrenic symptom severity, we also conducted ridge regression analyses with the predictors and dependent variables of BPRS symptom scores.

RESULTS

Behavioral Performance

Repeated-measure ANOVA results of performance indices are depicted in Figure 2 and summarized in in Supplemental Information (Table S3). There was a group-by-condition interaction effect on response accuracy (%Correct), indicating differential performance deficits of PSZ (i.e., lower accuracy in the HCP [$t_{[109]}$=−2.33, p=.022, d=−.44] but importantly not in the LCP condition [$t_{[109]}$=−1.53, p=.129, d=−.29]; see Figure 2). Similarly, σ had a group-by-condition interaction characterized by a significant group difference only in HCP condition (HCP: $t_{[109]}$=4.45, $p<10^{-4}$, d=.85; LCP: $t_{[109]}$=1.53, p=.130, d=.29). Unlike NC, PSZ had larger σ for HCP than LCP trials ($t_{[58]}$=2.12, p=.039, d=.28), indicating instability of controlled responses in PSZ for HCP. In contrast, μ and τ had group and condition effects but no group-by-condition interaction, indicating longer latency of PSZ than NC in both normal and slow responses regardless of the context processing load. Although group-by-condition interaction effect was not significant in τ, only PSZ had significantly larger τ in LCP than in HCP ($t_{[58]}$= 2.42, p=.019, d=.31).

Visual ERP Components

The cvN1 amplitude had no group difference in any condition and electrode, but a condition difference (LCP>HCP; Figure 3), perhaps because the green-cue had higher luminance than the red-cue(45). It also had significant group-by-electrode and a trend-level group-by-condition-by-electrode interaction effects, which were explained by differential condition-by-electrode interaction effects in the two groups; NC had the condition effect only in P7 ($t_{(51)}$=2.50, p=.016) while PSZ had the condition effect only in P8 electrode (t(56)=2.24, p=.029). The pvN1 peak amplitude had significant group (PSZ<NC) and condition (HCP>LCP) effects, but no other effect. The pvN1 peak latency had a group ($F_{[1,109]}$=7.76, p=.006, η^2=.07; PSZ>NC) and an electrode ($F_{[1,109]}$=5.60, p=.020, η^2=.05; PO7>PO8) effects, while cvN1 peak latency had no such effects. These findings suggest impairments in early visual processes in PSZ did not interact with the context processing demands of the task.

Proactive and Reactive Control ERP Components

The cfN2 amplitudes had group (PSZ<NC), electrode (Fz>F3>F4), group-by-condition interaction, and group-by-condition-by-electrode interaction effects (Figure 4). Follow-up tests found a significant group difference in HCP ($F_{[1,107]}$=8.02, p=.006, η^2=.07) but not in LCP ($F_{[1,107]}$=2.47, p=.119, η^2=.02). Such a differential group difference (i.e., group-by-

condition interaction) was observed in Fz ($F_{[1,107]}$=4.87, p=.030, η^2=.04) and F3 ($F_{[1,107]}$=9.49, p=.003, η^2=.08), but not in F4 electrode ($F_{[1,107]}$=.01, p=.937, η^2<.01). The prfN amplitude had group (PSZ<NC), condition (LCP>HCP), and a trend-level electrode effect (FCz>F3>F4). Group-by-condition and a group-by-electrode interaction effects were also significant for prfN. Follow-up analyses found prfN group differences in HCP ($F_{[1,108]}$=12.84, p=.001, η^2=.11) but not in LCP ($F_{[1,108]}$=2.80, p=.093, η^2=.03). Also, prfN group difference were significant at FCz ($F_{[1,108]}$]=16.96, $p<10^{-4}$, η^2=.14) and F3 ($F_{[1,108]}$=4.74, p=.032, η^2=.04), but not the F4 electrode ($F_{[1,108]}$=.92, p=.340, η^2=01).

Motor ERP Component

LRP amplitude was not different between conditions but largely reduced in PSZ compared to NC regardless of context processing loads (Figure 5). LRP onset-latency had no group effect ($F_{[1,101]}$=1.11, p=.294, η^2=.01) but showed a trend-level condition effect ($F_{[1,101]}$=3.59, p=.061, η^2=.03; HCP>LCP) and a significant group-by-condition interaction effect ($F_{[1,101]}$=5.32, p=.023, η^2=.05). Follow-up analysis found that PSZ had longer LRP onset-latency than NC in HCP ($t_{[101]}$=2.14, p=.035, d=.42) but not in LCP ($t_{[101]}$=.42, p=.677, d=.08). To further examine if this HCP-specific LRP problem relates to dysfunctional prefrontal-motor coordination for context-dependent motor control, we examined correlations between motor LRP and cognitive prfN amplitudes. We found that NC had significant correlation between LRP and prfN amplitudes in HCP ($r_{[51]}$=.35, p=.011) but not in LCP ($r_{[51]}$=.16, p=.261). PSZ showed no correlation in either condition (Figure 5D). Given the group-by-condition interaction pattern of the correlation (i.e., significant group difference in the correlation for HCP [z=2.19, p=.029] but not for LCP [z=1.49, p=.136]), the interaction between LRP and prfN might be indicative of specific deficits in prefrontal-motor coordination for reactive control in PSZ.

