CNS Activation by Noxious Heat to the Hand or Foot: Site-Dependent Delay in Sensory But Not Emotion Circuitry

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Becerra, L., M. Iadarola, and D. Borsook. CNS activation by noxious heat to the hand or foot: site-dependent delay in sensory but not emotion circuitry. J Neurophysiol 91: 533–541, 2004; 10.1152/jn.00326.2003. Recently, functional magnetic resonance imaging has been used as a novel method of evaluating the CNS response to noxious stimuli. In a previous study, a prolonged noxious thermal stimulus applied to the dorsum of the hand produced more than one hemodynamic response that was temporally segregated. The two major responses displayed activation in primary sensory regions (classic pain circuitry) and regions involved in emotion (reward/aversion circuitry), respectively. In the current study, we applied the same thermal stimulus separately to the dorsum of the left foot and the dorsum of the left hand in the same subjects and compared the hemodynamic responses to evaluate the effects of conduction distance on CNS activation within these two segregated systems. After stimulus delivery to the foot, the hemodynamic response in primary sensory networks occurs after a delay of 3.6 ± 1.3 s as compared with the response after hand stimulation. The relative delay of the hemodynamic response in reward/aversion regions is not significantly different between hand and foot stimulation (0.6 ± 2.1 s). These results within the primary sensory system are consistent with the greater conduction distance of the peripheral nerves from the hand versus the foot. The observation that the response within the reward/aversion pathways occurs with the same rapid temporal characteristics after either hand or foot stimulation supports the notion that the circuitry involved in the evaluation of aversive stimuli is rapid in onset and probably represents a major protective mechanism for survival.

INTRODUCTION

Functional magnetic resonance imaging (fMRI) has been used to map the CNS circuitry of the response to noxious stimuli and to explore the relative contributions of the “sensory” and “emotional” components of the pain experience (Price 2000). Recent work has demonstrated that the response to noxious stimuli has several components (Apkarian et al. 1999; Becerra et al. 1999, 2001; Kern et al. 1998).

After our initial report of more than one hemodynamic response to thermal pain (Becerra et al. 1999), we subsequently evaluated in another study the two main components (phases) and demonstrated a temporal segregation of responses in the CNS pathways involved in primary sensory processing (classic pain pathways) and emotional processing (reward/aversion pathways) (Becerra et al. 2001). Specifically, regions involved in emotion processing such as the sublenticular extended amygdala, the prefrontal cortex, and the ventral tegmentum, all activated during the first/early phase while regions such as the thalamus, primary sensory cortex, and insula involved in classic pain pathways were observed to activate during the second/late phase.

The present experiment was designed to further evaluate the multiphasic nature of the CNS response to noxious stimuli. For sensory/discriminative activation (classic pain pathways), represented by the late phase response, we predicted that the response should be segregated both spatially and temporally based on the location of the stimulation site (e.g., dorsum of the hand versus dorsum of the foot). Such a notion would seem obvious given the difference in distance between the two sites. Noxious heat activates C-fiber and Aδ-fiber nociceptors (Iggo and Ogawa 1971; Magee et al. 1999; Naka and Kakigi 1998; Opsommer et al. 1999; Treede 1999; Yarnitsky et al. 1992). These fibers conduct at speeds of 1–10 m/s. The relative distance between the hand and the foot may result in a relative delay of the CNS response of the foot with respect to the hand.

Reward/aversion circuitry has been reported to be activated across a number of different experimental conditions including drugs (Becerra et al. 2001), taste (Blood and Zatorre 2001; O’Doherty et al. 2002; Small et al. 2001), facial expression (Aharon et al. 2001; Elliott et al. 2000), and pain conditions including acupuncture (Hui et al. 2000) and noxious heat (Becerra et al. 2001). It has been suggested that this circuitry is important in survival because it prepares the individual for specific actions. Because there is no somatotopic information in these substrates (no spatial segregation), we wished to determine if activation in reward/aversion circuitry is site-independent. The possible mechanism for this is unclear and may be dependent on activation of separate pathways from the spinothalamic tract (conveying predominantly C and Aδ information) such as the spino-hypothalamic and -parabrachial-amygdaloid tracts (Bernard and Besson 1990; Burststein et al. 1996) or via fast feedback loops from cortical regions. No significant differences in temporal response (even within the limits of the fMRI signal) would support the notion of another process including one that emotional processing may indeed precede sensory processing as previously been proposed (see Zajonc 1980).

