Disruption of functional connectivity of M1 and cerebellum in Multiple sclerosis: a long-range functional dysconnection?

Adnan A.S. Alahmadi[1,2], Carmen Tur[1], Matteo Pardini[1,3], Peter Zeidman[4], Rebecca S. Samson[1], Egidio D'Angelo[5,6], Ahmed T. Toosy[1,7], Karl J. Friston[4], and Claudia Angela Michela Gandini Wheeler-Kingshott[1,6]

[1]NMR Research Unit, Queen Square MS Centre, Department of Neuroinflammation, UCL Institute of Neurology, London, United Kingdom, [2]Department of Diagnostic Radiology, Faculty of Applied Medical Science, KAU, Jeddah, Saudi Arabia, [3]Department of Neurosciences, Ophthalmology and Genetics, University of Genoa, Genoa, Italy, [4]Wellcome Centre for Imaging Neuroscience, UCL, Institute of Neurology, London, United Kingdom, [5]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy, [6]Brain Connectivity Center, C.Mondino National Neurological Institute, Pavia, Italy, Pavia, Italy, [7]NMR Research Unit, Department of Brain Repair and Rehabilitation, Queen Square MS Centre, UCL Institute of Neurology, London, United Kingdom

Synopsis

This study investigated changes in functional and effective connectivity with M1 and anterior cerebellum using psychophysiological interaction (PPI) and resting-state fMRI (rsfMRI), applied to a motor task fMRI dataset in healthy subjects and multiple sclerosis (MS) patients. Results show that M1 in MS patients has reduced long-range connectivity to the contra-lateral hemisphere and the cerebellum and vice versa. Furthermore, MS patients lose visuo-motor integration with parietal areas. This is in contrast to rsfMRI functional connectivity, where connectivity of M1 to areas identified by the PPI network is increased. Results indicate a task-specific disconnection reflecting increased disability, associated also with low frequency maladaptive increased rsfMRI connectivity.

Purpose

To investigate the relationship of task-dependent with resting-state fMRI (rsfMRI) functional connectivity of the motor network in multiple sclerosis (MS)

Background

Patients with MS have abnormal functional connectivity patterns compared to healthy subjects (HS) (1); these differences are based on rsfMRI signal correlations, which generally show increased functional connectivity in MS. However, it is unclear what this means in terms of distributed processing during a task and this is the focus of our investigation. The ultralow frequency correlations of rsfMRI data may or may not reflect task-related changes in effective connectivity mediated by physiological events at neuronal and synaptic levels. We therefore used Psychophysiological Interaction (PPI) analysis (2) to characterise task-dependent connectivity changes, where a task is seen as the modulator of connectivity. Given that in MS the motor system is heavily affected, we focused on motor areas, aiming to:

1. Define the changes in effective connectivity with the primary motor cortex (M1) and anterior cerebellum (aCBL), using PPI in the context of a visuo-motor task in HS and MS;

2. Compare these changes with the functional (rsfMRI) connectivity of M1 and aCBL within the PPI-defined ROIs, both in HS and MS.

Methods

18 Right-handed subjects (9 HS: 5 females; mean (sd) age 30 (3.75) years and 9 relapsing-remitting MS: 7 females; mean age 34 (2.23) years; median (range) expanded disability status scale (EDSS) = 3 (1.5, 6.5)) were recruited.

MRI: (3.0T Philips Achieva scanner) 1) T2*-weighted EPI: TE/TR=35/2500ms, voxel size=3×3×3mm^3, SENSE=2, Slices=46, FOV=192mm^2, volumes=200 (for task fMRI); 2) Same as 1) but with volumes=120 (for rsfMRI (3)); 3) PD/T2 clinical scan; 4) 1mm isotropic 3D-T1-weighted scan.

Task paradigm: visually-guided event-related task with 150 jittered trials, randomized with rest, squeezing a ball using their right hand.

fMRI pre-processing: slice timing; realignment; co-registration; normalization and smoothing.

