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Cerebellar volume deficits in medication-naïve obsessive compulsive disorder

Janardhanan C. Narayanaswamy [a,b], Dania Jose [b], Sunil V. Kalmady [b], Sri Mahavir Agarwal [a,b], Ganesan Venkatasubramanian [a,b,*], Y.C. Janardhan Reddy [a]

[a] Obsessive-Compulsive Disorder Clinic, Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bangalore 560029, India
[b] Translational Psychiatry Laboratory, Neurobiology Research Centre, National Institute of Mental Health and Neurosciences, Bangalore 560029, India

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ABSTRACT

Even though conventional neurobiological models of obsessive compulsive disorder (OCD) commonly demonstrate abnormalities involving fronto-striatal circuits, there is emerging evidence regarding the role of posterior brain structures such as cerebellum. In this study, we examined the cerebellar regional volume in a large sample of medication-naïve OCD patients compared to matched healthy controls (HC). In 49 medication naïve right handed OCD patients and 39 age and sex matched HC, sub-region wise volume of cerebellum was extracted from the T1 weighted images using Spatially Unbiased Infra tentorial Template (SUIT) toolbox and compared using hypothesis driven, region of interest approach after clinical assessment with standard scales. After controlling for age, sex and ICV, the subjects with OCD had significantly smaller cerebellum compared to HC, especially in the posterior lobe sub-regions - lobule VI and left crus 1. This study gives preliminary evidence for region specific cerebellar volumetric deficits in the pathophysiological of OCD. Regional cerebellar volume deficits conform to the abnormal connectivity of cerebellum to specific cortical regions and it is indicative of involvement of regions outside the conventional fronto-striatal circuitry. This might be important in the context of cognitive deficits seen in OCD.

1. Introduction

Traditional neurobiological models of obsessive compulsive disorder (OCD) highlight disturbances in fronto-striatal (FS) circuits as an explanation of the recurrent thoughts and compulsive behaviours (Menzies et al., 2008; Radua and Mataix-Cols, 2009). In the recent years, neuroimaging research has suggested involvement of regions outside the FS circuitry in OCD (Nabeyama et al., 2008; Pujol et al., 2004). A recent meta-analysis demonstrated that apart from the "conventional" fronto-striatal alterations, volume changes were present in widespread brain regions (Piras et al., 2015). In addition to this, there is growing evidence of widespread alterations in white matter fiber tracts in OCD (Piras et al., 2013). Overall, recent studies employing whole-brain analyses indicate that the neuroimaging alterations are more distributed, involving insular, parietal and cerebellar regions (Nabeyama et al., 2008; Pujol et al., 2004). In particular, the role of cerebellum, a crucial yet poorly studied structure in the context of OCD is gaining prominence (Nabeyama et al., 2008; Pujol et al., 2004). Contextually, cognitive task activation based fMRI studies have reported reduced activation of the cerebellum in patients with OCD with a reversal of this along with clinical improvement due to treatment (Nabeyama et al., 2008; Nakao et al., 2005; Sanematsu et al., 2010).

In summary, on integrating the current evidence of widespread brain structural and functional abnormalities, it is now being realized that the posterior regions such as cerebellum might have an important role in OCD (Menzies et al., 2008). Even though classically described as a structure important for motor coordination, converging evidence suggest that the cerebellum, through the cerebro-cerebellar circuits, has a pivotal role in cognition and emotion in addition to motor control (Strick et al., 2009). Importantly, the cerebellum has been shown to have a modulating effect on certain cognitive functions (Allen et al., 1997; Chen and Desmond, 2005; Daum and Ackermann, 1995; Honey et al., 2000; Stoodley and Schmahmann, 2010) including the ones that are impaired in OCD (Kuelz et al., 2004).

The cerebellum is organized into ten lobules (I–X) (Schmahmann et al., 2000). There are three recognized major anterior-posterior divisions or lobes within which the lobules are sub-divided: the anterior lobe (lobules I–V) is separated from the

* Corresponding author at: Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bangalore 560029, India.
E-mail address: venkat.nimhans@gmail.com (G. Venkatasubramanian).

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posterior lobe by the primary fissure, and the posterior lobe (lobules VI–IX) is separated from the flocculonodular lobe (lobule X) by the posterolateral fissure. The midline region is called the vermis and the lateral cerebellar regions are called the hemispheres. Most of the lateral cerebellar regions, also referred to as the neo-cerebellum, comprise of the hemispheric extensions of lobules VI and VII. Interestingly, cerebellum has functionally distinct and topographically segregated organization of motor, cognitive, and limbic functions (Stoodley and Schmahmann, 2010). The cerebellar motor abnormalities are related to lesions that involve the anterior lobe and parts of lobule VI while the cognitive difficulties are related to the posterior lobe impairments that affect lobules VI and VII (including Crus I, Crus II, and lobule VIIB) occurring due to the effects on cognitive network connections with cerebral association cortices. Vermis abnormalities affect the cerebro-cerebellar-limbic loops resulting in emotion related abnormalities observed in various neuropsychiatric disorders. Of particular relevance to neuropsychiatric disorders such as OCD is that the association area projections from the prefrontal, parietal, and temporal, and cingulate cortices have cerebellar homunculi mainly localized to lobules VI and VII (Kelly and Strick, 2003; Stoodley and Schmahmann, 2010). The projections of the prefrontal cortical brain regions such as the anterior cingulate cortex (ACC) to Crus I/II, lateral cortical projections to lobule VI and projections from limbic cortices to posterior vermis (Stoodley and Schmahmann, 2010) would be of relevance in OCD where cognitive and emotion related abnormalities are present. Specifically, lobules VI and VII probably mediate spatial tasks, executive function and affective processing through their connections with the relevant cortical regions (Honey et al., 2000; LaBar et al., 1999; Stoodley et al., 2012).

