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Attention to painful cutaneous laser stimuli evokes directed functional interactions between human sensory and modulatory pain-related cortical areas

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Abstract

The human ‘pain network’ includes cortical areas which are activated during the response to painful stimuli (termed category 1), or during psychological processes which modulate pain, e.g. distraction (termed category 2). These categories include parts of the parasyllian (PS), medial frontal (MF), and paracentral cortex (S1&M1). We now propose to test the hypothesis that causal interactions both within and between category 1 and category 2 modules occur during attention to a painful stimulus. Event-related causality (ERC) was calculated from local field potentials (LFP) recorded directly from these cortical areas during the response to a painful cutaneous laser stimulus in patients being monitored for epilepsy.

The number of electrodes involved in pairs with significant ERC in category 1 was greater for pre-stimulus versus post-stimulus and for attention versus distraction. This is consistent with our prior evidence that the category 1 ‘pain network’ changes rapidly with time intervals and tasks. In contrast, the interaction between categories was often unchanged or stable across intervals and tasks, particularly in MF.

The proportion of contacts involved in interactions with PS was greater during distraction versus attention while activation was less, which suggests that distraction involves an inhibitory process in PS. Functional interactions between categories were overwhelmingly in the direction from category 2 > 1, particularly for contacts in MF which often had a driver role. These results demonstrate that MF is densely interconnected throughout the ‘pain network’ so that stimulation of MF might be used to disrupt the ‘pain network’ as a therapy for pain.

Keywords

attention; human; pain; cortex; network; event related. causality

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INTRODUCTION

Cortical modules in the human ‘pain network’ classically include parts of the parasyllian cortex (PS), the medial frontal cortex (MF), and the S1&M1, which is made up of the primary somatic sensory cortex (S1) and the primary motor cortex (M1) [2;11;71]. Subdivisions within these cortical structures are activated by painful stimuli (termed category 1, e.g. S1); others are activated by psychological processes which modulate the response to painful stimuli, such as distraction (termed category 2, e.g. M1) [38;43;55;67].

Painful stimuli activate subdivisions of the PS around the sylvian fissure near the central sulcus (category 1)[2;3;11;22;33;43;66], while distraction from painful stimuli activates PS anterior to these structures including the frontal operculum, lateral orbitofrontal cortex and anterior insula (category 2)[2;3;33;66]. This is consistent with our findings that pain-related activation (desynchronization, ERD) is located around the sylvian fissure adjacent to the central sulcus, while areas anterior to this are not activated [60;62].

Distraction from pain activates the rostral pregenual cingulate cortex [3;83] and anterior cingulate cortex (ACC) (i.e. anterior to middle cingulate cortex (MCC))(category 2) [2;33;43;66;86]. These activations are anterior to those in the posterior MCC in response to painful stimuli (category 1)[3;33]. This is consistent with pain-related activations around the cingulate sulcus anterior to the central sulcus, while areas further anterior are not activated [60].

Our prior studies have shown synchrony and causal interactions between and within category 1 modules during attention to painful stimuli [51;61]. Among areas activated by painful stimuli, (category 1), pre-stimulus causal influences measured by fMRI are exerted by S1 upon both MF and PS ([37] cf [70]). These interactions may be consistent with evidence that lesions of category 2 areas lead to dramatically increased pain-related activations in category 1 and 2 areas ([30;78]). Therefore, causal interactions between these different cortical areas (categories 1 and 2) are unclear, although they have often been proposed (reviewed by [2;43;71]).

We now test the hypothesis that causal interactions both within and between category 1 and category 2 modules occur during response to a painful stimulus. As corollaries, we will test 1) whether these interactions are greater during attention versus distraction from the painful stimulus, 2) whether these interactions are dynamic or static which is stable across time and tasks, and 3) whether MF exerts an inhibitory effect upon PS during the response to a painful stimulus [30]. Event-related causality (ERC) was calculated from signals recorded directly from the cortical surface during the response to a painful cutaneous laser stimulus in patients being monitored for epilepsy through intracranial electrodes.

The ERC measures significant changes in SdDTF (Short time direct Directed Transfer Function), in the pre- or post-stimulus interval relative to an earlier baseline interval. SdDTF is a statistical multichannel measure for directed interactions between channels, similar to Granger causality [39;50]. Significant ERC values for an interaction from one neural structure (or signal) upon a second structure are evidence, but not proof, that the first structure exerts a causal influence, or plays a driver role upon the second.

MATERIALS AND METHODS

We have published patient characteristics, laser-evoked potentials and functional interactions in ongoing LFPs in these subjects in the companion paper [51]. All clinical, radiological, and recording techniques have previously been described in detail in that paper, and so are described briefly below.

The present study included three patients with medically intractable frontal lobe seizures. All seizure medications were discontinued 1 to 3 days after the implantation of the grid electrodes and reintroduced two to five days thereafter. Therefore, we could not rule out an effect of seizure medications in any subject [49]. 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 participation in this protocol.

