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Neuroimaging of emotional dysregulation in multiple sclerosis: relationship with alexithymia

van Assche Mitsouko[ab], Simioni Samanta[cd], Vrtička Pascal[efg], Sander David[ef], Schluep Myriam[ch], Vuilleumier Patrik[abf]

[a] Neurology Unit, Department of Clinical Neurosciences, Geneva University Hospitals (HUG), Geneva, Switzerland
[b] Laboratory for Neurology and Imaging of Cognition, Department of Fundamental Neurosciences, University of Geneva, Campus Biotech, Geneva, Switzerland
[c] Department of Clinical Neurosciences, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland
[d] Institution de Lavigny, Lavigny, Switzerland
[e] Laboratory for the study of Emotion Elicitation and Expression (E3 Lab), Department of Psychology, University of Geneva, Geneva, Switzerland
[f] Swiss Centre for Affective Sciences, University of Geneva, Campus Biotech, Geneva, Switzerland
[g] Centre for Brain Sciences, Department of Psychology, University of Essex, Colchester United Kingdom
[h] University of Lausanne, Lausanne, Switzerland

Summary

Patients with multiple sclerosis (MS) often show alexithymia, but the brain mechanisms underlying this emotional disorder remains unknown. We used functional magnetic resonance imaging (fMRI) to investigate alterations of emotion processing and emotion regulation in patients with MS, and their relationships with alexithymia. Nineteen MS patients with minimal disability and twenty healthy control (HC) participants took part in this cross-sectional study. During fMRI, participants viewed scenes conveying negative or positive emotions, and were asked to rate the intensity of their emotional state (1) after spontaneous viewing and (2) after emotion regulation (cognitive reappraisal). Self-reported questionnaires targeting alexithymia and other affective disorders were collected, in addition to functional and anatomical MRI. We compared brain activity and functional connectivity between each group during emotion processing and reappraisal. Moreover, we performed correlation analyses between affective questionnaire scores, subjective emotion ratings, brain activity, and structural integrity. Results showed a higher rate of alexithymia in MS patients. Globally, subjective ratings of emotional state were similar between MS and HC during both spontaneous perception and reappraisal. However, in both task conditions, the MS group showed increased responses to emotional scenes in the orbital inferior frontal gyrus, compared with controls. Moreover, during the reappraisal of negative scenes, these regions displayed increased functional connectivity with the amygdala, whose activity was positively correlated with alexithymia severity in MS. Our findings suggest a direct relationship between alexithymia and a lack of down-regulation of amygdala activity in response to negative emotions during reappraisal in MS. Moreover, they highlight compensatory mechanisms in minimally disabled MS patients, recruiting fronto-striatal circuits, which may serve to preserve homeostasis of amygdala activity and affective state.

Correspondence:
Mitsouko van Assche, PhD, Neurology Unit, Department of Clinical Neurosciences, Geneva, University Hospitals, Rue Gabrielle-Perret-Gentil 4, CH-1211 Geneva 4, mitsouko.vanassche[at]gmail.com

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Introduction

Impairments in cognition and social functioning are increasingly recognised in multiple sclerosis (MS) and contribute to handicaps in everyday life [1]. Such deficits may result from long-range disconnections induced by demyelinating lesions due to the disease [2, 3]. In particular, associated emotion perception disorders have been linked to dysfunctional activity within a network of brain regions comprising the ventrolateral prefrontal cortex (PFC) and the amygdala [4–7], respectively involved in the cognitive and affective evaluation of behaviourally relevant events [8–10].

Emotion regulation abilities are a key component of affective processes and psychological health. These may be impaired in MS and contribute to behavioural difficulties in patients and include alexithymia [11–14], characterised by the inability to identify and describe ones' own feelings. Emotion regulation mechanisms, such as cognitive reappraisal, primarily involve top-down modulatory inputs from the lateral PFC to the amygdala [15], leading to a decreased response of the amygdala to negative stimuli [16–20]. Healthy alexithymic subjects typically use poorly efficient strategies to regulate their emotions [21, 22] and display a reduced amygdala response to negative stimuli [23]. On the other hand, other regions within a distributed prefrontal-striatal-pallidalthalamic-limbic network also take part in the regulation of amygdala activity [15, 20, 24, 25]. For instance, in healthy participants, as well as in other neurodegenerative disorders, lower striatum activity has been repeatedly implicated in alexithymia [13, 23, 26]. However, in MS, current knowledge underlying the neural substrates of alexithymia is restricted to the sole finding of increased atrophy in the posterior corpus callosum [27], tentatively linked to impaired communication of affective information between the two hemispheres. On the other

hand, disconnection lesions commonly associated with MS might potentially disrupt top- down modulation of emotion processing by cognitive reappraisal, a hypothesis that remains to be explored.

Here we used functional magnetic resonance imaging (fMRI) to examine brain circuits mobilised in MS patients during emotion perception and regulation [28, 29]. Patients were probed for alexithymia as well as other affective disorders, enabling us to investigate their relationship with emotion perception and regulation abilities, and concomitant brain activity. We hypothesised that alexithymia in MS might be associated with dysfunctional patterns of activity in prefrontal areas and amygdala during reappraisal due to impaired connectivity between these areas as a result of white-matter lesions.

Methods

Standard protocol approvals, registrations and patient consent

This study was approved by the local ethics committee (University of Lausanne, Switzerland, CCER 27.07.10, "Etude en IRMf des capacités de régulation des patients avec sclérose en plaque"). All participants signed a written informed consent form, in accordance with the Declaration of Helsinki.

