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Original experimental

Salience, central executive, and sensorimotor network functional connectivity alterations in failed back surgery syndrome

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HIGHLIGHTS

- Failed back surgery syndrome (FBSS) is a chronic pain condition.
- Brain functional connectivity (FC) was altered in three resting state networks in FBSS.
- Alterations were seen in the salience, central executive, and sensorimotor networks.

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ABSTRACT

Objective: This study examined the altered patterns of functional connectivity in task-positive resting state networks in failed back surgery syndrome (FBSS) patients compared to healthy controls using functional magnetic resonance imaging (fMRI). This work stems from a previous study in which alterations in the task-negative default mode network were investigated.
Design: Participants underwent a 7-minute resting state fMRI scan in which they lay still, with eyes closed, in the absence of a task.
Setting: Scanning took place at the National Research Council's 3 Tesla MRI magnet in Winnipeg, Canada.
Subjects: Fourteen patients with FBSS and age- and gender-matched controls participated in this study. Three patients were removed from the analyses due to image artefact ($n = 1$) and effective pain treatment ($n = 2$). Eleven patients (5 female, mean age 52.7 years) and their matched controls were included in the final analyses.
Methods: Resting state fMRI data were analyzed using an independent component analysis, yielding three resting state networks of interest: the salience network (SN), involved in detection of external stimuli, central executive network (CEN), involved in cognitions, and sensorimotor network (SeN), involved in sensory and motor integration. Analysis of Variance contrasts were performed for each network, comparing functional connectivity differences between FBSS patients and healthy controls.
Results: Alterations were observed in all three resting state networks, primarily relating to pain and its processing in the FBSS group. Specifically, compared to healthy controls, FBSS patients demonstrated increased functional connectivity in the anterior cingulate cortex within the SN, medial frontal gyrus in the CEN, and precentral gyrus within the SeN. FBSS patients also demonstrated decreased functional connectivity in the medial frontal gyrus in the SeN compared to healthy controls. Interestingly, we also observed internetwork functional connectivity in the SN and SeN.
Conclusions: FBSS is associated with altered patterns of functional connectivity in the SN, CEN, and SeN. Taken together with our previous work, this reveals that a chronic pain condition can have a dramatic effect on the connectivity of multiple resting state networks.
Implications: These data suggest that a chronic pain condition—FBSS—is associated with disruptions to networks of functional connectivity in brain areas that are involved in numerous functions, including pain processing, sensation, and movement. It is possible that the alterations in these networks may contribute to other common chronic pain comorbidities, such as disrupted cognitions or anxiety. Previous research shows that during experimentally-induced pain, these networks can return to initial levels of functioning, indicating that these functional alterations are likely not permanent.

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1. Introduction

Failed back surgery syndrome (FBSS) is a complex chronic pain phenomenon that is often loosely defined as upper or lower back pain resulting after spinal surgery (see [1] for review). Although countless studies have been done to determine the neural correlates of pain in general, few have considered chronic pain alone, in the absence of noxious stimuli, or a task. In our previous work [2], we aimed to identify neural connectivity differences in FBSS patients compared to healthy controls in the absence of a task-based functional magnetic resonance imaging (fMRI) experiment using resting state fMRI. Resting state fMRI is used to identify brain regions that spontaneously and coherently fluctuate in activity (i.e., functional networks) while the participant is at rest, given the simple instructions to lie still with eyes closed, remaining awake. We previously found alterations in regions within, and pain-related regions outside of the scope of one network, the task-negative (i.e., anti-correlated with task performance) default mode network (DMN); however, there are networks of interest in addition to the DMN, namely the salience network (SN), the central executive networks (CEN), and the sensorimotor network (SeN).

Pain is considered to be a salient triune experience, comprised of sensory, affective, and cognitive components [3]. A resting state network associated with the integrations of these modalities is of interest in a chronic pain population; the SN is such a network [4]. The SN is comprised of the anterior cingulate cortex (ACC) and anterior insula [5,6]. Complementing this network is the CEN, a key network for performing cognitively demanding tasks; the dorsolateral prefrontal cortex (dlPFC) is a key region in this network, involved in modulating pain processing [7]. The final network of interest, the SeN, is fairly straight-forward in that it is responsible for motor and sensory functions and comprises the precentral and postcentral gyri, and the supplementary motor area [8]. This network has a fairly intuitive relationship to chronic pain as the most familiar component of pain is the sensory one. Stemming from our previous work, we have investigated three task-positive networks (i.e., correlated with task performance; SN, CEN, and SeN) of interest from our previous study with FBSS patients.

