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Neurological soft signs in recent-onset schizophrenia: Focus on the cerebellum

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ABSTRACT

Background: Previous structural neuroimaging studies linked cerebellar deficits to neurological soft signs (NSS) in schizophrenia. However, no studies employed a methodology specifically designed to assess cerebellar morphology. In this study, we evaluated the relationship between NSS levels and abnormalities of the human cerebellum in patients with recent-onset schizophrenia and healthy individuals using an exclusive cerebellar atlas.
Methods: A group of 26 patients with recent-onset schizophrenia and 26 healthy controls were included. All participants underwent a high-resolution T1-weighted MRI scan on a 3 Tesla scanner. We used a voxel-based morphometry (VBM) approach utilizing the Spatially Unbiased Infratentorial (SUIT) toolbox to provide an optimized and fine-grained exploration of cerebellar structural alterations associated with NSS.
Results: Compared with healthy controls, patients had significantly smaller cerebellar volumes for both hemispheres. In the patients' group, we identified a significant negative correlation between NSS levels and gray matter volume in the left lobule VI and the right lobule VIIa, corrected for multiple comparisons. Further, NSS performance was significantly associated with white matter volume in the left midbrain and corpus medullare and the right lobule VIIa. In contrast, no significant associations between NSS scores and cerebellar subregions in healthy subjects arose.
Conclusion: Our results demonstrate the benefits of SUIT when investigating cerebellar correlates of NSS. These results support the view that distinct parts of *sensorimotor* and *cognitive cerebellum* play an important role in the pathogenesis of NSS in schizophrenia.

1. Introduction

Minor motor and sensory deficits or neurological soft signs (NSS) are frequently found in patients with schizophrenia at any stage of their illness (Schroder et al., 1991; Thomann et al., 2009a; Hirjak et al., 2012; Thomann et al., 2014). According to recent evidence, NSS might represent a trait feature of schizophrenia (Bombin et al., 2005). Over the past two decades, neuroimaging studies of NSS in schizophrenia have revealed structural and functional alterations in cortical and subcortical brain areas (see meta-analysis for detail Zhao et al., 2013). These findings strongly support the hypothesis that NSS may be related to a disrupted cortico-cerebellar-thalamo-cortical circuit as conceptualized in the model of "cognitive dysmetria" (Andreasen et al., 1998).

The cerebellum is crucial for motor function, control of muscle tone and balance. Furthermore, the cerebellum is also interconnected with cerebral networks involved in cognition (Ramnani, 2006; Buckner, 2013; Koziol et al., 2014). When compared to healthy controls, patients with schizophrenia have shown reduced cerebellar volumes (Andreasen and Pierson, 2008). Yet to date, only few structural MRI (sMRI) studies have examined the relationship between NSS and cerebellar morphology (Bersani et al., 2007; Bottmer et al., 2005; Keshavan et al., 2003; Mouchet-Mages et al., 2007; Thomann et al., 2009a), yielding inconsistent findings. This inconsistency might at least in part be attributable to methodological aspects like image analysis procedures. In particular, the complex and convoluted morphology of the cerebellum including thinner striations of gray and white matter is a methodological challenge to ordinary region-of-interest (ROI)-based or whole-brain approaches (Kuhn et al., 2012a). Although there is some evidence suggesting an involvement of the cerebellum in the generation of NSS in schizophrenia, at present the question of if and how the cerebellar cortex and white matter contribute to the pathophysiology of NSS has not yet been addressed in a comprehensive way.

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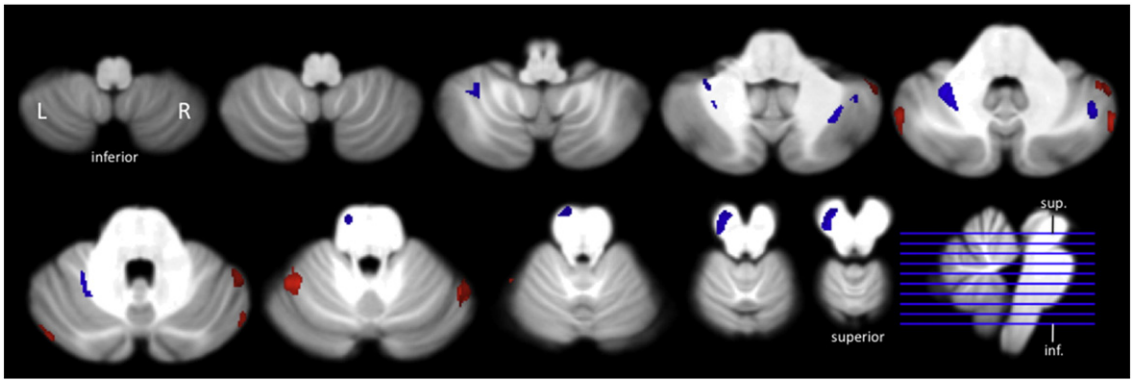

Fig. 1. Statistical maps displaying corrected clusters (FWE; red = grey matter, blue = white matter) of significant associations between NSS scores and cerebellar morphology.

