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Frequency of hospitalizations for pain and association with altered brain network connectivity in sickle cell disease

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Abstract

Sickle cell disease (SCD) is a hemoglobinopathy affecting more than 100,000 individuals in United States. The disease is characterized by presence of sickle hemoglobin and recurrent episodes of pain. Some individuals with SCD experience frequent hospitalizations and high burden of pain. The role of central mechanisms in SCD pain has not been explored. Twenty-five adolescents and young adults with SCD underwent functional MRI (fMRI). Participants were stratified into high or low pain groups based on the number of hospitalizations for pain in preceding 12 months. Resting state functional connectivity was analyzed using seed based and dual-regression independent component analysis. Intrinsic brain connectivity was compared between high and low pain groups and association with fetal hemoglobin, a known modifier of SCD, was explored. Patients in the high pain group displayed an excess of pro-nociceptive connectivity such as anterior cingulate to default-mode-network structures such as the precuneus, whereas patients in low pain group showed more connectivity to anti-nociceptive structures such

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as the peri- and sub-genual cingulate. Although a similar proportion of patients in both groups reported to be on hydroxyurea, the fetal hemoglobin levels were significantly higher in the low pain group and were associated with greater connectivity to anti-nociceptive structures. These findings support the role of central mechanisms in SCD pain. Intrinsic brain connectivity should be explored as a complementary and objective outcome measure in SCD pain research.

Introduction

Recurrent episodes of pain are the leading cause of visits to the emergency department (ED) and hospitalizations in sickle cell disease (SCD). With an estimated annual cost of \$2.4 billion for treatment, SCD pain leads to significant financial burden to the health care system³¹ and is associated with poor quality of life and early mortality^{16, 34, 38}. Although painful vaso-occlusive episodes (VOEs) are considered the hallmark of SCD, chronic daily pain is highly prevalent in this population³⁶. Most episodes of pain do not result in visits to the emergency department and hospitalization³⁶, however correlation exist between mean pain intensity scores in the ambulatory setting, the percentage of pain days and health care utilization for pain^{19, 36}. Differences in the patterns of pain start to emerge in young children with SCD which may change overtime, likely reflecting neuroplasticity of brain¹⁴. Not all patients display high pain burden^{34, 36} leading to uncertainty in the field as to why some SCD patients develop significant pain burden and others do not. There is a growing body of evidence in non-SCD pain conditions implicating the central nervous system as a contributor to chronic pain^{25, 26, 33}. SCD has been shown to be associated with increased sensitivity to pain both in human and mice models^{6, 20}. Interestingly, a recent study has also shown evidence of central sensitization in a murine model of SCD¹⁰.

Resting state functional connectivity (rsFC) studies of brain activity are being increasingly utilized to study chronic pain conditions^{2, 30}. RsFC involves correlating the time course of blood-oxygen level dependent (BOLD) MRI signal changes between various brain regions²¹. In the absence of external stimuli, this resting state activity provides insight into functionally interconnected brain networks while patients are at rest which is ideal for the assessment of spontaneous ongoing clinical pain. One network that has been implicated in the expression and modulation of spontaneous chronic pain is the Default Mode Network (DMN) which includes the inferior parietal lobule, the posterior cingulate cortex, precuneus, areas of the medial frontal gyri, the hippocampal formation, and the posterior lateral temporal cortex⁸. DMN structures are typically deactivated during various externally-focused or demanding cognitive processes. Chronic pain patients demonstrate disrupted DMN dynamics and diminished deactivation associated with tasks². Furthermore, pain patients with fibromyalgia show increased connectivity between the DMN and the insula³³, a brain region thought to integrate the multiple dimensions of pain⁷. In a recent study, reduction of this connectivity was associated with improved clinical pain following pharmacologic treatment with pregabalin²⁴. Other brain regions that are also involved in pain processing and modulation include the primary and secondary somatosensory cortices (SI and SII), various regions of the thalamus, and as well as the rostral and dorsal anterior cingulate cortex (ACC)¹. Previous neuroimaging studies in non-SCD pain populations indicate the salience network (SLN) as a key hub for pain processing which includes the

bilateral primary and secondary somatosensory cortices (SI and SII), anterior insula, primary motor cortex (M1), and the sensory motor area (SMA)³. Despite description of these functional neuroimaging characteristics in other pain populations these outcomes have not been investigated in SCD. While shared brain mechanisms between different chronic pain disorders have been postulated, recent findings suggest some alterations in functional connectivity may also show disease specificity.²³

The goal of this pilot study was to determine feasibility of MRI- rsFC approach in adolescents and young adults with SCD and to explore the association between pain and intrinsic resting state brain connectivity implicating the role of central mechanisms in SCD pain.

