EEG analysis reveals widespread directed functional interactions related to a painful cutaneous laser stimulus.


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Abbreviated title: ERC analysis of the pain network-initial EEG study

Keywords: attention, human, pain, cortex, network, event related causality.

Abstract 250 words

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Acknowledgements: We thank Anna Korzeniewska who made suggestions on this manuscript. This work was supported by the National Institutes of Health – National Institute of Neurological Disorders and Stroke (NS38493-11 to FAL).
None of the authors has conflicts of interest related to this work, which is in accordance with the statement of ethical standards for manuscripts submitted to *Journal of Neurophysiology*. 
ABSTRACT

During attention to a painful cutaneous laser stimulus, event-related causality (ERC) has been detected in recordings from subdural electrodes implanted directly over cortical modules for the treatment of epilepsy. However, these studies afforded limited sampling of modules, and did not examine interactions with a non-painful stimulus as a control.

We now sample scalp EEG to test the hypothesis that attention to the laser stimulus is associated with post-stimulus ERC interactions which are different from those with attention to a non-painful stimulus. Subjects attended to (counted) either a painful laser stimulus (laser attention task), or a non-painful electrical cutaneous stimulus which produced distraction from the laser (laser distraction task). Both of these stimuli were presented in random order in a single train. The intensities of both stimuli were adjusted to produce the similar baseline salience, and sensations in the same cutaneous territory.

The results demonstrated that EEG channels with post-stimulus ERC interactions were consistently different during the laser versus the electric stimulus. Post-stimulus ERC interactions were different for the laser attention than the laser distraction task. Furthermore, scalp EEG frontal channels play a driver role while parietal temporal channels play a receiver role during both tasks, although this does not prove that these channels are connected. Sites at which large numbers of ERC interactions were found for both laser attention and distraction tasks (critical sites) were located at Cz, Pz, and C3. Stimulation leading to disruption of sites of these pain-related interactions may produce analgesia for acute pain.
INTRODUCTION

It has often been suggested that pain sensations are the result of activity and functional interactions in ‘pain networks’ in the brain (2; 12; 43; 50; 59; 67). Our prior studies applied a painful cutaneous laser stimulus and measured functional interactions between local field potentials recorded directly from cortex through subdural electrodes implanted for seizure monitoring (45; 46; 54-57). These studies demonstrated the interactions between human cortical modules, such as S1 (primary somatic sensory cortex), PS (parasylvian cortex including S2 and insular cortex), and MF (medial frontal cortex including cingulate and supplementary motor cortex).

These interactions change dynamically with tasks, such as attention to- or distraction from a cutaneous laser stimulus (45; 56). However, these recordings did not sample many cortical modules, which seem to be involved in ‘pain networks’, and did not compare interactions between painful and non-painful (control) somatic stimuli (2; 43; 60). Therefore, the results did not demonstrate the extent of this ‘pain network’, or the degree to which it is specific to painful versus non-painful somatic modalities.

Our prior studies also identified cortical sites (critical sites), which have strong widespread functional interactions both within their module and with other cortical modules. At critical sites, the number of interactions for sites overall was elevated both during attention to the painful laser stimulus and during distraction from the stimulus (46). This result suggests that functional interactions at critical sites may exert powerful, task-independent causal influences throughout the ‘pain network’.

EEG and MEG recordings have previously been used to demonstrate non-phase locked changes in power in response to painful stimuli (4; 5; 24; 31; 52; 63; 68; 75). We have now tested the hypothesis that attention to the laser stimulus is associated with increased EEG functional interactions involving widespread cortical structures, which are different from the structures associated with attention to a non-painful electrical stimulus. The widespread.
functional interactions were quantified by the Event-Related Causality (ERC), an approach which has previously been used to study event-related interactions among brain areas (6; 38; 39; 44; 45). As a corollary of this hypothesis, we tested whether the analysis of the EEG would show evidence of pain-related ERC interactions characteristic of critical sites. Subjects attended (counted) either the painful laser stimuli or the non-painful electrical stimuli while both modalities of stimulation were presented in random order in a single train of stimuli. This protocol is similar to those that have been used in previous studies (9-11; 48; 51; 72).

In order to minimize the effect of location of the stimulus on the results, both stimuli were presented in the same somatotopic area. In order to minimize differences in expectancy of the stimuli, both were presented with random order and random inter-stimulus intervals. In order to minimize differences in intrusiveness, the stimuli were applied at intensities which produced the same salience for both stimuli, as determined for each subject in a separate session prior to the experiment. These features were designed to examine the extent to which ERC interactions are specific to painful versus non-painful stimuli.

METHODS

Participants:

Sixteen healthy volunteers (10 males and 6 females; aged 22-57 years) were recruited in the present study. Results derived from the present dataset have not previously been published. The methods of this study are consistent with the Helsinki Agreement. The Institutional Review Board of the Johns Hopkins University approved these studies and all subjects signed an informed consent for participation in this study.

Painful Laser and Non-Painful Electrical Stimulation:

The experiment was conducted in a silent, dimly lit room with the room temperature set to 22 to 24 degrees centigrade during the experiment. Subjects sat in a comfortable chair and
rested their arms on a table in front of them. Insert earphones (ER1-14A Eartips, Etymotic Research, Inc, Elk Grove Village, IL) delivered a constant white noise (60 to 80 dB) throughout the experiment (Click-Tone control module, Astro-Med, Inc. GRASS Instrument Division).

