PAIN® xxx (2014) xxx–xxx

www.elsevier.com/locate/pain

Brain mediators of the effects of noxious heat on pain

Lauren Y. Atlas [a,*], Martin A. Lindquist [b], Niall Bolger [c], Tor D. Wager [d]

[a] Department of Psychology, New York University, New York, NY, USA
[b] Department of Biostatistics, Johns Hopkins University, New York, NY, USA
[c] Department of Psychology, Columbia University, New York, NY, USA
[d] Department of Psychology and Neuroscience, University of Colorado–Boulder, Boulder, CO, USA

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

ARTICLE INFO

Article history:
Received 1 October 2013
Received in revised form 1 May 2014
Accepted 14 May 2014
Available online xxxx

Keywords:
fMRI
Mediation
Neuroimaging
Nociception
Pain
Connectivity
Human

ABSTRACT

Recent human neuroimaging studies have investigated the neural correlates of either noxious stimulus intensity or reported pain. Although useful, analyzing brain relationships with stimulus intensity and behavior separately does not address how sensation and pain are linked in the central nervous system. In this study, we used multi-level mediation analysis to identify brain mediators of pain—regions for which trial-by-trial responses to heat explained variability in the relationship between noxious stimulus intensity (across 4 levels) and pain. This approach has the potential to identify multiple circuits with complementary roles in pain genesis. Brain mediators of noxious heat effects on pain included targets of ascending nociceptive pathways (anterior cingulate, insula, SII, and medial thalamus) and also prefrontal and subcortical regions not associated with nociceptive pathways per se. Cluster analysis revealed that mediators were grouped into several distinct functional networks, including the following: somatosensory, paralimbic, and striatal-cerebellar networks that increased with stimulus intensity; and 2 networks co-localized with "default mode" regions in which stimulus intensity-related decreases mediated increased pain. We also identified "thermosensory" regions that responded to increasing noxious heat but did not predict pain reports. Finally, several regions did not respond to noxious input, but their activity predicted pain; these included ventromedial prefrontal cortex, dorsolateral prefrontal cortex, cerebellar regions, and supplementary motor cortices. These regions likely underlie both nociceptive and non-nociceptive processes that contribute to pain, such as attention and decision-making processes. Overall, these results elucidate how multiple distinct brain systems jointly contribute to the central generation of pain.

1. Introduction

The relationship between stimulus intensity and perception is lawful and robust in all perceptual domains, including pain [2,72]. However, although higher stimulus intensities usually lead to greater pain, there is nearly always variability in the stimulus–response relationship. Pain perception is strongly influenced by spontaneous fluctuations in arousal and attention [14,46,62], stimulus history [12,37,64], and other factors. Thus, a given stimulus intensity can be perceived or reported as painful or nonpainful depending on brain activity before [14,62], during [63], or after noxious stimulation [9,44]. The purpose of the present study was to examine how variations in noxious stimulus intensity are transformed into variations in pain, focusing specifically on responses during noxious stimulation itself. In particular, we sought to identify regions that mediate stimulus effects on pain and those that do not respond strongly to noxious stimuli but nonetheless play supporting roles in pain genesis.

Targets of spino-thalamo-cortical nociceptive pathways [32] and other nociceptive pathways (eg, spino-parabrachial and spino-reticular [83]) reliably track the stimulus intensity of painful events in human neuroimaging studies, including somatosensory (SI/SII), dorsal posterior [dpINS], anterior insular [aIns], and anterior cingulate [aCC] cortices and thalamus [5,35,60]. There is broad consensus that these "intensity coding" regions also generally correlate with pain [25,76], although the stimulus–response function between brain response and pain report may differ depending on the region [15,20,38,48,63].

* Corresponding author. Address: New York University, Meyer Hall, 6 Washington Place, Room 877, New York, NY 10003. Tel.: +1 (212) 998 3720.
E-mail address: laurenatlas@nyu.edu (L.Y. Atlas).

http://dx.doi.org/10.1016/j.pain.2014.05.015
0304-3959/

However, only a few studies have directly compared brain activity related to stimulus processing with activity related to pain, and findings are mixed on which areas are most strongly associated with each. One seminal study found that dpINS correlated preferentially with stimulus intensity and that aIns correlated preferentially with perceived pain [29], whereas another study found the opposite [6]. In addition, these previous studies do not provide models of how stimulus-related brain activity and pain-related brain activity are linked. Although these studies identify correlates of either noxious stimulus intensity or pain perception, we know little about the brain processes that transform stimulus processing into pain, and which processes might contribute to pain independent of stimulus processing.

We used whole-brain multi-level mediation analysis [7,80,81], a linear multivariate approach that relates stimuli, brain responses, and behavior in a single model, to understand the pathways that mediate the effects of noxious input on pain perception. We identified 3 classes of relevant brain processes: (1) mediator regions that link stimulus intensity with pain; (2) thermosensory regions that respond specifically to noxious input; and (3) pain-related regions that contribute to decisions about pain above and beyond the linear and nonlinear effects of noxious stimulus intensity and thus may reflect endogenous decision-making processes that contribute to variations in pain, such as arousal, attention, and magnitude estimation. We identify networks with distinct functional properties related to pain genesis, which could help create a clearer picture of the multiple systems involved in creating pain. This approach could also serve as a model for understanding sensory decision making in other perceptual modalities.

