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DACC Resting State Functional Connectivity as a Predictor of Pain Symptoms Following Motor Vehicle Crash: A Preliminary Investigation

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Highlights

- Pain severity after MVC predicted by resting state functional connectivity
- Positive dACC-premotor connectivity predicts greater pain severity
- Negative dACC-precuneus connectivity predicts greater pain severity

DACC Resting State Functional Connectivity as a Predictor of Pain Symptoms Following Motor Vehicle Crash: A Preliminary Investigation

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Abstract

There is significant heterogeneity in pain outcomes following motor vehicle crashes (MVCs), such that a sizeable portion of individuals develop symptoms of chronic pain months after injury while others recover. Despite variable outcomes, the pathogenesis of chronic pain is

currently unclear. Previous neuroimaging work implicates the dorsal anterior cingulate cortex (dACC) in adaptive control of pain, while prior resting state functional magnetic resonance imaging studies find increased functional connectivity (FC) between the dACC and regions involved in pain processing in those with chronic pain. Hyper-connectivity of the dACC to regions that mediate pain response may therefore relate to pain severity. The present study completed rsfMRI scans on *N*=22 survivors of MVCs collected within two weeks of the incident to test whole-brain dACC-FC as a predictor of pain severity six months later. At two weeks, pain symptoms were predicted by positive connectivity between the dACC and the premotor cortex. Controlling for pain symptoms at two weeks, pain symptoms at six months were predicted by negative connectivity between the dACC and the precuneus. Previous research implicates the precuneus in the individual subjective awareness of pain. Given a relatively small sample size, approximately half of which did not experience chronic pain at six months, findings warrant replication. Nevertheless, this study provides preliminary evidence of enhanced dACC connectivity with motor regions and decreased connectivity with pain processing regions as immediate and prospective predictors of pain following MVC.

Perspective: This article presents evidence of distinct neural vulnerabilities that predict chronic pain in motor vehicle crash survivors based on whole-brain connectivity with the dorsal anterior cingulate cortex.

Key Words: motor vehicle accident; traumatic injury; pain; fMRI; resting state; cingulate cortex

Introduction

Motor vehicle crashes (MVCs) are a leading cause of traumatic injuries in the United States – second only to falls – and account for over 20% of all severe injuries that require hospital care.[21] While a host of negative outcomes accompany MVCs, chief among these is the

experience of severe pain symptoms, which affect up to 80% of MVC survivors immediately after injury.[9] In terms of the long-term prognosis of pain outcomes, there is considerable variability. Large-scale and population-based studies demonstrate that anywhere from 12-40% of MVC survivors continue to suffer from pain months after injury.[47,57] As pain symptoms become chronic, defined as pain that is maintained at least six months after injury, risk for diminished quality of life and psychiatric illness increases.[3,24] Therefore, deciphering who is at risk for the emergence of chronic pain after injury provides an opportunity to intervene and positively affect overall health of MVC survivors. Currently, however, relatively little is known about what factors moderate the relationship between MVC-related injury and the development of chronic pain, demonstrating a need for more research to precisely elucidate which factors predict heterogeneity of pain outcomes in this population.[16]

Neurobiologically, the acute experience of pain involves activation in numerous discrete brain regions.[62] During injury, pain signals are sent from the periphery to the brain by way of the spinal cord and brainstem, which subsequently transmit these signals to the thalamus.[6] This information is then sent to the somatosensory cortex, involved in deciphering the location and intensity of incoming pain signals.[2,13,59] The amygdala and insula, which are involved in salience detection, processing, and experience of emotion[38,53,58], are also active and contribute to overall pain processing.[33,73]

In addition to these regions, which are principally involved in the appraisal of pain as a salient event[52], the spinothalamic system directly innervates higher cortical regions to manage and control the pain response, with a chief target being the dorsal anterior cingulate cortex (dACC).[44,72] The dACC receives direct[1,25] and indirect[10,49,74] connections from the brainstem, in addition to possessing a bilateral connection with the amygdala.[34,61,68,82] Based on this

