

Neuronal correlates of symptom formation in functional somatic syndromes: A fMRI study

Michael Landgrebe,^a Winfried Barta,^a Katharina Rosengarth,^b Ulrich Frick,^a Simone Hauser,^a Berthold Langguth,^a Roland Rutschmann,^b Mark W. Greenlee,^b Goeran Hajak,^a and Peter Eichhammer^{a,*}

^a Department of Psychiatry, Psychosomatics, and Psychotherapy, University of Regensburg, Germany

^b Department of Experimental Psychology, University of Regensburg, Germany

Received 17 December 2007; revised 7 April 2008; accepted 11 April 2008
Available online 20 April 2008

Functional somatic syndromes are characterized by high morbidity due to various, fluctuating symptoms without objective somatic findings. There is increasing evidence for the contribution of emotional and cognitive functions to symptom formation, which has been well established in the perception of pain. In addition to their involvement in various other cognitive and emotional processes, the anterior cingulate and insular cortex are thought to contribute to the so-called “pain neuromatrix”. Recent data suggest that these areas appear also to be involved in symptom manifestation in multiple chemical sensitivity. Here we used functional Magnetic Resonance Imaging (fMRI) to test whether this network is also involved in the induction of unpleasant perceptions by sham mobile phone radiation in subjectively electrosensitive patients. This design enabled us to completely dissociate the unpleasant subjective perception from any real physical stimulus. Fifteen subjectively electrosensitive patients and 15 age- and gender-matched healthy controls were exposed to sham mobile phone radiation and heat as a control condition. The perceived stimulus intensities were rated on a five-point scale. During anticipation of and exposure to sham mobile phone radiation increased activations in anterior cingulate and insular cortex as well as fusiform gyrus were seen in the electrosensitive group compared to controls, while heat stimulation led to similar activations in both groups. Symptom manifestation during sham exposure to mobile phone radiation was accompanied by specific alterations of cortical activity in anterior cingulate and insular cortex in subjectively electrosensitive patients further supporting the involvement of these areas in the perception of unpleasantness and generation of functional somatic syndromes.

© 2008 Elsevier Inc. All rights reserved.

Introduction

Somatoform disorders, functional somatic syndromes and psychosomatic diseases are characterized by a considerable discrepancy between subjective complaints of symptoms and objective somatic findings. But such a discrepancy is also known from other conditions such as insomnia, tinnitus or chronic pain, where the degree of suffering is not sufficiently explained by the amount and the severity of objective findings. This suggests the involvement of emotional and cognitive functions in the pathophysiology of these diseases.

For pain already in the early 1960ies modulatory effects on different levels of the ascending pain pathway have been described, which later became popular as the “gate control theory” (Melzack and Wall, 1965). Currently it is widely accepted that higher cognitive functions like attitudes, beliefs or expectations can modulate the perception of pain. Recent functional imaging data demonstrated a cortical network involved in these cognitive processes (Ploghaus et al., 1999; Wager et al., 2004). This so-called “pain neuromatrix” is sub-divided in a sensory-discriminative component encompassing primary and secondary somatosensory cortex (SI and SII), posterior insula, and nuclei in the lateral thalamus. In contrast, the anterior insula and the anterior cingulate cortex (ACC) have been associated with the encoding of subjectively perceived unpleasantness (Singer et al., 2004). These areas have also been shown to be involved in the representation of interoceptive perceptions (Craig, 2002), anxiety proneness (Paulus and Stein, 2006), and mediation of expectation-related information (Koyama et al., 2005). Furthermore, similar cortical circuits are involved in symptom generation in multi-chemical sensitivity (also known as “environmental intolerance”; Hillert et al., 2007) as an example of a functional somatic syndrome. Thus, it appears that these areas may represent a cortical network conveying emotional and cognitive aspects of unpleasant stimuli of varying modalities. One may speculate that under certain conditions this system may provoke symptoms even in the absence of afferent stimuli.

Abbreviations: ACC, anterior cingulate gyrus; EMF, electromagnetic fields; FWE, family-wise error; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; MFG, middle frontal gyrus; MOG, middle occipital gyrus; MNI, Montreal Neurological Institute; MSU, MNI Space Utility; SFG, superior frontal gyrus.

* Corresponding author. Department of Psychiatry, Psychosomatics, and Psychotherapy, University of Regensburg, Universitätsstrasse 84, 93053 Regensburg, Germany. Fax: +49 941 941 2075.

E-mail address: peter.eichhammer@medbo.de (P. Eichhammer).

Available online on ScienceDirect (www.sciencedirect.com).

