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Altered Cortical Processing of Observed Pain in Patients With Fibromyalgia Syndrome

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Abstract: Fibromyalgia syndrome (FMS) is characterized by widespread chronic pain, fatigue, sleep disorders, and cognitive-emotional disturbance. Patients with FMS exhibit increased sensitivity to experimental pain and pain-related cues, as well as deficits in emotional regulation. The present study investigated the spatiotemporal patterns of brain activations for observed pain in 19 patients with FMS and 18 age-matched, healthy control individuals using event-related potential analysis. Patients with FMS attributed greater pain and unpleasantness to pain pictures, relative to healthy control participants. An augmented late positive potential (LPP) component (>500 milliseconds) was found in patients viewing both pain and nonpain pictures, and this amplitude difference in the LPP covaried with perceived unpleasantness of pictures. Mid-latency potentials (250–450 milliseconds) demonstrated similar amplitude increases of positive potentials in the FMS patient group. By contrast, the short-latency positive potential (140 milliseconds) was reduced in patients with FMS relative to healthy control participants. Results suggest amplitude increases to mid- to long-latency cortical activations in patients with FMS, which are known to reflect emotional control and motivational salience of stimuli.

***Perspective:** Patients with FMS demonstrate increased activations associated with pain and nonpain pictures. The findings suggest that even innocuous, everyday visual stimuli with somatic connotations may challenge the emotional state of patients with FMS. Our study points toward the importance of cognitive-emotional therapeutic approaches for the treatment of FMS.*

***Key words:** Electroencephalography, event-related potential, chronic pain, hypervigilance.*

Fibromyalgia syndrome (FMS) is characterized by widespread chronic pain and tenderness, psychological disturbance, cognitive dysfunction and sleep disorders.[6,65] Patients with FMS demonstrate reduced pain thresholds[39,46,54] and augmented brain responses[15,29,57] during experimental pain. Patients also exhibit hypervigilance to pain[17] and deficits in affective processing[4,66] and emotional regulation.[61,62,66] It has been proposed that such dysfunctional emotional processing could play an important role in the development and maintenance of pain in FMS.[4,17,26,58]

Observing pain in others requires complex affective processing to empathize with the physical and emotional experiences of another, and pain-related stimuli elicit greater evaluation than nonpainful scenes because they are more novel and important for survival.[22] Despite the aforementioned psychological features of FMS, processing of observed pain remains poorly understood, although a recent study reported augmented hypervigilance for observed pain in patients with FMS, but normal levels of empathic concern.[63] The central sensitization theory of FMS suggests that sensory thresholds are decreased as a consequence of central alterations, potentially resulting from neuroplasticity changes, which lead to augmented processing of peripheral stimuli.[59] Underlying central alterations may affect the processing of observed pain in FMS, or alternatively,

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psychological factors may be more influential. Recent research has demonstrated that central sensitization may play a role in amplifying nonpainful somatosensory stimuli in patients with FMS,[21] whereas observed pain was shown to facilitate the detection of tactile stimuli in patients with FMS in a similar manner to healthy people.[63] The temporal resolution of event-related potential (ERP) analysis allows for insight into the precise timing of processing alterations for observed pain in patients with FMS. This could shed light on the complex relationship between central processing and observed pain in FMS.

ERP studies have investigated the temporal dynamics of neural responses to observed pain in healthy people, revealing modulation of both early (110–180 milliseconds after stimulus), and late (300–700 milliseconds after stimulus) ERP components.[22,33,35,44] Patients with FMS exhibit heightened autonomic and subjective responses to negative affective stimuli[4] and alterations to early ERP components[27] when viewing painful facial expressions, but it is not known whether any such changes are evident during observation of pain stimulation in others.

Existing ERP research for perceived pain points to modulation of cortical processing by top-down influences such as self-perspective[35,44] or relevant previous experience.[19] Such factors are also likely to play a role in differentiating patients with FMS from healthy populations. Previously, clinical populations with deficits in empathic processing such as autistic spectrum disorder and juvenile psychopathic patients were shown to exhibit reduced ERP components during observed pain relative to healthy people.[13,23] Conversely, because patients with FMS are generally hypervigilant to pain cues,[17] we would expect them to report greater observed pain for visual pain stimuli and to display corresponding modulation of cortical activations.

To investigate neural processing of pain-related visual stimuli in patients with FMS, ERPs associated with viewing of pain and nonpain pictures were analyzed. We hypothesized that patients with FMS, relative to healthy people, would attribute greater pain to pain scenes and manifest greater amplitudes in ERP components known to be associated with emotional control, such as the late positive potential (LPP).[31,53]

Methods

Participants

Nineteen female patients (age 40.01 ± 7.95 years, mean ± standard deviation [SD]) diagnosed with FMS took part in the study. Patients were recruited from outpatient fibromyalgia clinics at 2 regional National Health Service Foundation Trust hospitals: the Walton Centre, Liverpool, United Kingdom, and Wirral University Teaching Hospital, Wirral, United Kingdom. All patients fulfilled American College of Rheumatology criteria for diagnosis with fibromyalgia,[65] and those with additional disease or disorders that are not commonly comorbid with FMS were excluded. Patients were aged between 19 and 52 years, and mean duration of symptoms was 9.62 ± 6.97 years. Patients using medications with central nervous system effects who were not deemed suitable for withdrawal were excluded. Analgesics (such as co-codamol) were withdrawn for at least 3 days before recordings; withdrawal was managed by the clinical team during consultations. Mild analgesic medications such as paracetamol were permitted. At their request, 6 patients on low-dose antidepressant medication (eg, 10 mg citalopram or nortriptyline per day) were permitted to take part after undergoing withdrawal for 5 days before recordings. Six patients were using no medications for management of their FMS, and the remaining 7 patients either were using permissible doses of common medications with minimal central nervous efficacy or withdrew from nonpermitted medications, such as co-codamol, for at least 3 days before recordings. The medication profiles in the patient group are shown in Table 1 and reflect the difficulty in recruiting a homogenous cohort of patients with FMS to evaluate neural activity associated with observed pain in the absence of centrally acting medications.

Eighteen female controls (age 39.23 ± 7.99 years, mean ± SD) were recruited through Internet and campus advertisements. Volunteers were age matched to patients with FMS, and those taking regular medication or currently diagnosed with any disease or disorder were excluded. All patients and volunteers were compensated for time and travel expenses. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki. The study was approved by the National Research Ethics Committee of the United Kingdom and the Research Governance Committees of both National Health Service Foundation Trust hospitals.

