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Deficits in Go and NoGo P3 potentials in patients with schizophrenia

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ABSTRACT

Cognitive control processes elicited during a cued continuous performance test were evaluated using event-related potentials in 46 patients who were within the first 5 years of diagnosis of schizophrenia, and 29 healthy controls. Patients had longer reaction times, lower hit rates, and higher false alarm rates compared with controls. Patients had an overall P3 amplitude reduction that was more prominent on NoGo compared with Go trials. This greater P3 reduction on NoGo trials was present in central and parietal regions, but was absent in the frontal region, where the P3 reduction was comparable on NoGo and Go trials. Our findings suggest that the neural activity contributing to Go and NoGo P3s are both deteriorated in schizophrenia, but those contributing to central and parietal NoGo P3s are the most severely affected ones. We conclude that the cognitive control processes engaged during execution, and particularly during inhibition of a prepared motor response were disturbed in the early course of schizophrenia. Our findings might be related to our sample being in relatively early stages of schizophrenia and/or related to the use of atypical antipsychotics by most of our patients.

1. Introduction

Deficits in sustained attention, as measured using the continuous performance test (CPT) (Beck et al., 1956), have been consistently reported in schizophrenia (Cornblatt et al., 1989; Orzack and Kornetsky, 1966). Impaired CPT performance has been suggested as a biologic marker of schizophrenia because of its presence in patients with schizophrenia who were in remission (Asarnow and MacCrimmon, 1978; Wohlberg and Kornetsky, 1973), in those with first-episode schizophrenia (Francey et al., 2005; Keefe et al., 2006), in subjects at ultra-high risk for psychosis (Francey et al., 2005; Keefe et al., 2006), and in unaffected first-degree relatives of patients (Chen et al., 1998; Mirsky et al., 1995).

In the cued version of the CPT (AX-CPT), subjects are instructed to respond when the letter A (cue) is followed by the letter X (AX trial, target), and not to respond to any other letter sequences (AY, BX and BY trials, nontarget). B and Y are any letters other than A and X, respectively. The AX-CPT measures the representation, maintenance, and updating of task-relevant context information (cue and/or the goal of the task), and selection and execution of appropriate behavior (Braver et al., 1999). Thus, the AX-CPT has a particular demand on the cognitive control processes, which are suggested to involve prefrontal, frontal, and parietal structures (Dosenbach et al., 2008; Petersen and Posner, 2012; Riccio et al., 2002). Previous research has demonstrated that representation and maintenance of context information were associated with prefrontal cortex function (Barch et al., 1997; Cohen et al., 1997; Fuster, 1973; Fuster and Alexander, 1971).

Various versions of AX-CPT, with different ratios of trials, have been used. In one version of AX-CPT, the ratios of AX and AY trials are equal (10%) and subjects are instructed to respond only to AX trials. In AY trials, subjects have to inhibit their prepared response. This task gives the opportunity to compare cognitive control processes engaged during response execution and inhibition independent of their probabilities because the probability of executing a response following the letter A is equal to witholding it. Most studies reported that patients with schizophrenia had lower hit rates and longer reaction times compared to controls in this task (Fallgatter et al., 2003; Kleinlogel et al., 2007; Stratta et al., 2000; Zielasek et al., 2005). In a few studies, patients were additionally reported to have higher false alarm rates (Zielasek et al., 2005). In another version of AX-CPT (expectancy AX), the ratios of AX trials are high (70–80%) and the subjects are instructed to respond, but differently, to both targets and nontargets. This task produces a prepotent tendency to make a target response to an X and an expectancy to make a target response following A (Cohen et al., 1999; Servan-Schreiber et al., 1996). In this task, patients with schizophrenia, in contrast to controls, performed better on AY relative to BX trials, which implied a deficit in context processing (Braver et al., 1999; Javitt et al., 2000; MacDonald et al., 2003). Context processing deficits in schizophrenia were related to prefrontal cortex dysfunction (Barch et al., 2001; MacDonald et al., 2005), and were modeled as a

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dysfunctional dopamine-mediated modulation of the prefrontal cortex (Braver et al., 1999).

Event-related potentials (ERPs) are real-time measures of neural activity with high temporal resolution. Consequently, they are promising tools to explore brain dynamics that underlie deficits during CPT performance. One major ERP component elicited during CPT is the P3. The P3 is a positive deflection that occurs at 250–500 ms in the poststimulus period and is linked with attention processes during memory updating (Donchin and Coles, 1988; Polich, 2007; Polich and Kok, 1995). P3 amplitude is suggested to reflect the amount of attentional resources engaged in processing task-relevant stimuli (Polich and Kok, 1995). Various studies using CPT or Go/NoGo task reported that the P3 on Go trials has a centro-parietal distribution, whereas the P3 on NoGo trials has a more central distribution (Fallgatter and Strik, 1999; Jodo and Inoue, 1990; Pfefferbaum et al., 1985; Roberts et al., 1994; Simson et al., 1977; Strik et al., 1998). This anteriorization of NoGo P3 compared with Go P3 (NoGo anteriorization) has been proposed to reflect response inhibition and was attributed to an increase in the activity of frontal brain areas, particularly the anterior cingulate cortex (Enriquez-Geppert et al., 2010; Fallgatter et al., 2002; Strik et al., 1998).