Participants

Nineteen patients with relapsing-remitting MS and minimal disability (McDonald's diagnostic criteria [30]) took part in this study (see table 1). Inclusion criteria were: (1) mild to moderate neurological disability but unimpaired ambulation (Expanded Disability Status Scale [EDSS] ≤2.5 in all cases [31];); (2) no clinical relapse and no corticosteroid therapy for at least 6 weeks before inclusion in the study; (3) no other neurological diagnosis, major depression or psychiatric illness according to Diagnostic and Statistical Manual of Mental Disorders (DSM5) criteria; (4) no use of antidepressant, anxiolytic or antipsychotic drugs; and (5) no evidence of cognitive impairment on a complete neuropsychological examination.

Fourteen patients were treated with disease-modifying therapies (interferon β-1a or 1b in 8 cases, natalizumab in 3, fingolimod in 2, glatiramer acetate in 1) for a mean period of 3.8 years (ranging from 5 months to 10 years).

Table 1: Demographic and clinical data.

	Multiple sclerosis patients	Controls	p-value
Number of males/females	8/11	8/12	
Age (years)	33.5 ± 4	33.5 ± 4.5	0.60
Education (years)	14.4 ± 2.2	14.9 ± 2.5	0.59
Handedness (left/right-handed)	2/17	0/20	
Disease duration (years)	8.4 ± 5.2	–	
EDSS	1.5 (1–3)	–	
Disability progression	0.27 ± 0.1	–	
Anxiety/depression			
Hospital Anxiety and Depression scale-A	7.2 ± 3.1	7.1 ± 3.4	0.88
Hospital Anxiety and Depression scale-D	3.3 ± 2.9	2.8 ± 2.3	0.51
State-Trait Anxiety Inventory	41.9 ± 10.6	46 ± 10.3	0.23
Affective questionnaires			
Behavioral Inhibition System scale	30.8 ± 4.2	30 ± 4.2	0.54
Behavioral Approach System scale	64.4 ± 7.2	62.7 ± 8	0.49
Positive and Negative Affect scale			
(1) Positive	59.3 ± 13.3	57.6 ± 10.3	0.65
(2) Negative	37.5 ± 12.5	39.9 ± 9.4	0.49
Toronto Alexithymia Scale			
(1) Difficulty describing feelings	17.9 ± 6.2	13.5 ± 4	**0.01**
(2) Difficulty identifying feeling	14.2 ± 3.4	11.1 ± 3.7	**0.009**
(3) Externally oriented thinking	21.2 ± 4.6	15.6 ± 3	**0.000***
(4) Total score	53.4 ± 9.1	40.1 ± 8	**0.000***
Emotion Regulation Questionnaire			
(1) Reappraisal	28.7 ± 4.9	29.5 ± 5.9	0.64
(2) Suppression	15.1 ± 6.3	12.5 ± 4.9	0.16
Cognitive measures (BRB-N)			
Selective reminding		66 (54-70)	
(1) Long Term Storage	62 (34–71)		0.15
(2) Consistent long term storage	55 (21–71)	59 (42–70)	0.14
(3) Delayed recall	11 (5–12)	12 (9–12)	0.72
10/36 spatial recall		21 (13–28)	
(1) Total	24 (16–30)		0.21
(2) Delayed	9 (3–10)	8 (5–10)	0.70
Paced Auditory Serial Addition test	57 (31–60)	56 (23–60)	0.96
Symbol Digit Modalities test	57 (38–73)	59 (46–77)	0.31
Word list generation	27 (15–35)	32 (21–37)	**0.02**

Mean ± SD (t-tests), except for EDSS and cognitive measures (median (range); Mann-Whitney U-tests). * significant after Bonferroni correction.

Twenty healthy subjects with no previous history of neurological or psychiatric disorder were recruited as a control group (HCs; see table 1). Gender was balanced within and between groups, but not included as a covariate in our analyses given the small sample size precluding reliable conclusions about gender differences.

Affective measures

In addition to the Toronto Alexithymia Scale (TAS [32];), a set of questionnaires was administered in order to evaluate affective state more globally, including the Emotion Regulation Questionnaire (ERQ), the Behavioral Inhibition and Approach System Scale (BISBAS), the Positive and Negative Affect Scale (PANAS), and anxiety and depression scales (Hospital Anxiety and Depression Scale; State-Trait Anxiety Inventory).

Cognitive measures

The Brief Repeatable Battery of Neuropsychological Tests (BRB-N [33, 34]) was administered to all patients and 15 out of 20 controls, to assess verbal memory (Selective Reminding Test [SRT]), spatial memory (10/36 Spatial Recall Test), sustained attention/information processing speed (Paced Auditory Serial Addition Test [PASAT], Symbol Digit Modalities Test [SDMT]), and verbal fluency on semantic cues (Word List Generation [WLG]).

Experimental protocol

Participants underwent event-related fMRI during emotion perception and regulation, following a well-established protocol described extensively elsewhere [28, 29]. The task was controlled using E-prime 1.0 (Psychology Software Tools Inc., Pittsburgh). Subjects viewed photographs of emotional scenes (positive or negative valence from the International Affective Pictures System) under two conditions: "spontaneous viewing" and "reappraisal". The scenes involved social or non-social contents in equal distribution. In the "viewing" condition, for each picture, subjects rated the valence and intensity of their spontaneous emotional feeling, on a scale ranging from −2 (very negative) to +2 (very positive) in steps of 1, with 0 being neutral. In the "reappraisal" condition, they had to regulate their emotions by reinterpreting the meaning of the scene in such a way as to reduce its affective significance, for example by imagining the pictures were made up or taken from a movie scene, and hence unreal or not truly emotional. Again, participants rated the valence and intensity of their emotions, this time after emotional reappraisal. This type of emotion regulation strategy typically leads to a diminution of emotional intensities (scores closer to 0 [28, 29]).