Procedure

Participants were accompanied to the Sensory-Motor Laboratory in the Walton Centre National Health Service Foundation Trust to undergo electrode preparation. During the experiment participants were seated in a comfortable chair positioned 1 m from a 48.2-cm (19-in) computer monitor. The experiment consisted of a single recording encompassing viewing of 100 trials and lasting 20 minutes. Each trial (Fig 1) began with a 3-second resting interval, when subjects viewed a black fixation cross on a gray background, then a color photograph was presented for 3 seconds followed by a resting interval of 2 seconds and a 4-second response period. During the response period, a 7-point rating scale with anchors "no pain" to "worst possible pain" was presented. Participants were required to repeatedly click a mouse button to incrementally advance the scale to attribute the amount of pain they perceived to be evident in the scene.

The images used were similar to those used in previous studies.[1,22,30,33,37,38,40] Fifty pictures displayed hands or feet in situations containing pain, such as a knife cutting bread in a manner that would endanger the hand, or a foot standing on a shard of glass (Fig 1). A further 50 pictures depicted nonpain scenes, which were graphically matched to the aforementioned pain

Table 1. Demographic, Clinical, and Medication Profile Data of Patients With FMS

Patient Code	Age (y)	Duration of Symptoms (y)	FIQ	BDI	PCS	Medication Profile
FM01	40	12.00	64.70	16.00	16.00	β-Blockers
FM02	42	5.00	59.02	20.00	21.00	Diclofenac
FM03	39	3.00	71.99	21.00	20.00	Gabapentin
FM04	22	6.00	68.32	22.00	10.00	No medication
FM05	43	4.50	77.75	31.00	14.00	Tramadol, sertraline
FM06	44	15.00	61.92	8.00	1.00	Co-codamol
FM07	33	7.00	55.55	17.00	16.00	Co-codamol
FM08	43	4.00	72.15	21.00	12.00	Gabapentin, nortriptyline
FM09	41	18.00	19.11	5.00	14.00	Citalopram
FM10	48	6.00	39.22	14.00	3.00	Citalopram, tramadol
FM11	37	3.50	56.40	6.00	.00	Pregabalin, nortriptyline, co-codamol
FM12	49	3.00	25.36	5.00	2.00	No medication
FM13	52	10.00	48.96	14.00	19.00	Co-codamol
FM14	46	2.00	75.37	20.00	25.00	Co-codamol
FM15	45	18.00	48.42	6.00	5.00	No medication
FM16	30	4.00	82.56	41.00	28.00	No medication
FM17	26	6.00	74.74	20.00	5.00	No medication
FM18	32	16.00	69.67	33.00	33.00	Gabapentin, duloxetine, Co-codamol
FM19	37	4.50	80.23	37.00	31.00	No medication

scenes but contained no pain, such as a knife safely cutting bread. Pictures were presented in a pseudorandomized order, and the same picture type was not presented more than 3 times in succession. After the experiment, participants rated each picture in terms of affective valence (ranging from neutral to extremely unpleasant) and arousal (neutral to extremely arousing) using 9-point Self-Assessment Manikin scales.[10] Each participant also completed a series of questionnaires incorporating the Beck Depression Inventory (BDI),[5] Pain Catastrophizing Scale (PCS),[60] and the Fibromyalgia Impact Questionnaire (FIQ).[11]

Recordings

Electroencephalographic (EEG) data were recorded using a 64-channel Biosemi Ag-ACl active 2-electrode system (Biosemi BV, Amsterdam, The Netherlands). Electrode positions were allocated according to the extended 10–20 system with respect to 3 anatomical landmarks: the 2 preauricular points and the nasion. Two bipolar, flat Ag-ACl external reference electrodes were attached to the mastoid processes, and electrooculograms were recorded using bipolar electrodes positioned above and below the right eye. The recording bandpass filter was .16–100 Hz, and the sampling rate was 512 Hz.

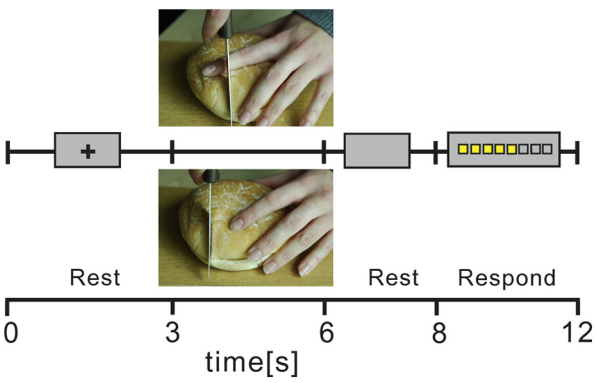

Figure 1. The flowchart of the experiment illustrates one trial beginning with a rest interval (3 seconds) followed by visual presentation of a pain or nonpain picture (3 seconds), followed by a second rest interval (2 seconds) and a response period (4 seconds). During the response period, patients used repeated mouse clicks to incrementally advance a scale and attribute the amount of pain they considered to be evident in the image.

EEG Data Analysis

EEG data were preprocessed using BESA v.6.0 (MEGIS Software GmbH, Gräfelfing, Germany). Data were initially spatially transformed into reference-free data using common average reference method,[41] and oculographic and electrocardiographic artifacts were removed using principal component analysis.[7] Data were visually inspected for the presence of movement or muscle artifacts, and epochs contaminated with artifacts were manually excluded. The experimenter (N.F.) was blinded to trial type when excluding artifacts from raw EEG data. The mean number of trials remaining after artifact correction was 42.6 ± 5.3 (mean ± SD) and 42.6 ± 5.0 for pain pictures, and 43.5 ± 4.5 and 42.3 ± 6.1 for nonpain pictures in patient and healthy control groups, respectively. There was no difference between FMS and healthy groups in the mean number of trials allowed for either picture condition ($P > .05$).

