

Clinical and neurophysiological patterns of impairments to emotion attention and empathy in multiple sclerosis

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Patients suffering from multiple sclerosis experience various cognitive and affective impairments, resulting in a negative impact on social behavior and personal independence to differing degrees. According to these often clinically subtle but conflicting cognitive-affective impairments, recordings of these socially relevant issues are still of demand to stratifying clinical and social support in a sophisticated way. Therefore, we studied specific cognitive and affective capacities in eleven patients with a predominant relapsing-remitting type of multiple sclerosis by applying paradigms of event-related potentials and a well-selected neuropsychological test protocol. Thus far, distinct cognitive disturbances of executive and attentional domains and the Wechsler Memory Test's four memory indices were found in multiple sclerosis patients. Concerning affective domains, patients showed discrete impairments of affect discrimination and affected naming as proved by specific testing (Tuebinger Affect Battery). Neurophysiologically, event-related potentials recordings in multiple sclerosis patients, were associated with decreased implicit emotion processing to cues of different emotion arousal at the early processing stage depending on attentional capacities and alterations of implicit emotion modulation at late processing stages. These clinical neurophysiological and neuropsychological data were correlated in part to quantitative magnetic resonance imaging brain lesions. Summarizing our data, our data indicate certain neurocognitive and neuroaffective dysfunctions in patients with multiple sclerosis, thus highlighting the validity of sensitive recording of less apparent neurologic disturbances in multiple sclerosis for optimizing the individual care management in patients.

Keywords

Multiple sclerosis; Emotion attention; Emotion empathy; Event-related potentials

1. Introduction

Approximately 70% of patients with multiple sclerosis (MS) at all stages and in all subtypes of the disease exhibit various cognitive dysfunctions during their illness [1–7]. Neuropsychological tests consistently reveal impairments to sev-

eral cognitive domains such as episodic and working memory, attention, executive functioning, and information processing speed as the significant areas [8–13]. Besides these cognitive impairments, patients suffering from MS are also at particular risk for affective disturbances such as perceiving and recognizing emotion with their sequelae to social interaction and affective functioning [14]. In addition, functional impairments, including disorders of affect and behavior, anxiety disorders, and substantial personality changes, including irritability, emotional lability, and apathy, account for up to 60% of MS patients for another leading contributor to morbidity and mortality [15]. In MS, disconnections in the frontal-subcortical brain tracts, known to also be involved in processing emotion signals, are observed [16]. However, the observed impairments in emotion processing in MS with failures incorrect identification of emotions might depend partly on the necessities of the functional integrity of a number of cognitive domains, including working memory, visual attention, visuospatial perception, and executive functions often compromised in MS [14]. In particular, impaired attention, executive function and working memory might be a matter of reduced process quality at the prefrontal cortex sites in forwarding cues of the emotional content of the inner and/or outer environment, so studying affective impairments at one hand, but also the consideration of possible confounding high order cognitive disturbances at the other hand, seems to be reasonable for implementing cognitive domains in studying emotion processing in MS, guiding a comprehensive approach in disentangling the features of affective impairments in MS.

Morphological and tractographical MRI studies in patients with MS suggested morphological changes of the white and gray matter within frontal, temporal and parietal lobes, suggesting disturbed structural integrity of the responsible frontal-parietal networks according to their functions along substantive cortical and subcortical pathways onto the result-

ing affective, but also cognitive impairments [17–19]. As far as these structural lesions and subsequent brain atrophy are well recognized as causing affective and cognitive decline [20], still circumscribed lesions as putative for distinct cognitive or affective disturbances have been criticized for several reasons. Nonetheless, some studies have been able to find significant correlations between clinical impairments of cognitive and/or affective domains and lesions located, for instance, in structures of the frontal lobes [21], the limbic system [22] and the left arcuatus fasciculus [23], are robustly identified in association with the observed high order domains of cognitive and/or emotion processing.

Beyond the structural analyses provided by cranial MRI, investigating the neurophysiological underpinnings of cognitive and/or affective impairments in MS would be of specific interest, particularly for capturing the affective impairments along their different time distribution lines. Using suitable paradigms could support this to evoke specific event-related potentials (ERP), but there are rare substantial reports on these issues. Specific investigations using the P300 component have given some interesting information on the neurophysiological background of cognitive impairments in MS [24–30]. In contrast, substantial reports about ERP patterns for emotion processing in MS are a subject of interest, particularly considering the previously conclusive findings of event-related potentials to physiological emotion processing in healthy subjects. The hallmark findings of ERP in emotion processing are early negativity shifts around 200 and 300 ms post stimulus to pictures with salient emotional contents of different arousal over temporo-occipital areas in healthy humans, indicative of an early facilitated sensory processing of affective cues at the bottom-up of the extended visual system independent of top-down control [31–34], and also indicative of augmented late positive potentials over parietal areas, indicating an intrinsically higher relevance of affective cues additionally on subsequent order stages of processing affective cues [35]. These robust findings along with various studies of healthy populations suggest a fairly conservative neurophysiological feature of emotion processing, which could be compromised by distinct neural lesions of the brain, offering a particular avenue for studying the neurophysiological background of emotion processing in neurological disorders as a sequela of topographically distinct brain lesions [36, 37].

The present study aimed to study this neurophysiological background of emotional disturbances in MS in more detail. Concerning recording early and high order emotion modulation by confined event-related potential paradigms, we hypothesized that patients with MS would show altered ERP of emotive cues of salient scenes at the early and also late processing as representative for affective processing at bottom-up and top-down stages, which should emphasize specific neurophysiological patterns as underpinning the clinically described affective impairments in MS patients. As a second hypothesis, impaired discrimination in emotions should also be found clinically, i.e., by testing the recognition of emo-

tions in the Tübinger Affekt Batterie (TAB) facial expression, which might support the primary hypothesis of electrophysiological patterns of disturbed affective processing. Concerning probing the prevalence and possible influence of cognitive deficiencies on affective impairments, we applied a broad neuropsychological test battery focusing on attentional, memory and executive functions in our study sample. Another aim of the present study was to identify substantial correlations between the investigated ERP patterns and the clinical and structural data provided by lesion load in cranial MRI, respectively.

2. Materials and methods

2.1 Patients and controls

We examined eleven ambulatory patients with a confined relapsing-remitting course of multiple sclerosis (RRMS), whereby three patients met the criteria of an advanced illness stage of the secondary chronic course of MS, according to the criteria of McDonald *et al.* [38, 39]. The patients have been recruited from institutional care of the department, comprising four male and seven female patients with a median age of 37.36 years. For control, eleven convenient, healthy subjects of the investigator institute surrounding comparable sex, age, and education level were considered without any neurological or psychiatric disorders. Patients enrolled in the study were diagnosed with clinically defined MS by an experienced neurologist according to the McDonald criteria [38, 39]. All the patients were in the course of treatment with disease-modifying agents, including interferon beta and glatiramer acetate. Exclusion criteria included severe cognitive or affective disorders as its entity according to ICD10, progressive forms of MS, the concomitance of other neurological or systemic disorders, severely decreased visual acuity and hearing loss.

Around clinical neuropsychological and psychophysiological testing, an MRI for further assessments of correlation of obtained data was performed within seven days. Patients were examined clinically with the MSFC (Multiple Sclerosis Functional Composite): walking distance, 9-hole-peg-test, Paced Auditory Serial Addition Test for assessment of overall motor and cognitive performance, and EDSS (Expanded Disability Severity Scale) for the graduation of daily dependency [40]. We informed all patients and controls about the design and aims of the study, and they gave their consent. All subjects performed the neuropsychological test battery and the event-related potentials recordings. The mean performing duration time of neuropsychologic testing and recording of event-related potentials was around three hours. Cranial MRI sessions for each MS patient did not extend over half an hour. The local ethics committee approved the study.