Although data exist with the DMN, it is important to broaden our understanding of the neural underpinnings of FBSS. The aim of the current study was to further examine the patterns of functional connectivity in additional resting state networks in FBSS patients.

2. Methods

2.1. Participants

Fourteen FBSS patients with chronic low back pain were referred by their physician from the neurosurgery department, but after removal of 3 patients (1 due to image artefacts, 2 for effective pain treatment), 11 patients (6 male, 5 female, mean age 52.7 ± 14.3 years, age range 33–72 years) remained. Eleven age- and gender-matched healthy controls (mean age 53.5 ± 15.0 years, age range 31–72 years) were also recruited. See [2] for information regarding inclusion and exclusion, duration of pain, medications used, and behavioural data (including depression, anxiety, and pain scores). All participants provided written informed consent prior to participation. The study was approved by the National Research Council Canada's Research Ethics Board, as well as the University of Manitoba's Research Ethics Board.

2.2. Data acquisition

The raw data in the present study were acquired for the previous report on the DMN [2]. As in the previous report, participants were instructed to lie in the MRI scanner with their eyes closed, remaining awake. Participants were not given further instruction as to what to think about. Images were collected using a homogeneous birdcage coil on a whole-body 3T Siemens TRIO MRI scanner (Siemens, Erlangen, Germany). The high-resolution anatomical (T1-weighted) images were collected using an MP-RAGE spoiled gradient echo sequence (TR/TE = 1900/2.2 ms, slice thickness = 1 mm with 0 gap between slices, 256×256 mm matrix, field of view [FOV] = 24 cm, and in plane resolution of 0.94×0.94 mm). Functional data were collected using a whole brain echo planar imaging (EPI) sequence (T2-weighted) in 140 volumes with the following parameters: 3 mm slice thickness, 0 gap, TR/TE = 3000/30 ms, flip angle = 90°, 64×64 matrix, FOV = 24 cm.

2.3. Data analysis

Data were preprocessed and analyzed as reported in our previous study [2] using BrainVoyager QX software (Brain Innovation, BV, Maastricht, The Netherlands), with the exception of selecting the CEN (left and right), SN, and SeN for the comparison between FBSS patients and healthy controls. Functional data were preprocessed using slice scan time correction, a trilinear/sync interpolation 3D motion correction, and temporal filtering. Motion parameters (i.e., translation and rotation in the x, y, and z planes) were regressed out of the data. Functional data were then co-registered with the structural data and spatially transformed to Talairach space. Individual-level data were run through an independent components analysis (ICA), followed by a self-organizing group ICA with 20 final ICs representing all participant data. ICA analysis was used to reduce bias as it takes functional connectivity from the entire resting state time series into account, and this analysis was done for the whole brain to reduce any bias introduced by pre-selecting regions of interest. From here, the SN, left and right CEN, and SeN components were identified. The left and right CEN were combined for subsequent analyses. Group comparisons were made separately for each of the three resulting components, comparing the functional connectivity between FBSS patients and healthy controls. Resulting contrast maps ($p < 0.05$) were subject to a cluster threshold estimator using Monte Carlo simulations (1000 iterations) to correct for multiple comparisons. Cluster data (peak and centre of gravity coordinates, p-values, and cluster size) were exported for each corrected map.

3. Results

3.1. Salience network

The two largest significant clusters in the SN were for the FBSS patients greater than the healthy controls contrast and had peak voxels in the ACC, and the thalamus, extending to the insula (Table 1 and Fig. 1A). The contrast for healthy controls greater than FBSS patients included a cluster in the cingulate gyrus, and bilateral clusters in the angular/supramarginal gyri.

3.2. Central executive network

For the CEN, only two significant clusters of functional connectivity were observed (Table 1). One cluster was observed in the cerebellum for the contrast in which healthy controls were greater than FBSS, and the other in the medial frontal gyrus (MFG), extending to the subgenual region of the ACC for the FBSS greater than healthy controls contrast (Fig. 1B).