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Emotional disturbances in multiple sclerosis: a neuropsychological and fMRI study

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Background: Emotional disturbances in multiple sclerosis (MS) are often explored in terms of affect recognition, with controversial results that likely reflect the high lesional heterogeneity. Patients' emotional experience, however, has seldom been studied and has never been explored using fMRI.

Objectives: To explore the emotional experience in MS and compare these data with fMRI measurements using for the first time real-life emotional scenes differing in valence and arousal.

Methods: Twenty-five right-handed women with relapsing-remitting MS and 27 right-handed age-, sex-, and education-matched healthy controls visualized during an fMRI session, emotional scenes taken from the international affect picture system (IAPS) and differing in valence (positive, negative, neutral) and arousal (ranging from calm to excited). During a post-scanning debriefing, participants were asked to look again at each image and score it in terms of valence and arousal sensation on a scale of 1 to 9.

Results: Cognitively well-preserved MS subjects presented a significantly more scattered emotional experience compared to controls in response to positive and negative pictures. In fMRI, MS patients also presented a higher variability of response when compared to controls in left inferior orbitofrontal cortex for positive stimulations. **For negative condition, no significant results were observed between the two groups. However,** a trend was detected in left amygdala, right fusiform gyrus, right caudate nucleus and right pallidum for negative stimulations.

Conclusion: In response to ~~positive and negative~~ emotional stimuli, MS subjects presented a scattered emotional experience subtended by a greater variability of brain response, highlighting an emotional pattern not previously reported in MS patients.

1. Introduction

Affective disorders are frequently reported in multiple sclerosis (MS) (Patten et al., 2005) and consist of long-lasting mood modifications and short-duration emotional disturbances (MONTREUIL and PETROPOULOU, 2003). However, the aetiology of these disorders remains difficult to elucidate. While some of them are more likely to be related to a psychological reaction to the disease (Feinstein et al., 1999; Stenager et al., 1994; Vleugels et al., 1998), others would appear to be linked to the organic state of the brain (Bakshi et al., 2000; Di Legge et al., 2003; Pujol et al., 2000). Recently, several cases of psychotic events at MS onset were described and were found to be associated with MRI changes (Berna et al., 2016; Blanc et al., 2010; Guernion et al., 2013), reinforcing the notion that affective disorders could be a direct consequence of the disease process.

From a neuroscience perspective, emotions are usually characterized by two components: the capacity to recognize others' emotions and the experience they elicit (Belzung, 2007). Functional magnetic resonance imaging (fMRI) studies have identified a large set of cortical and subcortical structures interacting during both these emotional processes (Kober et al., 2008; Phan et al., 2002), while there are other brain areas that seem to be specifically involved during one or other of these processes (Sabatinelli et al., 2011).

MS is the most prevalent demyelinating disease of the human central nervous system (Krieger and al. 2016), and, while commonly described in white matter locations, MS lesions can also involve grey matter (Trapp and Nave, 2008). Thus, the loss of grey matter in addition to the typical diffuse lesions in white matter directed our attention to the integrity of emotional networks in MS.

Studies on social cognition in MS have mainly focused on face emotion recognition and they showed that patients often have difficulty in identifying unpleasant expressions (Henry et al., 2009; Krause et al., 2009; Lenne et al., 2014). MRI studies provide evidence, firstly, that disconnection mechanisms as well as cortical thinning of specific brain areas may contribute to the impaired processing of facial expressions (Mike et al., 2013) and, secondly, that these results are not related to depression (Krause et al., 2009). Moreover, even when this processing is preserved, MS patients show a lack of functional connectivity between fronto-limbic structures during emotion recognition tasks (Jehna et al., 2011; Passamonti et al., 2009), indicating a fragility of emotional processing at a cerebral level.

Furthermore, emotional experience has seldom been studied in MS, yet this aspect is important for social functioning and quality of life (Ille et al., 2011). A preliminary study showed that MS subjects' feelings in response to negative sounds and pictures are less intense than those of healthy subjects (Di Bitonto et al., 2011) but no fMRI studies have yet focused on these disturbances.

The aim of our study was to explore, using fMRI, the emotional experience in women suffering from MS, using real-life emotional scenes due to their capacity to induce emotion across a wide range of valence (positive to negative) and arousal (calm to high). Taking into account the notion of varied valence and intensity can lead to a better understanding of the dynamics of emotional functioning, because disorders are more likely to be expressed through a distorted valence and intensity (e.g. a negative emotion experienced as more highly negative) than through the experience of a different emotion (Pasquier, 2013).

Moreover, given the heterogeneity of lesions and functional reorganization in MS, patients tend to vary markedly at clinical examination and in terms of motor (Lucchinetti et al., 2000) or cognitive dysfunction (Penner, 2016; Paul, 2016), and it is likely that this

variability also extends to the affective sphere. For example, emotional lability is one of the most prevalent emotional syndromes in MS (Ron, 2018). The French neurologist Jean-Martin Charcot, in 1867, already described an “emotional oscillation” when talking about pathological laughter and crying. Studying emotions on a large valence and intensity scale and using multiple dedicated tests allows us to assess this potential emotional variability.

In MS, functional heterogeneity in brain activations (i.e., decreased and increased recruitment in brain structures or networks) has been suggested as a possible explanation for the heterogeneity of cognitive profiles among patients (Schoonheim et al. 2015). However, it has also been shown, for example in dementia with Lewy bodies (DLB), that fluctuations of cognition are associated with a high variability in functional connectivity between brain network implicated in the cognitive function (Sourty et al. 2016). In light of previous studies, we hypothesized that MS subjects suffer from a modification of their emotional experience (Di Bitonto et al, 2011), and that these modifications are underlain by fronto-limbic changes, as revealed by fMRI (Passamonti et al. 2011).

We also hypothesized that these modifications could result mainly in an emotional variability when compared to controls, and are underlain by a functional reorganization in terms of increased and decreased fronto-limbic brain recruitment.

2. Participants and methods

2.1. Participants

Twenty-seven right-handed female relapsing–remitting MS patients (MS group) were recruited in the Department of Neurology of Strasbourg University Hospital. To be eligible for inclusion in the study, patients were required to have an Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) score of 5 or less, be receiving beta-interferon treatment and have been in a stable phase of the disease for at least 6 months. Two of the 27 patients had signs of a recent relapse and were therefore excluded from the study. The diagnosis of relapsing–remitting MS was made by a neurologist, according to the 2005 revision (Polman et al., 2005) of the original McDonald’s criteria. The 25 patients included were matched for age and education level with 27 right-handed healthy women (control group), recruited by the Clinical Investigation Centre of Strasbourg University Hospital or through a call for volunteers (see Table 1 for more information). Inclusion criteria applicable to all study participants were: no evidence of a major depressive episode, no history of major psychiatric disease or non-neurological disorders (other than MS in the case of the MS group), and normal or corrected visual acuity. The local ethics committee approved the study and each participant signed a written informed consent.