organization and in the context of acute pain response, the dACC has been identified as a critical region involved in integrating incoming signals governing the perception of pain (e.g., originating from the periphery by way of the brainstem) with those involved in salience detection and the generation of negative affect (e.g., originating from the amygdala.[54,72,77] Given the dACC's broader role in response inhibition and action planning [12,27], the principal role of the dACC in response to pain is believed to center on integrating pain and affective signals in order to mediate adaptive control of this experience.[72] This is supported by evidence from primate studies showing that the dACC is active in response to pain as well as when animals are fleeing from pain.[41,43,50] This suggests a role for the dACC in mediating the motivational response to pain. Humans with lesions in the cingulate cortex report reduced affective responses to pain without altering their perception of incoming pain signals, further suggesting that the dACC is involved in affective response to pain.[32] Evidence from functional magnetic resonance imaging (fMRI) studies in healthy volunteers also shows that perceived controllability of feeling pain tracks linearly with dACC engagement when pain is administered.[70] In the context of pain outcomes following MVCs, engagement of the dACC may therefore influence long-term pain prognosis given its role in pain regulation.

Indeed, there is evidence of altered dACC involvement in chronic pain based on data from cross-sectional fMRI studies examining dACC activation in individuals with fibromyalgia and chronic low back pain. Individuals with these conditions exhibit greater activation of the dACC during nociceptive processing.[19,35,66] Augmented engagement of the dACC during pain processing may compensate for greater anticipation and attention towards pain[19], as evidenced by the fact that dACC activation positively relates to greater subjective ratings of pain in these samples[66] and symptoms of pain catastrophizing – or characterizing pain as awful, horrible and

unbearable.[37] As pain processing involves many brain regions, functional connectivity (FC) studies have been useful for understanding alterations within larger networks, with specific focus on altered spontaneous low-frequency (< 0.1 Hz) fluctuations between regions at rest. This work also demonstrates altered connectivity between the ACC and pain processing regions in those with chronic pain. For instance, Cifre and colleagues found greater FC between the ACC and insula, and reduced ACC-amygdala and ACC-brainstem FC in those with fibromyalgia compared to healthy controls.[17] Enhanced ACC-insula connectivity may reflect greater interoceptive awareness of pain, while decreased ACC-amygdala and ACC-brainstem connectivity may represent abnormal bottom-up signaling of pain sensations and/or reduced descending modulation of pain.[17] Conversely, decreased FC between the insula and dACC is associated with greater reduction of pain symptoms when patients with fibromyalgia were administered milnacipran, a selective serotonin and norepinephrine reuptake inhibitor (SNRI) for their pain symptoms.[71] Together, this work demonstrates that greater FC between the dACC and pain processing regions (e.g., insula, thalamus, brainstem) characterizes chronic pain response, but that this FC is reversed when pain symptoms are treated. Based on this work, functional neurocircuitry between the dACC and brain regions involved in acute pain processing may be related to long-term pain outcomes; however, we are unaware of a study that has examined dACC-FC as a predictor of prospective pain severity following MVCs.

The current study tested whole-brain dACC-FC as a predictor of chronic pain symptoms assessed six months after a MVC. Pain ratings and rsfMRI were collected in-person acutely (e.g., within two weeks of the MVC) and pain ratings were collected again in-person six months later at a follow-up visit. We hypothesized that pain ratings across the two timepoints would be positively related to one another. In addition and based on prior neuroimaging work, we

hypothesized that baseline measures of rsfMRI, specifically positive connectivity of the dACC with regions involved in acute pain processing (e.g., the brainstem, thalamus, somatosensory cortex, amygdala and insula) would predict greater pain symptoms at baseline and prospectively predict greater pain symptoms at six months.

Methods

Participants and Procedures

Participants were recruited from the emergency department of the Level 1 trauma center at Froedtert Hospital/Medical College of Wisconsin in Milwaukee, WI. Participants were not admitted to long-term hospital care but were discharged following completion of acute care within the emergency department (ED). Inclusion criteria included: (1) MVC as mechanism of injury, (2) between the ages of 18-65, (3) ability to read and write English, and (4) ability to give informed consent. Participants were excluded if they had a head injury that resulted in loss of consciousness (Glasgow Coma Scale score < 13 on emergency department arrival). Additional exclusion criteria specific to fMRI scanning included: (1) presence of ferromagnetic material within the body, (2) pregnancy or actively trying to become pregnant, (3) fear of enclosed spaces (e.g., claustrophobia), and (4) inability to lie still for up to one hour. Participants were recruited over the phone from an ED discharge census and provided consent for participation when they arrived for rsfMRI testing and self-report scales two weeks after injury at a baseline appointment; self-report scales were again collected in-person six months later at follow-up. The Institutional Review Board (IRB) at the Medical College of Wisconsin approved all study procedures and participants were monetarily compensated for their time.