Cortical Recordings and Localization

Subdural electrode grids were placed over the S1 cortex, the PS cortex, and the medial wall of both the left and right hemisphere. The platinum-iridium circular contacts (2.3 mm diameter, 80–100 contacts) were arranged in a rectangular grid with a center-to-center distance between contacts 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, Inc., West Warwick, RI), digitally band-pass-filtered at 0.1–300 Hz, and then referenced to a single subdural contact chosen for its low activity. The signals were sampled and digitized at 1,000 Hz. The recorded signals were visually inspected and trials with artifact were excluded from the study.

Figure 1 shows the location of the contacts relative to the named landmarks of the underlying brain, including views of the convexity and the medial wall of the hemisphere, as in our previous studies [6;13;44;45]. The grids were placed over the right hemisphere in subject 2 and over the left in subjects 1 and 3, as shown in Figure 1. The SEP N20-P20 polarity reversal (heavy dashed line in Figure 1), as well as the three dimensional databases, were consistent in terms of the CS (red line in Figure 1) and sylvian fissure location in two subjects who had intra-operative pictures available (subjects 1 and 3). The radiological landmarks were determined as in previous studies [52;61] by use of standard anatomical approaches [23;58;62]. If the SEP polarity reversal was inconsistent with respect to the location of the central sulcus location, then 1) the 3D map and 2) the intraoperative observations were given priority.

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 Inc., Starnberg, Germany) with a laser beam wavelength of 2 μ m and a beam diameter of 6 mm. The energy level for the laser was selected to provoke a pain VAS of 4–5/10 during the attention task, as determined prior to the experiment. The duration of each laser pulse was 10 ms; the inter-stimulus interval was randomized to between 6 and 12 sec.

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 1) the number of stimuli under the attention task, or 2) two questions regarding their reading, under the distraction task. For each task, there were two separate blocks of stimuli; each block consisted of 38 laser stimulation pulses for a total of 76 laser stimuli per task [61]. The order of these blocks was randomized and counterbalanced across subjects. Ratings of the laser stimulus intensity were recorded at the end of each stimulation block. The ratings were made using a Visual Analogue Scale of Intensity, where 0 was no pain and 10 was the most intense pain imaginable. Laser stimuli evoked painful, pin-prick sensations in all three subjects.

To avoid fatigue or sensitization, each laser pulse was applied to a slightly different location. Nevertheless, an effect of habituation related to the interstimulus interval cannot be ruled out, although this effect was present during both the attention and distraction tasks [56;81].

Event-Related Causality (ERC)

Using the autoregressive models, Granger adopted the idea of causality introduced by Wiener and established the causality measure called Granger causality [29;87]. The causality introduced by Wiener considered two simultaneously measured signals in a statistical framework. If one can predict the first signal better by incorporating the past information from the second, then it is said that the second signal is causal to the first. Originally, the Granger causality was a bivariate function which was based on the temporal ordering of two time series. Therefore, a cause must always precede the effect. However, the Granger causality does not necessarily imply the true causality unless the influence from all other time series can be excluded.

Based on the statistical framework of Granger causality, recent advances have enabled the evaluation of the short time event-related causality in a multivariate system. ERC is a multivariate approach and is based on the SdDTF for estimating the changes in the multivariate causality that are event-related in the frequency domain. The SdDTF is developed by using a multivariate autoregressive modeling approach to estimate the direct causal interactions within a multivariate system. The SdDTF is an implementation of direct Directed Transfer Function (dDTF) and is used for the signals that are short in duration and have a large number of repetitions. In turn, the dDTF is a version of earlier measure, the Directed Transfer Function (DTF). The essential part of the ERC method is the statistical testing procedure which will reveal the significant changes in inter-channel relationships that are event-related. In the following sub-sections, we provide more detail for each of the above mentioned approaches which contributed to the development of ERC in the present and previously published studies [19;40;50].

1. Directed Transfer Function (DTF)—DTF is the first multivariate AR modeling (MVAR) based approach that was developed for analyzing the causal relationships for a multivariate system. DTF is related to the Granger causality; it measures the direction and strength of the causal interaction in both the time and frequency domain within a given system. In the case of two variables, the DTF is equivalent to the Granger causality [34] and, thus, it may be interpreted in terms of Granger causality. The signals, which were 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 [25]. The MVAR model used for calculation of the ERC includes all selected contacts, rather than including each of the cortical areas separately. The order for MVAR model was determined by the Akaike information criteria (AIC), which is an estimate for the number of coefficients that would optimize the MVAR analysis [1].

2. Direct Directed Transfer Function (dDTF)—Since DTF evaluates a linear combination of causal influences along all causal pathways—*direct* and *indirect*—originating from one site and terminating at another, either directly or by interaction with an unobserved site(s). Therefore, non-zero values of DTF between two variables do not necessarily imply that the causal influence between them is direct. The causal influence may be mediated by another variable(s), or by variable(s) that are not even observed in the system.

