Research report

Prefrontal function associated with impaired emotion recognition in patients with multiple sclerosis

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ARTICLE INFO

ABSTRACT

Multiple sclerosis (MS) is associated with the occurrence of white matter plaques in the central nervous system. These are frequently located in areas interconnecting areas associated with the processing of emotions. Although recent behavioral studies indicated social and affective disturbances in many of these patients, functional studies investigating specific emotional recognition in MS are lacking.

We used functional magnetic resonance imaging (fMRI) and lesion mapping in MS-patients to investigate correlates between these measures and emotional facial recognition. Eleven patients whose affective ability was impaired were compared with eleven unimpaired MS-patients and eleven healthy controls (HCs) using a facial expression matching task.

Decreased recognition performance was limited to the detection of unpleasant facial expressions (sad, fearful, angry). In evaluating the functional activation maps for the unpleasant facial expressions, we found decreased insular and ventrolateral prefrontal cortex (VLPFC) activation in the impaired group versus the unimpaired groups. We found a close relationship between the inability of solving the task and decreased activation of the left VLPFC and the left anterior insula. In addition, we found a correlation between decreased performance accuracy and the presence of lesions in the left temporal white matter.

These data suggest that emotion recognition deficits in MS-patients might be due to the interruption of processing emotionally relevant information, which leads to decreased activation of the VLPFC and the insula.

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1. Introduction

Recognizing emotions from facial expressions is essential for perceiving the intentions and dispositions of others. This can be considered a key skill for the understanding of relevant social information in everyday life [12]. Recent lesion and functional magnetic resonance imaging studies have delineated the functional anatomy of this ability [2] demonstrating that emotion recognition from facial expressions consists of different processes: initial visual perception, activation of an emotional state via somatic representation, appraisal of the socio-environmental context, decision about the social meaning, and regulation of possible responses [1,14]. Two approaches have been used to separately examine these processes: correlation of lesion locations with neuropsychological deficits and the correlation of activation intensity with recognition performance. However, it would be advantageous to apply both strategies in MS patients since inflammatory foci are widespread throughout the white matter of the CNS and an understanding of the disturbance of emotional recognition in MS might only be possible by employing different methodological approaches.

Functional imaging studies provided clear evidence for the early pathway used for processing facial information. However, downstream emotional facial recognition is incompletely understood. After activating early visual areas, facial stimuli are selectively processed in a special region of the fusiform gyrus, the fusiform face area (FFA) and in the facial part of the superior temporal sulcus or fSTS [18]. While the FFA is recruited more by invariant features of faces like identity, and thus seems to be involved in face recognition, the fSTS codes the more changeable aspects of the face, like lip speech, gaze fixations, and emotional facial expression [3]. It is well established that the amygdala plays an essential role in this processing emotional qualities of facial expressions. Additionally, the amygdala is involved in automatic attention capture by emotional

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stimuli as well as in filtering emotionally relevant information from perceptual cues [40].

While the amygdala seems to be critical for extracting emotional relevant information from external cues from the environment, the anterior insula is involved in creating an "emotional state", in which it integrates the visceroception of the internal body state and information from the environment to a "feeling state" [2]. To complete this "emotional state", the anterior cingulate cortex (ACC) generates the appropriate "motivational state" [15]. The entire network is completed with the involvement of the orbitofrontal cortex (OFC) which is crucial for the processing of non-conscious aspects of facial expressions and is involved in the regulation of control to the social stimuli [2].

The role of the OFC in the recognition of emotional facial expression is not clearly understood, although an involvement of this area in emotional facial recognition in healthy subjects has been demonstrated [23,24]. Moreover, the precise spatial differentiation of this area is inconsistent. We may divide the OFC into two subdivisions, the ventromedial PFC (VMPFC), more involved in stimulus driven processing of emotional materials, and the ventrolateral PFC (VLPFC), involved in more cognitive aspects of emotional material [2,27].