Here, using fMRI of the effects of a 46°C applied to the dorsum of the left hand and foot, we report on early and late phase activations observed in sensory/discriminative and motivational/affective circuitry.
METHODS

Subjects

Nine right-handed male subjects were recruited into the study [27.0 ± 3.8 (SD) yr old]. The Human Subjects Committee on experimentation approved the study, and the study conformed to the Helsinki agreement on experimentation in human volunteers. Experiments were performed at the same time of day to control for circadian variation (Strian et al. 1989). Full consent was obtained from subjects prior to the study, and subjects were remunerated for their participation.

Imaging

Scanning was performed using a 1.5 Tesla scanner (General Electric, Milwaukee, WI). A conventional three-dimensional sagittal, T1-weighted, SPOILED/GRASS gradient echo sequence was acquired (in-plane resolution: 1.2 mm, slice thickness: 2.8 mm, 60 slices) for registration to the Talairach Atlas (Talairach and Tournoux 1988). Twenty contiguous slices (7-mm thick) were prescribed perpendicular to the anterior/posterior commissure line, extending from the anterior frontal lobe to part of the cerebellum. A T1-weighted echoplanar inversion recovery sequence (TI = 1,100 ms, in-plane resolution: 1.57 mm) was acquired for high-resolution structural images to be used in preliminary statistical maps. Functional scans consisted of an asymmetric spin echo, T2*-weighted sequence (TR/TE 2,500/70 ms, flip angle: 90, in-plane resolution: 3.125 mm) performed on the same 20-slice prescription. One hundred volumes were acquired per functional scan resulting in a scan time of 4 min 10 s.

Paradigm

Two functional scans were performed on each subject. Each functional scan consisted of three thermal (46°C) stimuli for 29 s interspersed with 36 s at 35°C. The stimuli were applied to the dorsum of the left foot or the dorsum of the left hand. To avoid order effects, the stimuli were applied to the dorsum of the hand in the first scan followed by the foot, whereas the other four subjects received the stimuli to the foot first then the hand. Stimuli were produced using a Peltier thermode, 3 × 3 cm in size (Medoc, Haifa, Israel). After each scan, subjects rated their pain on a visual analogue scale (0 = no pain and 10 = max pain imaginable).

fMRI analysis

Functional data were motion corrected, globally normalized, and transformed into the Talairach space (Talairach and Tournoux 1988). Functional data were averaged across time. A 5-mm Gaussian filter was used to smooth the data and prewhitening was performed using FEAT (Image Analysis Group, FMRIB, Oxford, UK) (Woolrich 2000).

Temporal delays calculation

Several fMRI analysis tools based on a generalized linear model (GLM), such as FSL, add the first derivative of the hemodynamic response to correct for small delays of the actual brain response with respect to the model (Image Analysis Group, FMRIB, Oxford, UK). However, for longer delays, this approach fails. Fourier analysis allows the calculation of temporal delays of a function with respect to another regardless of the length of the delay. A description of this approach follows:

The definition of the Fourier transform \( F(\omega) \) of a function \( f(t) \) is

\[
F(\omega) = \int_{-\infty}^{\infty} f(t) e^{-i\omega t} dt
\]

The Fourier transform is a complex function (i.e., real and imaginary components)

\[
F(\omega) = \text{Re}(F(\omega)) + i\text{Im}(F(\omega))
\]

but also can be described in terms of a magnitude \( M(\omega) \) and a phase or angle \( A(\omega) \)

\[
F(\omega) = M(\omega)e^{iA(\omega)}
\]

where \( M(\omega) \) is a real function of positive values and \( A(\omega) \) is a function in radians (angle).

