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Abnormal cerebellar volume in acute and remitted major depression

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ABSTRACT

Abnormal cortical volume is well-documented in patients with major depressive disorder (MDD), but cerebellar findings have been heterogeneous. It is unclear whether abnormal cerebellar structure relates to disease state or medication. In this study, using structural MRI, we investigated cerebellar volume in clinically acute (with and without psychotropic treatment) and remitted MDD patients. High-resolution structural MRI data at 3 T were obtained from acute medicated (n = 29), acute unmedicated (n = 14) and remitted patients (n = 16). Data from 29 healthy controls were used for comparison purposes. Cerebellar volume was investigated using cerebellum-optimized voxel-based analysis methods. Patients with an acute MDD episode showed increased volume of left cerebellar area IX, and this was true for both medicated and unmedicated individuals ($p < 0.05$ cluster-corrected). Remitted patients exhibited bilaterally increased area IX volume. In remitted, but not in acutely ill patients, area IX volume was significantly associated with measures of depression severity, as assessed by the Hamilton Depression Rating Scale (HAMD). In addition, area IX volume in remitted patients was significantly related to the duration of antidepressant treatment. In acutely ill patients, no significant relationships were established using clinical variables, such as HAMD, illness or treatment duration and number of depressive episodes. The data suggest that cerebellar area IX, a non-motor region that belongs to a large-scale brain functional network with known relevance to core depressive symptom expression, exhibits abnormal volume in patients independent of clinical severity or medication. Thus, the data imply a possible trait marker of the disorder. However, given bilaterality and an association with clinical scores at least in remitted patients, the current findings raise the possibility that cerebellar volume may be reflective of successful treatment as well.

1. Introduction

There is now a vast body of research suggesting regionally abnormal brain volume in patients with major depressive disorder (MDD). Several meta-analyses considering automated and user-independent structural data analysis approaches, such as voxel-based morphometry (VBM), have consistently demonstrated gray matter volume (GMV) reductions in anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), and hippocampus in patients with MDD (Bora et al., 2012; Du et al., 2012; Lai, 2013; Zhao et al., 2014). These investigations have reinforced existing neuroanatomical models of affective disorder (Price and Drevets, 2012). MDD pathophysiology appears to be characterized by impaired structure and activity within a cortico-limbic circuitry, along with alterations in the functional organization of multiple brain networks implicated in emotional processes, attention regulation, and cognitive control (Kaiser et al., 2015).

The extant meta-analyses do not suggest prominent cerebellar contributions in MDD. This is surprising given that the role of the cerebellum in both cognitive and affective processing is now well-recognized. Indeed, distinct corticocerebellar circuits that link the cerebellum with cerebral association cortices and paralimbic regions have been shown to underly the cerebellar role in higher-level functions (Schmahmann et al., 2007; Stoodley and Schmahmann, 2009). Functional connectivity analyses have revealed that separate, topographically-organized subsystems of the cerebellum are involved in non-motor network function: cerebellar area VI and VII form circuits with frontal and parietal association cortices, and cerebellar area IX appears to participate in multiple cortical systems, including the so-called "default mode network" (Habas et al., 2009; Stoodley and Schmahmann, 2009; Stoodley and

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Schmahmann, 2010; Buckner et al., 2011). While disorder-specific, regionally-confined structural aberrations of the cerebellum have been demonstrated on a robust level of evidence in neurodevelopmental disorders, i.e. autism spectrum disorder, attention deficit hyperactivity disorder, and developmental dyslexia (Stoodley, 2014), such investigations are scarce in affective disorders. Only one study specifically investigated cerebellar structure in MDD, but analyses were confined to vermian volume and lacked gray/white matter parcellation (Yucel et al., 2013). Moreover, in that study, significant structural findings were only obtained in patients with an extensive history of pharmacological treatment (Yucel et al., 2013). Abnormal cerebellar structure has been reported by previous whole-brain investigations of altered GMV in depression (Vasic et al., 2008; Peng et al., 2011; Lai and Wu, 2015). However, with only one exception (Lai and Wu, 2015), these studies reported their findings with respect to the cerebellum as a whole, and did not consider the functional segmentation of the cerebellum into anatomically distinct subregions. The available evidence on altered cerebellar structure in MDD is even further limited given that VBM methods using conventional whole-brain templates for data normalization have been shown to be suboptimal for cerebellar imaging (Diedrichsen, 2006). Cerebellar segmentation may be particularly vulnerable to inaccurate normalization, where poor alignment of cerebellar subregions can occur as a consequence of standard template use. Given considerable cerebellar variability between individuals and relatively small sizes of cerebellar subdivisions, cerebellar segmentation is particularly susceptible to neuroanatomical imprecision (Diedrichsen, 2006; Kuhn et al., 2011).