MRI acquisition

Data were acquired on a 3T MRI system (Trio TIM, Siemens, Germany) with a 32-channel head coil. Whole-brain functional images were collected with a susceptibility weighted echo planar imaging (EPI) sequence (repetition time/echo time/flip angle = 2200 ms/30 ms/90°; field of view = 216 × 216 mm). Thirty-five axial slices were acquired in an interleaved ascending manner (slice thickness = 3 mm, interslice gap = 0.3 mm; voxel size = 3 mm^3 isotropic). High-resolution anatomical images were acquired using a T1-weighted, 3D sequence (MPRAGE; repetition time/echo time/flip angle = 2300 ms/2.98 ms/9°; field of view = 240 × 160 mm; slice thickness = 1mm; interslice gap=0.5 mm; voxel size = 1 mm^3 isotropic). Visual stimuli were back projected on a screen and head movements were prevented using an ergonomic air head-cushion.

MRI data preprocessing

Functional MRI data were preprocessed and analysed with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) in a conventional manner. All functional volumes underwent slice timing correction, spatial realignment, spatial normalisation to an EPI brain template, resampling to 3-mm isotropic voxels and spatial smoothing (Gaussian kernel, 8 mm FWHM). The data were scaled globally and a high-pass filter (cut-off = 128 s) was applied prior to data modelling. The anatomical volumes were spatially co-registered to the mean functional image resulting from spatial realignment.

First-level general linear model

Functional data were modelled using a generalised linear model (GLM) with one regressor for each combination of task condition (viewing, reappraisal), emotional valence (positive, negative) and social content (social, non-social; not analysed in the current paper), yielding eight regressors convolved with a canonical haemodynamic function. Six additional regressors were included to account for head movement during scanning, using realignment parameters from the pre-processing step. Main contrasts of interest were defined by these eight conditions minus the implicit baseline activity.

Second-level group analysis

Contrast maps were incorporated in a flexible factorial design of analysis of variance (ANOVA) for group analyses. The critical comparisons were performed by means of t-tests between each group of participants (HC, MS) for each emotion condition (viewing, reappraisal), and each combination of emotion condition and valence (pooled across social content). Brain areas commonly engaged by HC and MS participants were explored using conjunction analyses ($p < 0.05$ family-wise error [few] corrected). For between-group contrasts, whole-brain analyses were performed with a threshold $p < 0.005$ uncorrected at voxel level and a minimum cluster extent $k = 50$ voxels, providing a reasonable balance between type I and type II errors since the precise onset of affective mechanisms is unknown at each trial and may vary in subjects from a clinical population [28]. We further provide significance at threshold $p < 0.001$ for the sake of completeness.

Significant peak activity in the second-level t-tests was observed in a number of brain areas involved in emotion perception and regulation, including lateral PFC. Modulation of functional connectivity for this region of interest was further examined using the generalised psychophysiological interaction (PPI) approach (http://www.nitrc.org/projects/gppi [35];). We further restricted the PPI analyses on relevant regions involved in emotion regulation, based on independently defined coordinates obtained by automated meta-analysis (http://neurosynth.org; keyword: emotion regulation, map threshold $p < 0.01$ false discovery rate [FDR] corrected, used as an inclusive mask), with a statistical threshold $p < 0.005$ uncorrected at voxel level (min-

imum cluster size = 10 voxels) [28]. Changes in connectivity between lateral PFC (sphere, 8 mm diameter) and brain areas involved in emotion regulation was computed for each combination of emotional condition (viewing, reappraisal) and valence (positive, negative) against implicit baseline activity for each subject. The resulting contrast maps were then incorporated in a factorial ANOVA at the second-level for between-group analyses.

Results

Questionnaire data

MS patients scored comparably to HCs in all questionnaires with the notable exception of the Toronto Alexithymia Scale (TAS), where patients reported higher alexithymia scores for all subscales compared with controls (table 1). Among patients, 13 out of 19 (68%) had significant or probable alexithymia as assessed by the TAS (cut-off score>51). In patients, the total alexithymia score correlated positively with the disease duration (Spearman rho = 0.644, p = 0.003), HAD-D (rho = 0.688, p = 0.001) and STAI (rho = 0.63, p = 0.004), whereas it correlated negatively with the BAS (rho = −0.67, p = 0.002). These data corroborate previous reports highlighting the higher prevalence of alexithymic disorders in MS compared with the normal population, as well as their association with depression and anxiety [36].

Cognitive measures

Patients did not differ from controls in the cognitive tests, except for verbal fluency (Mann-Whitney U test, Z = 2.36, p = 0.02; table 1).

Emotional ratings during functional MRI

An analysis of variance (group, task, and valence as factors) revealed no significant differences in subjective emotional ratings of pictures between patients and controls (all p >0.13). The interaction between task and valence was significant (F(1,37) = 85.3; p <0.001), with a greater difference in ratings between positive and negative events during viewing (Δ = 2.4) than during reappraisal of emotional scenes (Δ = 1.7; t (1, 38) =9 .1; p <0.001). This indirectly confirms that all participants reliably regulated their emotional state according to the task instructions. No correlation was observed between emotional ratings and alexithymia scores (or other affective questionnaires) in the MS group (all p values >0.235).