Patients with multiple sclerosis show impairments in social interaction and report affective disturbances [19], but are rarely investigated for dysfunctions in emotion recognition. There is only one study by Beatty and collaborators [6] in which 21 MS-patients were studied with a facial affect matching task. They found significant impairments in emotion recognition in MS-patients compared with controls, but they explained it by a general impairment in facial identification. To test patients for this ability again, we investigated 61 patients with MS for emotion recognition in a prestudy [8, under review]. We found clear deficits in emotion recognition using the Florida Affect Battery (FAB; [10]), while these patients showed no impairments in the facial identification task.

Here, we investigated differences in emotional recognition among patients with high and no emotional recognition impairments or HCs. We correlated fMRI-data and behavioral performance data with lesion load and lesion location. The emotion matching subtasks of the FAB were adapted to the environment of the fMRI scanner.

We investigated the following questions:

(a) Are emotion recognition deficits in MS patients related to clinical data such as disability status, depression, cognitive impairments, lesion location and lesion load?
(b) Which cerebral areas associated with emotional recognition are differently involved among patients with behavioral impairments and patients without such deficits or unimpaired healthy controls?
(c) Does activation in regions processing emotional recognition correlate with task performance accuracy?

2. Methods

2.1. Participants

Patients with multiple sclerosis according to the McDonald Criteria [25] were eligible for the study, if they were clinically stable for at least 30 days and EDSS (Expanded Disability Status Scale; [20]) was ≤ 5. The patients were recruited from the Neurology clinic at Greifswald University. The study was approved by the ethics committee of the Medical faculty of the University of Greifswald. All participants gave written informed consent according to the guidelines of the Declaration of Helsinki.

Via ambulant testing of the facial expression part of the Florida Affect Battery (FAB; details provided in Supplementary Methods), we tested 61 MS-patients according to their affective ability [8, under review]. In the current study, the 5th subtest of the FAB (facial emotion matching task), where subjects had to match emotional expression from a previously shown portrait to one of four portraits (each showing another type of emotional expression) was adapted to the scanner environment. With the use of the facial expression part of the FAB, the perception of affect can be tested in five different tasks with increasing difficulty. In the first task, two neutral faces have to be categorized as being either of same or different identity. This task can serve as a perceptual control task. In the facial emotion matching task (the fifth subtest in the FAB), two cards are presented simultaneously during each trial: one with a single photograph of an individual depicting a particular emotion and the other with five photographs of faces of different individuals, each with a different facial expression. Participants are required to choose the face on the second card depicting the emotion shown on the first card.

Out of the 61 MS-patients tested with the facial expression part of the FAB, we selected 22 patients in order to form two groups ($N = 11$ for each group; see Table 1) that differ significantly in their emotion recognition performance: MS-patients with deficits in emotion recognition (impaired MS-patients; age: 42.7 ± 8.4 years ($\pm$standard deviation) and a group of MS-patients without such deficits (unimpaired MS-patients; age: 36.3 ± 10.0 years). Out of these 22 patients, 17 took immunomodulators: beta interferon ($n = 9$) and Glatiramer acetate ($n = 8$). A patient was defined as impaired in emotion recognition if the total number of right answers to the FAB was at least 2 standard deviations below mean of right answers of a control group of 11 HCs (age: 41.8 ± 5.8 years) without neurological or psychiatric history (recognition rate: $94.4 \pm 2.3\%$, recognition rate for Impaired MS-patients $85.6 \pm 5.3\%$, $t(1,21) = 5.12$, $p < 0.001$; recognition rate for unimpaired MS-patients $95.9 \pm 1.7\%$). All groups were balanced in respect to gender (nine women, two men). In contrast to their different results of the total facial part of the FAB, groups performed similar in the facial identity task (1st subtest of the FAB; see Supplementary Methods); percentage of correct responses: unimpaired MS-patients: $99 \pm 2.4\%$, impaired MS-patients: $97 \pm 4.0\%$, HCs: $98.7 \pm 2.8\%$; $F(2,32) = 1.41$, $p = 0.26$. In this field, intact facial discrimination independent of perceptual impairment was guaranteed. In contrast, the impaired MS-patients performed worse in every other subtest (2nd: $F(2,32) = 12.9$, $p < 0.001$; 3rd: $F(2,32) = 5.35$, $p < 0.01$; 4th: $F(2,32) = 7.67$, $p < 0.002$; 5th: $F(2,32) = 15.93$, $p < 0.001$).

