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Neurobiology of Disease

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Neurobiology of Disease 30 (2008) 270–280

White matter anisotropy related to electrophysiology of first episode schizophrenia during NoGo inhibition

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Received 30 October 2007; revised 24 January 2008; accepted 30 January 2008
Available online 23 February 2008

Patients with schizophrenia have reduced execution functions and white matter alterations indicating cerebral disconnectivity. Here we investigated the relationship between white matter integrity and event related potentials (ERP) during a continuous performance test (CPT). Anisotropy values were correlated with the brain electrical P300 microstate duration and P300 latency associated to the NoGo- and the Go-stimuli of the CPT in 11 patients with first episode schizophrenia and 11 matched healthy controls. Both groups showed significant positive correlations of the NoGo-microstate duration with the white matter signal in the superior frontal region, the optic radiation, the posterior cingulate, and the inferolateral fascicle. In addition, patients with first episode schizophrenia had significant correlations with the right radiation and the left genu of the corpus callosum, bilateral geniculate, and the left middle and the superior temporal regions. We interpreted these findings as a sign of functional correlates of extended circuits for the active inhibition of a motor response in the visual CPT as compared to controls.

Keywords: Continuous Performance Test; NoGo; Go; Inhibition; Diffusion tensor imaging; Anisotropy; Gray matter; White matter; Event-related potentials; P300; First episode schizophrenia

Introduction

Schizophrenia has been described as a disorder of disrupted connectivity in the fronto-thalamo-striato-cerebellar circuit (Andreasen et al., 1998). The basis of impaired connectivity may be subtle gray and white matter lesions, as described in the review paper authored by Shenton et al. (2001). Diffusion tensor imaging (DTI) is a relatively new approach to assess tissue structure and provides information about the white matter structure (Catani, 2006, 2007; ffytche and Catani, 2005). DTI measures diffusion of water molecules in three dimensions. Diffusion of water perpendicular to the direction of the axons is restricted by the myelin sheath and the cell membrane such that diffusion will be greater along the length of the axon than perpendicular to the axon. Thus, DTI measures diffusion-driven displacements of molecules during their random path along axonal fibers, expressed as fractional anisotropy (FA) or intervoxel coherence (IC) ranging from 0 (isotropic medium) to 1 (fully anisotropic medium) (Pierpaoli and Basser, 1996).

Previous studies using DTI have shown white matter changes in patients with chronic schizophrenia as compared to healthy controls by measuring FA (Begré and Koenig, 2007; Kanaan et al., 2005; Kubicki et al., 2005, 2007; Manoach et al., 2007) and IC (Hao et al., 2006; Kalus et al., 2005a,b; Szeszko et al., 2005). One study investigating differences in IC values of patients with first episode schizophrenia and matched healthy controls reported 3 significant clusters with higher IC values for the patient group and 11 significant clusters with lower IC values for the patient group (Federspiel et al., 2006). Only one study reported augmented FA in circumscribed tracts of the brain in patients with chronic schizophrenia with hallucinations as compared with FA in healthy control groups (Hubl et al., 2004), whereas two studies found no differences (Begré et al., 2003; Price et al., 2005).

Patients with schizophrenia appear to have abnormalities in both brain structures and information processing compared to healthy controls. In fact, diminished performance and enlarged error rates in patients with chronic schizophrenia (Cornblatt and Keilp, 1994), and in patients with first episode schizophrenia (Keefe et al., 2006; Mohr et al., 2003) are consistently present during the Continuous Performance Test (CPT). During CPT, with visual Go–NoGo-task the P300 latency of the event related potential (ERP) was prolonged after the inhibitory NoGo-stimulus in patients with first episode schizophrenia (Kleinlogel et al., 2007). Additionally, the duration of the NoGo-P300 was increased and its amplitude was decreased. These features were interpreted as

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Available online on ScienceDirect (www.sciencedirect.com).

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doi:10.1016/j.nbd.2008.01.013

consequences of a partially debilitated prefrontal cortex in these patients. The P300 duration of Go- and NoGo-stimuli are supposed to give insight into the duration of mental processes involving the prefrontal cortex (Brandeis and Lehmann, 1989; Michel and Lehmann, 1993; Pascual-Marqui et al., 1995). Electroencephalographic (EEG) parameters in patients with first episode schizophrenia may deviate from those in healthy subjects not only during CPT but also at rest, indicating increased neuronal activity in left and frontal brain regions (Lehmann et al., 2005).