ERPs associated with the onset of pain and nonpain pictures were averaged for the interval ranging from −200 milliseconds to 1,200 milliseconds relative to stimulus onset (717 time points). A 1,200-millisecond epoch was selected for ERP analysis because this period was found to adequately cover peaks in global field power and butterfly plots corresponding to the early-, mid-, and long-latency ERP components. The baseline period was from −200 milliseconds to 0 milliseconds relative to the onset of the picture, and EEG data were bandpass-

filtered from .5 to 40 Hz and downsampled to 256 Hz. Finally, data were exported to Matlab v.8.10 (The Mathworks Inc, Natick, MA) for statistical analysis using the EEGLAB toolbox.[20]

Grand-averaged global field power, scalp isopotential maps, and butterfly plots were used to define the center of time windows, ranging from 20 to 150 milliseconds and encompassing the peak activity for each component, to be exported for statistical analysis. For each component, a 2-way analysis of variance (ANOVA) for repeated measures (Group × Picture type) was performed across all electrodes to identify clusters of electrodes showing significant main effects or interactions. A 95% confidence level was used, and permutation analysis technique[47] with 2,000 permutations was used to correct for the performance of multiple tests over 64 electrodes. In each component, clusters of electrodes demonstrating significant ANOVA effects were concatenated, and the mean amplitude for the time window was exported for further statistical analysis using 2-way ANOVA in SPSS version 21 (IBM Corp, Armonk, NY). All values from ANOVA analyses were adjusted with Greenhouse-Geisser ε correction to account for violation of the assumption of sphericity.

Subjective ratings of pain, unpleasantness, and arousal for each type of image were analyzed using a 2-way (Group × Picture type) mixed ANOVA in SPSS. Post hoc t-tests were used to investigate significant interaction effects, and a 95% confidence level was used throughout. Participants whose picture ratings fell outside 3 SDs of the group mean were excluded from statistical analyses of the specific rating to prevent extreme values from adversely influencing results. To evaluate whether the previous medication profile of patients influenced picture ratings for pain, valence, and arousal, we analyzed ratings within the patient cohort using a 2-way mixed ANOVA (no medication; Withdrawn from common medications × Picture type) in SPSS.

To analyze whether clinical symptoms were related to the differences seen in ERP components of patients with FMS, Spearman correlation analysis was performed in the FMS patient group, with ERP amplitudes from electrodes demonstrating significant group effects and BDI, FIQ, and PCS scores. To further investigate whether subjective ratings for each picture type were related to the alterations in cortical processing, a 2-way mixed analysis of covariance (ANCOVA) was performed using the BMDP2V program (Statistical Solutions Ltd, Cork, Ireland) with subjective ratings of pain, unpleasantness and arousal implemented as covariates, and BDI, PCS, and FIQ scores were used as covariates in SPSS. Mediation analysis[3] was used to investigate whether the relationship between the amplitude of the ERP components and fibromyalgia group status or picture type would be moderated by subjective ratings of pictures as pointed to by ANCOVA analysis. We first determined the magnitude of the predictive power and significance for each relationship using linear regression analysis in SPSS. For results demonstrating significant mediation, a Sobel test was performed to confirm the effect of subjective ratings.

Results

Self-Report Ratings

Table 2 shows pain, affective valence, and arousal ratings (mean ± SDs) attributed to pain and nonpain pictures for patients with FMS and healthy control groups. A 2-way mixed ANOVA revealed a significant main effect of picture type on the amount of pain participants attributed to scenes, with greater pain attributed to pain pictures ($F(1,35) = 176.2$, $P < .001$). A significant group effect was evident ($F(1,35) = 4.6$, $P = .039$), and the Group × Picture type interaction effect was also significant ($F(1,35) = 4.5$, $P = .041$). Post hoc between-patients t-test analysis revealed that patients with FMS attributed significantly greater pain scores to pain pictures than did healthy control individuals ($t(35) = 2.26$, $P = .03$), but there was no difference between ratings of nonpain pictures ($t(35) = .92$, $P = .36$).

One healthy control individual was excluded from analysis of valence and arousal ratings because the ratings fell outside 3 SDs of the group mean. Subjective ratings of affective valence for each image showed a main effect of picture type ($F(1,34) = 84.66$, $P < .001$), with pain pictures scoring higher for unpleasantness. A main effect of group ($F(1,34) = 4.52$, $P = .041$) and a significant Group × Picture type interaction effect ($F(1,34) = 5.96$, $P = .021$) were also evident. Post hoc analysis revealed significantly greater unpleasantness ratings for pain pictures in the FMS patient group relative to the healthy control group ($t(34) = 2.3$, $P = .028$), but no difference was found between valence ratings for nonpain pictures ($t(34) = .45$, $P = .66$). For subjective ratings of arousal, a main effect of picture type was observed ($F(1,34) = 74.70$, $P < .001$), with pain pictures eliciting a stronger arousal response than nonpain pictures. However, no group effect was evident ($F(1,34) = 2.51$, $P = .12$). The Group × Picture type interaction effect approached, but did not achieve, significance ($F(1,34) = 3.9$, $P = .056$). ANOVA comparison of picture ratings for withdrawn (compared with nonmedicated) patients revealed no significant effects of medication on picture ratings for observed pain ($F(1,17) = .44$, $P = .52$), valence ($F(1,17) = .22$, $P = .64$), or arousal ($F(1,17) = .40$, $P = .53$). The expected effect of picture type was significant for all 3 measures, but no interaction effects were observed.

ERP Analysis

Figs 2A and 2B illustrate the butterfly plot and grand average global field power of ERPs, which were used to identify peak time points for the center of time epochs covering each component shown in Table 3. In both groups and conditions, ERPs consistently displayed a negative potential component from 110 milliseconds to 170 milliseconds over frontal-central regions (N1) and a corresponding positivity located over the occipital lobe (P1; hereafter the time period of these concomitant potentials is referred to as P1/N1). Subsequently, a positive potential was evident from 190 to 240 milliseconds over the vertex (P2), and a negative deflection from

Table 2. Mean Scores (± SD) for Pain, Affective Valence, and Arousal Attributed to Pain and Nonpain Pictures in Patients With FMS and Healthy Control Groups

	Patients With FMS		*Healthy Controls*	
	Pain	*Nonpain*	*Pain*	*Nonpain*
Pain	4.9 ± 1.2	1.5 ± .5	4.1 ± 1.2	1.4 ± .3
Valence	4.4 ± 2.0	1.3 ± .4	3.0 ± 1.6	1.2 ± .3
Arousal	4.1 ± 2.0	1.3 ± .6	3.2 ± 1.6	1.4 ± .8

260 to 330 milliseconds (N2) over the frontal-central region. This was followed by a positive potential component from 370 to 450 milliseconds (P3) and an LPP from 500 to 800 milliseconds, both located over the posterior parietal region. The spatiotemporal pattern of components reflects those seen in previous studies using ERP analysis of pain and nonpain pictures.[22,33,44,51] Scalp topographies for each component for pain and nonpain pictures and FMS and healthy control groups are shown at peak time intervals in Fig 2C.

