Clinical Neurophysiology 118 (2007) 1449–1459

www.elsevier.com/locate/clinph

Impaired rapid modulation of cerebral hemodynamics during a planning task in schizophrenia

Daniel Schuepbach *, Silvan Weber, Wolfram Kawohl, Daniel Hell

Psychiatric University Hospital Zürich, Lenggstrasse 31, P.O. Box 1931, 8032 Zürich, Switzerland

Accepted 8 March 2007
Available online 23 April 2007

Abstract

Objective: Patients with schizophrenia show deficits in planning, and the Stockings of Cambridge (SOC) is a task that assesses planning performance. This study was undertaken to investigate rapid changes of cerebral hemodynamics during separate phases of SOC in schizophrenia and normals by means of functional transcranial Doppler sonography (fTCD).
Methods: We included 21 patients with chronic schizophrenia and a control group of 20 healthy subjects in the study. They underwent fTCD of the middle (MCA) and anterior cerebral arteries (ACA) during performance of SOC.
Results: The main finding was that healthy subjects significantly modulated the early cerebral hemodynamic response along distinct conditions of SOC, whereas we observed no significant differences in patients. Normally, there was an up-regulation of cerebral hemodynamics during mental planning, and about zero values were observed during movement execution. Patients showed lower development of the early cerebral hemodynamic response during planning of SOC.
Conclusions: The findings of this study suggest a uniform pattern of cerebral hemodynamic regulation during a planning task in schizophrenia, whereas healthy subjects modulated such a response along a planning-movement execution sequence.
Significance: We provide novel evidence that modulation of cerebral hemodynamics is compromised in schizophrenia, and that fTCD constitutes a proper method to measure these alterations.

Keywords: Cerebral blood flow velocity; Frontal lobe; fTCD; Schizophrenia; Stockings of Cambridge

1. Introduction

Planning plays an important role in every day life, and one measure to assess planning capability is the Tower of London paradigm (TOL; Shallice, 1988), or a modern computerized equivalent, the Stockings of Cambridge (Owen et al., 1990). Performance of patients with schizophrenia during these tasks has been shown to be impaired on some measures, such as a prolonged time to execute a plan or more moves required to solve problems (Morris et al., 1995). The SOC has several advantageous features, such as separation of mental planning and movement execution, and it also offers the possibility to modulate problem difficulty. Available neuroimaging literature on TOL suggests an involvement of the prefrontal, parietal and temporal cortex, including also the cingulate cortex and subcortical areas (Dagher et al., 1999; Rowe et al., 2001). There are very few TOL neuroimaging studies in schizophrenia (Andreasen et al., 1992; Rasser et al., 2005), and some frontal dysfunction has been suggested. Conflicting results have arisen in recent years concerning the concept of so-called "hypofrontality" in schizophrenia (Weinberger et al., 1986; Andreasen et al., 1992), referring to the lower brain perfusion in prefrontal regions during executive tasks. Barch (2005) suggested hypo- or hyperfrontality in schizophrenia to be dynamic, depending, among other factors, on task load. Interestingly, no (neuroimaging) TOL study in schizophrenia has reported on the time course of cerebral hemodynamics during separate conditions of the task.

* Corresponding author. Tel.: +41 44 384 21 11; fax: +41 44 383 44 56.
E-mail address: daniel.schuepbach@puk.zh.ch (D. Schuepbach).

1388-2457/$32.00
doi:10.1016/j.clinph.2007.03.001

Such studies would be necessary to visualize the impact of separate cognitive (executive) conditions on brain perfusion. Most surprisingly, no study to date has provided kinetic data such as the steepness of the increasing slope (S_{inc}; Panczel et al., 1999) during separate conditions of a planning paradigm, leaving it open whether there is simply an up-regulation regardless of cognitive condition, or whether regulation is condition-dependent. These questions are relevant, because there is evidence that executive functions are complex cognitive processes that connect and control the flow of information between cognitive subsystems, monitoring perceptual inputs and coordinating goal-oriented activity (Shallice, 1988; Baddeley, 1992). Hence, a favorable strategy could be to separate a complex task such as planning into conditions of planning and execution of a plan. Most neuroimaging reports on TOL used a forced choice paradigm, i.e. subjects had to solve problems by indicating only the number of necessary moves (Rasser et al., 2005), leaving it open whether the correct solution was achieved by proper planning and execution, or simply by guessing.

