Functional connectivity alterations in the mesolimbic-cortical dopaminergic system: a potential marker of depression in multiple sclerosis

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BACKGROUND AND AIMS

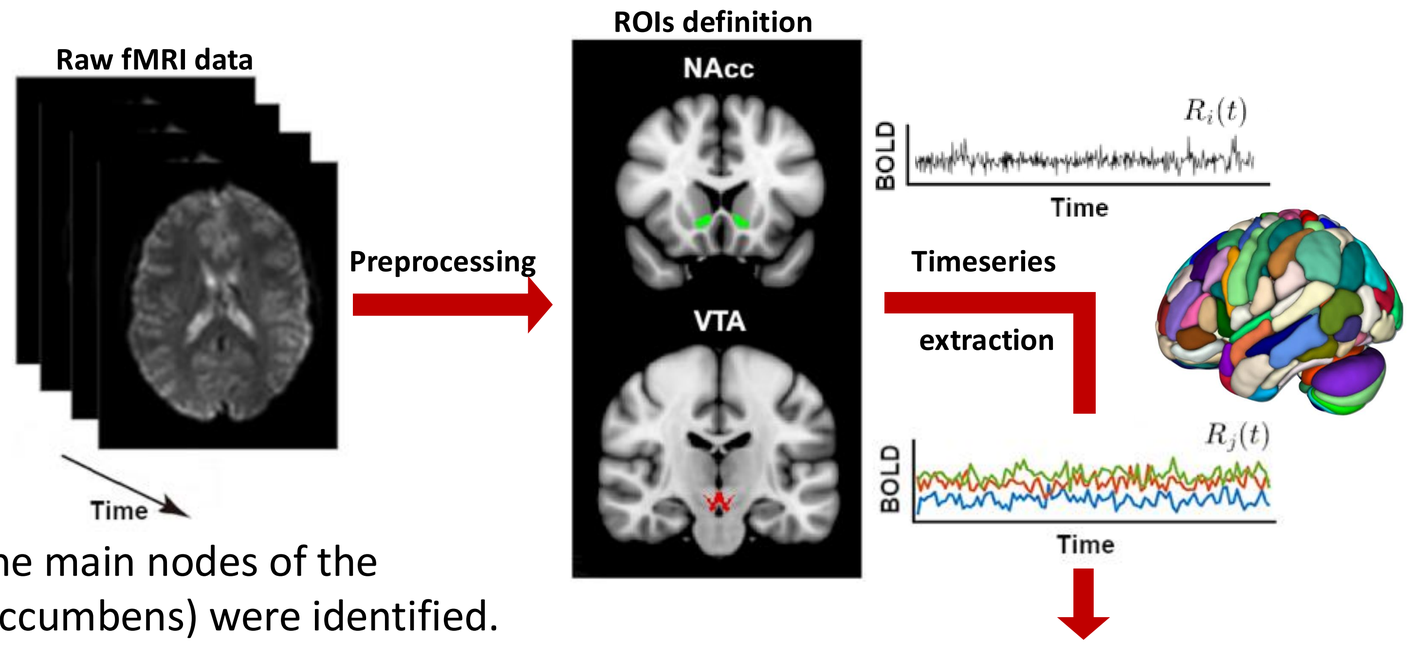
Depression is one of the most common and debilitating comorbidities in Multiple Sclerosis (MS), significantly impacting patients' quality of life. However, the biological basis underlying this clinical association is still poorly understood. Neurotrasmitter signaling change is assumed to play a core role in the pathophysiology of depression. In particular, a dysregulation of dopamine modulation and a disruption of functional connectivity between the key nodes of the mesolimbic-cortical dopaminergic system, commonly known as *reward circuit*, have been identified as a relevant study target to understand the onset of typical symptoms of major depression disorder, such as loss of motivation and pleasure. Based on these data, a similar functional disconnection has been hypothesized to occur in MS patients experiencing depression. Therefore, the main aim of the present study is to investigate the functional connectivity in the reward circuit in MS patients with depression, compared to MS patients without depression and healthy controls.

