Neural substrates of motor and cognitive dysfunctions in sca2 patients: a graph-theory approach.

G. Olivito[1,2,3] , M.Cercignani[3,4], M.Lupo [1,2], C.Iacobacci [1,2], S.Romano [5], M.Masciullo [6], M. Molinari[6], M. Bozzali[3], M. Leggio [1,2]

1. Ataxia Laboratory, IRCCS Santa Lucia Foundation, Rome, Italy; 2. Department of Psichology, Faculty of Medicine and Psychology, "Sapienza" University of Rome, Rome, Italy; 3. Neuroimaging Laboratory, IRCCS Santa Lucia Foundation, Rome, Italy; 4.Clinical Imaging Science Center, Brighton and Sussex Medical School, Brighton, UK; 5. Center for Experimental Neurological Therapies, Department of Neuroscience - Sant'Andrea Hospital - Rome, Italy; 6. Neurological and Spinal Cord Injury Rehabilitation Department A, IRCCS Santa Lucia Foundation , Rome, Italy.

INTRODUCTION

Spinocerebellar ataxia type 2 (SCA2) is an autosomal dominant neurodegenerative disease involving the cerebellum. The particular atrophy pattern results in some typical clinical features mainly including motor deficits. The presence of cognitive impairments in subjects with degenerative ataxia has long been debated (1). Recently, the cognitive performances of SCA 2 patients have been exhaustively investigated showing that the patients may have negative scores on all cognitive domains (2). The cerebellum is known to modulate cerebral cortical activity (3) and to contribute to distinct functional networks clearly related to higher level functions beyond motor control (4;5). It is therefore conceivable that one or more networks, rather than isolated regions, may be dysfunctional and that abnormal connectivity within specific cerebello-cortical circuits might explain the widespread deficits typically observed in SCA2 patients.

Methods

9 patients with SCA2 and 33 healthy subjects underwent an MRI acquisition protocol at 3T including resting-state functional MRI scans. RS-fMRI series were collected during rest for 7 min and 20s resulting in a total of 220 volumes. During this acquisition participants were instructed to keep their eyes closed, not to think of anything in particular, and not to fall asleep. RS-fMRI images were pre-processed for resting-state fMRI using Statistical Parametric Mapping 8 (SPM8 http://www.fil.ion.ucl.ac.uk/spm/) and in-house Matlab scripts. For each subject, the first four volumes of the fMRI series were discarded to allow for T1 equilibration effects. The pre-processing steps included correction for head motion, compensation for slice-dependent time shifts, co-registration to the corresponding MDEFT volume that was segmented into white matter, grey matter and CSF. Segmentation derived normalization parameters were used to warp the motion and slice-time corrected RS-fMRI images into Montreal Neurological Institute (MNI) coordinates provided with SPM8, and smoothing with a 3D Gaussian Kernel with 8mm3 full-width at half maximum.

Statistical Analysis

We used the "Networks-based statistics" (NBS) tool developed by Zalesky and co-authors (6). In order to obtain a connectivity matrix for each participant, we first identified a set of 116 nodes defined by the automated anatomical labelling (AAL) atlas (Fig1). Each node's mean time course was calculated as the average of the fMRI time series from all voxels within a certain region. Correlation matrices were then obtained calculating the correlation between all pairs of nodes' mean signals as previously described (7). In this way, we were able to assess differences in functional connectivity between specific cerebellar and cerebral "nodes".

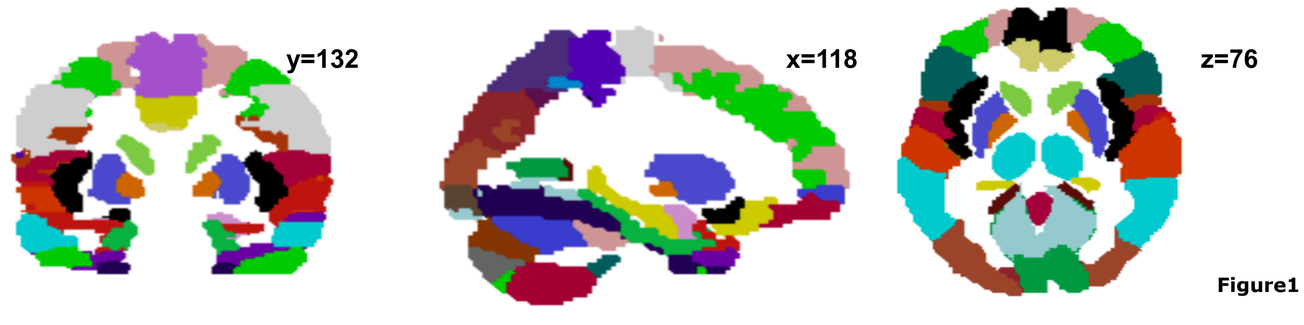

Figure1

Automated anatomical labelliing (AAL) atlas in the standard coronal (*y*), sagittal (*x*) and axial (*z*) views.

RESULTS

NBS analysis showed altered inter-nodal connectivity between cerebellum and different cerebral regions across the whole brain (Fig.2). Overall, 62 nodes and 110 edges showed differences in SCA2 brains compared to controls. Specifically, 57 edges and 35 nodes survived after Bonferroni correction for multiple comparisons. In particolar, inter-nodal *underconnectivity* was found between different pairs of nodes in the cerebellum and cerebral cortex, as listed in the panel1 and shown in Fig.2.

