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Impaired Midline Theta Power and Connectivity During Proactive Cognitive Control in Schizophrenia

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ABSTRACT

BACKGROUND: Disrupted proactive cognitive control, a form of early selection and active goal maintenance, is hypothesized to underlie the broad cognitive deficits observed in patients with schizophrenia (SPs). Current research suggests that the disrupted activation within and connectivity between regions of the cognitive control network contribute to disrupted proactive cognitive control; however, no study has examined these mechanisms using an AX Continuous Performance Test task in schizophrenia.

METHODS: Twenty-six SPs (17 male subjects; mean age 34.46 ± 8.77 years) and 28 healthy control participants (HCs; 16 male subjects; mean age 31.43 ± 7.23 years) underwent an electroencephalogram while performing the AX Continuous Performance Test. To examine the extent of activation and level of connectivity within the cognitive control network, power, intertrial phase clustering, and intersite phase clustering metrics were calculated and analyzed.

RESULTS: SPs exhibited expected general decrements in behavioral performance relative to HCs and a more selective deficit in conditions requiring proactive cognitive control. Additionally, SPs exhibited deficits in midline theta power and connectivity during proactive cognitive control trials. Specifically, HCs exhibited significantly greater theta power for B cues relative to A cues, whereas SPs exhibited no significant differences between A- and B-cue theta power. Additionally, differential theta connectivity patterns were observed in SPs and HCs. Behavioral measures of proactive cognitive control predicted functional outcomes in SPs.

CONCLUSIONS: This study suggests that low-frequency midline theta activity is selectively disrupted during proactive cognitive control in SPs. The disrupted midline theta activity may reflect a failure of SPs to proactively recruit cognitive control processes.

Keywords: AX-CPT, Electroencephalography, Functional outcomes, Proactive cognitive control, Schizophrenia, Theta

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Impaired cognitive function is linked to decreased objective quality of life (1) and daily functioning in schizophrenia (2,3). Disrupted proactive cognitive control is hypothesized to underlie the broad cognitive deficits observed in patients with schizophrenia (SPs). Therefore, understanding the mechanisms contributing to this proactive cognitive control impairment is an important step toward developing targeted treatments for the cognitive dysfunction observed in schizophrenia.

Cognitive control is defined as a set of processes required to pursue a goal, which includes context representation and maintenance, especially when distraction and/or strong competing responses must be overcome (4,5). Proactive cognitive control is a form of early selection in which goal-relevant information is actively maintained, requiring sustained activity of the lateral prefrontal cortex. The functioning of the dorsolateral prefrontal cortex (DLPFC) is thought to be a key component of proactive cognitive control (6,7), which is involved in the early, sustained maintenance of context information. This ability and corresponding DLPFC activation is consistently impaired in schizophrenia as evidenced by a reduction in blood oxygen level–dependent signal (4,8) and gamma activity (9), in addition to disrupted connectivity between the DLPFC and broader cognitive control network (CCN) (6), during cognitive control. It is unclear, however, whether the deficits in DLPFC functioning reflect a local failure (e.g., DLPFC fails to respond to input) or, rather, a failure of a preceding signal that would indicate the need for proactive cognitive control.

Electrophysiological studies have suggested that midline theta power reflects the operations of a conflict-and-control mechanism (10), and that theta connectivity facilitates both

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proactive and reactive cognitive control processes (11). The cerebral generators of midline theta power are currently actively investigated and may reflect activity from several brain regions (12–14); however, increasing evidence highlights the midcingulate cortex (MCC) as a key generator, including electroencephalography (EEG) source estimation (15,16), EEG-informed functional magnetic resonance imaging (17–20), magnetoencephalography (21), and invasive recordings in humans and monkeys (13,22–26). MCC is consistently implicated in the demand for control, either proactively or reactively, with varied theoretical accounts of its computational function (5,27,28). Given the roles of MCC and midline theta, the current study aimed to examine whether a deficit in proactive cognitive control was associated with disrupted midline theta activation.

