EXPLORING THE RELATIONS BETWEEN EMOTIONAL DISABILITY AND SUBCORTICAL ATROPHY IN PATIENTS WITH MULTIPLE SCLEROSIS

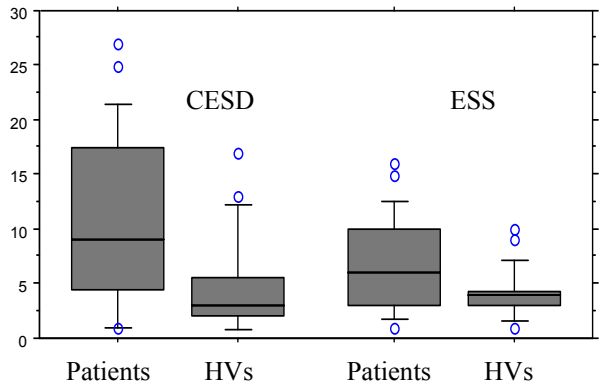
F. Bagnato[1], C. Pellicano[1], F. Cantor[1], A. Gallo[1], S. Auh[2], M. Ehrmantraut[1], I. Evangelou[1], V. Ikonomidou[1], R. Kane[3], J. Ohayon[1], S. Stern[1], and H. McFarland[1]

[1]NIB-NINDS-NIH, Bethesda, Maryland, United States, [2]Clinical Director Office-NINDS-NIH, Bethesda, Maryland, United States, [3]VA, Baltimore

Introduction: We investigated the relationship between atrophy of subcortical grey matter (GM) structures and depression in multiple sclerosis (MS). The reasons leading us to such an investigation were threefold: (i) the burgeoning evidence that subcortical GM atrophy affects patients with MS and is related to both physical and cognitive disability; (ii) the notion that volume loss and dysfunction of numerous GM subcortical structures has been linked to the occurrence of depression in otherwise healthy persons; (iii) the lack of existing literature on the relations between deep GM atrophy and depression in MS.

Methods: Twenty-four patients with MS (female/male = 17/7, age = 45.4±9.7 years, disability score at the Expanded Disability Status Scale or EDSS = 1.0-6.0) and 24 age-, sex- and education-matched healthy volunteers (HVs) participated in this study. Within a one-month period, each subject underwent the following procedures: (1) clinical routine 1.5Tesla Magnetic Resonance Imaging (MRI) to inspect for presence of contrast enhancing lesions in patients and rule out unsuspected lesions in the HVs; (2) physical examination rating disability for MS patients by means of the Expanded Disability Status Scale (EDSS), the Timed 25-Foot Walk (T25FW) and the 9-hole peg (9-HPG) tests (3) 3.0 T research brain MRI; (4) evaluation of depression and sleep disturbances. Depression was evaluated using the Center for Epidemiologic Studies Depression Scale (CESD) [1]. Sleep disturbances were assessed using the Epworth Sleepiness Scale (ESS). [2] MRI measures of white matter lesion volume (WM-LV), deep GM or whole brain volumes were obtained.
Differences in demographic, clinical and MRI characteristics between patients and HVs were assessed using a paired t-test (since matched for age, sex and years of education) and an unpaired t-test between patients with and without depression. Bivariate measurements of deep GM structures for each subject, one obtained from the left hemisphere (LH) and the other obtained from the right hemisphere (RH), were treated as two correlated observations. A linear mixed-effects model assuming a compound symmetric covariance structure was conducted to investigate the difference between patients and HVs as well as between patients with and without depression. The effect of group (i.e., patients and HVs) and side (i.e., LH and RH) were assessed. Prior to such an analysis the interaction term (i.e., group*side) was studied. When found to be significant, group and side effects were studied separately using paired or unpaired t-tests as appropriate. Within patients, Spearman correlation analyses were performed between each clinical measure, MRI variable and scores on the CESD and ESS. Partial correlations using clinical measures as controlling factors were also employed to investigate the relations between the CESD and ESS scores and each MRI variable previously found to be significantly related to any clinical or demographic measures.

Results: As shown by box plots in the figure below, compared to HVs, patients presented with higher scores on both the CESD (p=0.0013) and the ESS (p=0.018).
In examining patients with (n=7) and without depression, we found the former to have lower thalamic (p=0.037) and hippocampus (p≤0.030) volumes. No differences in WM-LV and whole brain volumes were seen between depressed and non-depressed patents.



	Controlling variable	p-value	r-value
Correlations Analyses with CESD			
LH-Thalamus	Age	0.010	-0.524
	Years of MS	0.024	-0.469
	EDSS	0.005	-0.561
RH-Thalamus	Years of MS	ns	
	EDSS	0.047	-0.419
	T25WF	0.020	-0.480
LH-hippocampus	T25WF	0.006	-0.554
RH-caudate	Years of MS	Not significant (ns)	
	EDSS	ns	
	T25WF	ns	
	9-HPT Left	ns	
Correlations Analyses with ESS			
LH-hippocampus	T25WF	0.012	-0.525

Significant relationships were found between the normalized volume of the LH-thalamus and disease duration, EDSS and T25WF; the normalized volume of the LH- hippocampus and T25WF; and the normalized volume of RH-caudate and age, disease duration, EDSS and T25WF. Owing to these findings, correlation analyses between the normalized volume of each one of those structures and the CESD or ESS were repeated employing a partial correlation analysis and using each one of the demographic or clinical variables as controlling factors. Partial correlation analyses obtained controlling for the effect of clinical and demographic variables, showed numerous significant associations between the depression level and GM atrophy. We present these results in the Table above.

Discussion: In patients with MS, subcortical atrophy of the structures of the limbic circuit may explain up to 30% of the variance of the degree of depression. This relationship is not influenced by the effect of physical disability, which could explain the occurrence of depression as an emotional reaction to the disease. The results support the hypothesis that, at least part of the MS-induced depression is associated to disease in topographically-specific areas Our findings demonstrate that the neurodegeneration which underlies the physical manifestations of the disease can also directly affect the emotional presentation of MS patients.

References: [1] Radloff LS. *Appl Psychol Meas* 1977;1:385–401; [2] Johns MW. *Sleep* 1991;14:540-545.