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Discrepancy between perceived pain and cortical processing: A voxel-based morphometry and contact heat evoked potential study

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HIGHLIGHTS

- A poor inter-individual relationship of contact heat evoked potentials (CHEPs) with rating of perceived intensity limits their applicability as objective measures of nociception.
- Accounting for gray matter volume between subjects in the insular cortex improved the relationship between CHEPs and rating.
- Differences in brain structure may underlie why some individuals demonstrate large amplitude cortical responses to noxious heat stimulation coupled with low pain ratings, and vice versa.

ABSTRACT

Objectives: The purpose of this study was to determine if local gray and white matter volume variations between subjects could account for variability in responses to CHEP stimulation.
Methods: Structural magnetic resonance imaging was used to perform voxel-based morphometry (VBM) of gray and white matter in 30 neurologically healthy subjects. Contact heat stimulation was performed on the dorsum of the right hand at the base of the thumb. Evoked potentials were acquired from a vertex-recording electrode referenced to linked ears.
Results: Controlling for age, total intracranial volume, and skull/scalp thickness, CHEP amplitude and pain rating were not significantly correlated between subjects. A VBM region of interest approach demonstrated a significant interaction between pain rating and N2 amplitude in the right insular cortex ($p < 0.05$, family-wise error corrected, FWE). In white matter, a significant interaction was localized in the right inferior frontal occipital fasciculus (IFOF, $p < 0.05$ FWE).
Conclusions: Accounting for gray matter volume in the right insular cortex, resulted in a significant relationship between CHEP amplitude and pain rating.
Significance: This finding suggests that the discrepancy between pain ratings and the amplitude of evoked potentials is not solely related to measurement artifact, but rather attributable, in part, to anatomical differences between subjects.

1. Introduction

At present, self-report (i.e., description and intensity) represents a clinical standard for the evaluation of pain. To detect subtle changes in somatosensory function, an objective assessment of pain is desirable. Electrophysiological analogues of conventional somatosensory evoked potentials acquired in response to electrical stimulation and central conduction in the dorsal columns, laser and contact heat evoked potentials (LEPs and CHEPs) represent objective methods to assess the integrity of small diameter afferents conveying temperature and pain sensation to the brain in the spinothalamic tract (Baumgartner et al., 2012). However,

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ratings as well as the amplitude of prominent cortical waveforms (e.g., N2P2) typically demonstrate high between-subject variability (Chen et al., 2006; Cruccu et al., 2008). Furthermore, while significant positive relationships between amplitude of evoked potentials and pain ratings have been reported (Beydoun et al., 1993; Chen et al., 2006; Garcia-Larrea et al., 1997; Iannetti et al., 2005), this too is highly variable – some individuals rating low intensity to stimulation but demonstrating large amplitude cortical potentials, and vice versa. The dissociation between pain rating and amplitude of prominent cortical potentials is also evident within an individual, shown in response to repeated and predictable stimulation (Iannetti et al., 2008). On one hand, these observations may be related, in part, to inherent difficulties rating noxious stimuli. For example, two individuals subjected to the same stimulation may lead to comparable EP amplitudes, but due to differences in their interpretation of scales used to rate pain intensity (e.g., 0–10), one individual reports an appreciably higher rating than the other. In such a case, the mismatch between CHEP/LEP amplitude and rating is prominently a function of measurement artifact, unrelated to differences in anatomy and physiology. However, central pain patients with thermal hyperalgesia demonstrate high prevalence of a similar phenomenon, often reporting high ratings coupled with small amplitude evoked potentials (Casey et al., 1996; Garcia-Larrea et al., 2002; Tinazzi et al., 2009; Wu et al., 1999). Collectively, these observations in healthy subjects and central pain patients raise the question whether a neural substrate underlies the discrepancy between ratings and evoked potential amplitudes.

By accounting for differences in sensitivity to noxious thermal stimuli (Emerson et al., 2014; Erpelding et al., 2012; Grant et al., 2010; Tseng et al., 2013), ability to modulate pain (Piche et al., 2013; Stankewitz et al., 2013; Teutsch et al., 2008), as well as the amplitude of evoked cortical responses to non-noxious afferent stimuli (Fjell et al., 2007; Liem et al., 2012; Muthukumaraswamy et al., 2010), structural magnetic resonance imaging (MRI) has highlighted an important relationship between normal brain anatomy and sensory function. Based on this knowledge, we intended to address the question whether between-subject variability in cortical structure could account for differences in responses to contact heat stimulation in healthy subjects. Specifically, we were interested in determining if estimates of gray and white matter volume explained, in part, why an individual perceived stimulation as low/high but generated an evoked cortical potential that was large/small. To this end, voxel-based morphometry (VBM) was used to explore associations between pain rating and CHEP amplitude in gray and white matter.

