



Analysis of synchrony demonstrates ‘pain networks’ defined by rapidly switching, task-specific, functional connectivity between pain-related cortical structures

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Abstract

Imaging studies indicate that experimental pain is processed in multiple cortical areas which are often characterized as a network. However, the functional connectivity within the network and the other properties of the network is poorly understood. Substantial evidence demonstrates that synchronous oscillations between two cortical areas may indicate functional connectivity between those areas. We now test the hypothesis that cortical areas with pain-related activity are functionally connected during attention to a painful stimulus. We stimulated with a painful, cutaneous, laser stimulus and recorded the response directly from the cortical surface (electrocorticography – ECoG) over primary somatosensory (SI), parasyllian (PS), and medial frontal (MF) cortex through subdural electrodes implanted for treatment of epilepsy. The results demonstrate synchrony of ECoGs between cortical structures receiving input from nociceptors, as indicated by the occurrence of laser-evoked potentials (LEPs) and/or event-related desynchronization (ERD). Prior to the stimulus, directed attention to the painful stimulus consistently increased the degree of synchrony between SI and PS regions, as the subject anticipated the stimulus. After the laser stimulus, directed attention to the painful stimulus consistently increased the degree of synchrony between SI and MF cortex, as the subject responded by counting the stimulus. Therefore, attention to painful stimuli always enhanced synchrony between cortical pain-related structures. The pattern of this synchrony changed as the patient switched tasks from anticipation of the stimulus to counting the stimulus. These results are the first compelling evidence of pain networks characterized by rapidly switching, task-specific functional connectivity.

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1. Introduction

Acute pain is a multidimensional experience associated with bloodflow or fMRI BOLD (blood oxygen level dependent) signals in multiple cortical structures in humans (reviewed by Rainville et al. (2000) and Davis (2000)), which have often been characterized as a ‘pain network’ or ‘neuro-matrix’ (Melzack, 1990; Gelnar

et al., 1999; Peyron et al., 1999; Apkarian et al., 2000; Casey, 2000; Strigo et al., 2003). A neural network consists of a collection of neural elements, their connections, and connectional weights which are often equated with neurons/modules in the brain, axons, and synapses, respectively (Churchland and Sejnowski, 1992). Functional connectivity within such a network may be conceived of as the network properties that enable its modules jointly to process inputs or outputs or both. However, the functional connections or connectional weights within the proposed ‘pain network’ have not previously been either demonstrated or measured.

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Functional connectivity between separate parts of brain in a network may be the result of synchronous oscillations of cortical neuronal activities (Singer and Gray, 1995). Synchronization of oscillatory electroencephalographic (EEG) activity between separate cortical regions in humans has been measured by the coherence or by similar functions (Rodriguez et al., 1999; Ohara et al., 2001). Our previous electrocorticographic (ECoG) studies have demonstrated electrical activation of SI, PS, and MF (ERD – event-related desynchronization (Ohara et al., 2004a)), in addition to the stimulus-locked responses evoked by a painful cutaneous laser stimulus (LEPs – (Lenz et al., 1998a,b; Ohara et al., 2004b)). We now test the hypothesis that these areas are functionally connected during attention to the laser stimulus. The ECoG activity was recorded during the unique opportunity provided by implantation of extensive subdural grids for surgical treatment of epilepsy. Inter-areal functional connectivity was inferred from synchrony between electrodes in different cortical areas. We report that ECoGs from these cortical areas are synchronized during directed attention to the painful stimulus and that the pattern of synchrony is task-specific.

2. Materials and methods

2.1. Patients

We studied two patients (subject 1: 21-year-old male, 2: 21-year-old female) with normal neurological and somatic sensory exams (Lenz et al., 1993), and with a normal neuropsychological battery, who had subdural grids placed over SI, PS, and MF cortex for treatment of medically intractable seizures (Figs. 2 and 3). Brain MRI revealed a small cavernoma in the right parietal lobe contralateral to the grid in subject 1 but was normal in subject 2. The protocol for these studies was reviewed and approved annually by the Institutional Review Board of Johns Hopkins Medicine. Both patients signed an informed consent.

2.2. Laser stimulation and experimental paradigm

Subjects wore protective glasses and lay on a bed with their eyes open, quietly wakeful, while a painful laser stimulus was applied to the dorsum of the hand (Thulium YAG laser: wavelength 2 μm , duration 1 ms, diameter 6 mm – Neurotest, Wavelight, Starnberg, Germany). To avoid sensitization or fatigue of nociceptors, the laser beam was moved at random to a slightly different position for each stimulus. We chose the laser energy level to generate a painful sensation of 3–4/10 on a scale of 10 (0 no pain, 10 most intense pain imaginable). The paradigm included separate conditions for attention to/distraction from the laser stimulus, each comprised of two runs of 40–50 randomly timed laser pulses. During the attention condition, the subject was asked to count the number of painful stimuli and to report both that number and the average pain intensity, after each run of laser pulses. During the distraction condition the subject read a magazine article and

answered question about it after the run. The average pain rating was estimated after each session using the scale described above.