Self-report Measures and Analysis

Participants completed a self-report index of pain at both baseline and six month visits using the Visual Analog Scale for Pain (VAS Pain)[56], a reliable and valid measurement for the reporting of unidimensional pain[22,29] and that has been used as a primary outcome measure of recurrent pain.[18] Upon presentation of the VAS Pain, participants were asked to rate how much pain they were currently experiencing on a continuous scale of 0-10 (0=no pain, 10=worst pain). In addition to the VAS Pain, all participants also completed a self-report rating of posttraumatic stress symptoms at both visits using the Impact of Events Scale-Revised (IES-R)[78], given high comorbidity between pain symptoms and posttraumatic stress disorder (PTSD).[7] The IES-R asks participants to rate how distressed they feel by common posttraumatic stress symptoms. In addition to clinical measures, participants were also asked about medications they were taken at the time of the fMRI assessment to determine opioid use for pain management

rsfMRI Acquisition, Preprocessing, and Analysis

All participants completed a 6-minute resting state scan during fMRI (e.g., rsfMRI) at their baseline appointment approximately two weeks after injury. During the scan participants viewed a white crosshair displayed on a black background and were instructed to keep their eyes open. Scanning was performed on a 3.0 Tesla short bore GE Signa Excite MRI system at the Medical College of Wisconsin. Functional T2*-weighted echoplanar images (EPI) were collected in a sagittal orientation with the following parameters: repetition time (TR)/echo time (TE)=2000/25ms; FOV=24mm; matrix=64x64; flip angle=77°; slice thickness=3.5mm. A high-resolution T1-weighted anatomical image was also acquired for co-registration with the

following parameters: TR/TE=8.2/3.2ms; FOV=240mm; matrix=256x224; flip angle=12°; voxel size=0.9375 x 0.9375 x 1mm.

Individual functional images were analyzed using the CONN functional connectivity toolbox[80] and images were preprocessed according to standard procedures. Briefly, images underwent spatial realignment, slice-time correction, structural segmentation and normalization, and motion correction. As small head movements can cause spurious noise and distance-dependent changes in signal correlations[64,65], frame-wise displacement (FD) was computed to rule out confounding effects of motion. Volumes with FD > 0.2mm (plus 1-back and 2-forward neighboring volumes) were 'scrubbed' (e.g., removed from analysis) and subjects with > 3 mm or 3 degrees of rotational cumulative movement were dropped from analysis. Images were normalized to the Montreal Neurological Institute (MNI) template and smoothed with a 4 mm^3 Gaussian kernel. To isolate rsfMRI signal, resulting data were bandpass filtered at 0.01-0.10 Hz, while signal from cerebrospinal fluid and white matter along with motion realignment parameters were entered as regressors of no-interest to control for these effects during scanning.

For whole-brain dACC-seeded analyses, an anatomical dACC mask was created from the ACC mask in the AAL atlas.[55,76] This ACC mask was edited using fslview (FSL v.5.0.9[45]) to exclude rostral ACC, such that ACC at and below the genu of the corpus callosum was excluded in-line with dACC versus rostral ACC boundaries.[12] Figure 1 illustrates spatial location of the dACC mask used as the seed region.

We first examined the relationship between dACC whole-brain FC and pain symptoms at baseline, controlling for age, gender, opioid administration at baseline (dichotomous variable), and time since injury for the baseline appointment. Second, we examined the relationship between dACC whole-brain FC and pain symptoms at six months, controlling for these same

covariates in addition to pain symptoms at baseline and PTSD symptom severity at six months (e.g., IES-R) given high comorbidity between the development of chronic pain and PTSD.[23,60,75] Age and gender covariates were included given wide range in age distribution and unequal gender distribution. Significant effects were examined using a height threshold of $p<0.001$ (uncorrected) and cluster threshold of $p<0.05$ corrected for multiple comparisons across the entire brain based on a false discovery rate (FDR) in-line with recent recommendations[26,63,81] and identical to other published methods.[20,40,48] To illustrate effects, connectivity values were extracted from significant clusters and input into SPSS (Version 25.0).