Table 3 shows mean amplitudes (± SD) and results of a 2-way mixed ANOVA for each significant cluster of electrodes in each ERP component. In the time epoch encompassing the P1/N1 component (135–155 milliseconds), a cluster of electrodes located over the right occipital region of the scalp demonstrated a significant group effect, with the healthy control group exhibiting a greater positivity relative to the FMS patient group. No significant effect of picture type or group was seen during the P2 component (210–230 milliseconds). However, the N2 (280–310 milliseconds) component exhibited a group difference, with patients with FMS demonstrating an exaggerated positivity over occipital electrodes relative to the healthy control group.

During the time period of the P3 potential (370–410 milliseconds), a stronger positive deflection was evident over right parietal electrodes in patients with FMS, relative to healthy individuals. A similar effect was seen over central-parietal electrodes during the LPP (500–650 milliseconds). Furthermore, during the LPP component, a picture effect was also seen in the same central-parietal electrodes, with pain pictures eliciting an augmented positive deflection relative to nonpain pictures. Fig 3 shows the scalp isopotential maps of ERP components for each group and picture type at peak time points, as well as average ERP curves from significant electrodes and bar charts illustrating mean amplitudes for each group and condition.

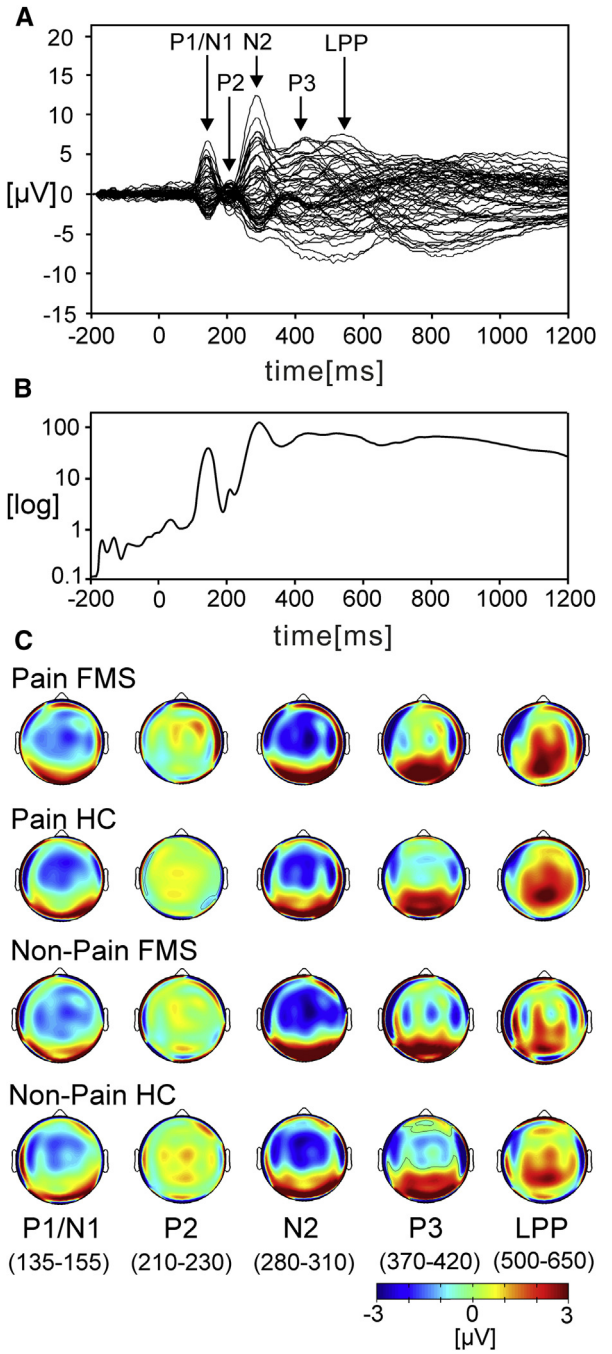

Figure 2. **(A)** The butterfly plot showing grand average amplitudes for each electrode in all subjects and both picture types; arrows indicate peak times used for the center of time windows of interest. **(B)** Grand-averaged global field power for all subjects and both picture types. **(C)** Mean topographic isopotential maps for time epochs encompassing components of interest for FMS patient and healthy control groups and for each picture type.

Correlation, Covariate, and Mediation Analysis

Spearman correlation analysis indicated that the amplitudes of electrode clusters demonstrating group differences in each component of interest were not correlated with BDI, FIQ, or PCS scores in the FMS patient group for either picture type. However, a 2-way mixed ANCOVA with valence, arousal, and subjective pain ratings implemented as covariates indicated that valence ratings significantly covaried with the group difference seen in the central-parietal cluster of electrodes in the time interval encompassing the LPP ($F(1,31) = 4.52$, $P = .042$). Similarly, valence ratings also demonstrated a significant covariation with the picture effect seen in the same component ($F(1,31) = 14.46$, $P < .001$). Neither pain nor arousal ratings demonstrated significant

Table 3. Clusters of Electrodes Showing Significant ERP Component Effects in 2-Way Mixed ANOVA

		FMS		Healthy					
	Time (ms)	Pain	Nonpain	Pain	Nonpain	Electrodes	ANOVA	F	P
P1/N1	135–155	.29 ± .78	.33 ± .75	.65 ± .72	.91 ± .96	CP6, P4, P6	Group	4.66	.038
N2	280–310	4.32 ± 3.18	4.73 ± 2.94	2.71 ± 1.91	2.73 ± 1.89	POz, Oz, O1, O2	Group	4.80	.035
P3	370–420	1.35 ± 1.08	1.19 ± 1.46	.42 ± 1.56	.31 ± 1.35	CPz, CP2, CP4	Group	4.34	.045
LPP	500–650	2.92 ± 1.04	2.06 ± 1.00	1.96 ± 1.31	1.42 ± 1.30	Cz, CPz, C2, CP2	Picture	37.56	.000
LPP	500–650	—	—	—	—	—	Group	5.06	.031