The relationship between Eqs. 2 and 3 can be seen in Fig. 1.

If a function \( f \) is delayed in time by a time \( t_0 \), then its corresponding Fourier transform \( F'(\omega) \) will be

\[
F'(\omega) = \int_{-\infty}^{\infty} f(t - t_0) e^{-i\omega t} dt
\]

Which can be rewritten as

\[
F'(\omega) = e^{-i\omega t_0} \int_{-\infty}^{\infty} f(t - t_0) e^{-i\omega t} dt = e^{-i\omega t_0} F(\omega)
\]

so

\[
M'(\omega) = M(\omega)
\]

and

\[
A'(\omega) = A(\omega) - \omega t_0
\]

Hence, the delay only affects the angle of the Fourier transform (Eq. 7), not its magnitude (Eq. 6), it imposes a linear component on it: \(-\omega t_0\).

If the hemodynamic model for the response (HR) has an angle \( H(\omega) \) and a voxel showing significant activation has an angle \( A(\omega) \), then the delay \( D_\omega \) can be estimated from

\[
D_\omega = A(\omega) - H(\omega)
\]

It is important to note that the temporal delay \( D_\omega \) is a measure of the displacement of the response in time, it does not necessarily measure

FIG. 1. Relationship among the different components of a Fourier transform: \( F \) is the Fourier transform of \( f(t) \). \( \text{Re}(F) \) and \( \text{Im}(F) \) are its real and imaginary components, respectively. Equivalently, \( A \) and \( M \) are its angle and magnitude.
delay in onset of activation or delay in peak activation. In our case, the measurement of the delay refers to the delay the HR has to experience to match the time course of a voxel. Figure 2 depicts two hemodynamic responses, one delayed with respect to the other by 10 s and their corresponding magnitude of their Fourier transforms. For these two HRs, the magnitude of the Fourier transform are identical. Figure 3 displays their angle function and the difference. The slope corresponds to the delay and comes to 10 s.

The method developed here utilizes a GLM approach, but it performs it on the magnitude components of the hemodynamic model and the data. The main advantage is that the magnitude of the brain response will not be affected by any delays as seen in Fig. 2. The corresponding statistical maps will reflect the similitude of the brain response to the hemodynamic model regardless of any possible delay. However, using GLM on Fourier transformed data might raise some issues about its validity, the Fourier transform is a linear transformation, hence GLM can be applied to the magnitude of the transformation.

If the GLM model is

$$y(t) = ax(t) + e$$

where $y(t)$ is the time course of a voxel, $x(t)$ is the HR, $a$ is a measure of the amplitude of the response, and $e$ is the error, assumed to be normally distributed. The Fourier transform of Eq. 9 is

$$Y(\omega) = aX(\omega) + \xi$$

The remaining question is if the noise characteristics are the same, FSL corrects for autocorrelation of the data assuring that the noise is normally distributed, the Fourier transform of a normal distribution is another normal distribution, therefore the noise in the Fourier transform remains normally distributed and allows for parametric statistics to be applied.

The activations maps determined from the magnitude data can in turn be used to determine delays based on areas of significant activation. Subtracting the angle function data of the foot from the hand results in a data set (the relative angle) containing information about the relative delay in brain responses. To calculate the delay, a linear fit of the relative angle data set yields a map of “slopes.” Significantly activated areas are used as a mask for the slope map to identify delays across different structures. This approach gives voxel-by-voxel delay
results. For primary somatosensory activation, however, this is not accurate because hand and foot are spatially represented at different locations; therefore to determine the delay, we need to extract the angle function corresponding to the hand and the foot from each data set to calculate the relative angle.