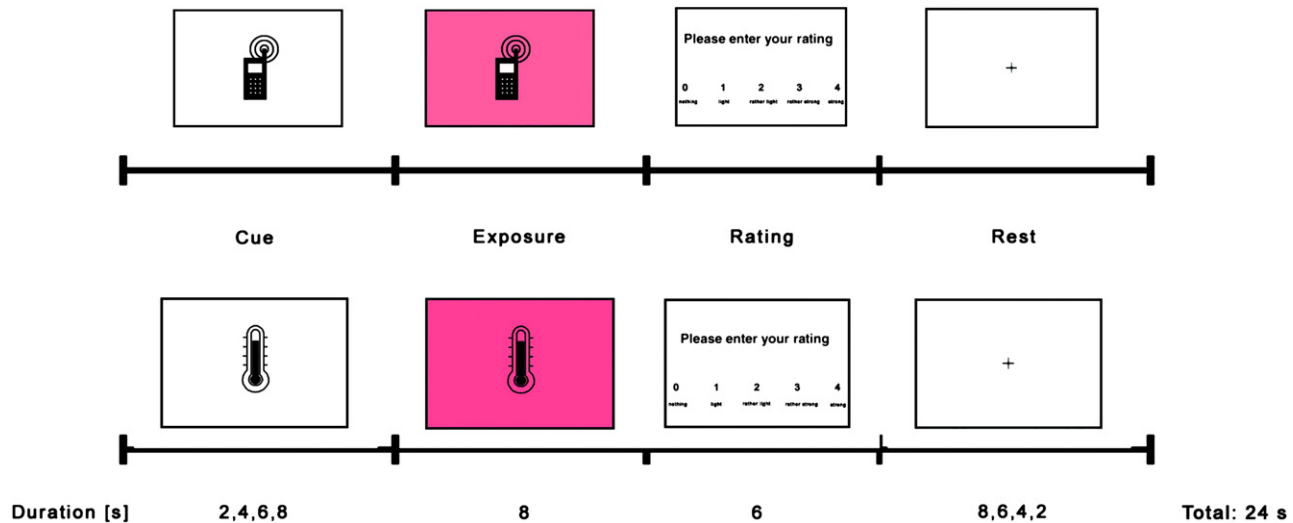


Fig. 1. Schematic trial diagram. Periods of anticipation and resting lasted 2 to 8 s in a pseudo-randomized manner. Stimulation and rating lasted 8 and 6 s, respectively. Each consecutive condition was announced by a symbol (cartoon of a thermometer or mobile phone). During the anticipation period, the background stayed white and turned into red during stimulation (either sham mobile phone radiation or heat stimulation). Total duration of each trial was 24 s.

In order to test this hypothesis the present study aimed at further characterizing the neural correlate of unpleasant perceptions both during exposure to real and virtual unpleasant stimuli. Therefore we investigated individuals suffering from the syndrome of “subjective electrohypersensitivity”. This syndrome is very common in Western populations (Levallois et al., 2002) and characterized by many fluctuating symptoms, high complaint level and the subjective belief that symptoms are caused by electromagnetic fields. In contrast, there are no objective medical findings in these patients which can sufficiently explain their symptoms nor were any kind of provocation studies able to elicit specific symptoms under controlled conditions (Rubin et al., 2005). As a condition that is characterized by a high complaint level without somatic correlate, subjectively electrohypersensitivity is ideally suited to investigate the role of a hypothesized cortical network modulating and probably generating unpleasant perceptions. We assumed that a dummy mobile phone might provoke symptoms in subjectively electrosensitive patients but not in healthy controls, because mobile phones are most often named by subjectively electrosensitive patients as a possible source of their health complaints. This fMRI paradigm enabled us to completely dissociate the subjective perception of unpleasantness from any real physical stimulus. We hypothesized that (1.) unpleasantness is related to ACC and anterior insular cortex activation even in the absence of any physical stimulus and that (2.) subjectively electrosensitive patients differ from controls in the activation of these areas during virtual exposure to mobile phone radiation.

Material and methods

Subjects

Fifteen subjectively electrosensitive patients (6 women, mean age 47.7 ± 10.5 years) and 15 gender- and age-matched control subjects (6 women, mean 46.9 ± 9.9 years) participated in the experiment. The group of subjectively electrosensitive patients represented a subgroup of 89 patients from an epidemiological study in southern Germany and Austria investigating the phenomenon of subjective electro-

hypersensitivity (see Landgrebe et al., 2008 for detailed information about inclusion criteria for the electrosensitive group). In brief, since diagnostic criteria for subjective electrohypersensitivity are lacking so far, main inclusion criterion was a high symptom load of unspecific health complaints which had to be alleged by the patients to be caused by exposure to electromagnetic fields (EMF) of various origin (e.g. mobile phone radiation, TV-towers, etc.). In the control group only individuals were enrolled which have never experienced any symptoms in context with EMF-exposure. All participants gave written informed consent. The study protocol was approved by the ethics committee of the University of Regensburg and conducted according to the Code of Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association (Declaration of Helsinki).

Experimental setup

The experiment has been designed to investigate cortical activations associated with unpleasant perceptions induced by sham exposure to EMF. All participants received a standardized instruction stating that the experiment has been designed to investigate “brain activation” associated with unpleasant perceptions induced by either heat stimulation or “mobile phone exposure”. Participants were instructed that “mobile phone exposure” will be delivered by a specifically constructed mobile phone, which works in the MR scanner and was fixed to the inner upper right surface of the head coil. None of the participants mentioned doubts about the feasibility of this experimental setup. After completion of the whole experimental series, all participants were briefed on the fact that a dummy mobile phone was used. Heat stimuli (42° , 45° or 48°) were applied by a thermode (Thermal Sensory Analyser, Medoc Inc., Israel) fixed to the subject's left wrist.

The experiment consisted of 48 trials (24 sham mobile phone exposures and 24 temperature exposures of 42°C , 45°C , and 48°C , each 8 times) with a duration of 24 s of each trial. Both conditions (temperature or sham mobile phone exposure) were presented in a pseudo-randomized order. In each trial, the given stimulus condition

