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Pain Does Not Follow the Boxcar Model: Temporal Dynamics of the BOLD fMRI Signal during Constant Current Painful Electric Nerve Stimulation

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Abstract

The temporal dynamics of the blood oxygen level dependent (BOLD) signal, especially for painful stimulations, is not completely understood. In this study, the BOLD signal response to a long painful electrical stimulation (a continuous painful stimulation of 2 minutes) is directly compared to that of a short painful stimulation (four 30-s periods of painful stimulation interleaved with 30-s rest) in an effort to further probe the relationship between the temporal dynamics of the BOLD signal during constant intensity pain stimulation. Time course analysis showed that both stimulation protocols produced three similarly timed peaks in both data sets, suggesting an early and delayed BOLD response to painful stimulation initiation, and a response related to stimulus termination. Despite the continuous stimulation, the BOLD signal returned to baseline in the two-minute task. Even with this signal discrepancy, however, the activation maps of the two pain tasks differed only slightly, suggesting that the bulk of the activation is determined by the sharp rise in BOLD signal with stimulus onset. These findings imply that the BOLD signal response time course is not directly reflective of pain perception.

Indexing Keywords

Pain; Functional MRI; Transcutaneous Electrical Nerve Stimulation; Time Factors; Image Processing; Blood Oxygen Level Dependent Signals

Introduction

Over the past two decades, blood oxygen-level dependent functional magnetic resonance imaging (BOLD fMRI) has played an important role in furthering our knowledge of pain processing in the human brain¹⁸. The majority of pain processing studies use short applications of either heat, cold, or electrical current in pain “tasks” lasting 1 to 30 seconds, interleaved with periods of “rest” where no stimulation is given. The data are then analyzed

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Disclosures

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by searching for areas of the brain where the BOLD signal matches a model consisting of the convolution of a Gaussian curve (or similar representation of the BOLD signal's hemodynamic delay) with the on/off pattern of the painful stimulation. This implies a key assumption⁶: the increase in BOLD signal consists of a single rise and fall that is independent of prior stimulations and maintains a constant level during a constant stimulus.

The BOLD response to painful stimulation may not fit this assumption, however. Prior work using a 30-second block design showed that the peak activity during each of four successive painful periods was less than the period preceding it¹⁰. It has been postulated that this decay may be due to the body's ability to accommodate to continuous stimulation^{4, 15}. This accommodation, if present, is likely due to the activation of endogenous antinociceptive circuitry. Consistent with this suggestion, previous data indicate that critical components of this circuit such as the Periaqueductal Gray are active during pain processing²¹.

Further evidence of the dynamic nature of the BOLD response to pain is suggested by multiple peaks in the BOLD signal; a phenomena attributed to a two-component (early and late) response to the stimulation^{319, 23} or to a state-change response occurring as a result of both initiation and termination of the painful stimulation⁸. BOLD imaging in general has a low overall signal-to-noise ratio that is further reduced for the deep structures involved in pain processing, with signal changes in many of the subcortical areas on the order of 1%. When this data is analyzed with a suboptimal model, significant areas of activation may be overlooked or inappropriately included. This underscores the importance of accurately characterizing the dynamic temporal BOLD response to pain, which may include multiple peaks in response to a single stimulation as well as signal decay during constant stimulation.

Our primary goal was to assess the temporal dynamics of the BOLD signal in relation to the initiation, duration, and termination of a painful electrical nerve stimulation through a region-of-interest based analysis. Based on our prior work¹⁰, our hypothesis was that the BOLD signal would rise with painful stimulation and then begin a slow decay noticeable only in long pain task. Secondly, because we hypothesized that the BOLD signal would monotonically decay during a long stimulation, we wanted to compare the pain maps of a long pain processing task with a typical short stimulus block design to determine if activation maps were sensitive to deviations from the assumed constant BOLD signal model.

Materials and Methods

Subjects

With Institutional Review Board approval from the University of Pittsburgh, informed consent was obtained from 15 right-handed, healthy subjects between the ages of 18 and 50 were recruited (11 male) from the general population via advertisements and word-of-mouth. Specific exclusion criteria included: pregnancy, a diagnosis of any neurologic disease, the use of any prescription medications or illicit substances, and any contraindications to magnetic resonance imaging.

