Dissecting Salience Network Responsivity to Evoked Nociception and Pain: Model Free Analyses

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Abstract

Dissecting the responses of brain changes to acute nociceptive stimuli includes understanding networks that dynamically interact to produce the experience of pain. Among these networks the salience, default, sensory, and cognitive/central executive networks are known to interact in monitoring external stimuli, assigning salience and diverting activity from self-reflection (default mode) to cognitive integration and planning potential reaction to pain (executive). Several studies of acute evoked pain report a pattern of activity reflecting the involvement of these networks. However, it has also been proposed that much of the activity seems to reflect a response to the saliency of pain rather than pain/nociceptive processing itself. These results stem from the assumption that the evoked fMRI signal arises from a single, canonical hemodynamic response induced by the stimuli. Using a model-free analysis we demonstrate that the observed fMRI response has a complex, dynamic nature not captured by model-based analysis. We provide evidence that these and other networks have a distinct temporal response. Results presented here suggest that proper modeling and characterization of the brain response is fundamental for a correct interpretation of brain activity in response to phasic/evoked noxious stimuli.

Introduction

The experience of pain is the result of an integration of sensory, emotional, autonomic and cognitive processes [1,2]. In recent years, a perspective of the large-scale distributed brain networks dynamically interacting to integrate and result in behavioral outcomes has provided a better understanding of brain function [3,4]. Three specific networks (salience (SN), default mode (DMN), and central executive (CEN)) are considered to be fundamental in an individual's interaction with the external world [5,6]. The DMN, a self-referential network, is switched off by the salience network when an external stimulus of relevant salience is experienced and enables activity of the central executive network to form a cognitive evaluation and planning a response [6-8]. Given the survival relevance pain plays, salience might have a critical role in processing pain [8]. Accordingly, it would be expected that a brain response to an acute painful stimulus might have temporal dynamics that differ due to the interaction among these different networks. Although the BOLD fMRI signal is a fairly slow signal, the temporal differences in network participation, and potential understanding of complex processes involved in how the brain interrogates pain, might be reflected in it. However, few reports of acute pain have studied potential differences in temporal dynamics. Indeed, most studies have assumed and modeled a single, canonical BOLD fMRI response across the whole brain to pain that has been based on sensory (viz. visual and motor) and cognitive studies [9]. Such results seem to indicate a strong involvement of the salience network [8]. Furthermore, it also has been suggested that the observed "pain" response (pain connectome) may incorporate a major response to the saliency of the stimulus rather than sensory aspects of pain processing [10].

In prior reports, we and others have reported that acute pain seems to elicit at least a biphasic response [11,12] and that each phase (an early and late phase) suggests representing spatial patterns involving different networks. Here we evaluate this concept in more detail and present converging lines of evidence

indicating that the evoked response to noxious stimuli is not well modeled by a single, canonical hemodynamic response but it actually represents a complex multiphase signal. Based on model-free analysis of evoked data across healthy subjects, it is possible to build appropriate models to characterize the dynamic response and provide a better characterization of the response. Specifically, in the first two sections we first provide an overview of *fMRI of Acute Pain in a Model-based and Model-free Analysis.* We then explore the generality of these observations in chronic pain.

Methods

Study Procedures

All studies were approved by the Institutional Review Board (IRB) (Massachusetts General Hospital, McLean Hospital, Boston Children's Hospital) and informed consent and assent of all participants and/or their legal guardians were obtained prior to their participation in these studies. All methods to acquire and manage data and Personal Health Information were performed in accordance with institutional guidelines and regulations.

Temporal Analysis

For temporal and network analysis (Figures 3 and 4), data from ref [12] was analyzed (N=10 male subjects, see reference for details) utilizing fsl 4.0 toolbox (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki). After computing ICA components of the noxious stimuli data using melodic's fsl, fslnets was utilized to extract time courses and compute between network connectivity and hierarchically organized. Time courses were averaged across subjects for 3 networks as displayed in Figure 4 along the temporal representation of the explanatory variable of the noxious stimuli (see ref [12] for further details).

A similar approach was used to determine temporal courses of the salience and default mode networks in pediatric patients (ref [18]) of brush evoked responses pre and post CRPS.

Salience Onset and Offset EVs were generated from the salience signal observed in 10 healthy subjects (ref [12] and displayed as blue line in Figure 4) by testing different "block" durations: We found a reasonable fit by using 5-second duration pulses for onset and offset "stimuli" convoluted with the standard hemodynamic response function (gamma function) utilizing fsl's tools. It is not clear why the salience response had an apparent stimulus duration of only 5 seconds; further studies are required to understand this observation.

The analysis of the pediatric CRPS data from ref [18] was carried out utilizing fsl tools, specifically feat was used with EVs generated from the healthy subjects or reference [12] and adapted to the timing of the pediatric brush stimulation. Statistical maps were thresholded for statistical significance utilizing a cluster-based approach with initial voxel threshold of 0.01 and cluster significance of 0.01, as described in fsl's feat webpage.

Data Availability

The datasets generated during and/or analyzed for the purposes of study are available from the corresponding author on reasonable request.

Results

fMRI Measures of Evoked Acute Pain - Model-based and Model-free Analysis

Model-based

We reported a temporal and spatial segregation of the brain response to acute painful thermal stimulation [12] (**Figure 1**). We interpreted the spatial maps associated with an early and late response to noxious stimuli as pathways involving emotional (early) and discriminative (late) processing. A closer look at such results in light of new understanding of brain networks seem to indicate that the main structures of the early response (anterior cingulate/anterior insula) are associated with the salience network while the late response seems to elicit activity in sensory/discriminative structures.

A follow up study by Chen and colleagues [11] of evoked (innocuous) brush and (noxious) thermal stimulation demonstrated clear fMRI signals for noxious heat that do not represent the standard hemodynamic response and that also show a complex response. Innocuous brush stimulation, however, provides a hemodynamic response close to the canonical one. They, however, did not model the signals with more than one hemodynamic response to delineate other brain structures potentially associated with the different signals. Nevertheless, application of sensory stimuli, be it noxious or innocuous, clearly raised the attention of the subjects and seems to be demonstrated in Chen's paper by a response that peaks about 6 seconds after the initiation of the stimulus. Only for noxious heat, it is possible to observe a second, delayed response appearing about 15 seconds post initiation of the stimulus.

