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Brain oscillations differentially encode noxious stimulus intensity and pain intensity

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ABSTRACT

Noxious stimuli induce physiological processes which commonly translate into pain. However, under certain conditions, pain intensity can substantially dissociate from stimulus intensity, e.g. during longer-lasting pain in chronic pain syndromes. How stimulus intensity and pain intensity are differentially represented in the human brain is, however, not yet fully understood. We therefore used electroencephalography (EEG) to investigate the cerebral representation of noxious stimulus intensity and pain intensity during 10 min of painful heat stimulation in 39 healthy human participants. Time courses of objective stimulus intensity and subjective pain ratings indicated a dissociation of both measures. EEG data showed that stimulus intensity was encoded by decreases of neuronal oscillations at alpha and beta frequencies in sensorimotor areas. In contrast, pain intensity was encoded by gamma oscillations in the medial prefrontal cortex. Contrasting right versus left hand stimulation revealed that the encoding of stimulus intensity in contralateral sensorimotor areas depended on the stimulation side. In contrast, a conjunction analysis of right and left hand stimulation revealed that the encoding of pain in the medial prefrontal cortex was independent of the side of stimulation. Thus, the translation of noxious stimulus intensity into pain is associated with a change from a spatially specific representation of stimulus intensity by alpha and beta oscillations in sensorimotor areas to a spatially independent representation of pain by gamma oscillations in brain areas related to cognitive and affective-motivational processes. These findings extend the understanding of the brain mechanisms of nociception and pain and their dissociations during longer-lasting pain as a key symptom of chronic pain syndromes.

Introduction

Noxious stimuli induce physiological processes which commonly translate into the perception of pain (Adair et al., 1968; Price, 1999; Stevens, 1957). However, the translation of noxious stimuli into pain can vary substantially (Baliki and Apkarian, 2015). In particular, in chronic pain, the relationship between pain and noxious stimuli is often loose (Baliki and Apkarian, 2015). Such dissociations, however, occur not only in chronic pain but can also be observed in healthy human participants during a few minutes of experimental painful stimulation (Schulz et al., 2015), which offers the opportunity to gain experimental insights into the differential representation of noxious stimulus intensity and pain intensity in the human brain.

In the brain, noxious stimuli activate an extended network of brain areas including somatosensory, insular, cingulate and prefrontal cortices as well as subcortical and brainstem areas (Apkarian et al., 2005; Tracey and Mantyh, 2007). The activity of many of these brain areas correlates with both stimulus intensity and pain intensity (Coghill et al., 1999; Derbyshire et al., 1997; Loggia et al., 2012; Porro et al., 1998). Moreover, neurophysiological recordings disclosed that these brain areas yield neuronal responses at different frequencies ranging from theta (4–7 Hz) via alpha (8–13 Hz) and beta (14–29 Hz) to gamma (30–100 Hz) frequencies (Gross et al., 2007; Hauck et al., 2007; Mouraux et al., 2003; Ploner et al., 2006; Zhang et al., 2012). The amplitudes of these responses also co-vary with stimulus intensity and pain intensity (Gross et al., 2007; Schulz et al., 2011; Tiemann et al., 2015; Timmermann et al., 2001; Zhang et al., 2012). However, how these brain areas and brain responses differentially relate to stimulus intensity and pain intensity is not fully clear yet. Comparatively few studies explicitly distinguished between brain responses related to noxious stimulus intensity and pain. Although the results were not fully consistent, they showed that somatosensory

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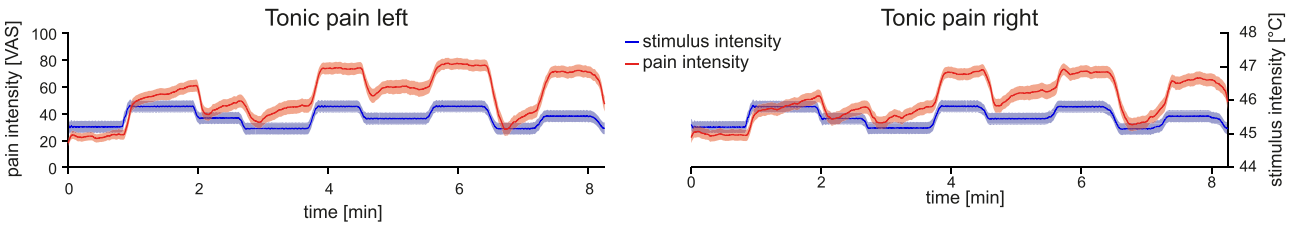

Fig. 1. Time courses of stimulus intensity and pain intensity. Group mean time courses of stimulus intensity and pain intensity during *tonic pain left* and *tonic pain right* conditions. The blue and red shaded areas depict the standard error of the mean. VAS, visual analogue scale. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

cortices were more closely related to stimulus intensity whereas insular, cingulate and prefrontal cortices and their subdivisions were related to both stimulus intensity and pain intensity (Atlas et al., 2014; Baliki et al., 2009; Bornhovd et al., 2002; Buchel et al., 2002; Kong et al., 2006; Moulton et al., 2012). In addition, neurophysiological studies demonstrated that under some (Gross et al., 2007; Zhang et al., 2012) but not all (Tiemann et al., 2015) conditions, neuronal oscillations at gamma frequencies are more closely related to pain than responses at other frequencies. Most recently, we showed that a substantial dissociation of stimulus intensity and pain intensity can already be observed during 10 min of tonic painful heat stimulation (Schulz et al., 2015). Stimulus intensity was encoded by beta oscillations over sensorimotor cortex whereas pain intensity was encoded by gamma oscillations over the medial prefrontal cortex. However, the spatial specificity of the encoding of stimulus intensity and pain intensity, i.e. whether the representations of stimulus intensity and pain intensity depend on the location of the stimulus, has remained unclear.