2.2 Neuropsychological testing

Patients of MS and controls were tested with the Tübinger Affekt Batterie (TAB) and adapted and validated the German version of the Florida Affect Battery [41]. This battery contains ten subtests, discriminating five different basic

emotions (happy, sad, angry, anxious, neutral) along visual, acoustic or intermodal (visual-acoustic) processing streams of responsible neural networks. In our study, the subtests 1–5 (1: facial identity discrimination; 2: facial affect discrimination; 3: facial affect naming; 4: facial affect selection; 5: facial affect matching) were engaged to study the recognition of the basic emotions in facial expressions. Additionally, probing cognitive domains along with attentional, executive and memory functions, we applied the test battery of attention probing (Test of Attentional Performance; TAP) containing five subtests (alertness, neglect, divided attention, covered shifting of attention; incompatibility) [42]. To test executive functions, we used the CKV (Computergestütztes KartensortierVerfahren), a German computerized version of the Wisconsin card sorting test by the computer-served card sorting procedure assessment disturbances of categorial properties [43]. The test evaluates executive functions, such as abstract thinking, development of strategies and playful action. Assessment of special memory capacities was tested by the revised Wechsler Memory Test (WMS-R) [44].

2.3 Event-related potentials

Studying the event-related potentials to emotional cues, we engaged computerized video movies made using Adobe® Premiere® software on a G3 Power Macintosh®. The videos presented 702 and 699 pictures as continuous streams of images. Videos were presented on a 21-inch EIZO F77 computer screen located approximately 100 cm before the subject, without perceivable inter-stimulus intervals (85 Hz refresh rate). Brain and ocular scalp potential fields were recorded with a multichannel 129 lead geodesic sensor net (Electrical Geodesics, Inc.), ensuring an evenly distributed sensor layout over the head surface with an intersensor distance of about 28–30 mm. Electrode impedance was kept below 30 k Ω . Data were recorded continuously with the vertex sensor as a reference electrode. The data were online bandpass filtered from 0.01–100 Hz and sampled at 250 Hz using Netstation software (5.2, EGI, Oregon, USA) and EGI amplifiers.

Event-related potentials for emotion encoding were recorded after applying a standardized set of paradigms [34, 35]. Colored pictures of the International Affective Picture System (IAPS) were presented to the subjects containing different emotional valences involving enjoyable (e.g., erotica, adventures, and sports) and very unpleasant contents (mutilations, human violence, and animal threat). Furthermore, pictures of a low level of arousal with different emotional valence, either neutral (e.g., household objects, neutral faces), less pleasant (e.g., babies, foods, and family scenes), and less unpleasant materials (e.g., loss, contamination, pollution) were presented [32]. All pictures were depicted in perceptually random sequences in each run of picture presentation. Four experimental conditions, each a constructed movie containing various examples of the IAPS, were administered (see Fig. 1). Conditions 1–3 each presented 702 pictures as a stream with a displaying duration of 333 ms per image, condition 4 presented 699 pictures with a displaying

duration of 1000 ms per image, drawn from a random order:

(1) Condition 1 was a ‘viewing only condition’ requesting the participant to fixate on the screen and watch the images, examining visual attention to emotional cues as indexed by an Early Negative Potential (EPN). In the second and third conditions, two different series of pictures of IAPS were displayed in the same manner (primary implicit visual task) but comprised with an explicit cognitive task focusing attention on non-affective stimuli (secondary explicit visual and/or auditory task). (2) In condition 2, a comparable movie was presented as a stream. Still, like an oddball paradigm, each picture was overlaid with vertical or horizontal lines. The patient required to count vertical lines, interspersed in random order and a probability of 20% of pictures overlaid with vertical lines (‘visual secondary cognitive attention’). (3) In condition 3, instead of lines, either a tone of low (800 Hz) or high (1000 Hz) frequency was presented with each picture, with the participant required to count high tones which were interspersed in random order and with a probability of 20% of pictures accompanied with a high tone (‘auditory secondary cognitive attention’). Participants were asked after each trial how many targets had been counted. In both conditions (2 and 3), the task-related non-affective stimuli were interspersed in a randomized order in the IAPS picture sequence with a mean lag of 6 IAPS pictures in between (range 2–10 pictures). (4) Condition 4 was similar to condition 1, but with a more extended presentation of 1000 ms per picture to examine Late Positive Potential (LPP) (‘second viewing only condition’). In this condition, the participant had been requested again to fixate on the presentation screen, as he did in the first trial, to capture early implicit encoding of affective cues (all four trials are depicted in Fig. 1).

Subjects were instructed carefully before each movie presentation, especially to stay fixated on the center of the screen. To minimize effects due to stimulus novelty, the subject was familiarized with the complete picture stimulus set. For all experimental runs, all subjects were informed clearly about the character and the task of each video presentation. Each subject was instructed to maintain focus on the center of the screen in each movie. Every video was followed by a break of approximately 5 minutes, in which the signal quality of the EEG sensors was checked. Afterward, task instructions for each experimental condition were given separately. Each presentation of the video lasted around 4 minutes. The subject room was dimly lit during a presentation of the videos.

2.4 Event-related potentials: data analysis

A 40 Hz, low pass filter was applied offline to the continuous EEG data. Stimulus synchronized epochs lasting from 42 ms before 332 ms after picture onset for 333 ms presented pictures, and pictures presented 42 ms before until 900 ms after 1000 ms were extracted. Off-line analysis of event-related potentials was performed by a Matlab-Analyzer package, excluding global artifacts like movements and correction for ocular movements after conversion to an average reference. Individual channel artifacts were detected based on the original