Functional data and the HR were Fourier transformed using Matlab (MathWorks, Natick, MA). The HR was obtained from convoluting a standard gamma function with a temporal function resembling the stimuli. To increase frequency resolution, data and HR were demeaned and zero-padded to 256 data points. Statistical analysis was carried out using FEAT, the FMRIB Easy Analysis Tool, and FILM with local autocorrelation correction (Woolrich et al. 2001). z statistic images were thresholded using clusters determined by $z > 2.3$ and a cluster significance threshold of $P = 0.05$ (Forman et al. 1995; Friston et al. 1992; Worsley et al. 1992). Figure 4 depicts the process followed in this report to obtain statistical and delay maps. Hand and foot statistical maps were compared with determine regions of interest (ROIs) of common activation. These ROIs were further used to extract the delays when comparing hand with foot.

**RESULTS**

Subjects rated their pain as $6.7 \pm 1.7$ for the hand and $6.4 \pm 2.3$ for the foot. These levels were not significantly different (Student’s $t$-test $P > 0.05$).

Table 1 summarizes activation detected in different structures after noxious thermal stimulation of the hand and the foot. Structures are arranged in Table 1 according to their function in pain processing (Iadarola et al. 1998). The table lists significance of activation ($z$ score) for each structure as well as its Talairach coordinates. Consistent with our previous study (Becerra et al. 2001), the response to the noxious thermal stimulus was biphasic for the foot as well as the hand with regions associated with emotion circuitry responding in the early phase and regions of sensory pain processing responding in the late phase. The delays quoted in Table 1 were calculated for the hand and foot using Eq. 8 as described in METHODS. For all the structures except the primary somatosensory area (S1; see METHODS for an explanation), delays were calculated from common ROIs as determined from an overlap map of hand and foot activation. For structures involved in sensory/discriminative processing of pain, an average delay of $3.6 \pm 1.3$ s was observed. This delay is significant ($P < 0.005$). For structures associated with affective/emotional processing of pain, the average delay between responses to hand versus foot stimulation was not significant ($0.6 \pm 2.1$ s; $P > 0.05$). As seen in our previous study, the only structure associated with emotional processing that did not respond in the early phase is the nucleus accumbens (NAc). The NAc had a delayed activation corresponding to the late phase; furthermore, it showed a negative signal change in response to the noxious stimulus. Neither temporal nor spatial differences between the hand and foot NAc activations were observed.

Figure 5 shows time courses of structures belonging to affective/emotional (A) and sensory/discriminative (B) circuitry. For clarity, only the response to the first stimulus is presented. Figure 5A presents activation in the inferior frontal gyrus after stimulation of the hand ($\cdot$) and the foot ($\cdot\cdot$) as well as the time evolution of the thermode temperature ($\cdot\cdot\cdot$). Both time courses respond rapidly and synchronously to the stimulus. In Fig. 5B, time courses corresponding to right insular cortex activation are displayed. Not only is there an overall

![Diagram](https://example.com/diagram.png)

**FIG. 4.** Fourier transform functional magnetic resonance imaging (fMRI) processing. After functional data has been preprocessed (see text), it was Fourier transformed (FT); the stimulus temporal variation was also Fourier transformed. Standard generalized linear model (GLM) analysis was used to determine statistical maps from magnitude data. Statistical maps in this case reflect the similarity of the response to the stimulus model regardless of any possible temporal delay. Any delay associated to the location of stimulation (e.g., hand vs. foot) does not affect the statistical significance of the activation.