2. Methods

2.1. Participants and procedure

2.1.1. Participants

Thirty healthy, right-handed participants were enrolled in the study. Participants were recruited from the New York metropolitan area through posted flyers, advertisements on Craigslist, and if they had previously participated in studies in our laboratory and volunteered to be contacted for future research. All participants provided informed consent in accordance with the Declaration of Helsinki, as approved by the Columbia University Institutional Review Board. Preliminary eligibility was assessed with a general health questionnaire, a pain safety screening form, and an functional magnetic resonance imaging (fMRI) safety screening form. Participants reported no history of psychiatric, neurological, or pain disorders. Three participants completed calibration but did not undergo scanning because of technical problems with the heat equipment (2 participants) or discomfort with the MR environment (1 participant). The fMRI imaging sequence was incorrect for 1 additional participant, leaving a final sample of 26 participants (9 female and 17 male, mean age = 27.8 years, range: 20–50 years).

2.1.2. Thermal stimulation and pain ratings

Thermal stimulation was delivered to the volar surface of the left (nondominant) inner forearm using a 16 × 16-mm Peltier thermode (Medoc, Inc.). Each stimulus lasted 10 seconds, with 1.5-second ramp-up and ramp-down periods and 7 seconds at target temperature. Temperatures were individually calibrated for each participant using an adaptive staircase procedure. During calibration and during the fMRI portion of the experiment, participants rated stimulation on a continuous scale from 0 to 8 (0 = no sensation; 1 = nonpainful warmth; 2 = low pain; 5 = moderate pain; 8 = maximum tolerable pain). This scale has been used in previous studies in our laboratory [7,8] and provides measures of pain threshold and tolerance. It is similar to the 0 to 5 scale used by Bornhovd et al. [15] and Buchel et al. [20] but provides a broader range to increase sensitivities to subtle variations in perception. We used a continuous visual analogue scale (VAS) during fMRI scanning, which provided further sensitivity to small fluctuations in pain.

The calibration procedure allowed us to derive each participant's stimulus–response curve for the relationship between applied thermal stimulation and reported pain, and to identify sites on the forearm with similar nociceptive profiles (ie, the 3 with the lowest average residuals based on the predicted stimulus–response function). During the fMRI experiment, heat was applied to the 3 sites that responded most similarly to changes in temperature, and temperatures were selected for each individual based his or her dose–response curve. Institutional review board restrictions precluded us from applying temperatures higher than 48°C, so all participants were required to have maximum tolerable pain levels fall within the range of 42°C to 48°C. One participant exceeded this range (maximum predicted temperature based on calibration, 50°C) but was included in the experiment and received a maximum stimulus of 48°C. No participants reported maximum tolerable pain that fell below 42°C.

2.1.3. fMRI task design

fMRI images were acquired during 6 functional runs (8 trials per run, 48 trials). The thermode was placed on a different skin site for each run, with 2 total runs per skin site. The task design is shown in Fig. 1. At the start of each trial, a square appeared in the center of the screen for 50 milliseconds, followed by a pair of faces from the Ekman set [34]. An emotional expression (Happy or Fearful) was Q4 presented for 33 milliseconds, masked by a neutral face presented for 1467 milliseconds. Face cues were evenly crossed with temperature.

As the conceptual focus of the present article concerns the mechanisms that link changes in temperature with changes in pain, our mediation analyses collapse across the face cues to examine pain-evoked responses during noxious stimulation period as a function of temperature. To test whether face primes were ignorable here, we controlled for the effects of face cues (main effects and interactions with temperature) on regions identified in our mediation analysis. This assessed the possibility that masked emotional faces induced variability in the temperature–pain relationship. No main effects of face primes were found on the regions that we report here, and all results reported were significant after controlling for face prime identity; thus, we do not report priming effects in detail. A full analysis of the face primes is awaiting replication and extension in future experiments, and is not the main focus of this article.

Cue presentation was followed by a 6-second anticipatory interval during which a fixation cross was presented on the screen. Thermal stimulation was then delivered via the thermode for 10 seconds (1.5-second ramp up from baseline [32°C], 7 seconds at peak destination temperature, 1.5-second return to baseline) at levels calibrated to elicit ratings of nonpainful warmth (VAS rating = 1; mean = 40.8°C, standard deviation [SD] = 2.03), low pain (VAS rating = 3; mean = 43.1°C, SD = 2.10), medium pain (VAS rating = 5; mean = 45.1°C, SD = 1.79), or high pain (VAS rating = 7; mean = 47.0°C, SD = 1.14). After thermal stimulation, a fixation cross was presented for a 14-second fixed interstimulus interval (ISI). The words "How painful?" then appeared on the screen for 4 seconds above an 8-point VAS. Participants rated the pain evoked by the preceding stimulus using an fMRI-compatible track-ball (Resonance Technologies, Inc.) with resolution equivalent to the screen resolution (ie, approximately 600 discrete values between

Please cite this article in press as: Atlas LY et al. Brain mediators of the effects of noxious heat on pain. PAIN® (2014), http://dx.doi.org/10.1016/j.pain.2014.05.015