American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY

(304) Regional gray matter predicts placebo response: a study of endogenous pain modulation in healthy individuals

J Craggs, A O'Shea, W Perlstein, D Price, R Staud, and M Robinson; University of Florida, Gainesville, FL

The use of placebos is known to be a powerful intervention. The structural brain correlates (i.e., cortical gray matter [GM]) associated with the magnitude of a placebo response is an understudied and important topic for understanding placebo and endogenous pain modulation. For this study, we used voxel-based morphometry (VBM) to identify brain regions primarily associated with the magnitude of a placebo analgesic response. Specifically, we examined the structural MRIs of 30 healthy participants (17 males) who were classically conditioned to experience an analgesic response to an inert cream (i.e., placebo analgesia). A preliminary analysis using hierarchical cluster analysis identified two magnitudes of placebo responses, moderate and robust (5% and 30% pain reduction respectively). No differences between groups were found in whole brain GM volume. However, robust responders had significantly more GM in several brain regions (minimum cluster criteria = $p \leq 0.001$, 10 contiguous voxels). These regions included the middle frontal gyrus (Brodmann areas [BA] 6 and 9), superior frontal gyrus (BA 8), cingulate gyrus (BA 24), precuneus (BA 7), inferior parietal lobule (BA 40), and several occipital areas. Furthermore, we found a significant correlation between the amount of regional gray matter and the magnitude of placebo response (e.g., $r = .629$, $p \leq 0.000$, BA 39 in the right hemisphere). These results suggest that even within an asymptomatic population gray matter volume may be a factor in facilitating endogenous pain modulation. Future research is needed to help clarify the structure/function relationship of brain regions, outside the traditional pain matrix, that may be involved in pain and its modulation. Research supported by grant 5R01AT001424 from the National Institute of Health.

(305) Phenotype matters: the importance of age, affect, medication, and pain characterization in the brain morphometry of chronic low back pain

A Dolman, M Loggia, R Edwards, J Kong, R Gollub, V Napadow, and A Wasan; Brigham and Women's Hospital, Boston, MA

Chronic low back pain (cLBP) is believed to be associated with alterations in brain morphometry. Studies have reported significant grey matter thinning, but they have not carefully controlled for important variables, such as affective disorder, pain medication, age, and pain phenotype. We propose that controlling for these factors may reduce the magnitude of the reported brain alterations in cLBP. We conducted cortical thickness and voxel-based morphometry (VBM) analyses in 14 cLBP patients with a discogenic component to their pain, not taking opioids or benzodiazepines, and not depressed or anxious. They were age and gender matched to 14 healthy controls (HC). An ROI-driven analysis was conducted, using 18 clusters from a previous arterial spin labeling (ASL) study identifying brain regions more active in cLBP subjects than HC during exacerbated back pain. Cortical thickness measurements were obtained from each subject's structural MRI scan after being processed within the automated FreeSurfer cortical reconstruction pipeline. VBM analysis was conducted within SPM8 contrasting grey matter volume between groups. MANOVA showed cLBP subject mild cortical thickening in the right paracentral lobule ($F(1,17)=3.667$, $p<0.067$) and significant thickening in the right rostral middle frontal gyrus ($F(1,17)=6.880$, $p<0.014$). These areas did not hold significance after including age as a covariate ($p<0.891$; $p<0.279$ respectively). A follow-up whole-brain analysis also did not identify significant clusters. VBM did not identify any significant clusters after controlling for multiple comparisons (uncorrected clusters $p<0.001$, false discovery rate correction $p<0.05$). Exploratory analyses identified a dichotomous trend in the correlation of age and cortical thickness of the right rostral middle frontal gyrus between cLBP subjects ($R=-0.027$, $p< 0.928$) and HC ($R=-0.805$, $p< 0.001$). Our pilot results suggest that affect, age, and concurrent medications may account for part of the previously reported brain alterations in cLBP. Follow-up studies should include a larger sample and explore possible cortical thickening.