Relationships between ERP components, Task Performance Indices, and Schizophrenic Symptoms

In the ridge regression analyses with dependent variables of performance indices and predictors of ERP components, we included the interaction term between the response-period prefrontal and motor ERPs (i.e., the product of prfN and LRP amplitudes [prfN*LRP]) as a predictor of fronto-motor coordination process of reactive control. Only the ERP component of prefrontal proactive control (cfN2) predicted performance accuracy. The mean and variability of normal responses (μ and σ) were primarily predicted by LRP amplitude and the fronto-motor interaction component (prfN*LRP). Lastly, the mean of slow response latencies (τ) was primarily predicted by prefrontal reactive control component (prfN). In the regressions predicting BPRS scores, we also found that prfN*LRP predicted severity of overall and disorganization symptoms of schizophrenia (see Supplemental Information for details; Table S4, S5, and Figure S2).

DISCUSSION

This study revealed that PSZ showed poor sensitivity of frontal brain responses to contextual information which predicted poor use of context to guide behavioral responses. Particularly in situations that required overriding prepotent responses based on contextual information

(HCP condition), PSZ had lower accuracy and larger RT variability (σ) than NC, but not when such control demands were low (LCP condition). In contrast, PSZ also had increased latency in normal and slow responses (μ and τ) regardless of context processing load, suggesting additional generalized deficits in motor preparation and attentional vigilance. During encoding of contextual cues PSZ had intact visual responses (cvN1) but reduced frontal cognitive responses (cfN2), pointing to deficient prefrontal proactive control processes but normal perception of simple and clearly discernable visual cue stimuli. In response to probe letters that followed cues, PSZ had diminished and delayed visual responses (pvN1) and reduced frontal responses prior to button presses (prfN), indicating deficits in visual processing of letter stimuli and prefrontal reactive control. PSZ also exhibited abnormal motor preparation processes that were associated with the speed of button presses to probes. In both LCP and HCP conditions PSZ had diminished motor potentials (LRPs) leading up to a behavioral response, but they showed a delayed LRP onset latency only for HCP trials, suggesting problems in controlled motor processes. None of the task performance and ERP indices were explained by antipsychotic medication dosage (see Supplemental Information).

Unlike previous reports(12) emphasizing sensory processing deficits (i.e., the bottom-up hypothesis of schizophrenia)(46), the present study revealed that response accuracy during a context processing task was predicted by prefrontal proactive control (cfN2) rather than neural responses for visual encoding of contextual cues (cvN1). Consistent with our recent findings that encoding period theta-frequency neural responses in prefrontal rather than visual cortices were predictive of WM deficits in PSZ(47), these results suggest that schizophrenia is associated with failures in context-cue encoding due to prefrontal proactive control deficits rather than simple visual deficits. Given the differential deficits of PSZ in cfN2, prfN, and LRP onset latency for HCP, proactive control for rule updating and reactive control of motor processes are the primary specific deficits underlying context processing deficits in schizophrenia.

Proactive and Reactive Control Deficits in PSZ

A previous ERP study using AX-CPT identified co-activations in the bilateral dorsolateral prefrontal (DLPFC) and parietal cortices as the neural sources of frontal N2 component during a cue-period(48). Therefore the cfN2 during the SRRT might reflect DLPFC-parietal activations for proactive control and the updating of WM for contextual rules. fMRI studies using the SRRT have shown activations in middle frontal, anterior cingulate (ACC), inferior frontal (IFC), and inferior parietal cortices for HCP trials(27, 49). Given the bilateral-frontal and frontocentral topography of prfN, it might reflect co-activations in the DLPFC-IFC-ACC network underlying reactive control for detection and resolution of response conflict by inhibiting a prepotent motor response(50, 51) and initiating a correct response according to contextual rules stored in WM(52). The context-dependent deficits in cfN2 and prfN components in PSZ suggest that they reflect prefrontal specific deficits involving both proactive and reactive controls. These findings partly replicate the previous AX-CPT fMRI findings that PSZ have deficient activations for proactive control (cue-period) but hyper-activations for reactive control (probe-period) in prefrontal-parietal network(16). The hyper- and hypo-frontality findings for reactive control in AX-CPT and SRRT might be due to

differences in task demands(53); SRRT requires more reactive controls than AX-CPT, not only inhibition of a prepotent automatic response but also initiation of a goal-relevant response.

In contrast to consistent findings of proactive control deficits, findings of reactive controls in PSZ are somewhat inconsistent. Unlike the EEG findings of reactive control deficits in the current SRRT and the recent AX-CPT(17) studies, recent behavioral findings of experimental studies using computerized conflict resolution tasks (i.e., the Stroop and Flanker tasks)(54-56) suggested intact reactive control abilities in PSZ. However, such tasks have the same rules requiring selective attention to task-relevant features of stimuli, while context processing tasks requires to use current mental representation of contextual rules varying across trials. Therefore, reactive control deficits in PSZ might arise from their difficulty in using mental representations rather than selective attention.