The multiphasic response appears to be independent of the type of noxious stimuli, Ibinson et al. [13] demonstrated a response to noxious electrical stimulation that was multiphasic and similar to the observed one with heat pain.

The data suggest that stimuli that are noxious further induce an additional response that it is delayed with respect to a first one that seems to be independent of the nature of the stimulus. In a recent study, [14] we aimed at assessing test-retest activation to painful stimuli, we utilized a two-phase model to characterize brain activity. Our results indicated that for graded pain stimuli, there's a differential response in the anterior insula (**Figure 2**) according to the intensity of the pain stimulus; the early phase, which seems to capture activity in the salience network, displays a graded activity according to the intensity of the nociceptive stimulus suggesting that the salient network encodes pain intensity. Interestingly, the late phase seems to be present in the anterior insula only when the nociceptive stimulus is clearly painful (7/10).

These results were obtained from analyzing fMRI experiments with a traditional general linear model (GLM) approach. Such approach tends to emphasize brain areas with temporal dynamics that better

match the model of choice. Given the complexity of the observed response to noxious stimuli in the brain, a model-free approach was utilized to provide an unbiased picture of brain dynamics not obtainable with traditional fMRI analyses.

Model-free Analysis

In order to further explore brain responses to noxious stimuli without imposing a specific response, we performed an independent component analysis, typically used in resting state analysis, of the evoked pain in 10 healthy subjects that were scanned while receiving 4 noxious stimuli of 46°C for 25 seconds with resting periods of 30 seconds at 35°C [15]. fMRI scans were pre-processed using standard approaches and a concatenated ICA analysis (fMRI Melodic Tool) was done with a fixed number of components (70). Following the ICA decomposition of the response of the subjects, brain networks were identified based on published results that characterize different networks and their corresponding connection [16]. **Figure 3** displays identified brain networks out of the 70 components obtained in our ICA analysis. The figure further displays a matrix of correlations between the different networks; from the diagonal up absolute correlations are color coded, from the diagonal down partial correlation between networks are displayed (partial correlation takes into account potential correlations of specific networks with the rest of networks) (the figure was generated with FSL's FSLNets tool). Some immediate, known dynamics are visible in the matrix; for example, the salience network (SN) and the posterior default mode network (pDMN) indicate a strong anticorrelation (r=-0.7) [5,6] and at the same time, the SN and the sensorimotor area representing the hand (rSMN) are strongly correlated. The dynamics indicated here between the DMN, SN and CEN have been extensively studied in resting state experiments [5,6] and are further emphasized here as a result of the noxious stimuli driving the signals across different networks.

We further inspected the temporal responses of specific networks based on the results of **Figure 3**. In **Figure 4**, the temporal response in 3 networks of interest; DMN, SN, and SMN are presented as well as a depiction of the explanatory variable of the noxious stimulus used in standard GLM analysis. DMN provides a signal that indicates de-activation when the stimulus was on as observed in other pain and cognitive experiments. The SMN signal seems to better match the GLM model.

The SN presents a striking signal in which it is quickly activated at the beginning of the stimulus returning to baseline and re-activated when the stimulus ends. Furthermore, the initial response is attenuated over time as the subjects become familiar with a painful but not threatening stimulus, suggesting adaptation to the stimuli over time. In a previous, similar study [17] we recorded subjects' ratings of the 4 noxious stimuli (**Figure 5**) and, although we did not detect differences between stimuli, there was a trend similar to what we observe in **Figure 4** with the second salience peak. Interestingly, the stimulus "offset" response seems to remain constant across all stimuli. We suggest that offset of the noxious stimuli results in pain relief and that, although a subject could have become familiar with the onset of pain, the relief when the stimulus finishes is constant.

fMRI of Evoked Pain in Chronic Pain Patients - Model-free Analysis

We have previously reported a study in pediatric patients suffering from complex regional pain syndrome (CRPS) [18]. In the study, patients were recruited after being diagnosed and scanned before and after a non-pharmacological treatment. The fMRI study was carried out performing evoked stimuli of the affected area producing allodynia (brush stimulation) or hyperalgesia (cold stimulation). Two fMRI scans for each type of stimulation were acquired; during each fMRI scan, the stimulus was delivered for 15 seconds twice with 30 seconds resting time. Pre-processing of fMRI data was performed as described in the original report [18]. Here, we analyzed the brush stimulation using an ICA approach as described above. Spatial maps that identified the SN and DMN were selected and time courses extracted based on a group-concatenated ICA analysis using melodic. **Figure 6** depicts the average temporal signal for patients pre- and post-treatment. For the SN, there is a clear initial signal that coincided with the onset and offset of the stimulus before treatment. For post-treatment, the initial SN response was similar to the pre-treatment signal but was mostly absent once the stimulus ended. Similarly, the DMN presented a strong signal when subjects were stimulated pre-treatment and was attenuated after treatment. VAS values pre- and post-treatment were 4.8±0.4 and 1.0±0.3, respectively. We interpret these signals as an indication in the pre-treatment phase that the initial brushing elicited a painful event that was salient upon its termination (pain relief). However, after recovering, although brushing provoked an initial salient response, it was not painful, and its termination did not represent a salient event. Furthermore, the DMN was not suppressed by the salient network as it was determined that this was not a painful event.

The significant attenuation of DMN's deactivation post-treatment, compared to its response before treatment, may support the notion that this network's activity is modulated by the saliency of the stimulus. The experimental temporal resolution of the fMRI datasets prevents us from elucidating the dynamical processing that takes place, and we can only speculate that the self-monitoring network (DMN) perceives an event (noxious stimulation) and the salience network assesses and determines is saliency inducing a proportionate disengagement of the DMN while prompting the central executive network to plan for action.