2.2. Apparatus and procedure

During the scanning period, participants had to perform a facial affect matching task as an adaptation of the 5th subtest of the FAB. During each of 60 trials, a photograph of a single individual showing one of five expressions (happy, sad, fearful, angry and neutral) was presented for 3 s, each expression presented twelve times in randomized order (for details see Supplementary Fig. 1). After presenting a fixation cross the second picture with four photographs of faces of different individuals was presented for 6 s and the participant was instructed to choose the face depicting the concordant emotion. The participant was instructed to press one of four buttons on a keypad. After responding, the chosen face was framed in color irrespective of correctness. Behavioral responses and response time were stored. The selection screen was followed by a 9 s fixation cross.

Scanning was performed with a 1.5 T whole body scanner (Siemens Symphony), consisting of anatomical MRI (T1-weighted: TR 368 ms; TE: 4 ms; T2-weighted: TR:

Table 1
Group characteristics. Differences in EDSS, PASAT and BDI were tested using unpaired t-test.

	Healthy controls ($N = 11$)	Unimpaired MS patients ($N = 11$)	Impaired MS patients ($N = 11$)	p
Age	41.8 ± 5.8 years	36.3 ± 10.0 years	42.7 ± 8.4 years	
Gender	Nine female, two male	Nine female, two male	Nine female, two male	
Course of disease[*]		10 RR; 1 PP	7 RR; 4 SP	
EDSS		Median 1.5 (range 0–3.5)	Median 3.5 (range 1–5)	0.07
PASAT		Mean 51.7 (SD 13.0)	Mean 37.1 (SD 14.4)	0.03
BDI		Mean 5.0 (SD 5.6)	Mean 14.4 (SD 9.6)	0.02

EDSS, Expanded Disability Status Scale; PASAT, paced auditory serial-addition task; BDI, Beck's Depression.

[*] RR, relapsing remitting; PP, primary progressive; SP, secondary progressive.
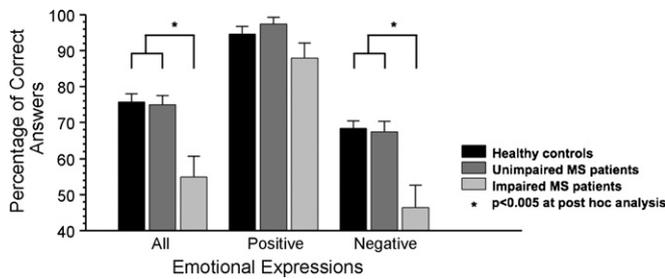
Fig. 1. Performance on facial emotion matching task. The total accuracy and the accuracy of identifying unpleasant facial expressions showed significant group differences ($p < 0.01$). Post hoc Tukey analyses showed that the performance of emotionally impaired MS-patients was significantly lower than both HCs and unimpaired MS-patients ($p < 0.005$), whereas accuracy between HCs and unimpaired MS-patients did not differ. These differences were observed in the total accuracy and the accuracy in identifying unpleasant facial expressions (sad, fearful, angry), but not the accuracy in identifying happy facial expressions.

3410 ms; TE: 123 ms; each scan 33 axial slices of 3 mm thickness and a T1-weighted MPrage-sequence; 1 mm × 1 mm × 1 mm) and echo planar imaging (EPI; TE: 50 ms; TR: 3000 ms; 33 axial slices of 3 mm thickness and 0.75 mm gap; matrix 64 × 64).

