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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).

Table 1
Peak neural functional connectivity differences for healthy controls and failed back surgery syndrome patients for the central executive, salience, and sensorimotor resting state networks.

	Region		Peak Talairach coordinates				*P*-value
		BA	*X*	*Y*	*Z*	Voxels	
Salience network							
HC > FBSS	Angular gyrus		38	−56	36	1286	<0.001
	Cingulate gyrus	32	−4	22	39	1071	<0.001
	Supramarginal gyrus		−52	−53	36	2618	<0.001
FBSS > HC	Thalamus		17	−8	12	6106	<0.001
	Anterior cingulate gyrus	32	5	40	0	10,504	<0.001
Central executive network							
HC > FBSS	Cerebellar tonsil		−28	−53	−36	1489	<0.001
FBSS > HC	Medial frontal gyrus	10	−7	37	−9	1289	<0.001
Sensorimotor network							
HC > FBSS	Medial frontal gyrus	10	5	61	−6	2162	<0.001
FBSS > HC	Precentral gyrus		−16	−20	66	1000	<0.001
	Putamen		−25	1	0	2600	<0.001

FBSS = failed back surgery syndrome; HC = healthy controls; BA = Brodmann area.

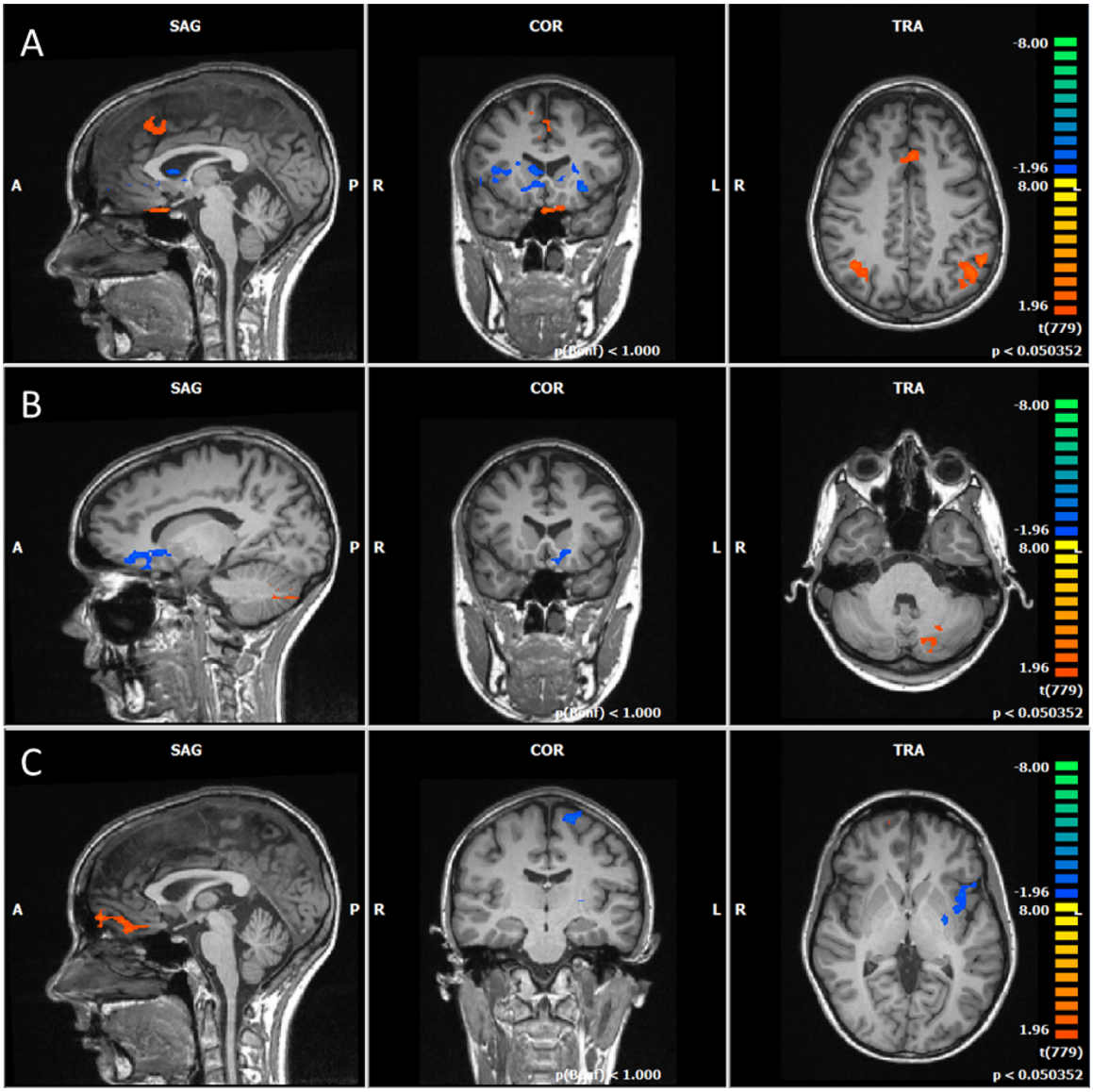

Fig. 1. Contrasts for HC > FBSS for (A) salience, (B) central executive, and (C) sensorimotor resting state networks in Talairach space. Orange regions indicate that functional connectivity is greater for healthy controls while blue regions indicate functional connectivity is greater for FBSS patients. All contrasts were corrected for multiple comparisons using Monte Carlo simulations. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.3. Sensorimotor network

Significant differences were also found in the SeN; FBSS patients had greater functional connectivity peaking in the precentral gyrus, extending to the postcentral gyrus, and the putamen, extending to the insula (Fig. 1C), while healthy controls had greater functional connectivity in the MFG.