ERP amplitudes (mean ± SD) for pain and nonpain pictures are shown with F statistics and *P* values.

covariation with the effects seen in any of the components. Similarly, clinical measures in the form of BDI, FIQ, and PCS scores did not significantly covary with group or picture type effects in any of the components analyzed. Supplementary Fig 1 illustrates the results of mediation analyses between FMS group status or picture

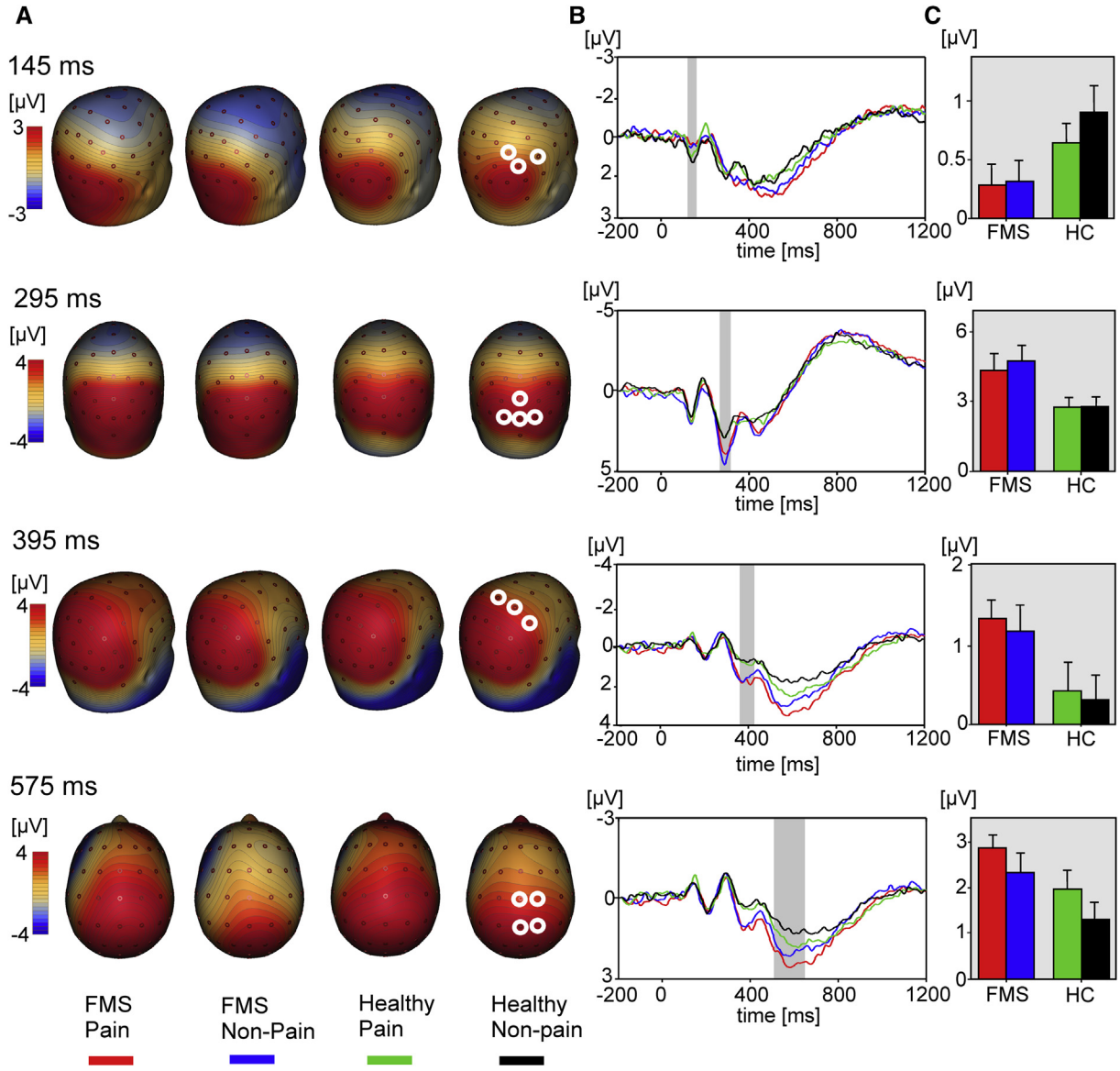

Figure 3. **(A)** Three-dimensional mean isopotential maps for each group and condition are shown at the peak time points for each component that demonstrated significant ANOVA effects. White circles indicate location of electrodes demonstrating significant differences in amplitude. **(B)** Mean ERP curves from select electrodes for each group and condition. Gray shaded areas signify the time epoch showing a significant ANOVA effect of ERP amplitudes. **(C)** Bar chart illustrating mean amplitudes and standard errors for select electrodes in each group and condition. Red denotes patients with fibromyalgia viewing pain pictures, blue represents fibromyalgia nonpain, green is healthy control individuals with pain pictures, and black denotes healthy control individuals for nonpain pictures.

type and LPP brain potential activations with valence ratings as mediating variables. Analyses indicate that valence ratings did not mediate the FMS group difference in central-parietal cortical activity during the time period of the LPP component, because the relationship between ratings and the brain potential was not significant. However, valence ratings did demonstrate a significant mediation of the relationship between picture type and amplitudes of the central-parietal LPP, confirmed by a Sobel test; $z = 2.19$, $P = .029$. Including valence ratings in the model led to significant reduction in the proportion of variance accounted for by picture type (see Supplementary Fig 1B).

Discussion

Patients with FMS attributed greater pain and unpleasantness to pain pictures than did healthy control individuals, which corroborates previous findings in patients with FMS using negative affective pictures.[4] Relative to healthy control participants, patients with FMS exhibited an augmented LPP over central-parietal electrodes, and pain pictures also elicited stronger ERPs in this LPP component for both groups. These amplitude differences covaried with subjective reports of unpleasantness of pictures. Further, patients with FMS demonstrated a similar pattern of augmented positive potentials in mid-latency components (N2 and P3), contrasting with reduced amplitudes in the short-latency (P1) visual component located over the occipital lobe.