2.3. Data acquisition

ECoG were recorded from up to 96 electrodes in subdural grids consisting of platinum-iridium electrodes (exposed diameter – 2.3 mm) embedded in a transparent silastic sheet at 1 cm Cartesian center-to-center intervals (Ad-Tech, Racine, WI). ECoG was amplified (12A5, Astro-Med Grass, Inc., West Warwick, RI), band-pass filtered at 0.1–300 and 30–300 Hz for the LEPs and somatosensory evoked potentials (SEPs), respectively, digitized at 1000 Hz, except for SEPs in subject 1 (1400 Hz). Frequency bands of ECoG were defined as follows: δ : 1–3 Hz, θ : 4–7, α : 8–12, β : 12–30, β_1 : 12–20, β_2 : 20–30, $\gamma > 30$. All ECoG signals were referenced to a single subdural reference electrode chosen for its relative inactivity and distance from the active electrodes.

2.4. Correlation with cortical gyral anatomy

For the purpose of functional mapping (Lesser et al., 1992), SEPs were recorded by electrically stimulating the median nerve just above the motor threshold (inter-stimulus interval 213 ms, duration 300 μs). The central sulcus (CS) and the sylvian fissure (SF) were determined by co-registration of the 3D post-implantation computed tomogram (CT) with the 3D pre-implantation MRI datasets (CT-MR, see figures) (Crone et al., 1998) and, for CS, by subdural ECoG SEP N20–P20 polarity reversal. SEP N20–P20 polarity reversal (dashed lines), and CT-MR were consistent in terms of CS location in both subjects.

2.5. Data analysis

Before subsequent analysis, ECoG signals from all electrodes signals were re-montaged to an averaged reference to minimize the influence of location and activity of the reference electrode (Crone et al., 1998). The time window for the analysis was 1200 ms, including a 200 ms pre-stimulus period.

2.5.1. Time–frequency analysis

We used a complex Morlet wavelet to obtain a time–frequency representation of the ECoG (Tallon-Baudry et al., 1996). The normalized complex Morlet wavelet, $w(t, f_0)$, is defined as:

$$w(t, f_0) = (\sigma^2 \pi)^{-1/4} \exp(-t^2/2\sigma^2) \cdot \exp(2\pi j f_0 t),$$

where j is the imaginary unit value, f_0 is the center frequency, and σ is the width of the wavelet. We used the constant ratio at $2\pi f_0 \sigma = 7.0$ as used in previous studies (Tallon-Baudry et al., 1996; Tallon-Baudry and Bertrand, 1999; Oya et al., 2002), and center frequencies ranged from 2 to 150 Hz in steps of 2 Hz. With those parameters, the width of the wavelet (2SD in time domain and in frequency domain) at a center frequency of 10 Hz, for example, was 222.8 ms and 2.9 Hz, respectively. The temporal resolution of this method has a reciprocal relationship with its frequency resolution. The time-varying power of the signal in a frequency band centered at f_0 , $E(t$,

f_0), is defined as the squared norm of the result of the convolution of a complex Morlet wavelet $w(t, f_0)$ with the signal $\text{sig}(t)$:

$$E(t, f_0) = |w(t, f_0) * \text{sig}(t)|^2,$$

where $*$ denotes the convolution operator.

The event-related band power change at frequency f_0 and time t was obtained as:

$$10 \cdot \log[E(t, f_0)/\text{Ref}(f_0)](\text{dB}),$$

where $\text{Ref}(f_0)$ was the median power envelope during the pre-stimulus period (200 ms) after subtracting the average evoked potential (LEP) from each of trials, then averaged across trials. The time window for this analysis was 1200 ms, including a 200 ms pre-stimulus period.

The phase difference between two signals (x, y) at frequency f_0 and time t , $\theta_y(t, f_0) - \theta_x(t, f_0)$, can be derived from the angles of their wavelet coefficients because

$$\exp(j(\theta_y(t, f_0) - \theta_x(t, f_0))) = \frac{w_x(t, f_0) \cdot w_y^*(t, f_0)}{|w_x(t, f_0)| |w_y(t, f_0)|}.$$

The synchrony between two signals (x, y) across N trials was defined as: $|1/N \cdot \sum_{\text{trial}} \exp(j(\theta_{y,\text{trial}}(t, f_0) - \theta_{x,\text{trial}}(t, f_0)))|$ (phase locking value, PLV), where N is the number of trials. PLV is a normalized index between 0 (two signals are independent) and 1 (constant phase lag between the two signals). The relative change of PLV from the pre-stimulus period (δPLV) was analyzed by subtracting the mean value during that period (200 ms).