2.2. fMRI task

2.2.1. fMRI data acquisition

Images were acquired on a 3T MRI scanner (Siemens Verio). For functional imaging, a T2*-weighted echo planar imaging (EPI) sequence was used (TR: 3 s, TE: 30 ms; Matrix: 64 x 64, voxel size: 3 mm isotropic, FOV: 192 mm x 192 mm, flip angle: 90°).

The slices covered the whole brain and were acquired at the anterior-posterior commissure line. High-resolution anatomical images (voxel size: 1 mm isotropic) were acquired for anatomical reference using a standard T1-weighted 3D MP-RAGE sequence.

During the scan, participants were shown 100 emotional pictures, selected from the International Affect Picture System (IAPS) database (Lang et al., 2008), differing in valence (positive, negative, neutral) and arousal (ranging from calm to excited). Pictures were presented using the same valence and arousal block design, alternating between emotional and neutral blocks, and in the same order for all subjects. Pictures were presented using Eprime 2 (Psychology Software Tools, Inc.), each picture appearing for 6 seconds.

To make sure that subjects really visualized the scene, they were asked to indicate whether or not the picture contained a human by pressing one of two buttons with their right index and middle finger. This decision task was designed to ensure a careful examination of each picture and was chosen because it is simple, unambiguous and requires a minimum of cognitive resources. The whole procedure was first performed outside the scanner before starting the fMRI experiment.

The emotional pictures were selected to be as close as possible to everyday life scenes. The neutral emotion pictures depicted natural scenes that were selected to be as close as possible to the visual complexity of the emotional pictures. This point is important as the neutral pictures constituted our control condition which served to eliminate the effects of visual perception.

2.2.2. fMRI data analysis

The fMRI data were analysed using SPM 12 (Wellcome Department of imaging Neuroscience, London, United Kingdom <http://www.fil.ion.ucl.ac.uk/spm/software/spm12>) for first-level analyses and SPSS 21 (IBM, Armonk, NY) for region-of-interest (ROI)-based second-level analyses.

All fMRI images were realigned to the first volume to correct for intra-scan movement and were then spatially normalized to the standard EPI brain template of the Montreal Neurological Institute (MNI). The data were finally smoothed using a 6-mm full-width at half-maximum isotropic Gaussian kernel.

The haemodynamic response (HR) for each image type (positive, negative and neutral pictures) was modelled by a canonical response. Each stimulus was convolved by event with the canonical haemodynamic response function (HRF). At the first level analysis, contrast images were computed for each subject using the effect of two block conditions: “positive versus neutral blocks” and “negative versus neutral blocks”. The six estimated head movement parameters were included as confounds.

2.2.3. Statistical analyses

fMRI analyses were conducted at two different levels: first a voxel-wise whole-brain analysis and then an ROI-based approach.

2.2.3.1. Whole brain analyses

The contrast images of each subject and for the two conditions (“positive versus neutral” and “negative versus neutral”) were analysed using the general linear model to explore the main effect of the task in each group independently (one-sample t-tests). Then, two-sample t-tests were conducted to identify significant differences between groups for each condition

We used a family-wise error rate (FWER) threshold to assess the intra-group analysis cluster-size required given the voxels that were significant at $P < 0.05$. For inter-group analyses we used a threshold of $P < 0.001$, uncorrected, 30 contiguous voxels.

2.2.3.2. ROI analyses

Based on an fMRI meta-analysis involving healthy volunteers (Sabatinelli et al., 2011), we identified 14 regions specific to emotional scene processing: orbitofrontal cortex (superior, middle, medial and inferior parts), superior frontal gyrus (medial part), anterior cingulate gyrus, amygdala, fusiform gyrus, superior and inferior temporal gyrus. Four other ROIs were added due to their implication in emotional experience and subjective feelings: basal ganglia (caudate nucleus, putamen and pallidum) and insula (Moonen et al., 2017; Phan et al., 2002). ROIs were obtained from the AAL atlas (Tzourio-Mazoyer et al., 2002). For each condition and each subject, the mean of the corresponding contrast image was computed for each ROI. Group analyses were finally conducted to compare mean values and disparities between groups.

2.2.3.3. Group comparison in terms of mean difference

The groups were compared in terms of mean difference for each ROI and each condition (positive versus neutral and negative versus neutral) using the Mann–Whitney test.

2.2.3.4. Group comparison in terms of disparity differences

The aim of this analysis was to investigate whether the dispersion of the values was significantly higher in the MS group when compared to the control group. To this end, for each ROI of each subject we computed a Z-score encoding the absolute deviation from the distribution observed in the control group. This was done by computing the mean and standard deviation in the control group for each ROI and for each condition. The absolute Z-score was calculated for each subject in both the control group and the MS group and these scores were then compared between the two groups using the Mann–Whitney test.

2.2.3.5. Multiple testing correction

The results of the statistical analyses were discussed according to three levels of significance: $P_{\text{unc}} < 0.01$ without correction, and $P_{\text{FDR}} < 0.05$ and $P_{\text{FDR}} < 0.1$ with false discovery rate (FDR) correction.

2.3. Behavioural data

2.3.1. Post-scanning subjective rating: collection of emotional experience

Immediately after the fMRI task, participants were shown each image again and were instructed to rate their subjective feelings in terms of valence (on a scale from 1 “very negative” to 9 “very positive”) and arousal (on a scale from 1 “very calm” to 9 “very excited”). Pictures were presented in the same order as in the fMRI task.

As for the fMRI analyses, two types of analyses were conducted for emotional experience: the mean value and the disparity (variability), with the same methodology as in the ROI analyses, and focusing on the behavioural responses.

2.3.2. Neuropsychological assessment

2.3.2.1. Cognitive assessment

Executive functions were assessed according Miyake’s model, using the computerized Test of Attentional Performance (TAP) (Zimmermann and Fimm, 2002) for inhibition (“incompatibility” subtest, analysed with difference between the number of errors observed in the compatibility vs incompatibility phase), flexibility (“flexibility” subtest) and the updating of the information (“working memory subtest”, Third level). The relevant criteria were the difference in the number of errors for the first two tasks, and the number of omissions for the last task. The WAIS-IV similarities subtest, a test of verbal abstraction, was also administered.

Processing speed was evaluated with the Symbol Digit Modalities Test (SDMT) (Smith, 1982), a very sensitive 90-second oral task, known to be predictive of global cognitive impairment in MS (Parmenter et al., 2007). The number of correct answers was chosen as the relevant criterion.