Overall Evaluation of Modeling Evoked fMRI Responses

Converging lines of evidence suggest that the response to evoked painful stimuli does not simply follow the standard GLM approach in fMRI of modeling the hemodynamic response. A complex pattern is observed that requires careful modeling to properly capture the signals and their associated brain structures.

Dissecting the Evoked Response to Acute Nociception in Chronic Pain Patients

Based on the results of **Figure 4**, we generated 2 explanatory variables (EV) to reproduce the signal observed in the salience network (**Figure 4** blue line) for the onset (**Figure 7,** blue) and offset phases (**Figure 7,** black) of noxious evoked stimuli. We then constructed EVs for the CRPS patients' brush response utilizing the onset and offset salience EVs generated form healthy subjects' data (ref [12]). A standard GLM-based analysis of the brush response for pre- and post-treatment brush scans using FSL feat tools was performed. Differences in activation for the 3 EVs (onset, offset, and standard EV based on

stimulus presentation) comparing pre- and post-treatment scans were evaluated and results are presented in **Figure 8**: **Panel A**. BRUSH corresponds to the standard “block” EV. For the EV representing the initial salience response (“Salience On” in **Figure 8, Panel B**), there were no significant differences in activation in pre- vs. post-treatment as evidenced from the group maps and from the comparison map. The results for the EV representing the offset of the stimulus (“Salience Off” in **Figure 8**, **Panel C**) displayed significant differences. Comparing pre- vs. post-treatment; the standard BRUSH results seem to indicate that cingulate and frontal areas are more active pre-treatment than post-treatment. Inspecting the Salience-On comparison between pre- and post-treatment indicates non-significant differences in activation, suggesting that although subjects have recovered from chronic pain, their brains remain alert to stimuli of the one affected area. On the other hand, comparison of activation of the Salience-Off response between pre- and post- demonstrates a significant difference due to a smaller response in the post-treatment scan. This result suggests that non-noxious stimuli do not elicit a salience response once the stimulus is finished. Although patients recovered from chronic pain, stimulation of the affected area elicited a salient response, alerting that an area previously sensitive to pain, has been touched, but upon realization that pain is no longer elicited, once the stimulus is stopped, the SN does not find such event as salient.

Summary

We present evidence that brain response to phasic noxious stimuli is a complex inter-dynamic process involving several networks resulting in a fMRI response that is not well characterized utilizing standard models. Using a model-free approach the temporal behavior of the different network provides a picture in which the sequential involvement of these can be delineated and characterized. Accordingly, our results seem to indicate that current approaches do not characterize the brain response to pain in an accurate way resulting in a distorted perception that the brain response mainly represents activation of the salience network. Further studies will provide a better understanding of the brain dynamics of pain processing; specifically related to properly identifying and explaining the reasons for the duration of the onset/offset of the salience response.

Declarations

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Author Contributions

LB performed data analysis, wrote the main manuscript text, and prepared figures; DB responsible for writing and editing. Both authors reviewed the manuscript.

Competing Interests

The authors declare no competing interests.

