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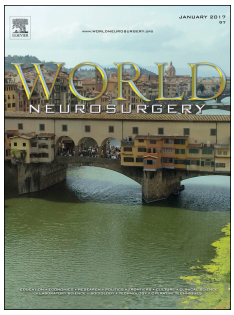

Resting-State fMRI Functional Connectivity of the Brain is Associated with Altered Sensorimotor Function in Patients with Cervical Spondylosis

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Resting-State fMRI Functional Connectivity of the Brain is Associated with Altered Sensorimotor Function in Patients with Cervical Spondylosis

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data, and interpretation of data; (2) drafting and revising the article; and (3) final approval of the version to be submitted.

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ABSTRACT

Objectives: To determine the relationship between functional connectivity using resting-state fMRI and neurological impairment in patients with cervical spondylosis and healthy controls.

Methods: A total of 24 patients with cervical spondylosis with or without myelopathy and 17 neurologically intact, healthy volunteer subjects were prospectively enrolled in a cross-sectional study involving observational MRI and evaluation of neurological function using the modified Japanese Orthopedic Association (mJOA) score. Seed-to-seed connectivity and seed-to-voxel connectivity were performed on fMRI data were performed using a general linear model of connectivity with respect to age and mJOA.

Results: Increased functional connectivity was observed with increasing neurological impairment in patients with cervical stenosis within sensorimotor areas, including precentral gyrus, postcentral gyrus, and supplemental motor regions (SMA), using both seed-to-seed and seed-to-voxel analyses. The anterior cingulate showed increasing connectivity with the SMA, thalamus and cerebellum with increasing neurological function. Similarly, the thalamus, cerebellum, and putamen presented with increasing connectivity to both the bilateral precuneus and posterior cingulate with increasing mJOA.

Conclusions: Patients with cervical spondylosis exhibiting neurological impairment experience similar changes in brain connectivity to patients with chronic traumatic spinal cord injury. Results suggest an increase in functional connectivity within sensorimotor regions with increasing neurological impairment decreased connectivity between the cerebellum, putamen, and thalamus to the anterior and posterior cingulate as well as frontal lobe regions.

INTRODUCTION

Cervical spondylosis (CS) is a common occurrence among the middle aged and elderly population, with an occurrence of around 80% in the total population[1]. Cervical spondylotic myelopathy (CSM), or spondylosis resulting in functional impairment, can occur with a wide variety of symptoms including problems in gait, hand coordination, and sensory changes. Static and dynamic forces exerted on the spinal cord, along with ischemia resulting from chronic vascular insufficiency, can cause progressive spinal cord damage in CSM patients[2]. Therefore, CSM is often considered a chronic condition that can result in long-term degenerative changes within the spinal cord.

As the fibers within the spinal cord originate or terminate within the brain, injury to the spinal cord can cause long-term changes in brain function. Consistent with the hypothesis that CS can alter brain function, studies using motor task-based functional magnetic resonance imaging (fMRI) have revealed increased activation within cortical motor regions in patients with CSM when compared to healthy controls [3,4]. Studies in traumatic spinal cord injury patients using resting-state functional magnetic resonance imaging (rs-fMRI), which leverages low frequency oscillations of blood oxygenation level dependent (BOLD) signal to measure patterns of brain activity at rest, have suggested an overall decrease in functional connectivity in spinal cord injury patients compared with neurologically intact participants; however, investigators have also noted localized increases in connectivity between sensorimotor regions and subcortical areas (e.g. thalamus) occurs in both subacute [5,6] and chronic injury [7,8], presumably due to a need for increased efferent drive or altered brain plasticity to compensate for injury to the cord.

In the current study, we extend our previous work by looking at differences in functional connectivity in patients with CS with and without functional impairment along with a cohort of

neurologically intact participants. We hypothesize that patients with CS will exhibit increasing brain functional connectivity within sensorimotor networks and decreased functional connectivity between subcortical regions and frontal lobe executive regions proportional to the degree of neurological impairment.

