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Prefrontal hyperactivation during a working memory task in early-onset schizophrenia spectrum disorders: An fMRI study

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ABSTRACT

Working memory (WM) dysfunction is increasingly recognized as a core feature of schizophrenia, but few studies have investigated prefrontal activation during WM tasks in early-onset schizophrenia spectrum disorder (EOS). Our aim was to explore prefrontal activation during a WM-task in EOS patients compared to healthy controls using functional magnetic resonance imaging (fMRI). Fifteen patients with EOS and 15 matched healthy controls performed a 0-back and a 2-back task while fMRI data were acquired. Results indicated that even though performance between patients and controls was comparable on both tasks, there was a hyperactivation in patients' ventrolateral prefrontal cortex (VLPFC) during the 2-back task compared to healthy controls. This pattern of activation suggests that, in patients with EOS, the VLPFC compensated in order to match performance of the controls. The activations in the EOS group may reflect the use of a compensatory, cognitive strategy while solving WM-tasks.

1. Introduction

There is a need to investigate patients with early onset schizophrenia (EOS; onset of psychotic symptoms before age 18), because most schizophrenia research focuses on patients with adult onset (AOS). Patients with EOS may provide valuable evidence towards understanding the pathogenic mechanisms and the phenotypic patterns of the disease, as they have less exposure to relevant and possibly confounding life events and to medication. In addition, studies on EOS may potentially provide knowledge about why EOS patients have a poorer prognosis than AOS patients. Although the prevalence of schizophrenia before the age of 13 is very low (approximately 1/100 schizophrenia cases) (Beitchman, 1985), the incidence of schizophrenia rises significantly towards the age of 18 (approximately 12–33/100 schizophrenia cases) (Krausz and Mullerthomsen, 1993; Hafner and Nowotny, 1995).

A large body of research has confirmed that patients with schizophrenia show deficits across a broad range of neuropsychological domains (Heinrichs and Zakzanis, 1998; Rund, 1998; Mesholam-Gately et al., 2009). Working memory (WM) is one of the most affected cognitive domains both in AOS (Honey and Fletcher, 2006) and EOS (Oie and Rund, 1999; Holmen et al., 2009). Several neuroimaging studies have revealed inadequate prefrontal activations in AOS during WM-tasks (e.g. Hugdahl et al., 2004; Glahn et al., 2005). A further investigation of EOS patients' brain activation during a WM task is important in revealing possible differences from AOS patients.

WM is essential for adequate adaptation to the ever changing environment, and is a cognitive function which reflects an individual's ability to maintain and utilize information in short-term memory (Baddeley and Hitch, 1974). Through neuroimaging studies in healthy humans, WM has primarily been associated with activation in the prefrontal cortex (PFC) and parietal cortex (Wager and Smith, 2003). However, findings of robust activations related to WM in the lateral premotor cortex and in the dorsal anterior cingulate reveal a highly complex network of activations during WM tasks (Owen et al., 2005). Concerning the PFC, several studies have indicated that the

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dorsolateral prefrontal cortex (DLPFC) is involved in manipulative functions in WM, while the ventrolateral prefrontal cortex (VLPFC) is related to processes of encoding, maintenance and inhibition (Tan et al., 2005). The dynamics of PFC activation during WM tasks is further complicated by the finding that activations are load dependent and better performance has been accompanied by both hypo- and hyper-activations (Callicott et al., 2003a; Johnson et al., 2006). It has been suggested that an inverted U-shape function reflects the relationship between performance and PFC activation (Callicott et al., 2003b; Karlsgodt et al., 2009); activation increases until cognitive load goes beyond working memory capacity, and then decreases as load increases.

To measure WM, Baddeley (1984) suggested using n-back tasks or similar tasks requiring maintenance, manipulation, monitoring and updating of information. The n-back is a task that presents stimulus sequences, such as letters or pictures. For each item in the sequence, people are asked to determine if the present stimulus matches the one presented n items ago. Imaging studies have suggested that when a task either gets too complex or the load on the WM system exceeds the level a person is able to process, the prefrontal system will break down, and compensatory functioning will be activated (Hugdahl et al., 2004).

Previous studies using 2-back tasks to investigate WM have found both hypo- (Barch et al., 2001; Perlstein et al., 2003) and hyper- (Callicott et al., 2000; Thermenos et al., 2005) activation in the PFC of patients with AOS compared to healthy controls, and some studies have also reported no difference of activation between the groups (Honey et al., 2002). Most of the studies have reported hyper-/hypo-activation in the DLPFC; however, the peak voxels in some of these studies are located in the VLPFC (e.g. Callicott et al., 2003a; Brahmbhatt et al., 2006). These diverse findings could reflect complex matters of human development in general and also developmental patterns of schizophrenia. One recent multicenter study (Schneider et al., 2007) reported VLPFC hyper-activation during a 2-back task in a first-episode schizophrenia sample. They argued that while retrieval, storage and maintenance processes seemed to be affected, executive manipulatory processes mediated by the DLPFC are spared.