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Figures

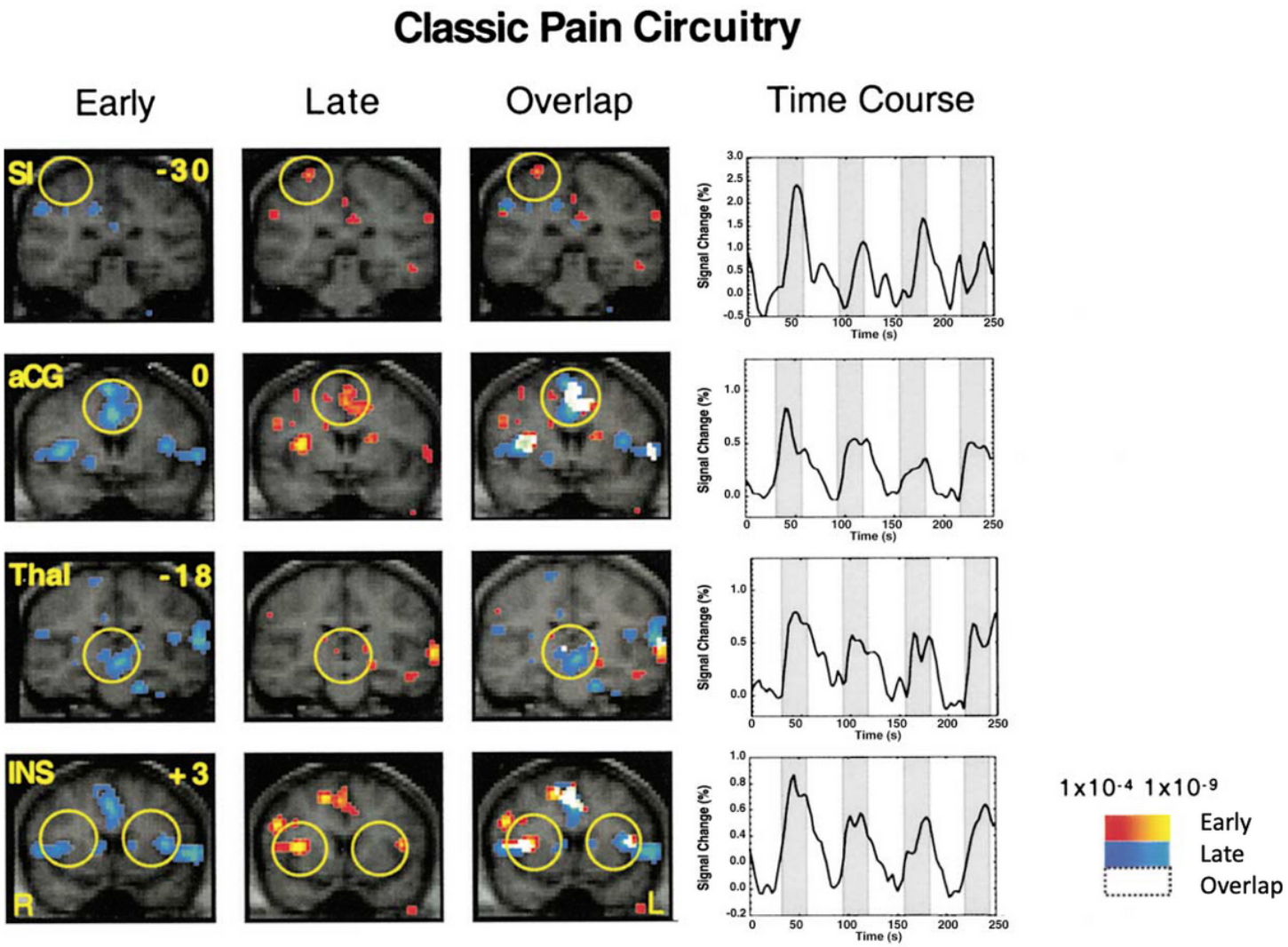

Figure 1

Segregated Brain Activity to Painful Stimuli (need to get permission from Neuron): Depicts spatial patterns of activation and time courses in response to acute painful stimuli utilizing a 2-hemodynamic model. The “early” phase displays an activation pattern involving several brain areas that belong to the salience network. The “late” phase indicated activity in sensorimotor area, as well as others associated

with the pain “matrix”. Time courses clearly show a non-canonical hemodynamic response. (Reproduced with permission from J. Wiley & Sons publisher)

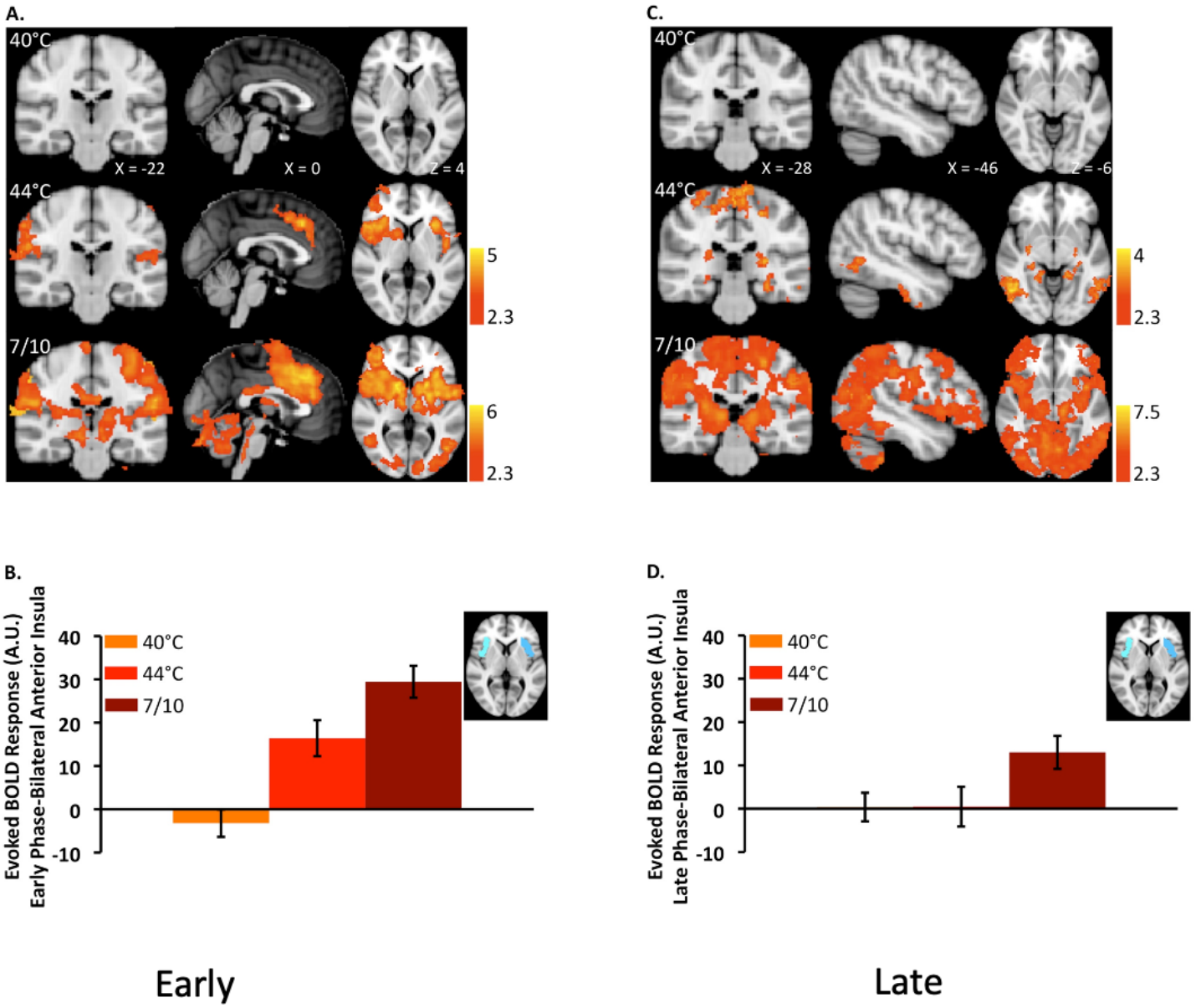

Figure 2

Pain Intensity encoding in early response to pain. Brain responses encoding pain intensity in the anterior insula with the salient component accounting for most of the encoding while the later temporal response only activates with high levels of pain (7/10) (Modified from Ref [14]).