The statistical significance of PLV was assessed by randomization tests on shuffled data (Lachaux et al., 1999). The variance was computed by shuffling the order of events for one of the two signals randomly for each trial without replacement. This process was repeated 200 times. For example, shuffle 23 out of 200 might lead to calculation of the PLV between the ECoG for event 23 in SI with that of event 146 in the PS electrode (Fig. 1). Therefore, the stimulus-locked laser-evoked activity of the two signals is preserved but the non-stimulus-locked correlation of signals related to any specific event is lost. The significance level of 0.05 was corrected by the number of frequency bins and cortical areas tested (Tallon-Baudry et al., 2001) (see Section 4.1).

We analyzed baseline PLV and δPLV for all possible pairs of electrodes, at which significant LEP peaks and/or α event-related desynchronization (ERD) (6–14 Hz for both subjects) were observed in our previous paper (Ohara et al., 2004a). Since LEPs and ERD were recorded from SI, PS, and the MF cortex, we focused on the analysis of baseline PLV and δPLV between those regions (outlined by blue lines in Fig. 2). Preliminary results showed that significant PLV and δPLV were observed commonly in two subjects in and/or around α -range (6–14 Hz) and in β -range (16–24 Hz). PLV and δPLV in γ -range (>30 Hz) were found for some electrode pairs, but their magnitude was small and inconsistent between subjects. Therefore, the analyses described below were limited in these two (6–14 and 16–24 Hz) frequency ranges.

We next tested the differences between attention and distraction in the proportion of synchronous (PLV or δPLV) electrode pairs for each region pair, such as SI–PS. When comparing such differences in synchrony, we adopted the sta-

tistical approach reported in previous studies of this kind (for example, see (von Stein et al., 1999; Bruns and Eckhorn, 2004)). We first carried out tests of proportionality of synchronous electrode pairs across the three cortical areas for subjects overall, with Bonferroni correction for multiple cortical areas. We then carried out tests of proportionality within each subject, individually considering pairs of cortical areas corresponding to those with synchrony overall. The null hypothesis of no attention-related change in synchrony was rejected only on the stringent condition that the differences in synchrony between attention and distraction were significant *both* over all subjects and within each subject.

In the subjects we analyzed, we often observed polarity reversal of LEPs across major sulci (e.g., the sylvian fissure). This suggests that the oscillatory activity from a single generator source could also be recorded in an opposite polarity at different electrodes. Therefore, we could not analyze phase relationship (phase lag), which reflects the polarity of potentials.

3. Results

Laser pulses used in the present study evoked a painful, pin-prick sensation in both subjects. Subject 1 rated pain intensity as 4–5/10 and 3–4/10 for two attention runs, and 3–4/10 and 2–3/10 for two distraction runs. Subject 2 reported pain intensity of 5/10 for both attention runs, and 0/10, 1/10, and 5/10 for the distraction runs (Ohara et al., 2004a). Despite the differences in laser-evoked pain we did not see significant differences in the PLV and δPLV among runs for each condition and patient. Therefore, we analyzed data together from 2 or 3 runs for each condition in each subject.

Fig. 1 shows PLV and δPLV between a pair of electrodes, one each in SI and PS areas, as identified by arrowheads in Figs. 2 and 3, respectively. The colors other than the background (A – dark blue PLV, B – green δPLV) indicate significant differences from the mean PLV or δPLV as determined for SI–PS pairs of electrodes in which the order of trials was shuffled.

In the β -range (16–24 Hz), event-related ERD, or decreased power, was observed in SI during attention and distraction (A – lower) (see (Ohara et al., 2004a)), while attention significantly increased the PLV during the pre-stimulus/baseline period (A – upper). In the α -range (6–14 Hz), ERD was observed during attention and distraction in SI (B – lower), and increased δPLV (B – upper) was observed during attention during the post-stimulus period. It should be noted that the peak increase of PLV (δPLV at approximately 300 ms) preceded the decrease in power change in SI (ERD at approximately 650 ms). Therefore, the change in power did not correlate with changes in PLV or δPLV , as in previous studies of synchrony between cortical structures (Tallon-Baudry et al., 2001; Knyazeva et al., 2005).

