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

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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.

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 cingulated 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.

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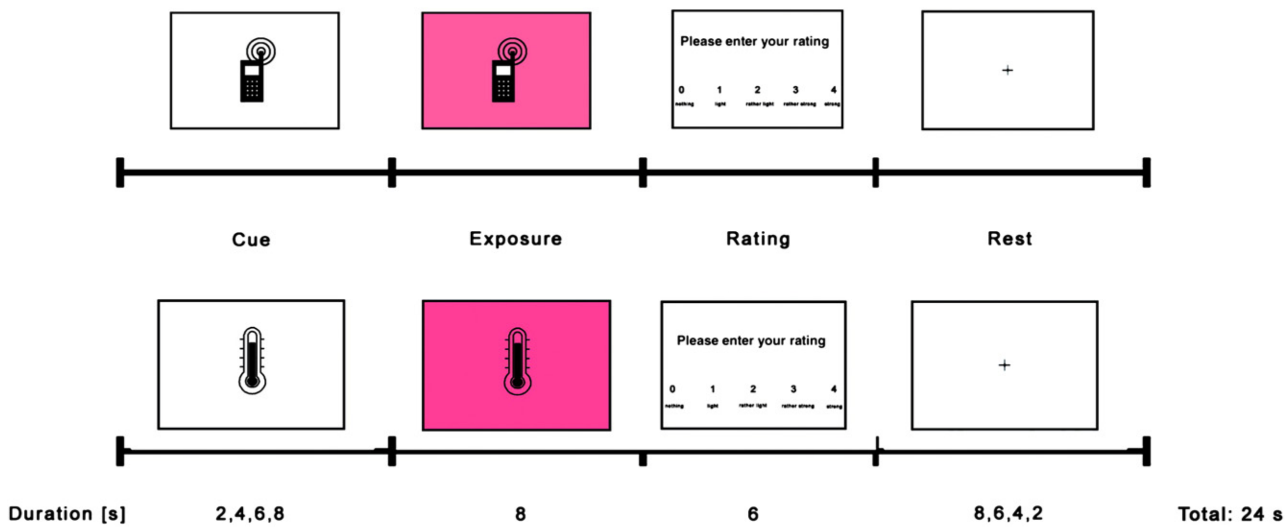

Fig. 1. Schematic trial diagram. Periods of anticipation and resting lasted 2 to 8 s in a pseudo-randomized manner. Stimulation and rating lasted 8 and 6 s, respectively. Each consecutive condition was announced by a symbol (cartoon of a thermometer or mobile phone). During the anticipation period, the 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 electrohypersensitivity (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 Word 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