Functional transcranial Doppler sonography (fTCD) of basal cerebral arteries has been successfully used to measure peak mean cerebral blood flow velocity (MFV) during planning tasks such as the Tower of Hanoi or the SOC in healthy subjects and patients with schizophrenia (Schuepbach et al., 2002a,b; Frauenfelder et al., 2004; Feldmann et al., 2006). One advantage of fTCD consists in the high temporal resolution, allowing pinpointing instant MFV changes (for review, see Stroobant and Vingerhoets, 2000; Duschek and Schandry, 2003), whereas the spatial resolution of this technique is restricted to the arterial territories. In this context it is of relevance to note that the arterial supply of the middle cerebral artery (MCA) comprises the lateral hemisphere of the frontal and parietal lobes whereas the territory of the anterior cerebral artery (ACA) involves the medial part of the hemisphere including the frontal pole and the cingulate gyrus (Tatu et al., 1998). There is evidence that relative MFV is significantly associated with cerebral blood flow (CBF) (Bishop et al., 1986; Dahl et al., 1992) and also with results of functional magnetic resonance imaging (fMRI) (Schmidt et al., 1999).

In this report, we wanted to implement the (temporal) pinpointing capability of fTCD during the SOC in schizophrenia. To the best of our knowledge, no neuroimaging study to date has investigated modulation of cerebral hemodynamics during TOL/SOC in normals or in patients with schizophrenia. The characterization of rapid cerebral hemodynamic response development during separate phases of a planning task is interesting. It does not only allow to study differences of brain behavior relationship between patients with schizophrenia and healthy subjects (i.e. between diagnostic groups), but may also shed light on rapid MFV changes occurring during a planning-movement execution- (control) sequence (i.e. within diagnostic groups). Experimental work by Klingelhöfer et al. (1992) demonstrated that MFV changes due to stimulation started to happen in less than 1 s in basal cerebral arteries. Therefore, we focused on the time interval of the initial 2 s during planning, movement execution and contro l of SOC. Such short time intervals have also, in the context of SOC, the advantage that imputation of missing values is reduced to a minimum (Feldmann et al., 2006).

In order to expand previous results on cerebral hemodynamics during SOC, this study addressed the following unanswered issues: (1) What is the MFV time course during planning, movement execution and control in patients with chronic schizophrenia and healthy subjects? (2) Is S_{inc} during planning, movement execution and control lower in patients with chronic schizophrenia than in healthy subjects? (3) Do patterns of S_{inc} differ across conditions within diagnostic groups?

2. Methods

2.1. Subjects

We included 21 right-handed patients with a chronic schizophrenia according to DSM-IV criteria in this study. Sociodemographic and clinical data are presented in Table 1. This sample slightly differs from the one used in the Feldmann et al. (2006) study: in order to improve the gender ratio between diagnostic groups, one more female patient was added and two male patients were removed from the latter. However, as compared to the original sample (Feldmann et al., 2006), these changes showed no major effect on presented MFV results and conclusions of this study. All were inpatients and under stable antipsychotic medication (amisulpride, clozapine, flupentixol, olanzapine, quetiapine, promazine, risperidone, zuclopenthixol). One patient was on antidepressive therapy (paroxetine). Concomitant medication consisted of biperiden hydrochloride. The following exclusion criteria applied: (1) affective or organic brain disorders, (2) substance abuse for the last 3 months prior to the examination or a lifetime diagnosis of substance dependence, including a positive urine test for psychotropic substances, (3) mental retardation, and (4) migraine and other headaches. Within 24 h of fTCD measurements, patients were clinically assessed by means of the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) and the Clinical Global Impression Scale (CGI) (Bech and Ahlfors, 1993). Secondary effects of antipsychotics on the extrapyramidal system were examined with the Extrapyramidal Symptom Scale (EPS) (Simpson and Angus, 1970) and the Barnes Akathisia Scale (BAS) (Barnes, 1989). Twenty right-handed healthy volunteers were included with sociodemographic features similar to the patients, and with known SOC performance and brain perfusion characteristics (Frauenfelder et al., 2004). Subjects were not allowed to consume caffeine or nicotine 2 h prior to the fTCD examination, and they were not familiar with the contents of the study. They denied any recent traumatic burden and gave their written informed consent. The local Ethic committee approved the study.