The concept of partial correlation coefficient (partial coherence in frequency domain), is a well known method that takes all other variables into account in regression analysis. The

partial coherence is introduced and incorporated in the computation of DTF to reveal the causal influence that is direct. Therefore, the DTF values are multiplied by the non-directional partial coherence and this step leads to the development of dDTF. As a result, the small or zero values of partial coherence and consequently the dDTF value indicate that interaction between a given pair of signals is mediated by other sites even if DTF has large values [40].

The original DTF and dDTF is not designed to analyze the data with very short duration, and, thus, it cannot be used to study interactions that occur on brief time scales. This particular limitation may be overcome when a large number of trials of a particular task is available [19]. The short time DTF (SDTF) is a modification of the original DTF and is adapted for analyzing the causal interactions that occur in a short time scale and has been applied to electrophysiological data [27;28].

3. Short-time direct Directed Transfer Function (SdDTF)—Finally, the SdDTF was introduced by combining the dDTF and SDTF. The SdDTF combines the advantages of dDTF and SDTF for estimating the directions, intensities, and spectral contents of direct causal influences between variables for recordings of short duration. Furthermore, a sliding window was applied, when computing the SdDTF; this approach provided a smoothed estimator for SdDTF. In this study, the length of the sliding window was set to 0.1 sec, and the step size for sliding window was set to 0.04 sec for the following consecutive windows. The length of the time window is chosen to be small enough to treat the data as stationary, yet large enough to take into account the jitter of the recorded signal interactions across different trials. The same approach was used also used in previously published studies [6;53].

4. Statistical Testing—ERC is determined by comparing SdDTF between the intervals of interest to the predefined baseline reference interval. This is analogous to the ERD/ERS approach well established in the signal analysis for the significant changes in the event-related power. The structures in living brain are always interacting and the meaningful analysis of changes related to particular events has to include comparison with its baseline activities. Since the SdDTF can be dynamically altering both during baseline and analyses periods, we did not assume stationarity. Therefore, we applied a formal bivariate spline smoothing model in the statistical testing to reduce the variability of the ERC, as in our previous studies [39;53].

To test the significant changes in the causal influences, including ERC, a semiparametric regression analysis was implemented. For each paired electrode combination, this test tested the SdDTF in every frequency and time between baseline and the interval of interest with Bonferroni correction for multiple comparisons [39;74]. The baseline in this present study was taken from the recording prior to the pre-stimulus interval and the duration for the interval was set to 1 second.

In addition, the ERC in this study was evaluated in the 6–14 Hz frequency range. This range was chosen based on frequency peaks observed in ensemble averages of the spectral power and coherence of LFP [51]. The power and coherence are directly reflected in the overall interactions between signals. Therefore, the LFP power and coherence peaks are expected to have the corresponding peaks in the time-frequency ERC plots [51]. The significant level was set to $\alpha=0.05$. The significant causal influence in the interval of interest was declared if the smoothed SdDTF values were significantly different from all those occurred in the baseline interval. The significant causal influences were color coded and shown in the time-frequency plot (Figure 2B).

All the statistical models were implemented in R using a freely available SemiPar software package (<http://www.uow.edu.au/~mwand/SemiPar.html>) and have been previously tested and used in similar multichannel human intracranial recordings [39;53]. All the programs for the ERC analysis were written in C language, developed in the Linux environment and run on a computer cluster which was implemented as one distributed system.

Event-Related Desynchronization (ERD) and Event-Related Synchronization (ERS)

The ERD was calculated as described in a previous paper [60]. We now describe the statistical method of determining changes in the average LFP power. First, the time series of average LFP power was segmented into a series of 100 ms epochs spanning 1 sec before and 1 sec after stimulus onset, and overlapping each other by 50%. The natural log-transformed power was analyzed with a separate mixed-effects regression model which was fitted for each channel using the power change value as the dependent variable and the post-stimulus epoch latency as the independent variable. The mean values and confidence limits were calculated from the anti-log to give the geometric mean percentage change from baseline and 95% confidence limits. If the confidence intervals did not include zero, a change in post-stimulus power was significant. We denoted a change in post-stimulus ECoG power only if four consecutive epochs were significant.

RESULTS

These studies were carried out on three subjects (2 female, 1 male, aged 21–51 yrs) who had subdural grids implanted for the surgical treatment of medically intractable epilepsy thought to arise from a frontal focus. Neurological examination was normal for all subjects [47], which included a standard sensory testing protocol [46]. Brain magnetic resonance imaging (MRI) was normal in subjects 1 and 2. The MRI in subject 3 revealed bilateral subcortical T2 changes which were consistent with enlarged peri-vascular spaces, which is a normal variant [65].

