Published in final edited form as:

Pain. 2011 March ; 152(3): 664–675. doi:10.1016/j.pain.2010.12.016.

Attention to painful cutaneous laser stimuli evokes directed functional connectivity between activity recorded directly from human pain-related cortical structures

C.-C. Liu^a, S. Ohara^a, P. J. Franaszczuk^b, and F. A. Lenz^a

^a Department of Neurosurgery, Johns Hopkins University, Baltimore, MD, USA

^b Department of Neurology, Johns Hopkins University, Baltimore, MD, USA

Abstract

Our previous studies show that attention to painful cutaneous laser stimuli is associated with functional connectivity between human primary somatosensory cortex (SI), parasyllian cortex (PS), and medial frontal cortex (MF), which may constitute a pain network. However, the direction of functional connections within this network is unknown. We now test the hypothesis that activity recorded from the SI has a driver role, and a causal influence, with respect to activity recorded from PS and MF during attention to a laser. Local field potentials (LFP) were recorded from subdural grid electrodes implanted for the treatment of epilepsy. We estimated causal influences by using the Granger causality (GRC), which was computed while subjects performed either an attention task (counting laser stimuli) or a distraction task (reading for comprehension). Before the laser stimuli, directed attention to the painful stimulus (counting) consistently increased the number of GRC pairs both within the SI cortex and from SI upon PS (SI > PS). After the laser stimulus, attention to a painful stimulus increased the number of GRC pairs from SI > PS, and SI > MF, and within the SI area. LFP at some electrode sites (critical sites) exerted GRC influences upon signals at multiple widespread electrodes, both in other cortical areas and within the area where the critical site was located. Critical sites may bind these areas together into a pain network, and disruption of that network by stimulation at critical sites might be used to treat pain.

Keywords

Attention; Human; Pain; Somatic sensory cortex; Network; Event-related; Laser evoked; potentials

1. Introduction

The response to painful stimuli occurs in brain areas including the primary somatosensory cortex (S1), parasyllian cortex (PS, including the secondary somatic sensory cortex [SII] and insula), and medial frontal cortex (MF, including the middle cingulate and supplementary motor cortex) [3,19,25,52,82,84]. Both electroencephalography (EEG) and (magnetoencephalography (MEG) studies have suggested that cognitive modulation of pain by attention involves early sensory processing in SII and insular cortex [51] and later

---

Conflict of interest statement

None of the authors has conflicts of interest related to this work.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

processing in the anterior cingulate cortex [8,30,41,83,87,106,107]. These structures, or their subunits, may constitute a pain network ([5,18,31,61,76,92] cf [64]).

A neural network consists of neural elements, their connections, and connectional weights, which are often equated with neurons/modules in the brain, axons, and synapses, respectively. 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 [21,69,84]. Synchrony between signals recorded from forebrain structures may indicate functional connectivity between these modules [88]. Studies of local field potentials (LFP) recorded directly from the brain have demonstrated significantly increased synchrony during the attention versus the distraction task [69]. Specifically, there was increased synchrony between SI and PS in the beta range (16–24 Hz) before the stimulus, and between SI and MF in the alpha range (8–16 Hz) after the stimulus.

The results of that study are consistent with a model in which SI plays a pivotal role in the processing of acute pain by receiving inputs from the periphery and then influencing activity in other pain-related structures such as the MF and PS cortex [3,38,82]. In addition, the blood oxygen level dependent (BOLD) activity before a painful stimulus is synchronous between areas including SI, anterior, and middle cingulate cortex, insula, and S2 [48]. We now test the hypothesis that activity in SI exerts a causal influence or driver role upon activity recorded from PS and MF during directed attention to the laser.

We estimated causal influences by the Granger causality (GRC) between LFPs recorded from cortical structures in response to an acute painful (cutaneous laser) stimulus. GRC [32] is based on the concept of linear predictability. Briefly, a signal Y is said to be causal of signal X when the predication error of the X is reduced by adding the past information of Y. The number of coefficients of past information is characterized by the auto-regressive model order which optimizes the description of the system. Recordings were made for a week before cortical resections for the treatment of patients with focal epilepsy through grid electrodes implanted directly over the cortex, under conditions of attention toward and distraction from the laser stimulus.

2. Methods

The present study included three patients with medically intractable frontal lobe seizures. Neurological examinations and brain magnetic resonance images were normal [57]. In addition, all seizure medications were discontinued for 36 hours after the implantation of the electrodes. Therefore, all subjects had substantial blood levels of these drugs at all points relevant to this study [58]. No subject had any medical or psychiatric condition other than epilepsy, or took medications other than anti-epileptic drugs. The protocol for these studies was approved by the Institutional Review Board of the Johns Hopkins University; all subjects signed an informed consent for this protocol.

2.1. Cortical recordings and localization

Subdural electrode grids were placed over the SI cortex, the PS cortex, and the medial wall of both the left and right hemisphere (Figs. 1 and 4). The platinum-iridium circular contacts (2.3-mm diameter, 80–100 electrodes) were arranged in a rectangular grid with a center-to-center distance between electrodes of 1 cm (Ad-Tech, Racine, WI) and were used to record LFPs directly from these subdural regions. All LFP recordings were amplified (12A5, Astro-Med, West Warwick, RI), down-sampled to 200 Hz, digitally band-pass-filtered at 0.1 to 300 Hz, and then referenced to a single subdural electrode chosen for its low activity. The signals were sampled and digitized at 1000 Hz. The recorded signals were visually inspected and trials with artifact were excluded from the study.

The positions of subdural electrodes relative to the central sulcus (CS) and the sylvian fissure (SF) were determined by the somatosensory evoked potential (SEP), N20–P20 polarity reversal, intraoperative observation and photographs (Fig. 1). In Fig. 1 (subjects 1 and 2), the orientation of the electrodes relative to the map of the underlying brain is the same as that shown in Figs. 4A and 5A (middle and right columns). For subject 3, the grids were implanted over the right hemisphere so that the map of the brain is the mirror image of that for the other subjects.

In Fig. 4A, left column the grid is shown superimposed upon 3-dimensional (3D) computed tomography (CT) and 3D MRI image, as in previous studies [10,23,54,55]. The SEP N20–P20 polarity reversal and intraoperative pictures were consistent in terms of CS location in 2 subjects who had intraoperative pictures available (subjects 1 and 3).

The location of the sulci, including the SF and CS, was based on anatomy of the convexity as estimated by SEP and 3D CT-MRI [65]. The sulcal anatomy, based on 3D CT-MRI data, was then used to make diagrams of the cortical surface (Fig. 1). The locations of SEP N20–P20 polarity reversal and of the N20 maximum were found slightly anterior to the CS location as determined from 3D CT-MRI. The positions of subdural electrodes on the interhemispheric surface were determined by superimposition of a parasagittal image from the preoperative T1 weighted MRI and the mid-sagittal plane of the postoperative 3D CT.

2.2. Laser stimulation and experimental paradigm

The subjects wore goggles and rested in a semi-reclining posture with their eyes open, quietly wakeful. Laser stimuli were applied to the dorsum of the hand (contralateral to the implanted grid electrodes) using a Thulium YAG laser (Neurotest, Wavelight, Starnberg, Germany) with a laser-beam wavelength of 2 μm and a beam diameter of 6 mm. The energy level for the laser was selected to provoke pain equal to 4–5/10, as determined before the experiment. The duration of each laser pulse was 10 milliseconds; the inter-stimulus interval was randomized between 6 and 12 seconds. An effect of habituation related to the interstimulus interval cannot be ruled out, although this effect will be present during both the attention and distraction conditions [63,102]. The analysis interval began 200 milliseconds before the laser and ended 1000 milliseconds after the laser. To avoid fatigue or sensitization, each laser pulse was applied to a slightly different location.