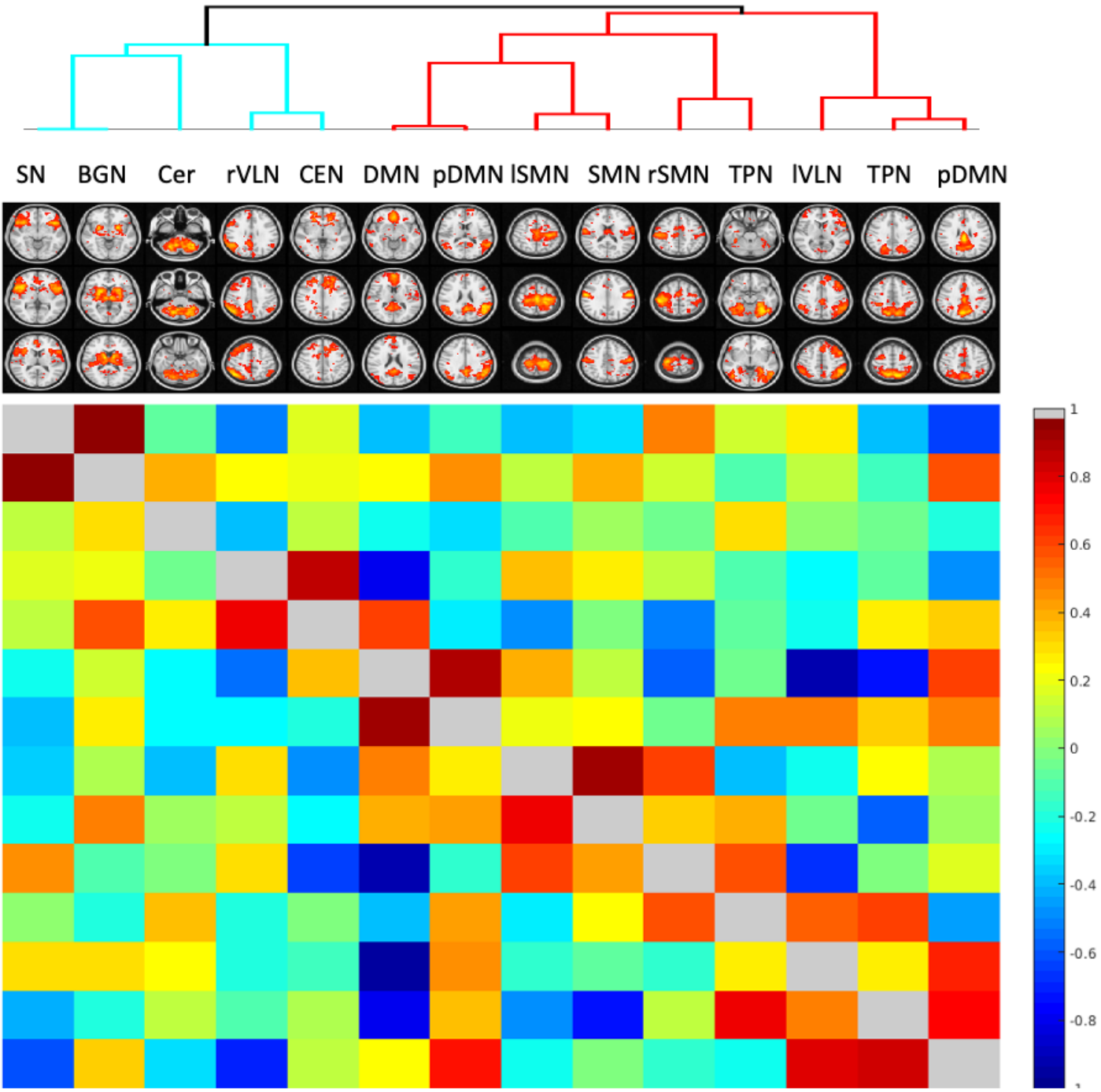

Figure 3

Brain Networks associated with evoked pain and their interactions. The figure displays the networks identified in an ICA decomposition of the response to evoked pain in healthy subjects (data from ref [12]). Correlated (red-yellow) and anti-correlated (blue-light blue) networks are further hierarchically clustered according to their temporal profiles. The diagonal separates full correlations (upper triangular matrix) from partial correlations (lower triangular matrix) among displayed networks.