Methods

Study population and pain phenotype

The study was reviewed and approved by the Institutional Review Board of Children's National Health System, Washington, DC. All participants or their parents provided written informed consent prior to the study. All participants completed functional MRI in the steady state of health. Exclusion criteria included (1) history of non-SCD chronic pain disorders such as irritable bowel syndrome and fibromyalgia; (2) known psychiatric disorders such as major depressive disorder or schizophrenia; (3) history of overt stroke or an abnormal neurological examination; (4) contraindication to MRI scanning and (5) known history of substance abuse. Patients on chronic transfusion due to abnormal transcranial doppler study, or hydroxyurea, and with silent infarct or SCD chronic pain were not excluded. The number of visits to the ED and hospitalizations for pain in the 12 months preceding recruitment was recorded from the electronic medical records and was utilized to assign pain groups. Visits to ED that resulted in hospitalization were counted only as the hospitalization. Traditionally, 3 or more episodes of acute painful episodes requiring health care utilization have been considered as a marker of severe SCD¹¹. In this study, patients with 3 or more episodes of pain requiring hospitalization were classified into "high pain hospitalization or high pain group" while those with two or less hospitalizations were classified as the "low pain hospitalization or low pain group". A convenience sample of 25 SCD patients was recruited to participate in this IRB approved study. An attempt was made to recruit patients with pain phenotypes on both extremes (i.e. patients either with relatively lower or higher rates of hospitalization for pain). Some patients in the high pain group were on long acting opioids for their daily pain which were not discontinued for neuroimaging.

MRI acquisition

Images were obtained in a 3.0T whole-body MR scanner Discovery, MR750 (GE Healthcare, Waukesha, WI) with 60cm bore, 32 receive channels, gradient strength 50mT/m and 200T/m/s slew rate and a 32-channel receive-only head coil array (MR Instruments, Inc. Minneapolis, MN). Five minutes of resting functional magnetic resonance imaging (fMRI) data were collected using T2* weighted BOLD pulse sequence in the axial plane (repetition time [TR]/echo time [TE] = 2500/25ms, acquisition matrix 64×64, field of view (FOV) = 240×240mm², 150 volumes, slices, voxel size = 3.75×3.75 × 3.0mm³ and acquisition time of

6:28mins). During the scan subjects were asked to close their eyes and rest comfortably without moving or falling asleep. Structural high resolution data were acquired using a 3D Inversion-prepared Fast Spoiled Gradient Echo (FSPGR) T1 weighted pulse sequence (TR/TE = 8.2/.3.2ms, inversion time [TI] = 450ms, flip angle = 12 degrees, receiver bandwidth = 31.25 KHz, FOV = 240×240mm², acquisition matrix = 256×256, voxel size = 0.94×0.94×1.2mm³, 128 slices, and acquisition time of 4:11mins).

Preprocessing

Preprocessing of fMRI data was performed using the SPM8 (Statistical parametric mapping; Wellcome Department of Cognitive Neurology, London, UK) software package running under Matlab7.10. Canonical preprocessing steps involved image registration, motion correction, normalization to MNI space and spatial smoothing using a Gaussian filter of full width half maximum value of 8mm.