In the analysis of this type of data, there is always concern that a common reference, such as our averaged

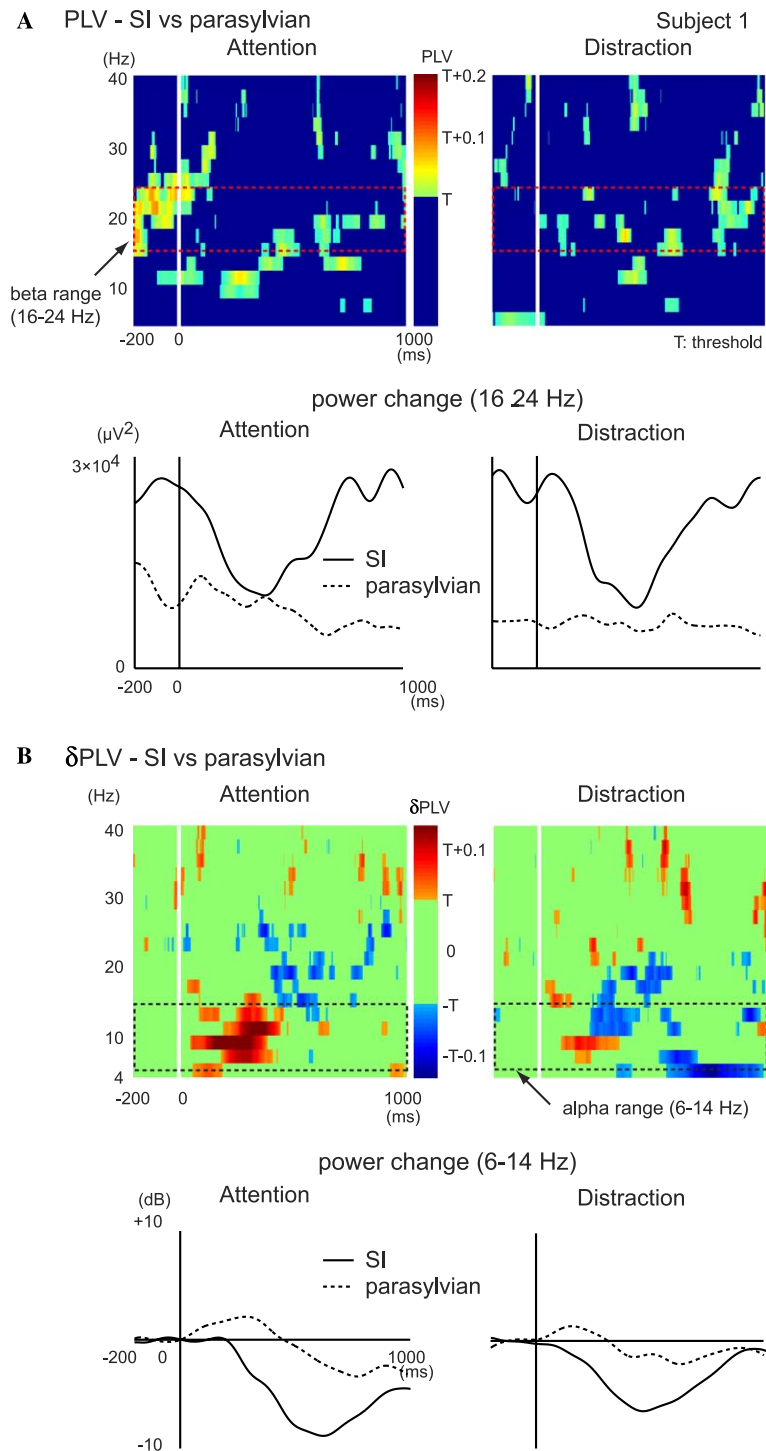


Fig. 1. PLV and δ PLV between electrodes in SI and parasyllvian (PS) regions in subject 1. (A) Time–frequency representation of PLV and power in the β -range (16–24 Hz). (B) Time–frequency representation of δ PLV and power in the α -range (6–14 Hz). The electrode locations chosen in SI and PS regions for PLV (A) and δ PLV (B) are indicated in the diagram of cortical anatomy in Figs. 2 and 3 by arrowheads, respectively. PLV (A) and δ PLV (B) above significant level (T, threshold) were demonstrated by the color other than background (blue for A, green for B). See the text.

reference, will automatically lead to synchrony between channels sharing the reference (Bruns and Eckhorn, 2004). Therefore, we tested the extent to which the averaged reference affects the signal recorded at any individual electrode. This was accomplished by computing the

PLV and δ PLV between the signal measured at each electrode (against the averaged reference) versus the averaged reference itself, across both subjects and three cortical regions. For the 81 electrodes in the present data, this PLV was significant in 2/81 electrodes (2%)