2.3.2.2. Self-report questionnaire

All subjects were asked to complete a French self-administered depression scale called EHD (*Échelle d’Humeur Dépressive*) (Radat et al., 2007). We assessed the following: anxiety, using the Hamilton Scale (Hamilton, 1959); alexithymia, using the French version of the 20-item Toronto Alexithymia Scale (TAS-20) (Loas et al., 1997); and fatigue, using the French version of the Modified Fatigue Impact Scale (MFIS) (Debouverie et al., 2007), which is commonly used in MS and has been validated in this population. On all these scales, the higher the score, the worse the symptoms.

2.3.2.3. Statistical analyses

Statistical analyses were performed using Excel and SPSS-21. Non-parametric statistical tests were used due to non-homogeneity of variance and non-normality of the distribution. A Mann–Whitney U test was performed for between-group comparisons of quantitative data. $P < 0.05$ was considered statistically significant for between-group comparisons of behavioural data.

For the MS group, Spearman’s rho was used to explore the correlation between significant brain areas’ responses and cognition, mood and disease characteristics. For the debriefing and fMRI data, the correlation analyses were conducted only for the results of the disparity analyses, as no significant differences were observed at the mean analysis level. For these univariate analyses an alpha level < 0.01 was considered statistically significant.

3. Results

3.1. Behavioural Data

No significant difference was observed between the two groups for the neuropsychological assessment, except for the SDMT, on which the MS group presented a significantly lower score than the control group ($P = 0.017$) (Table 1). The self-report questionnaire showed that the MS patients were more depressed ($P < 0.0001$), more anxious ($P = 0.001$) and more alexithymic ($P < 0.0001$) than controls; they also presented more fatigue symptoms ($P <$

	Multiple Sclerosis group n=25 Mean Score (SD)	Control group n=27 Mean Score (SD)	P-value
Demographic and clinical characteristics			
Gender	Female	Female	$P > 0.05$
Age, years	41.52 (9.9)	41.52 (10.0)	$P > 0.05$
Education, years	13.72 (2.1)	14.3 (3.1)	$P > 0.05$
Disease duration, years	10.36 (8.9)	NA	
EDSS score (median)	1(1-5)	NA	
Neuropsychological assessment			
Inhibition (Incompatibility Subtest, TAP)	2 (3.6)	0.85 (1.99)	$P > 0.05$
Flexibility (TAP)	2.16 (2.42)	1.70 (1.99)	$P > 0.05$
Working Memory (TAP, 3 level)	3.08 (2.61)	2.48 (2.19)	$P > 0.05$
Verbal abstraction (Similarities subtest, WAIS-IV)	9.4 (3)	9.8 (2)	$P > 0.05$

0.0001) (Table 1).

Information processing speed, SDMT	52.8 (12.1)	61.04 (8.2)	$P = 0.017$
Self-report questionnaire			
Depression, EHD score (/44)	22.04 (5.98)	15.44 (4.23)	$P < 0.0001$
Anxiety, Hamilton Scale (/56)	18.45 (12.29)	8.037 (7.11)	$P = 0.001$
Fatigue, MFIS (/100)	45.17 (24.15)	20.22 (7.34)	$P < 0.0001$
Alexithymia, TAS 20 (/100)	54.28 (11.64)	40.22 (10.97)	$P < 0.0001$

Table 1 Demographic, clinical and neuropsychological characteristics of the MS group and the control group

Abbreviations: N.A: not applicable TAP, Test of Attentional Performance; SDMT, Symbol Digit Modalities Test; EHD, Depressive Mood Scale (*Echelle d'Humeur Dépressive*); MFIS, Modified Fatigue Impact Scale; TAS, Toronto Alexithymia Scale

3.2. Post-scanning subjective rating

3.2.1. Analysis of the mean values

The results of the post-scanning subjective evaluation of positive, negative and neutral pictures did not differ between the MS patients and the control subjects for valence (unpleasant/pleasant) or for arousal when the raw values were compared between the two groups (see Table 2).

Table 2 Subjective evaluation of the response to positive, negative or neutral IAPS pictures: comparison of MS group and control group scores for valence and arousal

		MS group	Control group	P-value
		Mean score (SD)	Mean score (SD)	
Valence	Positive	7.45 (0.62)	7.24 (3.62)	0.22
	Negative	2.76 (0.81)	3.03 (1.51)	0.10
	Neutral	5.13 (0.44)	5.20 (2.60)	0.94
Arousal	Positive	4.65 (1.90)	3.92 (1.80)	0.12
	Negative	5.26 (1.70)	4.71 (1.49)	0.20
	Neutral	1.84 (1.09)	1.51 (0.79)	0.30

3.2.2. Analysis of disparity (variability)

For the valence dimension, MS patients scored differently their emotional experience in response to positive ($P = 0.001$), negative ($P = 0.0036$) and neutral ($P = 0.016$) IAPS pictures when compared to the control group. For the arousal dimension, MS patients scored differently their experience in response to positive ($P = 0.024$) and negative ($P = 0.003$) IAPS pictures but not in response to neutral IAPS pictures ($P = 0.097$), when compared to the control group (Fig. 1).

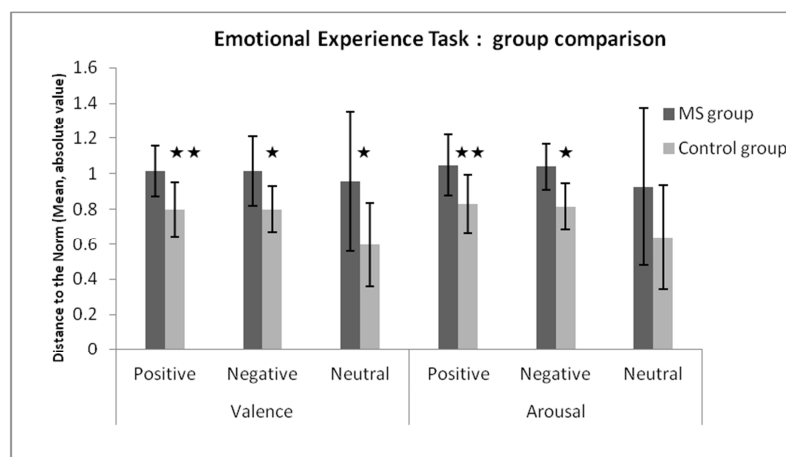


Fig. 1 – Dispersion of the subjective evaluation of responses to positive, negative and neutral IAPS pictures: comparison of MS group and control group scores for valence and arousal.

* Significant difference at $P < 0.05$ ** Significant difference at $P < 0.01$

3.3. Neuroimaging results

3.3.1. Within-group analyses

For the positive (Fig. 2, Supplementary table 1) and negative (Fig. 3, Supplementary table 2) conditions, both groups showed strong temporo-occipital and frontal activations (FWE, $P < 0.05$). The control group presented additional limbic activation, which included the amygdala (FWE, $P < 0.05$).