Anatomical MRI data

In the MS group, reduced whole-brain white matter volume was associated with higher EDSS scores (Spearman rho = −0.474, p = 0.04) and higher alexithymia scores (TAS-1: rho = −0.619, p = 0.005; TAS-2: rho= −0.517, p = 0.023; TAS total: rho = − 0.599, p = 0.007). In controls, higher white matter volume was associated with more efficient regulation of negative emotions, i.e., correlating with more positive emotional ratings after reappraisal of negative scenes (rho = 0.56, p = 0.01). There was no such correlation in patients (rho = 0.048, p=.844).

Functional MRI data

Shared brain activity between MS patients and HC

During spontaneous viewing of emotional scenes, both patients and controls commonly engaged a widespread set of regions, including the ventrolateral PFC (orbital and opercular inferior frontal gyrus-IFG), insula, anterior cingulate cortex (ACC), basal ganglia (dorsal striatum), and visual and sensorimotor areas, as well as posterior parietal cortex (conjunction analysis, p <0.05 FWE corrected; table 2A). During the reappraisal of emotional scenes, areas comparable to those during the viewing condition were again recruited in both groups (p <0.05 FWE corrected), except that the orbital IFG and the dorsal striatum were absent in this condition (table 2B).

HC > MS patient comparisons

When viewing either negative or positive emotional scenes, the HC group showed higher activity in a distributed network involving the ventrolateral PFC (triangular and opercular IFG) and the inferior parietal cortex (IPL), together with sensorimotor and visual areas (p <0.005; fig. 1, table 3B). Similarly, during the reappraisal of emotional scenes, HC showed higher activity in dorsal fronto-parietal, sensorimotor, and visual areas, again irrespective of emotional content (p <0.005; fig. 1, table 3, C and D).

MS patients > HC comparisons

During viewing of negative scenes, MS patients showed higher recruitment of more ventral prefrontal areas, including orbital IFG and subgenual ACC, together with the left caudate nucleus (p <0.005; fig. 2, table 4A). During reappraisal of negative scenes, these same ventral prefrontal areas (including orbital IFG and subgenual ACC) were again more recruited in patients, together with the intra-parietal sulcus (IPS) and occipito-temporal visual areas (p <0.005; fig. 2, table 4C; see also fig. 3A). When viewing positive scenes, MS patients showed higher activity in subgenual ACC, caudate nucleus, and visual areas, whereas increase in activity was restricted to visual areas during reappraisal of these scenes (p <0.005; fig. 1, table 4, B and D).

Functional connectivity analyses.

The orbital IFG was selectively engaged in MS patients (fig. 3A) and has been implicated in the regulation of amygdala activity in the normal population [10, 17]. Therefore, we examined its modulation and functional coupling with other areas involved in emotion reappraisal. Connectivity analysis showed increased functional coupling in patients compared with controls between the left orbital IFG and the left amygdala on the one hand (MNI coordinates: −24, −6, −10; p = 0.015 FWE-corrected, small volume correction; fig. 3B, table 5), and also with the right amygdala (MNI coordinates: 26, −4, −20; p = 0.021 FWE-corrected, small volume correction; table 5). The reverse comparison did not reveal any significant group difference. To explore whether amygdala activity was abnormally regulated in alexithymic patients, we performed a complementary correlation analysis revealing that activity within the left amygdala was positively associated with the “dif-

ficulty identifying one's feeling" alexithymic symptom in MS patients (TAS-2 subscale; rho = 0.599; p = 0.007; fig. 3C). This was also the case for the right amygdala (TAS-2 subscale; rho = 0.468; p = 0.044).

Discussion

Functional MRI was applied to investigate the brain mechanisms of emotion perception and regulation in minimally disabled MS patients, together with their relationship with alexithymia.

Alexithymia: link with questionnaires, disease progression and white matter damage

Alexithymic disorders, which reflect difficulties in recognising and reporting one's own emotions, were highly prevalent in the present sample of MS patients, in line with previous epidemiological studies [12]. Alexithymia total scores were associated with higher disease duration, disability and depression, as previously reported [37–39]. Moreover, alexithymia was correlated with the extent of white matter damage as assessed by whole-brain white matter volumetry, corroborating another recent study [24].

Emotional ratings

Across groups, emotional ratings were strongly related with whole-brain volumetric measures of white matter. In particular, higher white matter volumes were associated

Table 2: Conjunction analysis between MS and HC groups for emotion viewing.

	BA	T-Value	MNI coordinates			Cluster size
			x	y	z	
A. VIEWING						
Frontal/insular/subcortical						
L anterior insula		8.43	−30	22	4	376
R anterior insula		6.64	30	24	4	180
R orbital IFG	47	5.93	34	32	-10	
L SMA / ACC	6	11.8	−4	−6	54	1646
R dorsal ACC	32	7.46	8	20	40	
R opercular IFG	45	6.64	56	12	22	347
L putamen		6.34	−22	4	6	119
R putamen		5.90	22	6	8	99
Motor/sensori-motor						
L precentral gyrus	4	12.33	−34	−24	54	2886
L postcentral gyrus	2/3	10.98	−46	-30	56	
L middle frontal gyrus	6	9.10	−54	6	36	346
R precentral gyrus / middle frontal gyrus	6	5.96	40	−10	62	26
R postcentral gyrus	2/3	7.15	42	−28	44	342
Posterior parietal						
R SPL	7	5.08	14	−66	56	22
Visuo-perceptual						
R lingual gyrus	37	15.39	28	−48	-8	9279
R fusiform gyrus	19	13.65	28	−62	-8	
R middle occipital gyrus	18	13.37	32	−86	14	
B. REAPPRAISAL						
Frontal/insular						
L dorsal ACC	32	6.68	−4	22	42	
R opercular IFG	44	6.92	46	12	28	377
R triangular IFG	45	4.98	46	34	16	38
L anterior insula		5.57	−28	22	6	31
Motor/sensori-motor						
L SMA	6	11.30	−6	−6	54	1448
R SMA	6	10.51	2	0	58	
L middle frontal gyrus	6	9.34	−52	6	34	352
L precentral gyrus	4	12.29	−36	−22	56	3251
L postcentral gyrus/IPL	2/40	10.91	−40	−32	44	
R postcentral gyrus	2/3	6.65	46	−28	44	197
Posterior parietal						
R SPL	7	5.68	14	−66	56	141
R IPL	7	5.29	34	−54	50	
Visuo-perceptual						
lingual gyrus	37	15.78	28	−48	-8	10210
R middle occipital gyrus	18	14.42	32	−86	14	
R fusiform gyrus	19	14.05	26	−66	-8	

