RELEVANCE OF FUNCTIONAL CONNECTIVITY ABNORMALITIES TO COGNITIVE IMPAIRMENT IN NEUROMYELITIS OPTICA SPECTRUM DISORDER

[1,2]P. Preziosa, [1]P. Valsasina, [1]F. Savoldi, [1]G.C. Riccitelli, [2]M. Radaelli, [2]G. Comi, [3]A. Falini, [1,2]M. Filippi, [1,2]M.A. Rocca.

[1]Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, [2]Dept. of Neurology and [3]Dept. of Neuroradiology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy.

INTRODUCTION and PURPOSE

•Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune inflammatory disorder of the central nervous system.
•In 2015, new diagnostic criteria have been released:

1999

No symptoms of brain involvement

Wingerchuck et al., Neurology 1999 [1]

2015

New criteria: optic nerve, spinal cord, area postrema, other brainstem, diencephalic, or cerebral presentation

Wingerchuck et al., Neurology 2015 [2]

•Approximately 40-60% of NMOSD patients show cognitive impairment (CI) [3,4].
•The frequency of occurrence of CI in NMOSD and multiple sclerosis (MS) patients was found to be similar [3,5], or slightly lower in NMOSD than MS [6].
•The cognitive domains most frequently involved are long-term memory, information processing speed, attention and executive functions.
•Compared to NMOSD, MS patients tend to have more severe impairment in learning and memory tests [6].
•Despite the traditional notion of a relative sparing of brain tissue in NMOSD, previous MRI studies have shown significant damage of the normal-appearing white matter and grey matter [7] as well as atrophy of the thalamus [4] and visual cortex [8] in these patients.
•Structural imaging studies have detected hippocampal atrophy in NMOSD patients with CI [4].
•Using resting state (RS) fMRI, decreased RS functional connectivity (FC) in the default mode network and increased RS FC in basal ganglia and frontal regions have been described in NMOSD patients [9,10].
•Cognitive network RS FC correlates of CI in NMOSD patients have not been investigated yet.

Aim of this study was to compare RS FC within and among cognitive RS networks between patients with NMOSD, MS and healthy controls, using independent component analysis.

METHODS

Clinical assessment:
•NMOSD patients: defined according to the AQP-IgG+ 2015 International consensus diagnostic criteria [2].
Seventeen patients (65%) had T2-hyperintense lesions in the brain (typical AQP-IgG+ pattern: 3 patients).
•Control groups: 30 MS patients, 30 healthy controls (HC).
Inclusion criteria: right-handedness, no history of drug and alcohol abuse, no other major clinical and psychiatric conditions.
Neurologic examination: clinical history, EDSS rating, collection of AQP-IgG test (type and result).
Neuropsychological assessment:
-Attention and information processing speed: Symbol modalities test, Paced auditory serial addition task 2" and 3";
-Verbal and visual spatial memory: Selective reminding digit test; 10/36 Spatial recall test;
-Executive functions: Stroop test.
Abnormal test: score ≥ 2 SD below normative values.
Computation of a global and domain-related cognitive impairment index (CII) [11].
Cognitively impaired (CI) patients: abnormal scores in at least two neuropsychological tests.

fMRI acquisition and analysis:
•3.0 Tesla Philips Achieva: 200 RS fMRI scans acquired with a T2*-weighted EPI sequence (TR/TE=3000/35 ms, 30 slices, 4 mm thickness).
•Independent component analysis (ICA): GIFT software (http://mialab.mrn.org/software/gift). Identification of RSNs of interest by frequency analysis if IC time courses and a template-matching procedure.
•Connectivity among networks: Functional network connectivity (FNC) toolbox. Significant temporal correlations between all pair-wise combinations of components [12].

Statistical analysis:
•RS FC analysis (SPSS software):
-Calculation of a global RS FC Z-score for each network, and of regional Z-scores of RS FC for each cluster of the networks.
-Between-group comparison of RS FC: ANOVA models with *post-hoc* comparisons.
-Correlation between RS FC abnormalities and CII: Spearman's rank correlation coefficients.
•FNC analysis (SPSS software):
-Within-group connections between RSNs of interest: one-sample t test.
-Between-group comparison of connections between RSNs of interest: ANOVA models.

RESULTS

Table 1. Main demographic, clinical, and structural MRI characteristics of the study groups.