Painful Stimulus Paradigm

Painful stimulation was achieved by transcutaneous electrical nerve stimulation (ENS) of the lateral aspect of the right index finger with a standard intra-operative nerve stimulator (EzStim II, Life Tech, Stafford, TX, USA) at the 100-Hz tetany setting. ENS acts by direct non-specific activation on peripheral nerve fibers including C-fibers, as well as A-delta and A-beta fibers. It is for this reason that the digital nerve was chosen for stimulation, as only sensory fibers are present in this distal nerve bundle, avoiding possible confounding effects from muscle contraction. Noxious nociceptor activation by this mechanism may mimic neuropathic chronic pain, but nerve stimulation used in this study is strictly an experimental

model for acute pain occurring on a time scale of seconds to several minutes. Though reported as a tingling sensation at non-noxious intensity levels, painful ENS does not have a confounding sensory perception of relative temperature inherently present in studies using noxious thermal stimulation (and explored independent of the pain component of thermal stimuli¹⁶). The instantaneous on and off transitions for electrical stimulation is another advantage of this modality distinct from contact heat, though shared with laser-induced pain. This feature was anticipated to be helpful in examining the temporal profile of BOLD response with particular focus on the onset and termination of stimulation.

Immediately before moving to the scanner, all subjects were prepared for the painful stimulation. The current was slowly increased from 0 to a level that achieved a numerical verbal pain scale of 7/10, where 0 was no pain and 10 was the worst pain imaginable. The level was recorded and the patient was then positioned within the scanner. After positioning, a single 5 second painful stimulation was provided at the current previously used to ensure a continued pain rating of 7/10. The electric nerve stimulation was delivered at constant frequency and constant current (19 ± 12 mA, for all subjects included in the final analysis) throughout each stimulation period.

The data were collected as follows. Pain 1 consisted of a block design of four 30-s periods of painful stimulation preceded, interleaved, and ended with 30-s rest periods, giving a total time of 4.5 min. Pain 2 consisted of a rest period of 2 minutes followed by a single, continuous painful stimulation 2 minutes in duration and then 30 seconds of rest after the termination of the painful stimulus. The order of delivery was not randomized, however, Pain 1 and Pain 2 were separated by a four minute rest period which has previously been shown to prevent any confounding effects¹⁰. For a subset of the subjects, the numerical pain rating was recorded in off-line sessions at the beginning and the end of each stimulation in Pain 1, and every 30 seconds during Pain 2 to determine if an accommodation or sensitization process could occur during scanning.

Scanning Protocol and Data Acquisition

Patients were positioned into a 3.0-T Siemens Trio scanner. High resolution anatomic images were collected to provide greater precision for the localization of activity and the normalization of the functional images to a group map using a T1-weighted scanning technique (MPRAGE sequence, TR/TE/Flip=25/5ms/35°; field of view = 20 cm×20 cm; slice thickness = contiguous 2.8 mm; in-plane resolution = 1.2 mm; matrix = 256×192). FMRI scans were collected using a BOLD sensitive single-shot gradient echo, T2*-weighted sequence (TR/TE/Flip = 2s/30ms/90°; 64×64 matrix; slice thickness = 3 mm, in-plane resolution 3.125×3.125mm). Thirty-five axial slices with no gaps were acquired in an interleaved fashion for both tasks, giving whole brain coverage. In accordance with the descriptions above, the functional data sets for Pain 1 and Pain 2 consisted of 135 brain volumes each. Imaging continued during the four minute rest period between Pain 1 and Pain 2, however, this data was not used for further analysis in this work.

Individual Functional Map Analysis

All imaging data were preprocessed using FEAT (FMRI Expert Analysis Tool) Version 5.98, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl, version 4.1.6) and consisted of motion correction¹¹; non-brain signal removal²⁰; spatial smoothing using a Gaussian kernel of FWHM 5mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; and highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=30.0s). Furthermore, all individual subjects' functional images were registered to their T1-weighted, high resolution anatomic scans and

to the MNI152 standard space template using FLIRT (FSL's Linear Image Registration Tool)^{11, 12}.