ACC = anterior cingulate cortex; BA = Brodmann areas; IFG = inferior frontal gyrus; IPL = inferior parietal lobule; L = left, R = right SLP = superior parietal lobule; SMA = supplementary motor area, . p <0.05 familywise error corrected. Minimum cluster size = 20.

with more efficient emotional regulation during viewing of both negative and positive emotions. Thus, a rich network of white matter tracts supporting communication between distant brain areas is likely to support effective regulation strategies (e.g [40].), but also vulnerable to white matter lesions due to MS. In accordance with two other studies examining the association between alexithymia and emotion recognition, we did not observe any correlation between emotion ratings and alexithymia scores in patients [14, 37]. Moreover, average emotional ratings did not differ between patients and controls. One reason could be that the patients were only slightly impacted by the disease, owing to relatively short disease durations. Indeed, in our sample, the median EDSS score was 1.5. In previous studies with similar scores, no impairment was observed in emotion perception [7, 41]. Conversely, in a study involving patients with higher EDSS scores, impaired emotion perception was associated with longer disease durations [6].

Although these correlations provide indirect support to the notion that alexithymia may ultimately reflect impaired structural connectivity within distributed brain networks underlying the top-down regulation of emotional processes, we did not perform more detailed analysis using diffusion tensor imaging to identify the role of specific white-matter tracts. This limitation should be addressed in future follow up studies in MS patients and other neurological populations.

Compensatory activity in the orbital IFG during emotion perception and regulation

We hypothesised a dysfunctional recruitment of the lateral PFC in patients, due to its involvement in the regulation of amygdala activity during reappraisal. Remarkably, the ventrolateral PFC (BA47) was more activated in patients than controls during emotion reappraisal. This region is sensitive to emotional valence [10, 17] and has been repeatedly involved in emotion regulation [10, 19]. More particularly, it is part of an "external emotion control" pathway implicated in the modulation of amygdala activity following external emotional stimuli [42]. A second circuit also converges towards the amygdala, the "internal emotion control" pathway; in contrast to the former, this circuit modulates internally triggered affective states and implicates the orbito-frontal cortex instead (BA11). Abnormal functional connectivity within the external emotion control pathway has been previously documented in mood disorders [40, 42], similar to the present findings.

The ventrolateral PFC has also been implicated in past studies of emotion perception in MS, and was found to be more recruited in unimpaired than impaired MS patients or healthy controls [5, 6], in accordance with the present data. Here, we further observed increased functional connectivity between ventrolateral PFC and the amygdala in MS patients during the reappraisal of negative scenes. Previously, the ventrolateral PFC has been related with initiation [15], selection and inhibition mechanisms during reappraisal [16]. Because amygdala activity did not globally differ from controls, at least as revealed by the whole-brain analysis, our data might reflect an increased top-down input from the ventrolateral PFC towards the amygdala, aimed at normalising the activity of the latter region [10, 17]. In the past, this connectivity was found to be decreased in MS in the presence of increased activity in ventrolateral PFC during emotion identification [6]. More recently, damage to the uncinate fasciculus linking ventrolateral PFC with the amygdala has been implicated in social cognition disorders in MS [3]. From a functional point of view, which of the two mechanisms (increase or decrease of functional connectivity) is observed in a given study may depend on the effects of task demands and characteristics.

Relationship between amygdala activity and alexithymia in MS patients

Among our main findings, we report a significant positive association in patients between amygdala activity and alexithymia severity (subscale scores for difficulty identifying feelings) during the reappraisal of negative scenes. This might point to decreased down-regulation of limbic activ-

Figure 1: Healthy controls (HC) > MS patients, whole-brain contrast during the viewing and reappraisal of negative and positive emotional scenes (p <0.005 uncorrected, cluster size >50). L = left hemisphere, R = right hemisphere.