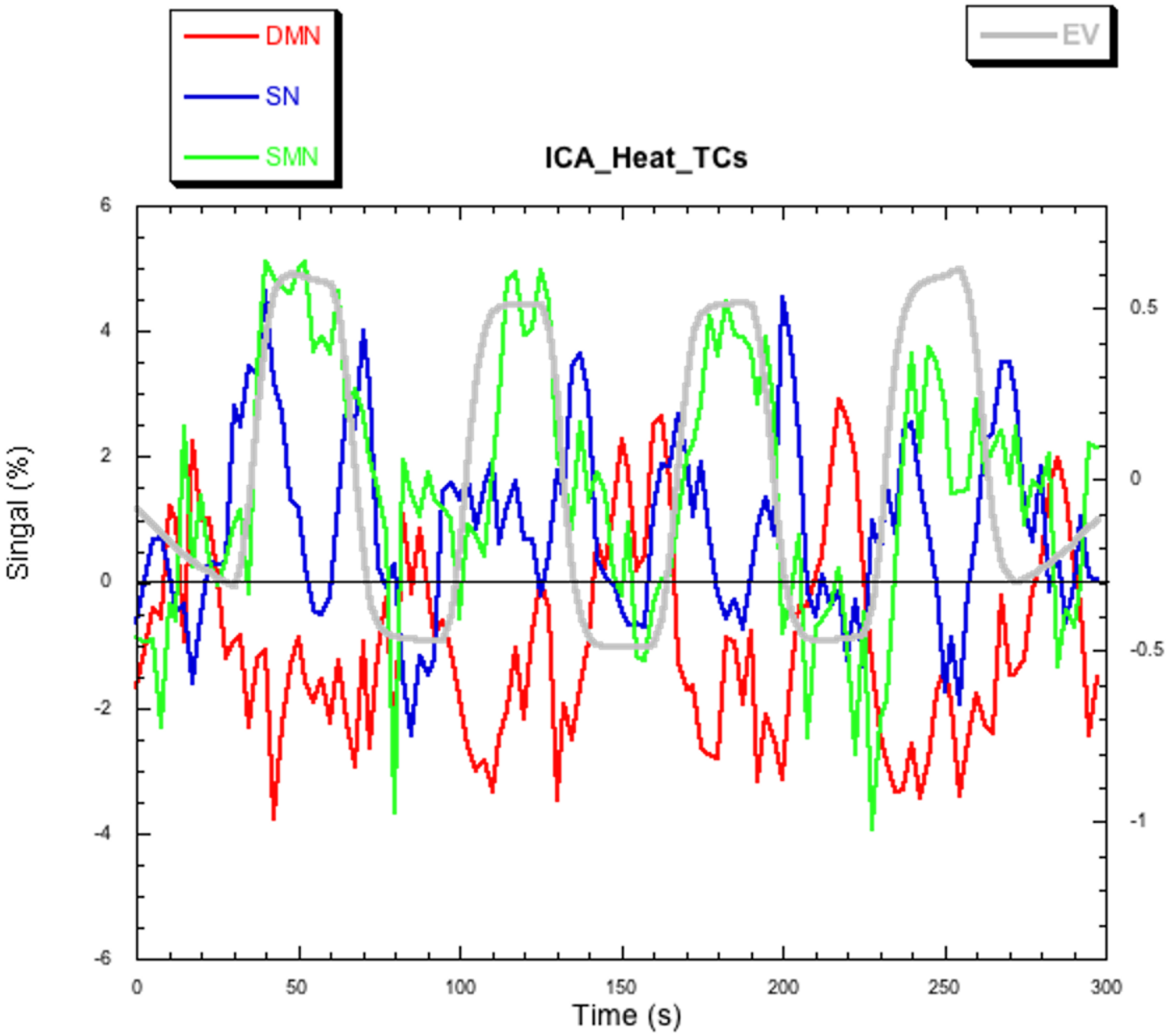

Figure 4

Temporal Profiles of Brain Networks Processing Pain. Average extracted time courses from DMN (red), SN (blue) and SMN (green) networks identified in Figure 3. In gray, the canonical explanatory variable constructed from the temporal profile of the stimuli temperature is indicated.

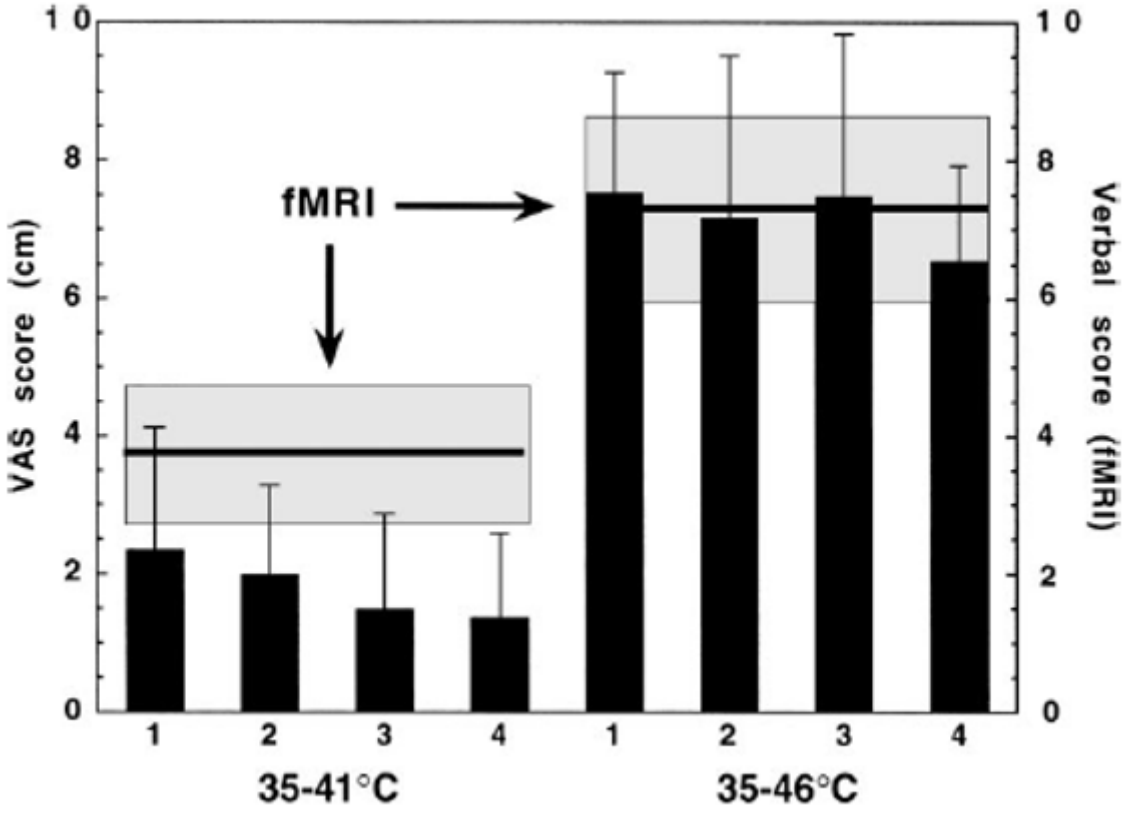

Figure 5

Behavioral Measures of Evoked Pain. Online VAS for innocuous (41 C) and noxious (46 C) in the scanner for a similar study. Both sets of stimuli indicated adaptation of pain intensity. (Reproduced with permission from J. Wiley & Sons publisher).