Seed-based Region of Interest (ROI) analysis

Seed-based ROI analyses were performed using the functional connectivity toolbox *Conn v. 1.3* (Cognitive and Affective Neuroscience Laboratory, Massachusetts Institute of Technology, Cambridge, USA) running on Matlab 7.10⁴¹. A priori seeds within the DMN including the inferior parietal lobule, precuneus, and posterior cingulate cortex were studied. In addition seeds from other pain regions including the insular cortex, thalamus, primary somatosensory cortex, secondary somatosensory cortex, amygdala, putamen, and the SLN were included in the analysis. These seeds were identified from previously published fMRI studies in chronic pain as listed in Supplementary Table 1^{3, 22, 32, 33}. Seed based ROI analyses were performed as in our previous studies^{28, 29}. Analysis steps included the addition of white matter and cerebrospinal fluid signals, as well as realignment parameters as covariates of no interest. A band pass filter (frequency window: 0.01–0.1 Hz) was applied to remove linear drift artifacts and high frequency noise. First level analyses were performed correlating seed region signal with voxel signal throughout the whole brain, thereby creating seed region-to-voxel connectivity maps. Connectivity maps were then used for second level (random effects) analyses with patient age as a covariate of no interest. Reported results were identified as significant at a Familywise error rate (FWE) cluster level corrected $p < 0.05$ derived from an uncorrected voxel level threshold of $p < 0.001$. For regions not meeting significance on the whole brain level, we used small volume correction (SVC) with a FWE cluster level corrected $p < 0.05$ derived from an uncorrected voxel level threshold of $p < 0.001$.

Independent component analysis

Group independent component analysis (ICA) was done using GIFT (Group ICA of Fmri Toolbox)⁹ and component estimates were validated using ICASSO²⁷ for 10 iterations. The number of independent components was limited to 20 to minimize splitting into subcomponents. Subject specific spatial maps and time courses were back reconstructed using spatio-temporal regression or dual regression option available in GIFT. Spatio-temporal regression (STR) regresses (i) the original subject data onto the aggregate ICA spatial maps to estimate subject specific time courses for each component (ii) then regresses the individual subject data back onto these time course matrices to estimate subject specific

spatial maps. Thus the original aggregate spatial map and the later estimated spatial maps represent the best approximation for the individual subject specific component maps. Group-level second level analysis was performed to link the differences in intrinsic resting state network connectivity networks among low vs. high pain groups using a two-sample t-test analysis in SPM8. As with our seed based connectivity approach, we performed both whole brain and SVC corrected analyses. Significant regions were identified at $p < 0.05$ FWE cluster level correction derived from an uncorrected voxel level threshold of $p < 0.001$.

Correlation with fetal hemoglobin

To further study the implications of brain connectivity changes on clinical measures, Fisher transformed r-values from significant seed based connectivity results and z-scores from significant ICA results were extracted and analyzed in SPSS v22. Scatter plots were inspected for outliers and connectivity r- or z-values were entered into a bivariate correlation with fetal hemoglobin percentage for the low -pain group. For this last analysis we excluded patients who were on chronic blood transfusion as chronic red cell transfusion will affect fetal hemoglobin levels. Results were deemed significant at $p = 0.05$.

Results

Patient demographics

Twenty five adolescents and young adults (ages 12–22 years) participated in the study (Table 1). Three individuals were not included in the analysis due to poor quality of the fMRI images. All patients in the low pain group ($n=14$) had sickle cell anemia while the frequent pain group ($n=8$) included one hemoglobin SC and one S-beta plus thalassemia patient. Patients in the high pain group were older than the low pain group but the difference was not statistically significant (18.5 years vs. 17 years; $P=0.3$). More than 50% of the patients in both groups reported to be on hydroxyurea therapy however the fetal hemoglobin (HbF) % was significantly higher in the low pain group (12.3 ± 9.8 vs 3.8 ± 2.3 ; $P=0.007$). Mean corpuscular volume was not different between the groups among the patients who were on hydroxyurea. As anticipated, the median (range) pain visits to ED (1.5 (1–7) vs. 0 (0–1); $P=0.028$) and hospitalizations (8 (3–11) vs. 0 (0–2); $P=0.0001$) were significantly higher in the high pain group (Table 1).

All participants were in the steady state of health during neuroimaging and none were experiencing an acute episode of pain. None of the participants had an obvious source of pain such as avascular necrosis of hip or leg ulcers. To characterize the pain experience of the patients in the high pain group further, we reviewed the most recent clinic visit note which occurred within 2–3 weeks of the imaging visit. Four of 8 patients in the high pain group had reported pain scores of 3–8 on a scale of 0–10, three patients reported intermittent pain in various areas while one patient reported frequent headaches. As per our clinical practice all participants had access to oral oxycodone for treating episodes of pain at home. Three participants in the high pain group were on long acting opioids which were not stopped for the neuroimaging.