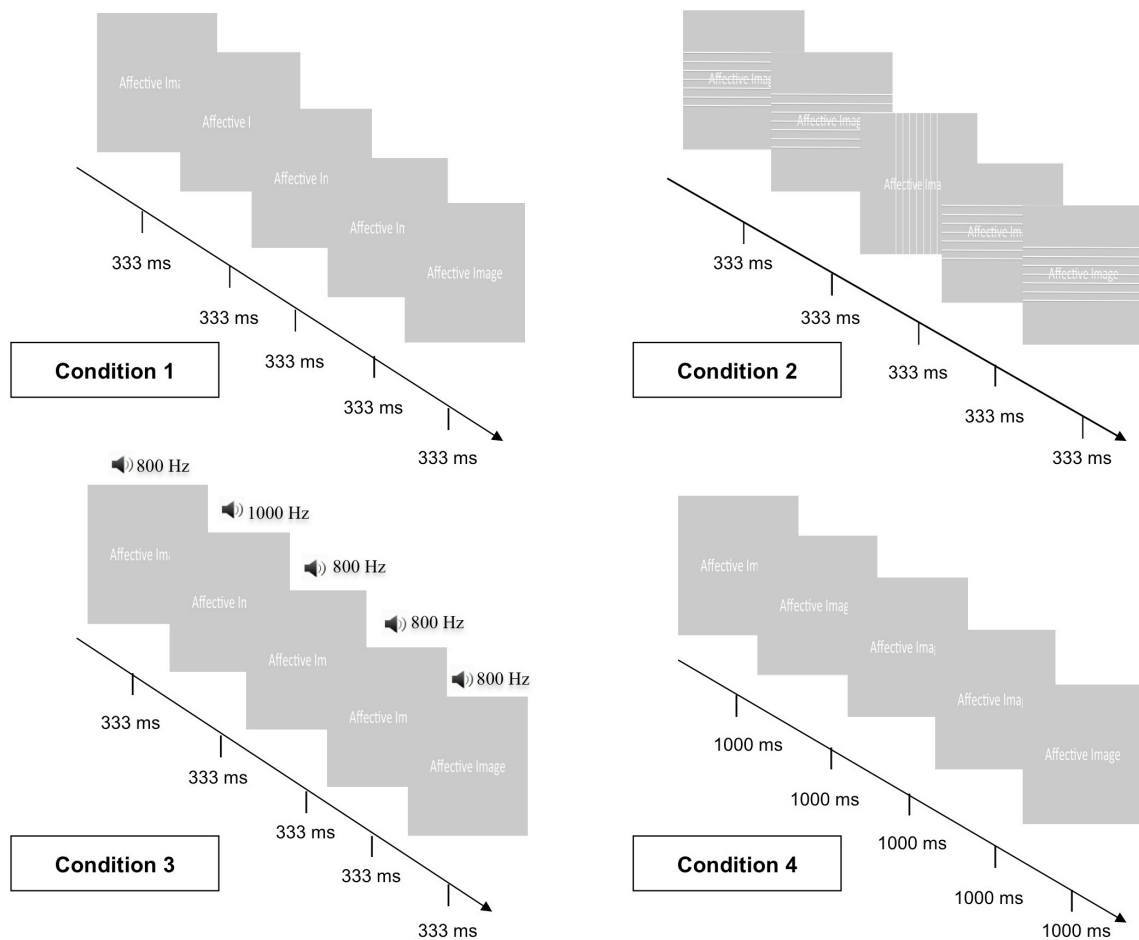


Fig. 1. Four conditions probing the EPN and LPP of emotional attention and the influence of cognitive distractions were performed. In condition 1, the patient viewed IAPS images changed at 333 ms intervals to capture EPN. In condition 2, each image was overlaid by horizontal or vertical lines, and in condition 3, each image was accompanied by two different tones (800 or 1000 Hz). In condition 4, images changed at longer intervals of 1000 ms to capture LPP.

vertex-referenced data set. For comparing ERP results between patients and controls, responses of each trial in each study task were calculated for all subjects in a first step to calculating a mean time range. After this, different ERP responses were calculated for each group (patients and control subjects) to distinguish possible group differences. The early selective processing for affective relative to neutral pictures was investigated in bilateral clusters over temporo-occipital areas [34]. According to each task and mean ERP responses of all recorded EEGs, we first calculated an overall grand average of all subjects and conditions to determine the exciting time ranges in which ERP responses were pronounced in each study run. In that way, the time to compare results of the early processing of affective stimuli focusing on the early posterior negativity (EPN) during implicit and during cognitive tasks should be limited to around 200 and 320 ms after picture onset. To extract the EPN from the EEG signal, separate average waveforms for pictures of low and high emotional arousal were calculated for each sensor and experimental condition.

The late selective processing appearing as enlarged late positive potential (LPP) amplitudes for affective relative to neutral pictures was investigated in bilateral clusters over the centro-parietal sensor area [35]. The LPP was also calculated after determining a mean time range of the grand average of all subjects, thus within a median time interval from 492 to 872 ms after picture onset.

Visual inspection determined that P300 waveforms were observed for the visual and the auditory attention task, differentiating an augmented P300 for target stimuli. P300 amplitude was calculated separately across separate average waveforms for each sensor of left and right centro-parietal clusters and experimental condition (non-target and target stimuli) for the visual and auditory attention task [34]. The P300 for visual stimuli was investigated in a time interval from 476 ms to 644 ms, and for auditory stimuli in a time interval from 284 ms to 480 ms.

2.5 Magnetic resonance imaging

We performed cranial magnetic resonance imaging (MRI) using a 1.0 Tesla scanner (Siemens, Erlangen) in each patient.

T1-weighted and dual-echo T2-weighted sequences, proton MR spectra and FLAIR sequences were recorded. The image matrix size was 256 m², the slice thickness of each axial scan was 3 mm. Cerebral lesion volumes were calculated by the obtained sequences semi-quantitatively using Image J (version 1.51, LOCI, University of Wisconsin, Madison, Wisconsin, USA), which represents a highly reproducible thresholding technique [45]. Lesions were segmented on computer displayed slices by delineating the regions of interests (ROI), and lesion volume was calculated by multiplying the total ROI area with the slice thickness. Each total lesion load (total lesion volume; TLV) was calculated, whereby a separate frontal lesion load (frontal lesion volume; FLV) was considered if appropriate. According to possible impacts of the amount of TLV of MRI lesions on neuropsychologic and —physiologic data, differentiation of patients with low lesion load (low lesion volume; LLV) and high lesion load (high lesion volume; HLV) with a dividing line at 3 cm was considered [46].

2.6 Data analysis

SPSS Version 16.0 (IBM Corp., Chicago, IL, USA) packaging was used for statistical analysis. Neuropsychological test results were compared by *T*-Test for independent samples and univariate analysis of variance (ANOVA), and ANOVA compared ERP data of the EEG recordings. Statistical significance was supposed for results with a level of 5% ($p = 0.05$), and a level of 1% ($p = 0.001$) was considered highly significant. Levene's test was applied for proving the basis of variance homogeneity. A calculation of Eta square (η^2) was applied to significant statistical variables of emotion domains (ERP, TAB) only in MS patients to assess the effect size. Testing possible correlative effects of different parameters, we applied Spearman's calculation of correlations coefficients. Improving the transparency and interpretation, TAP results were displayed in two ways: (1) comparison of MS and control group, and (2) comparison of norm data of test battery (*T*-values).

3. Results

3.1 Clinical data

All examined patients (four males and seven females) suffered from a primary relapsing-remitting course of Multiple Sclerosis (RRMS). Three out of these patients also gained the criteria of a secondary chronic progressive course of illness. The mean age of these patients was 37.4 years, and of the eleven healthy subjects was 36.5 years (see Table 1 for details). The latencies of the P100 of Visual Evoked Potentials (VEP) were 128.1 ms (+10.8) of the left and 126.3 ms (+10.3) of the right occipital derivation (+8.5). The mean duration time of illness course, the mean EDSS, and the mean scores of the MSFC subitems are depicted in Table 1.

3.2 Neuropsychological test battery

Studying the affective discrimination abilities by the TAB, patients with MS revealed significant deficiencies for discrimination (subtest 2; $t(12) = -3.74$; $p < 0.01$; $\eta^2 0.76$) and

Table 1. Overview of subjects basic data.

	MS	Control
Subjects (n)	11	11
Mean age	37.36 (+10.95)	36.5 (+8.5)
Sex	F: 7, M: 4	F: 7, M: 4
Mean duration of illness (years)	8.5 (± 4.3)	
EDSS	2.7 (+1.6)	
WD	5.7 (+3.4)	
NHPT	R: 19.1 (+3.7) L: 19.3 (+4.0)	
PASAT	43.25 (+13.8)	

Overview of demographic and clinical data of participants. Abbreviations: F, female; M, male; EDSS, Expanded Disability Status Scale; WD, walking distance; NHPT, nine-hole-peg-test (R, right side; L, left side); PASAT, Paced Auditory Serial Attention Test.

matching of facial affect expressions (subtest 5; $t(20) = -2.35$; $p < 0.05$; $\eta^2 0.87$). Regarding the remaining subtests of facial expression of emotions (subtests 1, 3 and 4), MS patients also yielded lower scores than control subjects, but these were beyond a statistical significance (see Fig. 2).

