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INTER-INDIVIDUAL DIFFERENCES IN PAIN PROCESSING INVESTIGATED BY FUNCTIONAL MAGNETIC RESONANCE IMAGING OF THE BRAINSTEM AND SPINAL CORD

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Abstract—The experience of pain is a highly complex and personal experience, characterized by tremendous inter-individual variability. The purpose of this study was to use functional magnetic resonance imaging (fMRI) to characterize responses in the brainstem and spinal cord to the same heat stimulus in healthy participants, to further our understanding of individual differences in pain perception. Responses to noxious heat stimuli at 49 °C were investigated in 20 healthy individuals by means of fMRI of the brainstem and spinal cord, at 3 Tesla, and were compared with brain fMRI and quantitative sensory testing. Blood oxygenation-level dependent (BOLD) responses were detected with a general linear model (GLM) and effective connectivity was examined with structural equation modeling (SEM). Reported pain ratings ranged from 18 to 84/100 across the participants. Consistent with previous research, brain fMRI results show that BOLD responses in a number of cortical regions are correlated with individual pain ratings. Correlations between pain scores and BOLD responses are also demonstrated in the spinal cord dorsal horn, locus coeruleus, and thalamus. SEM results demonstrate the network of brainstem and spinal cord regions that contribute to the pain response, and reveal differences related to individual pain sensitivity. The results of this study are consistent with the conclusion that individual differences in pain perception in healthy participants are a consequence of differences in descending modulation of spinal nociceptive processes from brainstem regions.

Key words: fMRI, pain, healthy, brain, brainstem, spinal cord.

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Abbreviations: ACC, anterior cingulate cortex; BOLD, blood oxygenation-level dependent; BPN, basilar pontine nuclei; C8, 8th cervical; fMRI, functional magnetic resonance imaging; FWE, family-wise error; GLM, general linear model; INS, insular cortex; LC, locus coeruleus; MIRT, Medical Image Registration Toolbox; mPFC, medial prefrontal cortex; NGc, nucleus gigantocellularis; NRM, nucleus raphe magnus; NTS, nucleus tractus solitarius; PAG, periaqueductal gray matter; PBN, parabrachial nucleus; PCC, posterior cingulate cortex; PFC, prefrontal cortex; RVM, rostral ventromedial medulla; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; SEM, structural equation modeling; TE, echo time; TR, repetition time.

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INTRODUCTION

Pain is a highly subjective experience consisting of sensory-discriminative and cognitive-emotional components, which can vary with a multitude of genetic and psychosocial factors even within healthy individuals (Fillingim, 2000; Price, 2000; Pincus and Morley, 2001; Greenspan et al., 2007; Fillingim et al., 2009; Coghill, 2010; Riley et al., 2014). Given this variability in pain perception, assessing an individual's pain in a clinical setting or for research to determine the effects of injury or disease presents a considerable challenge (Nielsen et al., 2009). The underlying factors are expected to include differences in emotional responses and how pain is evaluated, and influences on descending modulation of spinal nociceptive responses and receptive fields of neurons (Hayes et al., 1981; Coghill, 2010). As a result, the evidence to date consistently points toward the spinal cord and brainstem as playing pivotal roles in individual differences in pain perception. The purpose of this study was to characterize the blood oxygenation-level dependent (BOLD) functional MRI (fMRI) responses in the brainstem and spinal cord to the same heat stimulus in a group of healthy participants, in order to further our understanding of individual differences in pain processing.

A number of previous studies have investigated individual differences in human pain perception by using non-invasive functional neuroimaging methods or electrophysiology in combination with psychophysical testing (Porro et al., 1998; Tracey et al., 2002; Coghill et al., 2003; Seminowicz and Davis, 2006; Schulz et al., 2012; La Cesa et al., 2014). These studies have shown that subjective reports of pain intensity are closely related to the degree of neuronal activity in several brain regions important in the processing of pain. Coghill et al. (2003) observed that healthy participants subjected to a 49 °C thermal stimulus reported a large range of pain intensities (range 1.1–8.9 out of 10), as in previous studies (Nielsen et al., 2009; Coghill, 2010; Schulz et al., 2012). Brain functional MRI results revealed significantly larger BOLD responses in participants reporting higher pain intensities compared to those reporting lower pain, in the anterior cingulate cortex (ACC), primary somatosensory cortex (S1), and prefrontal cortex (PFC). Time-course profiles of pain intensities have also been observed to be positively or negatively correlated with BOLD response profiles in areas such as the ACC, S1, supplementary motor area (SMA) and medial prefrontal cortex (mPFC)