METHODS

Patient Population

A total of 24 patients with cervical spondylosis with or without myelopathy were prospectively enrolled in a cross-sectional study involving observational MRI and evaluation of neurological function. Patients were recruited from an outpatient neurosurgery clinic, and each had at least moderate cervical stenosis on standard cervical MRI, defined as no visible cerebrospinal fluid signal around the spinal cord at the site of maximal compression. All patients signed Institutional Review Board (IRB) approved consent forms, and all analyses were done in compliance with the Health Insurance Portability and Accountability Act (HIPAA). The cohort included 19 males and 5 females, with a mean age of 60 years (range 40 to 80). The modified Japanese Orthopedic Association (mJOA) score was used as a measure of neurological function.[9] The mean mJOA score for the patient cohort was 15.5 (range 9 to 18). Of the 24 patients, 6 were asymptomatic, while 18 presented with symptoms (mean mJOA of 14.7, mean symptom duration of 6 months). Asymptomatic patients initially presented with neck pain and were referred to the outpatient neurosurgery clinic by their primary care physician to evaluate the cervical stenosis visualized on their MRI of the spine. A cohort of 17 neurologically intact, healthy control (HC) volunteer subjects (11 males and 6 females with average age of 40 years, range 25-62) underwent the same MRI protocol for comparison. There was a significant difference in age between the groups (t-test, $P<0.001$), but not in body mass index (BMI, t-test, $P=0.3$) or sex (Chi-squared test, $P=0.3$). Patient and volunteer demographics are summarized in **Table 1.**

Resting-State fMRI Acquisition and Post-Processing

All functional MR images were collected on a Siemens Prisma 3T MR scanner (Siemens Healthcare, Erlangen, Germany) with a repetition time (TR)=1500ms; echo time (TE)=30ms; slice thickness of 4mm with no interslice gap; field-of-view (FOV) of 245mm with an acquisition matrix of 162x81 (50% phase encode sampling) for a voxel size of 1.5mm x 1.5mm x 4mm, interleaved acquisition; flip angle of 90°; parallel imaging via CAIPIRINHA with a factor of 4. Additionally, a 1mm 3D isotropic MPRAGE sequence was acquired for alignment with functional MRI data using standard acquisition parameters (TE=minimum, TR=1500-200ms, inversion time (TI)=1100-1500ms, flip angle 8-15 degrees, slice thickness = 1mm, FOV=25cm and matrix size of 256x256).

The CONN Toolbox (https://www.nitrc.org/projects/conn) [10] was used for functional connectivity analysis of the brain, which implements functions from the Statistic Parametric Mapping (SPM, http://www.fil.ion.ucl.ac.uk/spm/) toolbox. Because rs-fMRI is interested in low-frequency oscillations (≤ 0.1Hz, but generally lower than 0.08Hz) and because this study used a relatively fast TR (1500ms, or 1.5s), slice-timing correction was not applied as previous studies have suggested negligible effects on rs-fMRI results [11]. Functional realignment (motion correction, 12 degrees of freedom) and unwarping, registration of functional data to the structural volume, and registration of the structural volume to the standardized space defined by the Montreal Neurological Institute (MNI) averaged T1 brain [12] was then performed using the CONN pipeline. Segmentation of structural volumes, which included skull stripping and processing of tissue types (GM, WM, and CSF), were then performed. Artifacts Detection Tool (ART), an SPM package implemented in the CONN pipeline, was used to remove signal intensity spikes and fMRI volumes with excessive motion from the scan, with thresholds for signal intensity outliers set at 9 standard-deviations above or below the mean. A motion limit of

2mm translation and 2° rotation in any direction was also enforced. Spatial smoothing of the functional data was performed using an 8mm full width at half maximum (FWHM) Gaussian kernel. For denoising, signal from the WM, CSF, and motion parameters were regressed from the functional data, as well as being processed with a band-pass filter of 0.008 – 0.09 Hz. The bandpass filter was used to filter the signals to the range of interest to resting-state fMRI and reduce noise due to physiological effects, such as respiration and pulsation, and noise due to scanner drift.

Functional Connectivity Analysis

In order to evaluate associations between functional connectivity (FC) and neurological symptom variable (mJOA), both ROI-to-ROI (also termed seed-to-seed) connectivity and ROI-to-voxel (also termed seed-to-voxel) functional connectivity analyses were performed. ROI-to-ROI analyses implemented general linear models (GLMs) of the functional connectivity with respect to the symptom variable of interest. Age was included as a covariate in the GLMs to account for the effect of age on FC and the difference in age between the CS and HC groups. Seed and target ROIs were selected including the insular cortex (IC), the superior frontal gyrus (SFG), the middle frontal gyrus (MFG), the pre- and postcentral gyri, the superior parietal lobule (SPL), the supplementary motor area (SMA), the anterior and posterior cingulate (AC and PC, respectively), the precuneus, the cuneus, the thalamus, and the putamen. These regions were selected because of their well-documented functional activations in patients with SCI with regards to sensorimotor processing [13], and some of the regions showed structural alterations in patients with CS in a previous study [14]. Associations were evaluated between the functional connectivity and mJOA for all subjects (CS and HC), and for mJOA within the CS cohort

exclusively. Significance was set at P<0.05 (two-sided) for the individual connections with a false discovery rate (FDR)<0.05 based on the number of target regions.