2.3. Data analysis

The white matter lesion volume of each MS patient was evaluated in the axial T2 images by means of a manual region of interest delineation of hyperintense lesions by an experienced neurologist and a volume of lesion calculation within the MRIcron software package (http://www.sph.sc.edu/comd/rorden/mricron). Group differences in lesion volume, PASAT- and BDI- scores were analyzed using two sample *t*-tests performed with the Statistical Package for the Social Sciences (SPSS, version 16.0). Response time and number of correct responses were analyzed using analyses of variances (ANOVA) with facial expression (angry vs. sad vs. fearful vs. happy vs. neutral) as within subject variable and group impaired MS-patients vs. unimpaired MS-patients vs. HCs as between subject variable. Post hoc comparisons were calculated using Tukey's HSD test. Spearman rank correlation analysis between behavioral performance scores and EDSS, lesion volume, PASAT- and BDI were calculated. Each analysis was considered significant at $p < 0.05$.

With non-parametric mapping (NPM), the relationship between the location of the brain lesions and the behavioral performance can be calculated statistically in order to identify lesions that specifically correlate with observed impairments in the emotion matching task. Normalized individual lesion maps were integrated in the MRIcron NPM analyzing package (http://www.sph.sc.edu/comd/rorden/npm/index.html). With these data, we performed voxel-based lesion symptom mapping (VLSM; with Brunner–Munzel-test (for a detailed statistical overview, see [33]). Computed results were considered significant at $p < 0.001$ corrected for multiple comparisons.

The fMRI data were analyzed with the Statistical Parametric Mapping Program (SPM5; Wellcome Department of Imaging Neuroscience, http://www.fil.ion.ucl.ac.uk./spm) described in detail in the Supplementary Methods. For each subject, one sample t-test for each emotional expression (happy, sad, fearful, angry and neutral) was calculated and corresponding contrast images of each subject were entered into a second level random effects analysis for group evaluations. Statistical thresholds for ROI-analysis (amygdala, insula, ACC and OFC) were set at $p < 0.001$, uncorrected. A regression analysis was performed for analyzing the specific regions responsible for the accuracy of solving the facial emotion-matching task using the number of correct answers as covariate. In the same way, we performed correlation analyses with EDSS, lesion volume, PASAT- and BDI score to investigate possible activation differences related to disease or behavioral aspects.

3. Results

3.1. Behavioral data

During scanning, impaired MS-patients showed significantly less correct responses in the FAB than the other two groups ($F(2,31) = 9.33$, $p < 0.01$; data of all groups and conditions plotted in Fig. 1). Group differences in emotion recognition performance were more pronounced for the recognition of unpleasant facial expressions (HCs 68.4 ± 6.6 %, unimpaired MS-patients 67.5 ± 8.8 %, impaired MS-patients 46.5 ± 20.4 %; $F(2,31) = 9.16$, $p < 0.01$). Post hoc Tukey analyses demonstrated that performance was higher in controls than in impaired MS-patients ($p < 0.005$) but not different in unimpaired groups. Positive emotional expressions showed no differences between groups. Response times to happy facial expressions were significantly faster than to negative emotional expressions ($F(1,127) = 22.67$, $p < 0.001$).
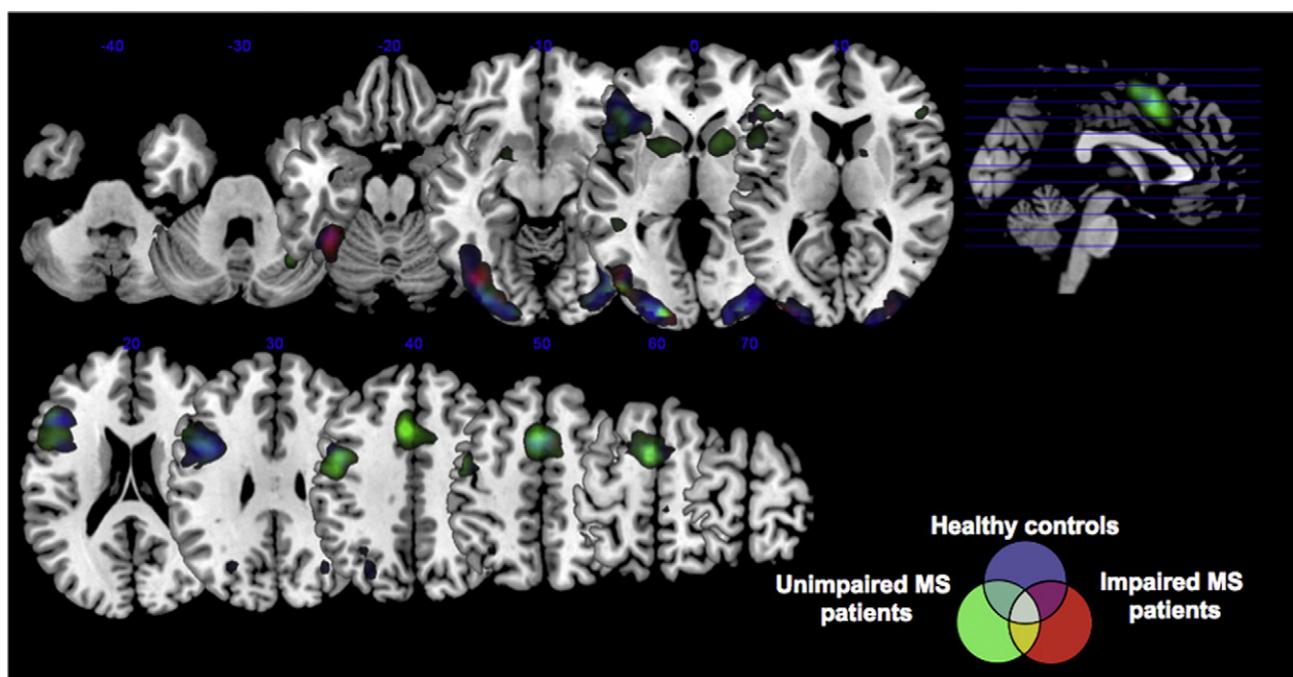