Functional activation was determined with general linear modeling using FEAT²⁵. To analyze each pain task, the pain stimulation paradigm was convolved with the default hemodynamic response function, which is a Gaussian impulse response function with lag time of 6 s. The first derivative of the stimulation time course was included in the model to account for small variability in the shape of the hemodynamic response function or imperfections in stimulus delivery timing⁹ and all six motion parameters were included in the model as effects of no interest. All data were pre-whitened during this first level analysis. Time-series statistical analysis was carried out using FILM with local autocorrelation correction²⁵. This data was then input into as first level analyses into the group map calculations described in the next subsection.

Additionally, individual maps using the median pain rating time course as the paradigm input were generated (again convolved with the default hemodynamic response function). These were also input into the below described analysis to determine if using the reported pain ratings instead of the assumed box-car would affect the overall group maps.

Group Functional Map Analysis

Average group activation maps were generated for the Pain 1 task (using the boxcar analysis and the actual pain ratings) and the Pain 2 task independently with a fixed effects model within FLAME (FMRIB's Local Analysis of Mixed Effects)^{5, 24}. These used a cluster-based thresholding correction for multiple comparisons determined by $Z > 3.25$ and a (corrected) cluster significance of $P=0.05$ ²⁶. Group difference maps were also generated directly comparing the response between the Pain 1 and Pain 2 tasks. For this, a fixed effects model was again used with statistic images thresholded by $Z>2.3$ clusters and a corrected significance of $P=0.05$.

Region of Interest Time Course Analysis

Regions of interest (ROIs) were generated for the cerebellum, contralateral and ipsilateral insula (Ins), contralateral prefrontal cortex (PFC), contralateral and ipsilateral secondary somatosensory cortex (SII), Brodmann Area (BA) 24 of the anterior cingulate cortex (ACC), BA 32 of the ACC, the contralateral thalamus, and the contralateral primary somatosensory cortex (SI). First, the center of mass for the activation in these areas from the Pain 1 group map (pain stimulation time course) was used to define a ROI sphere with a 6 cm diameter. This representative ROI was then inverse-transformed using the registration matrices generated by FLIRT back to the coordinates of each subject's functional-space images. The individual subject time courses for each area were then extracted, normalized to percent signal change, and finally averaged together to determine the group average time course for each ROI². This process was repeated for Pain 2 using the same ROIs from Pain 1. An additional ROI, located in the left lateral ventricle, was also created for each subject by the above procedure and used as a control comparison for time course analysis.

Results

All 15 subjects completed the entire scanning protocol. During motion correction, however, it was noted that Subject 1 moved over 1 mm in a stimulus-correlated manner and had activation maps that could not be interpreted. As a result, this subject was excluded from further analysis. None of the remaining subjects showed stimulus-correlated motion, nor had other issues with data quality, and thus the remaining 14 were used for subsequent analysis.

Dynamic Changes in Pain Rating During Stimulation

Analysis of the pain rating time course across the subset of four subjects showed that the pain rating at the beginning of each of the stimulations of Pain 1 was a median value of 7/10 and decreased to a 5 at the end of the 30 second stimulation. Interestingly, the Pain 2 stimulation started at a median value of 8 and then also fell to a rating of 5 by the end of the first 30 seconds of stimulation, which it maintained until the end of the Pain 2 stimulation. Thus, although some decrease in the pain intensity occurred during stimulation, the level remained at a pain score consistent with “pain” and with the successful generation of pain-related functional images^{8, 10, 17}.

Pain 1 Group Map

Pain related activation, as determined by general linear modeling using the block design of Pain 1 convolved with a Gaussian curve, was identified (Table 1) in the cerebellum, contralateral and ipsilateral insula, contralateral PFC, contralateral and ipsilateral SII, the ACC (BA 24 and 32), the contralateral thalamus, and the contralateral SI. The activation in selected areas are shown in Figure 1, and generally agrees with the results expected from the literature^{1, 18}. Utilization of the pain rating time course in the analysis GLM analysis did not significantly alter the Pain 1 map: no new areas of activation were identified, and the regional maximum Z-scores were overall similar (also shown in Table 1).

ROI-Based Time Course Analysis

The MR signal time course for each of the activated areas detailed above was investigated to determine the association between the BOLD signal and the stimulus duration, including the presence of multiple signal peaks linked to stimulus initiation and termination. An initial qualitative examination of the time course of each of the activated areas for Pain 1 showed an on/off pattern of BOLD signal change with a prominent peak at the start of stimulation (Figure 1, Pain 1 column). A closer visual inspection of the Pain 1 time courses suggested an additional peak in the BOLD signal that occurs around the time the painful stimulation ceases, although its intensity varies across brain areas and with repeated stimulations.