Visual Processing Deficits and Top-Down Visual Modulation in PSZ

We only partly replicated previous findings of visual encoding deficits in PSZ(12, 18); intact visual responses to contextual cues but deficient visual responses to probes. This might be due to differences in the visual stimuli used for cue. We used a simple visual cue (a rectangle in red/green color), while the previous studies used a letter(12) or an abstract shape(18). It appears that PSZ had visual encoding deficits for complex shapes but not for simple and easily discernable objects. Furthermore, PSZ might have had more difficulty in visual encoding of a letter that was presented for only 100 ms in the previous study(12), which challenged subsequent attentional processes. This might explain previous findings of associations of performance deficits with visual encoding deficits rather than prefrontal deficits. Our results show that both groups had larger pvN1 amplitudes in HCP than in LCP trials, suggesting that the prefrontal proactive control enhanced visual neuronal activity for controlled responses to probes. As indicated by the results from the supplementary analyses of cfN2-pvN1 ERP pairs (see Figure S3) that support the previous finding(12), PSZ might have relatively intact top-down modulation of visual processing.

Contribution of Deficits in Controlled Motor Processes to Context processing Deficits in PSZ

Consistent with LRP findings during Flanker tasks(57), PSZ had diminished LRP amplitudes regardless of response conflicts but increased LRP onset latency only for HCP trials, suggesting generalized and specific deficits of motor processes in PSZ. The onset latency of response-locked LRP represents amount of time between the onset of preparatory motor activities and the execution of the response. Therefore, the increased LRP onset latency might reflect deficient prefrontal reactive control of motor cortical activity to initiate a goal-relevant motor response in PSZ.

In line with the LRP findings, we also found general and specific abnormalities in Ex-Gaussian RT indices in PSZ, replicating recent findings of increased σ and τ in first-episode PSZ(58) that indicated unstable and dysregulated motor processes in schizophrenia. PSZ had HCP-specific abnormality in the RT variability index σ, which was primarily predicted by the interaction between prfN and LRP (prfN*LRP). Consistent with a recent fMRI finding

that smaller σ was predicted by larger activities of dorsal ACC(59) that might be the primary source of prfN, these findings suggest that deficient prefrontal-motor coordination for reactive control may cause unstable motor processes characterized by large trial-by-trial fluctuations in the latency of controlled motor responses. PSZ also had large increases in slow response latency (τ) which was predicted by smaller prfN and prfN*LRP. Large τ has been often associated with attentional lapse(58, 60), and recent fMRI studies found that attentional lapse is associated with diminished suppression of default mode brain network (DMN) activities(61, 62). Therefore, our finding of larger τ for LCP than HCP trials in PSZ might indicate their increased attentional lapse associated with not only deficient prefrontal reactive control but also inability to suppress spontaneous activities of DMN that tends to be larger in the easier trials leading to more mind-wandering(63). In addition, prfN*LRP predicted severity of overall and disorganization symptoms of schizophrenia. Given the recent fMRI finding that abnormal prefrontal-motor functional connectivity predicted overall schizophrenia symptom severity(64), the results suggested that failures in prefrontal-motor coordination underlying context processing deficits in PSZ relates to various schizophrenic symptoms as well as their cognitive deficits.