Despite the growing evidence regarding the important role of cerebellum in OCD, well-characterised region of interest studies of cerebellum in medication naïve patients have not been done to date. In the present study, we aimed to examine the structural volumetric differences of cerebellum and its various sub-regions in a large sample of medication naïve OCD patients in comparison to matched healthy controls (HC). We hypothesised that OCD patients would have significantly deficient cerebellar volume compared to HC. Taking into consideration the functional and topographical representation of various networks of cerebellum as described previously, we also hypothesised that there would be volume deficits predominantly in the regions confined to the posterior lobe.

2. Methods

2.1. Subjects

The study participants constituted 50 medication naïve adult patients with DSM-IV OCD (APA, 1994) and 40 matched HC. The patients were recruited from the National Institute of Mental Health And Neurosciences (NIMHANS), Bangalore, India. The study was conducted in accordance to the Declaration of Helsinki. The NIMHANS institute ethics committee approved the study. All the participants gave written informed consent for participation in the study. In the analysis, one subject from each group had to be excluded due to poor image quality of their MRI, thus leaving the final analysable sample to 49 OCD patients and 39 HC. None of the patients had prior exposure to psychotropic medications.

None of the subjects had any of the following: medical illness that may significantly influence CNS function or structure; significant neurologic disorder such as seizure disorder, cerebral palsy; history suggestive of delayed developmental milestones (suggestive of mental retardation);a family history of hereditary neurologic disorder that may complicate diagnosis; co-morbidity for DSM-IV psychoactive substance dependence; or a lifetime history of head injury associated with loss of consciousness longer than 10 min, seizures, neurological deficit, depressed skull fracture, surgical intervention, or central nervous system infection. Female subjects were neither pregnant nor were within the postpartum period.

2.2. Clinical measures

All patients were evaluated with the Mini International Neuropsychiatric Interview plus (MINI) (Sheehan et al., 1998), a short structured diagnostic interview, designed to diagnose psychiatric disorders as per for DSM-IV and ICD-10. Severity of OCD was measured using the Yale-Brown obsessive compulsive scale (YBOCS) that includes a symptom checklist, a 10-point severity rating scale, and item 11 for insight (Goodman et al., 1989). Each item is rated from 0 (no symptoms) to 4 (extreme symptoms) (total range, 0–40). It provides a specific measure of the severity of OCD symptoms that is not influenced by the type of obsessions or compulsions present. YBOCS item 11 measures insight regarding the illness. Its score ranges from 0 to 4 and a higher value indicate poorer insight. The Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) was used to quantify depressive comorbidity. It is a 10-point scale, each item rated from 0 to 6 with the overall score ranging from 0 to 60. Higher score implies more severe depression. The Clinical Global Impression scale (CGI) (Guy, 1976) was used to measure the global illness severity. It is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Only subjects who had YBOCS total score of more than 16 (clinically significant OCD) were recruited for the study. All subjects were right-handed as assessed by Annett's questionnaire (Annett, 1967), a 12-item handedness questionnaire. Healthy controls were administered the MINI (Sheehan et al., 1998) to rule out any Axis I psychiatric disorders.

2.3. MRI acquisition

MRI was done with a 1.5 T scanner (Magnetom 'Vision', Siemens, Erhlangen, Germany). T1-weighted three-dimensional magnetization prepared rapid acquisition gradient echo (MP-RAGE) sequence was performed (TR = 9.7 ms, TE = 4 ms, nutation angle = 12°, and slice thickness: 1-mm with no inter-slice gap, voxel dimension 1*1*1 mm isotropic) yielding 160 sagittal slices.

2.4. Cerebellum image analysis method

The origin of T1-weighted images was set to the anterior commissure using SPM8 (Wellcome Trust Centre for Neuroimaging, UCL, London; UK; http://www.fil.ion.ucl.ac.uk/spm) under MatLab 7.8.0 (The MathWorks Inc., Sherborn, MA, USA). Infra-tentorial structures namely cerebellum and brainstem were isolated from the surrounding tissue using the Spatially Unbiased Infra tentorial Template (SUIT) toolbox (Diedrichsen, 2006) (http://www.icn.ucl.ac.uk/motorcontrol/imaging/suit.htm), which uses the tissue-type and the proximity to cortical white matter to calculate the posterior probability of each voxel to belong to cerebellum or brainstem. The cropped anatomical images were then normalized where a non-linear deformation map to the SUIT template, using the cosine-basis function approach was performed (Ashburner and Friston, 1999). Images were then resampled into the SUIT atlas space using deformation map created in the normalization step, such that the overall probability mass were retained after normalization. Finally, using suit_lobuli_summarize function, all voxels within each