In this study, to overcome these limitations, we sought to investigate cerebellar volume in clinically acute (with and without psychotropic treatment) and remitted MDD patients. High-resolution structural MRI data at 3 T were obtained in 59 MDD patients and in 29 control subjects and cerebellar volume was investigated using cerebellum-optimized voxel-based analysis methods. In particular, we employed the Spatially Unbiased Infratentorial Toolbox (SUIT, http://www.icn.ucl.ac.uk/motorcontrol/imaging/suit.htm) for cerebellar segmentation and voxel-based analysis. SUIT provides a high-resolution atlas template of the human cerebellum which is spatially unbiased (Diedrichsen, 2006). The cerebellar template preserves anatomical detail of cerebellar subregions using automated nonlinear normalization methods, thus achieving a more accurate intersubject-alignment compared to whole-brain methods. SUIT has been successfully used to identify differences in cerebellar subdivisions in both psychiatric and neurological patient samples (Diedrichsen, 2006; Kuhn et al., 2011), and SUIT has been shown to be more sensitive to cerebellar structural differences compared to conventional whole-brain VBM (Diedrichsen, 2006; Kuhn et al., 2011).

We predicted that patients with MDD would show aberrant cerebellar volume in specific non-motor subregions, i.e. areae VI, VII or IX ("affective/cognitive cerebellum"). To explore whether cerebellar volume differences were related to the acute state of MDD or whether they represented trait characteristics of the disorder, we compared subgroups of patients with acute and with remitted MDD. Further, to differentiate disease- from medication-related cerebellar structural differences, we compared subgroups of MDD patients with and without antidepressant pharmacotherapy. Employing exploratory correlation analyses with psychometric scores, we additionally sought to assess the clinical relevance of altered cerebellar volume in MDD.

2. Materials and methods

2.1. Participants

59 patients with MDD and 29 healthy controls (HC) were included in this study (Table 1). All participants were right-handed. Patients were recruited among the in- and outpatients treated at the Department of Psychiatry and Psychotherapy III, Ulm University, Germany. Diagnostic assessments for all participants were performed by clinically trained and experienced raters (N.V., R.C.W. and N.D.W.) using the German version of the Structured Clinical Interview for DSM-IV (Axis-I and Axis-II disorders). Case notes were reviewed to corroborate a definitive diagnosis of MDD. Exclusion criteria for MDD patients were any lifetime or comorbid Axis-I and Axis-II disorders according to DSM-IV criteria, a past history or the presence of any medical or neurological disorder, presence of drug or alcohol abuse, a history of head trauma with loss of consciousness, and learning disabilities. HC participants were recruited among employees of the Department of Psychiatry and Psychotherapy III, Ulm University, Germany and were matched for gender and age. Exclusion criteria for HC were any neurological disease or any psychiatric disorder according to DSM-IV criteria, a positive family history for neurological and psychiatric disorders, or current drug treatment (except birth control pills). Depression severity was evaluated by means of the Beck Depression Inventory (BDI) (Beck et al., 1961) and the 21-item Hamilton Rating Scale for Depression (HAMD) (Hamilton, 1960). Of the 59 MDD patients, 43 patients were acutely depressed, i.e. fulfilled DSM-IV criteria for major depressive episode ("acute MDD"). The mean duration of the current episode was 2.8 months and the minimal duration was two weeks. Within this group of 43 acutely depressed patients, 29 patients were on an antidepressant drug regimen ("acute medicated MDD" group). Patients received antidepressant medication according to their psychiatrists' choice, following informed consent. At the time of inclusion, antidepressant medication had been administered for a mean period of 1.3 months in this subgroup. Treatment regimens were stable for at least 2 weeks prior to scanning. Of the 43 acutely depressed patients, 14 patients did not receive any psychotropic medication, i.e. were not on an antidepressant drug regimen ("acute unmedicated MDD" group). Of the 59 MDD patients, a subgroup of 16 patients was in clinical remission ("remitted MDD" group), as defined by HAMD-21 cut-off ≤8 (Riedel et al., 2010). All 16 remitted patients were on an antidepressant drug treatment at the time of the scanning, and had received antidepressant medication for a mean period of 2.5 months, with drug treatment stability for at least 2 weeks prior to scanning. All 59 MDD patients were electroconvulsive-therapy-(ECT)-naive. No patient fulfilled criteria for treatment-resistant depression (Berlim and Turecki, 2007; McIntyre et al., 2014). Demographics and clinical scores of the MDD subgroups are given in Table 2. Medication details are provided in the Supplementary material, Table 2. The

Table 1
Demographics and clinical variables for controls and patients with MDD (whole patient sample). BDI: Beck Depression Inventory; HAMD: Hamilton Depression Rating Scale; a: chi-square test; n.a.: not applicable.

	Controls (n = 29)		MDD patients (n = 59)		
	Mean	sd	Mean	sd	p-Value
Age (years)	34.5	10.7	37.5	11.3	0.245
Education (years)	14.9	2.6	12.9	2.0	0.0002
Gender (m/f)	11/18	n.a.	27/43	n.a.	0.944[a]
Duration of illness (years)	n.a.	n.a.	7.1	7.5	n.a.
Number of episodes	n.a.	n.a.	3.2	2.2	n.a.
BDI	1.5	2.4	24.2	11.8	<0.0001
HAMD	0.9	1.7	16.2	9.0	<0.0001