In summary, using an optimal task, RT variability analyses, and high temporal resolution ERP indices, the present study identified specific and generalized deficits in neural processes underlying context processing deficits in PSZ. Inaccuracy and instability of motor control predicted by deficient proactive prefrontal and reactive prefrontal-motor control activities in HCP condition indicated their specific context processing deficits associated with failures in using mental representations of varying contextual rules. In contrast, delayed response latencies and reduced visual and motor cortical activities observed regardless of task demands suggested generalized deficits in visuo-motor processes in schizophrenia. The identification of the specific and generalized cognitive/neural deficits may provide guidelines for future mechanistic studies and alternative interventions (e.g., cognitive remediation) of schizophrenia. Future studies analyzing interregional neural coordination may further clarify cortical dysintegration mechanisms underlying context processing deficits in schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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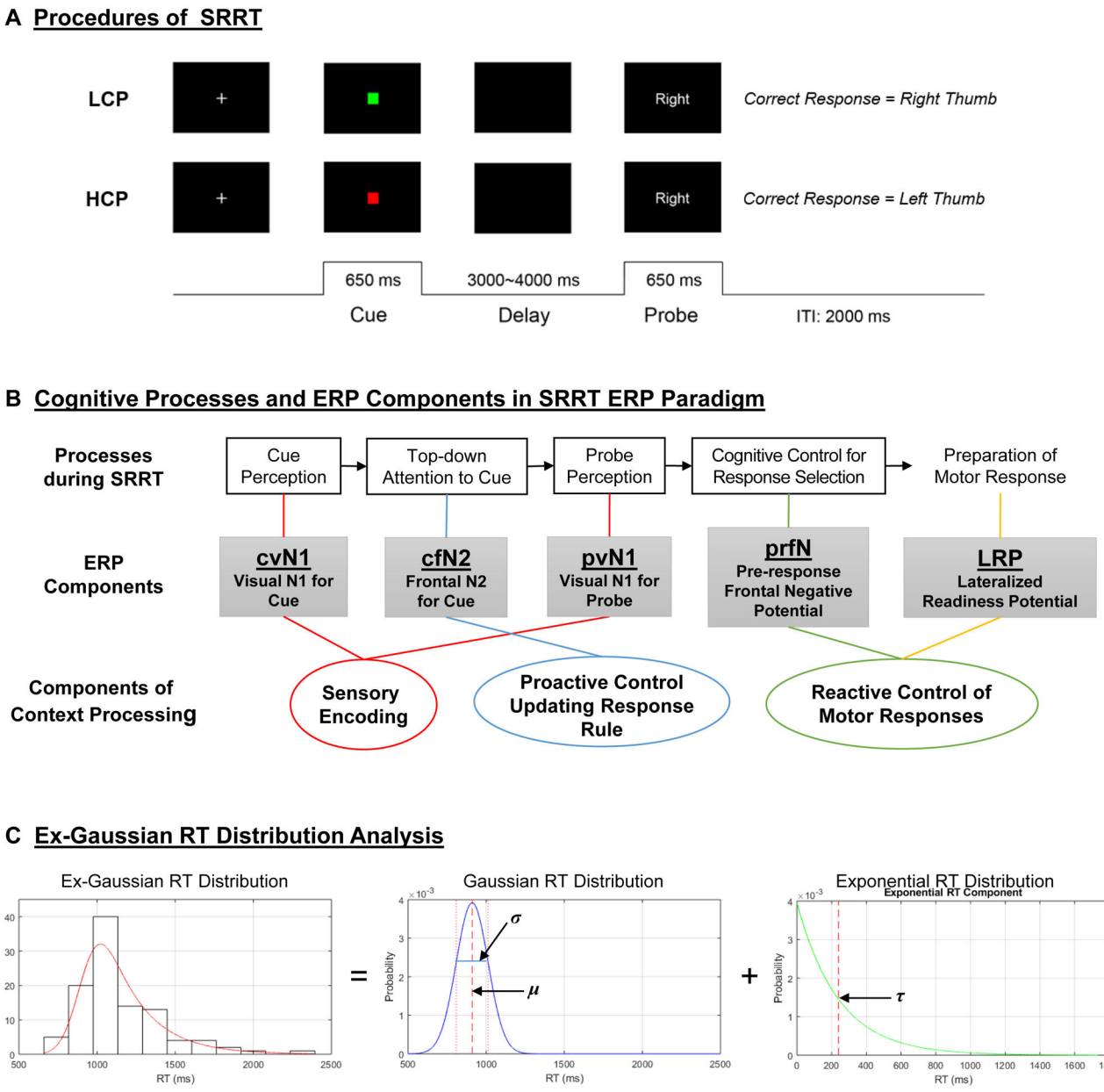

Figure 1.

A: Schematic of Stimulus Response Reversal Task (SRRT) with low context processing (LCP) and high context processing (HCP) trial types. In this task, subjects were asked to select responses to a directional probe word (“Left” or “Right”) according to a contextual cue (a red or green rectangle) presented prior to the probe. Each trial began with a central cross fixation which was followed by a green or red square cue that was presented for 650 ms. After 3000 to 4000 ms delay, a probe letter ("Right" or "Left") was presented for 650 ms. The next trial began 2000 ms after probe stimuli offset. **B:** A diagram depicting the sequence of cognitive processes and ERP components in the SRRT ERP paradigm that consist of context processing during the task. **C:** An example of Ex-Gaussian RT distribution from a subject’s correct response latency of SRRT HCP trials. Ex-Gaussian RT distribution

is a convolution of the two additive processes (i.e., Gaussian and exponential processes). The μ and σrepresent the mean and standard deviation of the normal (Gaussian) component of RT distribution, reflecting the mean speed and variability of normal responses. Thus, a large σ indicates increased trial-to-trial jittering of usual responses that might be caused by instability of motor processes. On the other hand, τ represents the mean of the exponential component of RT distribution, reflecting mean of extremely slow responses (i.e., outlier responses). Thus, a larger τ indicates a longer and thicker tail of exponential distributions of slow responses, which often occur due to attentional lapse. The mean and standard deviation of Ex-Gaussian distribution equal to $\mu + \tau$ and $\sqrt{\sigma^2 + \tau^2}$, respectively.