Subjects were instructed to keep their eyes closed and sit quietly while painful laser and non-painful electrical stimuli were delivered to their left arm. The laser stimuli were delivered using a Thulium YAG laser (Neurotest, Wavelight, Starnberg, Germany) with a laser-beam wavelength of 2 µm, a beam diameter of 6 mm, and a duration of 1 ms. The laser was applied to slightly different locations between stimuli to avoid fatigue or sensitization of nociceptors. The non-painful electrical stimuli were single pulse, constant current square-wave pulses (1 ms duration, Grass S12 Isolated Biphasic Stimulator) delivered through skin electrodes (0.5 cm diameter) with a 1 cm inter-electrode distance on the dorsum of the left wrist. The laser stimuli were all delivered on the dorsum of the left hand within the territory of the superficial radial nerve, while the non-painful electrical shock produced sensations in the same cutaneous territory.

For the laser stimulus, pain intensity and unpleasantness were rated separately on numerical rating scales, which were anchored by 0 for the absence of pain and 10 for the maximum imaginable pain. For the non-painful electrical stimulus, unpleasantness was rated on a numerical rating which was anchored by 0 for the absence of unpleasantness and 10 for the greatest imaginable unpleasantness. For both stimuli, salience was described as ‘the ability of the stimulus to capture attention’, and was rated on a numerical rating scale for which 0 was the absence of salience and 10 was the most salient stimulus imaginable.

For each subject, a series of laser pulses were delivered at 8 energy levels in increasing order as follows: 400, 480, 560, 640, 720, 800, 850 and 900 mJ. Prior to the experiment, the subjects were asked to rate the pain intensity for the given energy levels. For this study we selected the laser energy level which produced pain of around 5-6 out of 10 on
subject's pain intensity rating. In addition, at each given energy level, subjects were asked to
rate unpleasantness, and salience. The average energy level was 730 ± 170 mJ and
corresponding pain intensity ranged from 4-6/10.

In a separate session prior to the experiment, all subjects were introduced to the
electrical stimulus with a series of electric pulses at intensity levels from 5.5 to 18 mA. For
each level, subjects were asked to rate the unpleasantness and salience for the stimulus. For
each subject, the final intensity level for the electrical stimulus was selected so that the
electrical stimulus produced a salience rating equal to that of the selected laser energy level
(average current 12.8 ± 5.2 mA). For each subject these levels of electric and laser stimulation
were applied during all blocks of stimuli so that at baseline painful and non-pain stimuli were
considered to be equally salient for all the stimulation blocks.

**Experimental Design:**

Painful cutaneous laser and non-painful electrical pulses were delivered in four blocks
of 80 stimuli (40 of each stimulus type) in random order and random inter-stimulus intervals
of between 7 and 8 sec. The randomization procedures in the experimental design were
carried out in our studies by use of a standard random number generator (java.util.Random,
Oracle, Redwood Shores, California).

In this study, attention was directed as subjects were instructed prior to each block to
count either the number of laser stimuli (laser attention task) or the number of electrical stimuli
(laser distraction task). The arrangement of tasks consisted of two blocks of ‘attend to laser’
followed by two blocks of ‘attend to electric stimuli’, and vice versa. Therefore, there were a
total of four blocks (Blocks 1, 2, 3 and 4), and the first two blocks (Blocks 1 and 2) was
randomly assigned to either the laser attention task or laser distraction task, and counter
balanced across subjects. The task of counting stimuli was the same whether attention was
directed to the laser or the electrical stimulus. Besides counting the number of attended
stimuli, the experimental designs of directed attention to one of two stimulus modalities in a single train of stimuli have often been used in primate studies of the attentional modulation of painful stimuli (Bushnell, 1985; Miron, 1989; Bushnell, 1999; Tremblay, 1993; Longe, 2001). In studies of monkeys, attention was directed to a stimulus not by counting it, but by a reward for identifying it. Subjects were not told at the beginning of the first block of stimuli for the experiment that they would be asked to carry out ratings of the stimuli at the end of the block. Nevertheless, at the end of each block, subjects were asked to report the number of attended stimuli in that block and to rate the pain intensity, pain unpleasantness, and salience of the laser stimulus. In addition, the subjects were asked to rate unpleasantness and salience for the electrical stimulus. The effect of priority upon these ratings is described in the Results section.

Data Collection:
The EEG signals were recorded using 19 Ag-AgCl electrodes (Grass) placed on the scalp according to the international 10-20 system with a referential montage to a reference of linked earlobes, as shown in Figure 1 (Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, T3, T4, Pz, P3, P4, T5, T6, O1, O2). The number of electrodes is relatively small so that we were not able to group electrodes into meaningful sets, e.g. there is only one central electrode on either side. Signals were amplified and digitized at the sampling rate of 500 Hz (SynAmps 5083, Neuroscan). The timing for the onset of the laser and electrical stimuli were acquired and embedded in the EEG recordings. All the EEG recordings were visually inspected and trials with artifacts were removed before the analysis. The average event-related potential (ERP) waveforms were processed for each subject for both stimulus modalities and will be described in a subsequent report. EEG pre-processing was carried out using Matlab (The MathWorks) and EEGLAB (19).
Event-Related Causality (ERC):

Multivariate autoregressive (MVAR) modeling for causality analysis has become a primary technique for characterizing the ongoing activity of neuronal assemblies in the brain and their interactions in cortical networks, based on the theory of stochastic processes. Here, we briefly describe ERC methods that have already been described in detail in previously reports (6; 38; 39; 44; 45).