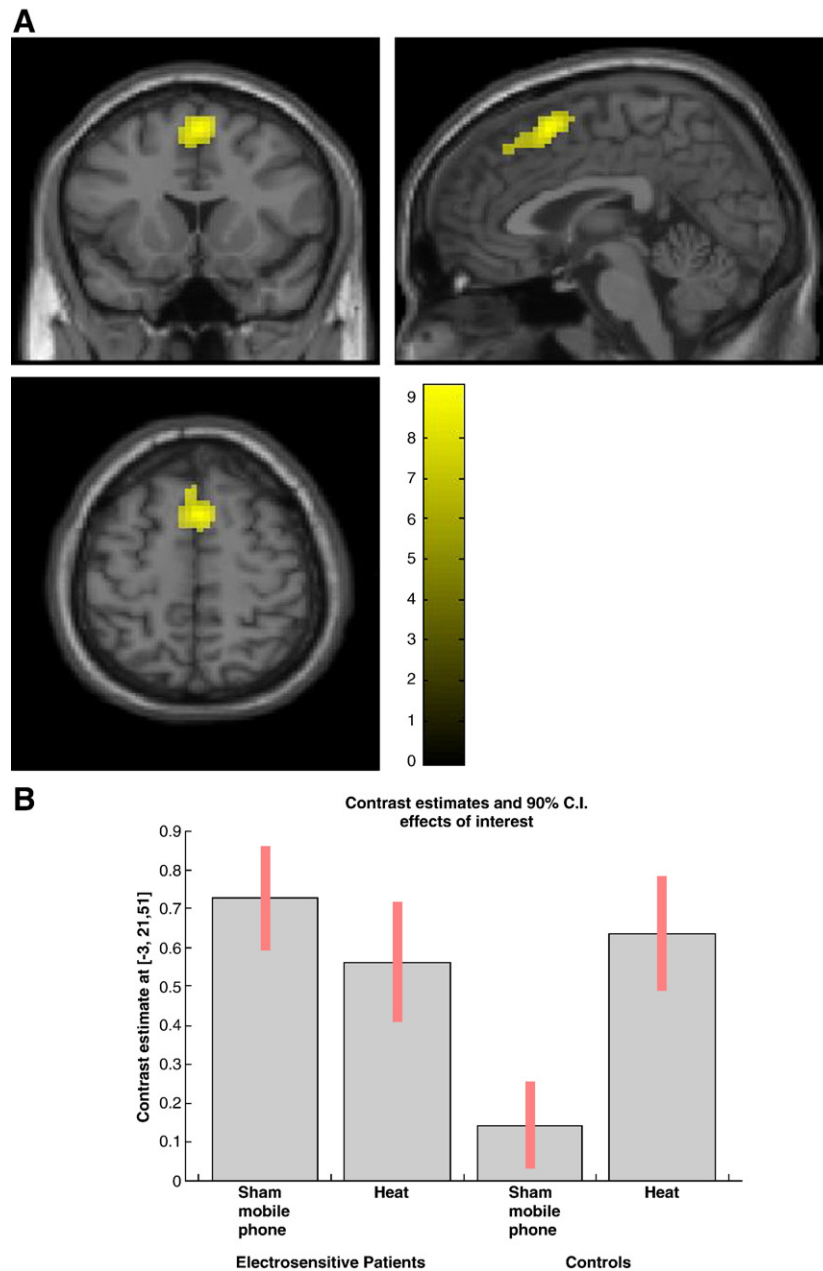


Fig. 2. Positive interaction “group X type of stimulation”. Shown are significantly activated areas in cingulate cortex [A] and the corresponding plot of the parameter estimates for the electrosensitive and control group (B; coordinates of peak voxel: $-3, 21, 51$; $p < 0.001$ uncorrected; Z-value of peak voxel = 4.55; $T = 3.28$).

was announced by an icon appearing on a white background (cartoon of mobile phone or of a thermometer) for 2–8 s. This cue was followed by the exposure period lasting 8 s, during which time the background switched to red. After stimulation participants had to rate the unpleasantness of the stimulus on a 5-point scale (6 s) followed by a resting period of 2–8 s (Fig. 1).

Imaging protocol

Scanning was performed on a Siemens Allegra 3 Tesla scanner with a one channel headcoil. Functional images were acquired using

a T2* weighted gradient EPI (TR = 2000 ms, TE = 30 ms, 34 slices, FoV = 192 mm, flip angle = 90°, $3 \times 3 \times 3$ mm voxel size, 722 scans). A high resolution T1 weighted image was also performed for each subject (TR = 2300 ms, TE = 2.91 ms, 160 slices, FoV = 256 mm, flip angle = 9°, $1 \times 1 \times 1$ mm voxel size).

Behavioral data analysis

For the temperature condition ratings were analyzed by using a 2×3 factorial ANOVA: group (electrosensitive vs. control) and rating (low, medium, high).

