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ORIGINAL PAPER

Dysfunctional pain modulation in somatoform pain disorder patients

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Abstract To date, pain perception is thought to be a creative process of modulation carried out by an interplay of pro- and anti-nociceptive mechanisms. Recent research demonstrates that pain experience constitutes the result of top–down processes represented in cortical descending pain modulation. Cortical, mainly medial and frontal areas, as well as subcortical structures such as the brain stem, medulla and thalamus seem to be key players in pain modulation. An imbalance of pro- and anti-nociceptive mechanisms are assumed to cause chronic pain disorders, which are associated with spontaneous pain perception without physiologic scaffolding or exaggerated cortical activation in response to pain exposure. In contrast to recent investigations, the aim of the present study was to elucidate cortical activation of somatoform pain disorder patients during baseline condition. Scalp EEG, quantitative Fourier-spectral analyses and LORETA were employed to compare patient group ($N = 15$) to age- and sex-matched controls ($N = 15$) at rest. SI, SII, ACC, SMA, PFC, PPC, insular, amygdale and hippocampus displayed significant spectral power reductions within the beta band range (12–30 Hz). These results suggest decreased cortical baseline arousal in somatoform pain disorder patients. We finally conclude that obtained results may point to an altered baseline activity, maybe characteristic for chronic somatoform pain disorder.

Keywords EEG · Beta-3 band · Pain modulation · Pain matrix · SI

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Abbreviations

EEG	Electroencephalogram
BA	Brodman area
rCBF	Regional cerebral blood flow
SMA	Supplementary motor area
PPC	Posterior parietal cortex
PFC	Prefrontal cortex
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex
ACC	Anterior cingulate cortex
rACC	Rostral anterior cingulate cortex
PAG	Periaqueductal grey
AI	Anterior insula
CBP	Chronic back pain patients
IBS	Irritable bowel syndrome
GI	Gastrointestinal
EOG	Electrooculogram
ICA	Independent component analysis

Introduction

The International Association of Study of Pain (IASP) defines pain as ‘an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage’. Within this definition, pain can be seen as a psychological state and an individually learned association of experiences with actual or potential tissue damage. It avoids tying pain to a simplistic stimulus-related experience (IASP 1994). Biologists characterise pain as a life-saving reaction warning against severely impairing events and as interplay of cognitive-discriminative, emotional-affective, vegetative and motor components [6, 7]. According

to recent neuroimaging investigations, pain perception is the result of active pain modulation. It is conceived as a complex interplay of cortical and subcortical structures, constituting the so-called pain matrix [4, 11, 20, 28, 36]. In contrast to healthy subjects, patients suffering from chronic pain disorder experience spontaneous pain with insufficient physiologic scaffolding and/or suffer from enhanced pain perception in response to innoxious stimuli [12]. Recent results attribute this phenomenon to a maladjustment/disequilibrium of nociceptive and anti-nociceptive processes within the ascending pain processing [4, 26, 27]. Accordingly, chronic pain disorder is associated with altered pain-related brain activity, characteristic for pain patients. Continuous EEG and functional low-resolution electromagnetic tomography (LORETA) studies detected neuropathic pain–associated enhanced theta (6–9 Hz) and beta (12–16 Hz) power in structures of the pain matrix. Authors suppose this spontaneous enhanced spectral power to serve as a physical underlying model of chronic neurogenic pain [38]. Sarnthein et al. yielded to replicate the enhanced spectral power within the frequency range of 4–9 Hz generated in the pain-associated areas in neurogenic pain patients compared to healthy controls [32]. Furthermore, frontal theta frequency bands show tight coupling with thalamic activity and seem to play a crucial role in pain processing. Consequently, neurogenic pain is supposed to be causative related to a dysfunctional thalamocortical interplay [33, 37]. Beside EEG investigations, numerous fMRI and PET studies confirmed the assumption of abnormal cortical activity within areas of the pain matrix [2, 8, 11, 16, 22, 39] and altered connection between cortical and subcortical structures [4, 9, 13, 34] in chronic pain patients. Despite considerable limited transferability of fMRI studies to scalp EEG power spectra analyses, both methods can identify cortical activity of certain areas. Previous fMRI and PET studies showed distinct cortical activation differences characteristic for pain disorder as mentioned earlier. Since the EEG analysed by means of LORETA serves as an alternative imaging technique of cortical activity, we assumed to identify pain disorder characteristic activity using the quantitative EEG (qEEG), potentially overlapping with the previously defined pain matrix.