Similar regions of interest were selected for the ROI-to-voxel connectivity analyses. The precentral gyrus, postcentral gyrus, the SMA, the AC, the precuneus, the SFG, the cuneus, the thalamus, the putamen, and the cerebellum, were selected as seed regions. For all ROI-to-voxel analyses, brain structures that were divided into left and right in the atlas were seeded for both sides and the main effect (equal weighting of 0.5 to both structures in the GLM) was used in the experimental design. For the cerebellum, the regions of the Automated Anatomical Labeling (AAL) [15] cerebellar atlas, which is based on parcellations of the cerebellum created by Schmahmann *et al* [16], were used to seed the listed cerebellar regions excluding the vermis (total of 10) for both the left and right hemispheres, to give a total of 20 ROIs and a weighting of 0.05 per ROI for the main effect in the GLM. For all analyses, a P-value threshold of 0.05 was used with two-sided tests. For each analysis there was a total of 10 ROIs, and thus a value of 0.05/10 = 0.005 was used as FDR-corrected P-value threshold for cluster size, wherein permutations of cluster sizes were used to determine the necessary cluster size so that the p-value for the cluster was FDR-corrected at the level of 0.005.

RESULTS

ROI-to-ROI Results

When computing the association between mJOA and FC for ROI-to-ROI results, mJOA presented with both negatively associated (increasing FC with worsening neurological symptoms) and positively associated (decreasing FC with worsening neurological symptoms) connections. For mJOA, the bilateral pre- and postcentral gyri, SMA, and SPL showed decreasing connectivity with the posterior cingulate, while the right putamen displayed increased connectivity with the bilateral thalamus, the left postcentral gyrus, and the left SPL, while the right thalamus had a positive association with the right MFG (**Fig. 1A**). When assessing the ROI-to-ROI connectivity within the CS cohort exclusively, similar trends emerged: the putamen displayed positive associations with the thalamus, and left SPL, while the right thalamus showed positive association with the left thalamus and the right MFG, while displaying a negative association with the left and right postcentral gyri (**Fig. 1B**).

ROI-to-Voxel Results

For the ROI-to-voxel functional connectivity analysis, multiple of the seed regions produced clusters where the functional connectivity was significantly associated with mJOA while accounting for age. For mJOA, results where both the overall group (**Table 2**), which included HC subjects, and the group of CS patients only demonstrated significant results have been displayed together side-by-side. The results were grouped into sensorimotor cortical regions (precentral gyrus, postcentral gyrus, SMA, **Fig. 2**), and subcortical regions (thalamus, putamen, cerebellum, **Fig. 3**). Additionally, regions that showed a significant association with mJOA only in the group that included HC subjects are shown in a separate figure (**Fig. 4**; **Table 3**).

ROI-to-Voxel Results: Sensorimotor Regions

For the sensorimotor regions, both the precentral gyrus and postcentral gyrus displayed a negative association between mJOA and FC (increasing FC with worsening neurological symptoms) with the precuneus and posterior cingulate for the left (**Fig. 2.A,B,D,E.i**) and the right (**Fig. 2.A,B,D,E.j**) hemispheres, which was similar across the HC included and CS patients only groups. The SMA displayed a larger area of negative association between mJOA and FC in the precuneus and posterior cingulate for left (**Fig. 2.C,F.i**) and right (**Fig. 2.C,F.j**) hemispheres in both groups in addition to a regions in the right primary sensorimotor cortex and superior frontal gyrus in both groups (**Fig. 2.C,F.l**), and a region in the left superior frontal gyrus (**Fig. 2.F.m**) and left anterior cingulate (**Fig. 2.F.n**) in the CS patients only group. Additionally, the SMA showed a positive association (increasing FC with increasing mJOA) with the anterior cingulate when including HCs (**Fig. 2.C.k**).

ROI-to-Voxel Results: Subcortical Regions and Additional Regions

For the subcortical seeds, both the thalamus and cerebellum displayed clusters with a negative association between mJOA and FC (increasing FC with worsening neurological symptoms), particularly with the left (**Fig. 3.m**) and right (**Fig. 3.n**) precentral and postcentral gyri in both the HC Included and CS patients only groups. The thalamus and cerebellum also presented with a significant positive association (decreasing FC with worsening neurological symptoms) with the anterior cingulate, which was larger for the thalamus (**Fig. 3.A,D.j** and **A,D.l**,) than for the cerebellum (**Fig. 3.C,F.j** and **F.l**) for both groups. Additionally, all three structures (the thalamus, cerebellum, and putamen) presented with a significant positive

association between mJOA and the bilateral precuneus and posterior cingulate (**Fig. 3.i,k**) for both groups. The Putamen displayed a large positively associated area around the pre- and postcentral gyri (**Fig. 3.B,E.o** and **B,E.p**, respectively).