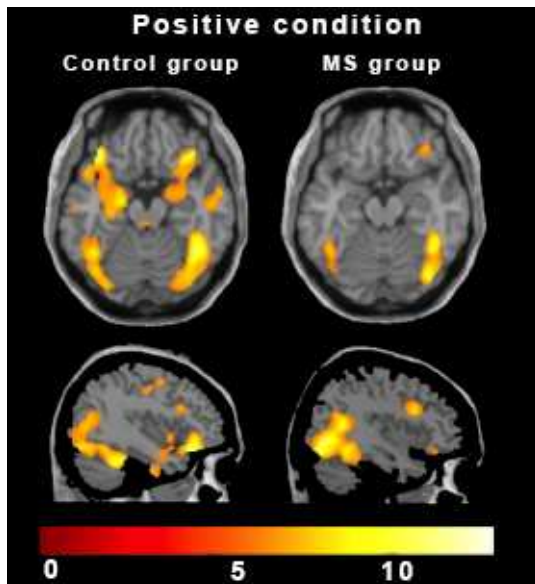


Fig. 2 — Brain activation relative to responsiveness to the positive condition: control group (left) and MS group (right); FWE corrected, $P < 0.05$.

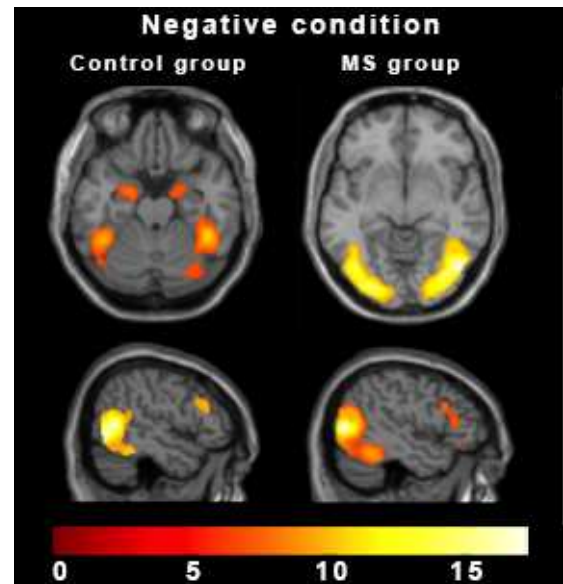


Fig. 3 — Brain activation relative to responsiveness to the negative condition: control group (left) and MS group (right); FWE corrected, $P < 0.05$.

3.3.2. Between-group analyses

a) Whole-brain analyses

No inter-group differences were observed (no activation over $P < 0.001$, uncorrected, with $k = 30$).

b) ROI analyses

Analysis of the mean: no inter-group differences were observed (all $P > 0.05$).

Analysis of disparity: in the positive condition, the results showed that, compared to controls, MS subjects presented abnormal variability in the left inferior orbitofrontal gyrus, both without correction ($P = 0.002$) and after multiple-comparison correction at $P_{FDR} < 0.05$ and $P_{FDR} < 0.1$ ($P = 0.0047$, FDR); in the negative condition, abnormalities involved the left amygdala ($P = 0.004$, uncorrected), the right fusiform gyrus ($P = 0.008$, uncorrected), the right caudate nucleus ($P = 0.009$, uncorrected) and the right pallidum ($P = 0.01$, uncorrected) (Table 3, Fig. 4). After multiple-comparison correction, this ROI survived with a threshold