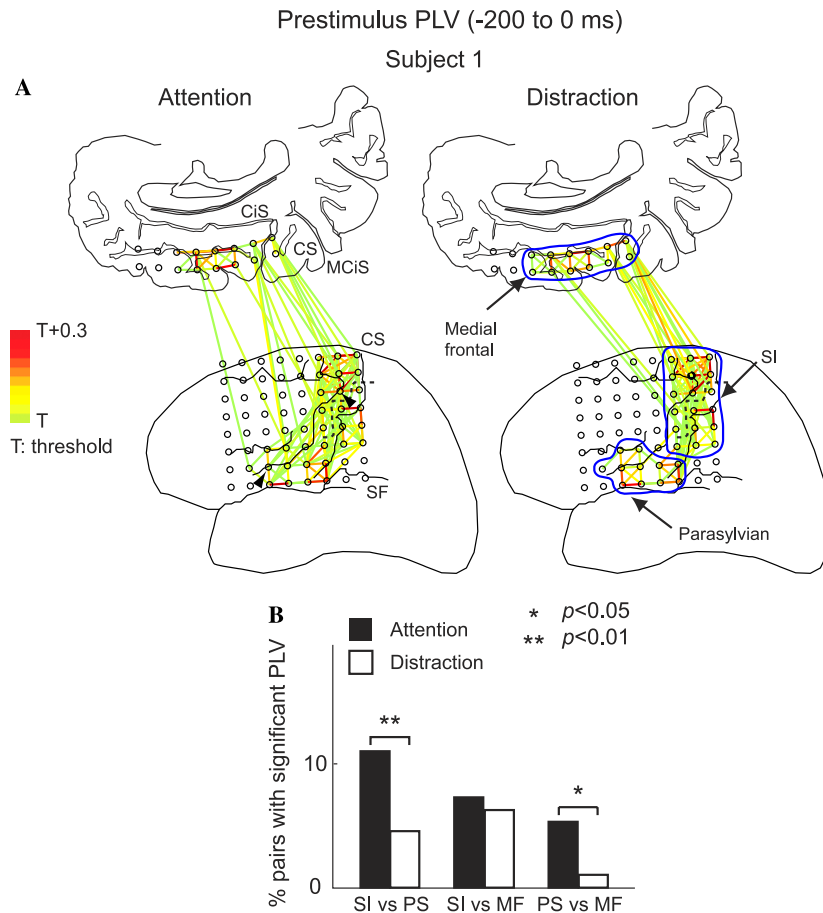


Fig. 2. PLV during the pre-stimulus period in β -range (16–24 Hz) in (A) subject 1 and (B) subject 2. PLV value above significant level (T, threshold) was demonstrated by the color of the line connecting a pair of electrodes. Scale was shown in color bars. Three regions analyzed (SI, PS, and MF) are circumscribed by blue lines. Note the clear difference between two conditions in degree of synchronization. Bar graphs indicate the proportion of electrode pairs between two regions where significantly increased baseline PLVs were recorded. Significant differences between the two conditions were consistently found between SI and PS regions. CS, central sulcus; SF, sylvian fissure; CiS, cingulate sulcus; MCiS, marginal branch of cingulate sulcus; PS, PS region; MF, MF region; N, no electrode pairs showing significant PLVs. Dashed lines in the diagram indicate SEP N20–P20 phase reversal, suggesting the location of the central sulcus.

and the δ PLV never reached a significant level (0/81). Therefore, the averaged reference does not account for a significant amount of activity in any individual channel in the present data.

3.1. Pre-stimulus PLV

In the β -range (16–24 Hz), at least one electrode pair with significantly increased baseline PLV was found (Fig. 2) between all 3 region pairs except for the distraction condition in the PS–MF region in subject 1. Fig. 2 shows higher proportion of synchronized pairs during attention than during distraction for PS–SI pairs ($P = 0.003$, Bonferroni corrected χ^2), and PS–MF pairs ($P = 0.020$) but not SI–MF pairs ($P > 0.9$). The results were next analyzed within subjects.

There was a higher proportion of synchronized pairs during the attention than the distraction condition for PS–SI pairs in subject 1 ($P = 0.036$, χ^2 test) and in sub-

ject 2 ($P = 0.004$). The same test for the PS–MF pair showed no significance for subject 1 ($P = 0.060$) or for subject 2 ($P = 0.085$). In summary, the proportion of electrode pairs for which baseline PLV values were significantly and consistently higher during attention than distraction for SI–PS pairs.