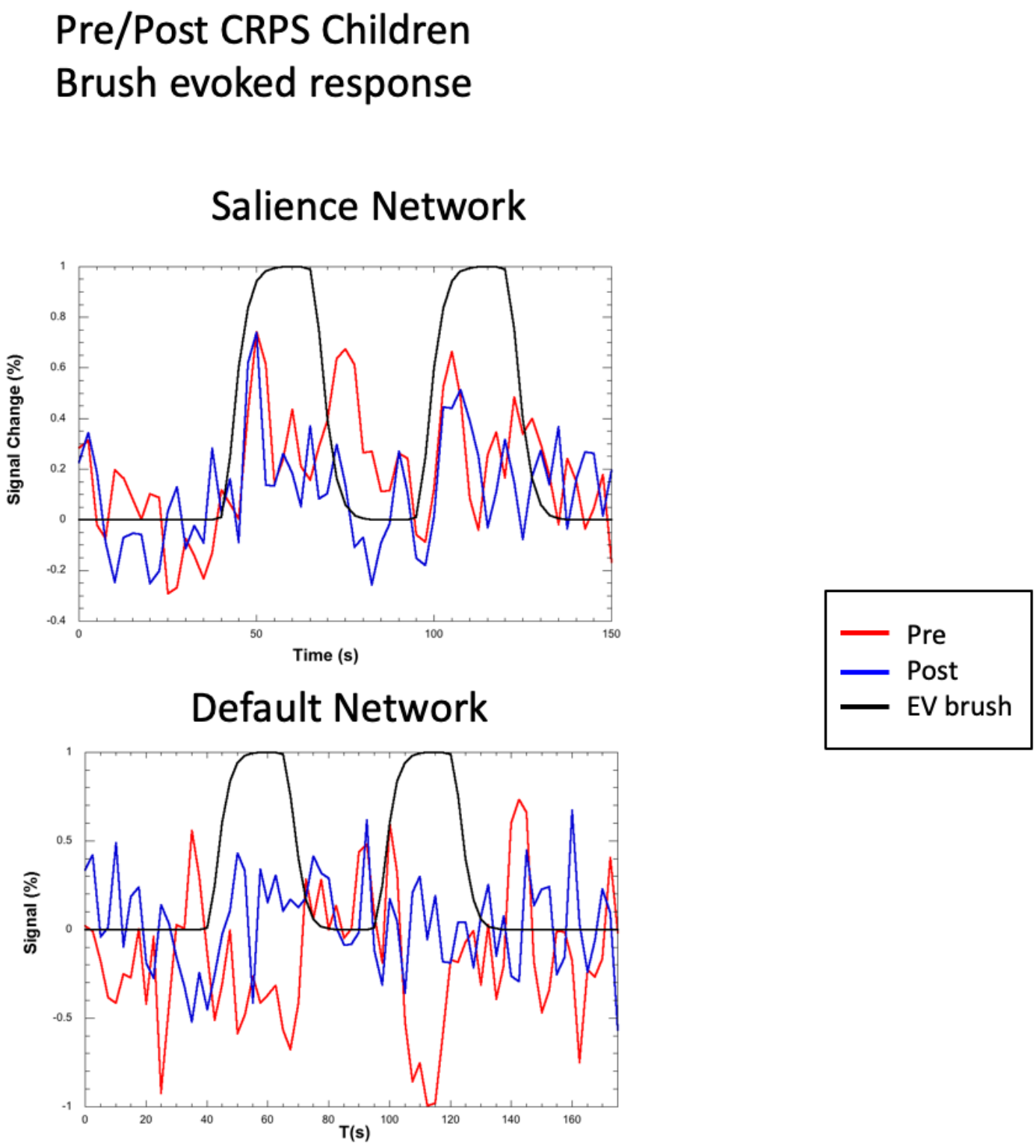

Figure 6

Temporal Profile of Two Brain Networks (DMN, SN) in CRPS. Pediatric patients experiencing pain (CRPS) to brushing pre- and post-treatment with most of their chronic pain relieved (data from ref. [18]). Before treatment, brushing affected area induced strong salient activation to the onset and offset of the stimulus with de-activation of the DMN. Post-treatment, although there was a salient initial response,

perhaps as a result of the learned experience, the “relief” saliency observed when the stimulus stops (as during pain) is no longer observed. Similarly, the DMN was not particularly activated.