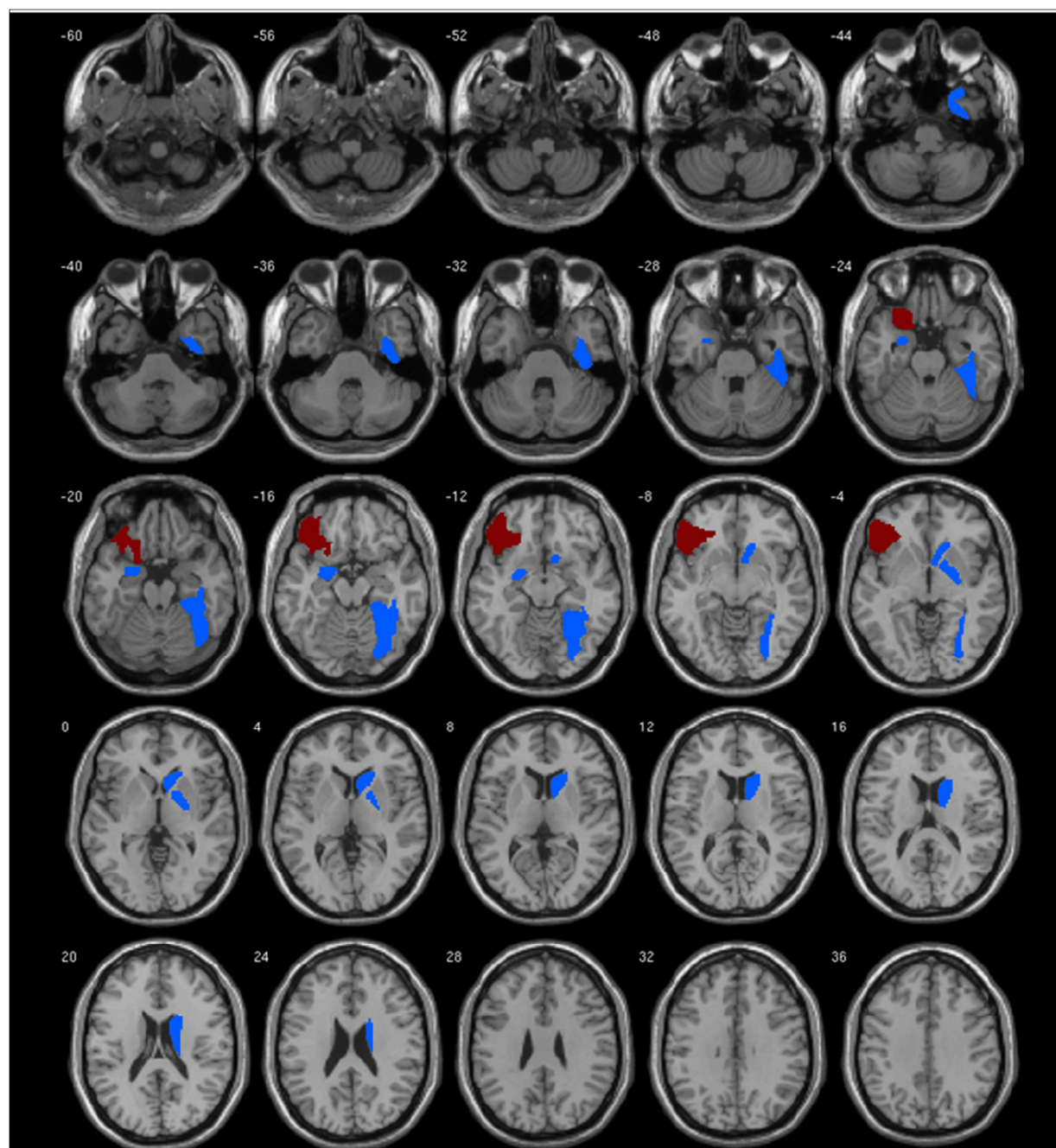
		MS group Mean (SD) of absolute z score	Control group Mean (SD) of absolute z score	Punc. value	P_{FDR}	MS group Mean (SD) of absolute z score	Control group Mean (SD) of absolute z score	Punc. value	P_{FDR}
Superior frontal gyrus, orbital part	L	1.07 (0.94)	0.77 (0.61)	> 0.01	> 0.1	0.96 (0.79)	0.75(0.64)	> 0.01	> 0.1
	R	1.16 (0.93)	0.77 (0.62)	> 0.01	> 0.1	0.92 (0.63)	0.66 (0.74)	> 0.01	> 0.1
Middle frontal gyrus, orbital part	L	1.08 (1.08)	0.74 (0.65)	> 0.01	> 0.1	0.70 (0.70)	0.69 (0.71)	> 0.01	> 0.1
	R	1.15 (0.93)	0.68 (0.73)	> 0.01	> 0.1	0.89 (1.01)	0.77 (0.62)	> 0.01	> 0.1
Inferior frontal gyrus, Orbital part	L	1.37 (0.94)	0.71 (0.69)	0.002*	0.047**	1.04 (0.73)	0.72 (0.68)	> 0.01	> 0.1
	R	0.97 (0.69)	0.68 (0.72)	> 0.1	> 0.05	1.02 (0.69)	0.80 (0.59)	> 0.01	> 0.1
Superior frontal gyrus, medial part	L	0.96 (0.66)	0.71 (0.69)	> 0.1	> 0.05	0.89 (0.74)	0.80 (0.58)	> 0.01	> 0.1
	R	0.86 (0.67)	0.76 (0.63)	> 0.1	> 0.05	0.88 (0.63)	0.81 (0.57)	> 0.01	> 0.1
Medial Orbitofrontal cortex	L	0.98 (0.80)	0.70 (0.70)	> 0.1	> 0.05	0.81 (0.52)	0.74 (0.66)	> 0.01	> 0.1
	R	0.87 (0.71)	0.73 (0.67)	> 0.1	> 0.05	0.84 (0.49)	0.70 (0.70)	> 0.01	> 0.1
Insula	L	1.20 (1.04)	0.78 (0.60)	> 0.1	> 0.05	1.26 (0.87)	0.77 (0.63)	> 0.01	> 0.1
	R	1.03 (1.06)	0.88 (0.43)	> 0.1	> 0.05	1.17 (0.91)	0.80 (0.57)	> 0.01	> 0.1
Anterior cingulate gyrus	L	0.93 (0.73)	0.76 (0.64)	> 0.1	> 0.05	1.22 (0.99)	0.79 (0.59)	> 0.01	> 0.1
	R	0.78 (0.7)	0.68 (0.72)	> 0.1	> 0.05	1.09 (0.94)	0.80 (0.59)	> 0.01	> 0.1
Amygdala	L	0.87 (0.90)	0.77 (0.62)	> 0.1	> 0.05	1.41 (0.80)	0.79 (0.60)	0.004*	0.067***
	R	0.89 (0.90)	0.79 (0.59)	> 0.1	> 0.05	1.15 (0.70)	0.78 (0.61)	> 0.01	> 0.1
Fusiform gyrus	L	1.32 (1.26)	0.76 (0.63)	> 0.1	> 0.05	0.87 (0.59)	0.69 (0.71)	> 0.01	> 0.05
	R	1.33 (1.37)	0.81 (0.56)	> 0.1	> 0.05	1.09 (0.64)	0.69 (0.71)	0.008*	0.067***
Caudate nucleus	L	1.22 (1.17)	0.72 (0.68)	> 0.1	> 0.05	1.19 (1.04)	0.81 (0.57)	> 0.01	> 0.05
	R	0.98 (0.85)	0.70 (0.70)	> 0.1	> 0.05	1.33 (0.96)	0.75 (0.64)	0.009*	0.067***
Putamen	L	1.10 (1.04)	0.78 (0.61)	> 0.1	> 0.05	1.28 (0.84)	0.79 (0.60)	> 0.01	> 0.1
	R	0.93 (0.99)	0.81 (0.56)	> 0.1	> 0.05	1.07 (0.68)	0.78 (0.61)	> 0.01	> 0.1
Pallidum	L	1.04 (1.01)	0.85 (0.51)	> 0.1	> 0.05	1.27 (0.78)	0.80 (0.58)	> 0.01	> 0.05
	R	0.98 (0.90)	0.87 (0.46)	> 0.1	> 0.05	1.27 (0.78)	0.74 (0.66)	0.01*	0.067***
Superior temporal gyrus	L	1.42 (1.05)	0.75 (0.65)	> 0.1	> 0.05	1.14 (0.83)	0.77 (0.63)	> 0.01	> 0.1
	R	1.24 (1.11)	0.81 (0.56)	> 0.1	> 0.05	0.92 (0.80)	0.74 (0.66)	> 0.01	> 0.1
Inferior temporal gyrus	L	1.18 (1.14)	0.64 (0.75)	> 0.1	> 0.05	0.73 (0.46)	0.66 (0.74)	> 0.01	> 0.1
	R	1.35 (1.44)	0.83 (0.54)	> 0.1	> 0.05	1.01 (0.65)	0.69 (0.71)	> 0.01	> 0.1

at $P_{FDR}<0.1$ but not $P_{FDR}<0.05$ (see Table 3).

Table 3 Between-group ROI analyses of disparity for the positive and negative conditions, with uncorrected P -value (P_{unc}) and after FDR correction (P_{FDR})

* Significant at $P_{unc}<0.01$, ** significant at $P_{FDR}<0.05$ *** significant at $P_{FDR}<0.1$

Fig. 4 – Axial view of the local brain responses, showing significantly scattered activations in the positive (red) and negative (blue) conditions in the MS group when compared to the control group at $P < 0.01$, uncorrected. **Notice that only the red region is statistically significant after correction ($P_{FDR} < 0.05$).**



3.4. Correlation results in the MS group

As inhibition, flexibility and working memory are strongly correlated to each other, we created a composite score (named “frontal composite”, see Table 4) in order to reduce the number of correlation analyses.