In the current study, we intended to better understand the relationship between cerebellar morphology and NSS in schizophrenia. In contrast to previous NSS studies on cerebellum, the present study has been extended by means of a novel method specifically designed to assess cerebellar morphology. We used the Spatially Unbiased Infratentorial (SUIT) toolbox (http://www.icn.ucl.ac.uk/motorcontrol/imaging/suit.htm) with a new template (Diedrichsen, 2006), which has less spatial variance across individuals and preserves anatomical detail of cerebellar subregions (three lobes and lobules I-X) using automated nonlinear normalization methods, thus achieving a more accurate intersubject-alignment compared to whole-brain methods. Previous sMRI studies in patients with neuropsychiatric diseases successfully used SUIT to identify morphological changes in cerebellar subregions (Diedrichsen 2006; Kuhn et al., 2011; Wolf et al., 2015; D'Agata et al., 2011). Moreover, these studies showed that SUIT is more sensitive to cerebellar changes compared to voxel-based morphometry (VBM) approaches.

This study had two goals: first, to assess structural cerebellar differences between patients with recent-onset schizophrenia and healthy controls and second, to examine the cerebellar phenotype underlying NSS total scores and NSS scores on the five subscales in both groups. We believe this to be important since some of the previous MRI studies on NSS in schizophrenia were only related to distinct motor domains (Baudendistel et al., 1995; Schroder et al., 1995, 1999). We predicted that schizophrenia patients would show higher NSS scores when compared to healthy controls. Drawing on scientific evidence linking cerebellar structure to NSS in schizophrenia, we further predicted that schizophrenia patients would exhibit reduced cerebellar volumes and that higher NSS levels would be tied to structural abnormalities in both anterior and posterior subregions of the cerebellum in this group.

2. Methods

2.1. Subjects

Twenty-six subjects with first-episode schizophrenia and twenty-six healthy controls matched for age, gender, ethnicity, and handedness were enrolled. Patients were consecutively admitted to the inpatient unit of the Department of Psychiatry, University of Heidelberg, and diagnosed as suffering from recent-onset schizophrenia according to ICD-10 and DSM-IV criteria. The patient group consisted of 7 women and 19 men, all Caucasians with a mean age of 23.38 years (SD = 3.87) and a mean of 12.07 (SD = 1.32) years of education. All patients had an initial onset of psychosis within two years prior to study entry. The mean duration of illness was 7.1 ± 2.77 months (range 2 to 15 months). Patients were treated with an atypical antipsychotic according to their psychiatrists' choice (mean dose of 435.11 ± 240.41 mg chlorpromazine equivalents (CPZ) (Woods, 2003)). The mean duration of total neuroleptic treatment was 2.33 ± 2.94 months (range 0.25 to 15 months). None of the participants had a lifetime history of neurological or medical illness, head injury, severe substance abuse or lifetime substance dependence according to ICD-10 or DSM-IV criteria. Twenty-six healthy controls were recruited through advertisements and screened for major psychiatric disorders before being included. Clinical evaluation included ascertainment of personal and family history and detailed physical and neurological examination. None of the participants

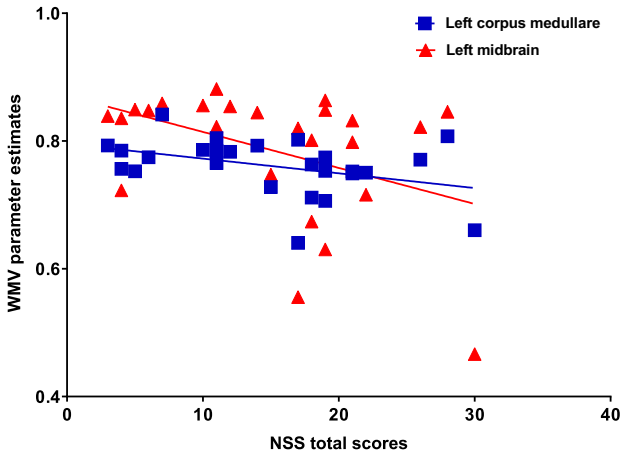

Fig. 2. Scatter plot of voxel-wise regression analysis of NSS total scores and local white matter volume (WMV) parameter estimates in schizophrenia.

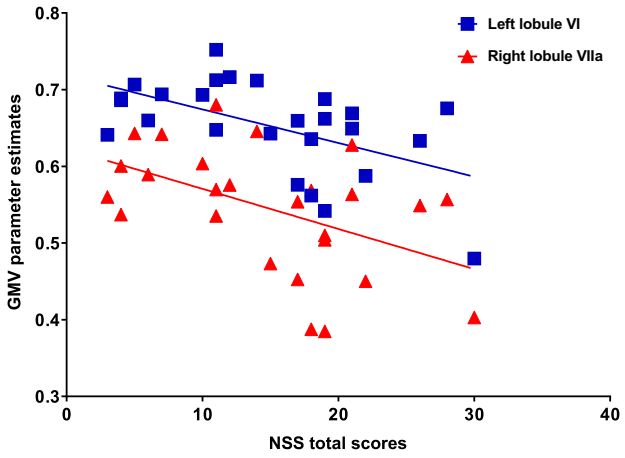

Fig. 3. Scatter plot of voxel-wise regression analysis of NSS total scores and local gray matter volume (GMV) parameter estimates in schizophrenia.