Fig. 2. Axial slices showing activity related to responsiveness to unpleasant facial expressions (sad, fearful, angry) for HCs (blue), unimpaired MS-patients (green) and impaired MS-patients (red). Each group had activations predominantly in occipitotemporal visual areas and in the prefrontal cortex. Activity was thresholded at $p_{corr} < 0.05$ with a minimal cluster size of 10 voxels.
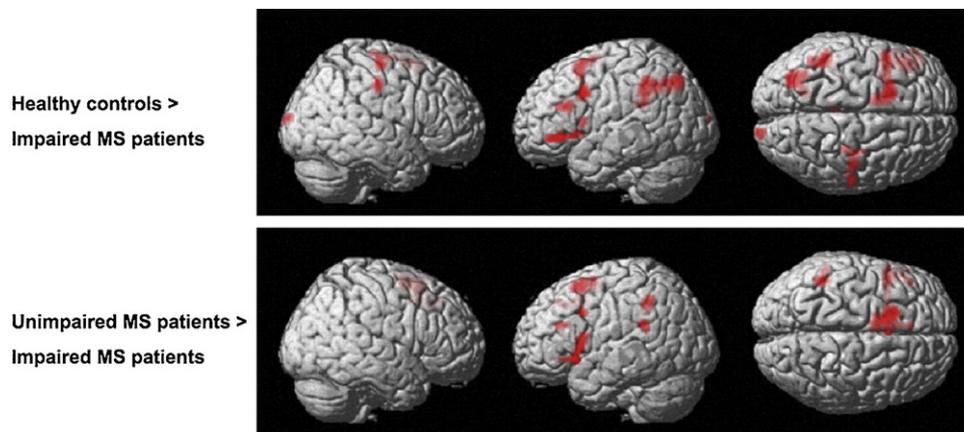
Fig. 3. Segmented brain surface with projected activation maps related to responsiveness to unpleasant facial expressions (sad, fearful, and angry) for healthy controls minus impaired MS patients (top) and unimpaired minus impaired MS patients (bottom). The differences were located predominantly in the left hemisphere (VLPFC, insula). Activity was thresholded at $p_{corr.} < 0.05$ with a minimal cluster size of 10 voxels.