(Porro et al., 1998; Kucyi et al., 2014). Regions of the default mode network (DMN), particularly the mPFC, are structurally and functionally connected to the periaqueductal gray matter (PAG), an area known to play a role in the descending modulation of pain. The connectivity strength between these two regions has been shown to be negatively correlated with an individual's sensitivity to pain (Kucyi et al., 2013). A recent combined brain and spinal cord fMRI study with 46 and 47 °C stimuli applied to the forearm demonstrated a positive correlation between PAG-spinal cord connectivity strengths and individual pain ratings (Sprenger et al., 2015). Moreover, an important link has been demonstrated between the rACC and descending modulation of pain, via the PAG and the rostral ventromedial medulla (RVM), in relation to placebo analgesia (Bingel et al., 2006; Eippert et al., 2009). The PAG provides input to the RVM and the locus coeruleus (LC), both of which project to the spinal cord dorsal horn. We therefore anticipate that the regions of the spinal cord and brainstem that engage in the descending modulation of spinal nociception are also involved with individual differences in pain perception (Tracey and Mantyh, 2007; Wager et al., 2011; Lapate et al., 2012; Sevel et al., 2015).

Behavioral pain responses are therefore known to vary across participants, but the underlying neuronal processes are not completely understood. It is expected that individual differences in pain responses should be reflected in fMRI results in the spinal cord and brainstem, as observed in the brain, and may be used to provide important information about each individual (Wager et al., 2013; Atlas et al., 2014). For the present study we apply the same noxious heat stimulus (49 °C) during every fMRI acquisition, and use the participants' reported pain ratings to identify the component of variability in BOLD responses that can be attributed to differences in pain perception. We also use the variation in BOLD responses across repeated acquisitions and across participants to identify coordination between anatomical regions, thereby reflecting effective connectivity, with structural equation modeling (SEM). The results show that measured BOLD responses in the brainstem and spinal cord vary across participants in a predictable manner in relation to the perceived pain. The variability cannot be attributed to measurement error, but rather demonstrates the neural correlates of individual differences in pain perception in the spinal cord and brainstem.

EXPERIMENTAL PROCEDURES

Participants

Twenty healthy volunteers, aged 18–45 years (median 21 years), were recruited from the local community. Complete data sets were not obtained in two of the participants, and behavioral and brain fMRI results are shown for 20 participants (11 female, nine male), whereas spinal cord and brainstem fMRI results are shown for 18 participants (10 female, eight male). Participants were screened to exclude anyone with existing pain conditions, taking prescription medication for pain relief, a prior injury to the brain, spinal cord, or peripheral nerves, or a history of claustrophobia or anxiety, or having any MRI safety risks (e.g., pacemaker, implanted metallic devices etc.). All research procedures were reviewed and approved by the institutional Human Research Ethics Board.

Experimental design

The primary purpose of this study was to investigate the neuronal responses in the brainstem and spinal cord to the same heat stimulus in a group of healthy participants, by means of fMRI. We also acquired fMRI data from the brain, and behavioral measures of pain responses, to confirm that the results are comparable with previous studies, and to compare fMRI results with behavior. In order to identify neural correlates of individual differences in pain perception, we applied thermal stimulation (49 °C) to the right hand, on the little finger side of the palm corresponding to the 8th cervical dermatome (C8). The thermal stimulus was produced with a Medoc TSA-II thermal sensory analyzer (Medoc Ltd, Ramat Yishai, Israel). Participants underwent an initial training session, immediately prior to the MR imaging session. While seated comfortably, each participant held the heated thermode and applied it to their right hand, to become familiar with the sensation. They then experienced the heat at several different temperatures (which were not disclosed to the participants), and were trained to use the 100-point pain rating scale, with verbal descriptors at intervals of 10:10, warm; 20, a barely painful sensation; 30, very weak pain; 40, weak pain; 50, moderate pain; 60, slightly strong pain; 70, strong pain; 80, very strong pain; 90, nearly intolerable pain; and 100, intolerable pain. A test run was also carried out after each participant was positioned comfortably within the MRI system, prior to imaging. This familiarization period was intended to yield reliable pain ratings, and to reduce variations that may be caused by anxiety across the repeated fMRI acquisitions.

fMRI

fMRI studies were carried out in a 3 Tesla Siemens Magnetom Trio MRI system, using a spine-array coil, 6-channel neck coil, and 12-channel head coil, for detection of the MR signal. Receiver coil elements were selected as appropriate for spinal cord/brainstem imaging, and brain imaging, as detailed below. Participants were positioned comfortably on the MRI bed, and were encouraged to remain relaxed and as still as possible throughout the studies. Participants viewed the pain rating scale projected onto a rear-projection screen, via a mirror attached to the head coil.

Stimulation paradigm. For each fMRI acquisition, participants experienced thermal stimulation consisting of 10 brief heat pulses, preceded and followed by "baseline" periods, as shown in Fig. 1. The thermode was initially held at a warm adaptation temperature of 41 °C for 50 s ("baseline" period). A series of brief heat