The laser pulses were delivered while subjects were attending to the stimuli by counting them or while distracted from the stimuli by reading for comprehension. At the end of each stimulation block, the subject was asked the number of stimuli under the attention condition, or 2 questions regarding their reading, under the distraction condition. The overall pain intensity was rated for each block of stimuli on a visual analogue scale (VAS), for which 10 represented the most intense pain imaginable and 0 represented no pain. For each task condition, the stimulation consisted of 2 separate stimulation runs; each run consisted of 38 laser stimulation pulses a total number of 76 laser stimulations per condition [69]. The order of these runs was randomized and counterbalanced across subjects.

The GRC spectral analysis was performed on the signal recorded under both attention and distraction task conditions. For each task condition, 3 intervals (1 pre- and 2 post-stimulus intervals) were analyzed separately. As in our previous studies of subdural recordings and the Thulium laser, the first consistent laser evoked potential (LEP) peak was a negativity (N2) that reached its maximum amplitude at time approximately 136 to 149 milliseconds, and a positive component that reached its maximum amplitude at 222 to 238 milliseconds [71,72].

2.3. GRC analysis

In this study, the GRC analysis was applied to signals recorded from electrode sites located over different cortical structures to evaluate strength of GRC interactions between these structures. The GRC was calculated in the 6- to 14-Hz frequency band which was based on the frequencies of peaks in ensemble averages of the LFP power, coherence, and GRC (Fig. 2). These frequencies were consistent with those of other studies of intracranial recordings [69,74,97], and were higher than those of recordings from the scalp [2,105].

To determine causality in the frequency domain, we used a multivariate autoregressive modeling (MVAR) approach. The signals acquired during the experimental trials were treated as if they were produced by a common stochastic process, and were used to estimate the MVAR model coefficients for that process [26]. The MVAR model order was determined by the Akaike information criteria (AIC) [1] as an estimate of the number of coefficients which would optimize the MVAR analysis.

If the first channel is a driver of the second channel, then this causal influence it will be identified by the GRC method, although the inverse is not necessarily true. In addition, all signals relevant to analyzed system must be observed before final conclusions can be drawn from this analysis. All selected channels are included in the MVAR model used for computation of GRC so that it is not computed for each of the cortical areas separately. Therefore, effects within modules, such as SI, will not determine GRC influences across the network.

In general, the significant GRC influences are observed for pairs of channels that are both active and correlated. However, larger activation or correlation within an area such as the SI does not necessarily influence the level or directionality of GRC because of the normalization of the signals before the computation of GRC. In fact, the coefficients of the MVAR model used in this analysis are calculated using correlation matrices for all observed channels. Therefore, the correlation may influence the magnitude of the GRC but will not determine the directionality of the GRC effect. This additional information about directionality of influences is determined by the GRC analysis.

The anatomical location and size of the 3 cortical areas were determined (1) to cover the brain area where the significant laser- evoked responses (ie, LEPs) or electrical activation (event-related desynchronization) were located [69], and, (2) to satisfy the inequality for MVAR model considerations [49]. The numbers of selected electrode sites were 30 in subject 1 (MF: 9, SI: 12, PS: 9), 30 in subject 2 (MF: 6, SI: 14, PS: 10), and 40 in subject 3 (MF: 10, SI: 19, PS: 11). After MVAR model estimation, the goodness of the fit of the model was evaluated by testing the white noise assumption for the model residuals [26]. All of the estimated MVAR models in this study were tested to insure that the data could be represented as an AR process.

The concept of GRC is based on the predictability of linear regressive modeling for stationary time series. If a time series X_t contains information in the past that helps in the prediction of Y_t then, X_t said to Granger causal of Y_t [32]. Suppose the acquired LFP recording contains p channels, we can write as the acquired signal X at time t as:

$$X_t = (x_{1t}, x_{2t}, x_{3t}, \dots, x_{pt})^T,$$

where the subscription of x indicates the index of channel and time, the superscript T denotes the matrix operation for transpose. The m order multivariate autoregressive model (MVAR) for this p channel LFP recording can be written as:

$$\sum_{k=0}^m A_k X_{t-k} = E_t$$

where E_t are uncorrelated error terms and their covariance matrix is Σ , A_k are $p \times p$ coefficient matrices. The coefficients were estimated by solving the Yule-Walker equations using Levinson, Wiggins, and Robinson algorithm [24,26].

Before the MVAR model estimation, each sample of raw LFP signals was averaged across trials, and this ensemble average was subtracted from the LFP signal for each individual trial. For each trial, the resulting signal was further normalized by subtracting the mean signal amplitude for each trial from the signal for that trial and divided by the standard deviation for that trial. This normalization has been shown to enable the comparison of causality between different intervals and different pairs of channels [26,49]. With estimated MVAR model coefficients and covariances, the spectral matrix for the LFP recording can be written as:

$$S(f) = |X(f)X(f)^*| = H(f) \sum H^*(f).$$

where the superscript asterisk denotes matrix transposition and complex conjugation, and $-H(f) = \sum_k^m A_k e^{-2\pi i k f}$ is also conventionally called the transfer function. The power spectrum for channel i is denoted as the element S_{ii} in the spectral matrix S . The off-diagonal elements of spectral matrix S are the coherence spectrum for any given pair of channels and can be written as:

$$C_{ij}(f) = |S_{ij}(f)|^2 / [S_{ii}(f)S_{jj}(f)]$$

where the subscript i and j denotes channel i and j . The GRC spectrum for pair channels X and Y was computed using bi-variate AR model for LFP time series X_t and Y_t was constructed using the same procedure above procedures. The GRC spectrum from Y_t to X_t is computed as:

$$F_{Y \rightarrow X} = -\ln \left[1 - \frac{\left(\sum_{YY} - \frac{\sum_{XY}^2}{\sum_{XX}} \right) |H_{XY}(f)|^2}{S_{XX}(f)} \right]$$

where $\sum_{XX}$, $\sum_{YY}$ and $\sum_{XY}$ are elements in covariance matrix Σ . $S_{XX}(f)$ is the auto-power spectrum for electrode site X at frequency f . Similarly, the GRC spectrum from X to Y is

$$F_{X \rightarrow Y} = -\ln \left[1 - \frac{\left(\sum_{XX} - \frac{\sum_{XY}^2}{\sum_{YY}} \right) |H_{YX}(f)|^2}{S_{YY}(f)} \right]$$

The value of GRC ranges from 0, no GRC influence from the other site, to 1, representing total GRC influence from the other site.

2.4. Statistical testing

There are uncontrolled factors that can influence GRC measures and can lead to false GRC relationships. This results in the need for statistical examination to determine whether the event-related GRC effects are outside a statistical threshold for the confidence interval of GRC interactions in the data. Consider the GRC from signals recorded from 2 separate electrode sites. We determined the empirical distribution of the data by shuffling or resampling the data through pairing the data from 1 of these original sites randomly with other sites and trials in the same block. Using the data recorded from the baseline period, this resampling was carried out repeatedly with replacement (bootstrap) to produce a set of “artificial trials” which were analyzed to determine variability of the GRC [60].

An empirical distribution was constructed from the GRC calculated for these artificial trials and was used to determine confidence intervals for statistical significance level of the GRC. The number of artificial trials for constructing the baseline distribution was experimentally chosen to be 1500, to ensure the reliability of this estimate of the distribution. The significant level was set to $\alpha = 0.05$ with Bonferroni correction for multiple comparisons across the number of site pairs and the number of frequency bins [26,37,40].

