RESTING-STATE AND STRUCTURAL MRI METRICS RELATED TO FATIGUE IN MS, MOGAD AND NMOSD

Valentina Camera, MD[1,2] ; Silvia Messina, MD, DPhil[1]*; Ricarda Menke, PhD[1]*; Romina Mariano, MD, DPhil[1]; Ludovica Griffanti, PhD[3]; Ruth Geraldes, MD, DPhil[1]; Stefano Meletti, MD, PhD[2] ; Maria Isabel Leite, MD, DPhil[1] ; Jacqueline Palace MD[1]

1. Nuffield Department of Clinical Neuroscience, University of Oxford, Oxford, UK
2. Department of Biomedical, Metabolic and Neurosciences, University of Modena and Reggio Emilia, Modena, Italy 3. Department of Psychiatry, University of Oxford, Oxford, UK

BACKGROUND

Fatigue is frequently reported by patients with multiple sclerosis (MS), aquaporin-4 antibody neuromyelitis optica spectrum disorder (AQP4-NMOSD) and Myelin-Oligodendrocyte-Glycoprotein antibody disease (MOGAD)[1,2] .

This might suggest a similar pathophysiological mechanism.

AIMS

- Assess the presence of a single Resting State Network biomarker of fatigue across MS, AQP4-NMOSD, MOGAD
- Assess the presence of diffusion or structural imaging measures related to fatigue across MS, AQP4-NMOSD, MOGAD

METHODS

- 16 MS, 17 MOGAD and 17AQP4-NMOSD patients attending the Oxford NMO Service underwent Modified Fatigue Impact Scale (MFIS), Hospital Anxiety and depression scale (HADS) and EDSS scoring, and a same-day 3T brain and spinal cord MRI (3D T1WI, T2WI, DWI, resting-state functional imaging).
- Cortical thickness (CT), white matter lesion load and subcortical structures volumetrics, fractional anisotropy (FA) and functional connectivity (FC) metrics were derived using Freesurfer and FSL.
- The linear relationship between the MRI measures and the total (t-), cognitive (c-) and physical (p-) MFIS scoring were assessed in the total cohort.
- The analysis were adjusted for correlated clinical regressors. Bonferroni correction was applied in the resting-state analysis.

RESULTS

DESCRIPTIVE CLINICAL RESULTS	MS N=16	MOGAD N=17	AQP4-NMOSD N=17	P-value
Female n%	10 (62.5)	8 (47)	13 (76.5)	Ns
Median disease duration, yrs (range)	11.5 (1-19)	2 (0-24)	9 (0-24)	Ns
Median number of prior attacks, (range)	4 (1-13)	2 (1-11)	2 (1-11)	Ns
Mean age ± SD	43.6 ± 6.8	42.1 ± 10.9	56.7 ± 13.4	0.0005
Total MFIS score ≥ 38, n (%) Mean total MFIS score ± SD Mean cognitive MFIS score ± SD Mean physical MFIS score ± SD	6 (37.5) 37.7 ± 16.3 16.4 ± 8.2 17.9 ± 8.4	5 (29) 29.5 ± 21 13.3 ± 9.7 13.5 ± 9.9	10 (58.8) 38.4 ± 18.4 14.8 ± 8.6 19.3 ± 8.6	Ns Ns Ns Ns
EDSS median (range)	2 (0-6)	1.5 (0-7)	3 (0-7)	Ns
HADS depression score, median (range) HADS anxiety score, median (range) Clinical depression, n (%)	2 (1-14) 5 (2-14) 2 (12.5)	3 (0-11) 7.5 (0-19) 1 (6)	4 (0-12) 7 (0-18) 1 (6)	Ns Ns Ns

STRUCTURAL and DIFFUSION MRI MEASURES

CORTICAL THICKNESS
No associations with total, cognitive and physical MFIS
No differences across disease groups

TOTAL DEEP GREY MATTER VOLUME associated with:

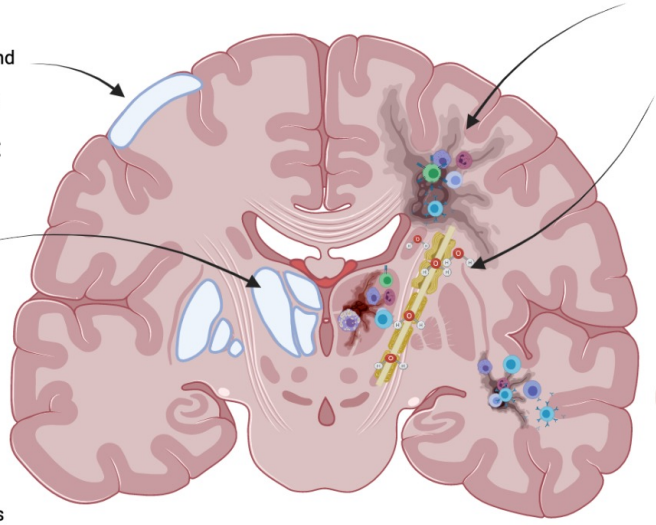
TOTAL MFIS B=-68, R2=0.19, p=0.011 (adjusted for age)

COGNITIVE MFIS B=- 140, R^2=0.18, p=0.014 (adjusted for age)

PHYSICAL MFIS B=-107, R2=0.14, p=0.054 (adjusted for age)

Significant results lost after further adjustments for EDSS and/or HADs

No differences across disease groups



COGNITIVE MFIS SCORE associated with:

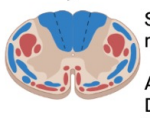
WHITE MATTER LESION LOAD
B=1186 ; R^2=0.22; p=0.034

TOTAL WHITE MATTER FRACTIONAL ANISOTROPY
B=-0.003, R^2=0.12, p=0.036

Adjusting for age, edss and HADs

No differences across disease groups

MFIS scores were not associated with:



Cervical spinal cord cross-sectional area

Spinal cord total, white matter, grey matter MTR

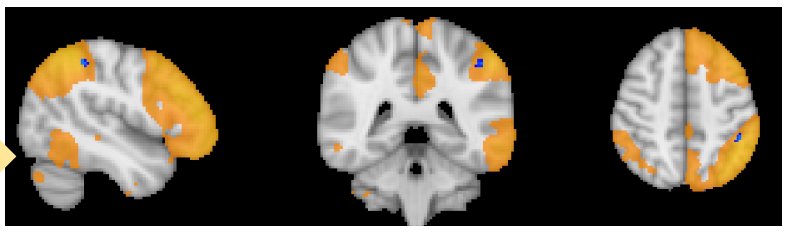
Average FC between Dorsal horns and Ventral horns

No differences across disease groups

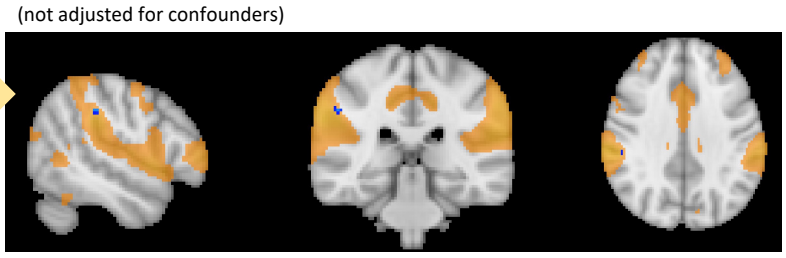
Created in BioRender.com

RESTING STATE FUNCTIONAL MRI FINDINGS	Whole cohort combined (MS+MOG+AQP)	MS vs (MOG+AQP)
Total MFIS	**A) Positive** relationship with FC of the **Fronto-Temporal (FT) network** with left middle temporal gyrus (p=0.033) **B) Negative** relationship with FC of **Salience network** in left anterior temporo-parietal cortex (p=0.026) **C) Negative** relationship with FC of the **Left Fronto-Parietal (FP) network** in left superior parietal cortex **(p=0.026)**	No significant differences
Total MFIS adjusted for AGE and EDSS	**D) Negative** relationship with FC of **Salience network** in left temporo-parietal cortex **(p=0.023)** *	No significant differences
Cognitive MFIS with or without adjustment for AGE + HADs total score	No significant results	No significant differences
Physical MFIS	**E) Positive** relationship with FC of **Sensory-Motor network** in the right pre-central motor cortex **(p=0.032)**	No significant differences
Physical MFIS adjusted for AGE and EDSS	**F) Positive** relationship with FC of **Sensory-Motor network** in the right pre-central motor cortex **(p=0.032)**	No significant differences
Physical MFIS adjusted for AGE, EDSS and HADs depression score	**G) Positive** relationship with FC of **Sensory-Motor network** in the right post-central gyrus (**p=0.018**)	No significant differences