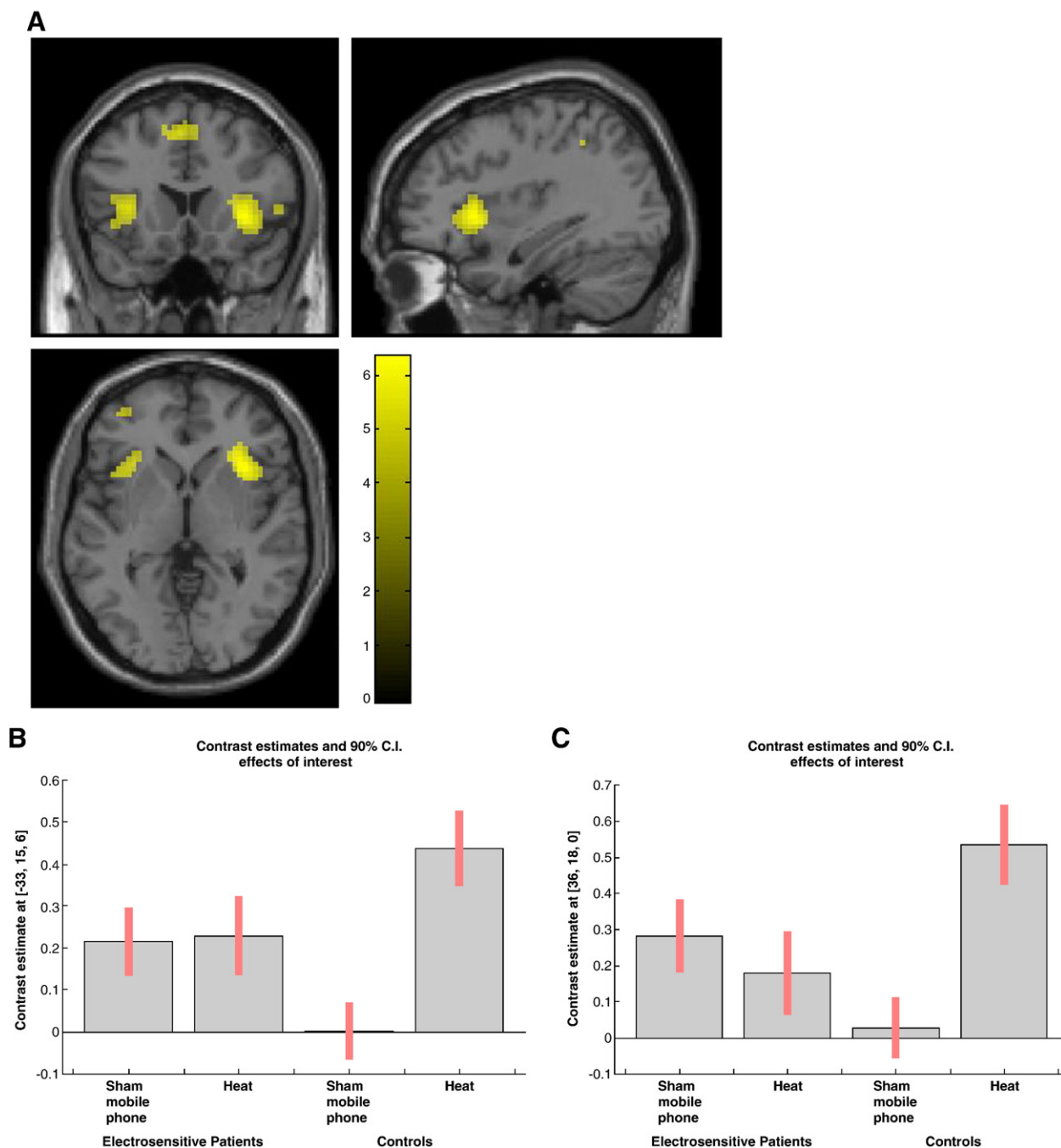


Fig. 3. Positive interaction “group X type of stimulation”. Shown are significantly activated areas in the left (coordinates of peak voxel: $-33, 15, 6$; Z -value=4.76) and right (coordinates of peak voxel: $36, 18, 0$; Z -value=5.34) insular cortex [A] and the corresponding plot of the parameter estimates for the electroSensitive and control group (B=left, C=right; $p < 0.001$ uncorrected; $T = 3.28$).

Group differences with respect to the stimulus condition (temperature and mobile phone exposure) were examined by two-sample t -test for independent samples. Statistical significance was determined by a p -value of less than 0.05.

fMRI data analysis

Data analysis was conducted by using the SPM5 software package running under Matlab. Since the experimental design aimed at

identifying cortical activations related to feelings of unpleasantness in relation to sham mobile phone exposure, we included only patients with a rating of ≥ 1.5 (intensity light to rather light; 11 out of 15) to guarantee a perception of unpleasantness under this condition. The remaining 4 patients reported no substantial perceptions for various reasons (e.g. the exposure period was too short to induce their typical reactions to EMF-exposure or that they have been distracted by the scanner noise). In contrast, all control subjects rated unpleasantness during mobile phone exposure as less than 1.5. In the control group,

Table 1

Brain areas showing significant activation of the interaction “group X type of stimulation” i.e. regions in which the contrast “mobile phone exposure vs. temperature” application was larger in the group of electrosensitives than in the control group ($p < 0.001$ uncorrected, $T = 3.28$)

Hemisphere and Region	Brodmann Area	Hemisphere	MNI coordinates			Z-values of maxima (cluster size in number of voxels)
			x	y	z	
Insula, IFG	44/45/47	R	36	18	0	5.34 (191)
Insula, IFG	45/47	L	−33	15	6	4.76 (101)
Cingulate Cortex, SFG, MFG	6/8//32	R/L	−3	21	51	4.55 (272)
MFG, SFG	10	L	−24	48	9	3.85(44)

The Montreal Neurological Institute (MNI) coordinates of the voxel with the highest Z-value is given for each cluster along with the Z-value of the magnitude of activation and the number of voxels contained within the cluster (in parentheses). Abbreviations (see text) for each brain structure assigned using the SPM5 extension MSU.

one subject had to be excluded because of stimulus correlated motion artifacts.

Motion correction and co-registration to the anatomical images were followed by normalization using the Montreal Neurological Institute T1 template and re-sampling the images to a $2 \times 2 \times 2$ mm resolution. Afterwards images were smoothed with an 8 mm Gaussian Kernel.

In the first level statistical design the anticipation period, the exposure period and the rating period were modeled for the stimulus conditions temperature and exposure and estimated with a boxcar convolved with the hemodynamic response function by using the general linear model. Anticipation periods were modeled as events, whereas exposure periods and rating

periods were modeled as blocks with a duration of 8 and 6 s, respectively.

We calculated individual T-maps for the contrast “thermal stimulation > baseline”, “mobile phone stimulation > baseline”, “temperature anticipation > baseline” and “sham mobile phone anticipation > baseline”.

In a random-effects analysis the main effects, interaction, single group effects and group differences were assessed using a 2×2 factorial ANOVA according to the factors group (patients vs. controls) and stimulation (heat vs. mobile phone exposure). For the anticipation single group effects and group differences one and two-sample *t*-tests were used. Clusters of ≥ 10 contiguous voxels (each surpassing an individual threshold of $p < 0.001$ uncorrected) large enough to pass a cluster-wise

Table 2

Brain areas showing significant activation in the contrasts “thermal stimulation versus baseline” for the control group and the electrosensitive group ($p < 0.05$ FWE corrected, $T = 5.37$), “mobile phone exposure versus baseline” for the electrosensitive group ($p < 0.05$ FWE corrected, $T = 5.37$) and “mobile phone exposure versus baseline” in the group difference “electrosensitive > control” ($p < 0.001$ uncorrected, $T = 3.28$)