3. Results

These studies were carried out in 3 subjects (2 female, 1 male, 21–51 years of age) who had subdural grids implanted for the surgical treatment of medically intractable epilepsy that was thought to result from a frontal focus. Subdural electrode grids were implanted over the left lateral frontal parietal convexity and medial wall of the frontal and parietal lobe (subject 1), the left lateral frontal parietal area (subject 2), and the right lateral convexity and medial frontal parietal area (subject 3). Neurological examination, including a standard sensory testing protocol [56], was normal for all subjects. Brain magnetic resonance imaging (MRI) revealed bilateral subcortical T2 changes consistent with enlarged peri-vascular spaces in subject 3 (Nadich et al., 1995), but was within normal limits in the others.

Laser stimulations evoked painful, pin-prick sensations in all 3 subjects. Table 1 reveals that the pain intensity ratings were similar in all 3 subjects during the counting task. The ratings were lower during reading in subjects 1 and 3, and substantially lower in subject 2; overall pain VAS scores were significantly ($t = 3.0$, $P = .024$) higher during counting (4.7 ± 0.5) than during reading (2.5 ± 1.6). Significantly higher alpha band power and N2 and P2 LEP amplitude were found across the 3 areas in all 3 subjects during attention versus distraction [70,73] (Table 3).

3.1. Ensemble analyses

Anatomical areas for this analysis were defined by the location of electrodes from which reproducible LEPs could be recorded. Cortical areas are defined by this criteria SI, PS, and MF, as indicated by gray areas on the cortical surface, as shown in Fig. 1 and by electrode positions marked as in Fig. 4 [71,72].

The power and coherence spectra were first computed from estimated MVAR models for each subject. Fig. 2A and B show the average power and coherence spectra for MF, SI, and PS cortical areas. The autopower of a signal is the square of the magnitude of the signal as a function of frequency [75]. The cross-spectrum of the 2 signals is composed of the magnitude (cross-power spectrum) and phase spectrum. The square of the cross-power is often divided by the product of the averages of the 2 autospectra to produce the coherence. The coherence is used to estimate the probability that the 2 signals are linearly related, ie, 1 signal could be described as a linear function of the other [6].

For all 3 subjects, the average power spectra showed that peak oscillatory activities during the experimental task period occurred within the alpha band (8–13 Hz), and the averaged coherence spectra showed that the alpha band oscillatory activities were often synchronous overall. The peaks in the averaged power spectra were 6.8 Hz, 7.8 Hz, and 8.9 Hz, and for the averaged coherence spectra were 7.1 Hz, 8.5 Hz, and 9.1 Hz for subjects 1, 2, and 3, respectively.

Fig. 2C shows the averaged significant GRC for all 3 subjects. It is clear that the peak averaged significant GRC also occurred within the alpha frequency band. The confidence interval for GRC was determined by the resampling approach described in Methods (Statistical analysis subsection), with a Bonferroni correction for multiple comparisons. The confidence interval was determined separately for both directions between each site pair pair (Table 2).

3.2. Pre-stimulus GRC

The analysis of significant GRC was carried out by dividing the pairs of electrodes into the following: 1) those located within the same area (“within-area,” separate gray areas in Fig. 4A, middle column); and 2) those in which the 2 electrodes were located in different areas and time intervals. These “between-areas” GRCs connect pairs of electrodes located in separate gray areas in Fig. 4A, such as SI and PS areas 0 to 200 ms intervals. The number of significant GRC pairs between different intervals was compared using the z test for 2 proportions.

The number of pre-stimulus electrode pairs with significant GRC is indicated by cortical area in Fig. 3, ie, SI, PS, MF. The basic anatomy of the left cortical areas in subjects 1 and 2 and electrode sites is shown in Fig. 4, which can be interpreted with reference to Fig. 1. The anatomy on the right cortical areas (subject 3) is oriented as the mirror image of that shown in Fig. 1. The proportion of GRC pairs of electrode signals was significantly larger for the post-stimulus than the pre-stimulus period during the counting but not the reading condition ($P < .05$) (Fig. 3). This effect is seen in SI but not in MF or in PS.

The proportion for the number of significant GRC pairs found during the pre-stimulus interval was scaled and denoted by the width of the arrow in Fig. 4A. The display of the surface of the brain is oriented as shown in Fig. 1, which also indicates the sulci shown in Fig. 4A.

In Fig. 4A, it is clear that the largest number of between-area significant GRC pairs indicates GRC from SI to PS for all 3 subjects under the counting task condition. For all 3 brain areas under study, the SI area had a significantly higher total number of significant output GRC pairs over the pre-stimulus period under counting than under the reading task condition ($P = .004$, $P = .005$, and $P < .001$ for subjects 1, 2 and 3, respectively), indicating that SI exerted a GRC input upon PS when subjects attended the laser stimulus by counting the number of stimuli.

The significant SI GRCs were mainly with the electrode sites located in the PS area ($P = .026$, $P = .012$, $P = .001$ for subject 1, 2, and 3, respectively). Fig. 4B (right) plots the number of significant input GRC pairs received from the SI and MF areas to the PS area under counting and reading conditions. This plot indicates that the PS area played a receiver role ($P = .032$, $P = .041$, and $P = .016$ for subjects 1, 2, and 3, respectively) under the counting task condition. Moreover, these input GRC pairs to PS were found more from the SI area than the MF area ($P = .012$, $P = .031$, and $P = .006$ for subjects 1, 2, and 3, respectively). Furthermore, results showed no significant difference in the MF area in terms of the number

of pre-stimulus GRC pairs between reading versus counting tasks, either within-area or between-areas.

Any pair of electrodes can have significant GRC in 1 of 2 directions, or have reciprocal GRC so that both directions show significance. Overall, the results show that the proportion for the significant reciprocal GRC was significantly higher within-areas than between-areas when subjects were performing the counting task ($P < .001$). There was no significant difference between the proportions of reciprocal GRC between within-areas and between-areas during the reading task condition.

3.3. Post-stimulus GRC: Between cortical areas

During the post-stimulus analysis interval (0–400 ms), the total number of significant GRC pairs overall found during the counting task was significantly higher than during the reading task ($P < .001$, $P < .001$, and $P < .001$ for subjects 1, 2 and 3, respectively; $P < .05$, z test for 2 proportions). Fig. 5 shows the distributions for the significant GRC pairs found during stimulus intervals between cortical areas. It can be seen that the largest numbers of significant GRC pairs were found between SI and PS during the counting task condition in all 3 subjects. In the post-stimulus interval, the SI cortical area showed more significant GRC pairs upon the other areas (PS, MF) more commonly than those areas had GRC significant pairs upon SI ($P = .022$, $P = 0.011$, $P = .031$ for subjects 1, 2 and 3, respectively). Furthermore, the numbers of significant GRC pairs found during post-stimulus intervals were summarized as the within-area and between-area in Fig. 6.

- The number of significant between-area GRC pairs (Fig. 6, right) was much higher for the late (200–400 ms) than the early (<200 ms) post-stimulus period. This is seen in the number of GRC pairs from SI to MF ($P = .001$, $P < .001$, and $P = .021$ for subjects 1, 2 and 3, respectively), and from SI to PS ($P = .001$, $P = .038$, and $P < .001$ for subjects 1, 2 and 3, respectively) versus SI as the receiver. Finally, the number of significant GRC pairs in the direction SI to MF and SI to PS was significant higher for the counting than the reading task condition ($P < .05$).

There were also remarkable differences between the numbers of within-area GRC pairs between the 2 post-stimulus intervals (Fig. 6, left). For all 3 subjects, the counting task condition had significant higher number of critical sites than the reading task condition for subjects 1, 2, and 3 ($P = .03$, $P = .027$, and $P = .012$, Fisher).

