Subjective pain perception mediated by alpha rhythms

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Abstract

Suppression of spontaneous alpha oscillatory activities, interpreted as cortical excitability, was observed in response to both transient and tonic painful stimuli. The changes of alpha rhythms induced by pain could be modulated by painful sensory inputs, experimental tasks, and top-down cognitive regulations such as attention. The temporal and spatial characteristics, as well as neural functions of pain induced alpha responses, depend much on how these factors contribute to the observed alpha event-related desynchronization/synchronization (ERD/ERS). How sensory-, task-, and cognitive- related changes of alpha oscillatory activities interact in pain perception process is reviewed in the current study, and the following conclusions were made: (1) the functional inhibition hypothesis that has been proposed in auditory and visual modalities could be applied also in pain modality; (2) the neural functions of pain induced alpha ERD/ERS were highly dependent on the cortical regions where it was observed, e.g., somatosensory cortex alpha ERD/ERS in pain perception for painful stimulus processing; (3) the attention modulation of pain perception, i.e., influences on the sensory and affective dimensions of pain experience, could be mediated by changes of alpha rhythms. Finally, we proposed a model regarding the determinants of pain related alpha oscillatory activity, i.e., sensory-discriminative, affective-motivational, and cognitive-modulative aspects of pain experience, would affect and determine pain related alpha oscillatory activities in an integrated way within the distributed alpha system.

Introduction

Pain is defined as a subjective unpleasant sensation associated with injuries or potential injuries (Chen, 2001). It implies that pain sensation is a multi-dimensional experience, e.g., sensory-discriminative experience involves sensations with qualities (e.g., stinging, burning or aching), identifiable locations, and durations, while affective-motivational experience involves the emotional unpleasantness that motivates the individuals to engage in a behavior to avoid further damages. The sensory and affective dimensions of pain experience are normally examined using the pain scales measuring subjective pain intensity ("how intense is the pain?") and unpleasantness ("how much does the pain bother you?"), respectively. Human brain imaging studies using functional magnetic resonance imaging (fMRI), Electroencephalographic (EEG) and magnetoencephalographic (MEG) have revealed consistent brain areas involved in painful stimuli processing, including the primary somatosensory cortex (SI), secondary somatosensory cortex (SII), anterior cingulate cortex (ACC), insula, prefrontal cortex (PFC), thalamus, and cerebellum (Bromm and Chen, 1995; Chen, 2001; Garcia-Larrea et al., 2003; Legrain et al., 2011; Schnitzler and Ploner, 2000b; Wiech et al., 2008). As expected, the multiple pain-related brain areas/pathways are important for different aspects of the pain experience.

It was suggested that the somatosensory cortices (SI and SII) contribute more to encoding information about sensory features (e.g., qualities, durations, and locations) (Hofbauer et al., 2001), whereas ACC and insula are more important for encoding information regarding emotional and motivational aspects of pain (Price, 2000; Rainville et al., 1997). Patients with ACC surgically removed could still feel the intensity of pain, but were no longer bothered by it (Foltz and White, 1962), whereas a patient with somatosensory cortex removed could still report pain distress despite difficulties in reporting sensory aspects of pain (Ploner et al., 1999). However, it did not indicate that these structures worked independently in encoding different

aspects of pain. Somatosensory cortex, ACC, and insula are highly interactive, which could even be supported by their anatomical connections as well as the experience of pain itself (Rainville et al., 1997). The unpleasantness of pain experience is highly influenced by the sensory features, e.g., the more unpleasantness the subjects feel with higher intensity of the stimulus. Nevertheless, despite of these associations, a partial segregation of sensory and affective aspects appears to exist, e.g., ACC and insula activities are possibly reflecting more about affective aspects of pain experience that provokes individuals to make efficient reactions (Geisser et al., 1994; Price, 2000).

Top-down cognitive and emotional factors, such as anticipation, attention, hypnosis, and placebos, could exert control over pain experience (e.g., sensory-discrimination and affective-motivation) and its neural substrate (Legrain et al., 2009; Schnitzler and Ploner, 2000a; Wiech et al., 2008). These cognitive activities, in part at least, by neocortical processes, may affect both sensory and affective experience, or they may modify primarily the affective-motivational dimension of pain perception. For example, both discriminative-sensory and affective-motivational dimensions were blocked when involving in excitement of games (Melzack and Casey, 1968), while hypnosis suggestions or placebos analgesia may only modulate motivational-affective dimension and leave the sensory-discriminative dimension relatively undisturbed (Rainville et al., 1999). Thus, more comprehensively, as revealed by Figure 1, the pain system involves sensory-discriminative, affective-motivational, and evaluative-cognitive sub-systems. Three pain circuits interact with each other, and especially cognitive functions are able to act selectively on sensory processing or motivational mechanisms.

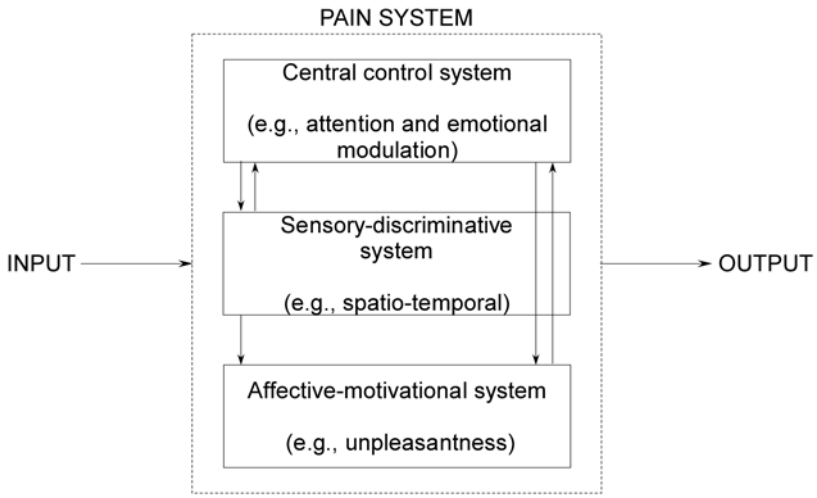

Figure.1 Pain perception determinants comprised of sensory-discriminative, affective-motivational, and evaluative-cognitive modulations. Sensory- and affective-related information flows to central control system for high-level recognition, and the cognitive modulation system could exert top-down manipulation over sensory- and affective- circuits of pain perception. Also note that the affective dimension of pain perception could be highly affected by sensory information of the painful sensory inputs.