Phase-locked responses were first estimated by averaging the raw EEG signals from all trials separately by task (laser attention task vs laser distraction task). These were then subtracted from the raw signals within each block. ERC analyses were performed on the resulting signals, by multivariate autoregressive (MVAR) modeling. This technique for subtracting phase-locked responses prior to ERC analysis, has been commonly used in the literature (6; 8; 37; 45; 47). It diminishes artifacts that can arise in the ERC analyses from phase-locked responses (73).

Directional interactions between brain areas were then estimated using Short-time direct Directed Transfer Function (SdDTF). SdDTF is an MVAR modeling approach that is based on the concept of Granger causality (28). In brief, for two observed time series X and Y, it is said that X is Granger causal of Y if the past knowledge of X significantly reduces the prediction error for Y. In this study, we refer to this as an electrode pair with a directed interaction, e.g. X \(>\) Y. The participation of any given electrode in network interactions can also be characterized by the total number of outgoing or incoming interactions with all other channels. The pattern of all directed interactions at any given time, as well as their evolution over time, can also be used to characterize the functional anatomy of large-scale cortical networks.

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 after versus before the stimulus (i.e. event-related change) (46).

SdDTF is superior to traditional spectral correlation approaches, such as coherence and partial direct coherence, because the latter methods do not provide information about the directionality of correlations (38; 45).

The order for the MVAR model used for SdDTF estimates was determined by the Akaike information criteria (AIC) (1), which was an estimate for the number of coefficients chosen to optimize the MVAR analysis. As described above, for each task condition the ensemble average was subtracted from each single trial in order to meet the criteria for MVAR modeling.

In the following sub-sections, we provide more detail for each of the above-mentioned approaches that contributed to the development of ERC in the present study.

1. Directed Transfer Function (DTF)

DTF is the first 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 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. The MVAR model used for calculation of the ERC includes all 19 electrodes.

2. Direct Directed Transfer Function (dDTF)

DTF evaluates a linear combination of causal influences along all causal pathways either directly or indirectly by interaction with an unobserved site. Therefore, non-zero values
of DTF between two channels do not necessarily imply that the causal influence between
them is direct. The causal influence may be mediated by another channel, or by channels 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 a 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.

The original DTF and dDTF is not designed to analyze the data with very short
duration and, thus, cannot be used to study interactions that occur on short time scales. This
particular limitation may be overcome when a large number of trials of a particular task is
available. 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.

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 and 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.
Because the state of the brain is constantly and spontaneously changing over time, it is important to select the baseline data within the same subject and task condition for the ERC analysis. The same baseline approach has also been used in scalp EEG and MEG recordings for analyses of spectral power changes (61; 62).

The relationship between neuronal assemblies can be understood by frequency representations of their oscillatory activities. The SdDTF was developed to estimate the directions, intensities, and spectral contents of the causal interactions. Therefore, the results from ERC analysis provide both the frequency and time information for significant causal influences found in time intervals of interest.

Post-stimulus ERC interactions were identified if the value for the SdDTF was significantly higher than a pre-selected baseline interval (i.e. one second interval starting two seconds before the stimulus). For each subject, all 19 channels were included in the MVAR models and a sliding window approach was used to smooth estimates of ERC. The size of the sliding window was set to 0.1 sec and was slid 0.04 sec at consecutive windows. This sliding window provides smoother estimates for the SdDTF at a cost of decreased temporal resolution for the ERC analysis.

To determine the statistical significance of changes in SdDTF, and thus the ERC, a baseline statistical test was applied in this study, and the significance level was set to $\alpha=0.05$, with correction for multiple comparisons. For every paired electrode combination, this test compared the values for the SdDTF in the frequency-time domain between baseline and the interval of interest using a semi-parametric regression model (16; 38; 45). A formal bivariate smoothing model for both the frequency and time was also used here to reduce the effects of the inherent noise in the recorded signals.

As in prior publications, we scanned across the 0 to 50 Hz range in order to be able to measure frequencies of ERC including the low gamma band, which is often functionally
significant (6; 38). In this study, significant causal influences were color coded by their magnitude as shown in time-frequency plots (Figure 2), across the 0 to 50 Hz band, which allows the possibility of detecting low gamma band ERC.

The computer programs for the above statistical tests were written in R language and have been previously tested and used in similar studies of multi-channel human recordings (46). All the programs for the ERC analysis were written in C language in-house, developed in the Linux environment, and run on a computer cluster, which was implemented as one distributed system.