- The significant pairs for SI area were significantly higher during the second post-stimulus interval than the first under the counting task ($P < .001$, $P = .002$, $P = .046$ for subjects 1, 2, and 3, respectively). In addition, the number of within-area significant GRC pairs during the combined (0–400 ms) post-stimulus interval were significantly higher for the SI during the counting task than the reading task ($P < .002$, $P < .001$, and $P < .003$ for subjects 1, 2, and 3 respectively), which suggests that the counting task induced higher degree of interactions within the SI area.

3.4. Critical sites

The electrode sites associated with multiple significant GRC pairs during post-stimulus intervals are indicated in Fig. 7, which Reading we refer to as “critical sites.” To estimate the extent of the connections of these critical sites, we combined the results for 2 post-stimulus intervals and used it for the subsequent analysis. For all 3 subjects, the counting task condition had significant higher number of critical sites than the reading task condition for subject 1, 2, and 3 ($P = .03$, $P = .027$, and $P = .012$, Fisher). The numbers of critical sites during reading overlapped with those during counting to a much greater degree than expected at random, as tested by hypergeometric probability (agreement test, [46]). The

numbers of critical sites during reading and counting was 21 and 49, among which 21 sites overlapped across conditions (representation factor: 1.9, $P < .0000001$).

Fig. 7 suggests that the locations for critical sites overlapped between the counting versus the reading task conditions for all subjects and brain regions ($P < .001$). The electrode sites associated with > 1 significant within-area GRC pairs were likely to have > 1 significant between area GRC pair for SI ($r = 0.71$, $P = .0011$, linear regression), and PS areas ($r = 0.65$, $P = .006$) but not for MF ($r = 0.51$, $P = .24$) under the counting task. There was no significant relationship between the within-area and between area connections of electrodes at critical sites during the reading task. In addition, the pain ratings recorded under counting task condition tended to correlate with the proportion of critical sites in SI area (Pearson correlation $r = 0.75$, $P = .086$). These correlations might also reflect the effects of attention during the counting task condition.

4. Discussion

These results demonstrate that attention to a painful stimulus leads to a consistent increase in GRC interactions between pain-related cortical structures during both the pre-stimulus and post-stimulus periods. SI consistently had significantly more GRC interactions upon PS during the attention versus the distraction task in the pre-stimulus period. During the post-stimulus period, SI had significant GRC interactions upon PS and MF during the attention task. During both the pre-stimulus and post-stimulus period, there were more within-area significant GRC pairs during attention than distraction for SI, but not for PS and MF. None of these GRC interactions between or within cortical areas had reciprocal relationships or feedback between-areas (Figs. 3–5), or between electrodes located in these areas (Fig. 6). This within-area GRC may be the result of a local network organized on the basis of neuronal response properties, as in the case of other primary sensory cortical areas [13].

The within-area results are consistent with the suggestion that pain is mediated through a hierarchical network of modules or local networks including SI, PS, and MF. In this view, SI mediates attention to the sensory aspect of pain through its connections with PS [22,38]. SI has significant GRC outputs to the cingulate cortex which mediate attention to the unpleasantness of the painful stimulus [3,82,85]. Lesions of modules in a hierarchical network lead to double dissociation, as lesions of each module produce a distinct abnormality, as in the case of language networks [14]. Separate abnormalities of pain sensation are found with lesions of insula which produce increased tolerance [7,34], and the middle cingulate cortex, which produce increased gain of experimental pain [33,96]. Binding of these dimensions of pain into a unified sensation may be mediated through functional connectivity between these modules or local networks [67,88]. This model may be defined, in part, by functional connections between the 3 cortical areas, or their subunits, or deep structures which were not observed in this study [3,77,86]. However, the phase reversals of LEPs in all 3 cortical areas suggest the nociceptive generator is near the cortical surface in each area [72].

Nociceptive inputs to SI have been demonstrated by human functional imaging [3,52,77], EEG, and MEG studies [42,79]. This is consistent with monkey studies of single neurons [20,43,44] and of intrinsic optical signals in SI [100,101]. Finally, our studies in human subjects demonstrate that LEPs overlap with the distributions of somatosensory evoked responses to vibration, and to electrical stimulation of nerves which can be used to localize the central sulcus [72].

4.1. Methodological concerns

The subjects in this study all had frontal lobe epilepsy as determined by clinical and scalp EEG criteria. This diagnosis may be associated with radiological and electrical abnormalities related to seizure onsets. However, previous studies of subjects with other kinds of epilepsy did not have observed differences in LEPs or ongoing LFPs at electrode sites located in structures with radiological or electrical evidence of seizure onsets [59]. This result suggests that recordings from the epileptogenic cortex in the presence of anti-epileptic drugs need not alter recordings of the response to the painful laser. The small number of subjects in this study is standard for intracranial recordings of monkeys, and is offset by the increased resolution of the present recordings.

There are a number of methodological limitations of this GRC analysis such as the effect of unobserved structures. In addition, the large number of electrodes limits this study to bivariate estimates of directionality, which will lead to an incomplete description of this network if it has substantial multivariate interactions [9,28].

Significant GRC might be detected between signals that are both active and correlated, but not truly causal. However, the coefficients of the MVAR model used in this analysis are calculated using correlation matrices for all observed channels, so that correlation can influence the magnitude of the GRC, but not the directionality. Finally, the 200-ms intervals in the present analysis will limit our temporal resolution. The alternative would have been the “sliding window” or “running average” [6,75], which may yield finer time resolution estimates which may yield finer time resolution estimates of Granger causality. However, by this approach the complexity of the statistical randomization tests increases to the point that the interpretation of the statistical results can be very unclear. In the present approach, the resolution associated with the 200-ms intervals is coarse, but the interpretation of the causal pairs and values within these intervals is clear.

Contrary to this study, an earlier study has reported the significant GRC between S1 and SII (part of PS) in response to a tactile but not a painful laser stimulus in healthy subjects carrying out a reaction time task [81]. In that study, responses were magnetic signals that were projected upon maps derived from source analysis of activity recorded during sensory and motor tasks. The differences in recording, mapping, and cognitive tasks may explain differences between these 2 studies.

4.2. Pre-stimulus activity

The present results are consistent with increased synchrony between S1 and PS before the stimulus while the subjects directed their attention to the painful stimulus [69]. Similarly, analysis of BOLD signals before a painful stimulus have shown evidence of synchrony or functional connectivity between pain activated structures such as SI, SII, and middle cingulate cortex [48]. Finally, prestimulus pain-related networks involved in the perception of pain have been identified by synchrony between BOLD signals recorded between PS (anterior insula), MF structures (anterior and middle cingulate cortex) and midbrain [11,78]. Shifts in cortical attention-related activity may result from thalamic inputs that reflect at the interaction of cognition (sustained attention task) and pain [45,47].

4.3. Post-stimulus activity

The present results are consistent with prior studies that demonstrate evidence of synchrony between LFPs recorded from pain-related cortical areas [68,69]. After the laser stimulus, the degree of synchrony between both SI and PS areas with MF was increased by directed attention to the stimulus [69]. The GRC pairs from SI upon PS after the stimulus are consistent with the dense, reciprocal interconnections of these 2 areas [15]. Joint

involvement of SI and SII in the sensory dimension of pain has previously been proposed [22]. Finally functional connectivity between these 2 separate cortical areas might be related to overlapping thalamocortical inputs from the ventral posterior nuclei in macaques [4,16,17,103].

The post-stimulus GRC significant pairs from SI to MF may be related to connections of SI with posterior parietal cortex and SII, which then project upon anterior and middle cingulate cortex [3,15,62,80]. Alternatively, the response to the painful stimulus may be related through connections from parietal cortex through the insula to the anterior cingulate [104]. Finally, the GRC pairs from SI to MF might be related to common input from the spinothalamic tract to human thalamic nuclei that project upon SI and MF [39,104].

