Altered cortical excitability in subjectively electro sensitive patients: Results of a pilot study

Michael Landgrebe, Simone Hauser, Berthold Langguth, Ulrich Frick, Göran Hajak, Peter Eichhammer

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

Received 14 March 2006; received in revised form 2 November 2006; accepted 13 November 2006

Abstract

Objective: Hypersensitivity to electromagnetic fields is frequently claimed to be linked to a variety of unspecific somatic and/or neuropsychological complaints. Whereas provocation studies often failed to demonstrate a causal relationship between electromagnetic field exposure and symptom formation, neurophysiological examinations highlight baseline deviations in people claiming to be electro sensitive. Methods: To elucidate a potential role of dysfunctional cortical regulations in mediating hypersensitivity to electromagnetic fields, cortical excitability parameters were measured by transcranial magnetic stimulation in subjectively electro sensitive patients (n=23) and two control groups (n=49) differing in their level of unspecific health complaints. Results: Electro sensitive patients showed reduced intracortical facilitation as compared to both control groups, while motor thresholds and intracortical inhibition were unaffected. Conclusions: This pilot study gives additional evidence that altered central nervous system function may account for symptom manifestation in subjectively electro sensitive patients as has been postulated for several chronic multisymptom illnesses sharing a similar clustering of symptoms. © 2007 Elsevier Inc. All rights reserved.

Keywords: Chronic multisymptom illnesses; Electromagnetic hypersensitivity; Intracortical facilitation; Transcranial magnetic stimulation

Introduction

Hypersensitivity to electromagnetic fields as an alleged cause of many unspecific somatic and/or neuropsychological complaints of patients is very common in western communities, with an assumed prevalence of up to 3% [1,2]. However, a clear definition of “electromagnetic hypersensitivity” and its diagnostic criteria is lacking so far [3]. The initial symptoms recognized in association with exposure to electromagnetic fields were dermatologic in nature, such as itching, burning, and various kinds of dermatoses frequently found on the face. This prior symptom constellation extended to a so-called “general syndrome” [4], including neurasthenic and/or somatic symptoms, such as dizziness, fatigue, headache, difficulties in breathing, or palpitations. Despite accumulating experience, a clear relationship between exposure to electromagnetic fields and these symptoms has not yet been established, and a majority of published provocation studies failed to demonstrate this relationship [5–8]. Due to these findings, symptom generation in these patients may be rather based on dysfunctional attributions of somatic symptoms to electromagnetic field exposure than to the exposure itself. The symptoms of subjectively electro sensitive patients are unspecific and overlap with many other syndromes of environmental intolerance, such as multiple chemical sensitivity or sick building syndrome [9,10], suggesting that hypersensitivity to electromagnetic fields should be considered as a form of a more general diagnostic entity labeled as chronic multisymptom illnesses (CMI) [11]. Despite serious scientific problems in definition

* Corresponding author. Department of Psychiatry, Psychosomatics, and Psychotherapy, University of Regensburg, Universitätsstrasse 84, 93053 Regensburg, Germany. Tel.: +49 941 941 2056; fax: +49 941 941 2075. E-mail address: peter.eichhammer@medbo.de (P. Eichhammer).

0022-3999/07/$ – see front matter © 2007 Elsevier Inc. All rights reserved. doi:10.1016/j.jpsychores.2006.11.007
and diagnostic criteria, the social impact of these illnesses is considerable, taking into account their high prevalence [1,2,4] and typical course, often ending in disablement [12]. Aggregated research concerning the pathophysiology of CMI has suggested that an aberrant function of centrally mediated processes may play a significant role in initiating and/or perpetuating symptoms [13]. In line with these findings, a growing body of literature reports imbalances in nervous system functions in patients with perceived electrical hypersensitivity [14–16]. To further address this issue, we used transcranial magnetic stimulation (TMS) to measure different parameters of cortical excitability (e.g., resting and active motor threshold, intracortical inhibition, and intracortical facilitation) [17] in patients claiming to be hypersensitive to electromagnetic fields. These parameters are assumed to reflect the integrity of distinct interneuronal circuits [18] and have proven to be sensitive to the detection of dysfunctional cortical regulation associated with different neuropsychiatric diseases or personality traits [19–21]. Here, we investigated whether electro sensitive patients display altered cortical excitability as compared to population controls, indicating a potential contribution of centrally mediated dysfunctional processes to symptom formation.

Materials and methods

Parameters of cortical excitability were measured in a group of people who claim themselves to be sensitive to electromagnetic fields (subjectively electrosensitive patients; \( n=23 \)) and compared to those of two control groups from a representative sample of the general population in the city of Regensburg. To recruit subjectively electrosensitive patients, an article was published in a local Regensburg newspaper reporting on the study and its objectives. People who perceived themselves as electro sensitive after reading this article were invited to participate in the study. Inclusion criteria for patients with subjective electrosensitivity were as follows: age between 18 and 64 years and articulation of serious complaints limiting activities of daily living. Complaints were subjectively interpreted as caused by explicitly named sources of electromagnetic fields (e.g., mobile phone base stations, TV towers, etc.).

