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The contribution of the contingent negative variation (CNV) to goal maintenance

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A B S T R A C T

The dot pattern expectancy (DPX) task has been strongly recommended as a measure of goal maintenance, which is impaired in schizophrenia patients. The current event-related potential (ERP) study was designed mainly to identify the ERP component that could represent the goal maintenance process of the DPX task as indexed by the error rate of the BX vs. AY (E_{BX-AY}). We focused our analysis on the cue-phased contingent negative variation (CNV) and found a significant association between the E_{BX-AY} and the amplitude of the difference wave of cue B vs. cue A (CNV_{B-A}) (for CP_3, $\beta = -0.262$, $P = 0.001$; for CP_Z, $\beta = -0.184$, $P = 0.025$; for CP_4, $\beta = -0.201$, $P = 0.015$). Lower E_{BX-AY} (better goal maintenance) was correlated with larger CNV_{B-A}. Further analysis found a significant association between the error rate of AY condition (E_{AY}) and the amplitude of CNV_A (for CP_3, $\beta = -0.180$, $P = 0.029$; for CP_Z, $\beta = -0.184$, $P = 0.024$; for CP_4, $\beta = -0.208$, $P = 0.011$) and a significant association between the error rate of BX condition (E_{BX}) and the amplitude of CNV_{B-A} (for CP_3, $\beta = -0.198$, $P = 0.016$; for CP_Z, $\beta = -0.165$, $P = 0.043$; for CP_4, $\beta = -0.151$, $P = 0.066$), but not the amplitude of the CNV_B (all $P > 0.05$). All these results together suggested that the cue-phased CNV could be used to represent the goal maintenance process. Future research needs to verify these results with schizophrenia patients.

1. Introduction

Cognitive deficit is one of the core features of schizophrenia. It is present prior to the first episode of the disorder and persists throughout the lifespan. It is refractory to most of the current antipsychotic treatment. The Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative, with its initial aim of developing behavioral measures to evaluate the treatment effect of new antipsychotic drugs on cognitive deficit of schizophrenia in clinical trials, has identified characteristically impaired cognitive domains and recommended a set of cognitive tasks for each domain (Barch et al., 2009; Carter et al., 2012). Among them, the dot pattern expectancy (DPX) task was strongly recommended as a new tool to measure goal maintenance, an important aspect of working memory (Barch et al., 2009; Carter et al., 2012).

The DPX task is an adaptation of the AX-CPT task. The stimuli of the DPX task are unfamiliar dot patterns, which are presented in pairs (cue-probe) (MacDonald et al., 2005). Subjects were required to make a target response to the probe X that is preceded by a cue A (AX condition, 70%) or make a nontarget response to all the other conditions (BX, 12.5%; AY, 12.5%; BY, 5%). To perform the task successfully, subjects have to maintain the cues in working memory so that they can guide the response to the subsequent probes. Because most Xs are targets, there is a prepotency for making target responses to all Xs. Individuals with impaired capability of goal maintenance have difficulty overcoming this prepotent target response on the BX condition and then would make more errors. Moreover, because most As are followed by target Xs, the maintenance of the As would produce a strong expectancy for the subsequent Xs and a preparation for a target response. Consequently, individuals with intact capability of goal maintenance would make more errors on the AY trials. It has been well established that

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higher relative error rate of the BX vs. AY (E_{BX-AY}) is a reliable measure of goal maintenance impairment in schizophrenia (Henderson et al., 2012).

The CNTRICS, in the current phase, has expanded its initial aims and is trying to develop functional magnetic resonance imaging (fMRI) and event-related potential (ERP) measures for future clinical trials (Carter et al., 2012). The DPX task was again strongly recommended as a neuroimaging paradigm for studying goal maintenance (Barch et al., 2009). In their recent fMRI studies, MacDonald and his colleagues (Lopez-Garcia et al., 2016) who developed the DPX task have reported significant activation of the prefrontal-parietal network for the contrast of cue B vs. cue A in healthy volunteers. Using the same contrast, they further found decreased activation of the same network in schizophrenia patients (Poppe et al., 2016). Although the ERP technique has higher temporal resolution than fMRI and is hence better suited for an investigation of brain response to different cues, it has never been used in previous studies on the DPX task.

In this ERP study, we tried to identify the ERP component(s) that could represent the goal maintenance process of the DPX task. We focused our analysis on contingent negative variation (CNV), a late cognitive component elicited by the cue-probe pairs when a response to the probe is required (Walter et al., 1964). Previous studies using the typical AX-CPT task have shown that the CNV is much larger (in the negative direction) to cue A (CNV_A) than to cue B (CNV_B) and that the CNV increases in the negative direction throughout the cue-probe interval (Dias et al., 2011). Although most previous studies on different versions of the AX-CPT task viewed this component as reflecting motor preparation, some researchers (Dias et al., 2003) have suggested that this component could reflect other processes, among which we believe is goal maintenance. Specifically, we hypothesized that a larger difference between CNV_A and CNV_B would be associated with better capability of goal maintenance (lower E_{BX-AY}). We further tested the CNV's associations with other behavioral measures such as the error rate of the BX condition (E_{BX}) and the error rate of the AY condition (E_{AY}) to validate the results.