An investigation of compensatory PFC functioning for WM tasks, as suggested for AOS, is important to reveal possible unique patterns in EOS. Bearing in mind the complex and diverse findings from AOS, the aim of our study was to investigate VLPFC and DLPFC hyper-activations in EOS patients compared with healthy controls during a 2-back task, and also to compare these activations with results from previous studies on AOS.

2. Methods

2.1. Participants

Individuals in the clinical sample were recruited from different psychiatric departments in the southern part of Norway. The inclusion criteria were as follows: age between 12 and 18 years, meeting the DSM-IV diagnostic criteria for a broad psychosis-spectrum disorder (schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic disorder and psychosis not otherwise specified [NOS]). All patients were interviewed by clinical psychologists who also had access to medical records and information from treating clinicians and family members.

Potential participants were excluded if they had a history of head injury or central nervous system pathology (loss of consciousness for greater than 30 min and/or any neurological sequelae) or had an estimated IQ less than 70. IQ was estimated for both groups using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 2007), using Norwegian norms. A total of 31 adolescents with psychosis were included in the larger study (Holmen et al., 2009). For the present fMRI analysis, 15 patients were included: 8 (53%) with a schizophrenic disorder, 5 (33%) with psychosis [NOS] (4 converted to schizophrenia when looking at outcome), 1 (7%) with schizoaffective disorder and 1 (7%) with schizophreniform disorder (converted to schizophrenia when looking at outcome). The demographics are displayed in Table 1. Psychopathological ratings on the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) revealed slightly more positive (13.5 ± 3.4) than negative (11.9 ± 4.5) symptoms and moderate general psychopathology (29.7 ± 6.1). The mean Global Assessment of Function (GAF; Pedersen et al., 2007) scale (split DSM-IV version) score was 47.2 ± 15.1 for global functions and 48.4 ± 12.4 for global symptoms. The mean duration of untreated psychosis (DUP) was 33.33 ± 52.1 weeks, and 11 patients (57.9%) had one psychotic episode, one patient (5.3%) had two psychotic episodes, two patients (10.5%) had three psychotic episodes and one patient (5.3%) had four psychotic episodes. The exclusion of 16 patients from the fMRI analysis was due to: not wanting to participate in the fMRI scanning (5), orthodontics (2) and head movement and other noise artefacts in the fMRI data (9).

Healthy comparison participants were recruited from schools in the patient catchment areas. Fifteen healthy participants were matched to patients on gender, age and length of mother's and father's education, and all were included for fMRI analysis. They were also screened for potential psychiatric disorders using the Mini-International Neuropsychiatric Interview screening module (Sheehan et al., 1998).

A complete description of the study was provided to the participants before written, informed consent was obtained from both the participants and their parents, if the participants were below 16 years of age. The study is also approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

2.2. Apparatus

Stimuli were presented to the participants using E-prime software (Psychology Software Tools, Inc; Pittsburgh, PA) in video goggles (VisualSystem; NordicNeuroLab, Bergen, Norway). The participants responded by pushing a response button (ResponseGrip; NordicNeuroLab, Bergen, Norway) and the number of correct answers was recorded.

2.3. Task paradigm

The experiment consisted of two types of tasks, a 0-back and a 2-back, presented in a block design, with each task having four ON and four OFF blocks in separate sessions. Each ON block (task) lasted for 52 s and each OFFblock (rest) lasted for 26 s. Numbers between 1 and 9 were used as stimuli and presented in pairs. There were three pseudo randomized targets in each block i.e. 12 targets in total during the sessions. During the OFF blocks, the screen was black with a fixation cross in the centre. Each stimulus was presented for 300 ms with a 2500 ms inter-trial interval (ITI). The screen remained blank through the ITI.

In the 0-back (control condition) session, the participants were asked to respond each time the pair of numbers shown on the screen were identical. In the 2-back (WM condition) session, the participants were presented pairs of identical numbers on every trial, and were instructed to push the response button when the pair of number was

Table 1
Characteristics of patients with schizophrenia compared to healthy control subjects[a].

	Patients	Healthy controls	Test statistics
Sex (female)	8 (53%)	8 (53%)	$p = 0.72$
Right handed	14 (93%)	14 (93%)	$p = 1.00$
Age	16.2 (1.3)	15.9 (1.6)	$p = 0.31$
Mother's education	14.1 (2.9)	15.9 (2.4)	$p = 0.13$
Father's education	14.1 (2.8)	14.2 (3.0)	$p = 0.96$.
FSIQ (WASI)	97.7 (16)	109 (13)	$p = 0.04$
Medication naïve	*5 (33%)*	15 (100%)	

[a] Mean (Standard Deviation) or number (percent) is presented.