	HC	NMOSD patients	MS patients	p	CP NMOSD	CI NMOSD	CP MS	CI MS
F/M	21/9	20/6	19/11	0.54*	13/4	7/2	13/7	6/4
Age [y] (SD)	42.3 (11.1)	43.6 (11.5)	37.3 (12.7)	0.07+	37.5 (8.6)	55.0++ (6.5)	36.4 (12.8)	39.2 (12.9)
Median EDSS (range)	-	4.5 (1.0-7.5)	2.0 (1.0-8.0)	0.51**	3.5 (1.0-7.5)	5.5 (1.5-7.0)	1.5 (1.0-8.0)	3.5 (1.5-8.0)
Mean disease duration [y] (range)	-	6.7 (1.0-30.2)	8.5 (1.0-25.0)	0.06**	7.2 (1.0-30.2)	5.7 (1.4-13.1)	8.3 (1.0-25.0)	8.8 (1.6-23.0)
T2 LV [ml] (SD)	-	1.9 (5.3)	7.1 (6.2)	<0.001**	2.6 (6.6)	0.8 (0.8)	7.7++ (6.8)	5.6 (4.3)
T1 LV [ml] (SD)	-	0.5 (1.4)	4.6 (4.3)	<0.001**	0.6 (1.8)	0.5 (0.6)	5.0++ (4.7)	3.6++ (3.1)

* Pearson's Chi-Square test; ** Mann-Whitney U test; + Kruskall and Wallis test.
++*Post hoc*: age of CI NMOSD and T2 LV of CP MS significantly higher than the other study groups; T1 LV of CP and CI MS significantly higher than T1 LV of CP and CI NMOSD.

Table 2. Results of neuropsychological evaluation of NMOSD and MS patients.

	NOMSD patients	MS patients	p	CP NMOSD	CI NMOSD	CP MS	CI MS
Cognitive impairment (%)	9/26 (35%)	10/30 (33%)	0.92*	-	-	-	-
Global CII (SD)	22.3 (9.1)	26.2 (7.6)	0.15**	27.6 (4.8)	12.1+ (5.6)	29.5 (6.2)	19.4+ (5.0)
Memory CII (SD)	12.2 (5.3)	13.2 (5.3)	0.52**	14.7 (3.3)	7.3+ (4.8)	15.1 (4.9)	9.5+ (3.8)
Attention CII (SD)	4.7 (3.6)	6.7 (4.0)	0.07**	6.70 (2.6)	0.77+ (1.4)	8.1 (3.5)	3.9+ (3.4)
Executive functions CII (SD)	5.5 (2.4)	6.2 (1.9)	0.38**	6.23 (2.1)	4.00+ (2.3)	6.35 (1.7)	6.0+ (2.1)

* Pearson's Chi-Square test; ** Mann-Whitney U test.
+*Post hoc*: CII scores of CI patients always significantly lower of the corresponding CP group; CII scores of CP NMOSD and CP MS not different; significantly lower global and attention CII scores in CI NMOSD than in CI MS.

• **RS FC analysis**: **Figure 1** shows the spatial patterns of the main cognitive networks detected by the ICA.

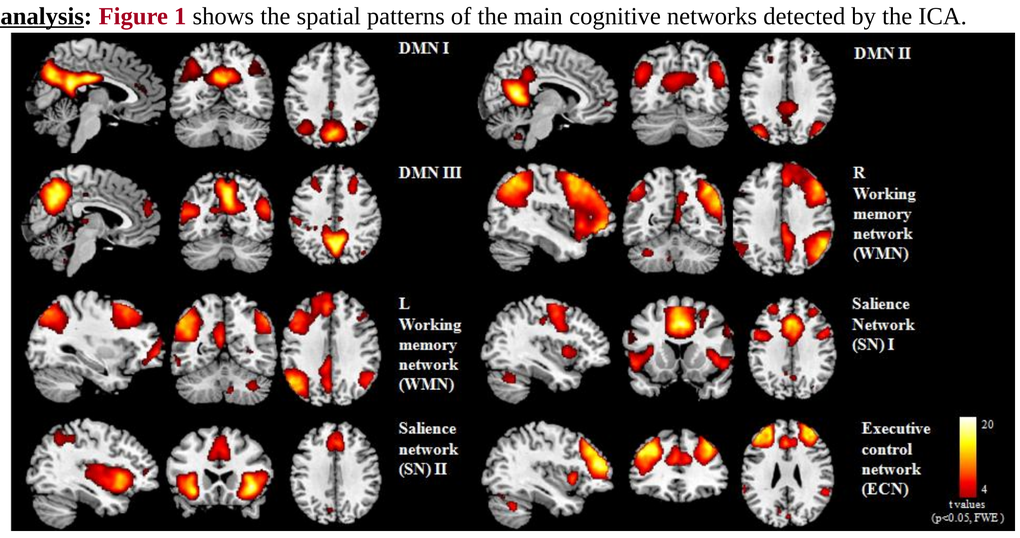

Table 3. Between-group differences of whole-network RS FC between HC, NMOSD and MS patients.