For the assessment of other interactions, several tests were performed additionally: paced auditory serial-addition task (PASAT [16]; unimpaired MS-group: mean 51.7 ± 13.0; impaired MS-group: mean 14.4 ± 9.6; different with $p = 0.03$); Beck's Depression Inventory (BDI [7]; unimpaired MS-group: mean 5.0 ± 5.6 and impaired group: mean 14.4 ± 9.6; different with $p = 0.02$) and Expanded Disability Status Scale (EDSS [20]; unimpaired MS-group: median 1.5 (range 0–3.5); impaired MS-group: median 3.5 (range 1–5); not significantly different with $p = 0.07$).

3.2. Functional neuroimaging data

3.2.1. Within-group analysis

Since behavioral data indicated only differences for unpleasant facial expressions (sad, fearful, and angry) fMRI-differences were only tested for this emotional dimension (Fig. 2, Supplementary Table 1 listing all clusters of activation). As predicted, significant activation was found predominantly in frontal and temporoocipital regions. In contrast, the impaired MS-patients only showed significant activation in regions involved in the early processing of emotional faces, including the fusiform face area (coordinates: $-36 -51 -18$; $t = 12.65$) and amygdala (coordinates: $-24 0 -12$;

$t = 4.31$). This suggests that emotion recognition deficits are associated with reduced activation of frontal and temporal cortical regions.

3.2.2. Between-group analysis

Whereas the comparison between HCs and unimpaired MS-patients revealed only a slight difference in the OFC, impaired MS-patients showed decreased activation in FFA, fSTS, ACC, insula and left OFC (BA 10, 47). fSTS, insula and left OFC (BA 47) activation were furthermore decreased in the impaired compared to the unimpaired patient group (Fig. 3, Table 2, Supplementary Table 2 listing all clusters of activation).

3.2.3. Correlation analysis

The percentage of correctly recognized unpleasant facial expressions correlated significantly with an increased activation of a cluster in the left BA 47 that mainly encompasses the VLPFC (coordinates: $-45 18 0$; $t = 4.91$) together with a small part of the left anterior insula (coordinates: $-45 15 0$; $t = 4.43$; see Fig. 4). None of the other predefined areas (FFA, fSTS, amygdala and ACC) showed a significant correlation. In correlating neuropsychological with behavioral data, accuracy of identifying unpleasant facial expres-

Table 2
Between-group ROI-analyses of areas involved in the processing of unpleasant facial expressions.

Region	Healthy controls > impaired MS patients						Unimpaired MS > impaired MS patients						Healthy controls > unimpaired MS patients					
	BA[a]	MNI coordinates			T[b]	k[c]	BA	MNI coordinates			T	k	BA	MNI coordinates			T	k
		x	y	z				x	y	z				x	y	z		
FFA		45	−48	−21	5.45	74					n.s.						n.s.	
fSTS	21	−60	−30	0	5.28	30	21	−63	−30	0	4.82	46					n.s.	
		54	−42	9	3.49	7		45	−36	3	4.25	26						
Amygdala					n.s.						n.s.						n.s.	
ACC		−6	18	27	3.71	12					n.s.						n.s.	
Insula	47	−45	15	0	5.09	42	47	−45	15	0	5.34	26					n.s.	
		30	−18	18	4.37	9												
		36	27	0	4.34	18												
OFC	47	−51	18	−3	7.51	36	47	−51	18	−6	6.14	55	10	−27	51	−3	4.31	24
	47	−51	33	−3	6.74	9	47	−51	33	−3	4.72	6						
	10	−30	51	0	5.00	19												
	10	−39	48	3	4.34	11												

Small volume correction for the a priori regions of interest using threshold $p < 0.001$ uncorrected for multiple comparisons. FFA, fusiform face area; fSTS, facial part of superior temporal sulcus; ACC, anterior cingulate cortex; OFC, orbital frontal cortex.