Multi-dimensional pain sensations were composed of sensory, affective, and cognitive experiences, could modulate the ongoing EEG oscillation across wide frequency bands, reflecting the mechanisms involved in cortical activation, inhibition, and probably bindings (Gross et al., 2007; Mouraux et al., 2003; Ploner et al., 2006b; Zhang et al., 2012), appeared as event-related desynchronization/synchronization (ERD/ERS). Specifically, the change of oscillatory activity within alpha frequency band is the reflection of an oscillatory mechanism that uses the modulation of 10 Hz oscillations to inhibit (alpha ERS) via neural networks or to release that inhibition (alpha ERD) in those networks (Jensen and Mazaheri, 2010; Palva and Palva, 2007). That inhibition/excitation is associated with parallel mechanisms of oscillatory bindings at higher/lower frequencies of those networks. Then, how could the different aspects of pain experience be reflected as changes of alpha oscillations?

And how could we identify the neural functions of pain induced changes of alpha activity? Thus, we firstly conduct a review about pain related alpha activities in previous studies, and then propose a model regarding the determinants of pain related changes of alpha oscillations.

Functional inhibition hypothesis could be applied on pain related alpha rhythms

As described by Hans Berger in the 1920s (Berger, 1929), alpha rhythmic activity within the frequency band of 8-14 Hz is the strongest electrophysiological signals measured from the surface of awake human brain. High levels of alpha activity were previously interpreted as cortical idling, since alpha activity increases in brain areas that are not engaged in a task. Recent accumulated evidence showed to be against the idling hypothesis, and proposed that alpha oscillatory activity could reflect sensory gating mechanism by inhibition of task-irrelevant areas and activation of task-relevant regions (Foxe and Snyder, 2011; Jensen et al., 2012; Jensen and Mazaheri, 2010; Schurmann and Basar, 2001). The spontaneous alpha oscillatory activity within occipital cortex is negatively correlated with the fMRI-blood oxygen level dependent signal, providing the direct evidence of the association between alpha activity and metabolic deactivation (Romei et al., 2008). The lower amplitude of alpha oscillatory activity is associated with the better information transfer through thalamocortical and cortico-cortical pathways (Pfurtscheller and da Silva, 1999). In particular, optimal task performance requires effective inhibition of task-irrelevant areas, which is reflected as high-level alpha oscillatory activity for a better resource allocation to the task-relevant areas (Ergenoglu et al., 2004; Foxe and Snyder, 2011; Jensen and Mazaheri, 2010; Rainville et al., 1999). Currently, alpha rhythm has been physiologically considered to reflect local cortical excitability, with lower amplitude for greater excitability (Fox and Raichle, 2007; Jensen and Mazaheri, 2010; Pfurtscheller and da Silva, 1999). However, it should be noted that such alpha inhibition hypothesis is mainly based on the evidence of alpha rhythms observed in

auditory and visual modalities.

Recent neurophysiological studies (Iannetti et al., 2008; Mouraux et al., 2003; Ploner et al., 2006b; Raij et al., 2004; Stancak, 2006) investigated the effects of transient painful stimulus on spontaneous alpha rhythms, and reported global suppression of alpha oscillations in somatosensory, motor, and visual areas. Such global suppression is quite in contrast with regionally specific suppression induced by inputs of other sensory modalities, indicating that pain modulates the cortical excitability of not only the sensorimotor system but also widespread cortical systems in general. Note that pain was defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage (Chen, 2001). Such a definition implies that pain is a unique experience which disrupts ongoing behavior, demands attention, and urges the individual to react. It broadly interferes with sensory, motor and cognitive processes. Correspondingly, pain may not only selectively modulate the function of the sensorimotor system but also modulate cortical systems in general. Such global suppression of alpha activity induced by pain reflects the particular alerting function of pain which opens the gate of sensory and motor systems for reacting to stimuli with existential relevance.

Painful stimuli could not only suppress alpha oscillatory activity, but also increase cortical excitability of the somatosensory system (Ploner et al., 2006a; Ploner et al., 2004). The effects of painful stimuli inputs on cortical processing of touch inputs was investigated, and reported that brief painful stimuli (prior to the tactile stimuli) yielded an increase of SI and SII response to following tactile test stimuli (Ploner et al., 2004). This study indicates that pain efficiently facilitates tactile processing by increasing the excitability of human somatosensory cortices, which may also reflect the alerting function of pain as a change of the internal state for preparing processing information with particular relevance. Furthermore, Ploner et al (Ploner

et al., 2006a) revealed a significantly negative correlation between painful laser stimuli induced modulations of alpha oscillatory activity and excitability of somatosensory cortex on a single-trial basis, providing direct evidence for the association of pain related alpha oscillatory activity and cortical excitability. Thus, pain induced modulations of both oscillatory activity and somatosensory excitability may represent a correlation of an alerting function.

Moreover, using a spatial attention paradigm requiring subjects to attend painful stimulus on one hand and ignore stimuli on the other hand, the pre-stimulus and post-stimulus alpha activity was modulated in a different way (May et al., 2012). Anticipatory alpha rhythms prior to the stimulus were lower over primary somatosensory cortex when attention was directed to the contralateral hand than to the ipsilateral hand, reflecting overall facilitation to process the painful stimuli on the attended hand. In contrast, post-stimulus alpha activity was consistently suppressed over widespread areas with attention direction, indicating the enhancement of cortical activations and intensified alerting function of pain. Such finding was quite consistent with the regulation of alpha activity by attention observed in other modalities, and provided evidence that functional role of pain related alpha activity also applies to the sensory gating mechanisms.

