FMRI BOLD Cerebellar Activation of First-episode Schizophrenia Patients during the Tower of London Task

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Introduction

Over the past decade there has been an increasing recognition that the cerebellum may play an important role in higher cognition, above and beyond its more traditionally accepted roles in motor and fine motor control. It has been suggested that the cerebello-cerebral-thalamic-cortical-circuit (CCTCC) incorporates a neuronal loop that serves to integrate motor and cognitive functioning [1]. Andreasen [2] suggests that any disruption of the CCTCC may lead to a ‘cognitive cerebellum’, which may underpin the cognitive symptoms of schizophrenia. A recent review of the literature revealed, however, that only 13 journal articles since 1988 have employed fMRI technology in studies of cerebellar function in schizophrenia patients [3]. Investigating the cerebellum is a very poorly studied area, particularly since traditional image co-registration techniques fail to take individual differences in cerebellar structure into account. The aim of the current study was to compare cerebellar BOLD activation across schizophrenia patients and healthy control subjects on a cognitive task (the Tower of London task or TOL), the cerebellar correlates of which are well-characterised [3].

Methods

Ten first-episode schizophrenia patients (including DSM-IV criteria) and 10 age/gender-matched control subjects were recruited using the TOL paradigm (Left Figure) whilst BOLD fMRI and dMRI brain images were acquired using a 1.5 T Siemens scanner. FMRI data were analysed to produce Z-maps using a regression model that took level of task difficulty into account. Each subject’s structural MR data was aligned with the ICBM template [4] in order to reduce individual proportional differences across subjects. This was followed by the extraction of the individual three-dimensional model of the cerebellum (C1). An average cerebellar model was formed by averaging the individual subjects' cerebellar models. This transformation was subsequently applied to the subjects’ functional Z-maps. Group (patient and control) averageing and correction of the Z-maps was performed and represented onto the average cerebellar model. A representation of the cerebellar areas as described by Schmahmann [5] in 1984 was produced by defining a set of regions based upon the surface of the Schmahmann, CON, SCZ

Schmahmann Atlas

Table: Clusters of significant positive BOLD response (dependent on number of moves) when performing the Tower of London task.

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Units/°</th>
<th>Zmax</th>
<th>Z threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>CON:</td>
<td>1599/238</td>
<td>7.30</td>
<td>4.00 (p&lt;0.001)</td>
</tr>
<tr>
<td>SCZ:</td>
<td>164/221</td>
<td>4.60</td>
<td>4.00 (p&lt;0.001)</td>
</tr>
</tbody>
</table>

Results and Conclusion

Table shows cerebellar lobule area and percentage of the cluster lying in the cerebellar lobule area, with the number of vertices in the cluster, and the maximum, mean and standard deviation of the Z-scores of the cluster. In healthy subjects, the main cluster of activation was confirmed for the posterior portion of the quadrangular lobule and the superior portion of the U-shaped semilunar lobule, which receives direct cortical and indirect tectocerebellar visual input (i.e. Crus I). A smaller cluster was confirmed for the right grical lobule extending into the biventer, which is patients' main focus of activation was confirmed for the right quarterde with extension into the grical lobule and biventer. Thus, our data provide further evidence for the notion of cerebellar contribution to higher level cognitive processing (p<0.07).

Middleton and Strick [8] comprehensively reviewed anatomical, physiological, behavioural and clinical data suggesting that the cerebellum, basal ganglia and multiple cortical areas, which include the primary motor cortex and subdivisions of frontal and temporal lobes. The authors concluded that the respective loops serve distinct brain functions ranging from motor control (motor primary, pre-motor, and oculomotor cortex) to complex and higher order cognitive processes (premotor, inferior temporal, and posterior cortical). Our previous findings [9] suggest an association of increasing BOLD and fCfvol in the dorsolateral prefrontal cortex, the inferior frontal cortex and the insula region, which may represent the neural circuitry that is subserving TOL processing. In the current study, task difficulty exerted a progressively increasing workload on spatial working memory with increasing number of TOL moves. Increasing executive demands on spatial working memory are known to shift activation to the right frontal cortex [10]. While healthy control subjects follow this pattern of right frontal cortical and contralateral cerebellar activation, first-episode schizophrenia patients exhibit a reversed pattern of BOLD response in this circuitry. A higher level of left frontal cortex and predominantly right cerebellar activation may indicate that patients are more likely to rely on alternative strategies (e.g. verbalisation) and are less able to maintain spatial working memory in order to perform the TOL at the same level as matched healthy control subjects do.

References