Magnetic resonance imaging (MRI) with high spatial resolution combined with EEG with high temporal resolution can join both advantages of structural and functional investigations. Studies using both MRI and ERP in patients with schizophrenia are rare. To our knowledge only five studies used this issue in parallel investigating patients with chronic schizophrenia (Egan et al., 1994; Ford et al., 2004; Gilmore et al., 2005; Johnston et al., 2005; Salgado-Pineda et al., 2003), and there is only one study using a Go/NoGo paradigm performed with patients with first episode schizophrenia in a combined structural (gray matter) and functional issue (Salgado-Pineda et al., 2004). However, there is no study focusing on putative correlations between the white matter structure and the task related ERP parameters evoked by the CPT in first episode schizophrenia.

The aim of this study was to investigate the relationship of executive function during the performance of a cognitive task and white matter connectivity in patients with first episode schizophrenia compared to healthy controls. We hypothesised an association for both groups between white matter connectivity measured by intervoxel coherence during diffusion tensor imaging and four ERP parameters measured during continuous performance test, such as the P300 microstate duration during NoGo and Go, and NoGo and Go latency to the P300 Peak (we use the following shortcuts hereafter: NoGo duration, Go duration, NoGo latency, Go latency). A correlation between fractional anisotropy and choice reaction time was recently investigated in healthy controls (Tuch et al., 2005). The authors suggested according to the "myelinisation hypothesis" that increased myelination would result in faster (or less variable) nerve conduction velocity, which would result in faster reaction time. Accordingly, the following four hypotheses were formulated: i) We expect a positive correlation between the IC values and the NoGo duration in patients and in healthy controls; ii) a negative correlation in patients and in healthy controls between the IC values and the NoGo latency; iii) a positive correlation in patients and in healthy controls between the IC values and the Go duration; and iv) a negative correlation of the Go latency with the IC values in patients and in healthy controls.

Materials and methods

Subjects

Eleven patients hospitalized with their first episode of schizophrenia, diagnosed according to ICD-10 diagnosis criteria (Bramer, 1988), were matched by gender and age (±6 months) with eleven healthy volunteers. Subjects were all right-handed. Patients with schizophrenia were recruited from the first episode ward of the University Hospital of Psychiatry in Bern; the control group consisted of normal volunteers from the region. Patients and their relatives were questioned about the development of psychotic symptoms, substance abuse, and any other psychiatric or medical conditions. All patients had at least first-rank symptoms, but one lacked auditory hallucinations. Three patients, including the one without auditory hallucinations, reported sporadic cannabis use. Four patients were not medicated. Table 1 contains a summary of the subject's characteristics. None of the healthy controls had a history of major medical or neurological disorders, substance abuse, or other psychiatric diseases, or received psychotropic medication before hospitalization. All patients and all healthy controls gave written informed consent, and the study was approved by the local ethics committee. For measurements in the MRI scanner, subjects received no specific instructions other than to relax and keep their head still. The use of restraining foam pads minimized head motion.

Continuous performance test

The investigation took place in an electrically shielded, sound attenuated and dimly lit room. The subjects were seated on a chair about 1 m in front of a computer screen.

The applied CPT-version was described earlier (Strik et al., 1998). It was a modified form of the classical cued CPT (Rosvold and Delgado, 1956; van Leeuwen et al., 1998) consisting of 12 different letters that were presented sequentially in random order on the computer screen. Each letter was presented for 200 ms in the center of the screen with an inter trial interval of 1450 ms. A sequence of two identical letters was avoided. The letters on the screen were 10 mm high. The letter O (cue) was presented as a signal to prepare a motor response (primer condition). Subjects were instructed to press a button with the index finger of their right hand as fast as possible, whenever the cue-letter O was followed by the target letter X (Go-stimulus). The reaction time was measured starting at the beginning of the presentation of X. It was also determined when a subject didn't press the button (omission). The other letters A–H, J, L thus required response inhibition if they immediately followed an O (NoGo-stimulus) and served as meaningless distractors if not preceded by an O. When a subject pressed the button after the NoGo-stimulus, this was counted as commission error. Every subject performed a short training session to ensure correct performance of the task. During the session 40 Go-pairs, 40 NoGo-pairs and 240 distractors, totally 400 letters, were presented, resulting in a recording time of 11 min.

EEG recording

Simultaneously with the CPT, the EEG was recorded with 21 electrodes placed according to the international 10-20-system. The

Table 1
Summary of subject's characteristics

	Patients	Controls
Sample size	11	11
Age, mean±SD, (years)[a]	25.2±5.5	23.4±3.3
Range	18.0–35.7	17.5–28.5
Sex	7 men; 4 women	7 men; 4 women
Duration of illness±SD, (days)	111.3±91.5	–
Range	14–270	
Medication	3 RIS, 1 OLA, 1 QUE, 1 HAL; 1 HAL+AMS	–
Duration on medication±SD, (days)	16.4±9.4	–
Range	4–35	

RIS = risperidone; OLA = olanzapine; QUE = quetiapine; HAL = haloperidol; AMS = amisulpride.

[a] Not significant as determined by Student *t*-test.