4.4. “Within-area” GRC and critical sites

The present results demonstrate that all 3 subjects had a higher proportion of significant within-area GRC pairs for SI during attention (counting) task than distraction (reading) task condition. Object based visual and tactile attention can alter the synchrony between pairs of neurons in visual cortex, and in SII in trained monkeys [29,89,93]. This synchrony may be related to local organization based upon response properties and receptive fields, as in the case of other primary sensory cortical areas [13]. If this synchrony represents functional connectivity, then within-area GRC may identify a local network or module which can change properties in response to sensory stimulation (Fig. 4 versus Fig. 5). These local networks in SI can lead to widespread changes in cortical processing, plasticity, and learning [35,36]. Critical sites may be connected in smaller local networks by synchronous activity, which is related to cortical networks or to thalamo-cortical interactions [5,66,90,91,99].

Some kinds of cortical activity clearly reflect cortical processing of thalamic inputs. For example, spatial attention evokes neuronal activity in Brodmann area 7B, which is a part of PS [27]. Thalamic activity may drive synchronous cortical activity through thalamic oscillations, or through common inputs from the spinothalamic tract to the thalamic somatic sensory relay nuclear complex to SI [94,95,103]. SI shows stimulus evoked responses that increase across the intensive continuum into the painful range (analog functions), whereas SII may show responses which increase with the stimulus, but only for stimuli in the painful range (binary functions) [12,98]. A similar dichotomy of stimulus–response functions has been observed in electrophysiological studies of the thalamic nuclei projecting to SI and SII [50,53]. Therefore, the combination of thalamic modules and cortical within-area and between area GRC pairs may produce the distinct functions that characterize these cortical modules.

Acknowledgments

This work was supported by the National Institutes of Health, National Institute of Neurological Disorders and Stroke (NS38493 to F.A.L.). The authors thank L.H. Rowland and J. Winberry for excellent technical assistance.

References

1. Akaike H. New look at statistical-model identification. *IEEE Trans Autom Control* 1974;AC19:716–723.
2. Andres FG, Mima T, Schulman AE, Dichgans J, Hallett M, Gerloff C. Functional coupling of human cortical sensorimotor areas during bimanual skill acquisition. *Brain* 1999;122:855–70. [PubMed: 10355671]
3. Apkarian AV, Bushnell MC, Treede R-D, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. *Eur J Pain* 2005;9:463–84. [PubMed: 15979027]

4. Apkarian AV, Shi T. Squirrel monkey lateral thalamus. I. somatic nociceptive neurons and their relation to spinothalamic terminals. *J Neurosci* 1994;14:6779–95. [PubMed: 7965079]
5. Apkarian AV, Shi T, Bruggemann J, Airapetian LR. Segregation of nociceptive and non-nociceptive networks in the squirrel monkey somatosensory thalamus. *J Neurophysiol* 2000;84:484–94. [PubMed: 10899221]
6. Bendat, JS.; Piersol, AG. Random data. New York: Wiley; 1976.
7. Berthier M, Starkstein S, Leiguarda R. Asymbolia for pain: a sensory-limbic disconnection syndrome. *Ann Neurol* 1988;24:41–9. [PubMed: 3415199]
8. Beydoun A, Morrow TJ, Shen JF, Casey KL. Variability of laser-evoked potentials: attention, arousal and lateralized differences. *Electroencephalogr Clin Neurophysiol* 1993;88:173–81. [PubMed: 7684966]
9. Blinowska KJ, Kus R, Kaminski M. Granger causality and information flow in multivariate processes. *Phys Rev E Stat Nonlin Soft Matter Phys* 2004;70:050902. [PubMed: 15600583]
10. Boatman D, Hall C, Goldstein MH, Lesser RH, Gordon B. Neuroperceptual differences in consonant and vowel discrimination as revealed by direct cortical electrical interference. *Cortex* 1997;33:83–9. [PubMed: 9088723]
11. Boly M, Balteau E, Schnakers C, Degueldre C, Moonen G, Luxen A, Phillips C, Peigneux P, Maquet P, Laureys S. Baseline brain activity fluctuations predict somatosensory perception in humans. *Proc Natl Acad Sci USA* 2007;29:12187–192. [PubMed: 17616583]
12. Bornhovd K, Quante M, Glauche V, Bromm B, Weiller C, Buchel C. Painful stimuli evoke different stimulus-response functions in the amygdala, prefrontal, insula and somatosensory cortex: a single-trial fMRI study. *Brain* 2002;125:1326–36. [PubMed: 12023321]
13. Brosch M, Schreiner CE. Correlations between neural discharges are related to receptive field properties in cat primary auditory cortex. *Eur J Neurosci* 1999;11:3517–30. [PubMed: 10564360]
14. Bullinaria, JA. Lesioned networks as models of neuropsychological deficits. In: Arbib, MA., editor. *The handbook of brain theory and neural networks*. Cambridge, MA: MIT Press; 2002. p. 635-8.
15. Burton, H. Second somatosensory cortex and related areas. In: Jones, EG.; Peters, A., editors. *Cerebral cortex*, vol. 5 sensory-motor areas and aspects of cortical connectivity. New York and London: Plenum; 1986. p. 31-98.
16. Burton H. Responses of spinal cord neurons to systematic changes in hindlimb skin temperatures in cats and primates. *J Neurophysiol* 1975;38:1060–79. [PubMed: 1177005]
17. Burton H. Corticothalamic connections from the second somatosensory area and neighboring regions in the lateral sulcus of macaque monkeys. *Brain Res* 1984;309:367–72.
18. Casey KL. Concepts of pain mechanisms: the contribution of functional imaging of the human brain. *Prog Brain Res* 2000;129:277–87. [PubMed: 11098696]
19. Casey, KL.; Bushnell, MC. Pain imaging. Seattle, WA: IASP Press; 2001.
20. Chudler EH, Dong WK, Kawakami Y. Cortical nociceptive responses and behavioral correlates in the monkey. *Brain Res* 1986;397:47–60. [PubMed: 3801865]
21. Churchland, PS.; Sejnowski, TJ. *The computational brain*. Cambridge, MA: MIT Press; 1992.
22. Coghill RC, Sang CN, Maisog JM, Iadarola MJ. Pain intensity processing within the human brain: a bilateral, distributed mechanism. *J Neurophysiol* 1999;82:1934–43. [PubMed: 10515983]
23. Crone NE, Miglioretti DL, Gordon B, Lesser RP. Functional mapping of human sensorimotor cortex with electrocorticographic spectral analysis. II. Event-related synchronization in the gamma band. *Brain* 1998;121:2301–15. [PubMed: 9874481]
24. Cui J, Xu LBSLD, Liang H. BSMART: a Matlab/C toolbox for analysis of multichannel neural time series. *Neural Netw* 2008;21:1094–104. [PubMed: 18599267]
25. Davis, KD. Studies of pain using functional magnetic resonance imaging. In: Casey, KL.; Bushnell, MC., editors. *Pain imaging*. Vol. 18. Seattle: IASP Press; 2000. p. 195-210.
26. Ding M, Bressler SL, Yang W, Liang H. Short-window spectral analysis of cortical event-related potentials by adaptive multivariate autoregressive modeling: data preprocessing, model validation, and variability assessment. *Biol Cybern* 2000;83:35–45. [PubMed: 10933236]