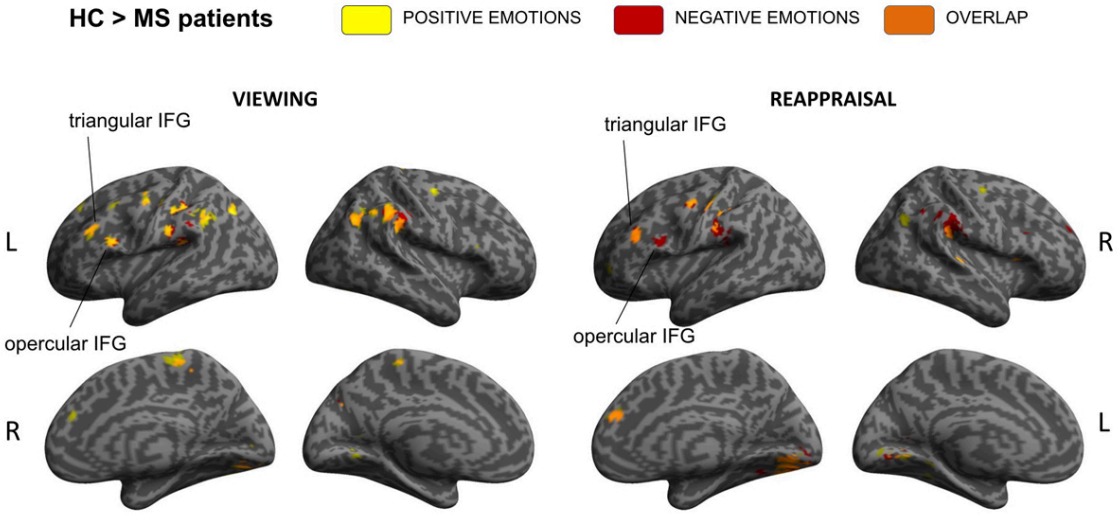


Table 3: Controls > MS patients, comparison of whole-brain activity during emotion viewing and reappraisal of negative and positive scenes.

	BA	T-value	MNI coordinates			Cluster size
			x	y	z	
A. VIEWING NEGATIVE SCENES						
Frontal						
L triangular IFG*	45	3.55	−46	32	28	104
L opercular IFG*	44	3.39	−50	14	24	101
Parietal						
R supramarginal gyrus*	40	4.10	56	-30	36	428
R angular gyrus*	39	3.88	42	-64	34	129
L IPL*	40	3.73	−40	-36	36	552
L supramarginal gyrus*		3.33	−50	-26	24	
Sensori-motor						
L postcentral gyrus*		3.29	−50	-10	50	100
L precentral gyrus		2.99	−40	-2	56	
R paracentral lobule		3.03	10	-34	60	59
L paracentral lobule		2.77	−4	-32	58	
Visual						
L middle occipital gyrus*		3.85	−20	-58	40	126
R lingual gyrus*	18	3.73	22	-76	-6	143
B. VIEWING POSITIVE SCENES						
Frontal						
L triangular IFG*	45	3.82	−44	32	28	148
R triangular IFG*	45	3.53	62	20	22	69
L opercular IFG*	44	3.58	−50	14	24	94
L superior frontal gyrus*		3.32	−14	36	42	56
R ACC*		3.27	4	44	26	63
Parietal						
R supramarginal gyrus*		4.19	48	-36	34	739
R angular gyrus*	39	4.05	40	-62	34	
R IPL*	40	3.68	56	-44	44	
L supramarginal gyrus*		3.77	−46	-28	26	759
Sensori-motor						
R middle frontal gyrus*	6	3.65	42	-4	56	81
L middle frontal gyrus*		3.24	−38	16	48	50
R SMA*	4	3.37	4	-22	62	252
R paracentral lobule*		3.32	10	-34	60	
L paracentral lobule	4	3.07	−4	-32	58	
Visual						
L middle occipital gyrus*		3.98	−20	-58	34	146
R lingual gyrus*	18	4.32	22	-76	-6	221
C. REAPRAISAL OF NEGATIVE SCENES						
Frontal						
L triangular IFG*	45	3.76	−42	32	26	182
L opercular IFG*	44	3.41	−46	14	22	92
R ACC*	32	3.72	14	46	24	121
Temporal-parietal						
R superior temporal gyrus*	22	4.87	66	-24	10	512
R supramarginal gyrus*		3.69	52	-34	32	
L temporo-parietal junction*	41	3.34	−42	-34	16	313
L supramarginal gyrus*		3.24	−56	-28	24	
R IPL*	40	3.29	56	-52	46	62
Sensori-motor						
L postcentral gyrus*	6	4.22	−50	-8	48	130
Visual						
R lingual gyrus*	18	5.26	20	-78	-6	763
L calcarine gyrus	18	3.07	−14	-62	4	94
L lingual gyrus	18	2.95	−6	-70	-2	
D. REAPRAISAL OF POSITIVE SCENES						
Frontal						
L triangular IFG*	48	3.56	−44	32	26	146
R opercular IFG*	45	4.00	38	16	16	123
R ACC*		3.34	8	46	24	98

ity with increasing alexithymia. Similarly, in a psychiatric sample of patients featuring emotional lability, activity in ventrolateral PFC as well as in a number of limbic areas increased during regulation of negative emotions [38]. The amygdala is well known to react reflexively to negative stimuli [39]. During successful reappraisal, the emotional impact of negative events is decreased thanks to a down-modulation of amygdala activity [10, 17–19]. A less efficient regulation strategy, emotional suppression, is on the contrary known to increase amygdala activity [17]. In our sample of patients, increased amygdala activity might thus reflect a deficit in applying a reappraisal strategy in the face of negative emotions, which would be commensurate with alexithymia level.