### Table 1. Temporal delays in hemodynamic responses to hand and foot stimulation

<table>
<thead>
<tr>
<th>Region (BA)</th>
<th>RL</th>
<th>IS</th>
<th>AP</th>
<th>Hand (z)</th>
<th>Foot (z)</th>
<th>Delay (F–H), s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary sensory/discriminative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INS(R)**</td>
<td>31</td>
<td>0</td>
<td>15</td>
<td>7.50</td>
<td>7.40</td>
<td>2.84 ± 1.80</td>
</tr>
<tr>
<td>INS(L)</td>
<td>−34</td>
<td>−9</td>
<td>12</td>
<td>5.43</td>
<td>3.98</td>
<td>0.77 ± 4.20</td>
</tr>
<tr>
<td>Thal**</td>
<td>3</td>
<td>12</td>
<td>−21</td>
<td>3.30</td>
<td>6.63</td>
<td>4.0 ± 2.10</td>
</tr>
<tr>
<td>S1(H)</td>
<td>44</td>
<td>56</td>
<td>−30</td>
<td>6.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1(F)**</td>
<td>0</td>
<td>59</td>
<td>−51</td>
<td></td>
<td></td>
<td>5.56 ± 2.37</td>
</tr>
<tr>
<td>Affective/emotional</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOb(11)</td>
<td>−10</td>
<td>−10</td>
<td>39</td>
<td>5.50</td>
<td>3.84</td>
<td>−0.46 ± 4.50</td>
</tr>
<tr>
<td>GFi(45)</td>
<td>9</td>
<td>40</td>
<td>27</td>
<td>5.01</td>
<td>5.55</td>
<td>1.91 ± 8.42</td>
</tr>
<tr>
<td>ACC(32)</td>
<td>0</td>
<td>38</td>
<td>9</td>
<td>3.67</td>
<td>7.04</td>
<td>−0.62 ± 2.00</td>
</tr>
<tr>
<td>NAc</td>
<td>−15</td>
<td>−9</td>
<td>9</td>
<td>7.78</td>
<td>6.76</td>
<td>0.91 ± 1.71</td>
</tr>
<tr>
<td>SLEA</td>
<td>12</td>
<td>−3</td>
<td>−54</td>
<td>4.64</td>
<td>3.90</td>
<td>1.41 ± 4.46</td>
</tr>
<tr>
<td>Cer**</td>
<td>28</td>
<td>−15</td>
<td>−54</td>
<td>5.05</td>
<td>3.47</td>
<td>5.1 ± 2.70</td>
</tr>
</tbody>
</table>

Selected activated regions where RL, IS, and AP are the Talairach coordinates (mm, + for right, superior and anterior), the $z$ values for the activated regions for each experiment is listed under hand and foot. Delay (F–H) lists the mean ± SD delay (s) for each region of interest between the hemodynamic model for the response of the foot and the hand stimulation. BA is the Brodmann area. Gob, orbital gyrus; GFi, inferior frontal gyrus; GPyC, precentral gyrus; ACC, anterior cingulate cortex; INS, insula; Thal, thalamus; S1, primary somatosensory cortex; NAc, nucleus accumbens; Cer, cerebellum. **, structures with significant delay differences between hand and foot activation.
delay in the response to the stimulus (---) for both stimulus sites, but the response to stimulation of the foot (---) is delayed with respect to the response to hand stimulation (---).

Relative angle information is depicted in Fig. 6. The linear fit yields a slope that corresponds to the delay between hand and foot. For the contralateral insular activation, there’s clearly a nonzero slope whose value corresponds to the delay presented in Table 1. For the anterior cingulate gyrus, the slope is small reflecting a relatively small delay between the hand and foot activation.

Selected activation maps for structures listed in Table 1 involved in sensory/discriminative and affective/emotional circuitry appear in Fig. 7. Positive activation is depicted in red-yellow and negative in blue-green (from less significant to more significant activation, respectively).

DISCUSSION

The temporal characteristics in the two phases in the CNS response to 46°C are affected distinctly depending on the stimulation site. Structures activated in emotional circuitry (the early phase) have hemodynamic responses that occur synchronously whether stimulation is to the foot or the hand. However, for structures involved in sensory/discriminative function (responding in the late phase), activation occurs with a significantly greater delay if the stimulus is applied to the foot rather than the hand. These differences, shown in Table 1, may reflect the existence of distinct regional processing of primary sensory (discriminative) versus emotional (affective) information.

