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Sex differences in connectivity of the subgenual anterior cingulate cortex

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ABSTRACT

We previously reported that women exhibit greater heat pain adaptation to a prolonged painful stimulus and greater habituation to repeated painful stimuli than men. The neural mechanism underlying this sex difference is unknown. However, Bingel et al. (2007) have shown that pain habituation after 8 days of daily pain testing is associated with an increase in pain-evoked activity of the subgenual anterior cingulate cortex (sgACC), suggesting that pain habituation may be mediated via connectivity between the sgACC and the descending pain antinociceptive system. Therefore, we investigated whether women have stronger functional connectivity (FC) and greater structural connectivity (SC) compared to men between the sgACC and the descending antinociceptive system. Our analyses revealed that 1) women exhibited greater FC between the sgACC and the periaqueductal gray (PAG), raphe nucleus, medial thalamus, and anterior midcingulate cortex (aMCC) than men; 2) men had stronger sgACC FC with the anterior insula and temporoparietal junction than women; 3) women and men exhibited comparable SC of the sgACC with the PAG, thalamus, aMCC, anterior insula, and amygdala; and 4) men have stronger sgACC SC with the hypothalamus than women. These data indicate that brain circuitry in women may provide for greater engagement of the descending modulation system mediating pain habituation. In contrast, in men, the salience network may be more engaged, which could support greater sustained attention to pain, thereby preventing pain habituation. Furthermore, the hypothalamus findings suggest a more powerful stress and endorphin-based system at play in men than women.

1. Introduction

Pain perception is determined by a complex interaction between ascending pain pathways transmitting nociceptive signals from the body to the brain and descending modulatory cortical and subcortical circuits. As such, in some situations pain can adapt to sustained noxious stimuli or can habituate to repeated noxious stimuli. This pain attenuation involves endogenous modulation mechanisms [11], including the descending pain modulation pathway, with main hubs in the periaqueductal gray (PAG) and the raphe nucleus that modulates the activity of nociceptive neurons in the dorsal horn through serotonergic projections [9,20]. Dysfunctional pain habituation, possibly due to impaired descending modulation, has been linked to chronic pain [40,77,81,100]. Thus, uncovering mechanisms of pain habituation has clinical implications.

A pivotal functional magnetic resonance imaging (fMRI) study has shown that pain habituation over the course of 8 days is associated with an increase in pain-evoked activity of the subgenual anterior cingulate cortex (sgACC) [24,25]. Given the role of the sgACC and the descending modulation network in pain habituation, these findings suggest a possible connection between the sgACC and the descending pain antinociceptive system mediating pain habituation. More recently, Hashmi and Davis reported that women exhibit greater heat pain adaptation to a prolonged painful stimulus and greater habituation to repeated painful stimuli compared to men [45]. The neural mechanism underlying this sex difference in habituation remains unknown, but is potentially mediated through sgACC connectivity with antinociceptive pathways.

The sgACC is defined as the part of the anterior cingulate cortex (ACC) below the genu or "knee" of the corpus callosum. The sgACC consists of BA25 as well as the subgenual parts of BA32 and of BA24 [50,102]. The term "subcallosal cortex" is often used interchangeably with sgACC. However, the subcallosal cortex is part of the sgACC [74] adjacent to the posterior parolfactory sulcus.

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Here, we will use the term sgACC because our study aimed to examine this region.

The aim of this study was to investigate whether there are sex differences in the functional (FC) and structural connectivity (SC) of the sgACC to other brain regions implicated in pain and its modulation. Using resting-state fMRI and diffusion-weighted imaging (DWI)-based probabilistic tractography, we tested the hypothesis that women have stronger FC and SC than men between the sgACC and brain areas implicated in pain processing such as the thalamus (Th), and regions associated in antinociception, including the PAG, raphe nucleus, insula, amygdala, and hypothalamus.

2. Methods

2.1. Participants

MRI data were examined from a cohort of 80 healthy right-handed subjects who provided informed written consent to experimental procedures approved by the University Health Network Research Ethics Board. The subject pool consisted of 40 women and 40 men aged between 19 and 36 years (mean age ± SD = 24.5 ± 4.9 years). Subjects were excluded if they reported any current or regular pain (other than menstrual cramps) in the last 6 months (eg, headache, toothache), pain lasting more than 3 months in the last year, any current or previous diagnosis of a psychiatric disorder (eg, depression, attention deficit hyperactivity disorder), any chronic illness, claustrophobia, braces or metal in their body, possibility of pregnancy, or medication/drug use at the dose, frequency, and duration potentially impacting pain or cognitive function.

The analysis of sex differences reported here represents a secondary analysis of a psychophysical and imaging dataset examined previously for pain-attention mechanisms [38]. For that study, subjects underwent a psychophysical session to determine heat and cold pain thresholds and temporal summation of heat pain. Stimuli were delivered to the left volar forearm with a 30 mm × 30 mm Peltier thermode (TSA-II NeuroSensory Analyzer, Medoc Ltd) to determine pain thresholds and temporal summation of heat pain. Thermal pain thresholds were measured using the methods of limits (for details see [38]). Temporal summation of heat pain was determined using 10 consecutive 48 °C stimuli delivered at 0.5 Hz (interstimulus interval temperature of 40 °C). For each subject, the first 2 blocks of 10 stimuli temporal summation testing were considered training runs, with the third block used to determine temporal summation based on the percentage change of pain rating (on a 0–100 numerical rating scale for "no pain" to "most intense pain imaginable") from the first to the 10th stimulus. Subjects also completed the pain catastrophizing scale questionnaire (PCS) [96].