To investigate the spatial specificity of the encoding of stimulus intensity and pain intensity, we applied painful tonic heat stimuli to the right and left hand of 39 healthy human participants. Concurrently, the participants provided continuous pain ratings and brain activity was recorded using electroencephalography (EEG). The results of linear mixed model analyses in source space show that stimulus intensity is stimulus location-dependently encoded by alpha and beta oscillations in sensorimotor areas contralateral to the stimulated hand whereas pain is encoded by gamma oscillations in the medial prefrontal cortex independent of stimulus location.

Materials and methods

Subjects

51 healthy human participants (age 24.7 ± 5.6 years (mean ± standard deviation), 24 female) participated in the experiment. All subjects were right-handed and gave written informed consent. Due to technical issues with the stimulation device, we had to exclude data sets of 12 subjects from further analysis. Thus, 39 participants (age 24.3 ± 5.6 years, 18 female) were included in the final analysis. Participants were screened for depression (Beck Depression Inventory II (Beck et al., 1996), 5.3 ± 4.3) and trait anxiety (State-Trait-Anxiety Inventory (Spielberger et al., 1983), female 33.6 ± 3.9, male 39.0 ± 8.0) to ensure that these traits were in the range of healthy subjects. Interviews confirmed that they did not suffer from neurological or psychiatric disorders or chronic pain and that they did not take any medication including analgesic drugs. The study was approved by the ethics committee of the Medical Faculty of the Technische Universität München and conducted in conformity with the declaration of Helsinki.

Paradigm

The subjects participated in two *tonic pain* conditions and two *visual control* conditions. In the two *tonic pain* conditions, painful heat stimuli with a duration of 10 min were applied to the dorsum of the left (*tonic pain left*) or the right hand (*tonic pain right*), respectively. Apart from the side of stimulation, the two tonic pain conditions were identical. In both conditions, the subjects were instructed to continuously rate the perceived pain intensity on a visual analogue scale (VAS) ranging from 0 to 100 anchored at *no pain* and *worst tolerable pain* using a custom-built finger-span device with the non-stimulated hand. The scale was simultaneously presented on a screen by a vertical red bar, the length of which represented the current pain intensity rating.

Painful heat stimuli were applied using a thermode (TSA-II, Medoc, Ramat Yishai, Israel). The time course of stimulation was similar for all subjects but the stimulus intensities were individually adjusted. Stimulus intensity was varied between three temperature levels (low, medium, high) of 0.5, 0.8 or 1.1 °C above an individually defined pain threshold temperature (see below). Thus, the stimulation continuously elicited sensations above pain threshold. In contrast to our previous study (Schulz et al., 2015) in which stimulus intensity was continuously adapted depending on the pain rating, the time course of stimulation was a priori defined in the present study. The three levels were applied using a sequence of 9 plateaus (Fig. 1) with 3 plateaus at each intensity. At each stimulus intensity, one plateau with a duration of 40, 50 and 60 s each was applied. The order of plateaus was pseudorandomized with the constraints that consecutive plateaus had differing stimulus intensities and that the sequence consisted of three consecutive triplets of low, medium and high stimulus intensities. The stimulation started at a baseline temperature of 40 °C, changes of stimulus intensity were implemented with a rate of 0.1 °C/s. Since stimulus intensities were individually adjusted, the time from the start of stimulation until the first plateau slightly varied between subjects. After the last plateau, the stimulus intensity decreased to the low intensity and stayed constant until the 10 min elapsed. The interval between the start of the first plateau and the end of the last decrease of stimulus intensity was included in the analysis resulting in an 8.2 min time window for analysis. Before the first tonic pain condition, individual pain threshold temperatures were determined. Over the course of 3 min, subjects were asked to adapt the stimulus intensity to their individual pain threshold using two keys of a keyboard to change the stimulus intensity with a rate of 0.5 °C/s. The pain threshold was defined as the average stimulus intensity during the last 10 s. The hand for which the threshold was determined was counterbalanced across subjects and the same threshold was then used to determine stimulation intensities for both hands.

To control for the sensory, motor and attentional components of the continuous pain rating procedure, we performed two *visual control* conditions (Baliki et al., 2006; Hashmi et al., 2013). In these two conditions, the temporally inverted time courses of the individual *tonic pain left* and *tonic pain right* ratings were visually presented as changes of the length of the vertical red bar over time. Subjects were instructed to continuously follow the length of the red bar using the finger-span device controlled by the right and the left hand, respectively. In both conditions, the thermode remained attached to the other hand at a neutral stimulus intensity of 32 °C.

The order of the *tonic pain left* and *tonic pain right* conditions was counterbalanced across subjects. The *tonic pain* conditions always preceded the respective *visual control* conditions. Stimulus presenta-