Cortical excitability parameters were measured subsequent to initial determination of individual subjective perception levels using magnetic stimuli [22]. For various reasons (e.g., refusal to give informed consent), not all probands participated in the subsequent determination of cortical excitability. Therefore, study groups are slightly smaller in the present study than in a previously published perception experiment [22].

Population controls were recruited according to their level of unspecific health complaints, which they had reported during a prior health survey [23]. In order to maximize differences in the complaint level of the two control groups, they were measured on a Rasch conform list of 36 unspecific health symptoms, which all had been alleged in the literature to be potentially related to electromagnetic field exposure. The most frequently reported symptoms encompassed fatigue, daytime sleepiness, headache, problems in concentrating, and neck pain. Latent class and latent trait analyses revealed that all symptoms, despite their heterogeneity concerning affected organ systems, measured all the same latent psychological traits [24]. Complaint scores range from 0 (no complaints at all) to a theoretical maximum of 108 (all 36 symptoms experienced in maximum intensity). One control group stemmed from the upper decile of that sample displaying a high symptom load (high complaint level; \( n=23 \)), whereas the second control group stemmed from the lowest decile with virtually no complaints (low complaint level; \( n=26 \); for details in study group recruitment and for a complete list of unspecific health complaints, see Frick et al. [22]). Mean scores in Table 1 reflect the prevalence of symptoms during the last 7 days prior to paired-pulse experiment.

Two population control groups with maximized differences concerning their levels of health complaints were chosen in order to gain maximum statistical power for potential differences in variables causing these

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic characteristics and cortical excitability parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subjectively electrosensitive patients (( n=23 ))</td>
</tr>
<tr>
<td>Age (years)</td>
<td>41.3±12.1</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>6/17</td>
</tr>
<tr>
<td>Major depression</td>
<td>1/23</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>1/23</td>
</tr>
<tr>
<td>Somatoform disorder (SOMS)</td>
<td>0</td>
</tr>
<tr>
<td>Complaint score (last 7 days)</td>
<td>10.9 (7.7)</td>
</tr>
<tr>
<td>ISI (ms)</td>
<td>Male (( n=6 )) Female (( n=17 )) Male (( n=5 )) Female (( n=18 )) Male (( n=20 )) Female (( n=6 ))</td>
</tr>
<tr>
<td>2</td>
<td>0.62±0.3</td>
</tr>
<tr>
<td>6</td>
<td>1.10±0.2</td>
</tr>
<tr>
<td>15</td>
<td>1.10±0.2</td>
</tr>
</tbody>
</table>

Demographic characteristics of subjectively electrosensitive patients and control groups, as well as parameters of cortical excitability, comorbidity rates, and Rasch scores of health complaints. Data are presented as mean±S.D.
health complaints (e.g., degree of electrosensitivity) and to minimize potential confounding factors due to the selection of an artificially “healthy” sample [25]. In order to differentiate electrosensitivity from somatoform disorders, the German standardized interview Screening für somatoforme Störungen (SOMS; screening for somatoform disorders) [26], a validated self-questionnaire, was applied. Major depression and anxiety disorders were assessed with the Composite International Diagnostic Interview, Short Form (CIDI-SF) [27]. The study was approved by the local ethics committee. Written informed consent was obtained from all participants.

Experimental procedure

Resting and active motor thresholds representing parameters of cortical excitability were measured by TMS, according to Rossini et al. [28]. In detail, this procedure was performed using two Magstim 200 stimulators (Magstim Co., Whiteland, Dyfed, UK) connected via a Bistim module to a figure-of-eight coil (a double-circular 70-mm coil). The coil was held in optimal position (i.e., with the junction of two wings tangential to the skull and with the handle pointing backwards and ~45° away from the midline). Thus, induced current in the brain was directed about perpendicular to the assumed line of the central sulcus. We recorded motor-evoked potentials (MEPs) from the right abductor digiti minimi at rest using surface electrodes in a belly-tendon montage (filters, 20 Hz–10 kHz; A/D rate, 5 kHz). MEP amplitudes were measured peak to peak. Fifty milliseconds of prestimulus electromyogram (EMG) were recorded to assess muscle relaxation. With a slightly suprathreshold stimulus intensity, the optimal position for eliciting maximal amplitude MEPs was determined and marked to ensure constant coil placement throughout the experiment.