The LPP was previously associated with late cognitive evaluation of painful stimuli[12,23,50]; for example, LPP activation was augmented during a pain judgment task but diminished during a distraction counting task.[22] In the present study, LPP responses for pain, relative to nonpain pictures, were enhanced for both groups in accordance with previous findings,[22,36] but the response for both types of picture was also significantly stronger in patients with FMS relative to healthy control participants. Clinical populations with deficits in empathic processing were previously shown to exhibit reduced LPP amplitudes relative to healthy people,[13] whereas the augmented LPP in patients with FMS appears to reflect heightened sensitivity to painful, and even nonpainful, somatic pictures.

The LPP was previously proposed as a marker for affective regulation,[31,53] and both the group and picture differences seen in LPP responses covaried with subjective valence ratings, which supports this hypothesis. Alterations to affective processing and emotional regulation are well documented in FMS,[4,61,62,66] and augmented LPP components were recently proposed as a mechanism for internal regulation of affective responses to perceived pain stimuli in highly empathic people.[36] Thus, the LPP appears particularly relevant for affective processing during observation of pain. Previously, cognitive-behavioral therapy in phobic participants was shown to improve emotional regulation and prolong exposure times to phobic picture stimuli and also to cause concomitant increases in the LPP.[42,43] LPP amplitude increases in patients with FMS may indicate upregulation of coping mechanisms for environmental pain cues, and appropriate psychological therapies to desensitize patients with FMS to environmental pain cues could have implications for reducing primary pain symptoms.[17,26] Furthermore, because the analysis revealed no correlations or covariation effects with other relevant factors such as BDI or PCS scores, it is unlikely that the differences seen in these components are related to concomitant affective disorders such as depression. Although ANCOVA analyses point to some relevance for emotional processing and this activation difference, mediation analyses revealed that valence ratings do not solely govern the degree of activation in this region during the LPP. However, mediation analyses did demonstrate a significant role for valence ratings in the differences seen in LPP activations between picture types. This finding indicates that perceived valence is at least partially responsible for the increased LPP component activations associated with pain pictures in both patients with FMS and healthy people.

The P3 component located over the right posterior parietal region was similarly augmented in patients with FMS relative to healthy control participants. Previously, the P3 component was linked with top-down processing relating to task relevance or motivational significance of stimuli,[49,53] which would suggest an increased allocation of top-down resources for both pain and nonpain pictures in patients with FMS. Thus, enhanced P3 activations could indicate a heightened significance for somatic cues in FMS, resulting in an augmented response to both types of pictures. Patients with generalized anxiety disorders exhibited a similar trend, with functional MRI (fMRI) studies revealing heightened amygdala activations associated with anticipation of aversive and even neutral visual stimuli.[34,52] Experienced physicians viewing pain pictures demonstrate reduced P3 amplitudes and subjective pain ratings for observed pain caused by desensitization of the salient aspects of such stimuli.[19] In effect, patients with fibromyalgia demonstrate the opposite phenomenon, in that they manifest augmented P3 responses, which suggests increased salience and attention for pain and nonpain somatic visual stimuli in patients with FMS.

The augmented P3 and LPP responses occurred over parietal electrodes. In the past the parietal cortex was functionally labeled as integrative or association cortex,[16] with perhaps a particular relevance for visuospatial or motor processing.[18,25] However, more recently the functional role of posterior parietal cortex in top-down processing for visual attention or salience has been highlighted (reviewed by Bisley and Goldberg[8]). In particular, the lateral intraparietal area acts as a multifaceted integrative interface, binding visuospatial, motor, and cognitive information into an organized topography to specify attentional priority according to demand.[28] Evidence suggests that P3 and LPP components are important for top-down processing of emotional or aversive visual stimuli,[31,32,53] and the underlying cortex is similarly recognized for

its integrative role in perception, action, and cognition,[8,28] which suggests that this cortical region could be particularly relevant for FMS mechanisms.

Patients with FMS showed reduced amplitudes of the P1 positive potential seen over right occipital electrodes relative to healthy control participants. Increased P1 amplitudes were previously seen in healthy people during observation of pain pictures relative to nonpain pictures,[22,56] which also accords with the activation profiles of fMRI studies.[1,40] By contrast, patients later demonstrated increased amplitudes for the positive potential located over the occipital region of the scalp during the period of the N2 component, which reflects the profile seen in P3 and LPP amplitude differences. A similar pattern of early impairment of visual processing followed by later augmentation of activations for perceived pain was recently demonstrated in an fMRI study of visual checkerboard stimuli with patients with FMS.[45] Therefore, early sensory processing appears to be affected in patients with FMS, although the spatiotemporal pattern of brain activations indicates predominantly augmented mid- to long-latency responses to both pain and nonpain stimuli.

The participants attributed their pain ratings 2 seconds after picture offset. Although this procedure is similar to previous ERP analyses of observed pain stimuli,[22] it is important to consider that any interlude requires the involvement of working memory to ascribe appropriate pain ratings to each picture. Previously, P3 and LPP components were shown to be involved in working memory processing,[2,55] and affective or arousing stimuli are better remembered than less arousing pictures.[9,64] Furthermore, as in previous studies,[23] ratings for affective valence and arousal of pictures were included after the period of recording to limit the duration of the experiment. Because these appraisals were made after the initial EEG presentations, familiarity or priming effects could influence the ratings attributed to images. Participants were not matched for menstrual cycle phase or menopausal status, which can influence pain in FMS,[14,48] and this should be considered for future research; similarly, a further limitation concerns the influence of social factors such as level of education,[24] because such data were not collected in the present study. The findings also point to the possibility that patients with FMS could also exhibit differences in processing of nonpainful negative affective images, and this prospect warrants further study.

Augmented mid-latency (P3) and long-latency (LPP) positive potential components over the parietal region of the scalp signified the strongest differences seen in FMS, which leads us to the conclusion that the period of late cognitive evaluation of pain cues is particularly affected in FMS. The augmented ERP responses were evident in patients with FMS across both pain and nonpain pictures, which is indicative of generalized hypervigilance to somatosensory stimuli. The significant covariance with affective valence ratings during the LPP, as well as previous research highlighting the importance of this component for affective regulation, emphasizes the relevance of this time period for alterations to processing of observed pain in patients with FMS. In the future, this late component may lend itself to the investigation of therapeutic interventions aimed at improving psychological and affective aspects of FMS.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpain.2015.04.008.