In Fig. 2, the distribution of PLV seems to be more spatially diffuse during the attention than the distraction task. A higher proportion of electrodes had significant PLV with an electrode in any other region for PS during attention (21/25) than during distraction (7/25) ($P < 0.001$) (χ^2 test, Bonferroni correction). Neither SI nor MF showed a significant difference. Therefore, attention to the stimulus during the pre-stimulus periods is associated with increases in the strength and spatial distribution of functional connectivity between SI and PS cortex. Fig. 2A suggests that the activation of SI was mostly in the somatotopically appropriate arm area, as in the other subject (not shown).

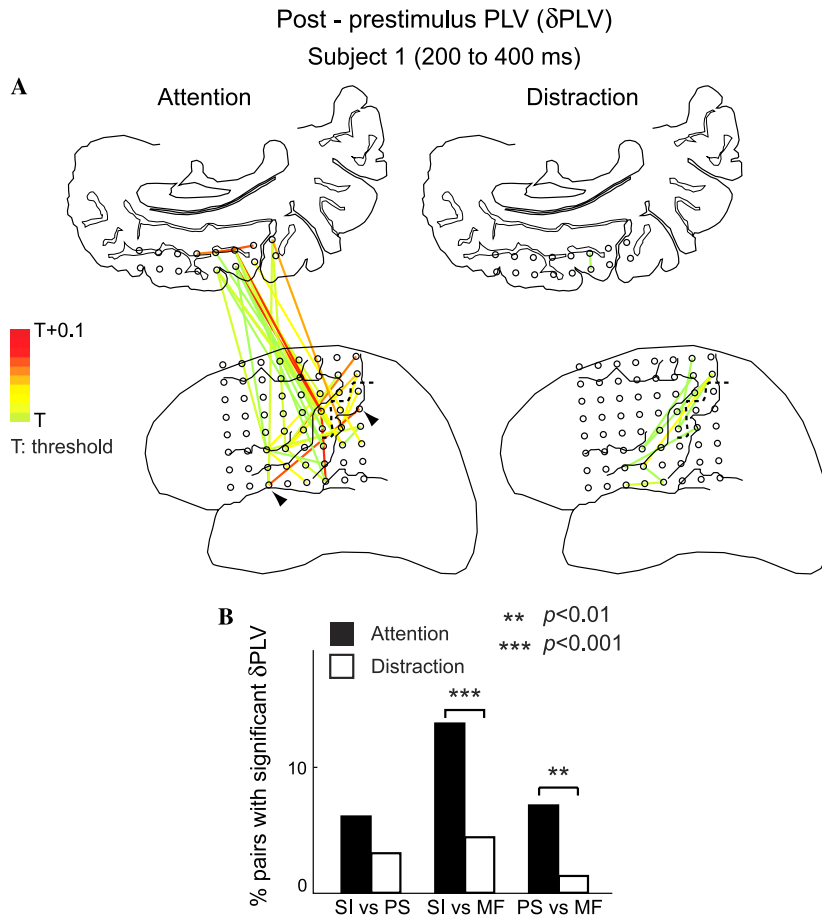


Fig. 3. PLV change from the baseline value (pre-stimulus period) (δ PLV) following laser stimulation in α -range (6–14 Hz) in (A) subject 1 and (B) subject 2. Significant δ PLV from the baseline value above significant level (T, threshold) is demonstrated by the color of the line connecting a pair of electrodes. Scale is shown in color bars. Conventions as in Fig. 2. The arrows in the diagram of cortical anatomy in subject 1 indicate the locations of electrodes in SI and PS regions demonstrated in Fig. 2. Note the clear difference between two conditions in both subjects. Bar graphs on the right hand side of the figure indicate the proportion of electrode pairs between two regions where significant δ PLV (increase) was found. Significant or nearly significant difference between conditions was found between SI and MF regions and between PS and MF regions.

3.2. Change from pre-stimulus to post-stimulus (δ PLV)

Fig. 3 illustrates a clear difference between attention and distraction conditions in the PLV change from pre-stimulus to post-stimulus (δ PLV). We analyzed the proportion of pairs with significant δ PLV in the α -range over the 200–400 ms for subject 1, and over the 100–300 ms for subject 2, based on the range of latencies of δ PLV measured across electrode pairs. Fig. 2 shows higher proportion of synchronized pairs for both subjects combined during attention than during distraction for PS–MF pairs ($P = 0.006$, Bonferroni corrected χ^2) and SI–MF pairs ($P < 0.001$), but not PS–SI pairs ($P = 0.221$). Again, results were analyzed within subjects for the pairs of cortical areas with significant δ PLV.

The significant difference in proportion of electrode pairs showing a significant δ PLV between attention and distraction was found for SI–MF pair for subject 1 ($P < 0.001$, χ^2) and subject 2 ($P = 0.005$). The same test for the PS–MF pair was significant for subject 2

(0.028), but not for subject 1 ($P = 0.060$). Therefore, we concluded that attention significantly increased the synchronization from the baseline for SI–MF pair. The most striking effect is the change from significant synchrony between PS and SI prior to the laser stimulus to significant synchrony relative to baseline between SI and MF after the stimulus.