**Statistical Measures:**

This manuscript is focused on the ERC which is measured by the probability that the post-stimulus period is different from the baseline period. There is no parametric value to be compared within individuals, only non-parametric tests of proportions of channels with significant ERC. The tests in which numbers of subjects are multiplied by the numbers of electrodes are overall tests of proportions, such as differences in proportions between the attention task versus the distraction task overall. Individual tests of proportions among subjects are summarized by the ratios in table 3. For any electrode, subjects are then taken as the independent variable and the presence of significant ERC for a subject is as the dependent variable which is examined statistically by tests of proportions.

In this study, the number of ERC’s found for all 19 electrodes and 16 subjects under different combinations of task and modality were used to estimate the 99% confidence intervals or the median using one-sample Wilcoxon signed rank test. This test is a non-parametric estimator of the confidence interval for the median of a population. Since it is a non-parametric test, it requires no assumption for the distribution of the measurement. The upper bounds for the 99% confidence intervals were used to
determine whether observed numbers of ERC pairs in a channel were significantly greater than expected at random. All the confidence intervals were computed using MINITAB (Minitab Inc., State College, PA, USA) (30).

RESULTS

Psychophysics Ratings:

For all subjects, application of a painful laser evoked sharp or pinprick pain sensations and the electrical stimulus produced a non-painful tingling sensation. For each subject, the final laser energy level was set to be around 5 to 6 on the pain intensity rating. The pain intensity was significantly greater (Table 1, 5.4±2 vs 1.9±3; p<0.01, paired t-test) when subjects attended to the laser (i.e. laser attention task) than when they attended to the electric stimulus (i.e. laser distraction task). The ability of the tasks to direct attention for the subjects was reflected in the low error rates for counting the total number of painful laser and non-painful electric stimuli for attention and distraction tasks (0.12±0.09 and 0.10±0.12). In addition, the range for the error rate did not reveal outliers in performance for attention (maximum, minimum: 0.14, 0.05) and distraction tasks (0.13, 0.0).

Prior to the study, the current level for non-painful electrical stimulus was selected to produce the same salience level as painful laser stimulus and this level was kept unchanged in all blocks for an individual subject. Therefore, before the study, the average salience level for both the laser and the electrical stimulus was 5.3±1.9. The salience level under the laser attention task for the laser (Table 1, salience 6.2±2.6) was similar to that for the electric stimulus under the laser distraction task (salience 4.8±2.0). This was consistent with prior demonstrations that non-painful somatic stimuli can be as salient as painful stimuli (42; 53).

A two-way ANOVA for task (Attention and Distraction) and modality (painful laser stimulus and non-painful electrical pulse) were performed for the ratings of unpleasantness.
and salience separately (Table 1). For the rating of unpleasantness, both factors (i.e. task and modality) revealed a main effect in the two-way ANOVA test (p=0.0001). Significant interaction effects between task and modality were also found (p=0.002). The post hoc comparisons using the two-sample t-test revealed that the unpleasantness ratings were significantly larger when the subject was asked to attend to the painful laser stimulus (5.4±2.3) than to the non-painful electric stimulus (1.9±1.5, p<0.001, two-sample t-test), i.e. an analgesic effect of distraction.

For the salience ratings, the ANOVA results showed a main effect for task (P=0.0001) but not for the modality. Therefore, the salience ratings were greater in the attention- than distraction task but were not significantly different between the laser and electric stimuli. The subjects had not been told that they would rate the stimuli until the end of the first block. Therefore, we tested for an effect of priority upon the ratings by comparing the ratings for the first versus the second block for the laser stimulus under the laser attention, and for the electric stimulus under the laser distraction task. These results are shown in Table 2 and demonstrate that differences in the ratings between these blocks were not significant (P>0.05, t-tests).

ERC Analyses:

Event-related causality was calculated in the post-stimulus interval for both tasks and stimulation modalities. Figure 2 shows ERC time frequency plots for four separate pairs of electrodes under either the laser attention or the laser distraction task. The plot in the left upper corner shows outgoing ERC for Fp1 and incoming ERC for Pz. ERC was consistently found at frequencies of less than 20Hz.

For the painful laser stimulus, the ERC analysis showed that the total number of ERC pairs was significantly greater in the attention versus the distraction task (3630/10944 vs
3402/10944 (denominator = 19 x 18 x 16 x 2), Chi-square, p<0.05). This significant difference was also found for non-painful electric pulses (3014/10944 vs 2999/10944, Chi-square, p<0.05). For both tasks, the ERC results for individual channels were presented by the task and stimulus modality in Table 3.

In Table 3, the results are given for the ERC analysis overall which indicates whether the numbers of ERC pairs (outgoing, incoming or total) are more common than the median (Methods: Statistical Measures). The table also includes the number of subjects who had significant ERC for the same electrode. The maximum number of subjects who could be expected to have significant ERC at any electrode at random was four as determined by combinatorial analysis (Binomial distribution with Bonferroni correction: 16 patients, probability of success 1/19). By this measure all ERC proportions were greater than 50% and involved more individuals than expected at random.