2.2. Brain imaging acquisition

All imaging data were obtained on a 3T MRI scanner (GE Medical Systems, Milwaukee, WI, USA) fitted with an 8-channel phased-array head coil. For each subject, we obtained 1) a whole-brain high-resolution scan using a T1-weighted inversion recovery prepped, 3-dimensional fast spoiled gradient echo sequence (flip angle = 15°; echo time [TE] = 3 ms; repetition time [TR] = 7.8 ms; inversion time = 450 ms; field of view [FOV] = 25.6 cm; 256 × 256 matrix; 180 slices; 1-mm slice thickness); 2) a resting-state fMRI scan using a T2*-weighted echo-planar imaging sequence (TE = 30 ms; TR = 2000 ms; FOV = 20 cm; 64 × 64 matrix; 40 slices; 4-mm slice thickness); and 3) 2 diffusion-weighted scans using 60 noncolinear isotropic directions (b = 1000 s/mm^2) and 10 non-diffusion-weighted images (b = 0 s/mm^2) (TR = 17,000 ms; TE = 83.3 ms; 96 × 96 matrix; FOV = 23 cm; 64 slices; 2.4-mm slice thickness). For the resting-state scan, subjects were instructed to not think of anything in particular and to keep their eyes closed.

2.3. Resting-state functional connectivity

2.3.1. Definition of seeds

A total of 6 bilateral spherical seeds were defined in sgACC regions that have previously been implicated in pain habituation [24,25]. Spheres have been commonly used as a seed shape in fMRI analyses [30,44,53,62,112]. The seeds were drawn as 3-mm spheres centered at Montreal Neurological Institute (MNI) coordinates: A: [−5, 25, −10]; B: [5, 25, −10]; C: [−5, 34, −9]; D: [5, 34, −9]; E: [−6, 33, −9]; F: [6, 33, −9]; G: [−5, 34, −4]; H: [5, 34, −4]; I: [−6, 27, 10]; J: [6, 27, −10]; K [−6, 30, −9]; N: [6, 30, −9] (see Fig. 1, note also that we did not use the letter "L" to avoid confusion with the "Left" designation in data display). We focused our study on FC between sgACC seeds and brain regions associated with the descending modulation system (ie, PAG, raphe nucleus, hypothalamus, amygdala, insula, and Th), although a whole-brain FC analysis allowed us to detect other brain regions to which the sgACC was functionally connected.

2.3.2. Preprocessing and correlation analysis

Because of the anatomical location of the sgACC, there was substantial blood-oxygen-level-dependent (BOLD) signal dropout (BOLD signal intensity below 65% of the mean intensity within nonzero intensity voxels; see Supplemental Fig. 1) within the sgACC region of interest for 10 men and 14 women, so these subjects were excluded from analysis. Thus, the resting state fMRI data analysis cohort was comprised of 30 men and 26 women (18–37 years old, mean ± SD age = 24.6 ± 5.1).

Seed-to-voxel correlational analyses were carried out by the functional connectivity (CONN) toolbox Version 13i (http://web.mit.edu.myaccess.library.utoronto.ca/swg/software.htm) and SPM8. The preprocessing pipeline of the functional images consisted of 1) motion correction, 2) registration to structural images, 3) spatial normalization to the MNI template, 4) smoothing with a Gaussian kernel of 6 mm, and 5) band-pass filtering of 0.01–0.1 Hz as recommended by the CONN toolbox.

After these preprocessing steps, the CompCor strategy [19] was implemented, which extracted signal noise from white matter and cerebrospinal fluid by principal component analysis. The analyses did not include global signal regression to avoid potential false anticorrelations (for discussion of this issue, see [73]). Motion parameters, cerebrospinal fluid, and white matter were included in the model and considered as variables of no interest.

2.3.3. Subject- and group-level statistical analyses

A first-level analysis was done using the CONN toolbox to perform spatial statistical analyses in each subject. A general linear model was applied to examine significant BOLD signal correlation with respect to time between each seed and each voxel. The toolbox converted the resulting correlation coefficients to Z scores using Fisher's Z transformation, for subsequent t tests.

A higher-level analysis using the CONN toolbox was performed to examine sex differences. To account for multiple comparisons, results were corrected using Monte Carlo simulations implemented in AlphaSim (http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim) at 10,000 iterations. AlphaSim confirmed that an image-wide threshold of $P < 0.05$ required a cluster corrected at $P < 0.001$ with 32 contiguous voxels for significance.

2.4. Probabilistic tractography

2.4.1. Seeds and targets definition

For each subject, we performed 2 probabilistic tractography analyses; each tract required the definition of a seed and a target. In our first analysis (analysis I), probabilistic tractography was performed using clusters of significant sex differences that were