Hemisphere and Region	Brodmann Area	Hemisphere	MNI coordinates			Z-values of maxima (cluster size in number of voxels)
			x	y	z	
<i>Thermal stimulation versus baseline for the control group</i>						
IFG, Insula	44/45/47	R	36	21	3	6.89 (203)
Insula, IFG	45/47	L	−33	15	6	6.36 (123)
IFG,MFG	6/8/9/44/45	L	−57	3	42	6.45 (80)
IPL, postcentral gyrus	1/3/40/43	R	66	−21	24	6.07 (21)
MFG	8/9/10/46	R	48	30	33	5.55 (67)
IFG, MFG	8/9	R	48	3	36	5.28 (38)
Cingulate gyrus, SFG, MFG	6/8/32	R/L	6	21	48	6.62 (231)
IPL	40	R	42	−48	45	6.29 (137)
MFG	6	R	30	6	57	5.31 (61)
IPL	40	L	−48	−36	48	5.58 (10)
<i>Thermal stimulation versus baseline for the electrosensitive group</i>						
Cerebellum	N/A	L	−27	−66	−33	6.27 (16)
IFG	10/47	R	48	45	21	5.89 (25)
IPL	40	R	48	−51	48	5.21 (43)
IPL, postcentral gyrus	40	R	57	−39	48	5.49 (14)
SFG,MFG	6/8	R/L	3	15	57	6.12 (83)
Postcentral gyrus, IPL	3/40	L	−42	−30	57	5.02 (18)
<i>Mobile phone exposure versus baseline for the electrosensitive group</i>						
IFG	45/47	R	51	21	3	5.35 (203)
IFG	45/47	L	−33	27	−3	5.69 (93)
Cingulate gyrus, MFG	6/32	R	9	24	39	5.04 (9)
Cingulate gyrus, SFG, MFG	6/8/32	R/L	−3	15	57	6.94 (203)
<i>Mobile phone exposure versus baseline in the group difference electrosensitive>control</i>						
IFG; MFG	45/47	R	54	24	3	3.89 (56)
Cingulate gyrus, MFG, SFG	6/8/32	R/L	−3	21	51	4.83 (151)

threshold of $p < 0.05$ FWE corrected were considered as significant. Where applicable we used the even more conservative voxel-wise threshold of $p < 0.05$ FWE corrected and report only clusters of 9 or more voxels. Active brain areas were labeled with anatomical loci and Brodmann areas by using the SPM5 extension MSU (MNI Space Utility).

Results

All participants tolerated the experiment without any side effects. Interestingly also in the electrosensitive group, no side effects were reported despite the exposure to the 3 T high frequency magnetic field and the gradient system during imaging.

Behavioral data

All three temperature levels were rated significantly different ($p < 0.05$) in both groups (control group mean (42° , 45° , 48°) = 2.24, 2.98, 4.3, respectively; electrosensitive group mean (42° , 45° , 48°) = 2.05, 2.95, 3.41, respectively). There were no significant group differences neither for ratings of unpleasantness during sham mobile phone exposure ($p < 0.174$) or during temperature exposure ($p < 0.595$) for the whole group. As stated above, only electrosensitive subjects with a rating of ≥ 1.5 in mean under the mobile phone exposure condition were included for all further analysis ($N = 11$), which led to a significant difference between both

groups for the rating under the mobile phone exposure condition ($p < 0.021$).

fMRI data

Exposure

The main effects analysis revealed a significant interaction between the factors group and type of stimulation with an increased activation in the bilateral insula, the cingulate cortex, the inferior frontal gyrus and middle frontal gyrus ($p < 0.001$ uncorrected; Figs. 2 and 3 and Table 1). There was also increased activation in superior frontal gyrus, which did not satisfy our significance criteria. This interaction indicates that the patients responded in a more pronounced manner to the sham mobile stimulation than did the controls. The opposite contrast did not yield any significant results.

Thermal stimulation

During thermal stimulation, similar activation patterns were found in the control and the electrosensitive group. The control group revealed significant increased activation ($p < 0.05$ corrected) in the bilateral inferior frontal gyrus, middle frontal gyrus, superior frontal gyrus, inferior parietal lobe, cingulate gyrus and insula as well as right postcentral gyrus (Table 2). The subjectively electrosensitive group showed increased activation in the left cerebellum and right inferior frontal gyrus as well as bilateral inferior parietal lobe, postcentral gyrus, superior frontal gyrus and middle frontal gyrus ($p < 0.05$