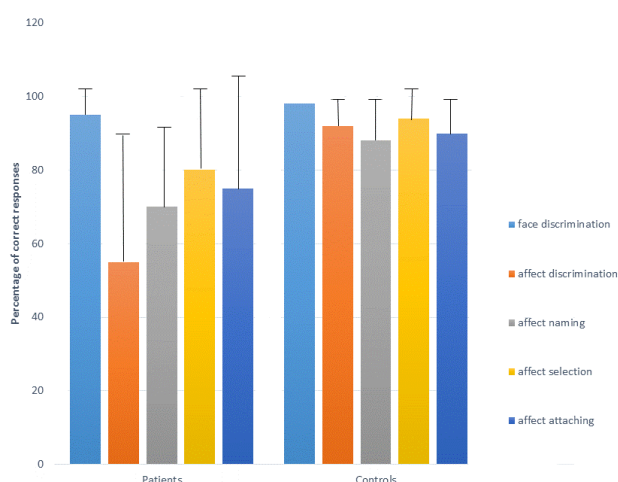


Fig. 2. Results of the Florida Affect Battery. The scores (in the percentage of valid responses) of subtest 1 up to 5 are displayed for patients at the left and controls at the right half.

Analyzing the cognitive abilities of attention, executive and memory functioning, MS patients showed impaired performance in different degrees (for a detailed overview of each result, see Table 2). In concern to attentional domains, the applied subitems of TAP revealed significant impairments in MS patients for tonic and phasic alertness with a significant main effect for the group of tonic alertness ($F(1,21) = 14.04$; $p < 0.01$), and also for the divided attention (significant: deficiencies for missings for general and for tones). Focusing the efforts of covered attention shifting, significant main effects were obtained for the factors condition (valid/invalid; $F(1) = 9.05$, $p < 0.01$) and group ($F(1,21) = 29.4$, $p < 0.01$), depending on reaction time. Depending on reaction time, the

Jeton test as representing the classical Stroop effect as part of executive functioning revealed a significant main effect on factor condition (interference/non-interference: $F(1,21) = 46.9$; $p < 0.01$) and factor group ($F(1,21) = 24.6$; $p < 0.01$). As a further investigation of executive functions, the CKV as the computerized version of the Wisconsin Card Sorting Test yielded significant scores for *perseverations* and *concept perseverations* (see Table 2). Also, patients exceeded the border value of false attachments by 2%, whereas control subjects scored normal with 14%. Finally, the memory capacities, tested by the WMS-R, exhibited significant group differences in all four memory indices (see Table 2).

3.3 Event-related potentials

Probing the event-relating potentials of the early capture of arousing affective contents as provided by cues of the IAPS, patients as well as controls elicited in all three conditions (1–3) an augmented early posterior negativity (EPN) over temporo-occipital regions of derivation as the neurophysiological response to pictures of high emotional arousal compared to pictures of low arousal, each displayed for 333 ms (condition 1).

Viewing pictures just as the primary task and focusing the attention on visual stimuli representing the secondary cognitive task (condition 2), MS patients elicited a pronounced negativity shift to highly arousing pleasant and unpleasant pictures in contrast to pictures of low arousal around temporo-occipital sites, which was beyond a clear statistical significance ($F(2,54) = 2.808$; $p < 0.068$). In contrast, control subjects elicited a significant pronounced negativity shift to highly arousing pleasant and unpleasant pictures at this trial ($F(2,54) = 7.002$; $p < 0.01$). The same ERP pattern in MS and healthy subjects remained if calculating the EPN only for emotional cues while only focusing the attention on target lines. This difference of ERP power remained significant when analyzing the between-group effect of the ERP ($F(2,54) = 7.306$; $p < 0.027$; $\eta^2 0.76$). Interestingly, viewing images of negative emotion valence during competitive overlaid lines as a secondary cognitive task was negatively correlated to the sum of successively counted events of vertical lines as a target condition in MS patients (-0.859 , $p < 0.01$) (see Fig. 3).

Viewing pictures simply as the primary task and focusing the attention on auditory stimuli representing the secondary cognitive task (condition 3), MS patients as well as healthy subjects elicited a significant pronounced negativity shift to highly arousing pleasant and unpleasant pictures in contrast to pictures of low arousal around temporo-occipital sites ($F(2,60) = 11.905$; $p < 0.01$; $F(2,60) = 5.047$; $p < 0.01$), whereby a between-group comparison showed a stronger EPN elicitation among healthy subjects ($F(2,60) = 10.829$; $p < 0.01$) (see Fig. 4). However, the within-group effect remains significant if considering only those EPN while focusing on the auditory target stimuli ($F(2,60) = 9.153$; $p < 0.01$; $F(2,60) = 9.599$; $p < 0.01$).

Analyzing the LPP during the presentation of pictures of the IAPS within a time frame of 1000 ms (condition 4), MS

patients showed no statistically significant augmentation of the LPP over centroparietal regions to pictures of the IAPS with a highly arousing pleasant or unpleasant content in comparison to pictures with a low arousing content for the time range of 492 up to 872 ms ($F(1,21) = 1.503$; $p = 0.231$), as it was for control subjects ($F(1,21) = 10.228$; $p < 0.01$). Analyzing the LPP at a between-group comparison, this finding remained significant for healthy subjects ($F(1,21) = 10.080$; $p < 0.01$) (see Fig. 5).

Considering the P300 as an index of successive cognitive discrimination for the synchronously displayed non-emotion tasks, patients ($F(1,21) = 12.876$; $p < 0.01$) as well as control subjects ($F(1,21) = 8.317$; $p < 0.01$) elicited a more robust positive ERP response around 300 ms to optically overlaid black lines of vertical orientation, as instructed as a target cue (Fig. 2). However, the visual P300 in MS patients has negatively correlated to several modules of the neuropsychologically probed attention domains, in particular the right hemisphere to alertness (trials with a warning tone, valid reactions: -0.725 , $p < 0.05$; trials with a warning tone, lapses: -0.725 , $p < 0.05$). ERP response to auditory target stimuli as displayed as a tone of 1000 Hz demarked a weak P300 for the target tones in patients ($F(1,21) = 2.126$; $p < 0.071$) and an augmented P300 in control subjects ($F(1,21) = 9.406$; $p < 0.01$). In comparison to visual P300, the auditory P300 showed some exciting correlations to clinical scores of alertness (trials with a warning tone, valid reactions, 674, $p < 0.05$; trials with a warning tone, lapses: 682, $p < 0.05$; trials with lapses of attention: -0.703 , $p < 0.05$; total mean of reaction time to incompatibility: -0.723 , $p < 0.05$). Behavioral data would show quite adequate attention of auditory target stimuli if a false rate of up to 20 % of missing targets were accepted.

3.4 Magnetic resonance imaging

Processing the MRI slices of ten patients with MS (one missing data set because of personal time constraints), six patients had a total lesion load (total lesion volume; TLV) below 3 cm^3 (low lesion volume; LLV), and four patients showed a total lesion load greater 3 cm^3 (high lesion volume; HLV). A distinct comparison in our sample did not yield any pronounced lesion load of the frontal cortex in comparison to the total lesion load, so further correlation analyses between MRI lesion load and neuropsychological as well as ERP evaluation were only employed for the total lesion load of the cerebrum (TLV) and the MRI-split subgroups with a lesion load more significant or smaller than 3 cm^3 (HLV and LLV).