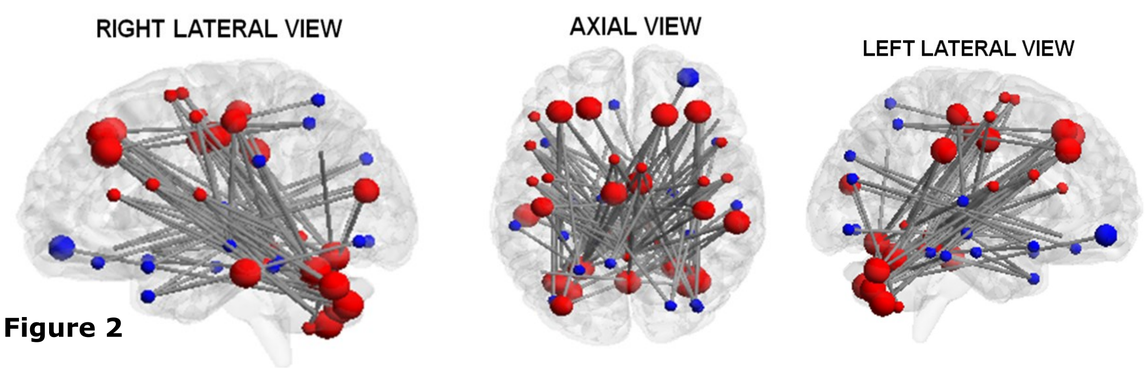

Figure 2

Edges and nodes of significant decreased functional connectivity in SCA2 patients as assessed by NBS analysis (FWE= .05). Regions of the cerebello-cortical (red) and cortico-cortical (blue) modules are shown in different colors. Bigger nodes correspond to cerebellar and cortical regions relevant to cognition and emotion; smaller nodes correspond to cerebellar and cortical regions relevant to motor control

Panel1

L_ CrusI-Frontal_Sup_R
CrusI-Frontal_Mid
R_CrusI-Temporal_Inf_L
CrusII-Frontal_Sup
CrusII-Frontal_Mid
R_CrusII-Temporal_Inf_L

Cer_III-Frontal_Inf_Oper
Cer_III-Rolandic_Oper
R_Cer_IV_V-Postcentral_L
Vermis_IV_V-Precentral
Vermis_IV_V-Postcentral

Cer_VI-Supp_Motor_Area
Cer_VI-Cingulum_Mid
L_Cer_VI-SupraMarginal_R
Cer_VI-Supp_Motor_Area

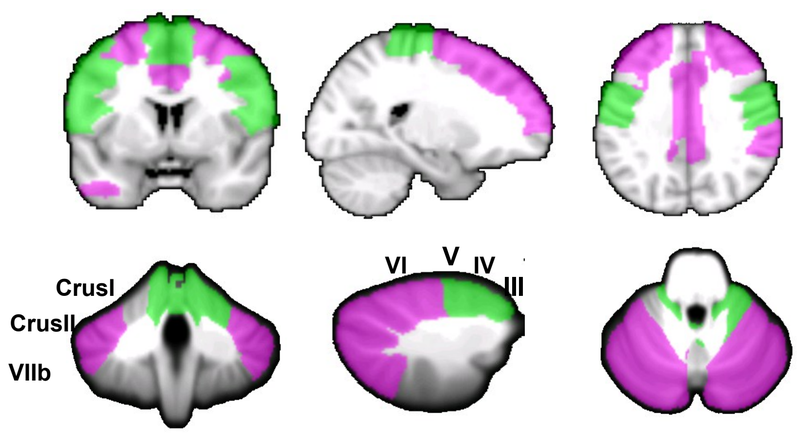

Figure 3

Anatomical representations of cognitive (violet) and motor (green) nodes in the cerebellum and cerebral cortex showing underconnectivity between each other.

According to the cerebellar functional topography, cerebellar nodes in the posterior cerebellum showed reduced functional connectivity with nodes in cerebral cortex regions related to cognition and emotion; cerebellar nodes in the anterior cerebellum and vermis showed reduced functional connectivity with nodes in the cerebral cortex regions related to motor control (Fig.3).

CONCLUSION

To our knowledge this is the first study investigating functional inter-nodal connectivity changes in SCA2 patients using graph-theory approaches. Interestingly, the observed pattern of inter-nodal underconnectity is consistent with the well-known functional segregation of the cerebellum in supramodal and sensorimotor zones (8).

We conclude that:

✓*-A cortical functional alteration derives from cerebellar structural degeneration typically associated with SCA2 pathology.*

✓*-The cerebellar dysfunction affect long-distance regions*

✓*-The clinical symptoms observed in SCA2 patients may be specifically related with connectivity changes between supramodal and sensorimotor cerebello-cortical nodes.*

References: 1)Fehrenbach RA, et al., Arch Neurol 1984; 2)Tedesco AM, et al., Brain 2011; 3)Middleton FA, Strick PL, Brain Res Rev 2000; 4)Allen G,et al., Neuroimage 2005; 5)Habas C, et al.,J Neurosci 2009; 6) Zalesky A, Fornito A, Bullmore ET, Neuroimage 2010; 7) Serra L, et al,, Plos One 2016; 8)O'Reilly JX, et al.,Cereb Cortex 2010.