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On the interpretation of temporal differences of BOLD fMRI responses to nociceptive stimulation

To the Editor: We have read with interest the paper by Becerra and colleagues in the January 2004 issue of the *Journal of Neurophysiology* (Becerra et al. 2004). In this article the authors use functional magnetic resonance imaging (fMRI) to investigate the temporal aspects of peripheral and CNS processing of nociceptive inputs. By applying noxious thermal stimuli to the dorsum of the hand and foot, they present two main findings. First, the hemodynamic response evoked in "primary sensory regions" by foot stimulation occurs with an average delay of 3.6 s compared with the response evoked when a matched stimulus is delivered to the hand of the same subject. Second, the response in "regions involved in emotions" does not show any temporal delay between hand and foot stimulation and precedes the response in somatosensory regions.

We would like to comment briefly regarding these findings and their possible interpretation.

Concerning the response observed in sensory regions, the authors affirm that a temporal delay of 3.6 s is consistent with the greater peripheral conduction distance after foot stimulation. Although one would expect to observe differences in the transit times for nociceptive information to reach the brain after hand and foot stimulation, the delay should be of the order of hundreds of milliseconds. This is based on the following considerations. The temperature of stimulation used by Becerra and colleagues (46°C applied to the skin for 29 s using a contact thermode) corresponds to the median thermal threshold of type II Aδ mechano-heat nociceptors (AMH-II units, thermal threshold 46–47°C, conduction velocity about 15 m/s), and is well above the median thermal threshold of C mechano-heat nociceptors (CMH units, thermal threshold of about 42°C, conduction velocity about 1 m/s) (Treede et al. 1995, 1998).

Even if we assume that the somatosensory input provided by their stimulus was exclusively mediated by CMH nociceptors and corresponding unmyelinated primary sensory fibers, this would still not explain the large delay reported. In fact, considering a 30-cm difference in peripheral nerve conduction distance between arm and leg, a CMH-mediated somatosensory input delivered to the foot would arrive at the spinal cord about 300 ms after a similar hand input—and temporal delays in this range have been reproduced in several experiments (e.g., Opsommer et al. 1999; Towell et al. 1996; Tran et al. 2002). One might also consider whether the extra time required to conduct the afferent volley along the spinal cord following stimulation of the foot might account for the reported temporal delay. However, we and others have demonstrated that selective C-fiber somatosensory input is transmitted between T12 and C5 spinal levels within 113–122 ms (Iannetti et al. 2003; Tran et al. 2002), obviating this as a possible explanation for their findings. In fact, the stimulus used is likely to have activated AMH-II nociceptors, which would further reduce conduction differences (Cruccu et al. 2000; Iannetti et al. 2001; Kakigi and Shibasaki 1991; Rossi et al. 2000).

For these reasons the time delay (of the order of seconds) observed by Becerra and colleagues simply cannot be ascribed to the different conduction distance after foot stimulation, which could account for a temporal difference of 500 ms at most. Possible explanations for the obtained results include the following. In normal subjects A-delta thresholds are higher in the foot dorsum than those in the hand (Agostino et al. 2000). The consequent delay at receptor level can be important, depending on the temperature rise time produced by the stimulator device used, and will contribute to the observed delay. Moreover, the blood oxygenation level–dependent (BOLD) response is linearly dependent on the magnitude of the incoming afferent volley (Arthurs et al. 2000), which is smaller after nociceptive stimulation of the foot than of the hand, as indicated by the lower amplitude of laser-evoked EEG responses, even if the perception is matched (Truini et al. 2005); this effect is expected to be enhanced when using slow rise time stimulators (Iannetti et al. 2004). The regional differences in physiological properties of peripheral nociceptors, and the intrinsic sluggishness and variance of BOLD signal and its underlying physiological mechanisms, imply that BOLD fMRI with relatively slow rise-time thermal stimulators is not the optimal experimental setting for exploring small time differences in neuronal responses.

Concerning the observation that "regions involved in emotions" are activated earlier than the "primary sensory" brain areas (e.g., see Fig. 5 in Becerra et al. 2004), this finding is based on the assumption that the BOLD response is similar throughout the brain. However, the BOLD response has been shown to vary across different brain regions (e.g., Lee et al. 1995; Robson et al. 1998); this variance, probably caused by underlying differences in vasculature, presents a formidable challenge to interpretation of absolute timing parameters (Miezin et al. 2000). In addition, the temporal difference between acquisition of different brain slices also introduces a possible confounding factor, and slice-timing correction is recommended when searching for small timing differences in explanatory variables (Smith 2001). Last, regarding the choice of brain regions for comparison to areas involved with processing the emotional aspect of pain, the inclusion of anterior insula as a "primary sensory/discriminative" region (see Table 1 and Figs. 5 and 6) is misleading. In man, this brain region has not been shown to receive direct connections from either VMpo or VPL (Blomqvist et al. 2000; Craig 2003; Kenshalo et al. 1988), the "classic" sensory pain pathway, and is in fact subject to substantial influences from anticipation (Ploghaus et al. 1999; Porro et al. 2002) and attention (Brooks et al. 2002). In experiments with a fixed interstimulus interval, anticipatory effects are significant, and unless explicitly modeled for may lead to erroneous findings.

In conclusion, considering the issues raised here, we believe that additional experiments are required to draw firm conclusions about the exact nature of the two main effects reported in this paper.

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