Alterations in Cerebellar Functional Connectivity in Social Anxiety Disorder

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Target Audience: Clinicians, and Researchers of Neuropsychiatric Disorders, Emotion Processing, Functional MRI and Resting State Networks.

Purpose: The Papez circuit[1] describes the collection of pathways associated with emotional processing. Amygdala as part of this circuit is currently considered as one of the key nodes of brain's emotion circuit[2]. However, cerebellar contribution to Papez circuit, although known from animal studies[3], has not been explored in patients with Social Anxiety Disorder (SAD), a prevalent neuropsychiatric disorder. The purpose of this study is to investigate the additional neural pathways underlying SAD by utilizing higher resolution imaging, improved sensitivity from multi-channel head coils and functional connectivity MRI (fcMRI).

Methods: 17 SAD patients (24.7±6.3 yrs, 8 males, all right-handed, no medication, Liebowitz Social Anxiety Scale: 77.9±14.1), and 17 age-, gender-, handedness-matched healthy controls (HC) (25±7.5 yrs) were imaged using a 3T scanner with the product 32-Channel head coil. 3D T1-weighted anatomical scan was acquired with 1.3x1x1.3 mm^3 voxel size, TR/TE/TI/FA=2530 ms/3.39 ms/1100 ms/7°. High-resolution (2x2x2 mm^3) resting-state scans were acquired using single-shot gradient echo EPI with 67 interleaved slices, TR/TE/FA=6000 ms/30 ms/90°. Data were realigned, slice-time corrected, normalized, spatially smoothed with a 3-mm kernel and temporally band-pass filtered (0.008 < f < 0.09) using SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK). Functional connectivity analyses were carried out using a Matlab-based in-house developed toolbox, CONN[4]. Regions of interest (ROIs) were 10-mm seeds placed on Left and Right cerebellum (±25, -81, -33), based on previously published foci[5] and were generated using WFU_PickAtlas[6]. Physiological and other spurious sources of noise were estimated using the anatomical Component based noise Correction (CompCor) method[7], and regressed out together with movement related covariates. Correlation maps were produced by extracting the residual BOLD time course from the source ROI, followed by computing Pearson's correlation coefficients between the source time-course and the time-courses of all other voxels in the brain. Correlation coefficients were converted to normally distributed scores using Fisher's r-to-z transform to allow for second-level General Linear Model analyses.

Results: Figure 1A shows correlations in left and right medial pre-frontal cortices and posterior cingulate cortex (part of default mode network, indicated by blue arrows) illustrating the connections to the left and right cerebellum (used as seeds). These correlations appear stronger in the SAD group. Notably, SAD>HC comparison revealed significant differences with peak cluster at left amygdala (-20 -10 -18) (blue arrow, Fig. 1B), t_{max}=4.44 with 486 voxels per cluster. HC>SAD contrast was not significant.

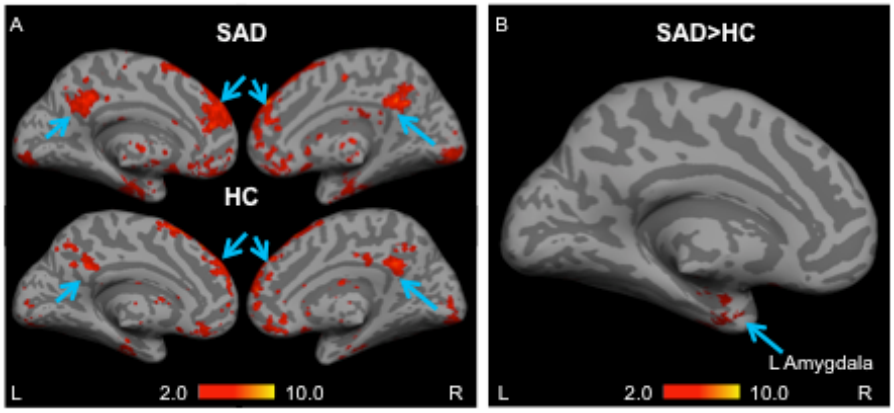

Figure 1: Statistically significant positive functional connectivity maps for cerebellum seeds (second-level analysis, n=17 per group) at within-group height threshold of whole-brain p<0.05, corrected for false discovery rate (Fig. 1A). SAD>HC revealed left amygdala (Fig. 1B). Between-group height threshold was p<0.05, cluster-level family-wise error corrected, p<0.05. Opposite contrast was not significant.

Discussion: Our results highlight the importance of coil sensitivity and high resolution for fcMRI acquisitions in order to provide useful application of neuroimaging to the realm of psychiatric disorders. We were able to identify hyper-connectivity in left amygdala in the SAD patient group compared to healthy controls. Furthermore, significantly stronger temporal correlations revealed between cerebellar seeds and amygdala in the patient group (which was not present in HC>SAD comparison), underscore the involvement of cerebellum not only in the context of SAD, but also as a key component for emotional processing in general.

Conclusions: We report cerebellar hyper-connectivity associated with SAD, specifically with left amygdala. Lateralization is an encouraging finding because hyperactivity in left amygdala has been reported previously in the context of depression (with task-based fMRI), which normalizes with antidepressant treatment[8]. Our findings could subsequently serve as guidelines for developing effective treatment strategies for SAD.

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