References

1. Akitsuki Y, Decety J: Social context and perceived agency affects empathy for pain: An event-related fMRI investigation. Neuroimage 47:722-734, 2009

2. Azizian A, Polich J: Evidence for attentional gradient in the serial position memory curve from event-related potentials. J Cogn Neurosci 19:2071-2081, 2007

3. Baron RM, Kenny DA: The Moderator Mediator Variable Distinction in Social Psychological-Research– conceptual, strategic, and statistical considerations. J Pers Soc Psychol 51:1173-1182, 1986

4. Bartley EJ, Rhudy JL, Williams AE: Experimental assessment of affective processing in fibromyalgia. J Pain 10: 1151-1160, 2009

5. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J: An inventory for measuring depression. Arch Gen Psychiatry 4: 561-571, 1961

6. Bennett RM, Jones J, Turk DC, Russell IJ, Matallana L: An internet survey of 2,596 people with fibromyalgia. BMC Musculoskelet Disord 8:27, 2007

7. Berg P, Scherg M: A multiple source approach to the correction of eye artifacts. Electroencephalogr Clin Neurophysiol 90:229-241, 1994

8. Bisley JW, Goldberg ME: Attention, intention, and priority in the parietal lobe. Annu Rev Neurosci 33:1-21, 2010

9. Bradley MM, Greenwald MK, Petry MC, Lang PJ: Remembering pictures: Pleasure and arousal in memory. J Exp Psychol Learn Mem Cog 18:379-390, 1992

10. Bradley MM, Lang PJ: Measuring emotion: The Self-Assessment Manikin and the Semantic Differential. J Behav Ther Exp Psychiatry 25:49-59, 1994

11. Burckhardt CS, Clark SR, Bennett RM: The fibromyalgia impact questionnaire: Development and validation. J Rheumatol 18:728-733, 1991

12. Chen C, Yang CY, Cheng Y: Sensorimotor resonance is an outcome but not a platform to anticipating harm to others. Soc Neurosci 7:578-590, 2012

13. Cheng Y, Hung AY, Decety J: Dissociation between affective sharing and emotion understanding in juvenile psychopaths. Dev Psychopathol 24:623-636, 2012

14. Colangelo K, Haig S, Bonner A, Zelenietz C, Pope J: Self-reported flaring varies during the menstrual cycle in systemic lupus erythematosus compared with rheumatoid arthritis and fibromyalgia. Rheumatology 50: 703-708, 2011

15. Cook DB, Lange G, Ciccone DS, Liu WC, Steffener J, Natelson BH: Functional imaging of pain in patients with primary fibromyalgia. J Rheumatol 31:364-378, 2004

16. Critchley MD: Le lobe parietal. Presse Med 61. 1604–1604

17. Crombez G, Eccleston C, Van den Broeck A, Goubert L, Van Houdenhove B: Hypervigilance to pain in fibromyalgia: The mediating role of pain intensity and catastrophic thinking about pain. Clin J Pain 20:98-102, 2004

18. Culham JC, Cavina-Pratesi C, Singhal A: The role of parietal cortex in visuomotor control: What have we learned from neuroimaging? Neuropsychologia 44:2668-2684, 2006

19. Decety J, Yang C-Y, Cheng Y: Physicians down-regulate their pain empathy response: An event-related brain potential study. Neuroimage 50:1676-1682, 2010

20. Delorme A, Makeig S: EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 134:9-21, 2004

21. Fallon N, Chiu YH, Li X, Nurmikko TJ, Stancak A: Ipsilateral cortical activation in fibromyalgia patients during brushing correlates with symptom severity. Clin Neurophysiol 124:154-163, 2013

22. Fan Y, Han S: Temporal dynamic of neural mechanisms involved in empathy for pain: An event-related brain potential study. Neuropsychologia 46:160-173, 2008

23. Fan YT, Chen C, Chen SC, Decety J, Cheng Y: Empathic arousal and social understanding in individuals with autism: Evidence from fMRI and ERP measurements. Soc Cogn Affect Neurosci 9:1203-1213, 2014

24. Fitzcharles MA, Rampakakis E, Ste-Marie PA, Sampalis JS, Shir Y: The association of socioeconomic status and symptom severity in persons with fibromyalgia. J Rheumatol 41:1398-1404, 2014

25. Fogassi L, Luppino G: Motor functions of the parietal lobe. Curr Opin Neurobiol 15:626-631, 2005

26. Geisser ME, Casey KL, Brucksch CB, Ribbens CM, Appleton BB, Crofford LJ: Perception of noxious and innocuous heat stimulation among healthy women and women with fibromyalgia: Association with mood, somatic focus, and catastrophizing. Pain 102:243-250, 2003

27. Gonzalez-Roldan AM, Munoz MA, Cifre I, Sitges C, Montoya P: Altered Psychophysiological Responses to the View of Others' Pain and Anger Faces in Fibromyalgia Patients. J Pain 14:709-719, 2013

28. Gottlieb J: From thought to action: The parietal cortex as a bridge between perception, action, and cognition. Neuron 53:9-16, 2007

29. Gracely RH, Petzke F, Wolf JM, Clauw DJ: Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 46:1333-1343, 2002

30. Gu X, Han S: Attention and reality constraints on the neural processes of empathy for pain. Neuroimage 36: 256-267, 2007

31. Hajcak G, MacNamara A, Olvet DM: Event-related potentials, emotion, and emotion regulation: An integrative review. Dev Neuropsychol 35:129-155, 2010

32. Hajcak G, Olvet DM: The persistence of attention to emotion: Brain potentials during and after picture presentation. Emotion 8:250-255, 2008

33. Han S, Fan Y, Mao L: Gender difference in empathy for pain: An electrophysiological investigation. Brain Res 1196: 85-93, 2008

34. Hoehn-Saric R, Schlund MW, Wong SH: Effects of citalopram on worry and brain activation in patients with generalized anxiety disorder. Psychiatry Res 131:11-21, 2004

35. Ibáñez A, Hurtado E, Lobos A, Escobar J, Trujillo N, Baez S, Huepe D, Manes F, Decety J: Subliminal presentation of other faces (but not own face) primes behavioral and evoked cortical processing of empathy for pain. Brain Res 1398:72-85, 2011