Seed-based Region of Interest (ROI) analysis

Group differences from the seed-based ROI analysis resulted in the high pain group displaying greater brain connectivity compared to the low pain group in the following regions (seeds in italics with seed references following): the *dorsal anterior cingulate cortex* and the right precuneus ($P_{FWE} = 0.001$); the *secondary somatosensory cortex* and the left precuneus [$SVC P_{FWE} = 0.002$;¹⁸]; the *inferior parietal lobule* and the mid cingulate cortex [$SVC P_{FWE} = 0.012$;¹⁷]; and the *right posterior insular cortex* and the right primary somatosensory cortex [$SVC P_{FWE} = 0.001$;³⁵] (Figure 1A, Table 2). In general these regions have been shown to be active when humans either experience experimental pain stimuli or have spontaneous chronic pain^{22, 33}. In contrast, the low pain group was found to have increased connectivity between the *left primary somatosensory cortex* and the subgenual anterior cingulate cortex when compared to the high pain group [$SVC P_{FWE} = 0.005$;⁴² (Figure 1B, Table 2)]. Interestingly activity in this subgenual anterior cingulate region is associated with endogenous analgesic mechanisms⁴.

Independent component analysis

From the resting state data, 7 independent components were identified from group ICA. These networks were identified as the: default mode network (DMN), salience network (SLN), sensory motor network (SMN), left frontoparietal control network (IFCN) and right frontoparietal control network (rFCN), medial visual network (MVN), and lateral visual network (LVN) (Supplementary Figure 1).

The DMN showed greater negative connectivity (anti-correlation) to the anterior insula in the low pain group as compared to high pain group (Figure 2A, Table 2; $SVC P_{FWE} < 0.05$). Interestingly this insular region showed greater pain evoked activations in chronic pain patients diagnosed with fibromyalgia¹³. In contrast, the SLN showed less negative connectivity to perigenual anterior cingulate cortex (pgACC) in the low pain group as compared to high pain patients (Figure 2B, Table 2; $SVC P_{FWE} = 0.008$). This region, when activated during placebo, has been previously shown to inhibit pain⁴.

Fetal hemoglobin and connectivity patterns

In an exploratory analysis, we investigated whether fetal hemoglobin levels within the low pain group may be associated with brain connectivity. Since chronic blood transfusions may alter the levels of fetal hemoglobin, we only examined this relationship in the low pain group patients who were not receiving chronic blood transfusions ($n=9$). The high pain group was not included in this analysis due to the inability to differentiate if the altered brain connectivity was related to high pain burden or low fetal hemoglobin. Interestingly, the low pain group displayed a negative correlation between HbF % and connectivity between the secondary somatosensory (SII) cortex and left precuneus ($r = -0.739$, $p = 0.023$ Figure 3A) i.e. patients displaying decreased connectivity between the SII-precuneus had higher fetal hemoglobin values. In contrast from our ICA connectivity analysis, the low pain group had a positive correlation between the level of connectivity between SLN to pgACC and fetal hemoglobin levels ($r = 0.67$, $p = 0.05$ Figure 3B) i.e. less anti-correlation between the SLN and the pgACC was associated with higher fetal hemoglobin levels. No other significant

correlations were found between brain RSN connectivity and the percent of fetal hemoglobin in either group.

Discussion

We report resting state brain functional connectivity analyses and the association with hospitalizations for pain in SCD. To our knowledge this is the first investigation linking brain connectivity patterns to pain in this population. SCD patients with higher rates of pain displayed greater pro-nociceptive connectivity between the dorsal/mid cingulate cortex to DMN structures including the precuneus and inferior parietal lobule. In contrast, SCD patients with infrequent pain showed greater connectivity between a sensory cortex region and the sub-genual cingulate cortex. These patients also showed less anti-correlation between the salience network and the perigenual anterior cingulate, another anti-nociceptive structure. In summary, patients with lower rates of hospitalization for pain displayed less pro-nociceptive connectivity and also greater anti-nociceptive connectivity while patients with higher rates of hospitalization for pain displayed opposite connectivity patterns.