RS network	Whole-network RS FC Z-score (SD)					p*
	HC	CP NMOSD	CI NMOSD	CP MS	CI MS	
DMN I	1.60 (0.32)	1.72 (0.23)	**1.38 (0.26)**	1.75 (0.27)	1.64 (0.40)	**0.04**
DMN II	1.39 (0.26)	**1.55 (0.20)**	**1.21 (0.24)**	1.48 (0.16)	1.55 (0.18)	**0.002**
DMN III	1.13 (0.25)	1.21 (0.17)	1.06 (0.21)	1.17 (0.16)	1.11 (0.17)	0.53
ECN	1.05 (0.21)	1.15 (0.16)	**0.94 (0.15)**	1.15 (0.14)	1.06 (0.20)	**0.02**
SN I	0.91 (0.17)	1.02 (0.14)	0.92 (0.14)	1.03 (0.12)	1.00 (0.15)	**0.04**
SN II	1.02 (0.17)	**1.13 (0.18)**	**0.86 (0.09)**	1.08 (0.15)	0.96 (0.11)	**0.001**
L WMN	1.16 (0.21)	1.24 (0.16)	1.09 (0.17)	1.21 (0.23)	1.20 (0.11)	0.34
R WMN	1.16 (0.18)	1.24 (0.15)	1.09 (0.19)	1.23 (0.16)	1.20 (0.16)	0.14

*ANOVA model; Red and blue: significant *vs* HC; **bold**: significant *vs* CP or CI, respectively.

Figures 2, **3** and **4** show the results of the between-group comparison of regional Z-scores of RS FC.

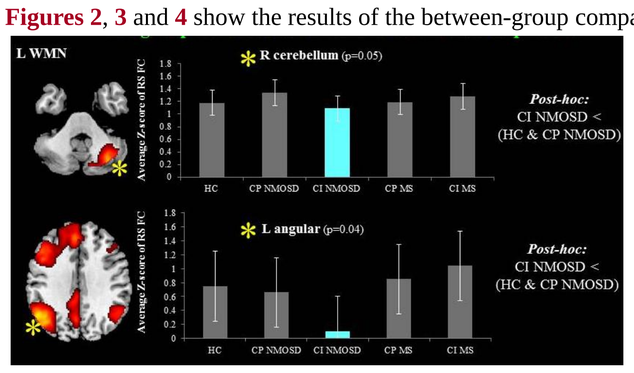

Figure 2. Effects driven from NMOSD patients.

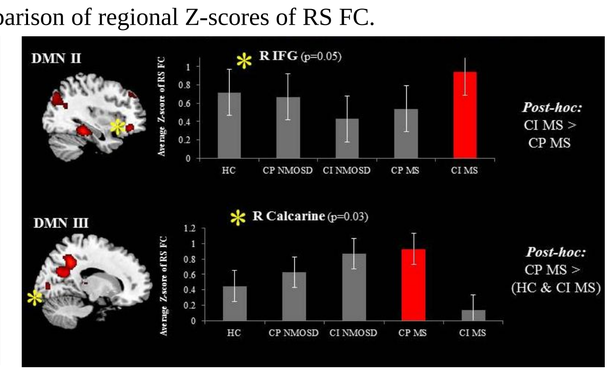

Figure 3. Effects driven from MS patients.

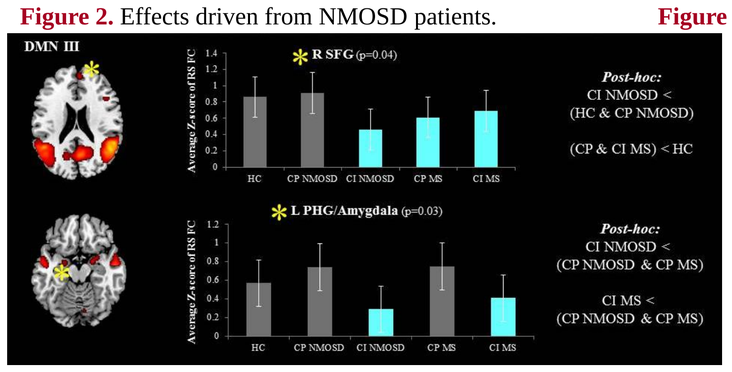

Figure 4. Effects in NMOSD and MS patients.