For the additional cortical areas that showed associations only in the HC Included group, the superior frontal gyrus (SFG) displayed a negative association between mJOA and FC (increasing FC with worsening neurological symptoms) with the left anterior cingulate (**Fig. 4.A.i**) and with the right SMA and precentral gyrus (**Fig. 4.A.j**). The precuneus displayed a negative association with the left and right precentral and postcentral gyri (**Fig. 4.B.k** and **B.j**, respectively).

DISCUSSION

There has been an increasing interest in the upstream cerebral functional alterations that are induced within the motor network as a response to spinal cord injury and their influence on disease pathogenesis and recovery. This phenomenon does not appear to be limited to any specific pathological process, as it has been described in both spinal cord injury caused by both acute trauma, and cervical degenerative disease. Alterations in cerebral functional activation have been observed in patients following traumatic SCI, where a host of sensorimotor regions have been reported as showing increased activation during functional tasks in fMRI studies [13].

Our previous studies utilizing task-based fMRI in CSM patients similarly demonstrated increased areas of cortical activation in simple motor tasks, such as dorsiflexion of the ankle and finger pinching [3,4]. This increased area of activation was postulated to be a compensatory mechanism designed to preserve neurological function as a result of spinal cord injury downstream within the motor network. The cortical representation maps reorganized after surgical decompression towards normal patterns, which paralleled neurological recovery [3,4], reinforcing the idea that the increased activation volume is a compensatory mechanism, which may be developed into measure of plasticity to guide neurosurgical intervention. While functional activation fMRI can be used to infer relationships between regional brain function and a particular task, resting state fMRI examines the low-frequency oscillation of brain regions at rest. One way to use this activity at rest is to examine the associations between patterns of activity across different brain regions, termed functional connectivity, which yields measures of brain plasticity and functional organization. To date, resting-state fMRI studies have shown increased functional connectivity between sensorimotor cortical and subcortical regions following traumatic spinal cord injury [5,7,8,17].

As alterations in cortical activation in CSM patients had already been established by our previous work, the present study sought to gain further insight into the dynamic process of neural plasticity by assaying the specific cortical and subcortical connections associated with CSM pathogenesis. The results from the current study indicate an overall increase in functional connectivity with worsening neurological symptoms (mJOA score) across sensorimotor regions. Additionally, results suggest involvement of supplementary areas, namely the precuneus, superior frontal gyrus, and anterior cingulate, which have been shown to be structurally altered in previous studies [14]. These results are also consistent with electroencephalography studies demonstrating larger cortical networks involved in motor volition in patients with spinal cord injury compared with healthy controls [18,19], further supporting the hypothesis that there is a need for increased brain plasticity in patients with spinal cord injury in order to overcome functional deficits.

Associations Between Functional Brain Measurements and Symptoms

For the primary sensorimotor structures, increased FC with worsening neurological function (decreasing mJOA score) was seen for the pre- and post-central gyri, and the supplementary motor area (SMA), to the regions of the precuneus and posterior cingulate. Additionally, the thalamus and cerebellum displayed strong increasing FC with worsening neurological symptoms to the pre- and post-central gyri, but displayed increased functional connectivity to areas of the posterior cingulate and precuneus and to areas of the anterior cingulate and superior frontal gyrus. The precuneus showed an increasing FC with worsening neurological symptoms to the pre- and post-central gyri, though this was seen only in the group that included both HC subjects and CS patients. Only the putamen demonstrated a decreasing

relationship of FC to neurological symptoms to the pre- and post-central gyri. The putamen also showed decreased FC to the precuneus and posterior cingulate. Similar patterns of FC were seen for both the CS-only and HC-included groups, which is an indication that age was successfully accounted for as a covariate in the GLMs and that the patterns are robust to inclusion of HC subjects in the analysis.

