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Reduced size of the pre-supplementary motor cortex and impaired motor sequence learning in first-episode schizophrenia

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Abstract

Increasing evidence suggests that schizophrenia is associated with various morphological and functional abnormalities of the frontal cortex. So far research has concentrated on the dorsolateral and orbitofrontal cortex. Behavioral evidence suggests however that regions responsible for higher motor control are compromised in schizophrenia as well. The current study assessed volumes of the anterior supplementary motor area (pre-SMA) and implicit motor sequence learning in 15 subjects with first-episode schizophrenia and 15 healthy matched controls. Pre-SMA volumes were assessed by three-dimensional structural magnetic resonance imaging (3D-MRI) and manual parcellation according to an established protocol. Implicit motor sequence learning was assessed using the Serial Reaction-Time Task (SRTT). Compared with control subjects, schizophrenia subjects had significantly smaller volumes of the left pre-SMA (16%). Subjects with schizophrenia were severely impaired on sequence-specific implicit motor learning. Size of the left pre-SMA of schizophrenia subjects was significantly related to impaired implicit learning. We conclude that subjects with first-episode schizophrenia have a morphological abnormality of the left pre-SMA that might predispose them to develop disturbances of higher motor control during acute episodes of psychosis. These structural and behavioral abnormalities might be conceptualized within a broader model that views schizophrenia as a disorder of disturbed coordination of thought and action.

Keywords: 3D-MRI; Pre-SMA; Procedural learning; Serial Reaction-Time Task

1. Introduction

The heterogeneity of behavioral and neurobiological abnormalities in schizophrenia has puzzled scientists and clinicians for decades. Andreasen (1999) has proposed a unitary model of schizophrenia whereby a fundamental cognitive deficit, termed "cognitive dysmetria" is assumed that underlies the

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diverse symptoms of schizophrenia and reflects a disorder in the cortico-cerebellar-thalamic-cortical circuit.

One crucial element within this target neural network is the supplementary motor area (SMA). The SMA is part of a functionally and anatomically segregated loop that funnels signals from distributed cortical motor areas via striatal and thalamic projections back to the SMA and thereby executes motor control (Alexander et al., 1986). There is now a consensus that the SMA may be divided into two cytoarchitectonically and functionally different areas (Picard and Strick, 1996; Rizzolatti et al., 1996). The anterior part of the SMA (pre-SMA) is known to interconnect with the prefrontal cortex and to play a role in the more complex, planning and decision components of movements whereas the caudal part (SMA-proper) is related to movement execution and projects to the primary motor cortex and spinal neurons (Luppino et al., 1993).

In schizophrenia evidence is still missing whether the SMA is affected by structural aberrations. There is, however, behavioral evidence for a disturbed functional integrity of the SMA in schizophrenia: schizophrenia subjects show reduced activation of the area during motor and mental tasks which elicit SMA activity in normal samples (Guenther et al., 1995; Schroeder et al., 1995; Crespo-Facorro et al., 1999b; Ortuño et al., 2004; Rogowska et al., 2004; Honey et al., 2005). The readiness potential (Bereitschaftspotential) during motor tasks which is thought to arise from the SMA, is reduced in schizophrenia subjects (Dreher et al., 1999). Disturbed performance of schizophrenia subjects has also been found on a number of tasks supposed to depend on the integrity of the SMA, like bimanual coordination (Bellgrove et al., 2001), saccardic eye movements (Karoumi et al., 1998), response inhibition (Bellgrove et al., 2005) and implicit motor sequence learning (Exner et al., in press; Green et al., 1997; Kumari et al., 2002; Schwartz et al., 2003). The latter task has repeatedly been shown to recruit primarily the SMA within a network of cortical, subcortical and cerebellar structures (Jenkins et al., 1994; Grafton et al., 1995; Hikosaka et al., 1996; Hazeltine et al., 1997; Sakai et al., 1998; Grafton et al., 2002). In an earlier study of our group subjects with combined basal ganglia and frontal lesions had disrupted implicit learning performance which was significantly related to pre-SMA volume (Exner et al., 2002).

In the present study pre-SMA volumes and implicit learning performance were studied in 15 subjects with first-episode schizophrenia and 15 matched healthy controls. The goals of our study were: 1) to investigate whether volume of the pre-SMA is reduced in schizophrenia, 2) to analyze whether implicit learning deficits of schizophrenia subjects (Exner et al., in press) are related to reduced size of the pre-SMAs of schizophrenia subjects.

2. Methods

2.1. Subjects

2.1.1. Subjects with schizophrenia

The sample comprised 15 inpatients with first-episode schizophrenia consecutively admitted to the Psychiatric Hospital of the University of Goettingen. Subjects fully met the criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*) (American Psychiatric Association, 1994) for a lifetime diagnosis of schizophrenia on the basis of interviews with the *Structured Clinical Interview for DSM-IV* (*SCID*) (Wittchen et al., 1997). Subjects with a history of head injury, neurological diseases or substance dependence or abuse (SCID) were excluded. All subjects were on antipsychotic medication (Table 1). Medication dose at testing was converted to chlorpromazine equivalents according to Bezchlibnyk-Butler and Jeffries (2001). One subject received anticholinergics and 7 subjects benzodiazepines in addition to their antipsychotic medication.

2.1.2. Healthy controls

Subjects with schizophrenia were compared with 15 healthy control subjects matched for age, sex and years of education (Table 1). Only subjects without a history of neurological or psychiatric disorder (as assessed by the *SCID*) were studied. Control subjects were paid for their participation.

After complete description of the study to the subjects informed written consent was obtained. The Ethical Committee of the Medical Faculty of the University of Goettingen had approved of the study design.