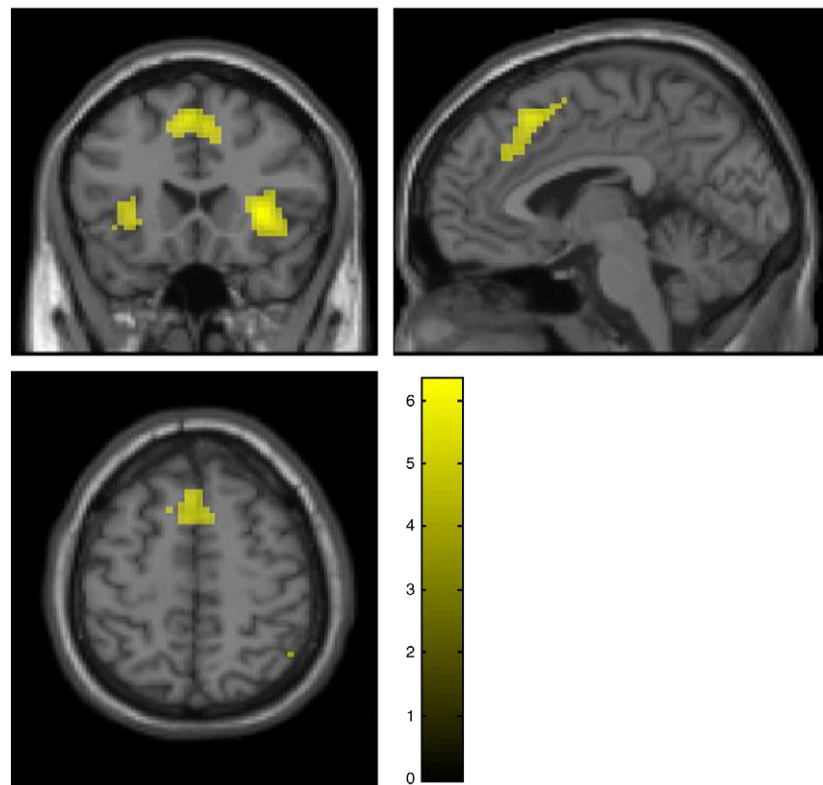


Fig. 4. Cortical activations in the electrosensitive group in the contrast “placebo mobile phone exposure versus baseline”. Significantly activated areas are found bilaterally in the inferior frontal gyrus (coordinates of peak voxel: 51, 21, 3 and -33 , 27, -3 , respectively; Z-values = 5.35 and 5.69, respectively) and the anterior insular cortex (coordinates 42, 24, -6 and -42 , 21, -6 , respectively) as well as cingulate cortex (coordinates of peak voxel: 9, 24, 39 and -3 , 15, 57, respectively; Z-values = 5.04 and 6.94, respectively; $P = 0.05$ FWE corrected, $T = 5.37$).

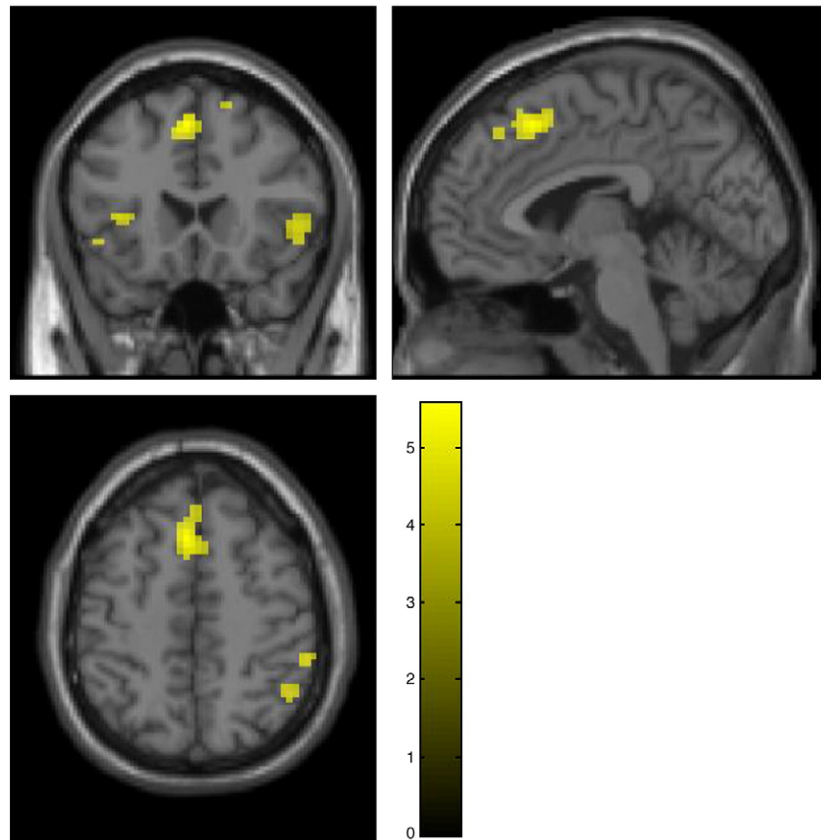


Fig. 5. Group comparison of the contrast “placebo mobile phone exposure versus baseline”. The significantly activated areas are shown in the right inferior and middle frontal gyrus (coordinates of peak voxel: 54, 24, 3; Z -value=3.89), insular cortex (coordinates: 33, 30, -3) and bilaterally in the cingulate cortex, superior and middle frontal gyrus (coordinates of peak voxel: -3, 21, 51; Z -values=4.83; $p < 0.001$ uncorrected; $T = 3.28$).

corrected; Table 2). There were no group specific differences concerning this contrast.

Sham mobile phone exposure

The contrast “sham mobile phone exposure versus baseline” led to increased activations in the subjectively electrosensitive group ($p < 0.05$ corrected; Table 2). There were significantly greater activations in the bilateral inferior frontal gyrus and anterior insular cortex, middle frontal gyrus, superior frontal gyrus and cingulate cortex (Fig. 4 and Table 2). The control group did not show any effect even if we applied a more liberal significance threshold of $p < 0.001$ uncorrected.

A group comparison for this contrast revealed that the subjectively electrosensitive group had increased activation in the right inferior frontal gyrus and anterior insular cortex and the bilateral middle frontal gyrus, superior frontal gyrus and cingulate gyrus ($p < 0.001$ uncorrected; Fig. 5 and Table 2).

Anticipation

Increased activation in the bilateral cerebellum, fusiform gyrus, middle occipital gyrus and temporal gyrus, the right inferior occipital gyrus, the inferior temporal gyrus and the superior temporal gyrus was observed in the control group during anticipation of thermal stimulation ($p < 0.001$ uncorrected; Table 3). The subjectively electrosensitive group showed enhanced activation in the bilateral cingulate gyrus, cuneus, precuneus, the right parahippocampal gyrus, supramarginal gyrus, superior temporal gyrus, inferior parietal lobe, middle occipital

gyrus, fusiform gyrus, middle and superior temporal gyrus and the right cerebellum ($p < 0.001$ uncorrected).

There was no activation during anticipation of sham mobile phone exposure in the control group. In contrast, the subjectively electrosensitive group showed increased activation in the right fusiform gyrus, inferior and middle temporal gyrus, and cerebellum ($p < 0.001$ uncorrected; Table 3).

Discussion

The aim of this study was to investigate whether (1.) activation of ACC and anterior insular cortex is related to feelings of unpleasantness induced by virtual physical stimuli and (2.) that subjectively electrosensitive patients differ from controls in the activation of these cortical areas during sham mobile phone exposure. Indeed, in subjectively electrosensitive patients but not controls, we found significant activations in bilateral ACC and lateral prefrontal cortex extending into anterior insula during sham mobile phone exposure. During the anticipation period, mainly parts of the temporal lobe including the fusiform gyrus were activated.