Abnormal subgenual ACC activity in MS patients

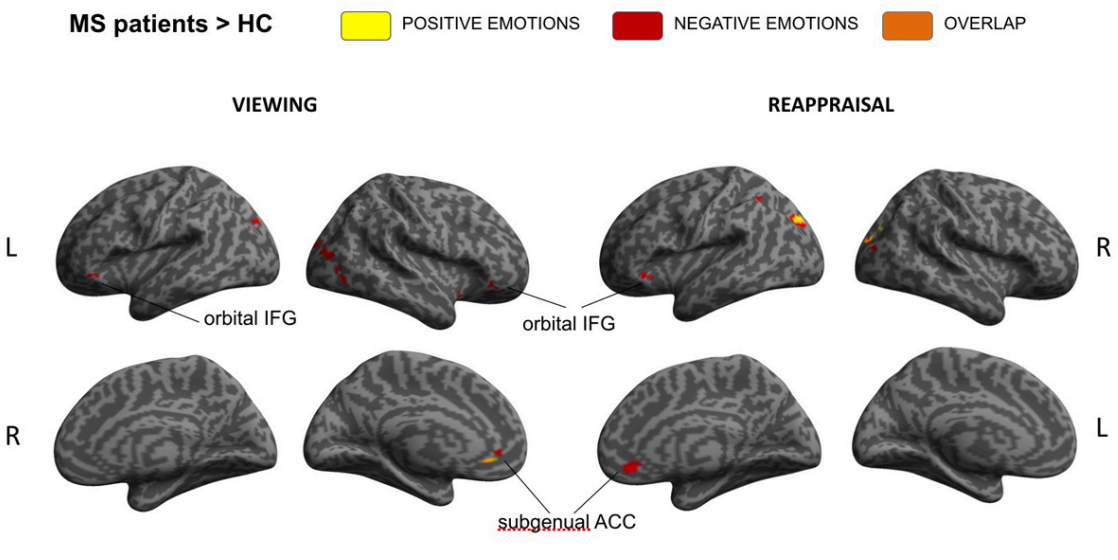
The subgenual ACC (or rostral ACC) was also globally more activated in patients, both during emotion perception and reappraisal, and irrespective of emotional valence. This region is a key part of the affective division of ACC, involved in the production of parasympathetic responses [43], as opposed to a more dorsal cognitive pathway [41, 44]. This affective ACC works together with other components of the limbic system (insular cortex and amygdala, notably) for the identification of emotional significance, whereas a more dorsal pathway including the dorsal aspect of ACC appears more related to the regulation of an emotional state evaluation [41, 44]. Here, a mobilisation of this affective component suggests additional compensation mechanisms that might aim at detecting emotional states in patients.

Overall, our results converge with recent meta-analyses suggesting that neural alterations in several limbic regions in alexithymic disorders, including amygdala, striatum, orbitofrontal, ventromedial and prefrontal areas [47]. However, it worth nothing that we did not observe significant group differences in the insula as reported in these previous studies, although this region was normally responsive to emotion in both controls and patients. Though speculative, this might argue against a key role of the insula in mediating the access of affective signals to conscious experience and deficits thereof in alexithymia, as speculated

	BA	T-value	MNI coordinates			Cluster size
			x	y	z	
L middle frontal gyrus	32	3.01	−40	54	0	52
Temporal-parietal						
R superior temporal gyrus*	22	4.33	66	-24	10	104
R supramarginal gyrus*		3.29		-36	30	74
R angular gyrus*	39	3.61	42	-62	32	79
L inferior parietal lobule*	3	3.51	−42	-30	34	91
L supramarginal gyrus		2.84	−50	-26	26	
Sensori-motor						
L postcentral gyrus*	6	3.92	−50	-8		189
R precentral/middle frontal gyrus*	6	3.74	40	-6		70
Visual						
R lingual gyrus*	18	5.17	20	-76		
R fusiform gyrus*	19	3.74	36	-70		901
L fusiform gyrus*	37	3.79	−18	-46		129

BA = Brodmann areas, IFG = inferior frontal gyrus, IPL = inferior parietal lobule, SMA = supplementary motor area, L = Left, R = Right. P<.005 uncorrected. Minimal cluster size k = 50. * Significant peak at p<.001 uncorrected.

Figure 2: MS patients > healthy controls (HC), whole-brain contrast during the viewing and reappraisal of negative and positive emotional scenes (p <0.005 uncorrected, cluster size >50). L = left hemisphere, R = right hemisphere.



by some theoretical models of emotional awareness [48], but instead points to abnormal modulation of affective processing due to altered top-down control circuits. This conclusion, however, requires replication in other populations.

Limitations

Our data should be interpreted with caution insofar as a relatively small sample of MS patients was included in the present study. However, we had strict selection criteria in order to recruit patients with only minimal neurological deficits, no major cognitive deficit and short disease duration. Moreover, our population appeared highly comparable to those reported in other MS studies. In the future, a larger cohort including different disease stages should be used in order to replicate as well as better understand the association between changes in functional connectivity, disease stage and emotion regulation impact on affective well-being, as well as their development. Ultimately, better understanding of how demyelinating lesions impact patients' ability to monitor their emotional state constitutes a crucial line of research to improve mental health care in MS.

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Potential competing interests

All authors report no conflict of interest

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Table 4: MS patients > Controls comparison of whole-brain activity during emotion viewing and reappraisal of negative scenes.

	BA	T-value	MNI coordinates			Cluster size
			x	y	z	
A. VIEWING NEGATIVE SCENES						
FRONTAL / SUB-CORTICAL / INSULAR						
L orbital IFG*	47	3.39	-50	28	-8	106
R orbital IFG*	47	3.23	50	34	-14	50
L subgenual ACC	32	2.99	-8	42	-6	52
L caudate nucleus*		3.40	-18	22	2	110
R anterior insula	38	3.05	36	12	-16	56
R temporal pole		2.70	36	12	-26	
VISUAL						
L superior occipital gyrus*	19	3.41	-24	-82	34	57
R inferior temporal gyrus*	37	3.41	40	-66	-6	58
R middle occipital gyrus*	19	4.09	36	-86	20	125
B. VIEWING POSITIVE SCENES						
FRONTAL / SUB-CORTICAL						
L caudate nucleus		3.00	-18	22	4	111
L subgenual ACC	32	2.82	-12	38	-8	
C. REAPRAISAL OF NEGATIVE SCENES						
FRONTAL						
L orbital IFG*	47	3.51	-36	30	-8	88
R subgenual ACC*	32	3.35	8	36	-14	69
PARIETAL						
L intra-parietal sulcus*		3.55	-24	-46	40	70
VISUAL						
L superior occipital gyrus*	19	3.64	-22	-74	26	144
R superior occipital gyrus*	19	3.84	22	-86	18	96
R middle occipital gyrus	18/19	3.12	36	-86	20	
D. REAPRAISAL OF POSITIVE SCENES						
VISUAL						
L superior occipital gyrus*	19	3.21	-22	-82	32	50
R superior occipital gyrus*	19	3.28	22	-86	18	79
R middle occipital gyrus		3.02	30	-70	26	