Only a few studies investigated response execution and inhibition processes in patients with schizophrenia using ERPs elicited during CPT. Fallgatter and Müller (2001) found no difference on Go and NoGo P3 amplitudes and latencies using microstate analysis, between patients with chronic schizophrenia and controls. However, as the study groups were enlarged, they observed P3 reduction in NoGo trials in patients compared with controls (Fallgatter et al., 2003). Both studies reported a reduction on NoGo anteriorization in patients with chronic schizophrenia. This research group also reported NoGo P3 reductions in chronic patients with cycloid psychoses (Ehlis et al., 2005b) and in chronic patients with systematic and unsystematic schizophrenias (Zielasek et al., 2005) compared with controls, but the reduction on NoGo anteriorization was only found in those with systematic schizophrenias. Kleinlogel et al. (2007) studied patients with first-episode schizophrenia and observed P3 reductions on NoGo and Go trials, and an increase in NoGo P3 latency. Importantly, their patients with first-episode schizophrenia showed increased NoGo anteriorization compared with controls. These researchers suggested that the reduced NoGo anteriorization might be an indicator of progressive deterioration over time in patients with schizophrenia (Kleinlogel et al., 2007).

Using auditory Go/NoGo tasks, Weisbrod et al. (2000) showed that NoGo P3 was left lateralized over frontal areas in controls, but not in patients with schizophrenia. They reported Go P3 as being normal. In accordance with their electrophysiologic data, patients showed a worse performance than controls on NoGo trials only. Kiehl et al. (2000) also showed that patients with schizophrenia had worse performance in only NoGo trials by using a visual Go/NoGo task. However, their P3 findings were somewhat different in that they found a right lateralized P3 in controls, but no lateralization of P3 in patients. They also found that Go P3 was larger than NoGo P3 in controls, but this difference was absent in patients with schizophrenia.

The present study investigated response execution and inhibition processes using ERPs elicited during AX-CPT (the version in which the ratios of AX and AY trials are 10% each) in patients who were within their first 5 years of diagnosis of schizophrenia. Thus, the mean duration of illness of our patients would be in between the first-episode patients of Kleinlogel et al. (2007) and the chronic patients of Fallgatter and Müller (2001), Fallgatter et al. (2003) and Zielasek et al. (2005) (mean durations of illness were 6.9 ± 5.3 years, 9.0 ± 8.4 years, and 8.7 ± 7.9 years, respectively). First, we expected to find P3 reduction, particularly on NoGo trials in our patients because NoGo P3 reduction was reported both in patients with first-episode and chronic schizophrenia. Secondly, we expected to find differences in the distributions of Go and NoGo P3s between patients and controls because distribution differences in P3s were reported in patients with first-episode and chronic schizophrenia, but with different characteristics. Thirdly, we expected to find lower hit rates and longer reaction times in patients compared with controls. Most of the studies using this task did not report increased false alarm rates in patients. However, considering their NoGo P3 reduction as a reflection of abnormal inhibitory processes, higher false alarm rates compared with controls could be expected. Our findings will give further information about the time course of changes in Go and NoGo P3 deficits in schizophrenia, which is important for understanding the disease pathophysiology and developing therapeutic approaches.

2. Methods

2.1. Subjects

Forty-six patients with schizophrenia and 29 control subjects participated in the study. Patients were interviewed using the Structured Clinical Interview for DSM-IV (SCID) data (First et al., 1997) and were required to meet the Diagnostic and Statistical Manual of Mental Disorders (fourth edition) (DSM-IV) criteria for schizophrenia. Patients were also required to have no prior brain injury or current psychiatric or neurologic disorder other than schizophrenia, and to have been stable on an antipsychotic drug for a minimum of four weeks. Exclusion criteria for patients included any organic disorder known to cause psychosis or cognitive impairment and alcohol/drug abuse during the last six months. Use of alcohol/drugs was based on the history taken from the patient and his/her family members. Patients were within the first 5 years of diagnosis of schizophrenia. Their mean duration of illness was 2.6 ± 1.5 years. The mean age at illness onset was 21.8 ± 4.9 years. The mean duration of untreated psychosis (DUP) was 7.6 ± 5.8 months. DUP was defined from the time of onset of first positive symptoms to the first hospitalization. Fifteen of our patients had only one psychotic episode, 27 had 2 psychotic episodes, and four had 3 psychotic episodes before the time of testing.

Psychopathology was evaluated using the Positive and Negative Syndrome Scale (PANSS) (Kay, 1991), Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984), and Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983).

Thirty-eight patients were receiving atypical antipsychotics, including amisulpride ($n=2$), aripiprazole ($n=3$), clozapine ($n=5$), quetiapine ($n=2$), olanzapine ($n=11$), risperidone ($n=13$), sertindole ($n=1$), and ziprasidone ($n=1$), and 5 patients were receiving typical antipsychotics, including fluphenazine ($n=3$), sulpiride ($n=1$), and zuclopenthixol ($n=1$). Three patients' data concerning the antipsychotic drug being used, duration of illness, and the scores on clinical scales were missing.

Controls were screened by using the Structured Clinical Interview for DSM-IV-R-Non-Patient Edition (First et al., 1997). All subjects gave written informed consent after procedures had been fully described. The study was approved by the Ethics Committee at Istanbul Medical Faculty, Istanbul, Turkey.

2.2. Continuous performance test

A cued CPT consisting of 8 different capital letters (A, B, C, E, H, M, O or Z) was implemented. Letters were presented sequentially in white against a dark gray background on a computer screen. Subjects were instructed to press the left mouse button with their right index finger whenever the letter A (cue) was followed by the letter Z (target, Go condition, 10%). Subjects must inhibit their prepared response when a letter other than Z followed the letter A (NoGo condition, 10%). Speed and accuracy were emphasized equally. CPT was conducted in seven blocks, each containing 100 stimuli (20% A, 20% Z, 60% the other six letters). The stimulus duration was 200 ms and the interstimulus interval was 1000 ms. Before the experiment, subjects were trained with blocks of 40 trials to ensure correct understanding of the

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