Reducing the stimulus intensity in steps of 1%, we defined resting motor threshold as the lowest intensity at which at least 5 of 10 consecutive MEPs were ≥50 μV in amplitude while the investigated muscle was at rest. Audiovisual electromyographic feedback was provided to control for muscle relaxation. Active motor threshold was determined as the lowest stimulation intensity that evoked an MEP≥250 μV during voluntary abduction of the small finger in at least 5 of 10 consecutive trials. A constant level of voluntary contraction was maintained by audiovisual feedback of EMG activity. Intracortical inhibition and facilitation were measured with a paired-pulse TMS protocol [17]. The intensity of the first (conditioning) stimulus was 10% below the active motor threshold. The second (test) stimulus was delivered at an intensity that produced MEPs of about 1 mV in the resting adductor digiti minimi muscle. Interstimulus intervals (ISIs) of 1–5 ms allow to measure aspects of intracortical inhibition, while ISIs of 7–30 ms allow to determine aspects of intracortical facilitation. Here, we used ISIs of 2, 6, and 15 ms, with each interval at least 10 times in random order. The interval between sweeps was 4 s. The effect of conditioning stimuli on MEP amplitude at each ISI was determined as the ratio of the average amplitude of conditioned MEP (cMEP) to the average amplitude of unconditioned test MEP (MEP) for each 10-trial block. MEPs were digitally recorded and analyzed with the program Vision Analyzer (Brain Products, Germany).

Statistical analysis

Statistical analyses of recorded MEP ratios were performed by an analysis of covariance model using two between-subjects factors (gender with two levels; group membership with three levels: subjectively electrosensitive patients, controls with low complaint level, and controls with high complaint level) and a within-subject factor for the three ISI times. Additionally, a contrast analysis comparing the subjectively electrosensitive group to the pooled low-complaint-level and high-complaint-level groups (population controls) was planned a priori. Gender was introduced as a between-subjects factor in order to control for uneven gender distribution over comparison groups (with males dominating the low-complaint-level group). Due to the exploratory character of this study, P values are given without adjustment for multiple testing. Calculations were performed with SAS module PROC GLM.

Results

All participants tolerated the study without any side effects. Demographic characteristics of the study population, as well as TMS parameters and Rasch scores of health complaints, are shown in Table 1. Among the low-complaint-level control group, no psychiatric comorbidity could be observed. From the high-complaint-level control group, 12 subjects fulfilled the criteria for major depression according to the criteria of the WHO CIDI-SF [27]. With regard to the subjectively electrosensitive group, one subject qualified for generalized anxiety disorder and major depression according to the criteria of the WHO CIDI-SF [27].

Average resting and active motor thresholds did not show significant differences between the three study groups, as has been reported elsewhere [22]. With regard to measures of intracortical inhibition, mean levels of inhibition and facilitation were found to be very similar at ISI times of 2 and 6 ms over all three groups. All three groups displayed the typical gradient of increasing facilitation with prolonged ISI intervals. But at an ISI time of 15 ms, there was significantly reduced facilitation, especially for the group of subjectively electrosensitive patients (Group × ISI Time interaction: F=2.48; df=4, 128; P=.047; Table 1 and Fig. 1). Further comparison of this effect by means of a t test contrasting the high-complaint-level group plus the low-complaint-level
Comparing patients with two distinct control groups differing in their levels of unspecific health complaints is thought to minimize potential sources of sampling bias due to a rigorous screening process focusing on artificially “healthy” control samples [21,25].

Aspects of cortical excitability are reflected by distinct electrophysiological parameters, such as motor threshold, intracortical inhibition, or intracortical facilitation. Each of these parameters can be attributed to different neuronal circuits and neurotransmitter systems and is modulated in a distinct way by various neuropsychiatric diseases [19,20]. Here we exclusively found changes in intracortical facilitation in subjectively electrosensitive patients, while all other measured parameters of cortical excitability were unaffected. Intracortical facilitation reflects the involvement of intracortical mechanisms and can be modulated by a variety of central-acting agents affecting distinct neurotransmitter systems, preferentially including glutamatergic ones [30,31]. Accumulating data based on a growing body of literature suggest that increase in intracortical facilitation may be associated with an increase in neuroplasticity, whereas lower neuronal excitability as reflected by reduced intracortical facilitation results in attenuation of neuroplastic changes and adaptation abilities [32,33]. Due to these findings, it is tempting to hypothesize that diminished intracortical facilitation, as demonstrated in our sample of subjectively electrosensitive patients, may reflect dysfunctional cortical regulation related to a deficiency in adaptive resources, which might account for a higher vulnerability of these patients to environmental influences. In line with our findings, predisposition to environmental maladaptation has been postulated by several studies as a characteristic feature of subjectively electrosensitive patients [14–16]. Part of this centrally mediated predisposition, as indicated by our TMS measures, might also contribute to an impaired ability of subjectively electrosensitive patients to discriminate exteroceptive sensory inputs from internal perceptions, finally leading to false-positive results in perception experiments [22]. Based on our results, we cannot postulate a causal relationship between alterations of cortical excitability (i.e., reduced intracortical facilitation) and symptom formation. However, considering that our neurobiological findings suggest attenuation of neuroplastic changes and adaptation, these data may indicate a neurobiological predisposition to higher vulnerability for environmental influences. In analogy to current neurobiological conceptualizations with regard to the pathophysiology of somatoform pain symptoms [34], neurobiological predisposition, together with miscellaneous intrapersonal and external factors, may contribute to symptom formation in electrosensitive patients. Assuming that reduced adaptive capacities may play a pivotal role in electrosensitivity, as suggested by our neurophysiological data, cognitive–behavioral therapy may increase the amount of adaptive resources, thus enabling