27. Dong WK, Chudler EH, Sugiyama K, Roberts VJ, Hayashi T. Somatosensory, multisensory, and task-related neurons in cortical area 7b (PF) of unanesthetized monkeys. *J Neurophysiol* 1994;72:542–64. [PubMed: 7983518]
28. Eichler M. A graphical approach for evaluating effective connectivity in neural systems. *Philos Trans R Soc Lond B Biol Sci* 2005;360:953–67. [PubMed: 16087440]
29. Fries P, Reynolds JH, Rorie AE, Desimone R. Modulation of oscillatory neuronal synchronization by selective visual attention. *Science* 2001;291:1560–3. [PubMed: 11222864]
30. Garcia-Larrea L, Peyron R, Laurent B, Mauguiere F. Association and dissociation between laser-evoked potentials and pain perception. *Neuroreport* 1997;8:3785–9. [PubMed: 9427371]
31. Gelnar PA, Krauss BR, Sheehe PR, Szeverenyi NM, Apkarian AV. A comparative fMRI study of cortical representations for thermal painful, vibrotactile, and motor performance tasks. *Neuroimage* 1999;10:460–82. [PubMed: 10493903]
32. Granger CW. Investigating causal relations by econometric models and cross spectral methods. *Econometrics* 1969;37:424–38.
33. Greenspan JD, Coghill RC, Gilron I, Sarlani E, Veldhuijzen D, Lenz FA. Quantitative somatic sensory testing and functional imaging of the response to painful stimuli before and after cingulotomy for obsessive compulsive disorder (OCD). *Eur J Pain* 2008;12:990–9. [PubMed: 18328752]
34. Greenspan JD, Lee RR, Lenz FA. Pain sensitivity alterations as a function of lesion location in the parasympathetic cortex. *Pain* 1999;81:273–82. [PubMed: 10431714]
35. Harris JA, Petersen RS, Diamond ME. Distribution of tactile learning and its neural basis. *Proc Natl Acad Sci USA* 1999;96:7587–91. [PubMed: 10377459]
36. Hasenstaub A, Sachdev RN, McCormick DA. State changes rapidly modulate cortical neuronal responsiveness. *J Neurosci* 2007;27:9607–22. [PubMed: 17804621]
37. Hesse W, Moller E, Arnold M, Schack B. The use of time-variant EEG Granger causality for inspecting directed interdependencies of neural assemblies. *J Neurosci Methods* 2003;124:27–44. [PubMed: 12648763]
38. Hofbauer RK, Rainville P, Duncan GH, Bushnell MC. Cortical representation of the sensory dimension of pain. *J Neurophysiol* 2001;86:402–11. [PubMed: 11431520]
39. Kaas, JH.; Pons, TP. The somatosensory system of primates. In: Steklis, HP., editor. *Neuroscience*. Vol. 4. New York, NY: Alan R Liss; 1988. p. 421–68.
40. Kaminski M, Ding M, Truccolo WA, Bressler SL. Evaluating causal relations in neural systems: Granger causality, directed transfer function and statistical assessment of significance. *Biol Cybern* 2001;85:145–57. [PubMed: 11508777]
41. Kanda M, Fujiwara N, Xu X, Shindo K, Nagamine T, Ikeda A, Shibasaki H. Pain-related and cognitive components of somatosensory evoked potentials following CO₂ laser stimulation. *EEG Clin Neurophysiol* 1996;100:105–14.
42. Kanda M, Nagamine T, Ikeda A, Ohara S, Kunieda T, Fujiwara N, Yazawa S, Sawamoto N, Matsumoto R, Taki W, Shibasaki H. Primary somatosensory cortex is actively involved in pain processing in human. *Brain Res* 2000;853:282–9. [PubMed: 10640625]
43. Kenshalo DR Jr, Chudler EH, Anton F, Dubner R. SI nociceptive neurons participate in the encoding process by which monkeys perceive the intensity of noxious thermal stimulation. *Brain Res* 1988;454:378–82. [PubMed: 3409021]
44. Kenshalo, DR.; Willis, WD. The role of the cerebral cortex in pain sensation. In: Peters, A.; Jones, EG., editors. *cerebral cortex*, Vol 9, normal and altered states of function. New York and London: Plenum Press; 1991. p. 153–212.
45. Kim JH, Ohara S, Lenz FA. Mental arithmetic leads to multiple discrete changes from baseline in the firing patterns of human thalamic neurons. *J Neurophysiol* 2009;101:2107–19. [PubMed: 19193769]
46. Kim SK, Lund J, Kiraly M, Duke K, Jiang M, Stuart JM, Eizinger A, Wylie BN, Davidson GS. A gene expression map for *Caenorhabditis elegans*. *Science* 2001;293:2087–92. [PubMed: 11557892]

47. Kobayashi K, Winberry J, Liu CC, Treede RD, Lenz FA. A painful cutaneous laser stimulus evokes responses from single neurons in the human thalamic principal somatic sensory nucleus ventral caudal—Vc. *J Neurophysiol* 2009;101:2210–7. [PubMed: 19244350]
48. Kong J, Loggia ML, Zyloney C, Tu P, Laviolette P, Gollub RL. Exploring the brain in pain: activations, deactivations and their relation. *Pain* 2010;148:257–67. [PubMed: 20005043]
49. Korzeniewska A, Crainiceanu CM, Kus R, Franaszczuk PJ, Crone NE. Dynamics of event-related causality in brain electrical activity. *Hum Brain Mapp* 2008;29:1170–92. [PubMed: 17712784]
50. Lee J, Dougherty PM, Antezana D, Lenz FA. Responses of neurons in the region of human thalamic principal somatic sensory nucleus to mechanical and thermal stimuli graded into the painful range. *J Comp Neurol* 1999;410:541–55. [PubMed: 10398047]
51. Legrain V, Guerit JM, Bruyer R, Plaghki L. Attentional modulation of the nociceptive processing into the human brain: selective spatial attention, probability of stimulus occurrence, and target detection effects on laser evoked potentials. *Pain* 2002;99:21–39. [PubMed: 12237181]
52. Lenz, FA.; Casey, KL.; Jones, EG.; Willis, WD, Jr. The human pain system: experimental and clinical perspectives. New York, NY: Cambridge University Press; 2010.
53. Lenz FA, Ohara S, Gracely RH, Dougherty PM, Patel SH. Pain encoding in the human forebrain: binary and analog exteroceptive channels. *J Neurosci* 2004;24:6540–4. [PubMed: 15269265]
54. Lenz FA, Rios M, Chau D, Krauss GL, Zirh TA, Lesser RP. Painful stimuli evoke potentials recorded from the parasyllian cortex in humans. *J Neurophysiol* 1998;80:2077–88. [PubMed: 9772262]
55. Lenz FA, Rios M, Zirh A, Chau D, Krauss G, Lesser RP. Painful stimuli evoke potentials recorded over the human anterior cingulate gyrus. *J Neurophysiol* 1998;79:2231–4. [PubMed: 9535984]
56. Lenz FA, Seike M, Richardson RT, Lin YC, Baker FH, Khoja I, Jaeger CJ, Gracely RH. Thermal and pain sensations evoked by microstimulation in the area of human ventrocaudal nucleus. *J Neurophysiol* 1993;70:200–12. [PubMed: 8360716]
57. Lesser, RP.; Gordon, B.; Fox, JM.; Hart, J.; Uematsu, S. Subdural grid electrodes in surgery of epilepsy. In: Luders, HO., editor. *Epilepsy surgery*. New York, NY: Raven; 1992. p. 399–408.
58. Levy, RH.; Mattson, RH.; Melega, W.; Perucca, E. *Antiepileptic drugs*. Philadelphia, PA: Lippincott, Williams & Wilkins; 2002.
59. Liu CC, Ohara S, Franaszczuk PJ, Zagzoog N, Gallagher M, Lenz FA. Painful stimuli evoke potentials recorded from the medial temporal lobe in humans. *Neurosci* 2010;165:1402–11.
60. Manly, BFJ. *Randomization, Bootstrap and Monte Carlo Methods in Biology*. New York, NY: Springer; 2007.
61. Melzack R. Phantom limbs and the concept of a neuromatrix. *Trends Neurosci* 1990;13:88–92. [PubMed: 1691874]
62. Mesulam, M-M.; Mufson, EJ. The insula of Reil in man and monkey. In: Peters, A.; Jones, EG., editors. *Cerebral cortex*. Vol. 4. New York, NY: Plenum; 1985. p. 179–226.
63. Mouraux A, Guerit JM, Plaghki L. Refractoriness cannot explain why C-fiber laser-evoked brain potentials are recorded only if concomitant A-delta-fiber activation is avoided. *Pain* 2004;112:16–26. [PubMed: 15494181]
64. Mouraux A, Iannetti GD. Nociceptive laser-evoked brain potentials do not reflect nociceptive-specific neural activity. *J Neurophysiol* 2009;101:3258–69. [PubMed: 19339457]
65. Naidich TP, Valavanis AG, Kubik S. Anatomic relationships along the low middle convexity: part 1—normal specimens and magnetic resonance imaging. *Neurosurgery* 1995;36:517–32. [PubMed: 7753352]
66. Nicolelis MA, Baccala LA, Lin RC, Chapin JK. Sensorimotor encoding by synchronous neural ensemble activity at multiple levels of the somatosensory system. *Science* 1995;268:1353–8. [PubMed: 7761855]
67. Nunez PL, Wingeier BM, Silberstein RB. Spatial-temporal structures of human alpha rhythms: theory, microcurrent sources, multiscale measurements, and global binding of local networks. *Hum Brain Mapp* 2001;13:125–64. [PubMed: 11376500]
68. Ohara S, Crone NE, Weiss N, Kim JH, Lenz FA. Analysis of synchrony demonstrates that the presence of “pain networks” prior to a noxious stimulus can enable the perception of pain in response to that stimulus. *Exp Brain Res* 2008;185:353–8. [PubMed: 18231782]