PPI statistical-analysis (figure-1) (using SPM12):

o The main effect of movement (for each subject) was entered into random effects analysis testing for group effects and between-group differences.

o A conjunction of motor activations (over both groups) was masked with anatomical regions of interest (ROIs) in left (contralateral) M1 and right (ipsilateral) aCBL.

o Centres of these two ROIs (seeds) were identified as the highest t-value (testing subject-specific movement effects) in each ROI. A subject-specific sphere of 8mm was selected for M1 and aCBL.

o Two PPI models were evaluated per subject including: M1 or aCBL responses as physiological factors, the main effect of motor task as the psychological factor, and the (PPI) interaction term, being the effect of interest.

o A second level analysis of PPI-M1 or PPI-aCBL effects was performed using one- or two-sample t-tests for within- and between-group comparisons.

o Maps were thresholded at the cluster level (one-sample=$P<0.05$, FWE; two-sample=$P<0.0001$).

rsfMRI statistical-analysis (figure-1) (using CONN (4)):

o Bivariate correlations measured ROI-to-ROIs rsfMRI connectivity with random effects analysis at group level.

o Source ROIs were M1 and aCBL, as in PPI, with targets being PPI network ROIs.

o ROI-to-ROIs significance used $P<0.05$, FWE.

Also, EDSS was used as a second level covariate.

Results

Main findings (see figures-2-5) are:

o In HS, the task-related (PPI) M1 network was organized around hubs for motor planning/execution, visual response and integration. Furthermore, clusters were symmetric in the brain and asymmetric in the cerebellum.
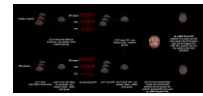
Figures

Fig.1. Infographic of the statistical analyses performed for the task fMRI, PPI and rsfMRI. The analyses from step (4) to step (9) were performed separately for M1 and aCBL.
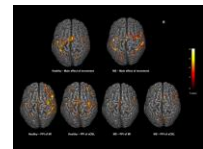

Fig.2. Examples of functional responses (activations) during the main effect of movement (top row). PPI connectivity to M1 and aCBL are also shown (bottom row).

Fig.3. PPI of M1 results in both HS and MS. Results are summarised for the purpose of illustrations into different ROIs; projected onto the SUIT flattened cerebellum for the cerebellar areas. Any Filled circles-connected ROIs; empty circles-ROIs that lost connectivity to M1 in MS but have greater functional activations; yellow-edged circles - comparisons HS>MS; blue-edged circles-ROIs that showed decreased connectivity to M1 with increasing disability.

Fig.4. PPI of aCBL in both HS and MS. Results are summarised for the purpose of illustrations into different ROIs; projected onto the SUIT flattened cerebellum for the cerebellar areas. Any Filled circles-connected ROIs; empty circles-ROIs that lost connectivity to aCBL in MS but have greater functional activations; yellow-edged circles - comparisons HS>MS; blue-edged circles-ROIs

o In MS, there was loss of task-related (PPI) connectivity with M1, preserving a motor hub but losing visuo-motor integration and cerebellar connectivity. Half of the connections of M1 and aCBL were lost within the M1 network, becoming largely lateralized. However, regional functional responses of disconnected ROIs were greater (mostly) in MS than HS.

o Two-sample *t*-tests showed that even when connectivity is preserved in M1 local hubs, this is reduced in MS and the reduction involves all domains. Furthermore, thalamic connectivity is reduced.

o rsfMRI connectivity of M1 was increased in MS. This was less evident for aCBL.

o Lower task-related (PPI) connectivity local to M1 and between aCBL and M1 was associated with increased disability. In contrast, rsfMRI showed an opposite correlation, where increased functional connectivity was associated with increased disability.

Conclusion

In this study, we identified effective (task-related) and functional (task-free) M1 and aCBL connectivity. Our results suggest that MS is characterised by a disconnection of long-range connectivity during task performance, while there are local compensatory attempts through increased activation (5). At ultralow frequencies, during rest, the same regions show increased connectivity, compared to HS. Given the task-related PPI disconnectivity and opposite correlation of connectivity with EDSS, we speculate whether increased rsfMRI functional connectivity in MS reflects a compensatory mechanism or may actually reflect a maladaptive frequency specific (task-related) functional disconnection, possibly also representing a reduction in white matter fibres' ability to support task connectivity in MS (6).

Acknowledgements

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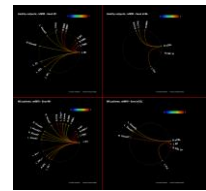that showed decreased connectivity to aCBL with increasing disability.

Fig.5. rsfMRI using ROI-ROIs analysis where the seeds are the ones used in the PPI and target areas are identified with the PPI results. The figure shows results in HV (top row) and MS (bottom row). A *t*-value bar is also provided.