A regression analysis was performed between the ROI that presented significant brain signal variability at $P_{FDR} < 0.05$, compared to controls and the clinical data. **These concerned the left inferior orbitofrontal cortex in the positive condition.** In the MS group, the total score on the similarities subtest correlated negatively with the functional brain variability signal in the left inferior orbito-frontal ROI in the positive condition. ~~In the negative condition, none of the ROIs that differed in terms of functional brain variability between the two groups (left amygdala, right fusiform gyrus, caudate nucleus and pallidum) showed a significant correlation.~~

Table 4 Spearman’s correlation coefficients between significant ROIs for each condition and the clinical or neuropsychological data.

	Positive condition Left inferior frontal gyrus, orbital part
Age	-0.01
Disease duration	0.20
Time since relapse	-0.19
EDSS score	0.17
Valence rating	0.24
Intensity rating	0.07
Depression	-0.16
Anxiety	-0.12
Fatigue	-0.11
Alexithymia	-0.24
Frontal composite	-0.122
Verbal abstraction	-0.549**
Processing speed	-0.17

**** $P < 0.01$**

Valence and Intensity ratings correspond to the studied condition (e.g. positive condition = subjective rating for positive pictures).

4. Discussion

This study focuses on the neurobiological causes of positive and negative affect experience in women with MS. The paradigm is based on Russell's circumplex model (Russell, 1980), which proposes that emotion can be experienced along a bi-dimensional axis of valence (positive, negative, neutral) and arousal (calm to strong). Emotional experience belongs, along with emotion recognition, to the behavioural aspects of emotion in the neurosciences (Belzung, 2007).

To our knowledge, this is the first study in MS to have examined both positive and negative emotion using fMRI, and in particular the experience dimension. Four previous studies focused on the neural basis of emotional disorders in MS, but only for negative facial expressions during an emotion recognition task (Jehna et al., 2011; Krause et al., 2009; Mike et al., 2013; Passamonti et al., 2009).

4.1. Behavioural data

In this study, the behavioural data objectified two different profiles. First, when we considered the mean post-scanning rating, MS subjects presented a similar emotional experience to that of controls. This highlights the validity of our fMRI protocol but at first sight would appear to contradict the results of Di Bitonto and colleagues (Di Bitonto et al., 2011), who showed that MS subjects had a less intense emotional experience when confronted with negative pictures and sounds.

However, when we considered the rating distance between the two groups, we found that the MS subjects had a more scattered emotional experience than that of our reference population for positive, negative and neutral IAPS pictures. These results confirm the original study (Di Bitonto et al., 2011), which found that emotional experience was modified in MS, and we extended these results to include both pleasant and unpleasant stimuli. If we consider emotion processing overall (i.e., recognition and experience), positive emotions are rarely affected in MS (only reported in (Cecchetto et al., 2014)). However, it is important to note that positive emotions are also less frequently studied than negative emotions; furthermore, when they are studied, subjects performing a facial emotional task are frequently presented with a happy face, a facial expression that is relatively easy to detect (Britton et al., 2006). This frequency and difficulty discrepancy between positive and negative emotions in all previously reported MS studies could lead to a bias in the statistical analyses and underestimate possible disturbances. The protocol used in our study, however, proposes positive and negative visual stimuli that are similar in terms of their frequency and complexity, and are close to real life emotional scenes (IAPS), allowing a more precise approach to the examination of emotional disorders in MS. Moreover, whereas face emotion recognition is considered universal (Ekman, 1992), the experience of a real life scene is far more subject to cultural variability (Dufey et al., 2011; Kitayama et al., 2006). Due to the heterogeneity of lesions and functional reorganization, patients with MS present variable symptoms that can differ between and within individuals, and this heterogeneity is a central aspect of the disease (Lucchinetti et al., 2000) (Rocca and Filippi, 2007). The emotional variability studies translated into z-scores and compared to our own healthy controls allowed us to assess heterogeneity in MS, while controlling for cultural differences.

4.2. fMRI data

The next main objective of this study was to understand the neuroanatomical substrate underlying these disturbances.

In each of the two groups, strong activations (though less intense in the MS group) were observed in temporo-occipital regions and frontal regions for both positive and negative pictures, in contrast to neutral pictures. These results are congruent with studies in healthy subjects that showed that affect-laden pictures do indeed recruit the same perceptive areas as neutral stimulation but with stronger activations. This may reflect top-down fronto-limbic modulatory effects for increased awareness and selective attention in response to emotional events (Kober et al., 2008; Phan et al., 2002).

In our study, strong amygdala activation was also observed in the control group, but not in the MS group, in both conditions. Whereas the role of the amygdala in emotion was previously thought to be restricted to negative stimulations (Adolphs et al., 2005; Wager et al., 2003), the current consensus emphasizes the central role of this structure for the detection and the processing of relevant and rewarding stimuli for the individual, regardless of their positive or negative valence (Liberzon et al., 2003). Surprisingly, when inter-group differences were examined, none of this mean activation differed significantly between the MS group and the control group. Consequently, we next focused group analyses on the study of the aforementioned emotional variability in MS, using the same approach as for the behavioural data.

4.2.1. Positive condition

These apparently inconsistent findings are most likely explained by more widely distributed and scattered cortical recruitment during the emotional induction task. When we examined haemodynamic signal variability in ROI analyses we found an abnormal signal in the left inferior orbitofrontal cortex (iOFC) during positive stimulation in fMRI, even after multiple-comparison correction.

The iOFC is one of the most polymodal cerebral regions and is situated on the ventral surface of the frontal cortex. It has heterogeneous connectivity, with inputs from a large number of visceral and sensory regions and reciprocal connections with core limbic structures, such as the amygdala, cingulate cortex, insula, striatum and periaqueductal grey (Kringelbach, 2005). This suggests that the orbitofrontal cortex (OFC) is able to integrate sensory and visceral information in order to modulate behaviour and take part in a functional network involved in emotional processing, including the orbital and medial part of the frontal cortex.

On the basis of a critical review of meta-analysis, Kringelbach, 2005 proposed a functional model of the OFC where the most anterolateral region is involved in assignment to the stimulus reward value and evaluation, leading to its influencing behaviour, whereas the most medial part of the OFC is devoted to storing this information. The subjective pleasantness experience would originate between these lateral and medial regions, where assigned reward is linked to hedonic experience and, more generally, could be an important gateway to subjective conscious experience. Moreover, several studies have suggested an involvement of the OFC in reward value (O'doherty et al., 2000) and subjective pleasantness (Kringelbach et al., 2003).

Thus, the abnormal brain response observed in the iOFC during visualization of positive stimuli in our study is congruent with OFC functions and could also explain the difference in subjective pleasantness observed during post-scanning rating, even if no correlation has been demonstrated between this region and the post-scanning rating.