Painful Laser Stimulus

Laser attention task

As described in the methods, for all 19 channels a one-sample Wilcoxon test was used to construct the 99% confidence intervals. In the laser attention task, test results for painful laser stimulus showed that the FP1, Pz, F3, C3, and Cz channels had significantly greater numbers of the ERC interactions than the median for the outgoing direction (one way Wilcoxon). By the same approach, the O2, Pz, Cz, P3 and T4 channels had greater numbers of the ERC pairs in the incoming direction. Lastly, the Pz, O2, Cz and C3 channels had greater numbers of ERC pairs for the total of ERC directions (p<0.01, one-sample Wilcoxon test), which has a different distribution from incoming and outgoing directions.

During the laser attention task, Fp1 and F3 had a significantly larger number of outgoing (Figure 3A: attention outgoing - hot colors) versus incoming ERC (Figure 3A,
attention incoming cold colors) and thus played a *driver* role (Fp1: 124/288 vs 75/288, F3: 116/288 vs 81/288; Chi-square, p<0.05). The denominator for these ratios was the number of possible ERC interactions in the direction of interest x the number of subjects (18 x 16 = 288).

The temporal T4 and T6 channels were found to have significantly larger numbers of incoming versus outgoing ERC and thus played a *receiver* role during the laser attention task (T6: 100/288 vs 72/288, T4: 105/288 vs 77/288; Chi-square, p<0.05). These results in the laser attention task are consistent with outgoing frontal ERC interactions and incoming parietal temporal ERC interactions.

During the laser attention task, outgoing interactions were found for both laser and electric stimuli at channels FP1, C3 and Cz (Table 3). This proportion of channels was not significantly different from random selection of channels (P=0.037, NS with Bonferroni correction $\alpha = 0.0083$) which suggests that different interactions subserve painful and non-painful sensations. In this task, Cz was found to have incoming ERC interactions in response to both laser and electric stimuli, which was not different from random selection (P=0.39). For the total interactions, C3 and Cz were found for both laser and electric stimuli modalities.

During the laser attention task, outgoing interactions were found for both laser and electric stimuli at channels FP1, C3 and Cz (Table 3). This proportion of channels was not significantly different from random selection of channels (P=0.037, NS with Bonferroni correction $\alpha = 0.0083$) which suggests that different interactions subserve painful and non-painful sensations. In this task, Cz was found to have incoming ERC interactions in response to both laser and electric stimuli, which was not different from random selection (P=0.39). For the total interactions, C3 and Cz were found for both laser and electric stimuli modalities.

**Laser distraction task**

In the distraction task, the test results for painful laser stimuli showed that the C3, Cz, T6, Pz and P4 channels had greater numbers of ERC interactions than the median in the outgoing direction (p<0.01, one-sample Wilcoxon test). The Cz, C4, O2, P4, C3 and T3 channels were found to have significantly greater numbers of the ERC pairs in the incoming direction. For the total of ERC directions (Table 3), the results showed that the Cz, C3, T6, P4 and Pz channels had greater numbers of ERC pairs.

F8 was found to have a significantly larger number of outgoing versus incoming ERC directions under the laser distraction task (F8: 65/288 vs. 87/288; Chi-square, p<0.05), and
thus played a *driver* role (Figure 3A). T3 was found to have a significantly larger number of incoming ERC in the laser distraction task (T3: 97/288 vs. 72/288; Chi-square, p<0.05), and thus played a *receiver* role (Figure 3A). Therefore, for the laser stimulus both laser attention and distraction tasks were characterized by outgoing frontal ERC and incoming temporal parietal ERC, although these results do not prove that frontal channels are functionally connected for parietal temporal channels.

During the laser distraction task, only outgoing T6 ERC interactions were found for both the laser and electric stimuli, which is not significantly different from random selection of channels (P=0.038, combinatorials NS with Bonferroni). No channels were found with incoming ERC interactions in response to both laser and electric stimuli which was not significantly different from random selection of channels (p=0.46). Therefore, for both tasks the interactions were not different for the painful versus non-painful stimuli.

**Non-Painful Electric Stimulus**

**Laser attention task**

In the attention task, test results for non-painful electric stimulus showed that the Fp1, Fp2, C3 and Cz channels (one-way Wilcoxon) had greater numbers of ERC pairs than the median in the outgoing ERC direction. The F4, Cz and T6 channels were found to have greater numbers of ERC pairs in the incoming direction of ERC. For the total of directions, the results showed the Fp1, Fp2, C3 and Cz channels had greater numbers of ERC interactions (p<0.01, one-sample Wilcoxon test).

For the non-painful electrical stimulus, the Fp1 channel was found to have a larger number of outgoing versus incoming ERC (Figure 3B), and thus played a *driver* role in the attention task (Fp1: 188/288 vs 162/288; Chi-square, p<0.05). In addition, the F3 channel was found to have significantly larger number of incoming versus outgoing ERC pairs, and thus played a *receiver* role in the attention task (F3: 170/288 vs 143/288; Chi-square, p<0.05).
Therefore, frontal channels were both *receivers* and *drivers* for the electric stimulus under the laser attention task, while for the laser stimulus *driver* channels were frontal (FP1, F3) and the *receiver* channels were temporal parietal (T4, T6). Therefore, the pattern of frontal *receiver* channels and temporal parietal *driver* channels found for laser stimuli during the laser attention task was not found for the electrical stimulus.

The comparison of ERC interactions which occur in both electric and laser stimuli is presented above under the painful laser stimulus for both tasks.