To better define the peaks, the Pain 1 signal in each ROI was averaged across the four on/off epochs (defined as a 30 seconds on/30 seconds off cycle of painful stimulation) and plotted in the second column of Figure 1. From this, the presence of the aforementioned initial peak with stimulation start (termed within as the “On-Peak”) is evident. Furthermore, the On-Peak dominated the BOLD signal during the task. An additional peak was clearly seen in all 10 of the activated areas from the Pain 1 task that occurred a few seconds after the painful stimulation stopped (termed the “Off-Peak”). Thus, the Pain 1 time course consists of an initial sharp On-Peak, a rapid decay towards the baseline, and a gradual rise in signal that ends with a sharp Off-Peak approximately 6 seconds after the end of the stimulation. Left to be determined, however, is whether Pain 1’s Off-Peak truly results from the stimulus termination, or if it is a peak that occurs 36 seconds after the initiation of the stimulus. Of note, these peaks were not present in the ventricular ROI, ruling out motion or other artifact as a source.

Using the ROIs defined by Pain 1, the BOLD signal time courses for Pain 2 were extracted and are presented in the Pain 2 column of Figure 1. A dominant initial peak, appearing to correspond to Pain 1’s On-Peak is clearly present. Also noted is the return of the Pain 2 signal back to baseline approximately 45 seconds after the start of the stimulation. After the stimulus ends, the Pain 2 signal shows a peak similar to the Off-Peak above and a prominent baseline undershoot, but determining the correspondence in signal changes between the pain tasks is still difficult, thus each time course was broken into pieces and plotted in Figure 2.

Figure 2 shows that there were important similarities and differences in the BOLD signals of Pain 1 and Pain 2. Again, both begin with an early response that returns to baseline in spite of continued stimulation (On-Peak) with obvious correspondence between the two (Figure 2, Column A). More distinct in the Pain 2 graphs of Figure 2 is that after the On-Peak returns to baseline, a second broad rise from approximately the 20 second mark until the 40 second mark is now present; we refer to this as the “Second-Rise” (Figure 1, Column B). The Second-Rise is not as prominent in the Pain 1 graphs, although signal increases are seen in selected areas. Plotting the time period containing Pain 1’s Off-Peak with the same timeframe for Pain 2 (Figure 2, Column C) shows that a true peak in the Pain 2 data corresponding to the Off-Peak timing found for Pain 1 is not seen; i.e., the Off-Peak is not simply a peak that is delayed 30 seconds from the start of the stimulation. Instead, by plotting the stimulus end of Pain 1 with the stimulus end of Pain 2 (Figure 2, Column D) an Off-Peak is evident in both data sets, confirming that the Off-Peak truly results from the cessation of the painful stimulus and is not a delayed peak linked to the initiation of pain. For all areas, a signal drop and undershoot below baseline then begins approximately 10 seconds after the end of the stimulus.

That the Off-Peak is related to stimulus termination is further confirmed by computing correlation coefficients between the Pain 1 and Pain 2 signals (Table 2) for each of the brain areas of Table 1. The On-Peaks (shown in Figure 2A) are strongly correlated with high coefficients – eight of the ten areas are above 0.9 and the overall average value is 0.9506. The Off-Peak in Pain 1 does not have a corresponding signal increase during the same time following stimulus as in Pain 2 (shown in Figure 2C); reflected by the average coefficient of 0.5941 for the Pain 1 off period versus the same timing of Pain 2 stimulation. Instead, the post stimulus period of Pain 1 strongly correlates to the post stimulus period seen in Pain 2 – as seen in Figure 2D. The average correlation coefficient across all ten areas of activation for this comparison is again high at 0.8656.

Effect of BOLD Temporal Dynamics on GLM-Based Activation Detection

When the Pain 2 data was analyzed with the traditional general linear model using a basic hemodynamic curve convolved with the single stimulation of the Pain 2 task, activation similar to that of Pain 1 was found in the SI, bilateral SII, bilateral insula, and the VI area of the cerebellum, in spite of the lack of continued BOLD signal elevation in the Pain 2 time courses. For the Pain 2 task, additional activation was found in the posterior cingulate cortex (PCC) and the Crus of the cerebellum, while no activation was identified in the thalamus, PFC, and the ACC. These are detailed in Table 3.