METHODOLOGY

Participants and Clinical assessment:

	HC	MS-nD	MS-D
Age, mean(SD)	39.0 (±13.3)	42.9(±8.21)	45(9.73)
Sex, Females/Males	18/12	17/13	22/8
DD, mean (SD)	-	8.94 (±9.12)	7.88 (±5.36)
EDSS, median (range)	-	1.75 (0-6.5)	2.25 (0-6.5)
SDMT-Tscore, mean (SD)	51.4(±10.1)	45.8(±11.4)	48.2(±15.5)
CVLT-Tscore, mean (SD)	59.1(±9.07)	54.8(±13.9)	47.7(±13.4)
BVMT-Tscore, mean (SD)	59.5(±13.6)	55.8(±12.9)	55.3(±14.4)
9HPT-DH, mean (SD)	20.4(±3.4)	23.1(±5.78)	23.3(±4.39)
9HPT-NDH, mean (SD)	20.7(±2.99)	25(±5.66)	26.2(±8.66)
25FWT, mean (SD)	4.46(±0.9)	5.74(±1.82)	6.84(±3.16)
HADS-D, mean (SD)	3.10(±2.02)	3.37(±1.96)	12.7(±1.60)
MFIS, mean (SD)	12.6 (±10)	20.6(±18.9)	52.0(±14.4)

90 subjects were prospectively enrolled in the study: 30 MS patients with depression (MS-D, HADS-D>11), 30 MS patients without depression (MS-nD, HADS-D<11) and 30 healthy controls (HC). All subjects underwent clinical evaluation and MRI acquisition with a 3T MR scanner (Siemens Prisma).



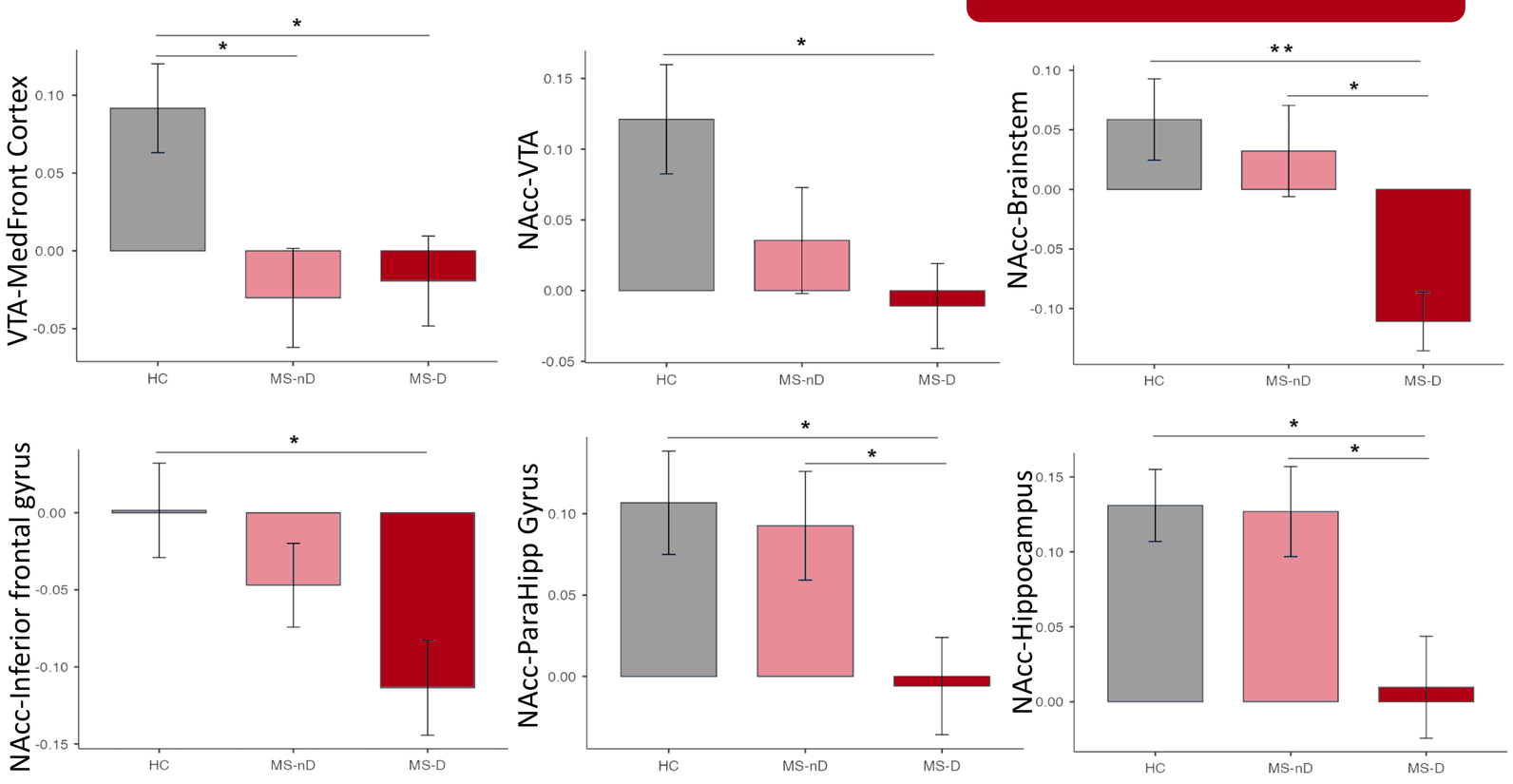
fMRI analysis:

Resting-state fMRI data were preprocessed with a standard pipeline including realignment, slice timing correction, smoothing and denoising, and analyzed with the CONN software. Two regions of interest (ROIs), corresponding to the main nodes of the reward circuit (VTA, ventral tegmental area; NAcc, nucleus accumbens) were identified. Their timeseries were extracted and correlated with BOLD activity across brain regions defined by the Harvard-Oxford Cortical/Subcortical atlas. Particularly, functional connectivity (FC) was evaluated by calculating the Pearson correlation coefficient between pairs of ROIs BOLD timeseries, which was then transformed to z-value with Fisher r-to-z transformation in order to improve normality. For the second-level analysis, FC measures were entered in an ANOVA, with age and sex as covariates, in order to assess significant differences between groups. Post-Hoc analyses were performed with a Bonferroni correction.

$$r(i,j) = \frac{\int R_i(t)R_j(t)dt}{\left(\int R_i^2(t)dt \int R_j^2(t)dt\right)^{1/2}}$$

$$Z(i,j) = tanh^{-1}\left(r(i,j)\right)$$

RESULTS



MS-D and MS-nD were significantly different for EDSS and HADS-D scores, but no differences were found in disease duration and lesion volumes. Significant differences of FC were found between groups including:

VTA-Medial Frontal Cortex (F=5.34, p=0.007); NAcc-VTA (F=3.19, p=0.04); NAcc-BrainStem (F=6.27, p=0.003); NAcc-Inferior frontal gyrus left (F=3.1, p=0.05); NAcc-Parahippocampal gyrus right (F=3.96, p=0.02); Nacc-Hippocampus right (F=4.83, p=0.01).

CONCLUSIONS

Preliminary results indicated altered FC within the mesolimbic-cortical dopaminergic system in MS-D patients compared to MS-nD and HC. The next phase of the study will include a group of 30 patients with major depression disorder but without MS to further investigate similarities and differences between groups and to better elucidate the pathogenic mechanisms underlying depression in MS.
These findings are expected to improve diagnostic accuracy and support the development of personalized and effective therapies.

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