**Laser distraction task**

The ERC results for non-painful electric pluses in the laser distraction task showed that the C4 and T6 channels had greater numbers of ERC interactions than the median in the outgoing direction. The F8 and O1 channels had greater numbers of ERC pairs in the incoming direction of ERC. For the total of directions of ERC, the Fp1, F4, C3, T6 and O1 channels were found to have significantly greater numbers of ERC pairs (p<0.01, one-sample Wilcoxon test).

For the laser distraction task and the electric stimulus, the C3 and C4 channels were found to have significantly larger number of outgoing versus incoming ERC pairs (Figure 3B), and thus played a *driver* role (C3: 166/288 vs 142/288, C4: 174/288 vs 150/288; Chi-square, p<0.05). No channel was found to have a significantly larger number of incoming versus outgoing ERC pairs in the distraction task (Chi-square, p<0.05). Therefore, for the laser distraction task central drivers were found for the electric stimulus, while for the laser stimulus and laser distraction task the driver channel was F8 was the driver and T3 was the receiver channel.

**Painful Laser Stimulus vs Non-Painful Stimulus**
For the laser attention task, the ERC analysis showed that the total number of ERC pairs was significantly greater for the painful laser stimulus than the non-painful stimulus (3630/10944 vs 3014/10944 (denominator = 19 x 18 x 16 x 2), Chi-square, p<0.01). For the laser distraction task, the total number of ERC pairs was significantly greater in the painful laser stimulus than the non-painful stimulus (3402/10944 vs 2999/10944, Chi-square, p<0.01).

As described above, the overlap between electrodes with greater numbers of ERC pairs than the median for both the laser and the electrical stimulus was not greater than expected at random. These results address both the numbers of ERC pairs and the topographical arrangement of the response to the electrical stimulus. The results are that the overlap of electrical and laser ERC pairs for either task is not significant, which demonstrates that these tasks are subserved by different structures during both tasks.

Channels with Reciprocal Interactions:

Examination of Table 3 suggests that many channels with significant ERC interactions have both incoming and outgoing interactions. Channels with reciprocal interactions are shown in Table 4. More of these interactions involved the laser stimulus than the electric stimulus (5/6 versus 1/6, P=0.08).

Critical sites:

Our prior studies of subdural recordings demonstrated the presence of critical sites that were associated with multiple significant ERC interactions in a laser attention distraction protocol (46). At critical sites, the numbers of ERC interactions during laser distraction and attention tasks were both larger than their median to a greater degree than expected at random. Therefore, to identify critical sites in the scalp data we looked for electrodes that
were associated with larger numbers of ERC interactions than the median during both the laser attention and laser distraction tasks by the one-sample Wilcoxon signed rank test (p<0.01). This is a stringent test since the chance of both conditions being met (P<0.01 for each condition) at random for any channel is very small. The results showed that the critical sites for this dataset were Cz, C3, Pz, and O2 channels (Table 3). The activity at these channels may reflect activity at critical sites in the brain as identified by subdural recordings (46).

DISCUSSION

We have now tested the hypothesis that attention to the painful laser stimulus is associated with increased functional interactions involving widespread cortical modules, which are different from the modules associated with attention to a non-painful electric stimulus. The results demonstrate ERC interactions, which are much more widespread than those described in our subdural studies of S1, MF and PS cortex (45; 46). The results also demonstrate that ERC of scalp EEG channels over the frontal lobe play a driver role while those over the parietal and temporal lobes play a receiver role for the laser stimulus during both the laser attention task and the laser distraction tasks. This pattern was not seen for ERC of the electrical stimulus in either task.

The channels with ERC in these results might be generated by particular cortical structures located within the brain. It is important to note that the precise structures involved in these ERC interactions cannot be inferred from the present results. Nevertheless, these results seem to be correlated with studies of subdural recordings that have demonstrated incoming ERC or receiver role for PS (parietal and temporal) cortex during post-stimulus intervals (45; 46). The present results do not prove that frontal channels are functionally related to parietal and temporal channels. Nevertheless, the present results also seem to be
related with fMRI studies, which found functional interconnections involving the fronto-parietal attention circuit during directed attention to pain (65), perception of pain (7), and rating of pain (36) (also see (7; 35; 64)).

Activations of these structures have been related to the salience of the stimulus, regardless of either the modality or the behavioral context of the stimulus (22; 23). The present results do not reflect differences in salience because the baseline intensity of the stimuli was adjusted to make baseline salience equal between the painful and non-painful somatic sensory stimuli. Differences in activations of these same cortical structures have been reported during attentional modulation of stimuli in different modalities (15; 27). The present ERC interactions are likely to be associated with endogenous components of attention because of the directed attention task, and because the stimulus intensities, locations, and frequencies were constant for all blocks of the experiment within each subject.

Methodological Considerations:

There are a number of limitations to ERC analysis. First, significant ERC roles might be detected between signals that are both active and correlated but not causal, as in the case of phase-locked activity. However, the coefficients of the MVAR model used in this analysis are calculated using correlation matrices, which include all observed channels. In this kind of analysis, correlation can influence the magnitude but not the direction of the ERC. These ERC calculations cannot account for the effect of unobserved channels or indirect interactions, which are outside the 19 channels included in this analysis. The present ERC causal interactions did not identify particular causal pairs, only the numbers of incoming or outgoing interactions by electrode. Finally, ERC detects and quantifies linear relations while some of the relationships that are present in the EEG may be non-linear.