4. Discussion

Data from the current study demonstrate that patients with FBSS have altered patterns of functional connectivity in three resting state networks: the SN, CEN, and SeN. Functional connectivity appears to be relatively consistent across these three networks, with increased functional connectivity in pain-related brain structures in the FBSS group, compared to healthy controls (see Table 1).

In FBSS patients, increased functional connectivity in the ACC within the SN may be explained due to the role of the ACC in emotional control and attention [9,10]; FBSS patients may have an enhanced awareness of the emotional aspect of pain [11]. As previously mentioned, the SN is involved in the attention of salient stimuli and the integration of this information. The current data supports the idea that the increased connectivity in the sensory and pain processing regions, such as the ACC and thalamus, are enhanced in FBSS patients due to the salient nature of pain associated with their condition.

In the SeN, we also observed increased functional connectivity in the precentral gyrus, extending to postcentral gyrus in the FBSS compared to the healthy controls. This finding logically follows from the role of the SeN and the key nodes that comprise this network. The SeN is comprised of the pre- and postcentral gyri and is involved in motor and sensory functions, specifically, the precentral gyrus is involved in motor functions while the postcentral gyrus is recruited for sensory functions [12–14]. Increased functional connectivity in the pre- and postcentral gyri suggests that sensorimotor integration may be heightened in FBSS patients.

Altered patterns of connectivity within the MFG were observed in both the CEN and SeN. However, in the CEN, the FBSS group revealed increased functional connectivity whereas in the SeN, the healthy controls demonstrated increased functional connectivity. However, upon closer examination, the centre of gravity of the MFG cluster in the CEN resides in the ACC (see Fig. 1). Further supporting this claim, 477 out of the 1289 voxels were contained within the ACC, while only 277 were contained within the MFG. Therefore, consistent with the patterns of functional connectivity observed in the SN, there is evidence to suggest that FBSS patients may have heightened experiences of the affective component of pain. The MFG is a region that makes up the prefrontal cortex with functions implicated in executive control and cognitive tasks [15]. The decreased connectivity observed in the MFG in FBSS within the SeN could be interpreted as downregulated cognitive processing [16], due to decreased resources available because of the increased load that pain places on the SeN.

In our previous work, results revealed that FBSS patients had an overall reduction in the DMN [2]. Interestingly, increased functional connectivity within the DMN was found in regions that are not part of the DMN, such as the anterior insula and dlPFC [2]. These regions are interesting because they are associated with pain processing but are not typically functionally connected with the DMN, suggesting a cross-talk effect of the DMN with other regions that are involved in processing pain [17–19]. Although we largely observed alterations within the networks relating to pain and its processing, we also observed some apparent between-network connectivity as well. Within the SN, there was decreased functional connectivity for the FBSS group within the angular/supramarginal gyri. Interestingly, the angular gyrus has been proposed as part of the DMN [20], which generally showed decreased functional connectivity in our previous study for the FBSS group [2]. We also observed functional connectivity differences in the SeN outside of the regular regions of this network in the MFG, as previously discussed, and in the putamen cluster that extends to the insula. The MFG is typically contained within the CEN while the insula belongs to the SN. These results support the presence of internetwork functional connectivity that can arise in a chronic low back pain condition, as recently reported in work by others [21]. In gaining understanding of the alterations in and between these networks, the mechanisms that underlie other common chronic pain comorbidities, such as disrupted cognitions or anxiety, may be elucidated.

Although the results of this study at first appear bleak—FBSS patients have altered brain connectivity—caution should be taken when interpreting these results. Research has shown that functional connectivity can be restored to “normal” patterns with the use of mindfulness-based interventions [22], cognitive-behavioural therapy [23], or surgery [24].

This study is limited by its relatively small sample size; however, the results obtained were robust ($p < 0.001$ for all data), even after corrections for multiple comparisons using Monte Carlo simulations (1000 iterations). Additionally, to aid in the external validity of these results, a random effects ANCOVA was run at the group level to control for differences between subjects.

5. Conclusions

In conclusion, our study builds on previous reports of functional connectivity alterations in FBSS [2]. In comparison to healthy controls, FBSS patients demonstrate alterations in the SN, CEN, and SeN. Specifically, regions involved in pain and pain processing in the FBSS group were shown to have increased functional connectivity. Cross-network functional connectivity appears to be prevalent across both task-negative, and task-positive resting state networks in at least one chronic pain population. This aids our overall understanding of FBSS and how inherently stable networks of functional connectivity are disrupted in a chronic pain condition.

Ethical issues

Informed consent was required and was obtained by all participants in this study. Ethic board approval was obtained for this study. This study protocol was not registered.

Conflicts of interest

The authors declare no conflicts of interest.

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