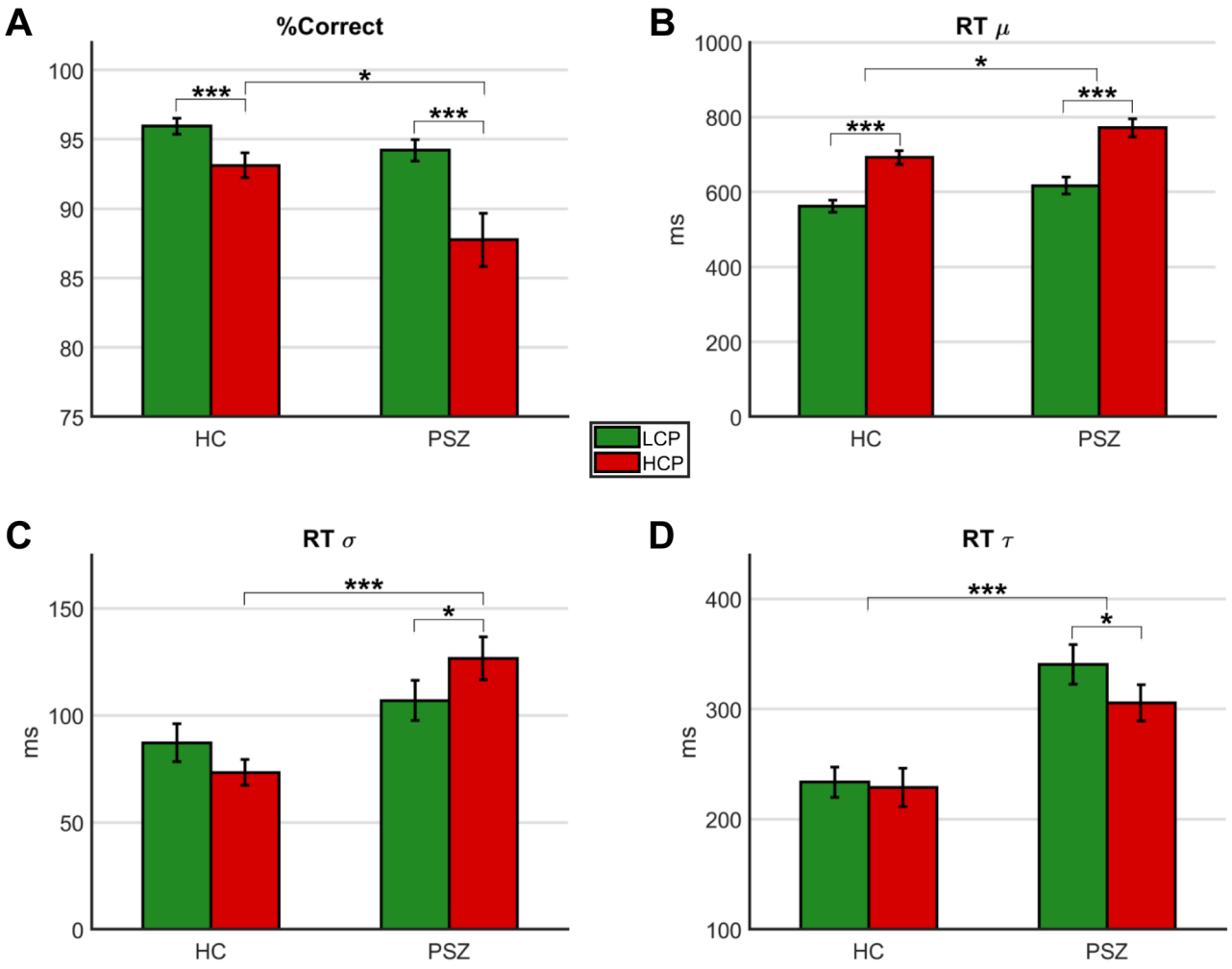

Figure 2.

Response accuracy (%Correct) and the three parameters of Ex-Gaussian RT distribution of SRRT. PSZ had response accuracy deficits only in HCP condition (**A**), suggesting a deficit specific to trials requiring controlled motor responses. Regardless of context-processing load, PSZ had longer mean latency than HC in normal (μ; **B**) and slow responses (τ; **D**) that were differentiated by deconvolution of a RT distribution into a Gaussian and an exponential RT distributions, indicating generalized problems in motor control in PSZ. In contrast, they had larger variability in normal responses (σ; **C**) than NC only for HCP trials, suggesting that PSZ had specific deficits of unstable motor controls especially on trials where they should override a prepotent response and initiate a context-relevant motor response. (Note: One schizophrenia patient who had difficulty in understanding how to perform the task and extremely low response accuracy was excluded from performance analyses; *: p<.05; *** p<.0005).