The rostral peri- and subgenual areas of the cingulate have been known for some time to modulate pain perception⁴. In particular, these regions are thought to be involved in analgesia during “top down” analgesic processes such as the placebo effect^{39, 44}. These areas are rich in endogenous opioid receptors which appear to be activated during placebo analgesia. We hypothesize that endogenous analgesic activity may “protect” or serve to lessen the development of chronic pain in SCD. In contrast, pro-nociceptive patterns of connectivity are seen in patients with fibromyalgia, such as connectivity between the DMN and pain regions including the insula and dorsal/anterior cingulate is indicative of greater clinical pain^{29, 33}. As both pharmacologic²⁴ and non-pharmacologic³² interventions that reduce DMN-insula connectivity have been associated with improved analgesia, interventions that target this aberrant pathology may also have therapeutic implications for this population.

Fetal hemoglobin, a known modifier of SCD, plays a protective role³⁴. Hydroxyurea is an effective therapy in reducing complications of SCD including severe painful VOs. One of the main proposed mechanisms of hydroxyurea includes increased production of HbF which in turn reduces polymerization of sickle hemoglobin and vaso-occlusion¹². In our study, while the proportion of patients reported to be on hydroxyurea was not different between the groups, the patients with infrequent hospitalizations overall had significantly higher fetal hemoglobin levels. We are unable to comment on the reasons for differences in hemoglobin F levels between the groups which may reflect noncompliance with hydroxyurea; however, pharmacogenetic differences cannot be ruled out^{5, 40}. Interestingly high fetal hemoglobin levels, which have been associated with lower pain rates in SCD patients, were also negatively correlated with connectivity between the secondary somatosensory (SII) cortex and left precuneus and positively correlated with connectivity between SLN to pgACC. While we could not discern if these connectivity patterns are causally related to higher fetal hemoglobin or vice versa, the correlation between hydroxyurea associated increases in fetal hemoglobin in the low pain group and greater anti-nociceptive connectivity patterns deserves further investigation.

These findings may have important implications for future studies of pain in SCD. The current state of knowledge of SCD pain suggests that multiple mechanisms such as central sensitization, peripheral sensitization and opioid-induced hyperalgesia may contribute to a pain experience of an individual and any combination of these processes may be at play at a given time^{15, 37}. Our findings support the possibility of central mechanisms playing a role in high pain burden in SCD. The association between hydroxyurea/ higher fetal hemoglobin and connectivity to anti-nociceptive activity also raises question if early initiation of hydroxyurea therapy could prevent neuroplastic changes speculated to be associated with chronic SCD pain.

Our findings should be interpreted with caution. Limitations of this study include small sample size, convenience sampling, the lack of formal evaluation for daily pain burden and psychological comorbidities. We utilized hospitalization for pain in the preceding 12 months as a marker of pain burden (number of daily pain days) since hospitalization for pain have been shown to correlate with the ambulatory pain intensity scores which in turn correlate with daily pain days.^{19, 36}. In addition one of our concerns includes the impact of sickle hemoglobin on the fMRI signal. While Zou et al. showed no relationship between hemoglobin concentration, resting cerebral blood flow and BOLD signal amplitude, they did observe diminished BOLD responses in children with sickle cell anemia compared to non-SCD children with posterior fossa tumor⁴³. To address this concern, we specifically compared fMRI connectivity and pain burden among SCD patients, wherein similar effects of sickle cells on the BOLD response would be shared in both high and low pain groups. However, the impact of sickle hemoglobin cannot be conclusively established in this pilot study as some of the patients were on chronic red cell transfusion even though the hemoglobin concentration was not different between the groups. Despite the limitations of present study, we propose that fcMRI should be explored as an effective methodology to investigate pain in a larger SCD population. Functional connectivity may have utility as a marker to evaluate therapies as it has been for some non-SCD pain conditions²⁴.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Perspective

Altered connectivity patterns associated with higher pain experience in patients with sickle cell disease suggest a possible role of central mechanisms in sickle cell pain. Resting state brain connectivity studies should be explored as an effective methodology to investigate pain in sickle cell disease.

Highlights

- Wide variability exists in the frequency of hospitalizations for pain among patients with sickle cell disease.
- This pilot study explored the association between hospitalizations for pain and intrinsic resting state brain connectivity in the steady state of health.
- Patients with frequent hospitalizations for pain showed patterns of increased pronociceptive and decreased antinociceptive brain connectivity.

Figure 1.