Calculating correlations of MRI lesion loads for clinical scores, a positive correlation was given to the EDSS and the total lesion load (TLV) (0.70 ; $p < 0.05$). Scores of the MSFC were without a significant correlation to the total lesion load (TLV) and the MRI-split subgroups of a low or high lesion load (LLV and HLV). Correlating the MRI lesion loads to neuropsychologic data of our sample, a negative correlation between the total MRI lesion load (TLV) and the *valid reactions* of the overall test within the TAP (-0.65 ; $p < 0.05$) was detected. On the other hand, positive correlations have been

Table 2. Overview of the neuropsychological results.

Test item	MS subjects	Control subjects	Statistic
●Tübinger Affekt Batterie (TAB)			
Subtest 1: face discrimination	98%	100%	
Subtest 2: affect discrimination	83%	97%	$t(12) = -3.74; p < 0.01$
Subtest 3: affect naming	88%	95%	
Subtest 4: affect selecting	93%	98%	
Subtest 5: affect matching	89%	96%	$t(20) = -2.35; p < 0.05$
●Test of Attentional Performance (TAP)			
Alertness: trials without warning tone-median of reaction time	327 ms	242 ms	$t(11) = 2.63; p < 0.05$
Alertness: trials with warning tone-median of reaction time	345 ms	230 ms	$t(10) = 2.53; p < 0.05$
Alertness: trials without warning tone-median of reaction time, t -value	34.8	46.45	
Alertness: trials with warning tone-median of reaction time, t -value	33.4	46.27	
D3: general test-median of reaction time	735 ms	676 ms	
D3: square test-median of reaction time	852 ms	791 ms	
D3: tone test-median of reaction time	599 ms	574 ms	
D3: general test-missings (median)	2.6	0.7	$t(13) = 2.99; p < 0.01$
D3: square test-missings (median)	0.9	0.5	
D3: tone test-missings (median)	1.7	0.3	$t(11) = 2.24; p < 0.05$
D3: general test-missings, t -value	41	50	
D3: square test-missings, t -value	49	53	
D3: tone test-missings, t -value	38	46	
Incompability: general test-false reactions	2	3.82	$t(20) = -2.14; p < 0.05$
Incompability: general test-false reactions, t -value	54.82	48.64	
●Covert Attention Shift			
PO1: warning stimulus left/target left-median of reaction time (valid)	366 ms	280 ms	$t(20) = 2.719; p < 0.05$
PO1: warning stimulus left/target right-median of reaction time (invalid)	442 ms	322 ms	$t(20) = 2.792; p < 0.05$
PO1: warning stimulus right/target left-median of reaction time (invalid)	405 ms	312 ms	$t(20) = 2.656; p < 0.05$
PO1: warning stimulus right/target right-median of reaction time (valid)	353 ms	272 ms	$t(20) = 2.554; p < 0.05$
PO1: warning stimulus left/target left-median of reaction time (valid), t -value	39	51	
PO1: warning stimulus left/target right-median of reaction time (invalid), t -value	39	50	
PO1: warning stimulus right/target left-median of reaction time (invalid), t -value	40	52	
PO1: warning stimulus right/target right-median of reaction time (valid), t -value	41	50	
●Stroop Test			
version 1 (first trial)	907 ms	709 ms	
version 1 (second trial)	735 ms	587 ms	
version 2 (third trial)	813 ms	670 ms	
version 2 (fourth trial)	809 ms	644 ms	
verbal interference (fifth trial)	1004 ms	850 ms	
colour interference (sixth trial)	1076 ms	905 ms	
verbal interference-general failure	2.2	1.7	
verbal interference-interference failure	1.8	1.5	
colour interference-general failure	1	1.4	
colour interference-interference failure	0.8	0.9	
●Computer-based Card Sorting Test (CKV)			
wrong matching	16%	14%	
perseveration score	17%	6%	
concept	6	6	
concept acquisition	6.7	6.6	
concept lost	0.7	0.6	
concept perseverations	0.4	0	
●Wechsler Memory Scale-revised (WMS-R)			
verbal	93	108	$t(17) = -3.13; p < 0.01$
visual	101	115	$t(20) = -4.67; p < 0.01$
general	94	113	$t(20) = -4.87; p < 0.01$
attention and concentration	93	108	$t(20) = -3.29; p < 0.01$

Detailed results of the neuropsychological test battery. If a comparison between both groups were statistically significant, the pertinent score data are inserted. For more details, please see the explanations in the result section of the article.

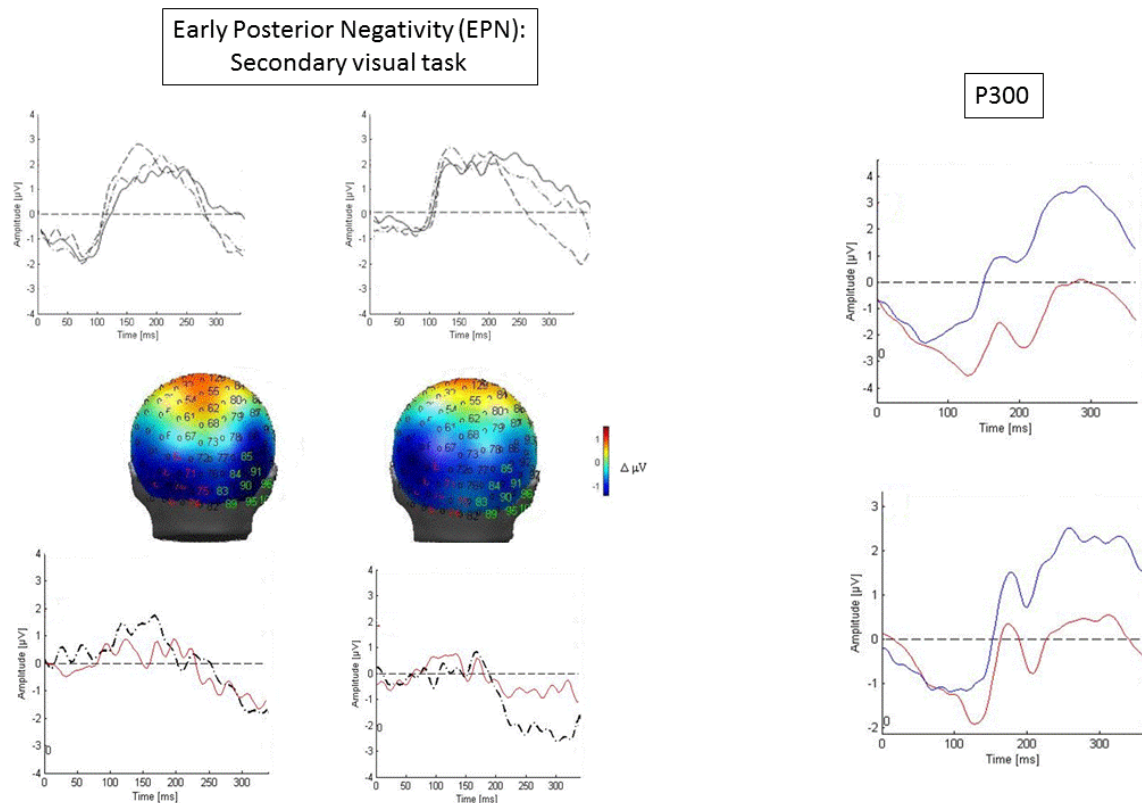


Fig. 3. Grand average of the Early Posterior Negativity (EPN) of condition 2 for competing for visual attention to affective and non-affective cues (IAPS viewing as the primary implicit task, and focusing horizontal and vertical lines as the explicit secondary task). At the left row, EPN in patients for all affective (dashed line: negative valence; dotted line: positive valence) and neutral (solid line) cues are displayed at the upper, its corresponding power map at the middle level. The EPN for affective (dashed line) and neutral (solid line) valence is displayed lower. In the same order, results of EPN for controls are displayed in the middle row. At the right row, corresponding P300 to target (blue line) and non-target (red line) cues of presented images are displayed. Time range of EPN: 200–320 ms (baseline: –42 ms).