Similar to the hypothesized role of increased area of activation found in functional activation studies in CSM [3,4] and SCI patients [13], the increased functional connectivity with worsening neurological symptoms between primary somatosensory cortex and supplementary areas (precuneus, thalamus, cerebellum, and superior frontal gyrus) may indicate some form of compensatory mechanism for the difficulty to accomplish motor tasks. This hypothesis is supported by a study in CSM patients performed by Hrabalek *et al*, where functional activation increases were not limited to primary sensorimotor cortex, but were found in the supplementary motor area, anterior cingulate, thalamus, basal ganglia, and cerebellum [20]. These areas were ostensibly recruited to assist the primary sensorimotor cortex in accomplishing motor tasks. This is reflected in the increased connectivity between these regions in the present study, where all the above regions show increased connectivity with worsening neurological symptoms to regions of the primary sensorimotor cortex, except for the putamen. This may be due to the inhibitory function of the putamen in motor planning and execution [21,22], indicating that the decreased FC with symptom severity exhibited by CS patients indicates decreased inhibition of motor movements, which complements the increased FC seen in other sensorimotor regions. Another relevant study evaluated positron emission tomography of the resting cerebral metabolic rate of glucose metabolism in patients with spinal cord injury, and found relatively increased

metabolism in the supplementary motor area, the anterior cingulate, and the putamen [23], all of which were shown to functionally altered in the current study.

Clinical Relevance of Functional Connectivity Measurements in CSM Patients

In SCI patients, the complex relationship between functional impairment, disease progression, and neurological recovery extends far beyond the spinal cord, and more study is required that investigates the role of the entire CNS. Cervical SCI has been associated with long-term reorganization and plasticity of the motor cortex that parallels recovery of finger dexterity[24,25], with increased expression of GAP-43 mRNA in the cortical areas involved in the functional recovery[26,27]. Task based fMRI studies involving SCI patients with impairment of gait function have demonstrated primary motor area representation for the foot expanded into the proximal leg and paraspinal representation [28]. As control of their lower extremity function improved through rehabilitation, the extent of cortical activation decreased and resembled normal control subjects. This is consistent with the aforementioned decreases in cortical representation encountered in CSM patients following surgical intervention that correlated with neurological recovery. [4,5]

Thus, the upstream cerebral alterations that occur in concert with spinal cord injury and recovery represent an emerging area of investigation with significant clinical relevance. FC provides additional information to cortical activation regarding the overall health of the entire sensorimotor network, and if validated with future study, could serve as a potential imaging biomarker in CSM patients. FC has already been evaluated in this capacity in the SCI population as increased resting-state FC between the primary motor cortex and SMA and premotor cortex has been associated with a good prognosis following SCI [29]. There is a distinct need to develop

noninvasive imaging techniques to better predict outcome following surgical intervention for CSM, and cerebral biomarkers have been understudied for this purpose, but appear to offer promise.

CONCLUSION

Patients with cervical spondylosis with neurological impairment experience similar changes in brain connectivity to patients with chronic traumatic spinal cord injury. The results suggest an increase in functional connectivity within sensorimotor regions with increasing neurological impairment decreased connectivity between the cerebellum, putamen, and thalamus to frontal lobe regions.

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FIGURE CAPTIONS

Fig. 1: (A) Correlation between ROI-to-ROI functional connectivity and mJOA for both CS patients and healthy controls. (B) Correlation between ROI-to-ROI functional connectivity and mJOA for CS patients only. Colors denotes value of the T-statistic, yellow-red denotes positive association (decreasing connectivity with worsening neurological symptoms), light blue-blue denotes negative association (increasing connectivity with worsening neurological symptoms). Position of ROIs displayed on midsagittal and mid-axial slices.

Fig. 2: Brain surface display of associations between functional connectivity (FC) and mJOA based on seeding of sensorimotor cortical regions (displayed on representative MNI brain slices in green) for group including HC subjects (left) and group consisting only of patients with CS (right): A) and D) precentral gyrus, B) and E) postcentral gyrus, C) and F) supplementary motor area (SMA). Blue-light blue denotes negative association between mJOA and FC (increasing FC with worsening neurological symptoms) which occurred in the precuneus and posterior cingulate for the left (i) and the right (j) hemispheres, in regions of the left (l) and right (m) primary sensorimotor cortex, and left superior frontal gyrus (SFG, n). Red-yellow denotes a positive association (increasing FC with increasing mJOA), which was seen in the anterior cingulate (k).

Fig. 3: Brain surface display of associations between functional connectivity (FC) and mJOA based on seeding of subcortical regions and cerebellum (displayed on representative MNI brain slices in green) for group including HC subjects (left) and group consisting only of patients with CS (right): A) and D) thalamus, B) and E) putamen, C) and F) cerebellum. Blue-light blue

denotes negative association between mJOA and FC (increasing FC with worsening neurological symptoms) which presented in the precentral and postcentral gyri (m and n). Red-yellow denotes a positive association (increasing FC with increasing mJOA), which was seen in the left and right anterior cingulate (j and l, respectively), left and right precuneus and posterior cingulate (i and k, respectively), as well as around the pre- and postcentral gyri (o and p).