Differences in brain connectivity patterns between sickle cell disease patients with high or low rates of pain requiring hospitalization using seed to whole brain connectivity analyses. A) Regions where the high pain group show greater connectivity as compared to the low-pain group. In general, the high pain group displayed greater connectivity between pro-nociceptive structures such as the insula and secondary somatosensory cortex. Greater connectivity was also seen in the high pain group between these pro-nociceptive pain structures and DMN regions (bilateral precuneus and inferior parietal lobule). B) In contrast,

the low pain group showed greater connectivity between the primary somatosensory cortex and an antinociceptive region of the cingulate (subgenual). Bar graphs on the right show mean difference in connectivity seen between the groups.

Figure 2.

Differences in resting brain network connectivity between sickle cell disease patients with high and low rates of pain using independent component analysis. (Upper panel) Patients in the low pain group display greater negative DMN connectivity (anti correlation) to the anterior insula as compared to the high pain group. (Lower panel) High pain patients show greater anti correlation between the SLN and an anti-nociceptive region of the anterior cingulate. Bar graphs on right show mean difference in connectivity seen between the groups.

Figure 3.

Fetal hemoglobin levels are associated with specific brain connectivity patterns in non-transfused SCD patients in the low pain group. A) Greater anti-correlation between the secondary somatosensory cortex and precuneus is associated with higher fetal hemoglobin levels. Patients displaying less pro-nociceptive connectivity have greater fetal hemoglobin levels. B) Greater connectivity between the SLN and the perigenual anterior cingulate is associated with higher levels of fetal hemoglobin. Patients with greater anti-nociceptive connectivity patterns have higher fetal hemoglobin levels.

Table 1

Demographics and characteristics of the study participants

Participant Characteristics		P	Low pain hospitalization group (2 hospitalizations for pain in preceding 12 months) (n=14)	High pain hospitalization group (3 hospitalizations for pain in preceding 12 months) (n=8)
Median age (range) in years		0.33	17 (12–20)	18.5 (13–22)
Laboratory Parameters	Gender	0.60	9 (64%)	6 (75%)
	Females, n (%)			
	Hemoglobin, (g/dL)	0.54	9.26 ($\pm$ 1.2)	8.83 ($\pm$ 1.7)
	Absolute Reticulocyte count, (k/mcL)	0.73	320 ($\pm$ 170)	288 ($\pm$ 231)
	Hemoglobin F, (%)	0.007	12.3 ($\pm$ 9.8)	3.8 ($\pm$ 2.3)
Disease modifying therapy	MCV (fL) (only in patients prescribed hydroxyurea)	0.23	93.7 ($\pm$ 10.8)	84.9 ($\pm$ 10.8)
	n (%)	0.74	8 (57%)	4 (50%)
	Hydroxyurea	0.25	23 ($\pm$ 3.1)	27 ($\pm$ 5.5)
	Dose (mg/Kg/day)			
Number of health care utilization visits for pain in preceding 12 months	Chronic red cell transfusion, n (%)	0.24	5 (35%)	1 (12%)
	Visits to the emergency department; median (range)	0.028	0 (0–1)	1.5 (1–7)
	Hospitalizations; median (range)	0.0001	0 (0–2)	8 (3–11)

All values are in mean $\pm$ SD unless specified otherwise

Table 2
Differences in resting state connectivity in SCD patients with high and low pain hospitalizations

Seed/Network	Connected Region	Cluster Size (number of voxels)	Z scores	P-value (FWE)	MNI Coordinates		
					X	Y	Z
Seed-based ROI Results							
<u>High Pain > Low Pain</u>							
	Anterior cingulate cortex	550	5.05	0.001	38	-66	40
	Right SII	166	4.14	0.002*	4	-62	42
	Right IPL	34	3.64	0.012*	-2	-12	42
	Right posterior IC	185	4.13	0.001*	60	-20	44
<u>Low Pain > High Pain</u>							
	Left SI	67	3.88	0.005*	6	40	-8
Independent Component Analysis Results							
<u>High Pain > Low Pain</u>							
	Default Mode Network	43	3.97	0.016*	-37	25	1
<u>Low Pain > High Pain</u>							
	Saliency Network	97	4.65	0.008*	-11	33	25

* Small volume correction.

ACC = anterior cingulate cortex, FWE = familywise error, IC = insular cortex, IPL = inferior parietal lobule, SI = primary somatosensory cortex, SII = secondary somatosensory cortex, High Pain = high pain hospitalization group, Low Pain = low pain hospitalization group