Moreover, information processed in the OFC is also destined to be involved in a regulatory mechanism via its role in inhibition response (Elliott et al., 2000) and anomalies in this step could lead to deviant behaviour.

In an fMRI study, Krause et al. reported a correlation between the decreased capacity of MS subjects to identify unpleasant facial expressions and a decreased activation in left BA 47, an iOFC region rich in von Economo neurons (VENs) (Krause et al., 2009). VENs are projection neurons located in the anterior cingulate and frontoinsula cortex, participating in *“the salience network in which information on the physiological states of the body reaches the fronto-insular cortex and is integrated into decision-making and value attribution processes in the ACC and prefrontal cortex”* (Butti et al., 2013). VENs are also involved in the recognition of emotional expression (Rosen et al., 2006) and in several neuropsychiatric diseases, such as autism spectrum (Allman et al., 2005), schizophrenia (Brüne et al., 2010) and dementia with Lewy bodies (Blanc et al., 2016).

4.2.2. Negative condition

During visualization of negative pictures, **no region varied significantly differently across** MS individuals compared to the control group. **However**, four ROIs tended to vary markedly both with an uncorrected threshold at $P < 0.01$ and after multiple-comparison correction at $P_{FDR} < 0.1$. This trend concerned abnormal variability of the haemodynamic signal in the left amygdala, the right fusiform gyrus, the caudate nucleus and the pallidum. **These regions are known to be important in emotional process, and to be altered in MS.**

For example, Passamonti and colleagues (Passamonti et al., 2009) reported that MS patients showed a lack of functional connectivity between prefrontal areas and the left amygdala when processing negative facial expressions relative to neutral stimuli. In the same way, Mike and colleagues (Mike et al., 2013) showed that the presence of white matter lesions in the uncinate fasciculus within an MS group was associated with poor performance in a facial emotion recognition task.

All our participants showed significant fusiform gyrus activations, which is logical because some of our IAPS pictures depicted emotional or neutral faces. ~~Indeed, through its substantial projections to primary and higher-order sensory areas, the amygdala modulates the affective representation of emotionally salient stimuli, by enhancing their perception via a top-down control~~ (Anderson and Phelps, 2001). Thus, the right fusiform gyrus, specifically activated by faces (McCarthy et al., 1997), shows enhanced activation in response to facial expressions, through an amygdala modulation (Vuilleumier et al., 2004). ~~This modulation, under the control of the amygdala (Vuilleumier et al., 2004), is an adaptive response because it influences forthcoming cognitive and perceptive processing, allowing individuals to coordinate an adapted response to their environment (Sander, 2013). The substantial variability of the haemodynamic response observed in the fusiform gyrus during the negative condition in the MS group shows that our patients were not able to adequately modulate the perceptive response to emotional stimuli. This result is congruent with.~~ In the intergroup analyses, MS patients present a trend to more variability in the haemodynamic response observed in the fusiform gyrus during the negative condition. In the same way, Mike and colleagues (Mike et al., 2013) ~~who~~ showed that poor performance in facial expression recognition in MS was correlated with fusiform area atrophy, but also with the lesion load in the right inferior longitudinal fasciculus, which connects the occipital lobe to the amygdala/temporal lobe, and the alteration of which is known to cause deficits in facial expression recognition (Philippi et al., 2009). ~~Diffusion tensor imaging (DTI) analysis could~~

~~help us to better understand the origin of the brain variability observed in the fusiform face area in our MS group.~~

A trend ~~Substantial brain variability~~ was also observed in the right caudate nucleus and putamen in the negative condition. The involvement of the basal ganglia has previously been reported in studies on healthy controls during the viewing of negative-affect-laden pictures depicting disgust or sadness (Phan et al., 2002). Studies of subcortical pathology have also highlighted this relationship, showing the affiliation of the basal ganglia in a striato-thalamo-cortical circuit involved in emotional processing (Péron et al., 2012). More precisely, the basal ganglia have been implicated in the modification of emotional experience in studies with patients suffering from Huntington's disease (Calder et al., 2000; Ille et al., 2011) and Parkinson's disease (Moonen et al., 2017). Moreover, several studies have provided evidence of the involvement of frontal-subcortical circuits in neuropsychiatric disorders, underlain by a specific chemoarchitecture and neurotransmitters acting as modulators in this functional activity (Tekin and Cummings, 2002).

In MS, basal ganglia atrophy has previously been associated with fatigue (Finke et al. 2015) and slower processing speed (Batista et al., 2012) but not with emotional aspects. Our study ~~tend to~~ extends these data, by showing that the basal ganglia could ~~are~~ also implicated in the modification of emotional experience in MS.

~~However, it is important to note that none of these results exceeded the statistical threshold after multiple comparison correction.~~

4.3. Brain variability during emotional processing and other characteristics

The haemodynamic variability ~~in the left orbitofrontal cortex~~ is independent of anxiety and depression, suggesting a coexistence and independence of mood and emotional disorders, as reported elsewhere (Passamonti, 2009; Krause, 2009). It is also important to note that our MS group was cognitively preserved, and so the aforementioned emotional disorder cannot, contrary to a suggestion by Lenne et al., 2014, be explained by a global cognitive deficit. The only correlation concerned the similarities subtest, possibly because it reflects a difficulty in verbalizing emotions (Wood and Williams, 2007). Some studies (Phan et al., 2003) have reported correlations between subjective ratings and specific brain regions, which was not the case in our study. Perhaps because this rating was proposed as a second step, after fMRI, subjects were not as close to the first subjective feeling experienced during fMRI, leading to a discrepancy between brain activations and the behavioural data. Moreover, the MS group was significantly more alexithymic than controls, and it also seems possible that for the same reason their reported experience did not correspond to their real feeling.

5. Limitations

Our study has several limitations. Firstly, the highlighted brain signal variability cannot be discriminated in terms of either hypo- or hyper-signal. ~~Secondly, for the negative condition we only showed some trends, but no brain structure exhibit statistical difference in their functional variability. This lake of statistical power might perhaps be related to the sample size of our populations.~~ Thirdly, a possible limitation is that the results of our study relate solely to a cohort of women. As behavioural and physiological sex differences in emotional experience are well documented, it has been strongly recommended that such differences be taken into account in functional brain imaging studies on emotion (Filkowski et al., 2016). In order to limit factors that could be a source of functional and clinical heterogeneity we

decided to include only women in our study. It would nonetheless be interesting to compare our results with a similar study on a group of men suffering from MS. Lastly, all the patients in our MS group were receiving β -interferon, and some preliminary clinical studies suggested that this treatment might favour the onset of emotional disorders (Group, 1993). However, a more recent long-term study supported the absence of any emotional worsening in MS patients treated with β -interferon (Porcel et al., 2006).