[a] BA: Brodman area.
[b] T: highest T score within a region.
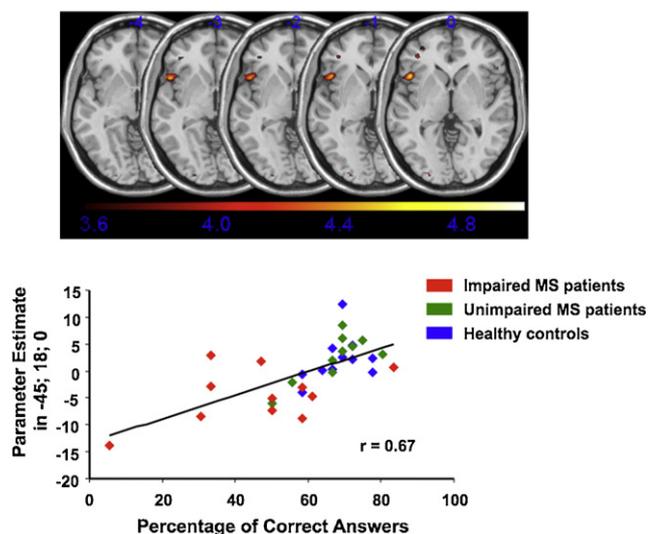[c] k: Cluster size in voxel (1 voxel = 27 mm^2).

Fig. 4. Regression analysis between signal intensity and the percentage of correct answers to unpleasant facial expressions. Of the regions of interest, only a cluster enclosing the VLPFC and the anterior insula showed significant activations (depicted on five axial slices with MNI *z*-coordinates; color-coded *t*-scale). Significant linear correlations were detected between blood oxygenation level-dependent (BOLD) intensities for each subject and parameter estimates of the highest activated voxels.

sions showed a trend for a negative correlation with activation of EDSS ($r = -0.43$; $p = 0.06$) and BDI ($r = -0.41$; $p = 0.08$) and a trend for a positive correlation with activation of PASAT ($r = 0.40$; $p = 0.07$).

EDSS, lesion volume, PASAT- or BDI-scores showed no relevant or significant correlation with the BOLD-signal strength in any of the ROIs, suggesting a specific role of the left VLPFC for emotion recognition performance, which is not influenced by general cognitive impairments or mood states.

3.2.4. Lesion measurements

Lesion volumes between unimpaired (5.1 cm^3; range 0.1–41.7) and impaired (3.3 cm^3; range 0.4–13.8) MS-patients were comparable ($t = 0.93$; $p = 0.36$). Recognition rates of unpleasant facial expressions showed no significant correlation to the lesion volume ($r = -0.26$; $p = 0.26$). Correlation analysis between lesion distribution and behavioral performance in recognizing unpleasant facial expressions revealed a most significant location in the left temporal white matter (coordinates: $-33 -53\ 20$; $z = 13.43$).

4. Discussion

The aim of our study was to identify the essential cerebral structures involved in emotion perception dysfunction in a group of MS-patients who was known to be impaired in emotion recognition. We used functional MRI during a facial affect matching task. Consistent with Beatty et al. [6], we found impaired emotion recognition. However, in contrast to their findings, no impairment was found in face identification, suggesting that the emotion recognition deficit is not due to a general impairment in discrimination of facial stimuli. We tested other possible influences like cognitive ability and depression, which differed between the groups but did not correlate with task accuracy.

The facial expression matching task used in our study is comparable to other studies evaluating dysfunction in the recognition of facial expressions in dementia [34] or schizophrenia [35]. Consistent with the current findings, these impairments were often most pronounced for recognizing unpleasant emotions from faces, while no deficits were observed for recognizing happy facial expression. One reason might be that recognizing a happy facial expression may

be easier and therefore can be better compensated [37]. The data of the current experiment would support such an interpretation.

For the unimpaired patient and HC-groups, the activation of all crucial regions of the neural system of emotion recognition is consistent with several neuroimaging studies of facial expression perception and judgement [29,31]. The anterior insula, which had been linked functionally to the VLPFC in respect to the ability to simulate the emotional state of others [36], showed decreased activation in those subjects who had problems in emotional facial expression recognition. This decrease correlated with lower emotion recognition performance. This finding is consistent with observations of insular activation in anticipation of emotionally aversive stimuli [30] and facial expression rating [11].