2. Materials and methods

This study's protocol was reviewed and approved by the Institutional Review Board of the Institute of Cognitive Neuroscience and Learning at Beijing Normal University. All subjects were Han Chinese and gave written informed consent for this study.

2.1. Subjects

One hundred and sixty-five healthy volunteers were included in the ERP study. This sample was collected from March 2015 to December 2016. All subjects were recruited by advertisement and were screened for any personal or family history of psychiatric disorders by experienced psychiatrists during an unstructured interview. All had normal or corrected-to-normal vision and were right-handed as assessed by the Edinburgh handedness inventory. None of the subjects reported taking any medication. Due to their excessive errors when performing the task (>3 standard deviations below the mean correct rates) and excessive noise in the ERP signal, 13 subjects were excluded from the final analysis. Table 1 shows a summary of demographic factors and cognitive performance on the DPX task for the subjects included in the final data analysis.

Table 1
Summary of demographic factors and cognitive performance for the subjects included in the final data analysis.

	Mean ± SD
Age (years)	27.01 ± 4.851
Gender (male/female)	118/34
Education (years)	12.13 ± 2.915
IQ[a]	110.10 ± 12.693
E_{BX-AY}	−0.044 ± 0.089
E_{BX}	0.032 ± 0.055
E_{AY}	0.076 ± 0.078

[a] IQ was measured by Wechsler Adult Intelligence Scale.

2.2. Cognitive task

The ERP task (Fig. 1) was very similar to the task that was described in our previous study (Zhang et al., 2015). Briefly, the stimuli were underlearned Braille font dot patterns, which were presented in pairs (cue-probe). 6 cues (1 valid and all others invalid) and 6 probes (1 valid and all others invalid) were used. The subjects were required to make a target response to the valid probe that followed the valid cue (AX condition), but to make a nontarget response to all other conditions (AY, BX and BY). The task was presented in 2 blocks, each of which included 120 trials (240 trials in total). The 120 trials of each block consisted of 84 (70%) AX trials, 15 (12.5%) AY trials, 15 (12.5%) BX trials, and 6 (5%) BY trials. Each trial started with a fixation cross for 350 ms, followed by a cue for 1000 ms, a delay of 2000 ms, and finally a probe for 500 ms. Between trials was a white intermission screen varying from 1600 ms to 1650 ms.

Behaviorally, the E_{BX-AY} (E_{BX} minus E_{AY}) was used as a main measure of goal maintenance (Henderson et al., 2012). Lower (more negative) E_{BX-AY} values (i.e., more errors on the AY trials relative to the BX trials) indicate better goal maintenance.

2.3. ERP acquisition

The electroencephalogram (EEG) was recorded with a 64 channel easy cap using a standard 10–20 system (Brain Products, Gilching, Germany) (band pass from 0.01 to 100 Hz, 500 Hz sampling rate). The reference electrode was on the right mastoid. The vertical electrooculographies (EOGs) were recorded with electrodes set below and above the right eye. The horizontal EOGs were recorded with electrodes set at outer canthi of each eye. The electrode impedance was maintained below 5 kΩ. During recordings, subjects sat in a comfortable chair inside a darkened, electrically shielded recording chamber, facing a computer monitor. Subjects were instructed to respond quickly and accurately by pressing a buttons on a keyboard.

2.4. Data analysis

Offline analyses were performed separately for the cue-phased and the probe-phased ERPs using the software BrainVision Analysis software (version 2.0; Brain Product, Gilching, Germany). EEGs were re-referenced to the whole brain (the average of all the electrodes). Preprocessing included both low-pass (0.01 Hz) and high-pass (30 Hz) temporal filtering, eye movement correction, segmentation into epochs 200 ms prior to the cue to 3000 ms after the cue (cue-phased), and artifacts removal (mean EEG voltage exceeding ±80 μV or peak-to-peak deflection exceeded ±80 μV). After artifact rejection, the average number of trials included in statistical analysis for cue A and cue B was 174 and 37 respectively.

The mean amplitude (2750 to 3000 ms, the last 250 ms before the appearance of the probe) for CNV_B, CNV_A and their difference waves (CNV_{B-A}, CNV_B minus CNV_A) was calculated at electrodes CP_3 and CP_4 according to the brain electrical activity map (see Fig. 2). Because many previous studies analyzed this component at the midline electrodes, we also included the electrode of CP_Z.

All data were analyzed using SPSS version 20.0. A repeated measures ANOVA was used to test the difference between CNV_A and CNV_B. In this analysis, electrode (CP_3 vs. CP_Z vs. CP_4) and condition (cue B vs. cue A) were entered as within-subject factors. Linear regression was used to test relationships between each behavioral