When the two task maps were compared statistically there were minimal differences (Table 4), suggesting that the sharp On-Peak corresponding to the painful stimulus onset is enough for functional map generation. The medial frontal cortex (BA 10) and a small portion of the occipital coneus (BA 19) showed greater correlation to Pain 1, even though neither of these areas was frankly active as determined by analysis of the Pain 1 response across subjects. When examining areas where the Pain 2 activation was greater than Pain 1, an additional medial frontal area (BA 11), an area in the left Crus, the right thalamus, an area in the middle temporal lobe (BA 21), and the posterior cingulate cortex were found to be statistically different.

Discussion

Our primary goal was to examine the temporal response of the BOLD signal in painful electrical nerve stimulation, determining if multiple peaks would be present and if they had dependence on stimulus initiation or termination. Multiple peaks in the time course for the typical on/off pattern of Pain 1 were found. The On-Peak is the bulk of the BOLD signal

change, especially for long stimuli, therefore the results are strongly tied to the stimulus onset.

One important design consideration in any study of pain is whether to maintain constant stimulus-energy intensity or to maintain constant pain rating by altering the stimulus energy. We chose to maintain a constant stimulus energy because of the unique technical challenges presented by the scanning environment (subject motion and image artifact), and because we wished to avoid any confounding brain activity resulting from the internal pain rating process and the communication of that rating with the outside world (be it through verbal or non-verbal means). Previous work has shown a linear increase in BOLD and blood flow signal changes with increasing frequency of electric nerve stimulation up to 100 Hz¹³. However, we expected that some pain intensity rating decrease would occur as it has been shown that current increases are needed to maintain pain rating in an ENS-induced long term potentiation and depression study¹⁴. Because the pain level did not cause the intensity to drop below the typically accepted pain threshold of 5 during the stimulation, we contend that a painful stimulation was maintained throughout. The finding within our subgroup that pain ratings actually increased for the initial stimulation of Pain 2 was not surprising and is likely due to long-term potentiation caused by high-frequency ENS¹⁴.

A review reveals that areas of the pain processing matrix (SI, SII, ACC, Thalamus, Insula) are activated across various experimental pain stimuli, including electrical, cold, heat, laser, and cutaneous pressure stimulation¹ with a reasonable consistency. Published BOLD time course data in response to pain is less commonly found in the FMRI literature. An On-Peak occurring approximately 6 s after stimulus onset is evident in previous studies using both heat and electrical stimulation.^{3, 8, 16, 23} It should be noted that it is a return towards baseline that gives the BOLD response waveform a peaked shape. In this regard, conflicting results have been shown with a similar On-Peak for non-painful ENS described as tingling⁸, and, conversely, a response more reflective of the classic boxcar waveform seen in response to brush stimulation²³. The effect we describe as the Off-Peak, occurring after stimulus termination, is even less frequently observed and discussed in the literature, but has been shown in other studies using both electrical and heat stimulation.^{8, 16} The presence of an "off" signal increase that may overlap the subsequent rest period, even after accounting for hemodynamic delays, implies that care must be taken to avoid underestimation of the degree of brain activation, as increased signal analyzed as part of the resting portion of a block design will cause the changes associated with stimulation to appear less significant.

The Second-Rise has also been demonstrated in other works.^{3, 8} When initially describing the presence of a double peak in heat-induced pain FMRI data, Beccera et al.³ found peaks corresponding to an early (first half) and late (second half) response to a 25 second stimulus. This has subsequently been analyzed using multiple component models by the same group^{16, 19, 23} as well as a potentially similar effect reported by others²², though BOLD time course data was not published in this study. We propose that our Second-Rise corresponds to their late response, but that the signal decay to baseline does not occur because the short-duration stimuli used end before it can occur (as with our Pain 1 data). Downar et al.⁸ also clearly show the presence of a Second-Rise in most of their electrical stimulation data, however they do not show a decay, even though their stimulation would be long enough by our model. We believe this discrepancy may be due to differences in the pre-processing of our image data. Downar et al. chose to use both voxel-wise linear regression and high-pass filtering to remove typical BOLD signal baseline drift in their data, while we only used the high-pass filtering technique. It has been our experience that high-pass filtering is sufficient, and we postulate that the additional regression could mask a slow decay to baseline if this was the predominant drift in the BOLD signal.