Contact Locations and Categories

The present analysis differentiated the category 1 and category 2 cortical areas (Figure 1) which were found at the locations described in the *Introduction*. Within subjects we identified these categories based upon the anatomy and physiology, particularly the ERD, as previously published [60;62]. Figure 1 shows that PS category 1 and PS category 2 contacts were within two contacts of the sylvian fissure at the central sulcus, and at the anterior extent of the grid, respectively. Category 1 or category 2 contacts were characterized physiologically by the presence or absence of ERD. In the case of MF category 1 and category 2, contacts were within two contacts of the cingulate sulcus, and at the paracentral lobule (category 1) and at the anterior extent of the grid (category 2). These contacts were characterized physiologically by the presence or absence of ERD.

The case of S1&M1 is somewhat different from PS and MF because S1 was in category 1 while M1 was in category 2, as explained in the *Introduction*. Contacts in S1 or M1 were posterior or anterior to the central sulcus, and within two contacts of the central sulcus; they were characterized by reproducible LEPs or pain-related ERD or both.

Ensemble Analyses

The power and coherence spectra were first computed from estimated MVAR models for each subject. The autopower of a signal is the square of the magnitude of the signal as a function of frequency [64]. The cross-spectrum of the two signals is composed of the magnitude (cross-power spectrum) and phase spectrum. The square of the cross-power is

divided by the product of the averages of the two auto-spectra to produce the coherence. The coherence is used to estimate the probability that the two signals are linearly related [5].

The ERC was calculated in the 6–14 Hz frequency band which was based on the frequencies of peaks in ensemble averages of the LFP autopower, coherence and ERC, as described below. The average power spectra showed that peak oscillatory activities during the experimental task period occurred within the alpha band (8–13 Hz)(subject 1 6.8 Hz, subject 2 – 7.8 Hz, and subject 3 – 8.9 Hz, see Figure 1 in [51]). The averaged coherence spectra showed that the alpha band oscillatory activities were often synchronous (7.1 Hz, 8.5 Hz, and 9.1 Hz).

Figure 2B shows the averaged significant MF>PS ERC for all three subjects. It is clear from this Figure that the peak averaged significant ERC also occurred within the alpha frequency band (8.3 Hz, 7.2 Hz and 8.6 Hz). The significant level for ERC was determined by the approach described in the *Methods*: (Statistical Testing) at $\alpha=0.05$. The significant ERC was determined separately for both directions between each site pair.

ERC Within and Between Cortical Modules

We first tested our hypothesis that there are significant causal interactions both within and between category 1 and category 2 modules in response to a painful stimulus. Figure 2A shows ERD for attention and distraction based upon recordings from a category 1 MF contact in subject 1 (adapted from Figure 1 in reference [51]). Figure 2B shows six grids, one for each of the attention and distraction conditions in each of the three subjects, as labeled. Each grid is composed of sixteen time-frequency plots of the ERC between the four contacts in category 1 MF and the four contacts in category 1 PS. The horizontal (time) scale of each plot covers 2 sec and is centered upon the time of the stimulus, and the vertical axis is frequency from 0 to 50 Hz, as labeled in the left lower plot of the distraction grid for subject 3. The ERC is the difference between the baseline period (1 sec before the pre-stimulus period) and the pre-stimulus and post-stimulus, separately. Decreases for the causal influences were not taken into consideration because the physiological interpretation of decreases in ERC during task performance is unclear.

If contact (or cortical area) X exerts a causal influence or driver role upon contact (or cortical area) Y, then we refer to this as a causal pair described by $X > Y$. The causal pairs were examined for consistency of proportions of contact pairs during the distraction versus attention task across all subjects. Within each subject, a greater response during a condition such as attention was identified by greater or equal number of causal pairs during attention than distraction. Therefore, category 1 MF was said to demonstrate a consistent causal influence upon category 1 PS during the attention task, and the pre-stimulus interval (Figure 2B). This MF > PS consistent causal pair is shown in Table 2 along the first row in the pre-stimulus column. Tables 2 and 3 show all consistent causal pairs in this analysis, which include those within categories (Table 2), and those between categories (Table 3), which is consistent with our hypothesis. The total number of consistent causal pairs was 27 so that the number of contacts involved in a causal pairs was 54.

Tables 2 and 3 also show the direction of consistent causal influences between cortical areas, during different interval, condition and category factors, as labeled. The contacts within both category 1 and 2 areas with consistent causal influences were significantly more common in MF (25/54, all $P < 0.03$, Chi square or Fisher exact, as appropriate) than in PS (13/54), in S1 (12/54), and in M1 (4/54).

Causal Pairs: Overall and Driver versus Receiver

The number of contacts in consistent causal pairs between category 1 and 2 areas (Table 3) was greater versus that within category 2 (Table 2) (24/54 vs 12/54, $P=0.014$). The proportion of contacts in consistent causal pairs was not apparently different within category 2 versus within category 1 areas (12/54 vs 18/54, $P=0.197$, Chi square). Therefore, interactions of category 2 areas are predominantly with category 1 and not within category 2.