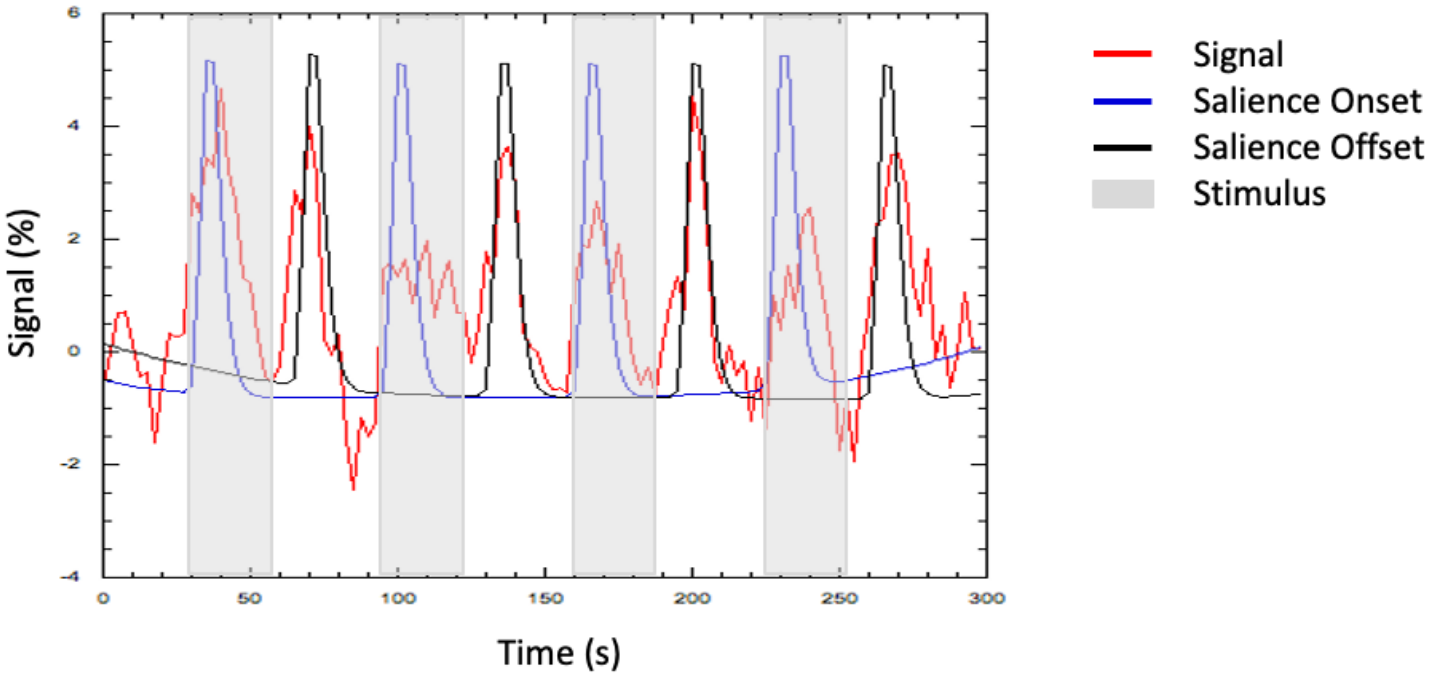

Figure 7

Onset and Offset Brain Responses. Construction of explanatory variables (EV) from the noxious heat experiments from data from Figure 4 (red) to be used to analyze the brush data of CRPS patients. Instead of using an “early” and “late” phase (as in references [12,14] an “Salience onset” (blue) and “Salience offset” (black) EVs are constructed. Gray Are represents duration of the noxious stimuli (46°C).

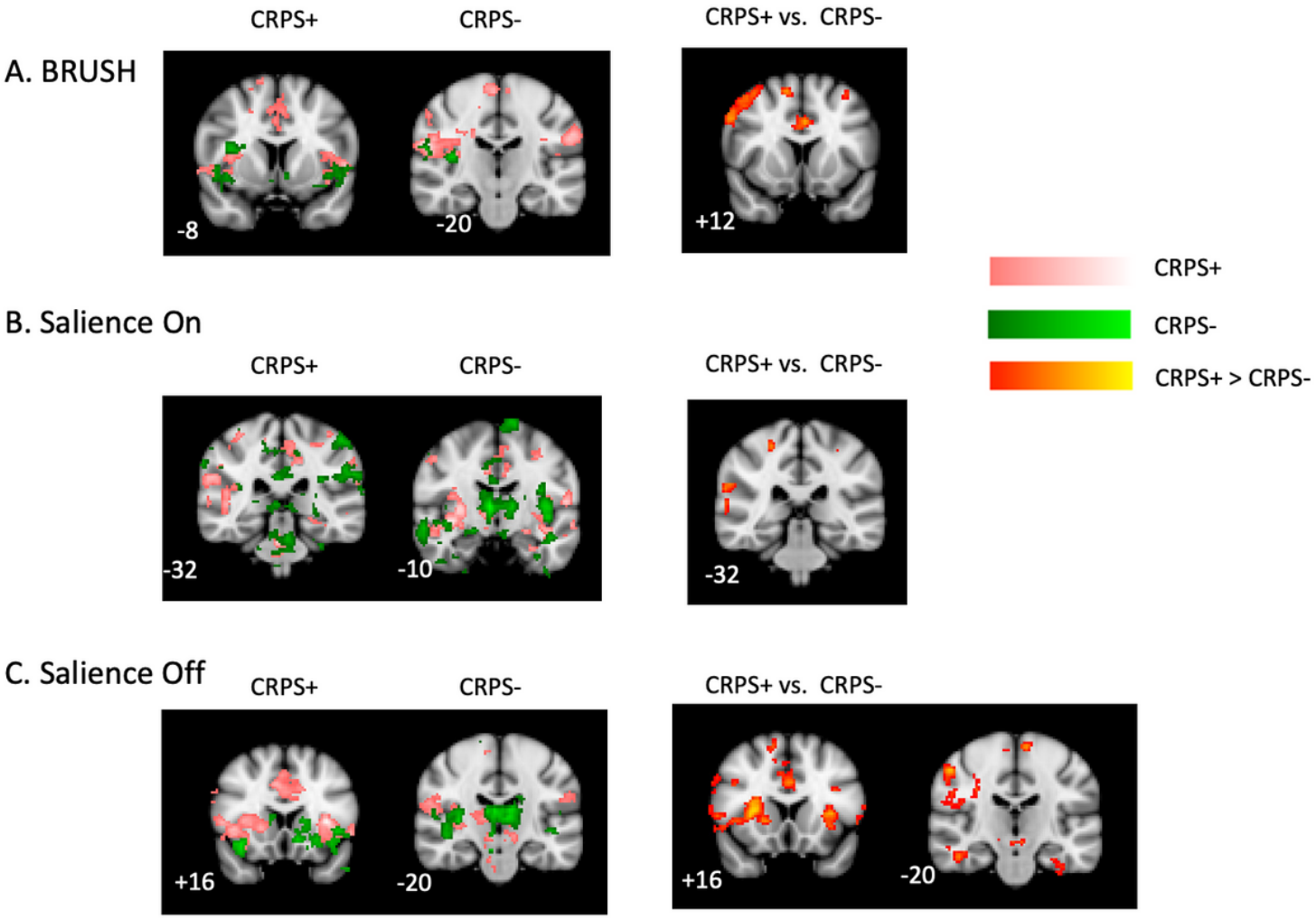

Figure 8

Activation maps for onset and offset analysis. The figure displays Panel (A) activation to brushing stimulation using a standard fMRI model (see Figure 7 for “brush” BOLD response model) for pre-(CRPS+) and post-treatment (CRPS-) as well as the comparison (CRPS+ vs. CRPS-). The ACC appears to be differentially activated in the standard analysis Panel (B) displays activation associated with the salience network response during the “on” phase of the stimulus. The difference between CRPS+ and CRPS- is small, indicating that although most of the allodynia associated with brush stimulation has disappeared in the CRPS- state, subjects still are aware of brushing and it is salient. Panel (C) Response of the salience network when brushing ceased (salience off) indicates a significant difference between CRPS+ and CRPS-. We interpret this result as an indication that stopping brushing in the CRPS- state is not associated with a relief (salient) event since the allodynia had almost if not completely resolve in the CPRS- state.