In this paper, we present an application of using a Fourier transform analysis for defining temporal delays. The advantage of this method, in contrast to other GLM methods, is that delays of any time may be accurately determined. Although the temporal resolution is set by the TR (2.5 s), it still allows proper sampling of the hemodynamic response. With the Fourier analysis described here, the determination of delays shorter than the specific TR is possible. Thus the observation of no temporal separation in the motivation/reward structures is not due to the lack of temporal resolution.

Response latency in somatosensory/discriminative regions is dependent on stimulation site

We previously reported that regions known to be involved in primary sensory or discriminative aspects of pain respond in the second phase of the biphasic CNS response to noxious heat.
The current study shows a significant difference in activation latency in all discriminative areas, including the thalamus and the primary somatosensory cortex, dependent on whether stimulation is to the left hand or left foot. Interestingly, the ipsilateral insula did not demonstrate any significant changes, whereas the contralateral insula did exhibit a latency shift. In our previous study, some regions, including the ipsilateral insula, demonstrated both early and late phase activation (Becerra et al. 2001), indicating a multifunctional response to pain which may explain the observed differences. This region has been reported to be involved both in pain (Craig et al. 2000) and other nonpain nonsensory functions (Evans et al. 2002; Feinstein et al. 2002; Winston et al. 2002).

Although an earlier fMRI study observed cortical activation after noxious heat applied to the hand and foot of normal volunteers (Berman et al. 1998), the authors did not address temporal differences. The results of this study focused on differentiating specific regional activation within the primary cortex after stimulation of the foot and hand areas. Differences in the time course of CNS activation after painful hand and foot stimulation have also been observed in vertex potentials after laser stimulation (Spiegel et al. 1996). In that study, a significant difference in electroencephalographic latency was observed dependent on whether stimulation was to the hand or the foot. The present study extends these observations and supports the notion that differences in CNS activation based on the site of stimulation can be measured using fMRI. In contrast, a magnetoencephalographic (MEG) study looking at cortical activation after laser stimulation to the hand detected early activation predominantly in S1 (Ploner et al. 2002). S2 and the anterior cingulate cortex displayed predominantly late activation. These results seem to contradict ours; however, they reported differences in brain activation that correlate with the perceptual (conscious) feeling of first and second pain after a brief (1 ms) but intense stimulation. They did not address differences in whole brain responses to prolonged pain, which may reflect complex neural pathway activations occurring early and late after the stimuli. Many of these activations are presumably subconscious. Similar MEG results were found in another study (Ninomiya et al. 2001) in which the authors found temporal segregation of activation in cortical (S1 and S2) and limbic structures (ACC). Interestingly, Maihofner et al. (2002) found insular cortex activating earlier than some cortical areas such as S2 and no activation in S1.

We provide evidence that the temporal profile of brain activation after painful sensory inputs can differentiate between stimuli applied to two regions of the body separated by ~50–70 cm. As noted in the INTRODUCTION, these differences may be explained on the basis of distance and differences in conduction velocities in pain fiber subgroups (Iggo and Ogawa 1971; Kakigi et al. 1991; LaMotte and Campbell 1978; Opsomer et al. 1999; Schmelz et al. 2000; Treede 1999; Treede et al. 1995). This may be sufficient to account for the temporal dispersion and within the temporal resolution of the fMRI signal.
Response latency in affective/emotional regions is independent of stimulation site

After noxious stimulation of the hand, activation in motivational/emotional circuitry is observed (Becerra et al. 2001). The activation pattern in this circuitry occurs rapidly prior to activation within sensory circuitry. In the present study, no significant differences in response latencies were observed when the hemodynamic responses within affective/emotional circuitry after a noxious stimulus to the hand were compared with those after the same stimulus to the foot. The reason for this is unclear, and there may be a number of proposed mechanisms.