Contacts with driver roles versus receiver roles in causal pairs within and between categories were more common within M1 (4/4 vs 0/4, $P=0.014$, Fisher), while differences were not significant ($P>0.24$ for each area, by Chi square or Fisher, as appropriate) for S1 (5/12 vs 7/12), MF (13/25 vs 12/25), or PS (5/13 vs 8/13). The proportion of driver contacts tended to be greater for M1 versus PS (4/4 vs 5/13, $p=0.053$, Fisher) and versus S1 (4/4 vs 5/12, $P=0.069$, Fisher), while M1 was not different versus MF (4/4 vs 13/26, $P=0.1$, Fisher). Therefore, M1 was always driver but MF had large numbers of contacts in both the driver and receiver roles, and was the most common driver overall.

Causal Pairs: Attention versus Distraction

We next tested a corollary of our hypothesis that these interactions are greater during the attention condition versus the distraction condition for this protocol. The number of contacts involved in consistent pairs between and within categories (Tables 2 and 3) was larger during distraction versus attention for PS (9/13 vs 4/13, $P<0.05$), but was not apparently different during distraction versus attention for M1 (1/4 vs 3/4, $P=0.22$, Fisher), MF (15/25 vs 10/25, $P=0.16$, Chi square), or for S1 (8/12 vs 4/12, $P=0.11$, Fisher).

During attention, contacts involved in interactions within the first or the second category (Table 2) were significantly more common than those pairs with interactions between category 1 and category 2 (Table 3) (20/30 vs 8/24, $P=0.015$, Chi square). In summary, causal pairs were commonly observed during distraction in PS (Figure 3), and during attention among causal pairs within categories 1 and 2 [59;61], which indicates a complex effect of condition, contrary to our corollary regarding the effect of attention.

The number of contacts is too small to test the significance of specific functional interconnections. Therefore, these interconnections are shown graphically by cortical area but without statistical testing in Figure 3 for attention versus distraction. The dynamic nature of these networks is demonstrated in Figure 3 by the reversal of $MF > S1 \& M1$ between attention and distraction.

Causal Pairs: Pre-stimulus versus Post-stimulus

The number of contacts involved in causal pairs was greater in the pre-stimulus versus post-stimulus interval within category 1 (14/18 vs 4/18, $P=0.001$, Fisher), which is consistent with dynamic 'pain networks' found in our prior studies of synchrony in category 1 [59;61]. The number of such contacts was also greater within categories 1 and 2 combined (20/30 vs 10/30, $P=0.0079$), but not within category 2 alone (6/12 vs 6/12, $P=1$, Chi square). The proportion of contacts in causal pairs involving both category 1 and 2 was greater during the pre-stimulus than the post-stimulus interval (16/24 vs 8/24, $P=0.021$, Chi square).

Differences in Interactions within and between Categories

Among causal pairs within category 1 or 2, MF was more common (11/30) versus M1 (2/30, $P=0.010$), but not PS (10/30) or S1 (7/30, $P>0.39$ in both cases). However, the most striking outcome of this analysis is that contacts involved in interactions between areas in different cortical categories were much more common in category 2 > category 1 causal pairs than

category 1 > category 2 causal pairs (22/24 vs 2/24, $P < 0.0000001$, Fisher). In addition, the number of contacts in category 2 > category 1 causal pairs was greater for MF (14/24) than for S1 (5/24, $P = 0.005$, Fisher), M1 (2/24, $P = 0.0003$ Fisher), and PS (3/24, $P = 0.001$ Fisher).

Interactions between category 2 > category 1 within the same cortical area were only found for MF > MF (see Figure 4, and Table 3 MF > MF₊), which was significantly greater than all other cortical areas combined (4/4 vs 0/4, $P = 0.014$, Fisher). The illustration of individual causal pairs in Figure 4A illustrates the predominance of MF in category 2 > category 1 causal pairs. Therefore, both distributed and 'local network' interactions show that category 2 MF areas are more likely to influence activity in category 1 than other cortical areas, which might make it an effective site for stimulation for the treatment of pain.

Stable Causal Pairs across Interval and Attention

We next tested whether causal interactions are dynamic or static, i.e. stable across time and tasks. Examination of Table 3 suggests that interactions between category 1 and category 2 can be stable, which we define as unchanging or changing in a reciprocal fashion across intervals and tasks. Reciprocity was identified by interactions in both directions between two cortical areas or categories in the same interval and task (e.g. MF > S1 and S1 > MF), and interactions within the same cortical areas and category (e.g. MF > MF). This analysis is based upon Table 4 which summarizes pairs of contacts with stable consistent interactions as a function of interval or task.

The number of MF contacts involved in stable causal pairs across intervals and tasks was significantly greater than for all other areas combined (Table 4, 17/22 vs 5/22, $P = 0.0003$). Furthermore, the proportion of contacts in MF involved in stable consistent causal pairs was greater than expected on the assumption that M1, S1, PS and MF contacts were each found with a probability of 0.25 ($P < 0.00001$, Binomial).