4. Discussion

We found that the directed attention to painful stimuli was always associated with increased synchronization. This synchrony occurred between SI and PS regions before the stimulus during attention. Following the painful stimulus, synchronization was increased by attention for SI–MF region pair. These results suggest that attention directed to painful laser stimulation leads to functional connectivity which is different between the pre- and post-stimulus interval corresponding to anticipation of and counting of the painful stimulus, respec-

tively. This is the first evidence of connectivity and the first measure of connectional strength between cortical pain-related areas and so is basic evidence for the existence of ‘pain networks’.

4.1. Methodological concerns

Any approach which employs a common reference leads to the concern that the use of such a reference will automatically lead to synchrony between electrodes (von Stein et al., 1999; Bruns and Eckhorn, 2004). In the present study, the activity at each electrode was measured against an averaged reference, as usual for studies of coherence or PLV between electrodes measuring either scalp EEG (Knyazeva et al., 2005; Summerfield and Mangels, 2005) or subdural ECoG (Bruns and Eckhorn, 2004). The validity of this approach depends upon widespread sampling, which makes the averaged reference a reference-independent estimate of the EEG sources (Bertrand et al., 1985; Srinivasan et al., 1999; Srinivasan, 1999, 2003; Bruns and Eckhorn, 2004). This is consistent with the lack of synchrony between the signal for each electrode (against the averaged reference) the averaged reference signal itself (Section 3).

The statistics of multiple comparisons is always a concern in studies of this type. In the present analysis, we corrected for the effect of different frequency bands and for different cortical areas, but not for different electrode pairs. Other studies of PLV or coherence have adopted a similar approach (Tallon-Baudry et al., 2001; Oya et al., 2002; Bruns and Eckhorn, 2004) or less stringent approaches (Classen et al., 1998; von Stein et al., 1999; Spencer et al., 2003; Brancucci et al., 2005; Summerfield and Mangels, 2005).

The significance of PLV or δ PLV without correction for multiple comparisons must be considered to be a liberal, if widely accepted, criterion for synchrony between any pair of electrodes. However, it is still a valid criterion for selecting electrode pairs with a degree of synchrony during attention versus distraction, which can be examined by tests of proportion. We adopted a very stringent condition for identifying differences in synchrony between attention and distraction. Specifically, the null hypothesis of no attention-related change in synchrony was rejected only if the difference was significant both across and within individuals (von Stein et al., 1999).

4.2. Pre-stimulus synchronization

The synchrony produced by tasks related to the painful stimulus is consistent with cortical neuronal synchrony during attention to sensory stimuli. One study showed a significant increase in neuronal synchronization between pairs of neurons in SII during attention to tactile stimuli (Steinmetz et al., 2000). Other studies

demonstrate increased synchronization between neurons in V1 and in V4 when monkeys attended to visual stimuli (Fries et al., 2001; Super et al., 2003).

The present synchronization of ECoG related to attention to painful stimuli is consistent with ECoG evidence of nociceptive inputs to these areas (Lenz et al., 1998a,b). Since the present study did not measure the response to non-painful somatic stimuli, it is unclear whether these stimuli would result in a similar pattern of synchrony. This is particularly so since the cortical areas included in the present study are activated by non-painful as well as by painful somatic stimuli (Casey et al., 1994; Coghill et al., 1994; Davis et al., 1998). These studies are also consistent with the involvement of these areas in attention to pain. In Brodmann’s area 7B, part of PS, neuronal activity anticipates the stimulus by increased firing as the noxious stimulus approaches the RF of the cell (Dong et al., 1994). Compromise of area 7B produces increased pain tolerance, perhaps related to inattention, which would suggest that the PS region is involved in mediating attention directed toward painful stimuli (Dong et al., 1996).

Pre-stimulus or baseline synchrony between pain-related cortical areas in the lower frequency bands is consistent with a broad range of evidence. The γ band has been often used to describe the phenomenon of cortical synchrony (Engel and Singer, 2001), usually to synchrony *within* cortical regions. One example of this effect is the enhanced local γ oscillations which occur during selective attention to sensory stimuli (Gruber et al., 1999; Gobbele et al., 2002). The lower frequency bands are better related to large-scale synchrony *between* cortical regions (Ermentrout and Kopell, 1998; Kopell et al., 2000; Varela et al., 2001), including separate regions known to be jointly involved in the task under study (Classen et al., 1998; Andres et al., 1999; von Stein et al., 1999; Mima et al., 2001; Ohara et al., 2001; Tallon-Baudry et al., 2001).