2. Methods

2.1. Subjects

Thirty neurologically healthy subjects participated in this study (13 females, 17 males). All subjects were prescreened for MRI contraindications and reported no acute or chronic pain at the time of examination. Subjects provided written informed consent and all procedures described below were in accordance with the Declaration of Helsinki, and approved by research ethics board at the University of Zurich (Ref. number: EK-04/2006).

2.2. Study protocol

2.2.1. Acquisition of pain rating and contact heat evoked potentials (CHEPs)

CHEPs and pain rating to contact heat stimuli were recorded following stimulation of the dorsal surface of the C6 dermatome at the base of the right thumb using the Pathway Pain and Sensory Evaluation System (Medoc Advanced Medical Systems®). 10 contact heat stimuli were delivered from a baseline temperature of 35 °C to a peak temperature of 52 °C, at an inter-pulse interval of 8–12 s. To familiarize subjects and limit the startle effect, individuals were exposed to contact heat stimuli on an untested site (e.g., forearm) before acquisition of evoked potentials. The contact heat stimulation thermode was repositioned (i.e., variable stimulation protocol) after each stimulus to reduce receptor fatigue. In response to an audio cue presented 2 s after contact heat stimulation, subjects rated perceived intensity according to a 0–10 numerical rating scale (NRS). Subjects were instructed not to blink in response to the stimulation, and withhold from blinking until hearing the audio cue. N2P2 was acquired from an active vertex-recording electrode (Cz) referenced to both earlobes (A1–A2). Previous studies have adopted a similar electrode configuration (i.e., single recording channel) for the acquisition of N2P2 (Chao et al., 2008, 2007; Chen et al., 2006), reporting significant intra-subject (i.e., test–retest) reliability for N2P2 amplitude (Kramer et al., 2012; Ruscheweyh et al., 2013). A ground strap electrode was secured on the upper arm of the stimulating side. A pre-trigger period of 100 ms preceded each recording, followed by a 1500 ms post-trigger, for a total 2000 ms epoch. All signals were sampled at 2000 Hz and amplified (20000×). Each stimulus was manually reviewed for artifact.

2.2.2. Automated detection of N2P2 amplitude

To enhance the signal-to-noise ratio of CHEPs, vertex recordings were bandpass (1–30 Hz) and wavelet filtered for automated detection of N2 and P2 amplitudes. The aim of wavelet filtering is to improve the signal to noise ratio, so as to allow automated detection of peak waveforms. Based on wavelet filtered CHEPs, single trial averaged N2P2, N2, and P2 amplitudes were determined. The advantage of single trial averaging compared to across trial averaging is that latency jitter does not affect the amplitude of responses. Rather, a measure of amplitude is extracted for each stimulus, and averaged across the total number of stimulations. In order to perform an unbiased single trial analysis of N2P2 amplitude from wavelet filtered CHEPs, an automated approach utilizing multiple linear regression with a dispersion term was performed in MatLab (Mathworks) (Hu et al., 2011, 2010). We applied the same techniques as described previously for CHEPs (Kramer et al., 2013).

2.2.3. Magnetic resonance image sequence

Using a Philips 3T Ingenia, a 3D-GRE T1-weighted (T1w) sequence was used to acquire a whole-brain, structural scan optimized for simultaneous assessment of the brain and spinal cord (Freund et al., 2010). The imaging parameters were: isotropic 1 mm^3 resolution, field of view 256 × 256 mm^2, matrix 256 × 256, 180 sagittal partitions, repetition time = 7.15 ms, echo time = 3.29 ms, inversion time = 858.65 ms, flip angle 8°, fat saturation, bandwidth 250 Hz/pixel and a scan time of 6 min 31 s. Prior to VBM analysis, MRI data from each subject was visually screened for movement artifacts.

2.2.4. Voxel-based morphometry (VBM)

To assess voxel-wise associations of gray and white matter volumes with N2, P2, and N2P2 amplitudes and pain ratings, VBM was performed in the framework of Statistical Parametric Mapping 8 (SPM8, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), applied on the acquired T1w 3D volumetric MRI data (Ashburner and Friston, 2000). First, a unified model inversion (unified segmentation) was used for bias correction and segmentation of MRI data into gray and white matter, and cerebrospinal fluid. Then Dartel was used to warp the gray and white matter segments into an optimal (average) space (Ashburner, 2007). The resulting gray and white matter images were modulated and affine transformed

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