(306) White matter microstructural integrity assessment in fibromyalgia using cardiac-gated diffusion tensor imaging

E Moana-Filho, I Tchivileva, and R Gracely; University of North Carolina, Chapel Hill, NC

Fibromyalgia (FM) pathophysiology remains largely unknown, with considerable neuroimaging evidence that brain functional and structural characteristics of patients differ from those of controls. Studies using diffusion tensor imaging (DTI) to assess white matter (WM) microstructure have shown significant differences across several brain regions for FM patients when compared to healthy controls (HC), which may indicate WM abnormalities. The main aim of this study was to assess global and regional brain WM characteristics in FM patients and HC using DTI. Eighteen female FM patients and 18 age- and gender-matched HC underwent a single magnetic resonance imaging (MRI) session where cardiac-gated DTI data with isotropic voxels (2 mm3) were acquired in a 3T scanner. To assess group differences in WM microstructure, we estimated DTI metrics such as fractional anisotropy (FA), mean diffusivity (MD) and radial diffusivity (RD) in a voxelwise fashion, and we performed a region of interest (ROI) analysis restricted only to the WM regions serving nociceptive pathways in the brain. Compared to FM, HC showed a trend towards greater FA values over the right anterior corona radiata (cluster size=116 voxels), while FM patients demonstrated an increased MD (cluster=11,511) and RD (cluster=7,938) in several WM areas ($p<0.1$). ROI analyses showed that, compared to FM, HC had greater FA values ($p=0.061$) and greater axial diffusivity ($p=0.077$) in the right primary somatosensory cortex. FM patients had greater MD ($p=0.036$) and RD ($p=0.079$) over the left corticospinal tract. Although these are preliminary results from ongoing research and further investigation is needed, our analyses of DTI metrics suggest that FM patients show WM abnormalities that may be associated to enhanced pain processing in supraspinal centers.

E20 Non-Opioid Analgesics

(307) The anti-inflammatory and analgesic activity of curcumin in a rat model of full thickness thermal injury

B Cheppudira, A Greer, A Mares, M Fowler, T Garza, L Petz, D Loyd, and J Clifford; US Army Institute of Surgical Research, San Antonio, TX

Each year there are approximately 45,000 burn injuries requiring hospitalization in the US, and opioids are the primary analgesic for these patients. However a range of side effects, as well as a high potential for addiction, often limit dose levels and frequency of use. There is therefore a need to develop effective non-opioid alternatives for treating burn pain. The purpose of this investigation was to assess the potential of curcumin, a naturally occurring anti-inflammatory agent that is highly abundant in the spice turmeric (Curcuma longa), as an analgesic for thermal injury pain. To accomplish this, male rats were subjected to a hind paw full thickness thermal injury protocol. The latency to paw withdrawal (PWL) from a noxious thermal stimulus or a mechanical stimulus was recorded prior to thermal injury (baseline), and at 24, 48, and 72 hours, and 1 week following thermal injury. We demonstrate that curcumin treatment attenuated thermal hyperalgesia and mechanical allodynia, as measured by an extended PWL. This effect was most pronounced after 1 week of treatment. Using multiplex cytokine antibody arrays, we also assessed the ability of curcumin to block heat-induced secretion of cytokines and other inflammatory mediators in cultured keratinocytes, the cell type most prevalent at the burn site. We demonstrate that curcumin suppressed heat induced secretion of GRO-α and IL-8 and both basal levels and heat-induced matrix metalloproteinase 1 and 3 (MMP-1 and MMP-3). Finally, we show that curcumin treatment suppressed heat induced p38 MAPK activity and both basal levels and heat-induced NF-κB p65 activity, as measured by levels of phosphorylated p38 and NF-κB p65, respectively. Our data indicate that curcumin may be an effective analgesic for thermal injury pain and that this effect could be mediated through suppression of inflammation at the site of injury.