Thus, the levels of pain related alpha activity could reflect cortical inhibition/activation, and the functional inhibition hypothesis could be also applied to alpha rhythms associated with painful stimulus processing. The painful stimulus induced global suppression of spontaneous alpha oscillatory activities could be well interpreted as widespread cortical activation and altering effect of pain.

Functions of pain induced alpha ERD/ERS were highly dependent on the cortical regions where it was observed

Alpha ERD was observed in response to various sensory modalities with scalp distribution specific to the explored sensory modality (Li et al., 2008; Pfurtscheller and da Silva, 1999; Pfurtscheller et al., 1994; Stancak, 2006), but also to various cognitive and motor tasks (Basar et al., 1999; Basar et al., 1997; Grabner et al., 2004; Klimesch, 1997; Kolev et al., 1999). For example, we could observe visual stimuli induced alpha ERD over visual cortex (Pfurtscheller et al., 1994), auditory stimuli induced alpha ERD over auditory cortex (Yordanova et al., 2001), and tactile stimuli induced alpha ERD over contralateral somatosensory cortex (Gaetz and Cheyne, 2006; Nikouline et al., 2000). This alpha ERD was thought to reflect the cortical activation of corresponding sensory cortex for the efficient processing of the incoming sensory stimulus. On the other hand, the cognitive task induced alpha ERD was not so regionally distributed (Basar et al., 1997; Grabner et al., 2004; Kolev et al., 1999; Wiech et al., 2008), and frequently observed over frontal and parietal regions. Thus, it hinted at the co-existence of sensory- and task- related alpha ERD with different scalp topography distributions.

Somatosensory alpha ERD in response to painful stimuli was observed (Hu et al., 2013; Ploner et al., 2006b; Raij et al., 2004), and the direct association between pain related alpha activity and somatosensory cortex excitability was proposed (Ploner et al., 2006a). Note that such association was restricted only to sensorimotor alpha oscillations, and alpha activity outside somatosensory system was not correlated with somatosensory excitability. Such pain induced modulations of alpha oscillatory activity within somatosensory cortex, reflecting functional state of somatosensory system, should mainly contribute to painful stimulus processing. At the same time, painful stimuli could also suppress alpha oscillatory activity over posterior parietal cortical areas (Iannetti et al., 2008; Mouraux et al., 2003; Peng et al., 2012). Mouraux et al (Mouraux et al., 2003) showed that both A-delta and C-fiber activation induced a widespread and long-lasting alpha ERD maximal at Pz electrode. Later, Iannetti et al

(Iannetti et al., 2008) applied trains of three identical laser stimulus with different intensities, and found that the magnitude of pain induced alpha ERD was not modulated by either intensity of perception or stimulus repetition. This finding is in striking contrast with laser evoked potentials (LEPs) that are significantly modulated by stimulus repetition and closely related to subjective pain intensity, and suggested that the alpha ERD reflects less about stimulus salience. The observed alpha ERD, maximal over posterior parietal cortical areas in these two studies, was reflecting more about specific attentional and mnesic processes that are task-related, since in the experiment the subjects were asked to rate the pain intensity or press a button as response.

To further comprehensively investigate task- and sensory- related alpha ERD during pain perception, two studies were presented in the current review (Hu et al., 2013; Peng et al., 2012). By employing a classical oddball experimental paradigm across auditory, visual, somatosensory, and pain modalities comprehensively, we observed that target stimuli induced alpha ERD displayed similar distribution over parieto-occipital regions, and the cortical information was flowed from generators of alpha ERD to P300, regardless of the sensory modalities. Such alpha ERD could also be interpreted as cognitive task related attention process without any modality difference. Interestingly, by further comparing the alpha ERD in response to frequent and infrequent painful stimuli, we confirmed the dissociation between a sensory-related alpha ERD maximally distributed over contralateral central electrodes, and a task-related alpha-ERD maximally distributed at posterior parietal and occipital electrodes (Figure 2). The cortical sources of these activities were estimated to be located at sensorimotor and bilateral occipital cortices respectively, indicating the independent generators of these two components of alpha ERD. Importantly, the time course of the alpha ERD elicited by target and non-target painful stimuli, revealed that functional segregation emerged only at late latencies

whereas topographic similarity was observed at earlier latencies. Thus, the observed alpha ERD induced by target painful stimulus, with overall distribution over parietal-occipital regions, was composed of sensory-related alpha ERD that was short-lasting and task-related component with higher intensity.

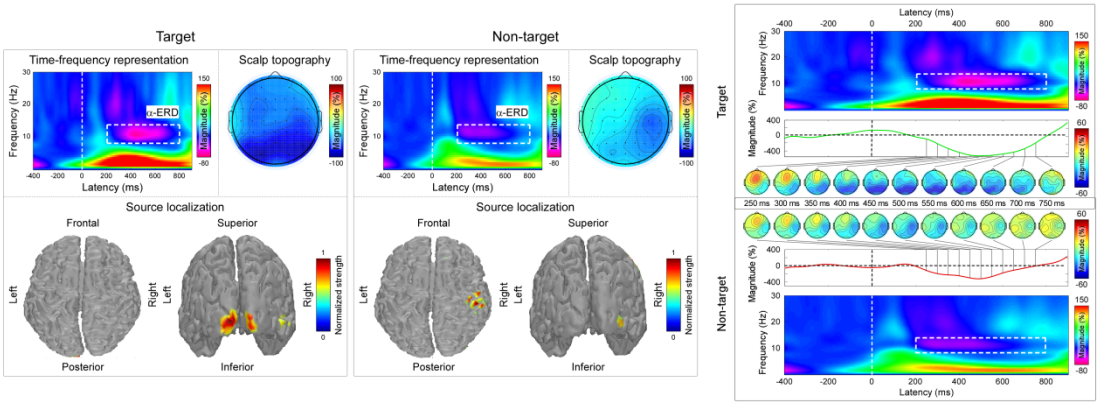

Figure 2. Dissociation of sensory- and task- related alpha ERD component in oddball pain paradigm (Peng et al., 2012; Hu&Peng et al., 2013).