69. Ohara S, Crone NE, Weiss N, Lenz FA. Analysis of synchrony demonstrates 'pain networks' defined by rapidly switching, task-specific, functional connectivity between pain-related cortical structures. *Pain* 2006;123:244–53. [PubMed: 16563627]
70. Ohara S, Crone NE, Weiss N, Lenz FA. Attention to a painful cutaneous laser stimulus modulates electrocorticographic event-related desynchronization in humans. *Clin Neurophysiol* 2004;115:1641–52. [PubMed: 15203065]
71. Ohara S, Crone NE, Weiss N, Treede RD, Lenz FA. Amplitudes of laser evoked potential recorded from primary somatosensory, parasympathetic and medial frontal cortex are graded with stimulus intensity. *Pain* 2004;110:318–28. [PubMed: 15275782]
72. Ohara S, Crone NE, Weiss N, Treede RD, Lenz FA. Cutaneous painful laser stimuli evoke responses recorded directly from primary somatosensory cortex in awake humans. *J Neurophysiol* 2004;91:2734–46. [PubMed: 14602841]
73. Ohara S, Crone NE, Weiss N, Vogel H, Treede RD, Lenz FA. Attention to pain is processed at multiple cortical sites in man. *Exp Brain Res* 2004;156:513–7. [PubMed: 15127169]
74. Ohara S, Mima T, Baba K, Ikeda A, Kunieda T, Matsumoto R, Yamamoto J, Matsushashi M, Nagamine T, Hirasawa K, Hori T, Mihara T, Hashimoto N, Salenius S, Shibasaki H. Increased synchronization of cortical oscillatory activities between human supplementary motor and primary sensorimotor areas during voluntary movements. *J Neurosci* 2001;21:9377–86. [PubMed: 11717371]
75. Oppenheim, AV.; Schaffer, RW. *Digital Signal Processing*. Englewood Heights, NJ: Prentice-Hall; 1975.
76. Peyron R, Garcia-Larrea L, Gregoire MC, Costes N, Convers P, Lavenne F, Mauguier F, Michel D, Laurent B. Haemodynamic brain responses to acute pain in humans: sensory and attentional networks. *Brain* 1999;122:1765–80. [PubMed: 10468515]
77. Peyron R, Laurent B, Garcia-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis. *Neurophysiol Clin* 2000;30:263–88. [PubMed: 11126640]
78. Ploner M, Lee MC, Wiech K, Bingel U, Tracey I. Prestimulus functional connectivity determines pain perception in humans. *Proc Natl Acad Sci USA* 2010;107:355–60. [PubMed: 19948949]
79. Ploner M, Schmitz F, Freund HJ, Schnitzler A. Differential organization of touch and pain in human primary somatosensory cortex. *J Neurophysiol* 2000;83:1770–6. [PubMed: 10712498]
80. Ploner M, Schmitz F, Freund HJ, Schnitzler A. Parallel activation of primary and secondary somatosensory cortices in human pain processing. *J Neurophysiol* 1999;81:3100–4. [PubMed: 10368426]
81. Ploner M, Schoffelen JM, Schnitzler A, Gross J. Functional integration within the human pain system as revealed by Granger causality. *Hum Brain Mapp* 2009;30:4025–32. [PubMed: 19479728]
82. Price DD. Psychological and neural mechanisms of the affective dimension of pain. *Science* 2000;288:1769–72. [PubMed: 10846154]
83. Qiu Y, Inui K, Wang X, Nguyen BT, Tran TD, Kakigi R. Effects of distraction on magnetoencephalographic responses ascending through C-fibers in humans. *Clin Neurophysiol* 2004;115:636–46. [PubMed: 15036060]
84. Rainville, P.; Bushnell, MC.; Duncan, GH. PET studies of the subjective experience of pain. In: Casey, KL.; Bushnell, MC., editors. *Pain imaging*. Vol. 18. Seattle, WA: IASP Press; 2000. p. 123–56.
85. Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC. Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science* 1997;277:968–71. [PubMed: 9252330]
86. Schreckenberger M, Lange-Asschenfeldt C, Lochmann M, Mann K, Siessmeier T, Buchholz HG, Bartenstein P, Grunder G. The thalamus as the generator and modulator of EEG alpha rhythm: a combined PET/EEG study with lorazepam challenge in humans. *Neuroimage* 2004;22:637–44. [PubMed: 15193592]
87. Siedenberg R, Treede RD. Laser-evoked potentials: exogenous and endogenous components. *Electroencephalogr Clin Neurophysiol* 1996;100:240–9. [PubMed: 8681865]
88. Singer W. Neuronal synchrony: a versatile code for the definition of relations? *Neuron* 1999;24:25–49.