There is ample anatomical evidence that the SI, PS, and MF thalamocortical circuits are extensively connected, both anatomically and physiologically (Burton, 1986). SI is connected with MF cortex through reciprocal connections from posterior parietal cortex and SII, to anterior and middle cingulate cortex (Van Hoesen et al., 1993). Synchronization within thalamic relay nuclei can lead to cortical synchronization across the range of EEG frequencies from α to γ (Nicoletis et al., 1995; Steriade et al., 1997; Apkarian et al., 2000).

4.3. Post-stimulus synchronization

Imaging studies have demonstrated pain-related changes in the relation between bloodflow signals in different cortical areas as studied by a correlation analysis (Faymonville et al., 2003) and by a principal component analysis (Lorenz et al., 2003). Specifically, the middle

cingulate area involved in pain affect (Rainville et al., 1997; Faymonville et al., 2000) has bloodflow changes correlated with those in bilateral insula, perigenual ACC, supplementary motor area, right prefrontal cortex, striatum, thalamus, and brainstem during hypnotic analgesia (Faymonville et al., 2003). Heat allodynia (capsaicin irritant), versus experimental heat stimulation, was associated with a decreased relationship between bloodflow of midbrain and medial thalamus which was correlated with increased activation in the left dorsal lateral prefrontal cortex (Lorenz et al., 2003). The present results are the first direct electrophysiological evidence of functional connectivity between cortical structures receiving input arising from nociceptors.

We report increased post-stimulus synchronization for SI–MF region pairs. The middle cingulate (within MF) is recently shown to be selectively activated by hypnotic manipulation of unpleasantness of painful stimuli (Rainville et al., 1997) and to be linked to widespread activation of the frontal lobe during the response to painful stimuli (Lorenz et al., 2003). However, the ACC is also implicated in attentional tasks not necessarily related to pain by imaging (Vogt et al., 1996; Davis et al., 1997; Derbyshire et al., 1998; Hsieh et al., 1999) and lesioning studies (Cohen et al., 1999). Therefore, the increased interaction of MF cortex with somatic sensory cortices during directed attention is consistent with the model that some parts of the ACC are ‘sources’ specific for attention while other parts of ACC and somatic sensory cortices may be ‘sites’ for attention-related modulation of inputs signaling pain (Posner, 2000).

Basic physiology provides mechanisms for cortical synchrony evoked by stimulation of thalamocortical systems. Low frequency stimulation of thalamic relay nuclei by natural stimulation of peripheral receptors, or by electrical thalamic stimulation, leads to progressively increasing, synchronized oscillations in cortex and in thalamic reticular nucleus (Von Knorring et al., 1979; Timofeev and Steriade, 1998; Steriade, 2001). High frequency stimulation of reticular nucleus can produce focal high frequency cortical oscillations (Macdonald et al., 1998), while low frequency stimulation leads to synchronized, progressively increasing, oscillations in cortex (Steriade, 2001). Lesions of the reticular nucleus impair directed attention (Weese et al., 1999) consistent with involvement of this nucleus in attention.

Widespread cortical activity may be synchronized by the intralaminar nuclei which receive input from the STT (Willis, 1985; Apkarian and Shi, 1994) and project to the anterior and middle cingulate, sensorimotor, and posterior parietal cortex (Vogt et al., 1987; Huffman and Krubitzer, 2001). Widespread, progressively increasing, synchronized cortical oscillations are observed in response to low frequency stimulation of intralaminar nuclei (Steriade, 2001), and stimulation of the intralaminar nuclei leads to alerting responses (Schlag and Sch-

lag-Rey, 1984; Minamimoto and Kimura, 2002), similar to the alertness evoked by novelty (Lenz et al., 2000). Therefore, a broad range of anatomic and physiologic evidence suggests that thalamic mechanisms may account for post-stimulus synchrony.

The present results demonstrate a significant change in synchrony between pre-stimulus and post-stimulus which are different pain-related tasks. The pre-stimulus task is anticipation of the stimulus which is associated with functional connectivity between SI and PS. The post-stimulus task is a response to the stimulus, i.e., counting, which is associated with increased synchrony between MF and SI. The effects of SI, PS, and MF lesions upon pain-related behavior suggest that these are separate processing modules within a hierarchical network (Churchland and Sejnowski, 1992; Davis et al., 1994; Talbot et al., 1995; Greenspan et al., 1999; Ploner et al., 1999). In view of these lesion studies, the present analysis of synchrony is the first compelling evidence that functional connectivity within hierarchical ‘pain networks’ is not fixed but changes rapidly as a function of the pain-related task.

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