The number of contacts involved in stable consistent causal pairs across intervals were more commonly located in MF versus other cortical areas (9/12 vs 3/12, $P = 0.039$). The numbers of MF contacts involved in consistent causal pairs was greater for attention versus distraction (Table 4, 8/10 vs 2/10, $P = 0.023$). Therefore, stable causal interactions were found for both local and distributed connections of MF, unlike the category 1 functional interactions which were dynamic (see above *Causal Pairs: Pre-stimulus ...* and [59;61]).

Relationship between Activation and Causal Pairs

Our prior studies have demonstrated both parietal and insular activations and increased pain ratings of a painful stimulus following a lesion of MCC [30]. These activations might be interpreted as disinhibition of PS resulting from a loss of an analgesic influence from the MCC directly or through unobserved structures [84]. Therefore, we examined the corollary of our hypothesis whether that MF exerts an inhibitory effect upon PS during the response to a painful stimulus [30]. This was approached by measuring the numbers of activated contacts during attention minus distraction (Figure 2A).

Pain-related activations of contacts in PS across patients were more common with attention versus distraction (11/12 vs 1/12, $P = 0.0001$, Fisher), but in none of the other areas. The number of contacts consistently involved in causal pairs was greater during distraction versus attention for PS (11/15 vs 4/15, 0.013, Fisher), but was not different by task for M1, S1, and MF. The pattern of increased connectivity and decreased activation of PS during distraction is consistent with the corollary of this hypothesis.

VAS Pain Ratings

Pain intensity VAS (Table 1) tended to be higher ($P=0.059$, Wilcoxon matched-pairs test corrected for the continuity) during counting (5: 4–5. Median: Minimum - Maximum) than during reading (3, 0–4). The VAS intensity rating during attention versus distraction in each of the three patients was directly related to the numbers of consistent ERC pairs with a contact in S1 (Figure 5A). The same result was found in PS (Figure 5B) but not in any other cortical area.

DISCUSSION

Our prior studies have provided evidence that synchrony or functional interactions between S1, M1, PS and MF change dynamically with task, such as the anticipation of the laser stimulus, attention to the laser, and distraction from the laser [59–61;63](see also [88]). The dynamic nature of the interactions in the present results is demonstrated during distraction versus attention in Figure 3 by the emergence of one ‘local network’ (PS>PS), the diminution of another (MF>MF), and by the reversal of the causal pair S1&M1 > MF. In addition, the present analysis has confirmed that the ERC between S1, PS and MF during the painful laser stimulus changes dynamically with time interval and task for category 1 cortical areas (Table 2).

These results have also demonstrated that the numbers of contacts in causal pairs are often static or stable, particularly for interactions of category 2 > 1 (Table 4). Prolonged BOLD functional interactions have been observed during ratings of painful laser stimuli, although these findings may be the result of the long intervals involved in the analysis of these interactions [7;37;38]. In the present results dynamic or static functional interactions are found depending upon categories and modules involved, which indicates that these interactions are not uniform throughout, consistent with the corollary of our hypothesis. The temporal features of these causal interactions may predict critical parameters of the ‘pain network’ which could include the time course of the pain, the attentive task, and the nature of therapeutic stimulation of the brain for the treatment of pain..

Causal interactions within modules, or local networks, might be due to the 1 cm spacing of electrodes relative to the location of the generators. The existence of such interactions is demonstrated by synchrony between spike trains of neurons which were widely distributed within modules in simian sensory and associational cortex [24;79]. Our ability to resolve such interactions is demonstrated by the LEP phase reversals in each category 1 module and the presence of closely spaced LEP generators on source analysis [4;62]. Finally, the MVAR analysis employed here will register altered magnitude, but not directionality in this case

Methodological Concerns

The subjects in this study all had frontal lobe epilepsy as determined by clinical criteria, which are an unavoidable feature of studies like this. However, previous studies of subjects with epilepsy did not have observed differences in LEPs or ongoing ERDs at contact sites located in structures with radiological or electrical evidence of seizure onsets [52]. This result suggests that recordings from the epileptogenic cortex in the presence of anti-epileptic drugs need not alter the response to the painful laser.

Significant ERC causal pairs might be detected between signals that are both active and correlated, but not truly causal, possibly in the case of pairs within the same module. 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 ERC, but not the directionality.

The response to the painful cutaneous laser may signal the salience of the stimulus, defined as ‘the ability of the stimulus to capture attention’ [57](see also [20;21;42;54;89]). Salience is also a property of non-painful somatic stimuli, and other modalities such as vision [20;21;57], which we did not control for (cf [62]). It should be also noted that these ‘results do not question the usefulness of LEPs ... to explore the effect of a given experimental factor on the transmission and processing of nociceptive input’ (e.g. distraction)[57].