Fig. 4. Brain surface display of associations between functional connectivity (FC) and mJOA based on seeding of cortical regions (displayed on representative MNI brain slices in green) that only produced significant associations with the overall group that included HC subjects: A) superior frontal gyrus (SFG), B) precuneus. Blue-light blue denotes negative association between mJOA and FC (increasing FC with worsening neurological symptoms) which occurred in the left cingulate (i) and the left and right precentral gyrus and SMA (k and j, respectively).

Table 1. CS patients and HC subjects cohort demographics for rs-fMRI. Differences from Table 2.1 are due to the exclusion of two CS patients.

Subject Population	**N**	**Age (mean years +/- SD)**	**Sex**	**BMI (mean +/- SD)**	**mJOA (mean +/- SD)**	**NDI (mean +/- SD)**
CS Patients	24	60 ± 10 years	19M / 5F	27.0 ± 6.2	15.5 ± 2.8	9.6 ± 10.6
HC Subjects	17	41 ± 13 years	11M / 6F	26.2 ± 3.0	18	

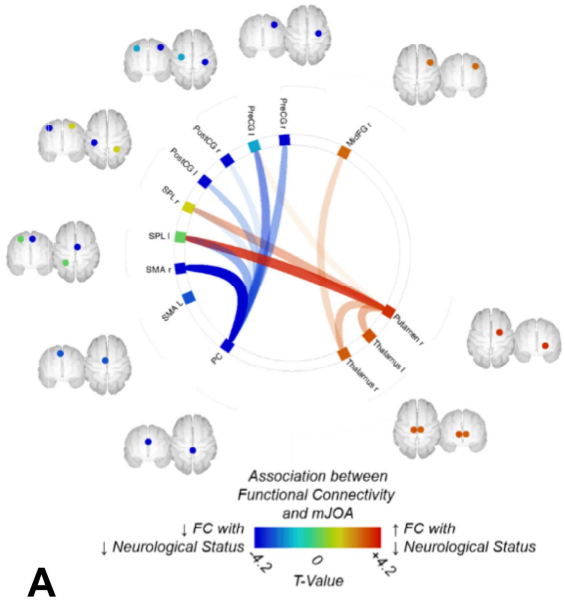
Table 2. Significant clusters from ROI-to-voxel FC analysis association between FC and mJOA for combined group of CS patients and HC subjects, accounting for age.

Seed ROI	Cluster Number	(x,y,z)	Cluster Size (mL)	Cluster P-FDR	Cluster T-Value
PreCG	1	(28, -68, 2)	10.45	0.00003	-6.03
PostCG	1	(6, -82, -32)	10.28	0.00003	-6.77
SMA	1	(-30, -64, -40)	6.29	0.00002	-8.05
	2	(-6, -52, 44)	5.69	0.00002	-4.70
	3	(16, -36, 16)	2.81	0.0006	8.49
SFG	1	(-14, -24, 80)	3.91	0.0004	-4.30
Precuneus	1	(-36, -26, 50)	7.65	0.00003	-4.16
Thalamus	1	(26, -14, 0)	11.30	0.00003	6.65
	2	(4, -24, 60)	4.09	0.00004	-3.74
Putamen	1	(22, -58, -32)	9.38	0.00001	7.52
	2	(-50, 42, 28)	7.82	0.00001	5.32
	3	(24, 0, 76)	3.85	0.00004	4.68
Cerebellum	1	(34, -10, 14)	16.65	0.00002	-4.44
	2	(38, -66, 0)	4.94	0.00003	-5.58
	3	(18, 8, 8)	4.34	0.00005	8.69

Table 3. Significant clusters from ROI-to-voxel FC analysis, association between FC and mJOA for group of CS patients only, accounting for age.

