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Research Report

Altered cerebellar–cerebral resting-state functional connectivity reliably identifies major depressive disorder

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ABSTRACT

In recent years, the cerebellum has been demonstrated to be involved in cognitive control and emotional processing and to play an important role in the pathology of major depressive disorder (MDD). The current study aims to explore the potential utility of selecting the altered cerebellar–cerebral functional connectivity as a classification feature to discriminate depressed patients from healthy controls. Twenty-four medication-free patients with major depression and 29 matched, healthy controls underwent resting-state functional magnetic resonance imaging. A promising classification accuracy of 90.6% was achieved using resting-state functional connectivity between predefined cerebellar seed regions and the voxels within the cerebrum as features. Moreover, the most discriminating functional connections were mainly located between the cerebellum and the anterior cingulate cortex, the ventromedial prefrontal cortex, the ventrolateral prefrontal cortex, the temporal lobe and the fusiform gyrus, which may contribute to the emotional and cognitive impairments observed in major depression. The current findings imply that the cerebellum might be considered as a node in the distributed disease-related brain network in major depression.

1. Introduction

Recently, a wealth of magnetic resonance imaging (MRI) studies have demonstrated the clinical value of employing multivariate pattern analysis (MVPA) methods to distinguish depressives from controls based on the functional neural bias (Craddock et al., 2009; Fu et al., 2008; Lu et al., 2012; Nouretdinov et al., 2011; Zeng et al., 2012). Some of these studies directly selected the altered functional connectivity of regions within the limbic–cortical circuitry as the classification features (Craddock et al., 2009), in accordance with the proposed pathological model of depression (Drevets et al., 2008; Mayberg, 1997). Other papers used whole-brain functional connectivity for the classification and investigated the most discriminating features to reveal the pathology of depression more clearly. For instance, Fu et al. (2008) selected whole-brain functional connectivity as a feature in an emotional task and demonstrated that the most discriminative features contributing to the classification were the connections between some limbic–cortical regions. Zeng et al. (2012) explored the distinct whole-brain resting-state functional connectivity of both depressed patients and controls and found that the altered cerebellar–cerebral connectivity unexpectedly played an important role in the classification,

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in addition to the connections between some well-reported limbic–cortical regions. By applying different features, these studies have achieved inspiring classification results, with accuracies of 95% (Craddock et al., 2009) and 94.3% (Zeng et al., 2012).

However, despite the overall impressive classification performance, previous studies have not systematically explored the effectiveness of identifying major depressive disorder (MDD) using the functional connectivity maps of the cerebellum as features. Indeed, the cerebellum has been shown to be involved in the pathology of depression by converging evidence. In addition to the structural abnormalities of the cerebellum observed in depression (Allen et al., 1997; Frodl et al., 2010; Lee et al., 2011; Liu et al., 2010; Peng et al., 2011; Soares and Mann, 1997), several functional MRI studies have found irregular activation patterns in the cerebellum, for instance, altered cerebellar–cerebral functional connectivity during the resting state (Alalade et al., 2011; Liu et al., 2012; Zeng et al., 2012) and abnormal cerebellum activation in MDD patients performing cognitive (Chantiluke et al., 2012) and emotional tasks (Fitzgerald et al., 2008; Frodl et al., 2010). Moreover, despite an early, intense dispute, the significant insight that the cerebellum not only subserves the prevailing motor coordination but also some other higher functions, i.e., cognition and emotion control, has achieved strong consensus (Allen et al., 1997; Gao et al., 1996; Konarski et al., 2005; Middleton and Strick, 1994). Clinical (Riva and Giorgi, 2000), anatomical (Kelly and Strick, 2003), and functional imaging (Stoodley and Schmahmann, 2010; Timmann et al., 2010) results have provided further evidence for this viewpoint in recent years. Furthermore, a provisional functional topography of the cerebellum was also mapped based on the specific districts of the cerebellum that are activated during cognitive and emotional tasks (Krienen and Buckner, 2009; O'Reilly et al., 2010; Stoodley and Schmahmann, 2009).

Cerebellum regions are tightly linked with cerebral structures via the thalamus in feedforward loops and via the pons in feedback loops (Stoodley and Schmahmann, 2010). These interconnections may form the anatomical and functional basis of the involvement of the cerebellum in cognition and emotion. Note that MDD is characterized by cognitive and emotional impairments, which implies that the altered cerebellar–cerebral functional connectivity seen in MDD patients might contribute to the cognitive and emotional deficits observed in MDD. To our knowledge, although abnormalities of the cerebellum in MDD patients have been discovered, the classification tasks focused on taking the connectivity maps of the cerebellum as features have not been previously investigated.

The current study aims to investigate the effectiveness of applying MVPA methods to discriminate major depressive patients from healthy controls based on the cerebellar–cerebral resting-state functional connectivity as a classification feature. We hypothesized that the altered cerebellar–cerebral connectivity patterns can reliably differentiate MDD patients from healthy controls. The most discriminative regions in the cerebrum abnormally connected to the cerebellum have been mainly well-reported in the pathology of MDD, and that these connections are associated with cognitive and emotional functions in the brain.

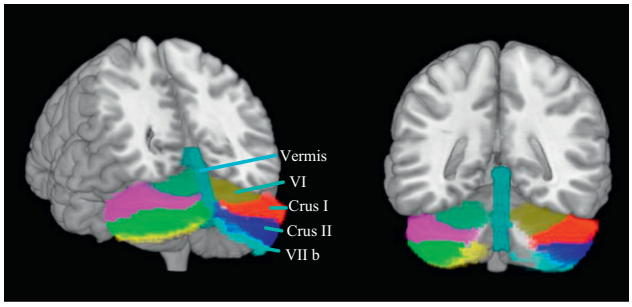

Fig. 1 – The nine cerebellar predefined seed regions. The cerebellar ROIs included the vermis, the bilateral lobule VI, Crus I, Crus II, and lobule VIIb.

2. Results

2.1. *Classification results*

The functional connectivity between nine predefined cerebellar regions of interest (ROIs) (see Fig. 1) and cerebrum voxels were assigned to nine respective groups of classification feature vectors. A support vector machine (SVM) with a linear kernel function was performed to discriminate the two groups (24 MDD patients and 29 healthy controls) by selecting 10 different feature vectors (including each of the nine groups

Table 1 – Performance of classifiers selecting the functional connectivity between nine cerebellar ROIs and voxels in the cerebrum as features separately and the union of all features.

Cerebellar ROIs	Training set correct rate (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)
Crus I_L	84.9	83.0	87.5	79.3
Crus I_R	100.0	88.7	87.5	89.7
Crus II_L	84.9	79.3	75.0	82.8
Crus II_R	83.0	81.1	79.2	82.8
Lobule VI_L	84.9	84.9	83.3	86.2
Lobule VI_R	100.0	79.3	79.2	79.3
Lobule VIIb_L	98.1	84.9	79.2	89.7
Lobule VIIb_R	86.8	86.8	91.7	82.8
Vermis	84.9	69.8	66.7	72.4
Union of all features	100.0	90.6	87.5	93.1

Note: R=right, L=left.