Left panel: Grand average time-frequency distributions, scalp topographies, and estimated sources of alpha ERD in response to frequent and infrequent painful stimuli were displayed in the left panel. Alpha ERD induced by infrequent painful stimuli showed maximal scalp topography distribution over posterior parietal and occipital regions, and were generated over bilateral visual cortex with talairach coordinates (x, y, z) of (-9,-99,-7) mm and (16 -95, -12) mm. In contrast, alpha ERD induced by infrequent painful stimuli showed maximal scalp topography distributions over contralateral central regions, with source localization over contralateral somatosensory cortex with coordinates of (-44, -5, 58) mm. Also note that the parietal-occipital alpha ERD that is task related showed much stronger intensities than contralateral SI alpha ERD that is sensory related.

Right panel: Time varying scalp topographies of alpha ERD in target and non-target conditions. Alpha ERD in response to infrequent and frequent painful stimuli showed similar scalp distributions maximal over contralateral central region during the early latency (from 250 to 350 ms), then they started to be different in the late latency

(from 400 to 750 ms), peaking at parietal and occipital region for the infrequent painful stimulus and at still over contralateral central regions for the frequent painful stimulus.

Therefore, we propose that even the pain could induce modulations of alpha activity over widespread cortical areas, which could be interpreted as alerting functions of pain, the specific functions of pain induced alpha ERD highly depends on the cortical regions where it is observed. Painful stimuli induced alpha ERD on somatosensory cortex, especially on contralateral hemisphere to stimulus side, is highly likely reflecting painful stimulus processing, whereas pain induced suppression of alpha activity over parietal-occipital regions should be reflecting the attentional and mnesic processes that are required by experimental tasks. Pain related experiments should be designed carefully to control the task-related alpha modulations, if they want to specifically investigate alpha activities relating to painful stimulus processing.

Attention modulation of pain experience could be well reflected as changes of alpha oscillatory activities

Attention is the behavioral and cognitive process of concentrating on selective aspects of the environment while ignoring others, which is also considered as the allocation of limited processing resources (Anderson and Ding, 2011; Bledowski et al., 2004). Previous studies (Frankenstein et al., 2001; Miron et al., 1989; Pessoa et al., 2003; Wiech et al., 2008) linking attention modulation of pain processes to behavior, have consistently shown that a painful stimulus is perceived as more intense and bothered, when attention is directed to the stimulus, while such painful stimulus is perceived less painful and bothered when attention is directed away from it. Such an effect of attention modulation on pain experience has also been applied in the psychological and behavioral treatment of pain, e.g., distraction from pain as powerful analgesic effect. Functional neuroimaging studies (Miron et al., 1989;

Pessoa et al., 2003; Petrovic et al., 2000; Quevedo and Coghill, 2007; Tracey et al., 2002; Yamasaki et al., 1999) have demonstrated the modulation of activities within those pain related cortical regions (e.g., SI, SII, ACC, and insula) by attention directed to the painful stimuli. These previous studies indicate that attention, as a typical cognitive modulation of pain, is effective in modulating both the sensory and affective sub-systems of pain experience.

When investigating the suppression or enhancement of cortical oscillations induced pain, the attention modulation of pain experience was also accompanied with changes of alpha rhythmic activity (Del Percio et al., 2006; Klimesch et al., 1998; May et al., 2012; Ohara et al., 2004). By using subdural electrocorticographic recordings (ECoG) from epilepsy patients, Ohara (Ohara et al., 2004) showed that the alpha ERD elicited by painful cutaneous laser stimuli occurred over more electrodes with greater magnitude, particularly over somatosensory and parasylvian (PS including SII and insula) cortices, when subjects' attention was focused on the laser stimuli (by counting stimuli) than when attention was distracted away (by comprehensive reading). The enhanced and intensified pain induced alpha ERD could be well interpreted as increased efficiency of the attended stimulus for an improved access to the higher processing resources. In contrast, Del Percio et al. (Del Percio et al., 2006) suggested that as an effect of distraction by performing either motor or arithmetic tasks, the alpha ERD before predictable painful stimuli reduced over frontal-central midline, together with significantly lower stimulus intensity perception and unpleasantness. It further supports the idea that an increased inhibition mediates the effect of distraction, while a decrease of inhibition effect mediates the attention process (Foxe and Snyder, 2011; Jensen and Mazaheri, 2010). These studies together indicated that attention/distraction that modulates subjective pain experience, could also induce changes of pain-related cortical alpha rhythms.

The attention modulation of pain related alpha activity was also observed in tonic pain studies (Peng et al., 2014). With the delivery of 5-min tonic heat painful stimuli, the effect of selective attention was characterized as a significant and consistent decrease of spontaneous alpha oscillatory activity over somatosensory areas contralateral to the stimulated side, by comparing the alpha activity in nociceptive-attended (rating the stimulus intensity at the end of each minute) and nociceptive-distracted (conducting arithmetic subtraction task) conditions (Left panel of Figure 3). Interestingly, such stable and persistent suppression of alpha rhythms over contralateral-central region was significantly correlated with subjective pain intensity (Right panel of Figure 3), indicating the close relationship between attention and pain-related alpha activity presented in tonic pain perception. Compared to tonic pain induced oscillatory responses in the gamma frequency band which reflects the summary effects of stimulus-related and attention-related processes, tonic heat pain related alpha oscillatory activity was mainly reflecting attention modulation, instead of sensory stimulus processing. Such tonic pain induced alpha oscillation suppression within SI may reflect a mechanism by which attention facilitates the preferential routing of important information in nociceptive processing through the corresponding cortical network. Thus, top-down attention modulation of pain perception could be reflected as changes of pain related oscillatory activities.