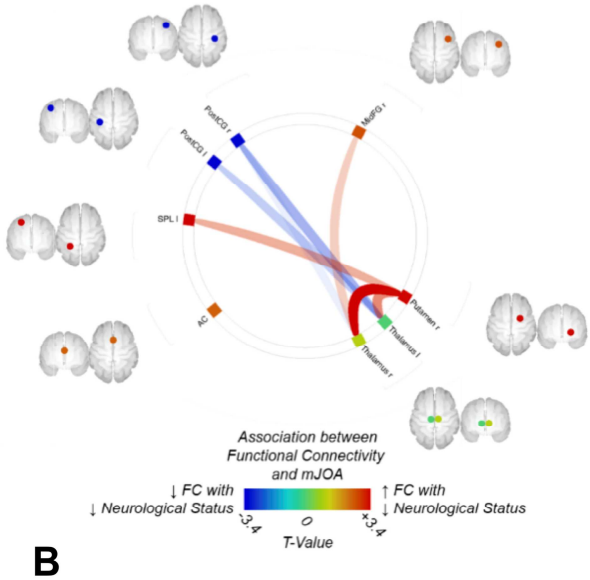
Seed ROI	Cluster Number	(x, y, z)	Cluster size (mL)	Cluster p-FDR	Cluster T-Value
PreCG	1	(2, -34, 8)	6.03	0.00005	-6.13
PostCG	1	(-18, -40, 40)	7.36	0.00004	-6.47
SMA	1	(-2, 32, 50)	2.49	0.003	-4.76
	2	(24, -6, 46)	2.38	0.003	-4.18
Thalamus	1	(24, -14, 0)	12.92	0.00002	7.34
	2	(-34, -20, -58)	6.69	0.00002	-4.04
Putamen	1	(-8, -42, 22)	10.38	0.00002	7.80
	2	(-44, -4, 34)	6.04	0.00002	5.30
Cerebellum	1	(18, -18, 74)	14.76	0.00002	-4.67
	2	(18, 8, 8)	8.08	0.00002	5.83