To mitigate the effect of phase-locked activity (e.g. ERPs) on our ERC analyses, we chose the most straightforward procedure that has been used in the literature to
remove phase-locked activity prior to SdDTF estimations (6; 8; 37; 45; 47). In particular, ERP subtraction is a required preprocessing step for multi-trial MVAR model fitting (21). In addition, spurious causality can be produced when the subtraction is not done (58). Nevertheless, we cannot completely rule out the possibility that our results were affected by this procedure (73).

Salience is a property of painful and non-painful somatic sensory stimuli, and of stimuli of special sense, e.g. vision (22; 23; 53). The response to the painful cutaneous laser may signal the saliency of the stimulus, defined as ‘the ability of the stimulus to capture attention’ (53)(see also (22; 23; 41; 49; 76)). We controlled for the effect of baseline salience of stimuli within each subject by matching the salience of the painful laser to that of the non-painful electrical stimulus through adjustments in the intensity of the stimuli. Salience of a stimulus was altered by task so that salience was not matched under different tasks. In addition, both stimuli were applied in the same somatotopic location. This method was designed so that the presence or absence of pain was the main difference between the two stimuli, which allowed us to examine our hypotheses regarding ERC interactions between painful and non-painful stimuli. The present results illustrate ‘the usefulness of laser-related activity … to explore the effect of a given experimental factor on the transmission and processing of nociceptive input’ (53).

ERC of painful versus non-painful stimuli:

As predicted by our hypothesis, the channels with ERC interactions were consistently different between painful versus non-painful stimuli for both laser attention and distraction tasks. These results were observed although the low resolution of scalp EEG recordings will lead to an overestimate of the number of cortical structures which play a driver or receiver role in response to both painful and non-painful stimuli. These results are consistent with a study of MEG recordings which reported different causal interactions between primary somatic...
sensory cortex, secondary somatic sensory cortex, and motor cortex between painful versus non-painful electrical stimulation (66). A similar dichotomy of interactions for painful and non-painful stimuli has also been demonstrated in the monkey somatic sensory thalamus (3).

The present results are consistent with imaging studies which have compared activations related to painful heat stimuli versus non-painful stimuli including vibrotactile (14; 26), moving tactile (17), and warm contact stimuli (13; 17; 33; 71). Across all reports, there were similarities and differences in activations between painful and non-painful stimuli. The most common similarities included pain and non-pain related activation of cortical areas SI and SII; the most common differences included pain-related activation of the anterior insula or the insula.

In one of these studies, correlation between the extent of activation in different areas was taken as a measure of functional connectivity (26), although it will not reflect the direction of causal interactions (see Methodological Considerations). By this measure, more pairs of areas were correlated in response to either painful heat or vibration than were correlated for both painful heat and vibration stimuli. The present results, together with the referenced studies, support the hypothesis that different networks subserve painful and non-painful somatic sensation, so that one modality could be disrupted by focal stimulation, while the other is not disrupted.

Cortical Modules, Critical Sites and Stimulation-Induced Analgesia:

EEG has previously been used to assess the response to painful stimuli. For example, EEG recordings have been used to demonstrate changes in EEG power at particular frequency bands in response to painful stimuli. Immersion of the hand in painfully cold water can provoke a contralateral parietal decrease in power (event-related desynchronization, ERD) in the alpha band (8-12 Hz) (24). At longer latencies, bilateral frontal and posterior increases in power (event-related synchronization, ERS) in alpha band were observed in
another study (5). Alpha ERD over the vertex has been observed in scalp EEG in response to
a painful cutaneous laser stimulus (52).

A prior study has examined causality based upon analysis of EEG recordings during
the response to painful stimuli (74). This study identified significant causal interactions
between midline and lateral 'centroparietal' channels during the response to a painful
cutaneous laser stimulus. These results may indicate causal interactions between the anterior
cingulate, secondary somatosensory cortex and insular cortexes.

A striking finding of this analysis is that channels with significant ERC are often
involved in reciprocal incoming and outgoing functional interconnections for a given task
(Table 4). The channels with reciprocal incoming and outgoing ERC might be due to jointly
oscillating modules within the 'pain network'. In general, oscillations in networks subserving a
sensory modality may contribute to the representation of that sensation (25; 69).

As a corollary of our main hypothesis, we tested whether analysis of the EEG would
show evidence of pain-related ERC interactions consistent with critical sites. The present
studies of channels involved in critical sites and in reciprocal interactions commonly involve
medial frontal, parietal or central channels. The location of these electrodes may be
consistent with the results of subdural recordings, which showed critical sites over the central
sulcus and medial frontal cortex. In the present analysis, none of the critical sites or sites with
reciprocal interactions was located over the frontal lobe. The location of such critical sites or
sites with reciprocal activity may be used to determine sites for transcutaneous magnetic
stimulation for the treatment of pain (40; 45). This strategy is based upon the assumption that
disruption of a cortical network can interfere with pathologic activity in a network by stimulation
of a single module (20; 34; 70), or a subcortical white matter pathway (18; 29; 34).
**FIGURE LEGENDS**

**Figure 1:** Diagram illustrating locations of EEG channels on the head. A. Schematic of a view of the cranium from above by the standard arrangement for EEG channels (10-20 system). B. Approximate location of electrodes on a lateral view of the head.