Increased activation of the fusiform gyrus during the anticipation period in subjectively electrosensitive patients compared to control subjects is probably due to increased processing of the cue and expectation of behaviorally relevant sensory input, which has also been found in specific phobias (Straube et al., 2006, 2007). In contrast to Wager et al. (2004), no activation of ACC or insular cortex were found during anticipation of either temperature or sham

Table 3

Brain areas showing significant activation in the contrasts “temperature anticipation versus baseline” in the control and the electrosensitive group as well as “mobile phone anticipation versus baseline” in the electrosensitive group ($p < 0.001$ uncorrected, $T = 3.85$)

Hemisphere and Region	Brodmann Area	Hemisphere	MNI coordinates			Z-values of maxima (cluster size in number of voxels)
			x	y	z	
<i>Temperature anticipation versus baseline in the control group</i>						
Cerebellum, Fusiform gyrus	19/NA	L/R	−18	−66	−24	4.5 (145)
	19/37	L	−54	−57	−3	4.08 (43)
IOG,MOG, ITG,MTG	19/37	R	57	−63	−3	4.36 (35)
MTG,STG	21/22/39	R	57	−54	6	4.54 (34)
<i>Temperature anticipation versus baseline in the electrosensitive group</i>						
Cingulate gyrus, Cuneus, Precuneus	7/19/23/29/30/31	R/L	0	−78	39	4.66 (588)
Fusiform gyrus, Parahippo-campal gyrus, MOG, Cerebellum	20/36/37	R	36	−42	−18	4.52 (129)
MTG, STG, Supramarginal gyrus, IPL	22/39/40	R	60	−54	18	4.13 (88)
<i>Mobile phone anticipation versus baseline in the electrosensitive group</i>						
	20/37	R	39	−51	−18	4.45 (92)

mobile phone exposure. However, our study has not been designed to specifically investigate anticipatory processes during pain stimulation. Rather heat stimulation was introduced as a control condition. Only one third of the thermal stimuli were painful, and therefore, the pain stimulus was probably not strong enough to induce avoidance behavior.

Another limitation of the study design, which may have contributed to the missing activation of the ACC and insular cortex during anticipation of pain may be the relatively short periods of anticipation, stimulation, rating, and resting. However, under the sham mobile phone condition, significant activations in ACC and anterior insula have been found. Furthermore, Wager et al. (2004) used similar time periods for anticipation and resting but much stronger pain stimuli. Therefore, it is likely that the missing activation under pain stimulation in our study is due to the comparatively weak pain stimulus, which has been introduced as a control condition.

Significant activations in ACC and anterior insular cortex during the exposure period have been detected in the electrosensitive group. These areas have been shown by several studies to be involved in pain perception (Koyama et al., 2005; Ploghaus et al., 1999; Wager et al., 2004), especially in conveying affective dimensions of pain like unpleasantness (Singer et al., 2004). Furthermore, the ACC has been demonstrated to be involved in the elicitation and control of sympathetic autonomic arousal (Critchley et al., 2003). Increased ACC activation may therefore be one possible explanation for alterations in autonomic function, which has been reported repeatedly in subjectively electrosensitive patients (Lyskov et al., 2001; Sandstrom et al., 1997, 2003). The anterior insula has been suggested to play a crucial role in interoception by representing internal bodily states of arousal and emotional awareness (Critchley et al., 2003, 2004). Increased insular activation has been linked to anxiety proneness (Paulus and Stein, 2006). Interestingly, cognitive assessments in subjectively electrosensitive patients have found evidence for increased rumination (e.g. ongoing thinking about possible health impacts of electromagnetic fields for themselves and others; Landgrebe et al., 2008), which may be a behavioral consequence of this anxiety proneness. Furthermore, it may be speculated, that the impaired ability of subjectively electrosensitive patients to discriminate external stimuli from internal perceptions, which seems to be a

characteristic finding in these patients (Landgrebe et al., 2007, 2008), is potentially also due to an increased awareness of internal perceptions. Finally, an altered self-representation of subjectively electrosensitive patients could further be reflected by the observed activation in Brodmann area 10, an area involved in the mediation of self-referential processing of emotional stimuli (Fossati et al., 2003).

Taken together we could demonstrate in subjectively electrosensitive patients during sham mobile phone exposure significantly altered activation in ACC and anterior insula. This activation was related to unpleasantness but not to any real physical stimulus. ACC and anterior insula have been shown to be involved in other functional somatic syndromes like multiple chemical sensitivity (Hillert et al., 2007). These areas convey various cognitive and emotional processes, which can be related to clinical key features of subjective electrohypersensitivity. Over-activation in ACC and anterior insula may be linked to dysfunctions of the autonomic system and anxiety proneness, activation of the fusiform gyrus points to increased processing of sensory cues. The extent to which these alterations in cortical function are causally involved in symptom generation in subjectively electrohypersensitivity remains unclear. However, our results fit well in the concept of development of functional somatic syndromes, where dysfunctional cognitions (e.g. rumination) and increased awareness of (physiological) bodily symptoms (“somatosensory amplification”; Barsky and Borus, 1999) play a pivotal role. Accordingly, cognitive behavioral therapeutic interventions have already been proven to be effective in these patients (Hillert et al., 1998; Rubin et al., 2006). Further studies will have to evaluate, whether such therapeutic strategies will “normalize” the observed alterations of cortical function in subjectively electrosensitive patients.

Similar cortical areas (i.e. ACC and anterior insula), which we showed to be linked to key symptoms of subjectively electrosensitive patients, seem to be also involved in anticipation of pain (Wager et al., 2004), symptom generation in multi-chemical sensitivity (Hillert et al., 2007), and specific phobias (Straube et al., 2006, 2007). Under physiological conditions, this system seems to be involved in the perception of unpleasantness of specific stimuli and in generating avoidance behavior, but conditioning may lead to dysfunctional activation, which in turn might generate symptoms in a specific context without external stimuli. Even if our data clearly

demonstrate the involvement of the mentioned cortical structures in subjective electrohypersensitivity, it is important to note that we cannot derive from our data, which mechanisms contribute to the development of the dysfunctional cortical activation patterns.