To sum up, the primary outcome of the recent research demonstrates that pain disorder patients show greater cortical activation in the pain matrix during pain perception [2, 8, 11, 14, 16, 22] and/or show altered power spectra bands at rest [32, 33, 37, 38]. However, the underlying mechanisms of chronic pain disorder are still not completely clarified and remain discussed contradictorily.

Today, the prior pain disorder treatment subsumes pharmacological [15, 23] interventions, which obtain frequently moderate effect sizes but are still associated with limited tolerability [21]. Hence, additional therapeutic approaches, reinforcing and supporting the conventional treatments are desired. Neuroimaging techniques are already applied as diagnostic tools [14, 17, 19, 30] and are aspired to be used as therapeutic interventions too [10, 18]. There are indeed initial but promising attempts to make the possible therapeutic potential of fMRI [10] and EEG [18] accessible. Since EEG neurofeedback represents a tolerable, financially economic and potentially effective [10, 18, 35] intervention alternative, the precise definition of pain disorder–specific cortical changes gains importance. Only the knowledge about what, in detail has to be changed in pathological brain activation in case of pain disorder constitutes the foundation to tap the full potential of neuroimaging-associated treatments.

The underlying hypothesis of this examination is an unbalanced pain modulating system, which may perform insufficiently in somatoform patients and potentially causes exaggerated reactions of the pain matrix. A hypoactive anti-nociceptive system closely related to the pain matrix would cause decreases during resting state and insufficient pain inhibition in case of painful as well as sub-painful stimuli experience. This lack of activity suppression—normally carried out by anti-nociceptive structures [3, 5] could cause hyperactivity in the pain matrix observed several times in former studies [4, 11, 25, 28, 36].

Since the EEG, featuring high temporal resolution represents an economic and applicable instrument [30], we aim to differentiate between pain patients and controls by means of scalp EEG spectral power characteristics. Hereby, we take the limitation of EEG analysis and logarithmic tomography methods as LORETA into account. These investigation instruments are restricted to the solution space of 2,394 voxel within the gray matter of the brain and feature a rather low spatial resolution. Consequently, we focus on cortical areas located within the cortical gray matter while changes in deeper areas are interpreted conditionally. We furthermore prefer to investigate cortical activation at rest for capturing exclusively the chronic pain symptoms and not to gain overlapping cortical activations caused by simultaneously occurring external induced and spontaneously pain perception. As a descriptive pilot study, it is designed to gain constitutive knowledge about potential pain disorder–associated dysregulations. It aims to detect cortical activity changes characteristic for somatoform pain disorder and to define a set of pain disorder–associated cortical structures, computable for LORETA analysis.

Methods

Subjects

15 right-handed individuals (average age: 50.07 years; 7 women, 8 men) treated at the Austrian General Hospital Department of Psychiatry and Psychotherapy were investigated between 2003 and 2005. At the time of EEG investigation, each patient met the ICD-10 criteria of somatoform pain disorder (F45.4/300.89) [12]. Patients reported continuous pain perception pertaining the whole body or multiple extremities, respectively. Five patients also fulfilled diagnoses criteria of fibromyalgia. They neither showed any clinically relevant depressive symptoms nor clinically relevant anxiety disorder symptoms. Diagnoses were obtained by semi-structures clinical interviews and screening questionnaires like Beck Depression Inventory (BDI), State Trait Anxiety Inventory (STAI I, STAI II), Symptom Check List (SCL-R-90) conducted by experienced clinicians. Since 1 week prior to the EEG recording psychoactive medication was stopped, our subjects can be regarded as drug free. The patient group was compared to 15 age- and sex-matched controls (average age: 50 years, 7 women, 8 men) recruited by print advertising. In each subject, a physical examination and psychiatric examination as well as laboratory tests were performed. Exclusion criteria were the diagnosis of entirely developed psychiatric disorders and/or reported consumption of centrally acting drugs. All of them gave consent to participate in the study, which was approved by the local research board.