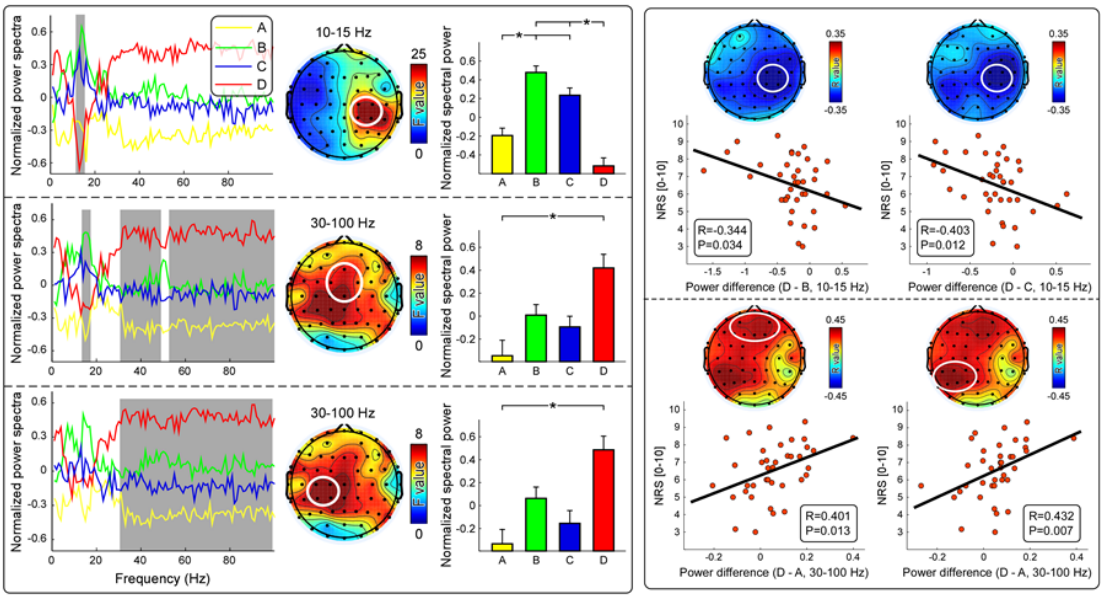

Figure 3. Attention modulations of tonic pain related oscillatory activities (Peng et al., 2014).

Panel Left: Comparison of normalized power spectra among four stimulation conditions (A: resting-sate, B: innoxious-distracted [non-painful inputs with attention distracted away from pain], C: noxious-distracted, D: noxious-attended). Significant differences of power spectra across stimulation conditions were dominantly observed at contralateral-central electrodes from 10 to 15 Hz (top), at frontal-central electrodes from 30 to 55 Hz and from 60 to 100 Hz (middle), and at ipsilateral-central electrodes from 30 to 100 Hz (bottom), which were marked in grey. The summarized spectral power, measured at contralateral-central electrodes (top) within alpha band (10-15 Hz, top), at frontal-central (middle) and ipsilateral-central (bottom) electrodes within gamma band (30-100 Hz), were compared among four stimulation conditions. Error bars represent, for each condition, ± SEM across subjects. Asterisk * indicates a significant difference ($P < 0.05$, Tukey's post hoc tests).

Panel Right: Relationships between tonic heat pain induced changes of spectral power and subjective pain intensity. Negative correlations between spectral power differences (left panel, D – B, D - C) within alpha frequency band (10-15 Hz) and subjective pain intensity were maximal at contralateral-central electrodes (C2, C4, CP2, and CP4). Positive correlations between spectral power difference (left panel, D

- A) within gamma frequency band (30-100 Hz) and subjective pain intensity were maximal at prefrontal-central (left: AF3, AF4, F1, Fz, and F2) and ipsilateral-posterior (right: CP1, CP3, CP5, P1, P3, and P5) electrodes. Each dot represents values from each subject, and black lines represent the best linear fit.

At the same time, attention to the painful stimuli leads to consistently increased functional interactions among those pain related cortical regions within the pain network (including SI, PS, medial frontal cortex [MF]) (Liu et al., 2011a; Liu et al., 2011b). Specifically, the attention directed to the painful stimuli would lead to the enhancement of the Granger causality from SI to PS prior to the painful stimulus presentation. Even after the laser stimuli, the synchronization from SI upon PS and MF increased with attention directed to the stimulus. The functional connectivity between SI and SII may be related to overlapping thalamocortical inputs from the ventral posterior nuclei in macaques (Apkarian et al., 2000; Burton, 1975, 1984), whereas the significant interactions from SI to MF may be related to common input from the spinothalamic tract to human thalamic nuclei that project upon SI and MF (Vogt et al., 1987). Thus, attention modulation on pain perception is also mediated through a hierarchical network composed of the pain related cortical areas, with SI exerting increased causal influence over PS and MF. It is quite likely that attention exerts its effect on pain perception through modulating the coherence of ongoing oscillations selectively for the neurons involved in encoding attended stimuli.

Therefore, the attention modulation of pain (i.e., clear influences on the sensory and affective dimensions of pain experience) could be mediated by changes of alpha oscillatory activities (Foxe and Snyder, 2011; Hauck et al., 2007; Hu et al., 2013; May et al., 2012; Ohara et al., 2004; Peng et al., 2014). The intensified alpha suppression within pain-related brain areas (e.g., somatosensory cortex) due to attention directed to pain, is quite likely reflecting attentional augmentation of painful information

processing. At the same time, the attention modulation in pain experience may be also accomplished by regulations of alpha oscillatory activities in high-level cognitive systems (e.g., prefrontal cortex), which exert manipulations over sensory- or affective- circuits of pain system through cortical functional interactions (Liu et al., 2011a; Liu et al., 2011b). In other words, the changes of alpha oscillatory activities that reflect the attentional influences on pain experience, could be observed in both pain-related areas and high-level cognitive areas, without distinct spatial distributions and cortical localization. Instead, the alpha response mediating attention modulation of pain should be identified by comparison of alpha responses in different experimental conditions, e.g., the difference of alpha response in pain-attended and pain-distracted conditions.

