Functional connectivity changes of Dentate Nucleus in Autism Spectrum Disorders: a resting-state fMRI study.

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TARGET AUDIENCE: Neuroscientists with an interest in the cerebellum and its connections to the cortex.

PURPOSE

Autism spectrum disorders (ASDs) are neurodevelopmental conditions characterized by core deficits in social functioning mainly including "Theory of Mind" (ToM) processes (1). The cortical underconnectivity theory has been reported as explanatory model for ASDs suggesting how functional connectivity among brain areas may be compromised in ASDs patients hampering their ability to accomplish cognitive functions and social task successfully (3). The cerebellum has emerged as one of the key brain regions underlying these processes by means of its connections with cerebral cortex areas related to social functioning. Since the cerebellum is known to influence cerebral activity via cerebello-thalamo-cortical (CTC) circuits it has been proposed that cerebello-cortical 'disconnection' could in part underlie autistic symptoms (4). In the present study we used resting state functional MRI (RS-fMRI) in patients with ASD. Since the Dentate Nucleus represents the sole cerebellar output channel partecipating in CTC circuit, we tested potential connectivity changes between the DN and CTC circuits targets using a seed-based approach in order to explore the relationship between cerebello-cortical connectivity and ASDs pathology.

MATERIAL AND METHODS

Six adults with ASDs [mean(SD) age=23.1(4.9)] were included in the study, together with 25 typically developing (TDA) subjects mean(SD) age=25.8(2.8); M/F=14/11], recruited as control group. All participants underwent a 3.0T MRI acquisition protocol, including a 3D modified driven equilibrium Fourier transform (MDEFT) and 220 fMRI volumes collected with T2* weighted echo planar image (EPI) scans. RS-fMRI data were pre-processed using SPM8 (Wellcome Department of Imaging Neuroscience; http://www.fil.ion.ucl.ac.uk/spm/), and filtered to remove potential bias and high frequency variations. Pre-processing included correction for head motion, compensation for slice-dependent time shifts, normalization to the EPI template in MNI coordinates provided with SPM8, and smoothing with a 3D Gaussian Kernel with 8mm^3 full-width at half maximum. The left and right DN masks were separately defined according to the spatially unbiased atlas template (SUIT) of the cerebellum and brainstem (5) (Fig.1). Each ROI was extracted using utilities from the FMRIB software library (FSL, www.fmrib.ox.ac.uk/fsl/) and resliced into EPI standard space. The mean time course of the voxels within each ROI was extracted for each participant and used as a regressor in a 1st level SPM analysis, thus localising the voxels in the brain showing a significant correlation with it. In order to explore differences in connectivity between ASD patients and TDA group, we ran a second level analysis comparing between the two groups the contrast images for positive correlation obtained at the first level, using a two-sample T-Test model. Results were considered significant at $p < 0.05$ FWE correction.

Figure 1. Coronal (A) , sagittal (B) and axial (C) view of the generated left (red) and right (yellow) ROIs superimposed to the spatially unbiased atlas template of the cerebellum and brainstem (SUIT).

RESULTS

Different patterns of functional connectivity were detected between left and right cerebellar dentate nucleus and contralateral and ipsilateral cerebral cortex areas. Significant functional correlation was also observed between each seed and regions of the cerebellum itself. When comparing the left DN functional connectivity between ASDs patient and TDA group, the most significant pattern was found in the right supramarginal gyrus and left precuneus (Fig 2A). When comparing the connectivity pattern of the right DN, the most significant pattern of functional changes were found with the left postcentral gyrus and both left and right precuneus (Fig 2B).

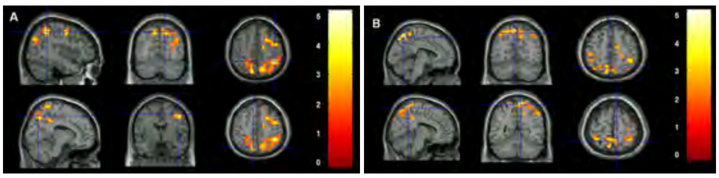

Figure 2. Two-sample T-Test comparing between the two groups the contrast images for positive correlation obtained at the first level. Results were considered significant at $p < 0.05$ FWE correction. A) Decreased functional connectivity in ASDs patients compared to controls between the left dentate nucleus and cerebral cortex. B) Decreased functional connectivity in ASDs patients compared to controls between the right dentate nucleus and cerebral cortex areas.

DISCUSSION

These rs-fMRI data define the pattern of connectivity between cerebellar DN and CTC targets. Using a seed-bsed approach, we were able to provide evidence that the functional connectivity of the DN is altered in ASDs patients. The prominent finding is the bilateral precuneus showing altered functional connectivity with the DN in patients compared to controls. The precuneus comprises a core region of the Default Mode Network, known to be relevant during cognitive processes related to social deficits seen in ASD, e.g ToM (6). Additionally, the Temporo-Parietal Junction, whose anterior division includes the SMG, is known to be a component of the posterior DMN and to be crucial for representing mental states, particularly false beliefs (7). Our conclusion is that the cerebellum may play an active role in shaping cerebral cortical default network by providing a mechanism to modulate the cerebral cortical default structures. This may suggest that the dysfunction reported within the cerebral–cortical network tipically related to social features of ASDs may be related to an impaired cerebellar modulation that prevent the cerebral cortex from receiving those cerebellar feedback inputs necessary for a successful adaptive social behavior.

REFERENCES

1. Baron-Cohen, 1995; 2.Coricelli, 2005; 3. Just MA, Cherkassky VL, Keller TA, Minshew NJ, 2004; 4. Rogers TD, McKimm E, Dickson PE, Goldowitz D, Blaha CD, Mittleman G, 2013; 5.Diedrichsen J, Balsters JH, Flavell J, Cussans E, Ramnani N., 2009; 6. Assaf M, Jagannathan K, Calhoun VD, Miller L, Stevens MC, Sahl R, O'Boyle JG, Schultz RT, Pearlson GD, 2010; 7. Saxe R,2006.