It has been previously postulated that the early response (On-Peak) is associated with protective mechanisms and descending control, while the Second-Peak reflects the conscious response to pain³. This explanation does not suggest why the BOLD signal would again decay to baseline after the Second-Peak, however. When coupled with the assumption that activation causes a consistent BOLD signal increase, our pain time course data would suggest that the BOLD signal within pain-activated areas should remain elevated since the stimulus remains painful throughout. Additional work is needed since several possible explanations exist for this phenomenon. First is that neuronal habituation can occur in either the peripheral or central nervous system, decreasing the experienced intensity of the constant stimulus. Similarly, activation of descending analgesic pathways, which may not have time to be effective with shorter duration stimuli, may reduce the supraspinal experience of pain during prolonged stimulation. Given the fact that our pain rating scores did show a decrement from 7–8 to 5 over the course of the stimulation, some element of the above is likely occurring. Alternately there may be delayed microvascular changes that occur, including a maintained increase in regional cerebral blood flow (which caused the initial BOLD signal increase) that is followed by a slowly reactive increase in regional cerebral venous blood volume, thus causing the decrease in BOLD signal. This theory is further compatible with the BOLD signal decrease to below baseline following the Off-Peak, however future work using various modalities of painful stimuli and imaging techniques capable of following changes in cerebral blood flow independent of cerebral blood volume is needed to investigate this possibility.

The repeatable presence of the multiple peaks suggests that they are a part of the experience of pain processing, with important implications for the design of the response timing in future studies. To illustrate this complicating effect, consider the following. Chen et al.⁷ found a two-phase peak to heat pain, including a gradual rise with an eventual second peak 17 seconds after the onset of the stimulus, which roughly corresponds with the timing of our “Second-Rise”. However, because their stimulus was approximately 10 seconds long, this peak was also about 7 seconds after the end of their heat stimulus, thus could also have been an effect similar to what we have described as the “Off-peak”.

The multiphasic peaks and signal decays detailed above are violations of the linearity assumptions presented in the introduction, and can cause ambiguous signal changes, as in the example above. Yet simple GLM based analyses of pain fMRI data that assume a constant BOLD signal change block design are commonly used within pain fMRI literature. This leaves one to question the effect these violations may have on the activation maps. Overall, the Pain 1 and Pain 2 maps were qualitatively similar, with only minor differences on statistical difference map examination (although activation that is visually larger in both extent and maximum z-score in Pain 1). The similarity in the pain maps follows from the fact that the bulk of the BOLD signal change is present in the On-Peaks. The minor differences are likely due to the decay seen after the Second-Rise in Pain 2 – the return to signal baseline weakens the z-scores of the model and decreases the intensity of the “activation”. Additionally, the use of the median pain rating time course in the analysis did not seem to affect the areas found to be activated or the overall level of activation, furthering the above argument. Future work will closely compare the derived three-peak model to the standard “boxcar” and the pain rating models to more formally investigate the importance of proper model specification.

In conclusion, analysis of the temporal dynamics of the BOLD signal revealed significant limitations associated with the use of a simple integrated signal approach in the study of electrical pain BOLD fMRI; the BOLD signal does not maintain a constant level during continued painful stimulation, as assumed in many studies. The multi-peak BOLD signal response that was previously reported for heat pain is present in electrically-induced pain

epochs, although this may go entirely undetected depending on the length of the painful stimulation. A two-peak model may not sufficiently characterize the response to electrical nerve stimulation, when an Off-Peak can confound the signal within the rest period.

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Perspective

This article demonstrates that the blood oxygen level dependent signal for a painful stimulation contains multiple peaks and does not maintain the constant level during stimulation that is assumed in typical analysis. While these dynamics should be accounted for in future studies due to their ability to confound results, their presence did not significantly alter the overall group maps.

Figure 1.