Category 2 >1 Bias of Causal Pairs between Categories

It is notable that contacts involved in connections between cortical areas in different categories (Table 3) were overwhelmingly in the direction from category 2 > 1 as opposed to category 1 > 2. The increase in pain-related activations during functional imaging studies during distraction involved the lateral orbitofrontal, and anterior PS cortex anterior to pain-related activations [2;3;22;33;43;66]. Similarly, functional imaging studies demonstrate that distraction from painful stimuli activates rostral pregenual cortex [33;66], ACC [2;3;33;43;83], and MCC [3;26;83]. These structures were anterior to the pain-related activations along the cingulate sulcus [2;43;68]. These category 2 sites largely exert their influence upon category 1 sites other than those in their own cortical area.

In the S1&M1 region, S1 is activated more commonly than M1 in response to painful stimuli [2;43]. The analgesic effect of motor cortex stimulation demonstrates that M1 can modulate acute and chronic pain [41]. Although areas involved in modulation of painful stimuli must receive signals related to those stimuli, this input does not seem to come from areas in category 1, and may be transmitted from unobserved structures such as the thalamus [9;10;43;76] or posterior or inferior parietal cortex [84]. Therefore causal interactions within and between category 1, and category 2, and unobserved modules occur in response to a painful stimulus, which is the complex conclusion to testing our hypothesis.

MF versus PS Interactions and Distraction

Overall, the effect of attention was more complex than anticipated by the corollary of our hypothesis since the main effect was increased causal interactions in PS during distraction. In this study, PS showed decreased activation but increased functional interactions during distraction, while during attention increased activation was associated with decreased interactions. This suggests that an increased inhibitory process mediates the effect of distraction while a decreased inhibitory effect (disinhibition) mediates the increased activation of attention, consistent with the corollary regarding the interaction of MF and PS. Disruption of this inhibitory effect by cingulotomy might explain the increased activation of PS which has been observed following cingulate lesions [30].

Modulation of activity in PS by input from MF has been suggested by our prior psychophysical and PET study of the response to painful stimuli before and after a bilateral cingulotomy of the MCC. Following the cingulate lesion, there was an increase in pain ratings and increased activation of the parietal and insular cortex ipsilateral to a painful stimulus [30]. In view of the present results, the cingulate lesion may produce activation through disinhibition of PS, and the effect of attention may occur through a similar disinhibitory process, which is dependent upon MCC [30].

In our prior studies, the relationship between VAS versus ERD or synchrony was measured for each block of the attention and distraction trials [60;61]. By that analysis, ERD or synchrony related to PS was a complex function of distraction and distraction-related analgesia between individuals. Studies of larger numbers of individuals may be able to sort out the process linking these variables.

The present results support an attention-related inhibitory process in PS but do not specifically support the possibility that this process involves MF, since both PS and MF are as likely to be a driver as a receiver. It is possible that functional interactions between PS and MF could be mediated through unobserved structures [14;68;72], or through functionally discrete subdivisions within PS [30;31], and within MF [30;85]. Examples of these subdivisions may include category 2 areas in anterior PS cortex and anterior ACC cortex, which may be involved in a modulatory ‘pain network’ [84].

The Modulatory Role of MF

The participation of MCC in pain processing is suggested by activation of this area in response to acute pain [15;17]. The extent of pain-related function along the caudal-rostral axis of MCC and ACC is suggested by functional imaging studies demonstrating widespread blood flow or BOLD activation between individuals [15;17]. Cingulate generators of LEPs are supported by source analysis of scalp EEG [12;36;80;82]. Recordings directly from the surface of the cortex localize the generator in the MCC, just anterior to the M1 [45;62;73].

Attention-related tasks (e.g. verbal fluency or Stroop) will also activate widespread MF areas [15;17]. Direct comparisons identify interleaved subunits within the ACC and MCC which are activated by attention versus pain-related tasks [69]. Therefore, the present results may be the result of widespread functionally discrete subunits or modules in MF which subserve pain and attention.

In comparison with other cortical areas, MF accounts for the largest number of contacts involved in consistent causal pairs (Tables 2 and 3), particularly in the case of attention (Figure 3) and category 2 > category 1 (Figure 4). These consistent connections were often stable across time intervals and attentional tasks (Table 4). Furthermore, functional interactions from category 2 > category 1 within the same cortical category were only found for MF (e.g. MF > MF_‡ in Table 4)[15;17]. These results strongly suggest that MF is the pivotal module in the ‘pain network’.

The efficacy of electrical or magnetic stimulation therapies for conditions including pain may result from activation and disruption of a single module [18] [77], or from activation of a network by stimulation of either a single module [18;35;77], or a subcortical white matter pathway [16;32;35]. In psychiatric disease, effective stimulation disrupts widespread networks as measured by the extent of stimulation-evoked change on cognitive testing [48], or by activation and functional interactions on functional imaging [75]. Therefore, stimulation of MF could disrupt the ‘pain network’ and so diminish acute pain, such as postoperative pain [8].

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Figure 1.