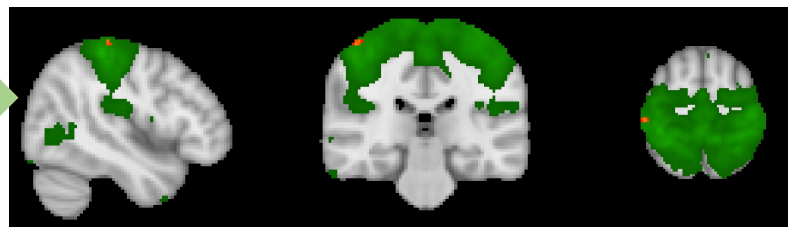
HADs=Hospital Anxiety and Depression scale. MFIS=Modified Fatigue Impact scale. MOG=MOGAD. AQP=AQP4-NMOSD.
*Salience network was not found associated with HADs depression score, however adding in HADs depression reduced power to see sig effect



C) NEGATIVE relationship between the total MFIS score and FC of the **Left Fronto-Parietal (FP) network** (orange) with the left the superior parietal cortex (blue) p=0.026 (not adjusted for confounders)



D) NEGATIVE relationship between total MFIS score and FC of the **Salience network** (orange) with the left parieto-temporal cortex (blue) p=0.023 (adjusted for AGE and EDSS)



G) POSITIVE relationship between the physical MFIS score and the FC of the **Sensory-Motor network** (dark green) with the the right post-central gyrus (red) p=0.018 (adjusted for AGE, EDSS, HADs depression score)

SUMMARY and INTERPRETATION

- Functional and structural imaging metrics associated with fatigue do not appear to differ across MS, MOGAD and AQP4-NMOSD
- The Salience network appears important in total fatigue and the Sensory-Motor network for physical fatigue perception
- Alteration of the Sensory-Motor network, including postcentral gyrus, precentral gyrus and supplementary motor areas, has previously reported in MS fatigued patients[3]
- Deep grey matter (DGM) volume loss was associated with fatigue although this did not survive multiple adjustments for covariate which could be related to powering and DGM damage may contribute to a functional connectivity alteration within the Salience network[4].
- Cognitive fatigue was associated with WM lesion load and total WM FA after adjustment for covariates. As reported in previous studies, the reduced white matter integrity might interfere with the cortical and DGM connections within the Salience network in cognitive fatigued patients[4,5].
- It appears fatigue may be a disconnection between perception of activity (reversable or irreversible) and future research should focus on rehabilitative strategies

REFERENCES
1. Penner IK, Friedmann P. Fatigue as a symptom or comorbity of neurological diseases. Nat Rev Neurol, 2017, 13 (11):662-675; 2. Yeo T, et al. Factors associated with fatigue in CNS inflammatory diseases with AQP4 and MOG antibodies. Ann Clin Tran Neurol. 2020, 7 (3): 375-383; 3. Manjaly ZM et al. Pathophysioogical and cognitive mechanisms of fatigue in multiple sclerosis. Journal of neurology, neurosurgery and psychiatry. 2019, 90 (6): 642-651; 4. Uddin L. Salience processing and insula cortical function and dysfuction. Nat Rev Neuroscie, 2015, 16 (1): 55-61; 5. Genova HM et. al. Examination of cognitive fatigue in multiple sclerosis using functional magnetic resonance imaging and diffusion tensor imaging. PloS one. 2013, 8 (11): e78811-e78811

ACKNOWLEDGEMENTS: We thank the European Charcot Foundation Research Fellowship for funding Dr Valentina Camera, the Highly Specialised Services NHS England and the MS society.

DISCLOSURES: VC grants from European Charcot Foundation and received support for scientific meeting from Janssen; SM,RM, RM, LG, SM, RG , nothing to disclose; JP support for scientific meetings/talks and honorariums for advisory work from Merck Serono, Novartis, Chugai, Alexion, Roche, Medimmune, Argenx, UCB, Mitsubishi, Amplo, Janssen and grants from Alexion, Chugai, MedImmune, and Amplo.