Selected slices from the Pain 1 group activation map on the MNI standard brain along with group average time courses for each region of interest (ROI) for the entire Pain 1 and Pain 2 tasks. The response to a single stimulation from the Pain 1 task is plotted in the Pain 1 Ave column and was obtained by averaging across all four stimulations. The prominent On- and Off-Peaks are evident in the Pain 1 Ave and Pain 2 graphs for the activated brain areas, but is absent in the ventricular (control) area. Similar activation was seen in the other areas of Table 1.

Figure 2.

Comparison of the time courses for each of the BOLD signal peaks evident in Figure 1. The time courses from the Pain 1 and Pain 2 tasks from Figure 1 are separated into four graphs based on their timing from the start of the stimulation. Column A highlights the On-Peaks for both tasks, showing the first 14 seconds of the stimulation. In Column B, the BOLD signals from 12 seconds post-stimulus start to 40 seconds post start are shown. Notice this encompasses the beginning of the Off-Peak for Pain 1, since it begins at the 36 second post-stimulus initiation. The Off-peak of Pain 1 is plotted with the same post-stimulus initiation timing for Pain 2 in Column C, while Column D compares the time surround the stimulus

off timing for both Pain 1 and Pain 2, showing that the Off-peak results from the cessation of stimulation.

Table 1

Areas of Significant Activation for the Pain 1 Task.

Brain region	Laterality	Decay Coordinates (mm)				BA
		Z-Max	Z-Max	X	Y	Z
SI	L (contra-)	11.2	9.85	-56	-22	44 1
SII	R (ipsa-)	7.93	8.10	58	-18	18 40
SII	L	7.81	10.6	-52	-22	14 40
ACC (24)	L	5.48	4.86	-2	-12	44 24
ACC (32)	Midline	4.54	4.94	0	26	28 32
Insula	R	7.75	7.46	44	-4	6 13
Insula	L	6.77	6.31	-38	-4	10 13
Thalamus	L	6.59	6.43	-16	-24	-4
PFC	R	4.52	4.58	4	18	58 9
Cerebellum	R	6.99	7.55	18	-54	-24 VI

Table 2

Comparison of Correlation Coefficients for Figure 2. (c = contralateral, i = ipsilateral)

Brain region	A. On-Peaks	B. Second Rise	C. Pain 1 Off vs Pain 2	D. Off-Peaks
SI	0.9513	0.7410	0.7030	0.9626
iSI	0.9850	0.4306	0.5646	0.9195
cSI	0.9905	0.6304	0.6750	0.9439
ACC (24)	0.9755	0.5893	0.6360	0.9100
ACC (32)	0.9143	−0.1094	0.3263	0.8728
iInsula	0.8973	0.4861	0.6569	0.8352
cInsula	0.8847	0.4024	0.5907	0.8940
Thalamus	0.9783	0.7471	0.8449	0.8494
PFC	0.9532	−0.1652	0.4767	0.7739
Cerebellum	0.9760	0.2733	0.4670	0.6950
Average	0.9506	0.4026	0.5941	0.8656
Ventricle	0.6300	0.6766	0.7763	0.7077

Table 3

Areas of Significant Activation for the Pain 2 Task.

Brain region	Laterality	Z-Max	Coordinates (mm)				BA
			X	Y	Z		
SI	L (contra-)	6.63	-46	-40	58	2	
SII	R (ipsa-)	4.52	56	-26	20	40	
SII	L		-64	-22	20	40	
PCC		5.75	0	-32	22		
Insula	R	5.56	56	16	-10	13	
Insula	L	5.61	-50	-4	0	22	
Sup Front Gyr	R	5.63	52	-50	40		
Cerebellum	R	4.56	22	-52	-26	VI	
Cerebellum	L	4.51	-40	-58	-30	Crus	

Table 4

Areas of Significant Differences in Activation between Pain 1 and Pain 2.

Brain region	Laterality	Coordinates (mm)				BA
		Z-Max	X	Y	Z	
Occipital Cortex	R (ipsa-)	3.94	-10	-90	-15.2	19
Medial Frontal Cortex	Bilateral	4.9	8	54	-16	10
Medial Frontal Cortex	Bilateral	3.77	4	68	-20	11
PCC	Bilateral	3.9	0	-28	28	23
Middle Temp Lobe	R	3.95	66	-28	-12	21
Supramarg Gyrus	R	3.99	52	-52	36	
Thalamus	R	3.85	6	-32	2	
Cerebellum	L	3.96	-16	-80	-28	Crus I