BA = Brodmann areas, IFG = inferior frontal gyrus, ACC = anterior cingulate cortex, L = Left, R = Right. P<.005 uncorrected. Minimal cluster size k = 50. * Significant peak at p<.001 uncorrected.

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Figure 3: Functional connectivity analysis of orbital IFG. (A) The left orbital IFG is more recruited in MS patients compared with healthy controls (HC) during the reappraisal of negative emotions. (B) A functional connectivity analysis with the left orbital IFG as seed indicates higher connectivity with bilateral amygdala in MS compared with HC (p <0.005). (C) In MS patients, the magnitude of activation within the left amygdala correlates positively with alexithymia scores at the TAS-2 (difficulty identifying feeling; Pearson correlation). L = left hemisphere.

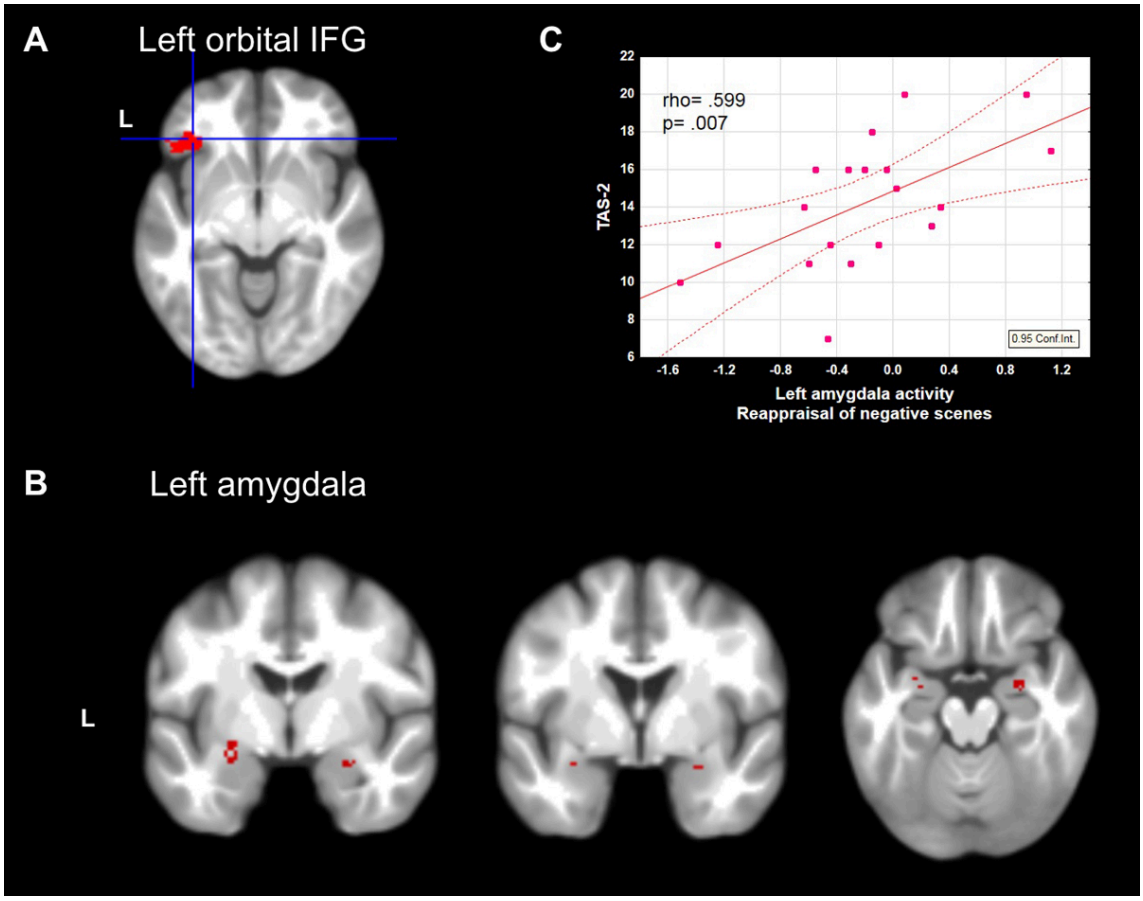

Table 5: Functional connectivity analysis with the left orbital IFG as seed region (MNI coordinates: -36, 30, -8) during the reappraisal of negative scenes within the emotion regulation network defined by Neurosynth.

	BA	T-Value	MNI coordinates			Cluster size
			X	Y	Z	
MS patients > HC						
L amygdala		3.02	-24	-6	-10	17
		2.98	-30	-2	-18	
R amygdala		2.87	26	-4	-20	13
L superior medial frontal gyrus	32	3.45	-10	40	18	13
HC > MS patients	-	-	-	-	-	-

p<.005 uncorrected, minimum cluster size = 10 voxels. MS = multiple sclerosis, HC = healthy controls. L = Left, R = Right.

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