Procedure

All participants underwent a 3-min vigilance-controlled EEG, a 4-min resting EEG with closed eyes and a 1-min EEG with opened eyes. During the whole EEG recording, subjects were lying in an electrically shielded room and were invited to relax. To prevent patients from falling asleep during the vigilance-controlled condition, they were aroused by auditory stimuli (tapping) as soon as drowsiness patterns occurred in the EEG.

Data acquisition

The EEG was recorded by means of a 21-channel Nihon Kohden 4321 G polygraph with a time constant of 0.3 s, high frequency response of 35 Hz, frequency range of 0.5–35 Hz, amplification of approximately 20,000 times and a maximal noise level of 2 μV peak-to-peak. The electrodes were attached to the scalp according to the international 10/20 system. The vertical electrooculogram (EOG) was recorded from an electrode at mid-forehead to the average of one electrode below the left eye and one electrode below the right eye. The horizontal EOG was recorded from the outer canthi. EEG recordings from 19 leads and two EOG recordings were digitised online by a 12-bit Burr Brown AD converter within a Hewlett-Packard Vectra system with a sampling frequency of 102.4 Hz. Spectral analysis was performed for 5-s epochs (512 sample points) this way resulting in a frequency resolution of 0.2 Hz, by using the Fast Fourier Transform Technique in floating-point arithmetic to maintain precision.

Data preprocessing

Artefact-free 5-s epochs were selected after minimising ocular artefacts by means of an automatic artefact identification method as described in Anderer et al. [1]. Before spectral analysis was conducted, the EEG recordings were transformed to average reference. The mean spectral curves contain data from 1.3 to 35 Hz quantified into 36 EEG variables: total power, absolute and relative power in 12 different frequency bands.

Mapping

For EEG mapping, 19 single values obtained from the 10/20 electrode set are mapped onto a 64×64 numerical matrix. Each interpolated value is based on the cubic distance from the values at the four nearest electrodes. Low-resolution electromagnetic tomography (LORETA) was applied to the 19-channel EEG data and squared current density source of eight frequency bands was determined: delta = 1.5–6 Hz, theta = 6–8 Hz, alpha-1 = 8–10 Hz, alpha-2 = 10–12 Hz, beta-1 = 12–18, beta-2 = 18–21, beta-3 = 21–30, total band = 1.5–30. LORETA is based on realistic head geometry (Talairach human brain atlas) and the smoothness constraint. The solution space is divided into 2,394 current density values or voxels and is restricted to the cortical gray matter and the hippocampus.

After data preprocessing, two-tailored voxel-by-voxel Student's *t*-tests were performed. Since this is a descriptive as well as explorative investigation, it has to be mentioned that uncorrected *t*-values are reported and have to be interpreted appropriately.

Results

The comparison—somatoform pain patients minus controls—yield exclusively decreases in EEG power spectra. Large cortical areas showed significant (uncorrected) reductions ($P < 0.05$) of spectral power in all frequency bands, except delta and alpha-2 bands. Due to multiple testing, all results were corrected by Bonferroni correction.

Apart from beta-3 band, results obtained within other frequency bands lost their significance.

Theta (6–8 Hz): theta bands are associated with some sleep states, states of quiet focus, for example meditation as well as voluntary behaviours and alert states. PPC (BA 7), precuneus (BA 31) and SMA (BA 5, 6) display less theta-power in somatoform patients.