Results

Participants

Based on inclusion/exclusion criteria, a total of 22 participants consented to and were included in the study. Participants were between the ages of 18-62 (M=31.82, SD=11.28); *n*=17 participants were female (77%). In terms of race and ethnicity, *n*=11 (50%) were Caucasian, *n*=8 (36%) African-American, *n*=2 (9%) Hispanic, and *n*=1 (5%) unknown. As a result of the MVC, 12/22 (54.55%) experienced injuries involving more than one area on the body, while the location of injuries included the back (12/22; 54.55%), neck (9/22; 40.91%), head (4/22; 18.18%), arms (3/22; 13.64%), hips (2/22; 9.09%), legs (2/22; 9.09%), chest (1/22; 4.55%), and abdomen (1/22; 4.55%). In terms of concomitant conditions, at the time of admittance into the ED, 16/22 (72.73%) had no current medical conditions, 3/22 (13.64%) had asthma, 1/22 (4.55%) had high cholesterol, 1/22 (4.55%) had hypertension, and 1/22 (4.55%) had anemia. No participants had a history of chronic pain prior to the injury.

At baseline, participants were asked to rate the severity of their pain associated with the injuries sustained during the MVC. Pain ratings ranged from 0-5.50 (M=2.57, SD=1.83) at baseline, and 0-7.00 (M=1.34, SD=1.80) at six months. The number of participants who reported pain 6 months after injury was 12/22 (54.55%) as qualified by a pain rating > 0, indicating presence of pain. A total of 7/22 (31.82%) participants reported either identical pain severity compared to baseline or an increase in pain severity at 6 months. Pain ratings at baseline were positively correlated to pain ratings at six months ($r(20)=0.44$, $p=0.04$). A total of six participants (27%) were taking opioids at baseline for pain management.

As time since injury may affect pain severity ratings, we also assessed the correlation between time since injury for both baseline and 6 month appointments and pain severity ratings. Two time since injury measures were calculated using difference scores reflecting: (1) baseline data collection date – date of injury, and (2) 6 month data collection date – date of injury. Time since injury for baseline assessments averaged 13.64±2.87 days, and time since injury for the 6 month assessments averaged 202.30±17.97 days. There was a trending relationship between time since injury at the baseline assessment and pain severity ratings at that time ($r(20)=0.41$, $p=0.06$), although time since injury for 6 month assessments and pain severity ratings at 6 months were not associated with one another ($r(20)=-0.04$, $p=0.87$).

Symptoms of PTSD ranged from 0.58-8.08 (M=4.47, SD=2.15) at baseline to 0-9.75 (M=2.50, SD=2.61) at six months. Severity of pain and PTSD symptoms were not related at either baseline ($r(20)=0.15$, $p=0.52$) or six months ($r(20)=0.39$, $p=.07$).

rsfMRI Predictors of Pain at Baseline

Pain symptoms at baseline were predicted by positive connectivity between the dACC and a cluster traversing the precentral gyrus/primary motor cortex (M1) and premotor cortex (peak MNI: 30, -14, 70; Z=7.45; volume= 1,440 mm^3; p=0.004 FDR-corrected). Spatial location of significant FC cluster in the precentral gyrus is displayed in Figure 2, Panel A.

rsfMRI Predictors of Pain at Six Months

Pain symptoms at six months were predicted by negative connectivity between the dACC and the precuneus (peak MNI: -6, -74, 32; Z=5.25; volume=1,272 mm^3; p=0.004 corrected). Spatial location of significant FC cluster in the precuneus is displayed in Figure 2, Panel B.

Discussion

The present study tested resting state FC of the dACC as a predictor of pain severity six months following a MVC. Several important findings emerged from this investigation: first, pain severity at baseline was predicted by positive connectivity between the dACC and precentral gyrus, while pain severity at six months was predicted by negative connectivity between the dACC and the precuneus. Although pain symptoms were positively related to pain symptoms six months later, neural predictors were significant after controlling for severity of symptoms at baseline. In effect, results demonstrate that dACC FC is a robust neural predictor of pain outcomes six months after injuries associated with MVC.

The findings that positive connectivity between the dACC and the precentral gyrus/primary motor cortex (M1) predicted greater pain severity is consistent with prior literature. For instance, altered stimulation of the M1 in individuals with chronic pain has been

widely reported on, related to altered compensatory movements that develop based on injuries.[15] As pain severity at the baseline timepoint was associated with positive connectivity between the dACC and M1, this suggests that movement dysfunction, mediated by the M1, may play a greater role in disrupted pain modulation acutely.