The more cognitive demand is required, the more lateral regions are activated [27,21]. Typically, the VLPFC has been described to be important for the processing of facial expression tasks [23,17]. A meta-analysis [38], which compared emotion induction tasks and cognitive tasks found that in emotion induction tasks, activation of area BA 47 was most often reported [29]. In a study of the recognition of emotional expressions with the FAB in patients with dementia, Rosen et al. [34] found that tissue loss in BA 47, detected with voxel based morphometry (VBM), correlated with inability to recognize negative emotions.

Although anatomically, Brodman area 47 is part of the VLPFC [28], voxelwise anatomical region correction assigns parts of the insular region to BA 47 as well. Other cytoarchitectonic, anatomical classifications define these regions as orbitoinsular [39]. Our findings are in agreement with this orbitoinsular activation pattern observed during emotion recognition. Interestingly, this frontoinsular cortex contains so called von Economo cells, which are suggested to play an important role in social cognition [4]. Thus, we hypothesize that the orbitoinsular cluster, comprising both the VLPFC and parts of the anterior insula, is the crucial region responsible for the deficits in emotion perception in impaired MS-patients.

In examining emotional, social, and cognitive interactions, Olsson and Ochsner [27] suggested a more functional-anatomical system of activation. They proposed a frontal framework with three dimensions: a medial-lateral dimension processing internal/emotional to external/cognitive, a ventral–dorsal dimension representing the stimulus driven to a reflective dimension, and an anterior to posterior dimension to lessen complexity. According to this model, the VLPFC BOLD-effect observed in the control groups corresponds with the stimulus driven external characteristic of the emotion perception task; decreasing recruitment leads to decreased accuracy.

In patients with MS, both cognitive and affective disturbances are believed to be due to the distribution of lesions [32], to the total lesion burden [9], or to cerebral atrophy [22]. In our study, the two MS-groups did not differ significantly in total lesion volume, nor did the total lesion load correlate with any activation during task performance.

With VLSM, the relationship between anatomical lesions and behavioral impairments can be tested voxelwise [33,5]. This method enables to ascertain which lesions are crucial for neuropsychological impairments like emotion perception dysfunction. This is superior to other studies that subdivide the brain into different subregions and correlate their regional lesion volume with behavioural data [22]. To our knowledge, the method used in this study has never been used to correlate neuropsychological data with lesion maps in MS-patients.

Using voxel-based lesion symptom mapping, we found that the most significant lesion was found in the left temporal periventricular white matter. Therefore, we suggest an impairment in information transmission from temporal visual processing areas to frontal regulation areas. In this white matter area, several projections pass, interconnecting the OFC and the STS [13,26].

An interruption of these connections may lead to a blockade in information processing and impairs the extraction of emotional meaning from the emotional stimulus material.

Combining the results of fMRI and VLSM methods, our data demonstrate that decreased activation of the VLPFC and the anterior insula is correlated with decreased accuracy in the emotion perception task. Furthermore, recognition failure correlated with white matter lesions in the temporal lobe. The combination of both methods suggests that temporal white matter lesions might cause an impaired interconnection of temporal facial processing and ventro-lateral prefrontal emotional facial recognition.

Critically, we are aware of several limitations. First, although emotion recognition in our data was not correlated with depression or cognition, only studies with more participants can rule out these covariates definitely. Second, we did not focus on grey matter abnormalities. Studies combining VLSM and VBM would be necessary to understand possible interactions. Third, structural connectivity analyses like fiber tracking is needed to understand MS related white matter fiber abnormalities.

Nevertheless, this study strongly suggests emotion recognition abnormalities in a subgroup of MS patients. More research is needed to understand more about the underlying cause. But knowledge about disease related neuropsychological impairments is useful for the handling of everyday life, both for patients and their therapists.

Disclosure

The authors report no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbr.2009.08.009.

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