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NISAD Schizophrenia Research

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

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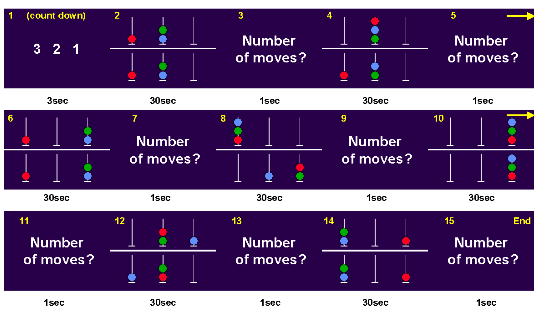
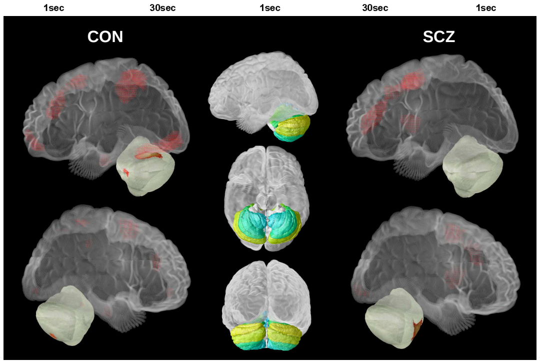
Introduction

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 gait and fine motor control. It has been suggested that the cortical-cerebellar-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 dysmetria", which may underpin the cognitive deficits and impairments seen in schizophrenia. A recent review of the literature revealed, however, that only 13 journal articles since 1988 have employed fMRI technology study to cerebellar functioning in schizophrenia patients, leaving the cerebellum a very poorly investigated structure 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 cerebral correlates of which are well characterised [3].



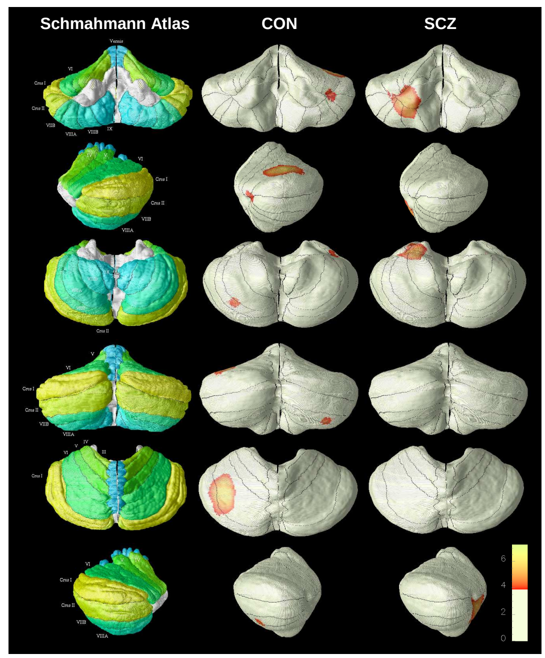


Left Figure: Example of a Tower of London sequence presented in the MR scanner. Each sequence consisted of four 'zero move' problems and three 'active' problems presented in an alternate order for 30 s, respectively. Subjects were required to silently calculate the minimum number of moves required to solve each problem by comparing the upper with the lower part of the display. Verbal responses were recorded for 1s following the presentation of each Tower of London problem. (Yellow labels are for the purpose of illustration only and did not appear in the original presentation mode). Below: Task difficulty-dependent positive BOLD response (critically thresholded at Z=3.88 ~ P<0.05 corrected for multiple comparisons) for 10 first-episode schizophrenia subjects (SCZ) and 10 matched healthy control subjects (CON) mapped into glass model of cerebral cortex and on average structural model of the cerebellum.

Right Figure: Task difficulty-dependent BOLD cluster of significant cerebellar activation mapped on average structural model of the cerebellum for first-episode schizophrenia subjects (SCZ) and matched healthy control subjects (CON). Cerebellar anatomy according to Schmahmann lobule atlas registered on colinRR cerebellum.

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

L/R	Lobule [% of cluster]	Units	Vol.	Z_{max}	Z_{mean}(SD)
CON:					
L	VI [71.9%]; Crus I [28.1%]	**1599**	**7753**	**5.9**	**4.8 (±0.6)**
L	Crus I [37.5%]; Crus II [33.2%]; VI [25.5%]; VIIB [3.8%]	**184**	**738**	**4.2**	**4.0 (±0.1)**
R	VIIB[85.1%]; VIIIA[14.9%]	**121**	**508**	**4.6**	**4.2 (±0.2)**
SCZ:					
R	Peduncle [48.9%]; VIIIB [19.5%]; VIIIA [13.6%]; VIIB [4.3%]; VI [3.6%]; V [3.3%]; Crus II [3.2%]	**1264**	**5778**	**5.4**	**4.6 (±0.4)**



Methods

Ten first-episode schizophrenia patients (according to DSM-IV criteria) and 10 age/gender-matched control subjects performed the TOL paradigm (Left Figure) whilst BOLD fMRI and sMRI brain image volumes 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 ICBM53 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 cerebellar cortex [5]. .An average model of cerebellar cortex was formed by averaging the individual subjects' cerebellar cortex models. This transformation was subsequently applied to the subjects' functional Z-maps. Group (patient and control) averaging and correction of the Z-maps was preformed and represented onto the average cerebellar model. A representation of the cerebellar areas as described by Schmahman [6] was produced by defining a set of regions based upon the surface of the of the Montreal Neurological Institute intensity-averaged single-subject MRI atlas. This template was then mapped onto the group averaged cerebellar model. Clusters of BOLD functional information were then classified and quantified based on the percentage of the cluster lying within a cerebellar lobule.

Results and Conclusion

Table shows cerebellum 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 posterior and superior portion of the the left semilunar lobule, which receives direct cortical and indirect tectocerebellar visual input (i.e. Crus I). A smaller cluster was confirmed for the right gracile lobule extending into the biventer while the patients' main focus of activation was confirmed for the right peduncle with extension into the gracile lobule and biventer. Thus, our data provide further evidence for the notion of cerebellar contribution to higher level cognitive processing [e.g.7].

Middleton and Strick [8] comprehensively reviewed anatomical, physiological, behavioural and clinical data suggesting distinct circuits involving 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 (primary motor, pre-motor, and oculomotor cortex) to complex and higher order cognitive processes (prefrontal, inferior temporal, and posterior cortex). Our previous findings [3] suggest an association of increasing BOLD and rCBF in the dorsolateral prefrontal cortex, the inferior parietal cortex, the lentiform nucleus and the cerebellar tonsils, thus representing the neural circuitry that is subserving TOL processing. In the current study, task difficulty exerts 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 [9]. 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) due to impaired spatial working memory in order to perform the TOL at the same level as matched healthy control subjects do.

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