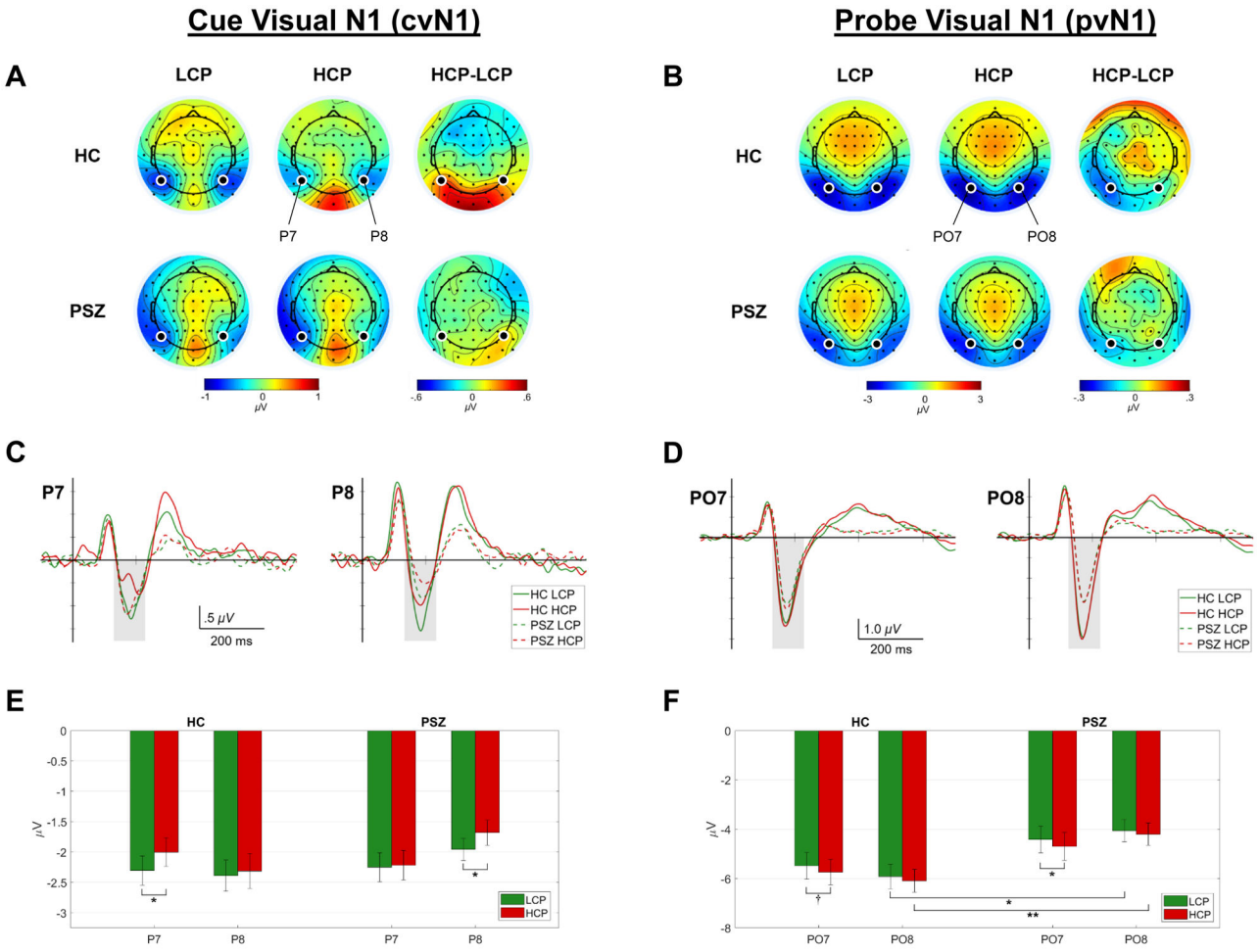

Figure 3.

Visual ERP components for cue (left) and probe (right) stimuli. **A** and **B:** Topographic distributions of the visual N1 components in response to cue and probe stimuli (cvN1 [left] and pvN1 [right]) in HC and PSZ, which were quantified by mean amplitudes within the time-windows (130-230 ms after stimulus onsets) for LCP and HCP conditions as well as the HCP-LCP difference. The cvN1 was maximal at P7 and P8, while the pvN1 was maximal at PO7 and PO8. **C** and **D:** ERP waveforms time-locked to the onsets of visual stimuli, where the time-windows used for the peak amplitude and latency quantification are marked by shaded areas (130-230 ms after onsets of the visual stimuli). **E** and **F:** Peak amplitudes of the cue and probe N1 components measured in P7/P8 and PO7/PO8 electrodes. No group difference was observed in the cvN1, which was larger for LCP (green) than HCP (red) cues; HC had the significant difference between cue types at P7 while PSZ showed the cue-type effect at P8. The pvN1 was diminished in PSZ compared to HC, especially in PO8, but both groups had larger pvN1 amplitudes in HCP condition (†: p<1.0; *:*p*<.05; **: *p*<.005).