6. Conclusion

Our study provides the first evidence of a modification in the pleasant ~~and unpleasant~~ emotional experience in women suffering from MS and highlights the underlying brain mechanisms. These mechanisms were expressed as a marked and abnormal variability in the MS group compared to controls, centred on prefrontal areas for positive emotions. ~~For negative emotion, no statistically difference were observed~~ between the two groups, only a trend. These concerned more temporo-sub-cortical areas (amygdala, basal ganglia and fusiform gyrus). This brain variability during emotional tasks could be explained by brain disconnection or alexithymia. Our aim is now to study the anatomical connectivity in MS patients using DTI analysis. Moreover, the comparison of functional connectivity and anatomical connectivity between patients with a high level of alexithymia and those with a low level could help us to better understand this emotional profile.

Besides, an appropriate emotional experience is the basis of efficient decision making in everyday life (Elsinger and Damasio, 1985), and contributes to good social functioning (Bar-On et al. 2003). High rates of divorce (Pfleger, 2010) and unemployment (Julian et al. 2008) are observed in MS, and this could be a reflection of dysfunctional emotions making the subject's entourage perplexed when faced with unstable emotional reactions. In view of the potential effects of emotional disturbances on patients' social and professional life and also on their quality of life (Philipps et al. 2011), these aspects should be taken into account in clinical practice.

Compliance with ethical standards

The authors report no conflict of interest.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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Supplementary material

Supplementary table 1 Coordinates (in MNI standard space) and activation significance (Z statistics at $P >$

	Cerebral region	Side	k*	T**	MNI coordinates		
					x	y	z
Control group	Temporal middle	R	4521	13.06	48	-70	6
	Temporal middle	R		12.12	54	-60	18
	Temporal inferior	R		11.96	48	-54	-24
	Temporal middle	L	2692	12.99	-48	-70	8
	Cerebellum 6	L		9.95	-38	-44	-30
	Temporal inferior	L		9.88	-44	-52	-24
	Frontal inferior orbital	L	3306	11.85	-36	28	-16
	Hippocampus BA 34	L		8.81	-20	-10	-20
	Medial geniculum body	L		8.36	-18	-26	-4
	Frontal inferior orbital	R	1975	9.81	36	28	-18
	Undefined BA27	R		8.11	18	-34	-4
	Frontal inferior triangularis	R		7.58	42	30	-2
	Precuneus	L	309	8.84	-2	-50	50
	Frontal middle	R	540	8.78	44	-2	54
	Precentral	R		6.63	38	0	32
	Cerebellum 9	R	82	7.56	6	-56	-40
	Cerebellum 8	R	79	7.44	12	-72	-38
	Temporal middle	R	343	7.4	52	-14	-12
	Temporal middle	R		7.36	62	-4	-14
	Frontal superior	L	126	7.34	-20	40	50
	Occipital lobe	R	168	7.1	8	-98	6
	Precentral	L	258	7.04	-42	-10	44
	Precentral	L		6.77	-40	0	50
	Temporal middle	R	3393	13.38	48	-66	0
Multiple sclerosis group	Temporal middle	R		10.83	46	-58	8
	Occipital inferior	R		10.79	38	-78	-12
	Occipital middle	L	1215	9.41	-46	-72	2
	Fusiform gyrus	L		8.5	-44	-54	-18
	Occipital inferior	R		7.48	-38	-74	-8
	Frontal inferior triangularis	R	566	8.28	40	12	24
	Frontal inferior opercularis	R		8.04	54	20	34
	Frontal inferior triangularis	R		6.91	58	18	24
	Frontal inferior orb	R	60	7.47	36	34	-18
	Occipital superior	R	113	6.93	18	-98	16
	Thalamus	R	9	5.7	8	-16	4

0.05, corrected) for cluster-based contrast in the positive condition for each group.

* k: cluster size in voxels (1 voxel = 9 mm²) ** T: highest T score within a region

L: left; R: right

	Cerebral region	Side	k*	T**	MNI coordinates		
					x	y	z
Control group	Occipital middle	L	15301	17.44	-46	-74	6
	Temporal middle	R		15.98	48	-70	4
	Cuneus	R		14	20	-94	8
	Frontal inferior triangularis	R	149	8.62	34	8	32
	Frontal inferior opercularis	L	448	7.88	-40	16	24
	Frontal inferior triangularis	L		7.03	-42	26	12
	Hippocampus	L	140	7.41	-18	-6	-22
	Frontal inferior triangularis	R	199	7.27	52	34	18
	Frontal inferior triangularis	R		6.7	52	24	26
	Frontal inferior orbital	L	78	6.57	-38	30	-14
	Parahippocampus (amygdala)	R	104	6.34	20	-6	-22
	Frontal superior medial	L	13	5.83	-4	62	30
Multiple Sclerosis group	Temporal inferior	R	5337	11.69	48	-70	-6
	Fusiform	R		11.14	44	-48	-16
	Temporal inferior	R		10.92	46	-58	10
	Occipital middle	L	4665	10.16	-48	-72	2
	Occipital inferior	L		9.85	-26	-86	-6
	Fusiform	L		9.14	-44	-56	-16
	Parietal inferior	R	133	7.16	28	-48	50
	Frontal inferior operculis	R	429	7.07	40	14	28
	Frontal inferior triangularis	R		6.28	54	26	24
	Precentral	R		6.21	42	4	38
	Frontal middle	R	12	5.89	44	0	58
	Parietal superior	L	33	5.82	-26	-52	50
	Cerebellum 7b	L	12	5.69	-10	-74	40

Supplementary table 2 Coordinates (in MNI standard space) and activation significance (Z statistics at $P > 0.05$, corrected) for cluster-based contrast in the negative condition for each group.

* k: cluster size in voxels (1 voxel = 9 mm²)

** T: highest T score within a region

L: left; R, right

Supplementary data

Differences in fMRI activation patterns between fatigued and non fatigued patients

No differences were observed with a corrected threshold at $P < 0.05$, FWE.

With an uncorrected threshold at $P < 0.01$ and $k=30$:

- For the positive condition, no differences were observed between the two groups ($P < 0.001$, unc, $k=30$);
- For the negative condition, the fatigued group presented a decreased activation in the left vermis 1-2 ($x=-2$; $y=-40$; $z=-20$) ($P < 0.001$, $k=71$), in the right superior frontal gyrus ($x=38$; $y=50$; $z=2$) ($P < 0.001$, $k=32$) and in undetermined white matter ($x=12$; $y=-34$; $z=20$, with $k=39$).

Consequently, it seems that in response to negative stimulation, some areas are impacted differently according to the presence or absence of fatigue.