36. Ikezawa S, Corbera S, Wexler BE: Emotion self-regulation and empathy depend upon longer stimulus exposure. Soc Cogn Affect Neurosci 9:1561-1568, 2014

37. Jackson PL, Brunet E, Meltzoff AN, Decety J: Empathy examined through the neural mechanisms involved in imagining how I feel versus how you feel pain. Neuropsychologia 44:752-761, 2006

38. Jackson PL, Meltzoff AN, Decety J: How do we perceive the pain of others? A window into the neural processes involved in empathy. Neuroimage 24:771-779, 2005

39. Kosek E, Ekholm J, Hansson P: Sensory dysfunction in fibromyalgia patients with implications for pathogenic mechanisms. Pain 68:375-383, 1996

40. Lamm C, Batson CD, Decety J: The Neural Substrate of Human Empathy: Effects of Perspective-taking and Cognitive Appraisal. J Cogn Neurosci 19:42-58, 2007

41. Lehmann D: Principles of spatial analysis. In: Gevins AS, Remond A (eds): Handbook of Electroencephalography and Clinical Neurophysiology: Methods of Analysis of Brain Electrical and Magnetic Signals. Amsterdam, Elsevier, 1987, pp 309-354

42. Leutgeb V, Schafer A, Kochel A, Schienle A: Exposure therapy leads to enhanced late frontal positivity in 8- to 13-year-old spider phobic girls. Biol Psychol 90:97-104, 2012

43. Leutgeb V, Schafer A, Schienle A: An event-related potential study on exposure therapy for patients suffering from spider phobia. Biol Psychol 82:293-300, 2009

44. Li W, Han S: Perspective taking modulates event-related potentials to perceived pain. Neurosci Lett 469:328-332, 2010

45. Lopez-Sola M, Pujol J, Wager TD, Garcia-Fontanals A, Blanco-Hinojo L, Garcia-Blanco S, Poca-Dias V, Harrison BJ, Contreras-Rodriguez O, Monfort J, Garcia-Fructuoso F, Deus J: Altered functional magnetic resonance imaging responses to nonpainful sensory stimulation in fibromyalgia patients. Arthritis Rheumatol 66:3200-3209, 2014

46. Lorenz J, Grasedyck K, Bromm B: Middle and long latency somatosensory evoked potentials after painful laser stimulation in patients with fibromyalgia syndrome. Electroencephalogr Clin Neurophysiol 100:165-168, 1996

47. Maris E, Oostenveld R: Nonparametric statistical testing of EEG- and MEG-data. J Neurosci Methods 164:177-190, 2007

48. Martinez-Jauand M, Sitges C, Femenia J, Cifre I, Gonzalez S, Chialvo D, Montoya P: Age-of-onset of menopause is associated with enhanced painful and non-painful sensitivity in fibromyalgia. Clin Rheumatol 32:975-981, 2013

49. McCarthy G, Donchin E: A metric for thought: A comparison of P300 latency and reaction time. Science 211:77-80, 1981

50. Mella N, Studer J, Gilet AL, Labouvie-Vief G: Empathy for Pain from Adolescence through Adulthood: An Event-Related Brain Potential Study. Front Psychol 3: 501, 2012

51. Meng J, Hu L, Shen L, Yang Z, Chen H, Huang X, Jackson T: Emotional primes modulate the responses to others' pain: An ERP study. Exp Brain Res 220:277-286, 2012

52. Nitschke JB, Sarinopoulos I, Oathes DJ, Johnstone T, Whalen PJ, Davidson RJ, Kalin NH: Anticipatory activation in the amygdala and anterior cingulate in generalized anxiety disorder and prediction of treatment response. Am J Psychiatry 166:302-310, 2009

53. Olofsson JK, Nordin S, Sequeira H, Polich J: Affective picture processing: An integrative review of ERP findings. Biol Psychol 77:247-265, 2008

54. Petzke F, Clauw DJ, Ambrose K, Khine A, Gracely RH: Increased pain sensitivity in fibromyalgia: Effects of stimulus type and mode of presentation. Pain 105:403-413, 2003

55. Polich J: Updating P300: An integrative theory of P3a and P3b. Clin Neurophysiol 118:2128-2148, 2007

56. Proverbio AM, Adorni R, Zani A, Trestianu L: Sex differences in the brain response to affective scenes with or without humans. Neuropsychologia 47:2374-2388, 2009

57. Staud R, Craggs JG, Perlstein WM, Robinson ME, Price DD: Brain activity associated with slow temporal summation of C-fiber evoked pain in fibromyalgia patients and healthy controls. Eur J Pain 12:1078-1089, 2008

58. Staud R, Robinson ME, Vierck CJ Jr, Cannon RC, Mauderli AP, Price DD: Ratings of experimental pain and pain-related negative affect predict clinical pain in patients with fibromyalgia syndrome. Pain 105:215-222, 2003

59. Staud R, Spaeth M: Psychophysical and neurochemical abnormalities of pain processing in fibromyalgia. CNS Spectr 13:12-17, 2008

60. Sullivan MJL, Bishop SR, Pivik J: The Pain Catastrophizing Scale: Development and validation. Psychol Assess 7: 524-532, 1995

61. van Middendorp H, Lumley MA, Jacobs JW, van Doornen LJ, Bijlsma JW, Geenen R: Emotions and emotional approach and avoidance strategies in fibromyalgia. J Psychosom Res 64:159-167, 2008

62. van Middendorp H, Lumley MA, Moerbeek M, Jacobs JW, Bijlsma JW, Geenen R: Effects of anger and anger regulation styles on pain in daily life of women with fibromyalgia: A diary study. Eur J Pain 14:176-182, 2010

63. Vandenbroucke S, Crombez G, Harrar V, Brusselmans G, Devulder J, Spence C, Goubert L: Fibromyalgia patients and controls are equally accurate in detecting tactile stimuli while observing another in pain: An experimental study. Atten Percept Psychophys 76:2548-2559, 2014

64. Versace F, Bradley MM, Lang PJ: Memory and event-related potentials for rapidly presented emotional pictures. Exp Brain Res 205:223-233, 2010

65. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P: The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 33: 160-172, 1990

66. Zautra AJ, Fasman R, Reich JW, Harakas P, Johnson LM, Olmsted ME, Davis MC: Fibromyalgia: Evidence for deficits in positive affect regulation. Psychosom Med 67:147-155, 2005