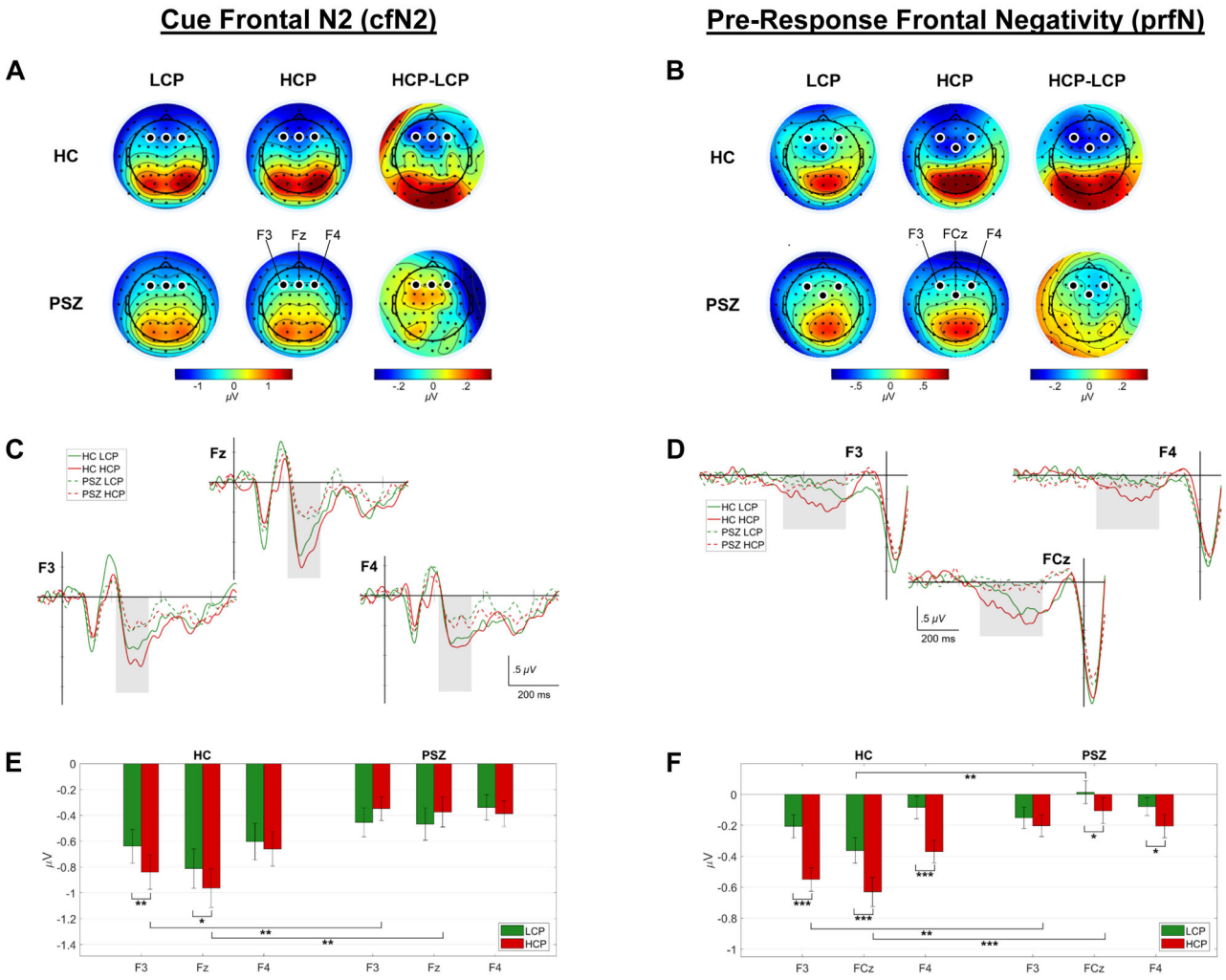

Figure 4.

Cue-period frontal N2 ERP component (cfN2) representing prefrontal proactive control (left) and pre-response frontal negativity (prfN) component representing prefrontal reactive control (right). **A** and **B:** Topographic distributions of cfN2 and prfN components in HC and PSZ, which were quantified by mean amplitudes within the time-windows (cfN2: 220-350 ms after cue onsets; prfN: 500-200 ms before response onsets) for LCP and HCP conditions as well as the HCP-LCP difference. The cfN2 was quantified at F3, Fz, and F4, while the prfN was quantified at F3, FCz, and F4 sites. **C** and **D:** ERP waveforms time-locked to the cue and response onsets, where the time-windows used for the mean amplitudes are marked by shaded areas. **E** and **F:** Mean amplitudes of the cfN2 and the prfN components were larger for HCP than LCP condition. The components were diminished in PSZ compared to HC, but only in the HCP condition. These differences were observed at F3 and Fz (cfN2) or FCz (prfN) sites. The condition effect was absent (cfN2) or diminished (prfN) in PSZ compared to HCs. These results suggested that PSZ had deficits in prefrontal proactive and reactive controls that were specific to HCP demands. (*: $p<.05$; **: $p<.005$; *** $p<.0005$).