Current studies investigated attention modulations of pain mostly assessed the alpha activities within a wide range of alpha frequency bands (May et al., 2012; Ohara et al., 2004; Peng et al., 2014), e.g., 7-14 Hz. However, with more and more evidence showing that functional significance of alpha ERD/ERS is a differential reactivity of lower and upper alpha frequency bands to dissimilar attentional cognitive demands (Bazanova and Vernon, 2014; Klimesch et al., 1997; Klimesch et al., 1998; Nir et al., 2012; Petsche et al., 1997), it is likely that the alpha activities mediating the attention modulations of pain experience would display different reactivity in lower and upper alpha frequency bands, which should be investigated in future studies. In addition, recent studies suggested that the phase of alpha oscillations is important for regulating information transmission (Busch et al., 2009; Jensen et al., 2012; Mathewson et al., 2011), thus allowing for effective network communications (Palva and Palva, 2007; von Stein et al., 2000; Wang et al., 2012). How phase of ongoing alpha activity biases visual perception has been demonstrated by recent studies (Busch et al., 2009), whether such an association also exists in pain perception is still not clear. Indeed, the dynamics for phase of alpha activities may provide

complemented information regarding attention modulations of pain experience.

In short, we propose that the effects of attention on pain perception could be mediated by changes of alpha rhythms. Attention could significantly modulate pain related alpha rhythms displayed as intensified and prolonged alpha suppression with directed attention, and such modulation could predict subject's pain perception to some degree since enhanced efficient processing was obtained with the selective attention.

Determinants of pain related changes of alpha oscillatory activities

Cognitive modulation (e.g., attention, hypnosis, expectation, and placebo) of subjective pain perception is presented in behavioral experience as well as cortical activities within pain related areas (Benedetti et al., 2005; Koyama et al., 2005; Legrain et al., 2009; Melzack and Casey, 1968; Pessoa et al., 2003; Valentini et al., 2013; Wiech et al., 2008). Similar with attention modulation in pain sensation, hypnosis suggestions specifically directed toward increasing or decreasing the perceived intensity of the burning pain sensation modulated activation intensity of SI, whereas suggestions directed toward changing the unpleasantness of the pain had no effect on pain-related activity in SI, but produced instead a robust modulation of activity in ACC that is correlated with the subjects' perception of unpleasantness (Croft et al., 2002; De Pascalis et al., 2006; Rainville et al., 1999). Expectations about the upcoming painful stimulus could also enable the pain systems to adjust adequate sensory, cognitive, and motor responses (Koyama et al., 2005). Behaviorally, when the subject was expecting a low-intensity painful stimulus, the same stimulus would be rated less intense, and vice versa (Wiech et al., 2008). The expectation period before the noxious stimulus is always characterized by increased activations within pain related cortical regions (Fairhurst et al., 2007; Jensen et al., 2003; Ploghaus et al., 1999; Porro et al., 2002). Crucially, the expectation of high pain intensity would

induce increased activation in contralateral S1, bilateral ACC, medial prefrontal cortex, and anterior insula, together with higher subjective pain intensity (Fairhurst et al., 2007; Keltner et al., 2006; Koyama et al., 2005; Porro et al., 2002). In contrast, the expectation of low- but application of high- level intensity of noxious stimulus was reflected as less activation within brain areas related to pain processing. Thus, neural processes during pain experiences are highly affected by prior knowledge regarding the upcoming stimulus. The placebo effect, involved in attention and expectation process more or less, could decrease pain intensity and cortical response to pain within ACC, insula, and thalamus (Bingel et al., 2006; Petrovic et al., 2002; Wager et al., 2004).

These findings based on fMRI and Positron Emission Tomography (PET) techniques have shown clearly how cognitive variables (hypnosis suggestions and anticipation) affect sensory and affective dimensions of the pain perception system. For short, “discriminative matrix” and “emotional matrix” are defined as the collection of brain areas encoding the sensory-discriminative aspect (e.g., qualities, locations, and durations) and affective-motivational aspect (e.g., unpleasantness to motivate individuals to engage in a behavior to avoid further damages) of pain experience. What we do not know is whether the modulation of the emotional matrix and discriminative matrix is reflected by variation of alpha rhythms in the node of these matrices. This is a relevant issue why synchronization/desynchronization of thalamocortical and cortico-cortical pathways may be the physiological mechanisms to coordinate the activity/inhibition among the nodes of the sensory matrix and among the nodes of the affective matrix. Possibly due to the high temporal resolution of EEG activity, alpha synchronization/desynchronization may be a physiological mechanism underlying the activation/inhibition revealed by low temporal resolution/high spatial resolution fMRI-PET techniques. As introduced earlier, the attention modulation on pain perception could be underlined by changes

of pain related alpha rhythms. Thus, we also propose that changes of pain related alpha rhythm could mediate the cognitive modulations. But due to the limitations of scalp EEG technique, the pain sensory/cognitive induced modulations of alpha oscillations within deep brain regions (e.g., insula) could not be easily detected, which could be solved by the combined techniques of EEG-fMRI.

Actually, besides attention modulation on pain perception mediated by alpha rhythms, there are also several studies investigating how high-level cognitive variables modulate pain perception based on cortical oscillatory activities, which have been listed as follows.

(1) Anticipatory cortical processes could be probed by EEG oscillatory activations within the alpha band (Babiloni et al., 2005; Babiloni et al., 2006). The suppression of alpha power before a painful stimulus reflected as ERD could index an anticipatory process, and such anticipatory suppression of the alpha rhythms (within low and high alpha frequency band) over the contralateral primary sensorimotor cortex predicts subjects' subsequent evaluation of pain intensity (Babiloni et al., 2006). It is quite in line with the idea that contralateral somatosensory cortex is implicated in sensory-discrimination of painful stimulus processing.