In addition to theta activity, prefrontal cortex–related gamma activity is disrupted in SPs during working memory and cognitive control (29), particularly in the DLPFC. This failure to maintain oscillatory activity may form the basis for deficits in top-down support to task-relevant circuits across the brain (30), an effect that is also present in persons experiencing a first episode of schizophrenia (31). Notably, in healthy control participants (HCs), higher frequencies (gamma) establish synchronization in local cortical networks (32,33), whereas lower frequencies (such as theta) establish synchronization over longer distances (34) and modulate power in the gamma spectrum (35). Thus, the disruption in gamma oscillations in SPs, particularly in the lateral frontal region, may be related to alterations in low-frequency activity, such as midline theta (36). There is emerging evidence that not only is theta disrupted during cognitive function in SPs (37,38), but the coupling between theta and gamma is also impaired (39), suggesting that SPs exhibit deficits in theta activity as well as the coordination of theta and gamma signaling.

While recent research highlights that theta-band dysfunction represents a key deficit of schizophrenia (40), to date no study has comprehensively examined theta activity during proactive cognitive control using the AX Continuous Performance Test (AX-CPT) in SPs. The central hypothesis of the current study is that deficits in proactive cognitive control result from aberrant theta and gamma power and phase clustering within and between regions within the CCN. These deficits, in turn, affect everyday functioning.

METHODS AND MATERIALS

Participants and Assessment Measures

SPs were recruited from the University of New Mexico Psychiatric Center. All participants provided informed consent according to institutional guidelines at the University of New Mexico. Refer to Supplemental Methods for additional information on inclusion and exclusion criteria and clinical assessments.

Multisensory AX-CPT Task

The Presentation software package (Neurobehavioral Systems, Berkeley, CA) was used for stimulus presentation and recording of behavioral data. Prior to EEG assessment, participants received instructions and completed practice until their performance indicated an understanding of task (see Supplementary Methods for details). Participants monitored a continuous series of visual cues (the letters A, R, V, P, S, and E; duration, 500 ms) and auditory probes (the letters X, Q, F, I, M, and U; duration, 500 ms) and were instructed to respond "yes" when the letter X follows the letter A (Figure 1). The total number of trials collected was as follows: 280 AX trials (70% of the total trials) and 40 of each of the remaining trial types (AY, BX, BY; each 10% of the total trials). A visual cue was used with an auditory probe, as previous studies indicate that this combination results in maximum cross-modal cueing effects (41). Non-A (hereafter referred to as "B cues") and non-X (hereafter referred to as "Y probes") letters were selected to be visually or aurally distinct from their respective counterparts. The interstimulus interval was 3220 ms jittered by 460 ms. The intertrial interval was 4520 ms, again jittered by 460 ms. Figure 1 provides further details of the task. The following contrasts were examined: B versus A cues, AX versus AY probes, and AX versus BX probes. See Supplemental Methods for further details.

Behavioral Analyses

AX Continuous Performance Test. Accuracy (percent correct) and median reaction time (RT) for correct trial data were computed for cues (A and B) and three of the probe trial types (AX, AY, and BX). A series of 2 × 2 (group [SPs vs. HCs] × condition [e.g., A cues vs. B cues]) mixed-measures analyses of variance examined RT and accuracy differences across the following planned contrasts: B versus A cues, AX versus AY probes, and AX versus BX probes.

RT and Functional Outcomes. The relationship between the three functional outcome measures [University of California–San Diego Performance-Based Skills Assessment–Brief (UPSA-B) (42), Schizophrenia Quality of Life Questionnaire 18 (S-QoL 18) (43), and Specific Levels of Functioning Scale–Informant Report (SLOF-I) (44)] was examined, and correlations indicated that the UPSA-B and S-QoL 18 were relatively independent ($r = -.04$). Therefore, three separate multiple regressions were conducted using two RT metrics of proactive cognitive control (B–A cue RT and BX–AX RT) as the independent variables and functional outcome measures as the dependent measure accounting for medication (olanzapine equivalent), extrapyramidal symptoms (Abnormal Involuntary Movement Scale, Barnes Akathisia Rating Scale, and Simpson–Angus Scale), and smoking history (Fagerstrom Test for Nicotine Dependence).

Electrophysiological Data Processing

Data were collected on a Biosemi EEG system (Amsterdam, Netherlands) utilizing a 128-electrode EEG cap and a sampling rate of 512 Hz. EEG data were collected in a shielded room with active electrodes, with no observed spectral peaks at 60 Hz. Similar to previous publications (45), the data underwent standard preprocessing steps using MATLAB (MathWorks; The MathWorks, Inc., Natick, MA) and EEGLAB, an open-source toolbox available for EEG signal processing (46). See Supplemental Materials for details. Data were epoched relative to stimulus onset (−2000 to +2000 ms), and artifacts were identified and removed using a combination of automated and