ABNORMAL BRAIN CONNECTIVITY IN ADULT PATIENTS WITH PEDIATRIC-ONSET MULTIPLE SCLEROSIS AND MILD DISABILITY

A. GIORGIO[1], J. ZHANG[1], M. L. STROMILLO[1], F. ROSSI[1], M. MORTILLA[2], E. PORTACCIO[3], B. HAKIKI[3], M.P. AMATO[3], N. DE STEFANO[1]

[1]Department of Medicine, Surgery and Neuroscience, University of Siena; [2]Radiology Unit, Anna Meyer Children's University Hospital, Florence; [3]Department of Neurology, University of Florence

Background

Natural history studies have shown that pediatric-onset MS (POMS) reaches irreversible disability, despite slower progression, at a much younger age than adult-onset MS (AOMS). However, it is unclear whether young adult POMS shows more pronounced brain tissue damage and/or disrupted connectivity with respect to AOMS of similar age and disability

Objective

To assess brain tissue integrity and connectivity in young adult POMS patients with mild disability in comparison with age- and disability-matched AOMS patients

Material and methods

Multimodal brain MRI was acquired on a 3T MR scanner in POMS (n=15, age=24.8±7 years, disease duration=9.8±6.2 years) and age-matched AOMS (n=14, age=27.8±3 years, disease duration=5.2±2.2 years) and NC (n=20, age=27.1±4 years). The two MS groups had similarly mild disability (median EDSS: 1 in both). MRI analyses were performed with tools of FSL (FMRIB Software Library, Oxford University). Anatomical connectivity (AC) along white matter (WM) tracts was assessed from diffusion tensor imaging (DTI) images with TBSS while intra- and inter-resting state network [RSN] functional connectivity (FC) was evaluated with independent component (IC) analysis (ICA-AROMA/MELODIC/dual regression and FSLNets, respectively). FSL-VBM was used to assess local grey matter (GM) volumes. Voxelwise analysis of variance was performed with nonparametric permutation testing ($p<0.01$, corrected).

Results

T2-lesion volume

T2-LV in POMS was greater, although not significantly, than in AOMS (10.7±12 cm^3 vs 6.6±4.5 cm^3, p=0.8).

Anatomical connectivity

Compared with NC, both POMS and AOMS showed altered DTI measures. In particular, in POMS patients there was lower fractional anisotropy (FA) in clusters along inferior longitudinal fascicle (ILF), inferior fronto-occipital fascicle (IFOF), fornix (Fx), cerebellum, forceps major, posterior corona radiata (PCR) and WM of the middle frontal gyrus (Fig 1a-d). In addition, POMS patients also had higher axial diffusivity (AD) in PCR and Fx (Fig 1e-f) and higher radial diffusivity (RD) in PCR, ILF, IFOF, Fx, splenium of the corpus callosum, posterior thalamic radiation and forceps minor (Fig 1g-i). In the comparison between POMS and AOMS, the former showed higher AD and higher RD in the PCR (Fig 2a-b).

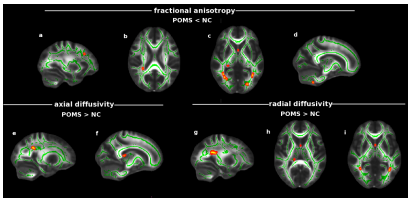
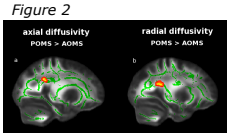


Figure 1

Figure 2



Grey matter volume

Compared with NC, both POMS and AOMS showed reduced GM volume mapping on the thalami. No significant difference was found between POMS and AOMS.

Short-range intra-network functional connectivity

No between-group differences were found in any RSN.

Long-range inter-network functional connectivity

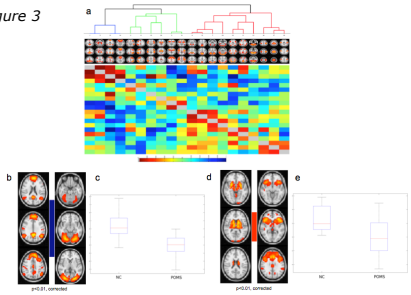
Hierarchical clustering

All averaged between-RSN correlation matrices were clustered hierarchically using their temporal similarity and led to different functional RSN groupings, represented by different colors (NC and POMS [Fig 3a], AOMS and POMS [Fig 4a], AOMS and NC [not shown]). Full correlations (below the diagonal) allow for the influence of other networks on RSN pairs while partial correlations (above the diagonal) represent a more direct relationship between RSN pairs.

NC vs POMS

There were two significant differences for full correlation, the first (negative correlation, blu bar in Fig 3b), between default mode network (IC8) and secondary visual network (IC7), the second (positive correlation, red bar in Fig 3d) between basal ganglia network (IC20) and salience network (IC3), with smaller connection strength in POMS than in NC (-4.06 vs -2.6, p=0.0016; 0.1 vs 2.0, p=0.01) (Fig 3c and e).

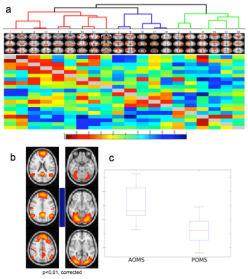
Figure 3



AOMS vs POMS

It was shown one significant difference for partial correlation in the (negatively correlated, blu bar in Fig 4b) connection strength between anterior default mode network (IC8) and secondary visual network (IC7), with a decrease in POMS compared to AOMS (-0.82 vs -0.22, p=0.0098) (Fig. 4c).

Figure 4



Conclusions

In spite of longer disease duration, POMS patients have a macroscopic (i.e., lesions and atrophy) brain tissue damage similar to that of AOMS patients with similar age and mild disability. However, in POMS patients there is a decrease in AC in the corona radiata, home of the motor pathways, which are clinically eloquent for physical disability, and also in the long-range FC of a relevant hub for cognition such as default mode network. Overall, such abnormal connectivity might explain in POMS patients at a relatively early disease stage their unfavourable long-term clinical outcome.

References 1. Renoux et al., N Engl J Med 2007, 356:3603-13. 2. Tenembaum et al., Curr Opin Pediatr 2010, 22:726-30. 3. Rocca et al., HBM 2014, 35:4180-92. 4. Akbar et al., PlosOne 2016, 11(1): e0145906. 5. Akbar et al., MSJ 2015, 22 96):792-800. 6. Krupp et al., Neurology 2007, 68(Suppl 2):S7-S12. 7. Smith et al., Neuroimage 2004,23 Suppl 1: S208-19. 8. Oguz et al., Neuroinformatics 2014, 8: 1-11. 9. Giorgio et al., J Neurosci 2015, 35(2): 550-558.