Images for the contact location in brain areas for each subject are as labeled. Categories 1 and 2 are indicated by open and closed circles, respectively. The blue abbreviations indicate the approximate location of sulci as follows: **CiS** – cingulate sulcus, **CS** – central sulcus, **MCiS** – marginal branch of the cingulate sulcus, **SF** - sylvian fissure.

Figure 2.

Time-frequency representation of ERD/ERS(A) and ERC (B) spectral responses to painful stimulation. **A.** Painful thermal stimulation induced transient power increase (ERS, hot colors) in the alpha and beta range at the peak latency of 100–150 ms in subject 1 (adapted from Figure 1 in [60]). Following ERS, the power decrease (ERD, cold colors) in the theta to beta range occurred. Note that both ERD, including alpha ERD, were more pronounced during the attention task than the distraction task. The borders of the significant ERC time–frequency plots between electrode contacts are colored blue, red and yellow to indicate the time intervals when ERC was found. Blue indicates the pre-stimulus, red denotes poststimulus and yellow denotes both pre-stimulus and poststimulus ERC. Time zero is indicated by a tic on the horizontal (time) axis. **B.** Grids of time frequency plots of the ERC,

where the presence of a significant increase in the ERC, is indicated by hot colors while white indicates that the ERC is subthreshold for such an increase (see text).

Figure 3.

Representation of the number of functional interactions between cortical areas during attention (**A**) and distraction (**B**). The maximal number of consistent causal pairs is 27 which is one half the number of contacts involved in a causal pairs ($n=54$). The diameter of the circles and width of arrows reflects the number of interconnections within that cortical area, and between those cortical areas, respectively, as divided by the total number of interconnections overall ($n=54$). Specifically, the dot indicates $0/54$, the largest circle indicates $5/54$, and the largest arrow indicates $3/54$.

Figure 4. Representation of the number of functional interactions between cortical areas: between category 2 and 1 (**A**), and within category 1 and 2 (**B**). Other conventions are as in Figure 3.

Figure 5. Regression of VAS intensity rating versus number of pairs with significant ERC. Results are shown for S1 (A) and PS (B) include attention versus distraction tasks in each subject.

Table 1

Pain intensity ratings by patient, task and run number.

Patient	Attention		Distraction	
	First run	Second run	First run	Second run
1	4/10	4/10	3/10	4/10
2	5/10	5/10	0/10	1/10
3	5/10	5/10	4/10	3/10

Table 2

Consistent causal pairs within the category 1 and category 2 cortical areas, as labeled.

	Prestimulus	Poststimulus
Category 1 – Attention	$S1 > S1^{\#}$, $S1 > MF^{\#}$, $PS > S1^{\#}$, <u>$MF > MF^{\#}$</u> , $MF > PS$.	$S1 > PS^{\#}$, $MF > S1^{\#}$.
Category 1 – Distraction	$S1 > MF$, $PS > PS^{\#}$.	
Category 2 – Attention	$M1 > PS$, <u>$MF > MF^{\#}$</u> .	$MF > MF^{\#}$.
Category 2 – Distraction	$MF > PS^{\#}$.	$M1 > PS$, $PS > PS^{\#}$, $PS > MF^{\#}$.

Fonts and symbol: Underline sensory versus nonsensory-related. *Italic* Prestimulus versus Poststimulus, **Bold** attention versus distraction,

[#] consistent reciprocal relationship between cortical areas (e.g. $PS > S1$ and $PS > S1$),

^{*} reciprocal between prestimulus and poststimulus.

⁺ consistent within area connectivity.

Table 3

Consistent causal pairs between category 1 and category 2, as labeled.

	Prestimulus	poststimulus
Category 2 > Category 1 - Attention	$MF > SI, MF > MF^{\ddagger}$	$MF > SI, MF > MF^{\ddagger}$
Category 1 > Category 2 - Attention		--
Category 2 > Category 1 - Distraction	$M1 > MF, M1 > PS, MF > MF^{\ddagger}, PS > S1, PS > MF$	$MF > S1, MF > MF^{\ddagger}$
Category 1 > Category 2 - Distraction	$S1 > MF$	

Conventions as for Table 2.

Table 4

Stable consistent causal interactions across categories and areas as a function of interval and condition. Stable interactions are defined in which one connection or a reciprocal connection (e.g. PS>S1 and PS > S1) is found across intervals or attention condition.

	Pre and poststimulus intervals	Attention and distraction conditions
Across cortical categories & across areas (Table 3)	$MF > SI.$	$MF > SI.$
Across cortical categories & within areas (Table 3)	$\underline{MF} > \underline{MF}^{\dagger}, \underline{MF} > \underline{MF}^{\ddagger}.$	
Within cortical categories & across areas (Table 2)	$PS > MF^{\dagger}, MF > SI^{\dagger}$	$S1 > MF^{\dagger},$
Within cortical categories & within areas (Table 2)	$\underline{MF} > \underline{MF}^{\ddagger}.$	$\underline{MF} > \underline{MF}^{\ddagger}.$

Conventions as for Table 2.