Alpha-1 (8–10 Hz): alpha-1 is associated with awake relaxation. The insula (BA 13), PFC (BA 44, 45, 46) and temporal areas (BA 22, 38) showed decreases.

Beta-1 (12–18 Hz): Within the beta-1 band associated with normal waking consciousness, the PFC (BA 44, 45, 46), the SMA (BA 6) as well as frontal regions (BA 9, 10) displayed decreases.

Beta-2 (18–21 Hz): Beta-2 band seems to be related to active, busy or anxious thinking and active concentration. The SMA (BA 6) and the SI (BA 1, 2, 3), primary motor cortex (BA 4), and few parts of frontal areas (BA 9. 10) showed decreases (Table 1).

Spectral power decreases within the beta-3-band remained significant after Bonferroni correction.

Beta-3 (21–30 Hz): Within the highest section of beta-waves decreases, remaining significant after Bonferroni correction were detected in the SI (BA 1, 2, 3), SII (BA 40, 43), PFC (BA 44, 45, 46, 47), SMA (BA 6), ACC (BA 32, 24), amygdala, hippocampus, insula and PPC (BA 7), in frontal regions (BA 8, 9, 10, 11, 25), occipital areas (BA 19), temporal areas (BA 20, 21, 22, 37, 38, 39, 41, 42) and limbic parts (BA 29, 36, 35, 28, 34) (Figs. 1, 2).

Discussion

Most of the current knowledge about pain disorder–specific cortical activity is obtained by neuroimaging studies using fMRI or PET, which is therefore only partially transferable to EEG data. fMRI and PET register hemodynamic signatures, while the EEG directly measures extracranial field potentials, which are both signs of brain activity. The coherence between hemodynamic activity and local neuronal synaptic field potentials is limited and contrary discussed [24]. At least it is assumed that electrical, hemodynamic and metabolic parameters are coupled in both space and time [29]. Considering this limitation, we employed the EEG to examine the regional cortical activity at rest in somatoform pain patients, aiming to explore neuronal properties of this psychiatric disorder.

Fortunately, the present study yielded to identify significant activation differences, discriminating between patients and controls at rest. Statistically relevant power spectra differences mainly occurred in the left hemisphere and represented exclusively reductions. Since, only beta-3 specific decreases remained significant after the correction for multiple testing, we focus on these results to back up the scientific relevance. The frequency range of beta-3 is associated with alertness and cortical activity. Hence, a reduction of this range can be interpreted as less cortical activation. Accordingly obtained results suggest reduced cortical activity in the SI, SII, PFC, SMA, ACC, the amygdala, hippocampus, insula, PPC, frontal regions, occipital areas, temporal areas and limbic parts. Compared to the formerly identified pain matrix [2, 4, 11, 20, 22, 36], the present set of decreased cortical areas show a striking overlap. Nevertheless, the exclusively descriptive character of these results has to be kept in mind. Although the striking congruence with the pain matrix becomes obvious, the present results cannot be conclusively interpreted as pain perception associated, since no pain stimulus condition was conducted.

Sarnthein et al. [32, 33] used a comparable EEG design and detected activation increases in neuropathic pain patients, which is putatively inconsistent with our results reflecting activation decreases. They reported a generally slowed resting EEG, as well beta and theta overactivity. Stern et al. [38] found activation increases in the insula, the ACC, inferior PPC, the SI, the SII and the supplementary somatosensory cortex, reasoning that neuropathic pain is associated with overactivation in the pain matrix. The diametrical differences between the current results and those of Sarnthein et al. [32] and Stern et al. [38] are obvious but seem to be allegeable by different pain disorder syndromes/systems. While neuropathic pain is caused by "primary lesion, dysfunction, or transitory perturbation in the peripheral or central nervous system" [32, 33], somatoform pain disorder is characterised as a long-lasting and agonising pain without sufficient physiologic foundation. According to the differing cortical manifestations occurring in the present study and those of Sarnthein et al. [32] and Stern et al. [38], neuropathic pain seems to be obviously not equate with somatoform pain disorder. Different pain syndromes seem to result in different cortical representations. Somatoform pain disorder seems to be associated with a hypoactive anti-nociceptive system [3], whereas neuropathic pain symptoms presented in Sarnthein et al. [32] seem to arise from direct as well as continuous cortical overactivation caused by primary lesions. In addition, patients in Stern et al. [38] were not free from centrally acting medication which is known to effect cortical activity patterns [31].

