
G. Olivotto1,2, M. Leggio1,2, F. Laghi1, R. Baiocchi1, A.M. Tedeschi1, S. Clausi1,2, C. Mastrovasio1, M. Molinari1, A. Cercignani1,4,5, M. Bosi6,7
1. Aversa Laboratory, IRCCS Santa Lucia Foundation, Rome, Italy. 2. Department of Psychology, Faculty of Medicine and Psychology, “Sapienza” University of Rome, Rome, Italy. 3. Department of Developmental and Social Psychology, Faculty of Medicine and Psychology, “Sapienza” University of Rome, Rome, Italy. 4. Neuroimaging Laboratory, IRCCS Santa Lucia Foundation, Rome, Italy. 5. Neurological and Spinal Cord Injury Rehabilitation Department. A. IRCCS Santa Lucia Foundation, Rome, Italy. 6. Clinical Imaging Science Center, Brighton and Sussex Medical School, Brighton, UK.

Introduction
Autism spectrum disorders (ASDs) are neurodevelopmental conditions characterized by core deficits in social functioning mainly including “Theory of Mind” (ToM) processes (1). The complex neural network subduing these processes consists of specific frontal lobe portions, tempo-parietal areas and subcortical structures (2). 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 successfullly (3). The cerebellum has emerged as one of the key brain regions underlying these processes by means of its connections with the cerebral cortex areas related to social functioning. Since the cerebellum is known to influence cerebral activity via cerebellum-thalamo-cortical (CTC) circuits it has been proposed that cerebellum-cortical ‘disconnection’ could in part underlie autistic symptoms (4). However, the role of CTC circuits in the pathophysiology of ASDs, needs to be further elucidated. Functional connectivity between spatially distinct brain regions can be investigated using resting state functional MRI (RS-fMRI). Since the dentate nucleus (DN) represents the sole cerebellar output channel participating in CTC circuits, in the present study we tested potential connectivity changes between the DN of the cerebellum and CTC circuit targets using RS-fMRI in patients with ASD, in order to explore the relationship between cerebellum-cortical connectivity and ASDs pathology.

Methods
Six adults with ASDs [mean(SD) age=23.1(4.9)] were included in the study and 25 typically developing (TDA) subjects [mean(SD) age=25.8(2.8); M/F=14/11] were recruited as control group. All participants underwent a 3.0T MRI acquisition protocol, including T1 and BOLD RS-fMRI scans. RS-fMRI data were pre-processed using SPM8, and filtered to remove potential bias and high frequency variations. The left and right DN masks were separately defined according to the spatially unbiased atlas template of the cerebellum and brainstem (5) (Fig.1). Each ROI was extracted using utilities from the FMIRI software library (FSL; www.fmrib.ox.ac.uk/fs/1) and resliced in 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 patient 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.

Results
Different patterns of functional connectivity were detectable between left and right cerebellar dentate nucleus and contralateral and ipsilateral cerebral cortex areas. Significant functional correlation was also detectable between each seed and regions of the cerebellum itself. When comparing the pattern of left DN functional connectivity between ASDs patient and TDA group, decreased functional connectivity was found between left and right dentate nucleus and regions of both contralateral and ipsilateral cerebral hemispheres. Specifically, the second level analyses showed patterns of decreased functional connectivity (FC) of the left DN with the posterior right supramarginal gyrus (RSMG) and, ipsilaterally, the left precuneus (Fig 2A). When comparing the connectivity pattern of the right DN, significant functional changes were found between the right DN and the left postcentral gyrus and both left and right precuneus (Fig 2B).

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).

Figure 2. A) Differences in functional connectivity were found in ASDs patients compared to controls between the left dentate nucleus and contralateral and ipsilateral cerebral cortex areas (shown in red) (FWE p < 0.05). The most significant pattern was found in the right supramarginal gyrus (x=42; y=-62; z=48) and left precuneus (x=-6; y=64; z=60). B) Differences in functional connectivity were found in ASDs patients compared to controls between the right dentate nucleus and contralateral and ipsilateral cerebral cortex areas (shown in light blue) (FWE p < 0.05). The most significant pattern was found in the left postcentral gyrus (x=14; y=-44; z=72), left (x=-6; y=64; z=60) and right precuneus (x=86; y=52; z=70).

Conclusion
The presented RS-fMRI data provide evidence that DN FC is altered in ASDs patients. In the present study, the prominent finding is the bilateral precuneus showing altered resting state connectivity with the DN in patients compared to controls. The precuneus comprises a core region of the Default Mode Network, a 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). Since the cerebellum is known to influence the cerebral cortex activity via CTC pathways, it 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 typically 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 behaviour. In conclusion, we suggest that the cerebellum may contribute to social perception in ASDs via interaction with key cortical social brain regions, such as cortical default structures.

References