**Figure 2:** Examples of time-frequency plots of ERC for different pairs of electrodes with the painful laser stimulus. Both displays are shown under the laser attention and laser distraction conditions with respect to the laser, as labeled. In the ERC time-frequency plots hot colors indicate significant increases in the raw ERC value. On the color scale, the numbers indicate the maximum and minimum values of ERC. All colored pixels indicate a significant change in ERC and the maximum ERC indicates the highest strength of directed interaction for the pair of channels.

**Figure 3:** Schematics of the incoming or outgoing ERC for the laser (A) or electric modality (B) by channel. These schematics display the numbers of ERC interactions involving each channel as summed across subjects, and displayed by the direction of ERC (incoming and outgoing) and by task (laser attention or laser distraction). On the color scale, the maximum and minimum values indicate the number of ERC interactions for each channel. The channel labels were plotted for the channels showed the significantly greater numbers of ERC interactions than the median. The critical sites were indicated by * next to the label. Note that critical sites had larger numbers of total ERC pairs related to the laser stimulus during both the attention and distraction tasks. Therefore, not
all critical sites had larger numbers ERC pairs for all incoming and outgoing directions.
<table>
<thead>
<tr>
<th></th>
<th>Laser: attention vs distraction task</th>
<th>Electric: attention vs distraction task</th>
</tr>
</thead>
<tbody>
<tr>
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<td>5.4±2.0 vs 1.9±1.3*</td>
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</tr>
<tr>
<td>Unpleasantness</td>
<td>5.4±2.3 vs 2.0±1.7**</td>
<td>0.9±0.8 vs 1.9±1.5**</td>
</tr>
<tr>
<td>Salience</td>
<td>6.2±2.6 vs 2.0±1.4**</td>
<td>2.0±1.7 vs 4.8±2.0**</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.001

Table 1: Psychophysical measures of pain and salience for the laser and electric stimuli under the laser attention and distraction tasks. Note that attention and distraction tasks always refer to the laser stimulus.
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<td>Block 1</td>
<td>Block 2</td>
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Table 3: Channels with significantly larger number of ERC pair (one way Wilcoxon, p=0.01) are listed in increasing order. The ratios next to the channel labels represent the proportion of the subjects showed consistent results with the overall result.
<table>
<thead>
<tr>
<th></th>
<th>Painful Laser</th>
<th>Non-painful Electric</th>
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<tbody>
<tr>
<td>Post-stimulus: Attention</td>
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<td>Cz</td>
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<tr>
<td>Post-stimulus: Distraction</td>
<td>F7, O1</td>
<td>F4, T6, O1</td>
</tr>
</tbody>
</table>

Table 4. Channels with significant ERC incoming and outgoing interactions by task.


58. Oya H, Poon PW, Brugge JF, Reale RA, Kawasaki H, Volkov IO and Howard MA, III. Functional connections between auditory cortical fields in humans revealed by Granger causality...


Painful Laser Stimulation

Attention
Fp1 -> Pz

Distraction
C4 -> Cz

F3 -> P4

P4 -> Cz

0 0.5 1 (sec)

50 (Hz)

38.8

-44.1

-49.3
A  
Painful Laser Stimulation

B  
Non-painful Electric stimulation

Attention  Distraction

outgoing
incoming

\[ \begin{align*}
\text{Fp1} & \quad \text{F3} \\
\text{C3'} & \quad \text{Cz'} \\
\text{Pz'} & \\
\end{align*} \]

\[ \begin{align*}
\text{C3'} & \quad \text{Cz'} \\
\text{Pz'} & \\
\text{P4} & \quad \text{T6} \\
\end{align*} \]

\[ \begin{align*}
\text{Cz'} & \quad \text{T4} \\
\text{P3} & \quad \text{Pz'} \\
\text{O2} & \\
\end{align*} \]

\[ \begin{align*}
\text{Cz'} & \quad \text{Cz'} \\
\text{T3} & \quad \text{P4} \\
\text{Pz} & \quad \text{O2} \\
\end{align*} \]

\[ \begin{align*}
\text{Fp2} & \quad \text{Fp1} \\
\text{Cz} & \quad \text{C3} \\
\text{F4} & \quad \text{T6} \\
\text{F8} & \quad \text{O1} \\
\text{C2} & \quad \text{T6} \\
\text{O1} & \\
\end{align*} \]
**Laser:** _attention vs distraction task_  

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<th>Distraction</th>
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<td><strong>Laser</strong></td>
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<td>Saliency</td>
<td>6.1±0.34</td>
<td>6.2±0.61</td>
</tr>
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<table>
<thead>
<tr>
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<tr>
<td><strong>Electric</strong></td>
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<td>0.8±0.5</td>
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<td>Fp1 - 9/16</td>
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Table 4. Channels with significant ERC incoming and outgoing interactions by task.