Further contradicting results were obtained in restrictly conferrable fMRI studies, revealing activation increases in pain patients contrasted with controls—but only at the first glance. Studies reporting pain disorder–associated activations in the pain matrix continuously used comparisons between two conditions—resting and pain-stimuli condition [2, 8, 11, 16]. In contrast to those, the present

Table 1 Voxel-by-voxel *t*-tests between somatoform pain disorder patients and age- and sex-matched controls (*n*: 2 × 15) for seven EEG-frequency bands (delta, theta, alpha-1, alpha-2, beta-1, beta-2 and beta-3) recorded under vigilance-controlled condition with eyes closed

Frequence	*t*-value	Lobe	BA	Hemisphere
Differences of power spectra: pain disorder patients minus controls				
Delta (1.5–6 Hz)				
Min	−1.96	Parietal lobe	31	Left
Max	0.35	Frontal lobe	8	Right
Theta (6–8 Hz)				
Min	−2.41*	Frontal/parietal lobe	5	Left
		Frontal lobe	6	Left + right
		Parietal lobe	7	Left + right
		Limbic lobe	31	Left
Max	0.08	Frontal/limbic lobe	32	Right
Alpha-1 (8–10 Hz)				
Min	−2.35*	Frontal lobe	45	Left
		Frontal lobe	10, 11, 9, 47, 46, 45, 44	Left
		Temporal lobe	22, 38	Left
		Sub-lobar	13	Left
Max	−0.56	Temporal lobe	20	Left
Alpha-2 (10–12 Hz)				
Min	−1.49	Frontal lobe	10	Left
Max	1.11	Occipital lobe	19	Right
Beta-1 (12–18 Hz)				
Min	−2.17*	Frontal lobe	44	Left
		Frontal lobe	10, 9, 6, 46, 45, 44	Left
Max	0.19*	Temporal lobe	37	Left
Beta-2 (18–21 Hz)				
Min	−2.24*	Frontal lobe	9	Left
		Frontal lobe	4, 6, 10, 11, 45, 47	Left
		Parietal lobe	3, 7, 1, 6	Left
Max	0.21	Temporal lobe	39	Right
Beta-3 (21–30 Hz)				
Min	−3.07**	Parietal lobe	40	Left
		Parietal lobe	1, 2, 3, 43	Left
		Parietal lobe	7	Left + right
		Frontal lobe	6, 8, 9, 10, 11, 25, 47	Left + right
		Frontal lobe	4, 44, 45, 46	Left
		Occipital lobe	19	Left
		Temporal lobe	20, 21, 22, 37, 38, 39, 41	Left
		Temporal lobe	42	Left + right
		Limbic lobe	24, 28, 32, 34	Left + right
			29, 35, 36	Left
		Sub-lobar	13	Left
Max	−0.24	Parietal lobe	40	Right

* $P < 0.5$, uncorrected

** $P < 0.5$, uncorrected, which would remain significant after Bonferroni correction

investigation employed a two-group comparison (somatoform patients vs. controls) during one condition—the resting state. This difference is probably due to the assumed discrepancy between our and previous analyses. Nonetheless, this seeming contradiction fit with our assumed hypotheses of dysregulated pain modulation, mentioned earlier. A potential hypoactive anti-nociceptive system would reflect at rest, less cortical activity and would advance activation of the pain matrix, especially in case of pain exposure. The current results do not serve as conclusive confirmation but indeed as further and valuable contribution to explore this hypothesis and its applicability.