found between the TLV and the rate of *false reactions* (0.69; $p < 0.05$) and *missing reactions* (0.645; $p < 0.05$) in TAP. Significant correlations between the CKV and the MRI lesion load subgroups were found for *conceptual registration* (–0.68; $p < 0.05$) and *conceptual loss* (–0.68; $p < 0.05$), and for trends, the item *all scores* (0.58; $p = 0.079$), *correct responses* (–0.60; $p = 0.068$) and *false responses* (0.60; $p = 0.068$), *perseveration* (0.57; $p = 0.085$), and *conceptual perseveration* (0.58; $p = 0.077$). Furthermore, there was a negative correlation between the MRI lesion load subgroups and *attention and concentration* (–0.64; $p < 0.05$), furthermore a positive between *visual performance* (0.68; $p < 0.05$), as tested by the Wechsler Memory Scale (WMSR). Finally, the quality of facial affect matching was negatively correlated to TLV of MRI (–0.709; $p < 0.05$).

Concerning correlative relations between ERP and MRI data, the auditory P300 showed a significant negative correlation to the TLV of MRI lesion in MS patients, i.e., for the amplitude of the P300 of the left centroparietal areas to the total lesion load (–0.67; $p < 0.05$), and the P300 of both hemispheres to the MRI-split subgroups of patients with HLV (left side: –0.64; $p < 0.05$; right side: –0.56; $p = 0.092$). Statistically relevant correlative effects of the early posterior nega-

tivity and the late positive potentials to MRI lesion loads and clinical and neuropsychologic data were not found.

4. Discussion

We investigated eleven patients of multiple sclerosis (MS) with a predominately primary relapsing-remitting illness course (RRMS) (three already advanced to a secondary illness course) with clinically moderate functional disability and eleven healthy controls on specific affective capacities to emotion attention and empathy, but additionally also cognitive functions, by robust neurophysiological and additional neuropsychological tools. Principal electrophysiological findings of disturbed emotion modulation as displayed by indicative ERP paradigms were impairments in perceiving affective cues on early stages were apparent in conditions of concurring cognitive tasks, whereby impairments in processing affective cues at late stages were already detectable without comprising concurrent explicit cognitive processing efforts. Therefore, our ERP findings suggest disturbed bottom-up and top-down processing lines of implicit encoding of affective cues in MS patients of our study due to reduced available neural resources of attentional domains to

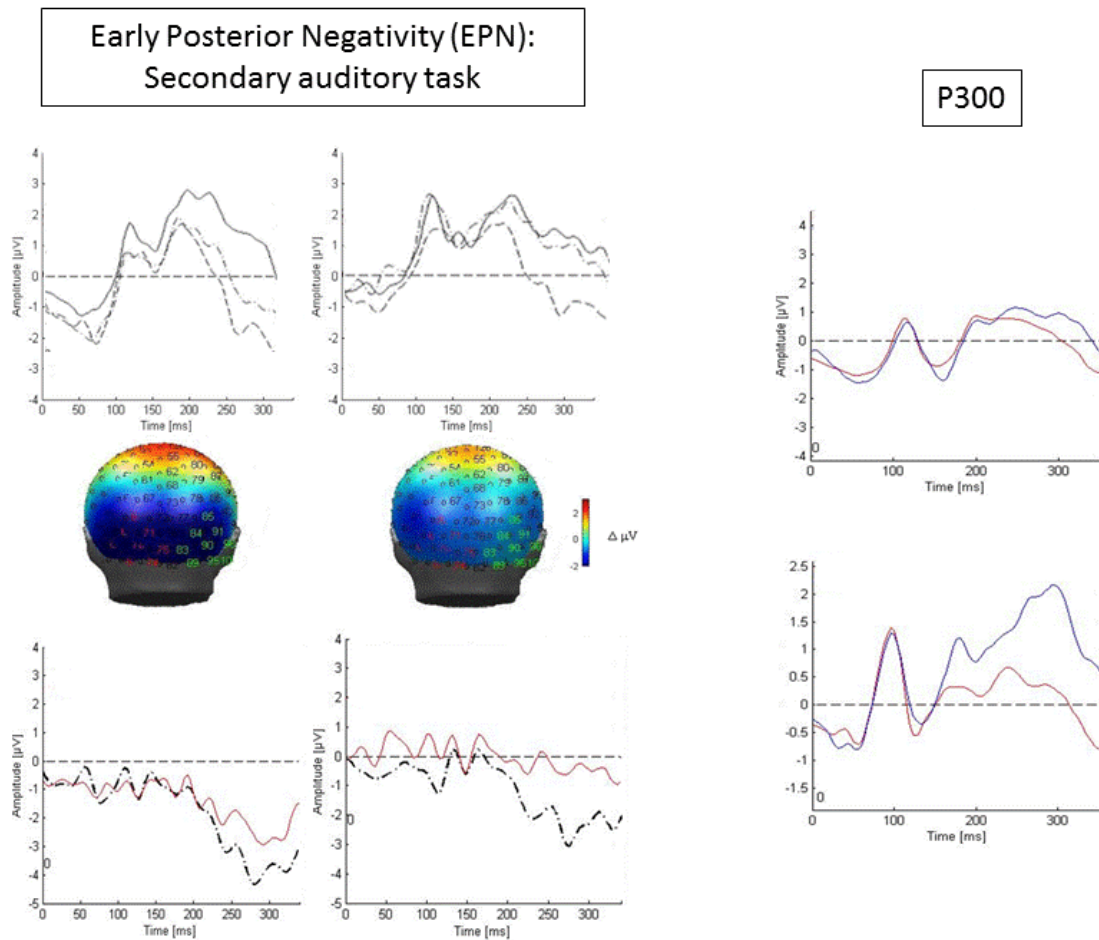


Fig. 4. The Early Posterior Negativity (EPN) of condition 3 for competing for attention to viewing affective and non-affective cues as the primary implicit task and listening to differing tones (800 vs. 1000 Hz) as the explicit secondary task. Similar to Fig. 3, EPN in patients for all affective (dashed line: negative valence; dotted line: positive valence) and neutral (solid line) cues are displayed at the upper level of the left row, and its corresponding power map at its middle level. The EPN for affective (dashed line) and neutral (solid line) valence is displayed at the lower-left level. EPN for controls is displayed in the middle row. At the right row, corresponding P300 to target (1000 Hz, blue line) and non-target (800 Hz, red line) cues are displayed. Time range of EPN: 200–320 ms (baseline: -42 ms).

emotional and cognitive cues at different but sequential processing stages. The recorded visual and auditory P300 suggested a preserved modulation in patients with a low MRI lesion volume and a disturbed modulation in patients with a high MRI lesion load. These electrophysiological findings in our sample of MS patients were accompanied by clinical impairments in emotion recognition in terms of discrimination and matching of emotion face expressions as proved by the Tübinger Affekt Batterie (TAB). Concerning cognitive domains, neuropsychological findings in MS patients of our study indicated cognitive impairments and several domains of memory, attention and executive functions, accompanied by an increased reaction time in nearly all neuropsychological test items. However, the neuropsychological findings of the cognitive domains did not correlate to the electrophysiological impairments as displayed by the affective ERP paradigms of the early posterior negativity (EPN), the late positive potential (LPP), and the P300 to non-emotional cues.