We also found that negative FC between the dACC and precuneus predicted greater pain severity six months after injury. The precuneus is one of the major 'hubs' of the default mode network (DMN), defined as correlated activation between the medial prefrontal cortex, posterior cingulate cortex, and precuneus at rest. Thus, effects specific to the precuneus is unsurprising given the reliance on a resting state paradigm in our design. Increased engagement of the DMN is related to self-referential thinking, planning, and monitoring of internal and external states outside of cognitive or affective demand.[11] The precuneus in particular is associated with consolidating information during rest and the forming of cohesive mental representations.[14] Activation of the precuneus diminishes during unconscious states[14] and during the switch from rest to externally-focused tasks.[31]

While not traditionally associated with pain processing[28], the precuneus mediates individual differences in pain sensations, or reported conscious experience of pain.[36] In healthy individuals, the experience of pain in the laboratory through the use of controlled thermal heat results in robust engagement of pre-established pain regions, specifically the somatosensory cortex, ACC, and insula.[36] However, in these same individuals, subjective report in feeling this pain correlates positively with engagement of the precuneus only (i.e., as opposed to other pain-centric regions).[36] Other work supports a role for the precuneus in tracking individual differences in pain ratings, but reports opposing effects, such that greater pain sensitivity is related to *dis*-engagement of the precuneus.[77] This latter study also demonstrates that greater sensitivity to pain

corresponds positively to engagement of the dACC while simultaneously corresponding to disengagement of the precuneus[77], suggesting that these brain regions may be part of a functional network. In contrast, there is little evidence that the precuneus is active during pain when perception of pain is not taken into account[36], while there is further evidence that later processing of pain (vs. early processing of pain on the order of milliseconds) corresponds to increased precuneus activation.[36] Thus, the unfolding of the perception of pain over time as it moves from unconscious to conscious awareness may be moderated by precuneus involvement. The role of the precuneus in information integration and "co-perception", or the integration of our internal and external selves, thus provides the best explanation for the involvement of the precuneus in mediating the internal perception of pain.[14,46]

This theory with respect to the role of the precuneus in pain processing is further supported by prior research involving those with chronic pain. Patients with chronic pain have increased functional connectivity between the precuneus and thalamus[42] and precuneus and sensorimotor cortex[8], but decreased connectivity between the precuneus and insula.[39] Other studies find increased overall DMN connectivity (including the precuneus) with the thalamus in those with chronic pain[51], suggesting overall strengthening of connections between pain processing and self-referential thinking. Enhanced MPFC-precuneus connectivity and MPFC-thalamic connectivity is directly associated with pain rumination in some of this work[51], suggesting that precuneus connectivity may be associated with integrating pain into a current state of mind. Finally, other studies have found that patients with chronic pain over-engage the precuneus within the larger DMN, perhaps showing greater reliance on this region during times of rest related to the integration of pain states.[4] Limited neuroimaging longitudinal studies involving those with chronic pain have been done, although findings from this work also

implicates the precuneus. Individuals who experience persistent chronic pain over one year exhibit decreased connectivity between the insula and precuneus.[5] In the present study, variability in the functional connection between the dACC and precuneus was a reliable marker of individual differences in future pain, furthering the role of the precuneus in the perception of pain. Weakened correlation between brain regions that regulate pain (i.e., dACC) and those associated with the internal perception of pain (i.e., precuneus) may therefore provide a "neuro-profile" of persistent perception of pain.

Contrary to hypotheses, we did not find evidence that dACC-FC with other brain regions involved in pain processing – specifically the brainstem, thalamus, somatosensory cortex, amygdala, and insula – predicted pain severity six months after injury. Although these regions are involved in the acute processing of pain, FC between the dACC and these regions was not a useful predictor of chronic pain symptoms. The current analysis controlled for symptoms of PTSD, a disorder associated with affective disturbances involving atypical insula and amygdala engagement.[30,67] That is, regions involved in the affective components of pain perception (e.g., insula, amygdala) may also be involved in affective symptoms of PTSD. By controlling for the contribution of stress symptoms in the present analysis, results isolate dACC-FC perturbations specific to the ability to predict chronicity of pain symptoms in comparison to comorbid conditions, which may help explain the lack of findings with other nociceptive regions that have shared disturbances with PTSD.

