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Research report

Transcranial magnetic stimulation over human secondary somatosensory cortex disrupts perception of pain intensity

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ABSTRACT

Pain is a complex sensory experience resulting from the activity of a network of brain regions. However, the functional contribution of individual regions in this network remains poorly understood. We delivered single-pulse transcranial magnetic stimulation (TMS) to the contralateral primary somatosensory cortex (S1), secondary somatosensory cortex (S2) and vertex (control site) 120 msec after selective stimulation of nociceptive afferents using neodymium:yttrium–aluminium–perovskite (Nd:YAP) laser pulses causing painful sensations. Participants were required to judge either the intensity (medium/high) or the spatial location (proximal/distal) of the stimulus in a two-alternative forced choice paradigm. When TMS pulses were delivered over S2, participants' ability to judge pain intensity was disrupted, as compared to S1 and vertex (control) stimulation. Signal-detection analysis demonstrated a loss of sensitivity to stimulation intensity, rather than a shift in perceived pain level or response bias. We did not find any effect of TMS on the ability to localise nociceptive stimuli on the skin. The novel finding that TMS over S2 can disrupt perception of pain intensity suggests a causal role for S2 in encoding of pain intensity.

1. Introduction

The ability to quickly and accurately discriminate the intensity and location of a noxious stimulus on the body is essential for survival. Non-invasive functional neuroimaging techniques have shown that noxious stimuli elicit responses in a number of brain structures including primary (S1) and secondary (S2) somatosensory cortices, anterior cingulate cortex (ACC) insular and prefrontal areas (Apkarian et al., 2005). Although some authors consider these regions to be specifically involved in generating painful percepts (e.g., Ploghaus et al., 1999), their functional significance is debated (Mouraux et al., 2011). Although responses in S1 and S2 are thought to subserve the discriminative components of pain sensation (e.g., location and intensity), their functional roles remain largely undefined.

Experimental studies investigating the neural mechanisms of pain intensity discrimination have found evidence for the

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involvement of both S1 and S2 (Bornhövd et al., 2002; Coghill et al., 1999; Frot et al., 2007; Grundmann et al., 2011; Iannetti et al., 2005; Kanda et al., 2003; Porro et al., 2007; Timmermann et al., 2001; Valmunen et al., 2009). For example, Frot et al. (2007) recorded evoked potentials from intracranial implanted electrodes in S2, and found that S2 responses correlated with perceived pain intensity. Similarly, Bornhövd et al. (2002) reported that BOLD responses in S2 distinguished between different intensities of noxious stimulation. Nevertheless, the role of S2 in pain intensity coding remains controversial. If an area displays a response graded with the stimulus intensity, this does not necessarily imply that the area is important for intensity encoding. The relation could reflect a dimension correlated with perceptual intensity, such as salience or arousal, rather than perceptual intensity itself (e.g., Carmon et al., 1976). For example, almost all the correlations between intensity of pain perception and nociceptive evoked electroencephalography (EEG) responses can be explained as well by accounts based on stimulus salience as by accounts based on pain intensity (Iannetti and Mouraux, 2010). Other studies have also found evidence for S1 involvement in pain intensity encoding (Coghill et al., 1999; Timmermann et al., 2001), but these studies again provide correlational, rather than causal evidence.

More generally, correlations between neural activity and perceptual intensity cannot show that an area or process plays a causal role in intensity encoding. Because transcranial magnetic stimulation (TMS) directly interferes with neural activity in the stimulated area, TMS studies are often thought to offer stronger causal evidence than correlations observed in neuroimaging studies. Table 1 summarises the results of recent relevant studies which stimulated S1 or S2, and assessed effects on judgements of location or intensity of experimental pain. Kanda et al. (2003) reported that TMS over S2 did not affect pain ratings, while TMS over S1 boosted pain ratings. Grundmann et al. (2011) reported that cathodal tDCS delivered to S1 altered sensitivity to cold sensations thought to be mediated by A-delta fibres (Grundmann et al., 2011), but their stimuli were not within the painful range.

To our knowledge, only one previous study has found a significant effect of TMS over S2 on pain intensity. Valmunen et al. (2009) delivered rTMS over a range of cortical sites including S1 and S2. They found that rTMS over S2 but not S1 increased heat pain thresholds on the face. However, Valmunen et al. used thermal contact-heat stimulation, which inevitably involves a combination of both nociceptive and tactile afferent input. Moreover, tactile and nociceptive systems interact strongly at several levels in the CNS. Thus, their findings cannot conclusively demonstrate a selective effect of S2 stimulation on *nociceptive* processing.

Previous research using TMS to investigate the role of S1 and S2 in the perceived location of pain has also yielded mixed findings. Porro et al. stimulated at one of four locations on the hand dorsum, and asked participants to name the stimulated spot (A, B, C or D) on each trial. They found that TMS over S1 significantly impaired participants' ability to localise painful stimuli (Porro et al., 2007). Kanda et al. (2003) used a pointing task in which participants were required to point to the stimulated site on their hand dorsum on an image of their hand. They found no effect of TMS over S1 or S2 on pain localisation judgements (Kanda et al., 2003).

Overall, the existing literature investigating the contributions of S1 and S2 to pain perception is fragmented. To our knowledge no studies have directly compared multiple intervention sites and multiple dimensions of pain perception using an appropriate and fair method that is sensitive to intensity and location encoding. To resolve these ambiguities, we developed an experimental design to systematically investigate the neural basis of sensory pain in the cerebral cortex. Specifically, we sought a design (1) that was causal rather than correlational, (2) that used comparable tasks and psychometric judgements to test two-alternative forced choice judgements of pain intensity and location (3) that would be equally sensitive to contributions of multiple cortical areas and (4) that used nociceptive laser stimulation to specifically activate A-delta fibres without a tactile component. We therefore used single-pulse TMS over S1, over S2, or in a vertex (sham) condition, to disrupt neural processing of pain sensations. Participants judged either the location or the intensity of each stimulus.

2. Materials and methods

2.1. Participants

Nineteen healthy volunteers (17 right handed, two left handed, 10 females; aged 20–32 years) participated for payment. All participants gave written informed consent, and the local ethics committee approved the experimental procedures.

2.2. Stimuli

2.2.1. Thermal stimulation

Painful stimuli were delivered by an infrared neodymium:yttrium–aluminium–perovskite (Nd:YAP) laser with a wavelength of 1.34 m (ElEn, Florence, Italy). This method was used in order to selectively activate A-delta and C nociceptive terminals located in the hairy skin. We used a spot size of 7 mm, a pulse length of 4 msec and two energies (2.75 J and 3.25 J), designed to elicit clear painful pinprick sensations, related to the selective activation of A-delta nociceptors. Previous studies, and a pilot in eight participants, confirmed that this combination of stimulus energy and spot size reliably elicit pinprick sensations. Before the experimental session began, participants reported the intensity of the two stimuli on a numerical scale ranging from 1 to 10, with 1 defined as "no pricking sensation" and 10 as "the most intense pricking sensation imaginable". The 2.75 J stimulus elicited a mean rating of 3.5 ± 1.0 J, and the 3.25 J stimulus a mean rating of 5.7 ± 1.2 J.

Stimuli were delivered to the left hand dorsum, at either a proximal or a distal locus. The proximal and distal loci were separated by 15 mm with approximately 8 mm between the centres of each site on the proximal or distal line (see Fig. 1). This distance was selected both on the basis of previous studies (Porro et al., 2007; Schlereth et al., 2001) and our pilot study, to elicit an intermediate level of accuracy, avoiding

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