Our ERP findings, delineating aberrant neurophysiological processing of affective cues with salient contents of differing valence and arousal in subjects suffering from a predominately subcortical lesioning, are quite interesting in terms of the repeatedly reported ERP modulation for emotions of different valence and arousal apparent over temporo-occipital and parietal areas in early and late stages of encoding [31, 34]. The prominent feature is early negativity (EPN) over temporo-occipital regions within a time range between 150 and 300 ms after picture onset, which is accompanied by an augmentation for contents of evolutionary importance (erotics, mutilations or threats), reflecting the intensity of affective engagement of motivational systems such as approachment or avoidance within an initial transitory processing phase of selected elaboration processing of emotional stimuli [47]. Source analysis suggests an activation of the extended visual system, indexing an early facilitated sensory processing of affective cues [33]. Encoding af-

Late Positive Potential (LPP)

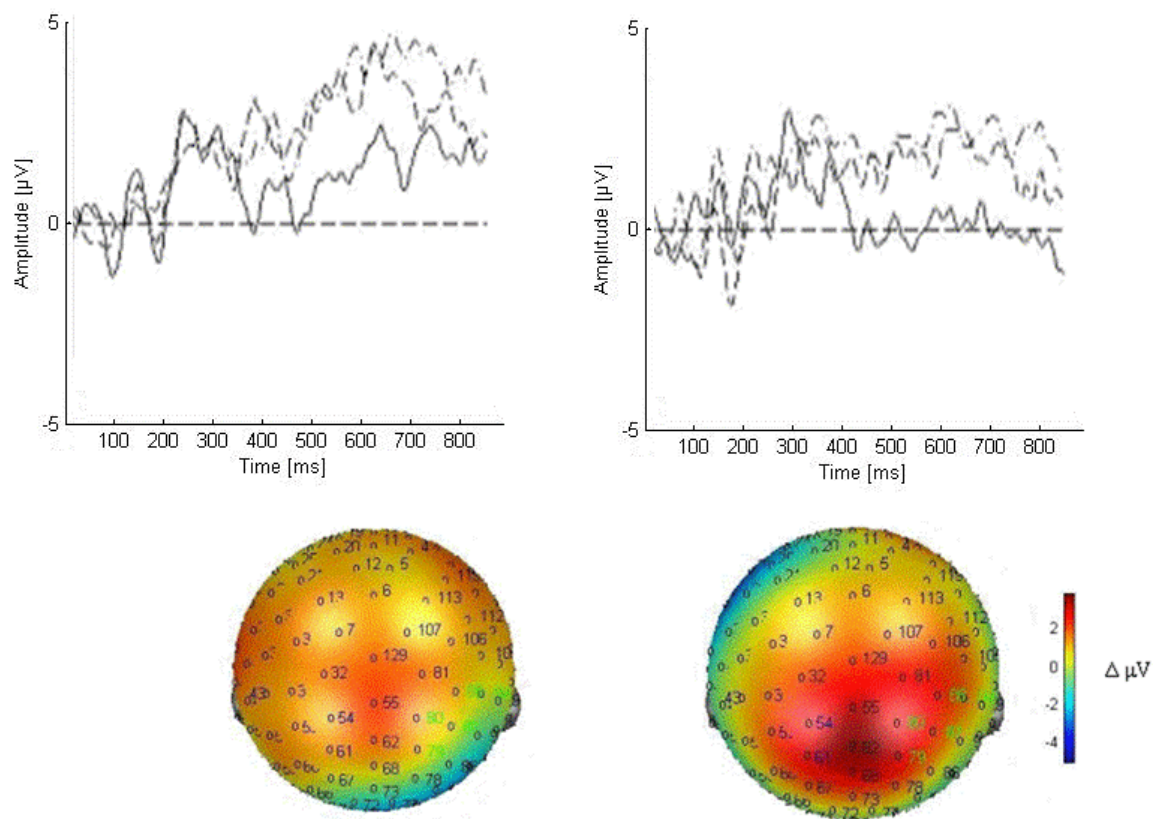


Fig. 5. Grand-averaged Late Positive Potential (LPP) of condition 4 for viewing pictures of the IAPS with different emotional valence (pleasant: dashed line: unpleasant: dashed-dotted line: neutral: solid line) as an implicit task. ERP and its corresponding power map of patients are depicted at the left row, and ERP and power map of controls are depicted at the right row. Time range of LPP: 492 to 872 ms.

ffective cues at these early stages reflects an automatic routine of capturing emotional stimuli independent of top-down control [34]. Indeed, intracranial recordings at inferior temporal and fusiform gyrus described a robust object-selectivity during initial processing (around 200 ms), despite a second object within the image [48]. Onward processing of visually presented affective cues with higher emotional arousal is associated with enlarged late positive potentials (LPP) relative to low arousing ones over parietal areas, indicating an intrinsically higher relevance of affective cues relative to neutral objects' high-order stages stimuli processing [35]. According to these well-evaluated findings of neurophysiologically detectable features of implicit affective processing, our sample of MS patients showed an impaired implicit emotional discrimination to presented visual affective cues of evolutionary relevance at the early stage of stimuli encoding in concurrently forced attention to non-affective cues, delineating the limitations of cue processing at bottom-up stages if the attentional load is subject of a critical threshold of available neural resources mainly demanded selected attention.

The failure of augmented LPP in our patient sample suggests a psychophysiological feature of disturbed implicit processing of affective cues at onwarding high-order stages, indicating a compromised allocation of processing resources in a capacity-limited processing stage associated with stimulus representation working memory [35, 49, 50]. Similarly, the reduced EPN to emotion cues in cases of forced selective attention to non-emotion objects indicates interference effects of competition for shared processing of those concurrent implicit emotional and explicitly cognitive tasks in the visual stream, unmasking a limited availability of processing resources for high-level constraints and thus unmasking the obligatory discriminative capturing of emotional significance in our sample of MS patients [51, 52]. The preferential processing of high-priority stimuli in the environment is an essential function of selective attention. Still, an inter-item competition among neural maps in the ventral stream of cue attention representing foreground task-stimuli and background emotion stimuli, as applied in our paradigm, obviously differed in favor of top-down attention processes for

focusing visual attention on task-relevant central stimuli so that emotionally relevant stimuli could no longer elicit the ERP signature of preferential emotion processing in our patients [47, 53]. Nevertheless, the finding of an augmented EPN to affective cues with a less constraining straightforward task suggests some preserved resources of visual attention to affective cues of evolutionary relevance along bottom-up pathways, similar to the observation of long preserved resources of hierarchical lower attention, such as attention span in patients with MS within the early phase of illness course [12, 35].

Concerning our neuropsychological findings of impairments in attention functions, these observations might be of interest in the discrepancy of the lesion-depending alterations of the P300 in our patient sample. ERP such as the P200 and the P300 is of particular interest for studying specific neurophysiological patterns of cognitive impairment in MS. A recent study of MS patients in a study by Waliszewska-Prosol *et al.* [54] showed higher P200 amplitudes, suggesting increased cortical and subcortical activity as a compensatory mobilization of more extensive neural networks to ensure better stimulus analysis. Accordingly, Senkowski and Herrmann [55] found a more substantial P200 amplitude for tasks with a higher difficulty level of a visual discrimination task. On the other hand, as a frequently analyzed ERP component in cognitive neuroscience, P300 is often associated with increased latency and/or decreased amplitude of this ERP, even suggesting a prognostic indicator for the progression of cognitive impairment in MS [56]. Honig *et al.* [57], and Piras *et al.* [58], argued that the consideration of structural issues in cognitive decline is relevant. They found a close correlation between changes in visual and auditory P300 and the number of plaques (lesion load) in MS [57, 58]. Thus, finding reduced P300 amplitude in auditory target stimuli at left parietal sites in MS patients with higher lesion load on MRI, as found in our study sample, is more consistent with the cognitive impairment neuropsychologically observed in the patients. This observation reflects the limitations or susceptibility of the functional complexity of the cerebral system in directing attention efforts to working memory, as seen, for example, in a study of working memory with the Sternberg memory scanning task in MS [59]. There, patients with lower scores in neuropsychological tests of working memory also showed a reduced positive shift in their reactions to memory probes. The reduced positivity shift was more strongly accentuated for auditory stimuli and related more to the probably higher demand on phonological working memory. Correspondingly, other clinical findings often pointed to signs of a disturbed phonological loop in patients with MS. The findings in our study seem to be associated with a reduced capacity of verbal working memory [60].