Discussion

To the best of our knowledge, the results of this study give initial evidence that subjectively electrosensitive patients differ from the general population in terms of their cortical excitability parameters. In detail, the main finding is that patients with perceived electromagnetic hypersensitivity displayed an altered cortical excitability indexed by a significantly reduced intracortical facilitation as compared to two control groups, while all other measured parameters of cortical excitability (i.e., resting and active motor threshold, intracortical inhibition) remained unaffected. Group with the subjectively electrosensitive group revealed that the ISI time of 15 ms remained statistically significant, resulting in a t value of 2.38 (df=70; P=.0255). Statistical differences were more pronounced between the high-complaint-level group and the subjectively electrosensitive group than between the low-complaint-level group and the subjectively electrosensitive group.

Gender did not directly influence intracortical excitability but could be shown to interact with group membership (interaction: F=6.54; df=1, 64; P=.003). In the low-complaint-level group and the subjectively electrosensitive group, both genders displayed a very similar gradient of their ISI Time × Facilitation Gradient, but in the high-complaint-level group, this gradient differed somewhat between males and females. As this effect was not a priori in the center of our study design and might be associated with gender-specific illnesses causing the high-complaint-level in this special group, it will not be further discussed and will only be regarded as a statistical adjustment procedure to control for gender-specific influences on the diminished facilitation observed in subjectively electrosensitive patients.
patients to better deal with environmental stressors. This hypothesis is in line with findings demonstrating that cognitive–behavioral therapy leads to substantial clinical improvement in these patients [35–37].

Moreover, we do not know whether changes in cortical excitability reflect a genuine unspecific dysfunctional processing that is potentially associated with diminished adaptive capacities or reflect a specific vulnerability to the exposition of electromagnetic fields produced by devices such as mobile phones. This issue should be addressed in further studies investigating whether cortical excitability is differently modulated by electromagnetic field exposure in subjectively electrosensitive patients as compared to healthy controls. Interestingly, electromagnetic field exposure has recently been shown to modulate cortical excitability in healthy volunteers as measured by TMS [38].

Previous studies demonstrated that cortical excitability, as detected by TMS, correlates with cortical regulation and specific behavioral traits [21]. In line with these findings, our results suggest that subjectively electrosensitive patients are characterized by a distinct neurophysiological pattern, which is quite different from that of subjects with anxiety-related personality traits [21]. Additional support for this finding comes from recent studies demonstrating that diseases primarily related to CMI and probably encompassing syndromes such as subjective electrosensitivity only show a modest link to classical psychiatric disorders [11]. With regard to our study, only two subjects fulfilled the criteria of major depression or anxiety disorder, strongly suggesting that alterations in cortical excitability in subjectively electrosensitive patients do not result from the additive presence of psychiatric diseases. These findings further point to the limits of clinically and phenomenologically based classification strategies in recruiting homogeneous samples of subjectively electrosensitive patients and may also explain why most provocation studies failed to demonstrate any consistent results (for recent reviews, see Rubin et al. [8] and Seitz et al. [39]).

Nevertheless, the results of our study have still to be interpreted with caution since the sample size is limited and, as a consequence, the potential effect size might not be estimated very precisely. Potential confounding effects of gender differences between study groups have been adjusted for in the analysis of variance model. However, to overcome aforementioned limitations, replication in a larger sample is necessary in order to confirm these preliminary results. Moreover, in future studies, functional imaging may help to visualize our neurophysiological data and may contribute to further investigation of which specific brain areas are engaged in mediating vulnerability to electromagnetic fields.

Taken together, our study gives further evidence that TMS is a useful tool to elucidate alterations in cortical processing underlying different diseases and behavioral traits. In this context, we could demonstrate for the first time that subjectively electrosensitive patients display changes of centrally mediated processes indicated by reduced intracortical facilitation, which may contribute to symptom manifestation.

References