(2) When investigating changes of pain related oscillatory activities in hypnosis, it has been shown that compared to the low-hypnotizability subjects, high-hypnotizability subjects showed a reduced cortical activity, suggesting a relationship between hypnotizability and cortical activity related to painful stimuli (Del Percio et al., 2013). Indeed, the relationship between EEG activity and hypnotic susceptibility was firstly advanced by De Pascalis et al. (1987&1989) (De Pascalis et al., 1987; De Pascalis et al., 1989), who showed that low- and high- hypnotizability subjects displayed differences of 40-Hz EEG asymmetry during the recall of emotional events in waking and hypnosis states. Later, painful

stimuli were applied to investigate the relation between cortical oscillations in response to pain, with and without hypnosis and hypnotic analgesia, and the subjective experience of pain (Croft et al., 2002; De Pascalis et al., 2004, 2006). It has been shown that only gamma activity (32–100 Hz) over prefrontal scalp sites predicted subject pain ratings in the hypnosis suggestion condition only for low hypnotizable subjects, and such correlation was independent of performance and stimulus intensity measures. This finding provides evidence that hypnosis interferes with pain/gamma relation over prefrontal cortex that may be the source of hypnosis modulation. It is quite possible that prefrontal cortex then exerts regulation of sensory- or affective- circuits of pain system through cortical functional interactions.

(3) By comparing resting-state EEG activity before, during, and after placebo procedure, Hunkene et al. (Huneke et al., 2013) have shown that resting alpha activity is modified by placebo analgesia. Post-treatment alpha oscillatory activity increased significantly in the placebo group only, and such alpha activity might have been generated in medial components of the pain network, including dorsal ACC and medial prefrontal cortex, and left insula. Such increased alpha oscillatory activity could be interpreted as inhibition of affective systems of pain perception with the treatment of placebo analgesia.

Even the pain-related cortical areas including SI, SII, insula, ACC, and prefrontal cortex, have been observed to be modulated by cognitive manipulations, the prefrontal cortex is more likely to represent a pivotal source of modulation (Bar, 2003; Buschman and Miller, 2007; Johnston et al., 2007; Tomita et al., 1999). Such an assumption is mainly based on its anatomical significance, i.e., it is highly interconnected with affect, motivation, and motor systems. Crucially, it receives sensory information from all modalities, and enables a direct translation of PFC outcome to behavior. The cognitive modulations may exert manipulations over

sensory and affective circuits of pain through connectivity between PFC and other pain-related regions, which could be mediated through alpha rhythms.

Taken together, painful sensory inputs would induce changes of alpha oscillatory activity within the distributed alpha system. Specifically, with the application of a painful stimulus, the observed alpha suppression over contralateral to stimulus side would mainly contribute to the sensory-discriminative aspect of pain perception. Even that pain induced modulations of alpha rhythms over insular and ACC were not reported before because of the low signal to noise ratio to detect the changes of alpha activity within these regions, we still propose that painful perception would change alpha activity over these regions reflecting the affective-motivational dimensions of pain. As well, variable cognitive modulations of pain perception would also induce changes of alpha oscillatory activities over parietal, SI, SII, ACC, insular, and frontal regions. As shown in Figure. 4, we could get the following hypotheses: (1) several factors would affect and determine pain related changes of alpha activities, including sensory-discriminative, affective-motivational, and top-down cognitive modulations; (2) the distributed alpha system receives and processes the pain related information, and of course sensory, affective, and cognitive circuits interact and influence each other; (3) the observed alpha oscillation suppression over SI and SII may reflect the discriminative-sensory dimension of pain perception, and the observed alpha ERD/ERS over insular and ACC may reflect the affective-motivational dimension of pain perception, but alpha rhythms over sensory- and affective matrices also may reflect some kind of cognitive modulation effects; as for the pain related alpha ERD/ERS over prefrontal or parietal regions, it may mainly reflect the cognitive modulations such as anticipation/expectation. However, the referred pain related alpha ERD/ERS should be separated from experimental task related components, and careful experiments should be designed to investigate specific components.

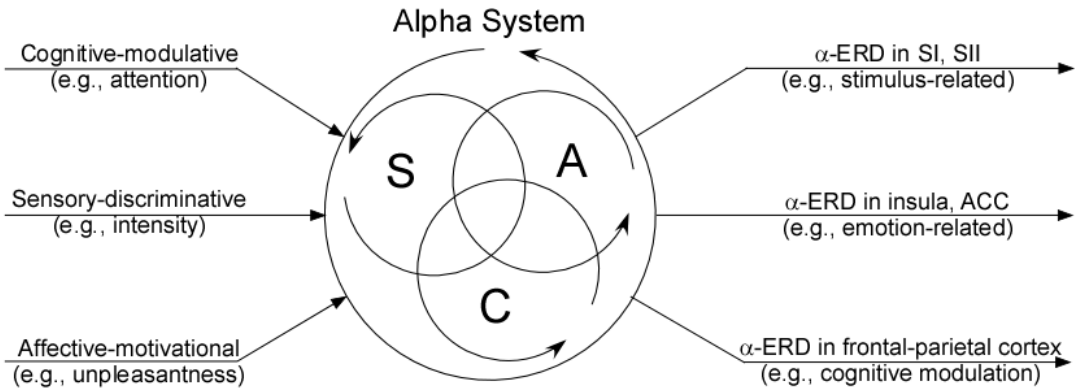

Figure 4. Factors contributing to pain related alpha activities and output of alpha system in pain perception.