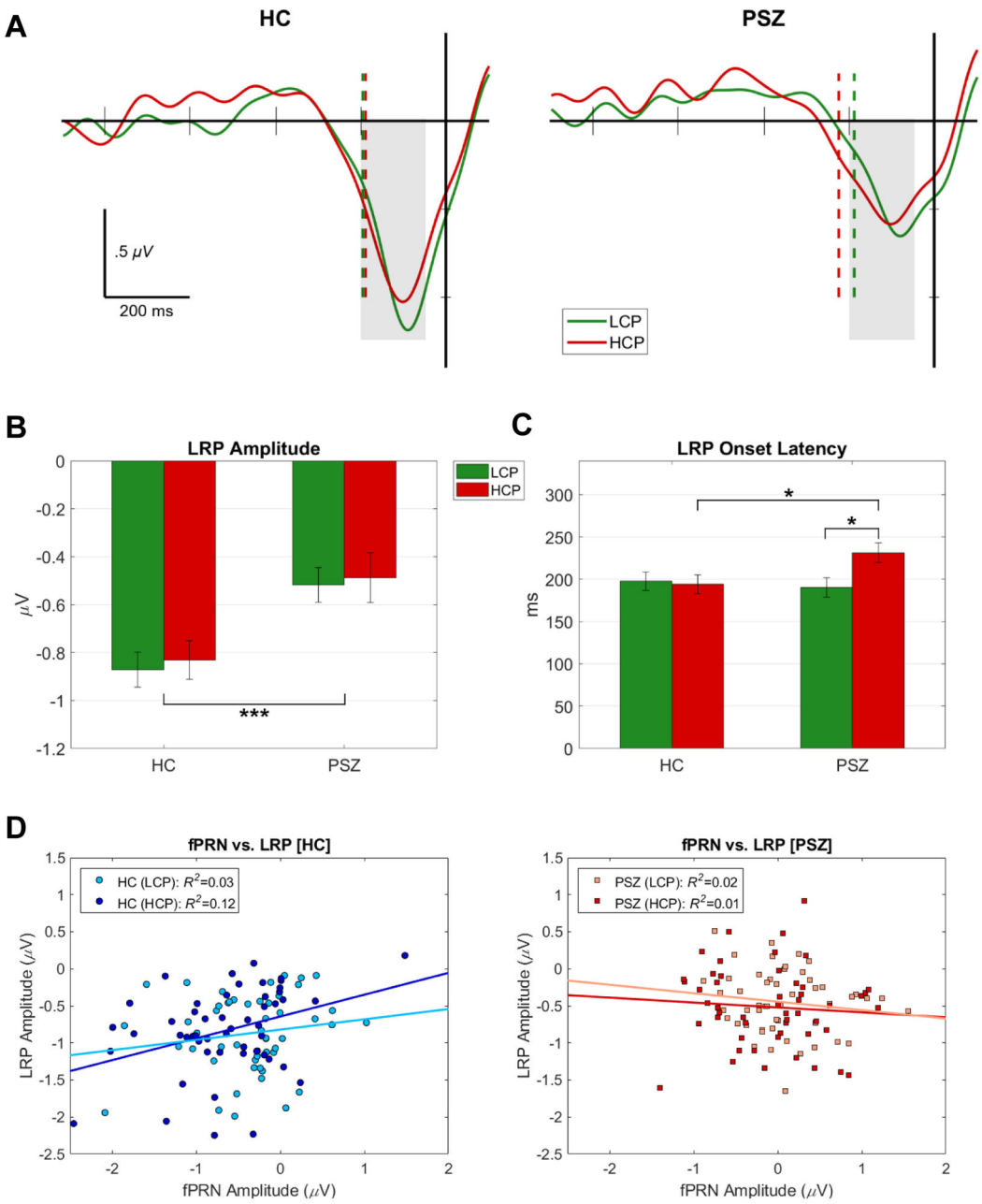

Figure 5.

Lateralized readiness potentials (LRPs) time-locked to button response onsets and measured as the difference between electrodes over the motor cortex of left and right hemispheres (C3 and C4). **A:** LRPs were maximal around 100 ms prior to response onsets. Two time-windows marked by the two shaded areas were used for LRP quantification for the mean amplitudes (200-50 ms before responses) and the onset latency (350-50 ms before responses) because the onset latency were often substantially earlier than the ranges of the peak LRP amplitudes as observed in previous studies(20). The dashed lines represent LRP onset latency indicating the time-point when the LRP reached 50% of its maximum amplitude. **B:** PSZ had largely diminished LRP amplitudes regardless of the task condition.

C: PSZ had longer LRP onset latency than NC only in the HCP condition. **D:** The relationships between pre-response frontal negativity (prfN) ERP component representing prefrontal reactive control and lateralized readiness potential (LRP) component representing preparatory motor cortical activity during LCP and HCP conditions in two groups. NC had significant positive correlation between prfN and LRP amplitudes in HCP ($r_{[51]}$=.35, p=.011) but not in LCP condition ($r_{51]}$=.16, p=.261), while PSZ failed to show an associations in either context processing condition (HCP: $r_{52]}$=−.08, p=.582; LCP: $r_{52]}$=−.14, p=.340). These results suggested that NC might have increased prefrontal-motor coordination underlying reactive control for context-processing in HCP trials, while PSZ failed to have such coordination.