Although the results obtained appear to fit satisfyingly the hypotheses of dysregulation of pain-associated cortical structures, some limitations of this study have to be mentioned. The EEG represents an economic investigation

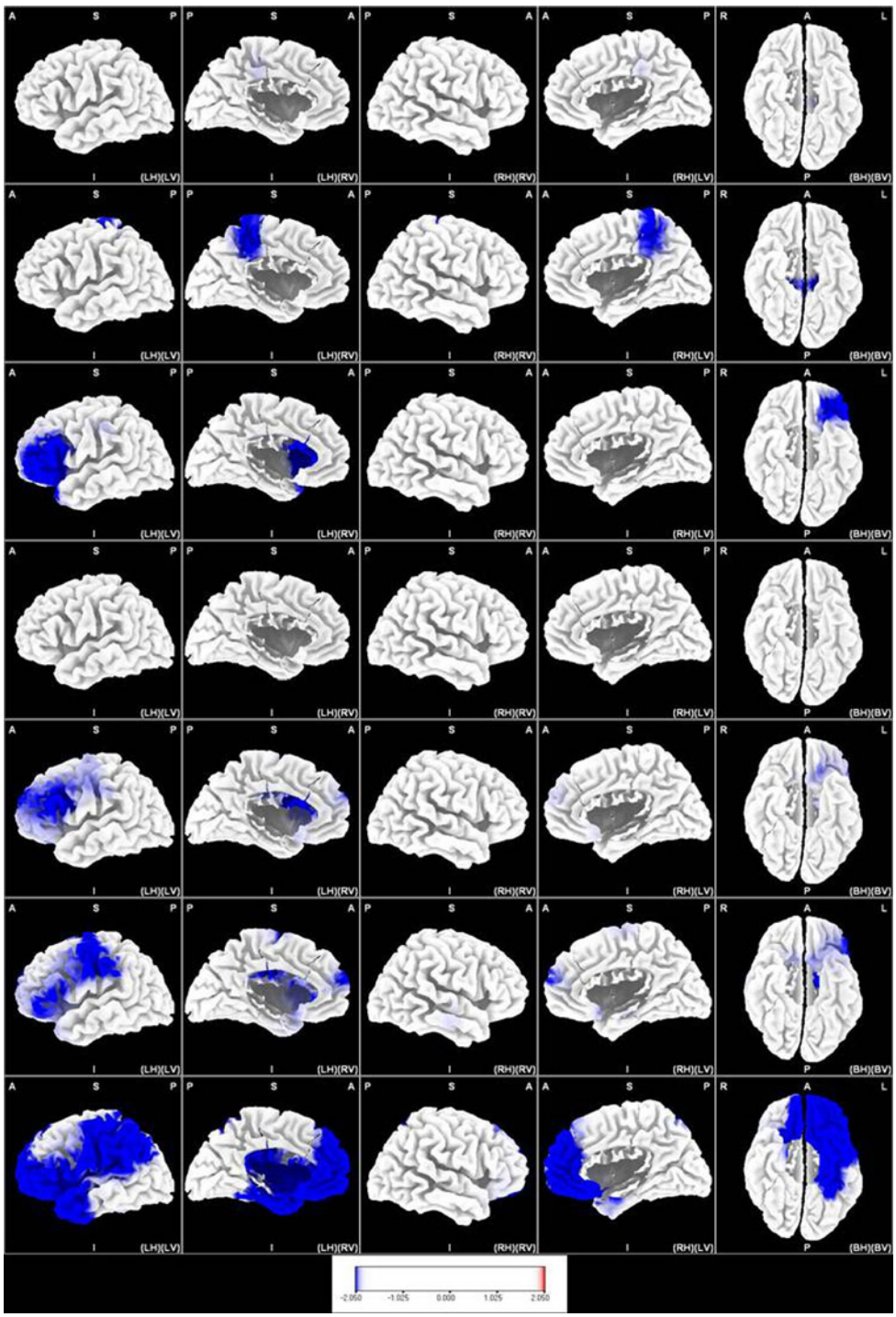

Fig. 1 Surface rendered EEG LORETA images depicting statistical parametric maps (SPMs) based on voxel-by-voxel *t*-tests between somatoform pain disorder patients and age- and sex-matched controls (n: 2 × 15) for seven EEG-frequency bands (delta, theta, alpha-1, alpha-2, beta-1, beta-2 and beta-3) recorded under vigilance-controlled condition with eyes closed seen from different perspectives. Significant decreases are shown in *blue colour* ($P < 0.05$, $df = 28$). columns left-right: *1*, *2* left hemisphere, left and right view, *3*, *4* right hemisphere, right and left view, *5* basal view; rows top-down: *1* δ, *2* θ, *3* $\alpha 1$, *4* $\alpha 2$, *5* $\beta 1$, *6* $\beta 2$, *7* $\beta 3$; *A* anterior, *P* posterior, *S* superior, *I* inferior, *R* right, *L* left

instrument with high temporal but low spatial resolution. Further processing of scalp EEG data by LORETA is restricted to a solution space of 2,394 voxel within the gray matter of the brain. Since the pain matrix exceeds the gray matter, the present investigation is restricted to a subgroup of pain-associated areas. As a consequence of multiple testing, the results have to be corrected by Bonferroni correction to minimise the alpha-error. All results except those corresponding to beta-3 band became insignificant after the correction. Since Bonferroni is a very strict correction technique, only material group differences remain significant. Hence, results obtained within the high beta power can be seen as strong and statistically relevant.

All included subjects were derived of centrally acting antidepressants to exclude possible EEG patterns caused by psychotropic drugs and overlapping with pain disorder–associated cortical changes. Nevertheless, potential withdrawal-specific EEG alterations cannot be excluded. Urine