Results of this study should be considered in light of several limitations. First, a relatively small sample size was used in the present study; therefore, findings require replication. Second, pain was assessed using a singular VAS rating at baseline and six months and therefore does not reflect the average pain over a duration of time. Pain severity can be measured both in terms of

pain intensity and unpleasantness to further validate pain ratings. Related, this sample experienced relatively lower levels of pain. Future studies should consider incorporating average VAS ratings over a period of time to account for subtle fluctuations in the reporting of pain, include individuals with more severe pain symptoms, and use more robust measures of pain that include ratings of unpleasantness. This investigation is also limited to pain outcomes following MVC and, thus, findings may not be generalizable to other types of injury. As this preliminary investigation focused exclusively on the dACC, future work should also consider investigating other nociceptive regions as predictors of chronic pain. Finally, in this sample the qualitative nature of the MVC was similar across participants, making it difficult to ascertain whether rsfMRI FC varied as a function of properties of the MVC. Without a control group, we were also unable to conclude that rsfMRI results are directly related to the MVC in this sample.

Despite these limitations, this study provides evidence of distinct neural vulnerabilities that predict chronic pain based on positive versus negative whole-brain connectivity with the dACC. The dACC is implicated in acute pain response[54,77] and has been viewed as a target for the treatment of chronic pain specifically.[69] This study provides added evidence of the importance of dACC in pain as a target of treatment by demonstrating that dACC-FC may be able to predict those most at risk for chronic pain. Ultimately, this work supports dACC connectivity as a potential biomarker of chronic pain.

Figure Legends

Figure 1

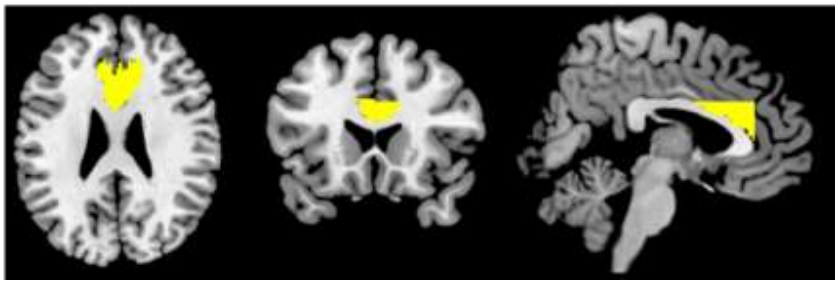

Figure 1. dorsal anterior cingulate cortex mask

Figure 2

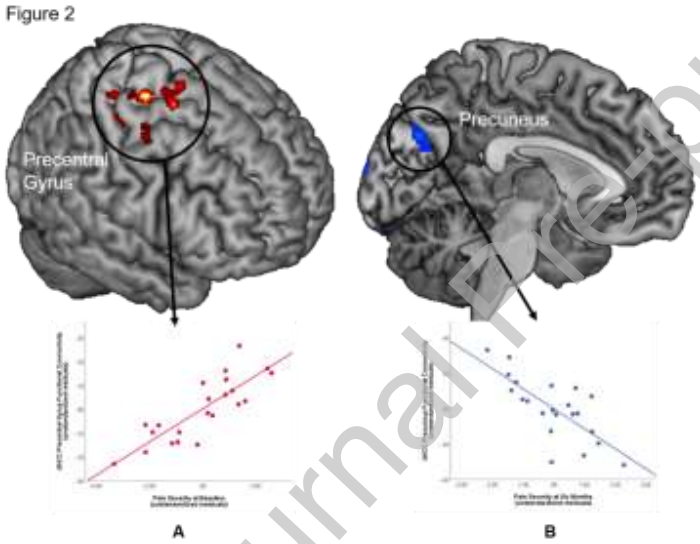

Figure 2. (A) Greater pain severity at baseline is associated with increased functional connectivity between the dACC and precentral gyrus/premotor cortex (peak MNI coordinate: 30, -14, 70). (B) Greater pain severity at six months is associated with decreased functional connectivity between the dACC and precuneus (peak MNI coordinate: -6, -74, 32). Display threshold is $p<0.001$ whole-brain uncorrected (cluster $p<0.05$ FDR-corrected). All effects control for opioid use at baseline, time since injury at baseline, age, and gender. Effects at six months additionally control for pain symptoms at baseline and PTSD symptoms at six months.

dACC=dorsal anterior cingulate cortex; MNI= Montreal Neurological Institute;

PTSD=posttraumatic stress disorder.

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