In one formulation of the CNS response to acute pain, differences in conduction velocities and CNS response are thought to be the basis for “first” and “second” pain (Campbell and LaMotte 1983; Lewis and Pochin 1937; Price et al. 1977; Thunberg 1902). In this formulation, the faster Aβ fibers are involved in transmitting discriminative information, and the slower conducting C fibers are involved in affective aspects of pain processing. This explanation might, however, suffer from being an oversimplification of the mechanism. Both fiber types conduct “noxious sensations” that have an aversive component. It is unlikely that fiber subtype relates to specific affective and sensory activations.

Afferent pain inputs to these brain regions have been well described in animal electrophysiology and anatomical reports (Bernard and Besson 1990; Bester et al. 1997; Burstein et al. 1996; Gear et al. 1999; Schmidt et al. 2002; Shi and Davis 1999). Early activation within affective/emotional circuitry may be the result of peripheral inputs reaching motivational/affective structures from fast-conducting central fiber systems (Treede et al. 1998). Because the temporal segregation of activation observed after hand versus foot stimulation in the sensory pathway was not observed in the emotional/affective pathway, the results indicate that central processing must account for either no difference or a difference not measured by fMRI.

The activation patterns observed may represent a more complex interaction between cognitive and subconscious processing in reward/aversion and sensory/discriminative pathways. One formulation is that the delayed processing in sensory networks reflects a very fast activation pattern not measured by the fMRI signal and the delay observed relates to further cognitive CNS processing.

Another potential reason for the early activation being observed in subcortical regions includes the possibility of anticipatory behavior. A number of studies have implicated anticipation of pain in cortical regions (Ploghaus et al. 1999; Porro et al. 2002). However, none of these studies measured changes in subcortical regions such as the NAc. This also does not rule out the contribution of anxiety to the activation patterns observed (see Ploghaus et al. 2001).

It is useful to consider the widely held interpretation that the brain’s response to threat, including pain, is anticipatory and evaluative (Melzack and Casey 1967). Patrick Wall and Ronald Melzack first noted this possibility in their classic paper on the gate theory of pain (Melzack and Wall 1965). An organism’s survival is dependent on determining the salience of the threat or reward associated with a given stimulus. Activation in emotional circuitry may reflect this type of evaluation [i.e., feeling before knowing (Zajonc 1980)]. The same regions that have been consistently implicated in the organization of motivational responses to rewarding stimuli (Bozarth and Wise 1986; LeDoux 1998; Robbins and Everitt 1996; Schultz et al. 1997; Wise 1998) are implicated in the motivational responses to aversive stimuli (Fenu et al. 2001; Gallagher et al. 1988) including painful stimuli (Becerra et al. 2001). Such responses probably serve to increase the animal’s level of arousal in anticipation of the perceived threat and are protective. Indeed, in support of this, none of these same regions are activated by a nonnoxious thermal stimulus (Becerra et al. 2001). Furthermore, one of the regions activated in both early and late phases of our previous study, the periaqueductal gray, is known to be important in endogenous modulation including inhibition of afferent pain signals (Heinricher et al. 1987). This is an example of an apparent protective mechanism possibly tied into a circuit that is permissive to allow action/escape response rather than simply pain control.

Conclusions

The data presented suggest that differences in stimulus location do not affect the latency of activation within motivational circuitry, whereas the latency of the sensory/discriminative response to acute pain is stimulus site-dependent. An understanding of the emotional/motivational response to pain has important consequences and seems independent of conscious awareness (for a review, see Becerra et al. 2001). Such differences may have implications for future pain experiences that may produce significant behavioral manifestations [e.g., pain associated with torture (Thomsen et al. 2000) or pain inflicted on the newborn (Ruda et al. 2000) or after child abuse (Goldberg et al. 1999) or physical and sexual abuse in adults (Green et al. 1999)]. Such experiences may not only contribute to increased pain levels but also to functional illnesses associated with pain such as depression (Wilson et al. 2001).

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References