Figures 5 and 6 show the results of FNC analysis in NMOSD and MS patients, respectively.

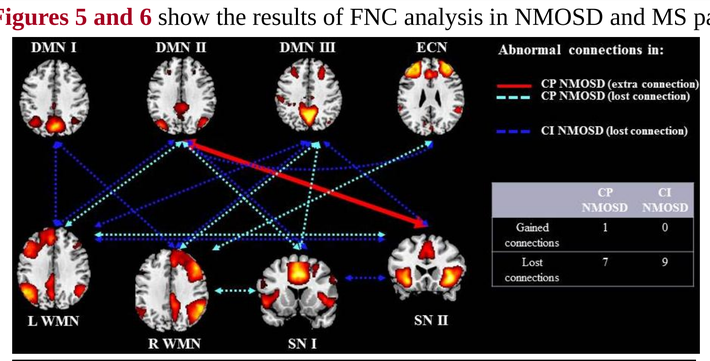

Figure 5. FNC analysis – NMOSD patients.

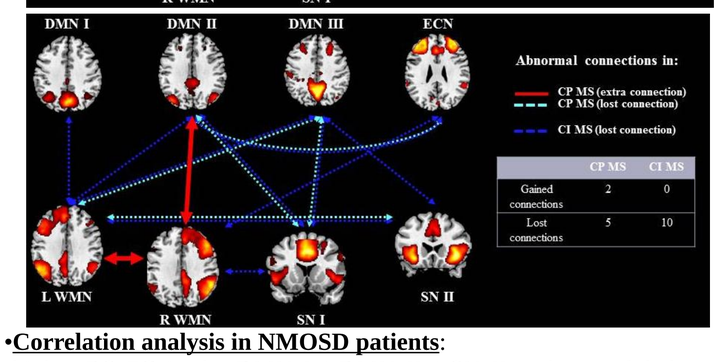

Figure 6. FNC analysis – MS patients.

•**Correlation analysis in NMOSD patients**:
-higher RS FC in the DMN I / DMN II / SN II *vs* better global, memory and attention CII scores (r=range 0.46-0.63, p=range 0.01-0.001);
-lower RS FC in the ECN *vs* worse global (r=0.44, p=0.02) and attention CII scores (r=0.45, p=0.02);
-lower RS FC in the R PHG of the DMN *vs* lower global (r=0.42, p=0.03) and attention (r=0.45, p=0.01) CII scores.
•**Correlation analysis in MS patients**:
-higher SN I RS FC *vs* better global CII score (r=0.39, p=0.03), lower T2 LV (r=-0.39, p=0.03) and lower T1 LV (r=-0.41, p=0.02).

CONCLUSIONS

• The prevalence and features of CI are similar between NMOSD and MS patients.
• CI NMOSD patients experience reduced global and regional RS FC in the main cognitive networks (especially the DMN, Sn and ECN), whereas CP NMOSD patients have increased RS FC in the DMN and SN.
• MS patients have global RS FC modifications at a lesser extent than NMOSD. At a regional level, a complex pattern of RS FC abnormalities contributes to characterize CI MS patients, with both regions of increased as well as decreased connectivity.
• The FNC analysis shows a trend towards a loss of inter-network connectivity in both patients'groups. The loss of connections is more marked in CI patients, while extra-connections are present in CP patients only.
• The correlation analysis shows that increased RS FC might have a compensatory role, whereas reduced RS FC is associated with worse cognitive performances.
• In MS patients, the progressive accumulation of structural damage might result in inefficient functional reorganization.

REFERENCES

[1] Wingerchuck et al., Neurology 1999; [2] Wingerchuck et al., Neurology 2015; [3] Blanc et al., Arch Neurol 2008; [4] Liu et al., Neurology 2015; [5] Vanotti et al., Arq Neuropsiquiatr 2013; [6] Kim et al., Mult Scler 2015; [7] Rocca et al., Neurology 2004; [8] Liu et al., Eur Radiol 2014; [9] Liang et al., Clin Neurophysiol 2011; [10] Liu et al., Eur J Radiol 2011; [11] Camp et al., Brain 1999; [12] Jafri et al., Neuroimage 2008.