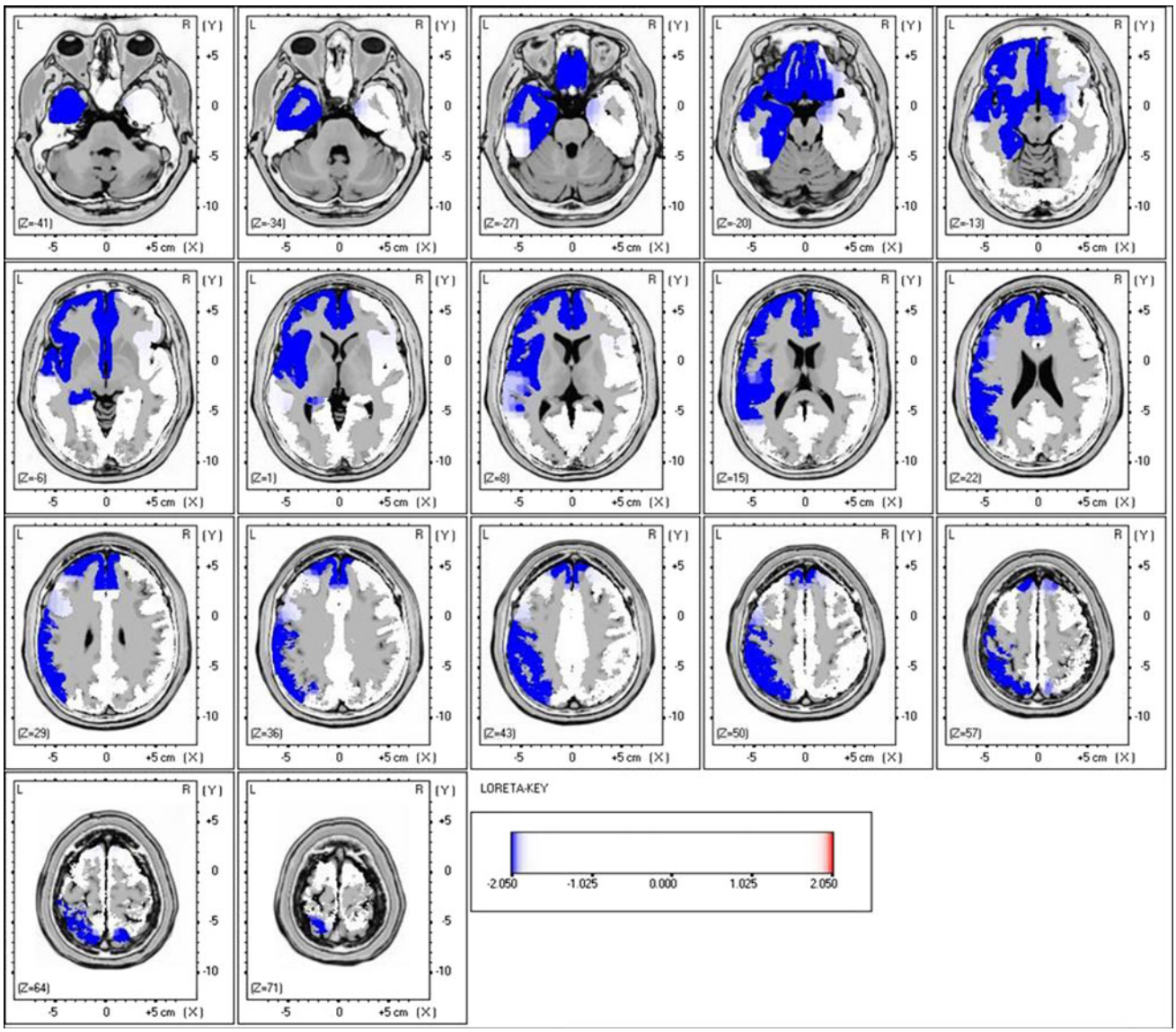

Fig. 2 Differences: somatoform pain disorder patients minus age- and sex-matched healthy controls (n: 2×15) in the fast beta frequency band (beta-3: 21–30 Hz) shown as statistical parametric maps (SPMs) based on voxel-by-voxel t-tests. Significant decreases are shown in *blue colour* ($P < 0.05$, $df = 28$). Structural anatomy is shown in *grey scale*. Axial slices in Talairach space are seen from above with the nose on top [X from left (L) to right (R); Y from posterior to anterior; Z from inferior to superior]

toxicology was done to affirm the patient status being drug free at the time of EEG recording. Regarding the design one remark has to be mentioned. In the present examination, exclusively resting state condition was performed and recorded. Consequently, this study offers exclusively descriptive results on pain disorder–associated cortical decreases.

Since there is no comparison of baseline and pain condition, we cannot attribute the observed cortical decreases to pain experience in a causative manner. But we can indeed define cortical deviations characteristic for pain disorder at rest.

Conclusion

So far, recent research provided evidence that pain perception is a rather complex interplay of pro- and anti-nociceptive activity than a simple on–off mechanism. Hence, further studies investigating the characteristics of this particular interaction are necessary. These analyses should cover group comparisons at rest as well as during stimulus conditions and use further mathematical analyses, e.g. ICA (independent component analysis) to identify possible relations between different pain structures. Further

reliable and valid evidence based research on this relevant topic is desirable.

The present EEG investigation yielded to describe activity decreases characteristic for somatoform pain disorder at rest. These decreases were located in areas, being partially enclosed in the pain matrix. Furthermore, the hypotheses of dysregulated cortical activity in pain patients at rest could be fortified in a descriptive manner. These results serve as further contribution to our knowledge about altered cortical activity in somatoform pain disorder.

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