89. Steinmetz PN, Roy A, Fitzgerald PJ, Hsiao SS, Johnson KO, Niebur E. Attention modulates synchronized neuronal firing in primate somatosensory cortex. *Nature* 2000;404:187–90. [PubMed: 10724171]
90. Steriade M. Impact of network activities on neuronal properties in corticothalamic systems. *J Neurophysiol* 2001;86:1–39. [PubMed: 11431485]
91. Steriade, M.; Jones, EG.; McCormick, DA. *Thalamus organisation and function*. Vol. 1. Amsterdam: Elsevier; 1997.
92. Strigo IA, Duncan GH, Boivin M, Bushnell MC. Differentiation of visceral and cutaneous pain in the human brain. *J Neurophysiol* 2003;89:3294–303. [PubMed: 12611986]
93. Super H, van der TC, Spekreijse H, Lamme VA. Internal state of monkey primary visual cortex (V1) predicts figure-ground perception. *J Neurosci* 2003;23:3407–14. [PubMed: 12716948]
94. Swadlow HA. Influence of VPM afferents on putative inhibitory interneurons in S1 of the awake rabbit: evidence from cross-correlation, microstimulation, and latencies to peripheral sensory stimulation. *J Neurophysiol* 1995;73:1584–99. [PubMed: 7643169]
95. Swadlow HA, Beloozerova IN, Sirota MG. Sharp, local synchrony among putative feed-forward inhibitory interneurons of rabbit somatosensory cortex. *J Neurophysiol* 1998;79:567–82. [PubMed: 9463422]
96. Talbot JD, Villemure JG, Bushnell MC, Duncan GH. Evaluation of pain perception after anterior capsulotomy: a case report. *Somatosens Mot Res* 1995;12:115–26. [PubMed: 7502602]
97. Tallon-Baudry C, Bertrand O, Fischer C. Oscillatory synchrony between human extrastriate areas during visual short-term memory maintenance. *J Neurosci* 2001;21:RC177. [PubMed: 11588207]
98. Timmermann L, Ploner M, Haucke K, Schmitz F, Baltissen R, Schnitzler A. Differential coding of pain intensity in the human primary and secondary somatosensory cortex. *J Neurophysiol* 2001;86:1499–503. [PubMed: 11535693]
99. Timofeev I, Steriade M. Fast (mainly 30–100 Hz) oscillations in the cat cerebellothalamic pathway and their synchronization with cortical potentials. *J Physiol* 1997;504:153–68. [PubMed: 9350626]
100. Tommerdahl M, Delemos KA, Favorov OV, Metz CB, Vierck CJ Jr, Whitsel BL. Response of anterior parietal cortex to different modes of same-site skin stimulation. *J Neurophysiol* 1998;80:3272–83. [PubMed: 9862921]
101. Tommerdahl M, Favorov O, Whitsel BL. Optical imaging of intrinsic signals in somatosensory cortex. *Behav Brain Res* 2002;135:83–91. [PubMed: 12356438]
102. Truini A, Rossi P, Galeotti F, Romaniello A, Virtuoso M, De LC, Leandri M, Cruccu G. Excitability of the Adelta nociceptive pathways as assessed by the recovery cycle of laser evoked potentials in humans. *Exp Brain Res* 2004;155:120–3. [PubMed: 15064893]
103. Usrey WM, Reid RC. Synchronous activity in the visual system. *Annu Rev Physiol* 1999;61:435–56. [PubMed: 10099696]
104. Vogt BA, Pandya DN. Cingulate cortex of the rhesus monkey: I. Cortical afferents. *J Comp Neurol* 1987;262:271–89. [PubMed: 3624555]
105. von Stein A, Rappelsberger P, Sarnthein J, Petsche H. Synchronization between temporal and parietal cortex during multimodal object processing in man. *Cereb Cortex* 1999;9:137–50. [PubMed: 10220226]
106. Yamasaki H, Kakigi R, Watanabe S, Hoshiyama M. Effects of distraction on pain-related somatosensory evoked magnetic fields and potentials following painful electrical stimulation. *Brain Res Cogn Brain Res* 2000;9:165–75. [PubMed: 10729700]
107. Yamasaki H, Kakigi R, Watanabe S, Naka D. Effects of distraction on pain perception: magneto- and electro-encephalographic studies. *Brain Res Cogn Brain Res* 1999;8:73–6. [PubMed: 10216275]

Fig. 1.

Orientation of surfaces of the left hemisphere is shown for subjects 1 and 2 in Figs. 4, 5 and 7, and the right hemisphere for subject 3 (see text). Sulci labeled in blue include the sylvian fissure (SF), cingulate sulcus (CiS), and marginal branch of the cingulate sulcus (MCiS). Black arrows indicate the central sulcus (CS).

Fig. 2. Ensemble spectral measures for crosscorrelation analysis and Granger causality (GRC) analysis for all 3 subjects: (A) Averaged power spectra where the vertical axis has an arbitrary scale to indicate the concentration of power in 1 frequency range. (B) Coherence spectra where 1 indicates a perfect linear relationship and 0 indicates the absence of such a relationship, C GRC (see Methods, GRC analysis subsection).

Fig. 3. Numbers of pre-stimulus versus post-stimulus within-area Granger causality (GRC) pairs during the counting versus the reading condition, as labeled. Difference between the numbers of pairs of electrodes within cortical areas that are linked by significant GRC, between the pre-stimulus versus post-stimulus periods.

Fig. 4.

(A) 3D images for the electrode placement (left column), for the distributions for the number of significant Granger causality (GRC) pairs found over 3 (gray) brain areas as labeled during the pre-stimulus interval under reading (middle column), and counting task conditions (right column). For each subject, the width of the large green arrows between cortical areas indicates the number of GRC pairs between the 2 cortical areas joined by the arrow. In this calculation, the number of GRC pairs is divided by the maximum number of electrode pairs observed for that subject across all combinations of cortical areas and both task conditions. The arrow, indicating the largest number of significant pairs for each subject, is indicated by the thickest line in the right panel for each row, which corresponds to the number at the left end of each row under the subject number, eg, subject 1 maximum = 4, for SI > PS. Blue lines and abbreviations indicate the approximate location of sulci, while the CS is indicated by a small, black arrow. (B) Total number of outgoing GRC influences for SI area to PS and MF (left) and total number of incoming GRC influences for PS area from SI and MF under reading (black) and the counting (gray) task conditions.

Fig. 5. Bar plots for the number of significant Granger causality (GRC) pairs found within-area and between area found over 3 brain areas during 2 post-stimulus intervals (0–200 ms) and (200–400 ms) under reading and counting task conditions. Conventions as in Fig. 4.

Fig. 6. Distributions for the number of significant Granger causality (GRC) pairs found over 3 cortical areas during post-stimulus intervals from 0 to 200 milliseconds, and from 200 to 400 milliseconds for both reading (left) and counting task conditions (right).

Fig. 7.

A plot shows the number of significant Granger causality (GRC) pairs found for each electrode site over 3 brain areas during 2 post-stimulus intervals (0–400 ms) for reading (left) and counting (right) task conditions. Only the electrode site with more than 2 significant GRC pairs is shown. Labels and conventions as in Fig. 1.

Table 1

Pain intensity ratings by subject, task, and run number.

Subject	power (mJ)	Attention		Distraction	
		First run	Second run	First run	Second run
1	640	4/10	4/10	3/10	4/10
2	560	5/10	5/10	0/10	1/10
3	640	5/10	5/10	4/10	3/10

Percentages and proportion of electrode pairs with evidence of significant reciprocal causality over the total number of electrode pairs showing causality.

Table 2

	Within area			Between areas			
	SI	PS	MF	Total	SI-PS	SI-MF	MF-PS
<i>Counting</i>							
Patient 1	0%	0	8	3	0	0	0
	0/8	0/19	1/13	1/32	0/24	0/34	0/13
Patient 2	12	3	13	15	0	0	17
	3/26	2/6	1/8	6/40	0/31	0/20	1/6
Patient 3	3	10	0	3	0	0	0
	1/34	1/10	0/34	2/78	0/66	0/44	0/18
Overall	6	3	4	6	0	0	3
	4/68	3/35	2/55	9/150	0/121	0/98	1/37
<i>Reading</i>							
Patient 1	0%	0	50	10	0	0	0
	0/3	0/5	1/2	1/10	0/6	0/5	0/4
Patient 2	0	50	33	14	0	20	0
	0/9	1/2	1/3	2/14	0/9	1/5	0/6
Patient 3	8	0	0	4	0	0	0
	1/12	0/20	0/6	1/38	0/15	0/13	0/11
Overall	4	4	18	5	0	4	0
	1/24	1/27	2/11	3/62	0/30	1/23	0/21

Non-zero percentages are shown in bold.

Table 3

Summary by subject of alpha band power change, LEP amplitude and laser energy during attention versus distraction.

Subject	Significant power change in alpha band (8–13 Hz)	Significant changes in LEP amplitude	Laser energy level (mJ)
1	Yes	Yes	640
2	Yes	Yes	560
3	Yes	Yes	640