S: Sensory-discriminative; A: Affective-motivational; C: cognitive-modulative. Input of sensory-, affective-, and cognitive- related information to alpha system could induce modulations of spontaneous alpha rhythms, displayed as alpha ERD/ERS reflecting cortical excitability/inhibition. Its neural functions for modulations of alpha activity in pain were highly dependent on the cortical regions where it was observed, e.g., alpha ERD/ERS over somatosensory cortex would be mainly reflecting sensory processing in pain, whereas alpha ERD/ERS over insula or ACC would be largely relating to the affective aspect of pain. Both sensory- and affective- related modulations of alpha activity could be highly affected by top-down cognitive manipulations as well as task requirements during the experiments. Specifically, the alpha ERD/ERS over prefrontal cortex or parietal cortex should be highly considered as cognitive-related component reflecting top-down manipulations on pain.

Outlook

Based on our current understandings and assumptions regarding the dynamics of pain induced modulations of alpha rhythms (appearing as alpha ERD/ERS), open questions and interesting lines of further research will be discussed as follows.

(1) How the phase of alpha rhythms reflects pain perception would be an interesting topic, considering that previous studies about pain related alpha activity were mainly

talking about its amplitude. Actually, it was suggested that the phase of alpha oscillatory activity could even underlie the mechanism of prioritizing and ordering input according to its relevance, indicating the functional significance of phase of alpha rhythms (Dustman, 1964; Jansen and Brandt, 1991; Jensen and Mazaheri, 2010; Kolev et al., 2001; Sauseng and Klimesch, 2008). With the evidence showing how phase of ongoing alpha activity biases visual perception, it is quite likely that such an association also exists in pain perception. The dynamics of phase of pain related alpha activity may provide complementing information regarding how individual's pain perception process modulates spontaneous alpha oscillatory activities. For example, it would be interesting to investigate how the phase of alpha activity within somatosensory cortex influences subjective pain intensity, as well as how the phase of alpha rhythm with ACC modulates the unpleasantness feelings in pain perception.

(2) Cortical oscillations are considered to reflect cyclical variations of the neuronal excitability, with particular frequency bands reflecting different neural functions, e.g., gamma oscillations for the formation of transient cortical assemblies and integration (Rossiter et al., 2013; Tallon-Baudry and Bertrand, 1999; TallonBaudry et al., 1997) while alpha oscillations for cortical inhibition or activation (Mouraux et al., 2003; Pfurtscheller and da Silva, 1999; Ploner et al., 2006b). Thus, cross-frequency coupling would be of particular interest to integrate functions across multiple scales (Cohen, 2008; Cohen et al., 2009; Wang et al., 2012), which could be evaluated using synchronization index. Distinct patterns of power and cross-trial phase coherence in multiple frequency bands in pain sensation deserve future investigations, especially for the coupling between alpha and gamma frequency oscillations. With more and more evidence showing the coupling between alpha and gamma oscillations (de Lange et al., 2008; Jensen and Colgin, 2007; Wang et al., 2012), whether the amplitude of gamma oscillations in pain sensation is modulated by the phase of alpha rhythms remains an important question for the further study. Considering that

painful stimulus could not only induce suppression of alpha oscillatory activities (Mouraux et al., 2003; Ploner et al., 2006b) but also enhancement of gamma activities within somatosensory cortex which could even predict the subjective perception (Gross et al., 2007; Schulz et al., 2011; Zhang et al., 2012), the understanding of the coupling between painful stimulus related alpha and gamma activities would allow for the understanding of how the nociceptive sensory network structures its temporal activity pattern so as to optimize the processing of painful information.

(3) Alterations of ongoing alpha oscillatory activities in chronic pain should be investigated in future studies. For example, hepatic encephalopathy patients showed a decreased peak frequency of somatosensory alpha activity and a delayed alpha rebound in painful stimulus processing (May et al., 2014). Such kinds of alteration could not only broaden our understanding about the pathophysiological mechanisms, but also provide new insights about the corresponding diagnosis and treatment. Such kind of findings could be broadened to other kinds of chronic pain situations of clinical importance. If the alterations of alpha activity really exist in some chronic pain situations, we may even modulate patients' levels of alpha activity using neuro-feedback, to relieve pain perception.

(4) The association between modulations of alpha activities and behavioral performance was shown in previous studies (Babiloni et al., 2008; Brandt et al., 1991; Lange et al., 2012; Linkenkaer-Hansen et al., 2004; Rahn and Basar, 1993a, b; Zhang and Ding, 2010). With the application of neuro-stimulation techniques outside the skull, such as Transcranial Magnetic Stimulation (TMS), it is possible to selectively modulate brain oscillatory activity. If such modulation could induce changes of behavioral performance in a task, it provides direct evidence for the functional role of oscillatory activity instead of some kind of correlative relevance. TMS induced

changes of alpha oscillatory activities in brain areas have been shown to differently modulate behavioral performance in a visual attention task (Hilgetag et al., 2001). Accordingly, it is also quite possible that the alpha activity has a causal role for the painful stimulus processing, e.g., modulations of alpha activity using TMS within somatosensory cortex may induce changes of subjective pain intensity, and boosting of alpha activity induced by TMS within ACC may influence the unpleasantness of pain perception. Such kinds of study could lead to new ways of pain relief and management.

(5) Lastly, variable cognitive modulations of pain perception and pain related activities have been shown quite clearly in previous behavioral and functional imaging studies, but the cortical basis for these modulations still has not been established well. For example, hypnosis suggestions to modulate pain intensity or unpleasantness would induce changes of activations within somatosensory cortex and cingulated cortex respectively (Rainville et al., 1999), proving the dissociation between sensory and affective circuits of pain. How such hypnosis modulation reflects the changes of oscillatory activity is still not known clearly. We may compare the cortical oscillation activity (e.g., alpha and gamma oscillations) or network activities (e.g., coherence or connectivity in sensory and affective circuits of the pain system) in hypnosis and control conditions. At the same time, the possible relationship between changes of oscillatory activities induced by hypnosis suggestion and physiological response to the noxious stimuli could be assessed, to verify the association between oscillatory modulations and behavioral relevance in pain perception.

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