In conclusion, anticipation and expectation of sham mobile phone exposure is accompanied by increased activations in ACC, anterior insula as well as fusiform gyrus, which seems to be related to symptom generation in subjectively electrosensitive patients. We suggest, that this neural network fulfills the role of mediating avoidance behavior under physiological conditions, but in case of dysfunctional over-activation is able to generate symptoms in functional somatic syndromes, somatoform disorders or other psychiatric disorders like specific phobias.

Acknowledgments

This study was supported by a grant from the German Federal Ministry for the Environment, Nature Conservation, and Nuclear Safety (UFOPLAN project StSch 4357). fMRI-scanning was performed at the 3 Tesla scanner of the University of Regensburg supported by BayernBrain3T.

References

- Barsky, A.J., Borus, J.F., 1999. Functional somatic syndromes. *Ann. Intern. Med.* 130, 910–921.
- Craig, A.D., 2002. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat. Rev., Neurosci.* 3, 655–666.
- Critchley, H.D., Mathias, C.J., Josephs, O., O'Doherty, J., Zanini, S., Dewar, B.K., Cipolletti, L., Shallice, T., Dolan, R.J., 2003. Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. *Brain* 126, 2139–2152.
- Critchley, H.D., Wiens, S., Rotshtein, P., Ohman, A., Dolan, R.J., 2004. Neural systems supporting interoceptive awareness. *Nat. Neurosci.* 7, 189–195.
- Fossati, P., Hevenor, S.J., Graham, S.J., Grady, C., Keightley, M.L., Craik, F., Mayberg, H., 2003. In search of the emotional self: an fMRI study using positive and negative emotional words. *Am. J. Psychiatry* 160, 1938–1945.
- Hillert, L., Kolmodin, H.B., Dolling, B.F., Arnetz, B.B., 1998. Cognitive behavioural therapy for patients with electric sensitivity— a multi-disciplinary approach in a controlled study. *Psychother. Psychosom.* 67, 302–310.
- Hillert, L., Musabasic, V., Berglund, H., Ciumas, C., Savic, I., 2007. Odor processing in multiple chemical sensitivity. *Hum. Brain Mapp.* 28, 172–182.
- Koyama, T., McHaffie, J.G., Laurienti, P.J., Coghill, R.C., 2005. The subjective experience of pain: where expectations become reality. *Proc. Natl. Acad. Sci. U. S. A.* 102, 12950–12955.
- Landgrebe, M., Hauser, S., Langguth, B., Frick, U., Hajak, G., Eichhammer, P., 2007. Altered cortical excitability in subjectively electrosensitive patients: results of a pilot study. *J. Psychosom. Res.* 62, 283–288.
- Landgrebe, M., Frick, U., Hauser, S., Langguth, B., Rosner, R., Hajak, G., Eichhammer, P., 2008. Cognitive and neurobiological alterations in electromagnetic hypersensitive patients: results of a case-control study. *Psychol. Med.* 26, 1–11.
- Levallois, P., Neutra, R., Lee, G., Hristova, L., 2002. Study of self-reported hypersensitivity to electromagnetic fields in California. *Environ. Health Perspect.* 110 (Suppl 4), 619–623.
- Lyskov, E., Sandstrom, M., Hansson, M.K., 2001. Neurophysiological study of patients with perceived 'electrical hypersensitivity'. *Int. J. Psychophysiol.* 42, 233–241.
- Melzack, R., Wall, P.D., 1965. Pain mechanisms: a new theory. *Science* 150, 971–979.
- Paulus, M.P., Stein, M.B., 2006. An insular view of anxiety. *Biol. Psychiatry* 60, 383–387.
- Ploghaus, A., Tracey, I., Gati, J.S., Clare, S., Menon, R.S., Matthews, P.M., Rawlins, J.N., 1999. Dissociating pain from its anticipation in the human brain. *Science* 284, 1979–1981.
- Rubin, G.J., Das, M.J., Wessely, S., 2005. Electromagnetic hypersensitivity: a systematic review of provocation studies. *Psychosom. Med.* 67, 224–232.
- Rubin, G.J., Das, M.J., Wessely, S., 2006. A systematic review of treatments for electromagnetic hypersensitivity. *Psychother. Psychosom.* 75, 12–18.
- Sandstrom, M., Lyskov, E., Berglund, A., Medvedev, S., Mild, K.H., 1997. Neurophysiological effects of flickering light in patients with perceived electrical hypersensitivity. *J. Occup. Environ. Med.* 39, 15–22.
- Sandstrom, M., Lyskov, E., Hornsten, R., Hansson, M.K., Wiklund, U., Rask, P., Klucharev, V., Stenberg, B., Bjerle, P., 2003. Holter ECG monitoring in patients with perceived electrical hypersensitivity. *Int. J. Psychophysiol.* 49, 227–235.
- Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R.J., Frith, C.D., 2004. Empathy for pain involves the affective but not sensory components of pain. *Science* 303, 1157–1162.
- Straube, T., Mentzel, H.J., Miltner, W.H., 2006. Neural mechanisms of automatic and direct processing of phobogenic stimuli in specific phobia. *Biol. Psychiatry* 59, 162–170.
- Straube, T., Mentzel, H.J., Miltner, W.H., 2007. Waiting for spiders: brain activation during anticipatory anxiety in spider phobics. *NeuroImage* 37, 1427–1436.
- Wager, T.D., Rilling, J.K., Smith, E.E., Sokolik, A., Casey, K.L., Davidson, R.J., Kosslyn, S.M., Rose, R.M., Cohen, J.D., 2004. Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science* 303, 1162–1167.