Our neuropsychological results are in line with previous findings of neurocognitive disturbances in patients with MS [1, 13, 61]. Patients in our sample showed impairments of different neuropsychological capacities, particularly within

attentional and memory and executive domains. Furthermore, patients were associated with impairments of processing resources of recognizing emotions in facial expressions, which is in line with the previous findings [10, 14, 62, 63]. Recent works indicated that these deficits also occurred in those with intact facial recognition, suggesting a rather specific affective than perceptual impairment [62–65]. These studies identified specific deficits in labeling sad, fearful, and angry facial expressions, as we found in our sample of MS patients performing the TAB. Despite the strong evidence of the neural substrates of impaired discrimination of emotional characteristics of facial expressions, in the particular prefrontal cortex (PFC) with the dorsolateral and ventromedial prefrontal cortex (DLPFC, VMPFC), the anterior cingulate and the amygdala-hippocampus-complex [66–68] disturbed transfers of responsible networks including interhemispheric transfer pathways of affective information may crucially account for impaired affect recognition and its significance in social cognition in patients with MS.

The analysis of correlations between neuropsychological and neurophysiological impairments to brain lesions in our considered cranial MRI was dominated by cognitive rather than affective impairments. This observation remains ambiguous concerning the different variables of affective behavior applied in our study sample, so there was a significant negative correlation to lesion load and emotion recognition in the TAB, but not for the ERP data. This observation of restricted correlations to MRI patterns for impaired emotion domains may be ascribed to the heterogeneity of topographic distribution [59] and properties of functional compensation [69]. However, several studies on the impact of brain lesions along topographic peculiarities like the number of brain lesions were often beyond a consistent relation to clinical issues, which have been assumed sequelae of neural reserves with strong compensatory potentials to cover the loss of network integrity. On the other hand, conventional MRI might be less sensitive to assess certain high order domains, so advanced MRI with higher resolution of affected brain tissues might be recommended in studying affective disturbances in MS, as microstructural measures in normal-appearing white matter indeed provide more neuroimaging information [20, 70]. Nevertheless, the lower yield of correlative effects between MRI and neurophysiological data of emotion processing in our study may also be a matter of our small patient sample, so further investigations using similar or at least comparable ERP protocols in study samples with a greater amount of patients might be of interest in clarifying this issue.

5. Limitations

Our study results are subject to some restrictions which should be considered. The power of our study results might be subject to relatively small sample size, i.e., eleven patients and eleven controls, which calls for a further evaluation of our study protocol even to a representative sample size. The

fact that three patients already met an advance to a secondary illness course in the meantime might be of less data impact if considering the moderate clinical degree of impairment as displayed by the EDSS. Nevertheless, we study a relatively homogenous sample of a particular brain disorder by applying robust clinical and neurophysiological study items, which delivers statistically feasible data, suggesting a valid subject in calculating the primarily hypothesized assumption of affective disturbances in MS. Therefore, further studies with a comparable protocol and a greater sample size might not only replicate but even differentiate some details of our findings due to a more representative statistical power. Another critical point of our study might be to concern the tremendous amount of variables in our protocol, i.e., besides the ERP trials in studying the neurophysiological appearance of affective disorders, accompanied by a broad set of neuropsychological tests and MRI data. To better understand our specific protocol, it is crucial to consider the growing use of clinical, neurophysiological and neuroradiological measurement tools in diagnosing and critical evaluation of individually afflicted functional areas in MS patients. Indeed, the optimal amount of chosen variables in characterizing such domains of affect regulation and possible cognitive influences like attentional and executive functions might challenge future research in MS.

6. Conclusions

The present work identified specific neurophysiological features of impairments in emotional attention and clinical features of a disorder in the discrimination of affective facial expressions, which contribute interesting information to the background and understanding of the neural mechanisms of affective disorders in MS. The functional deficits in our sample, which can be assumed to be moderate overall at an EDSS of 2.7, corresponding to the discrepancy in the maintenance of attentional performance for simple demand levels, which may already be the subject of compensatory neuronal activities the implemented networks of emotion regulation. Our approach to studying specific ERP to the neurophysiological underpinnings of impaired affective processing seems to be performed here the first time, particularly highlighting our results and their weighting, mainly topographical rather than temporal aspects of emotion processing in MS have become known. The detection of specific ERP in MS to assess the neurophysiological background and thus the degree of neuronal degeneration could therefore be of interest in the early course of the disease, but a growing topic for calculating the individual potential of disease progression in affective abilities. Noteworthy, in contrast to the well-documented cognitive impairments, affective disorders are detected comparatively even less frequently, despite their decisive influence on neuropsychiatric entities such as depressive or anxiety disorders and core aspects of social cognition such as emotion recognition in facial expression or the Theory of Mind [14, 15, 63]. Specific studies of affective impairment, as provided by sensitive clinical inventories

and specific neurophysiological markers such as the ERP of early and late emotion processing stages, can be used for individual statements on the therapeutic efficacy of drug modifying therapeutics, neurorehabilitative and psychotherapeutic applications to achieve a conflict resolution in favor of a decrease in the premature consumption of neuronal reserves in cognitive and affective networks [20, 71].

Abbreviations

ANOVA, Analysis of Variance; CKV, Computergestütztes KartensortierVerfahren; DLPFC, dorsolateral prefrontal cortex; EDSS, Expanded Disability Severity Scale; EEG, Electroencephalography; EPN, Early Negative Potential; ERP, Event-related potentials; IAPS, International Affective Picture System; FLAIR, Fluid-attenuated inversion recovery; ICD10, International Classification of Diseases, Version 10; LPP, Late Positive Potentials; MRI, Magnetic Resonance Imaging; MS, Multiple Sclerosis; MSFC, Multiple Sclerosis Functional Composite; RRMS, relapsing-remitting course of multiple sclerosis; TAP, Test of Attentional Performance; TAB, Tübinger Affekt Batterie; VAP, Visual-evoked potentials; VMPFC, ventromedial prefrontal cortex; WMS-R, revised Wechsler Memory Test.

Author contributions

MA, SK, CK and AH designed the research study. MA and SK performed the research. NH provided help and advice on the MRI recordings. MA and SK analyzed the data. MA, SK and CK wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All human participants were raised and handled at the Department of Neurology and the Department of Biological Psychology, both University of Greifswald. All human experiments were carried out in accordance with the guidelines of the European Community Council Directives 86/609/EEC and approved by the Mecklenburg-Vorpommern government and the Ethical Committee of the University of Greifswald. The approvals of study participation were obtained with the informed consent of all participants. The institutional review board of the Ethical Committee of the University of Greifswald approved this study.

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Conflict of interest

The authors declare no conflict of interest.

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