CS Patients and Healthy Controls



A

CS Patients Only



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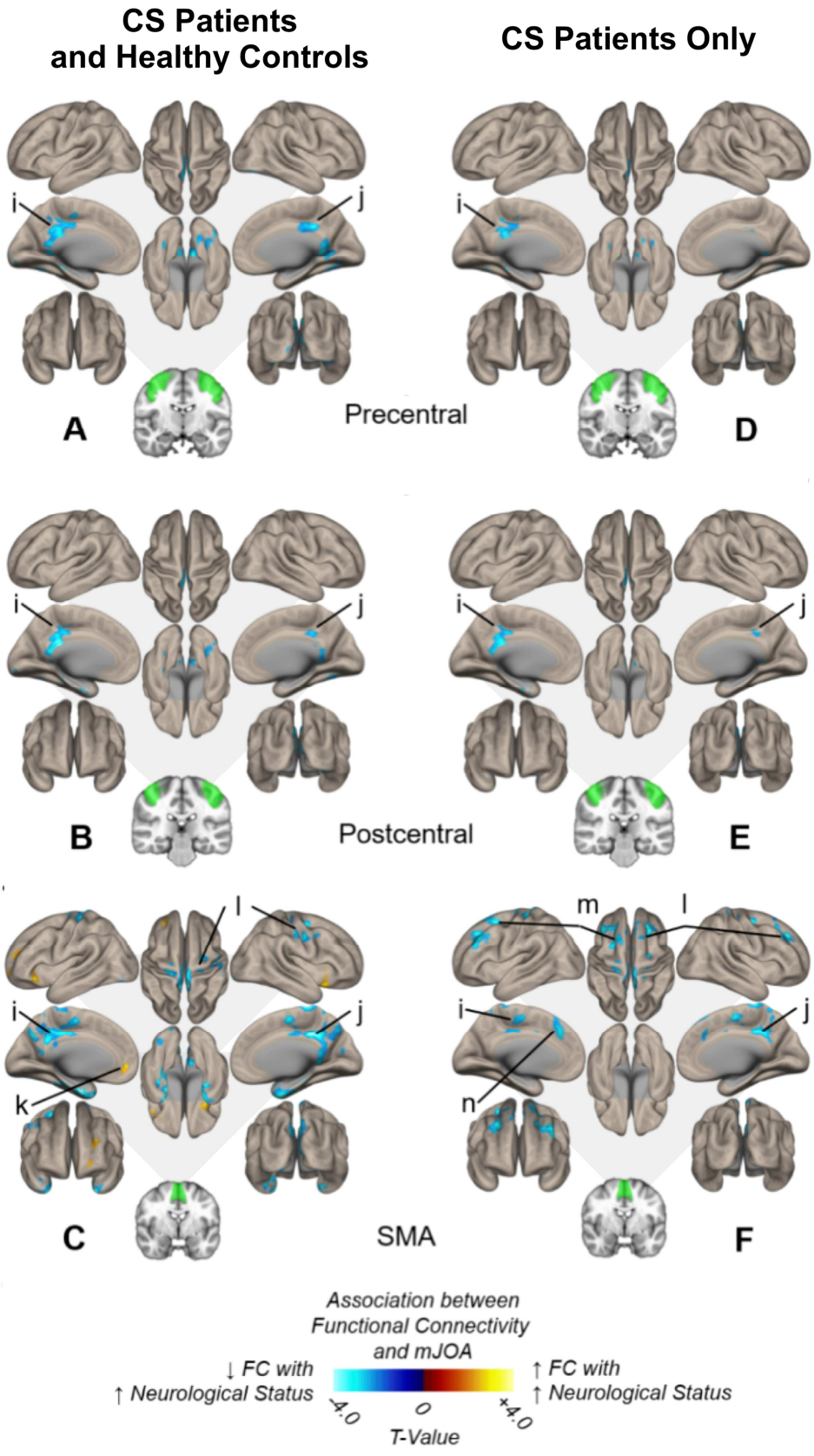
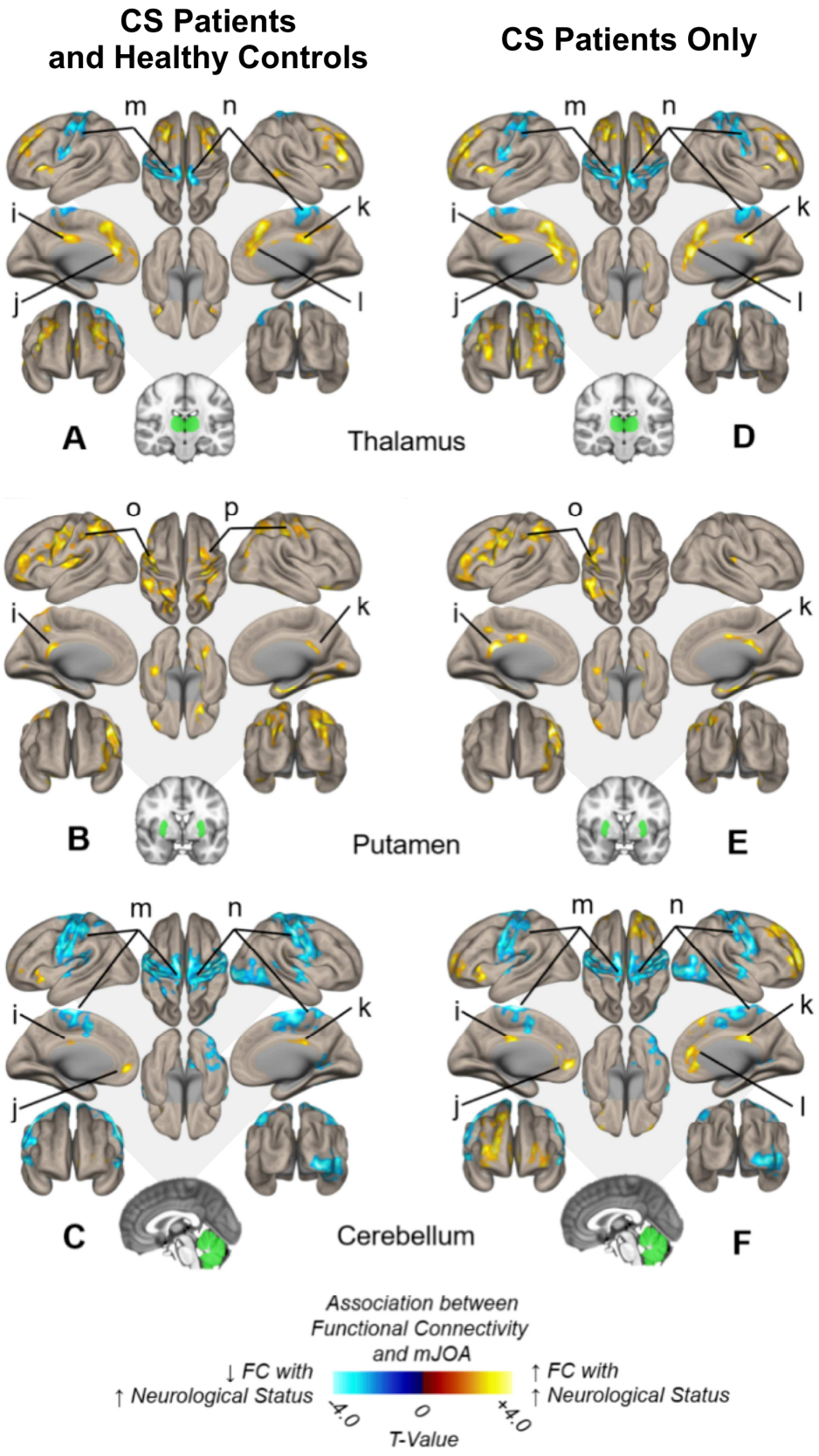
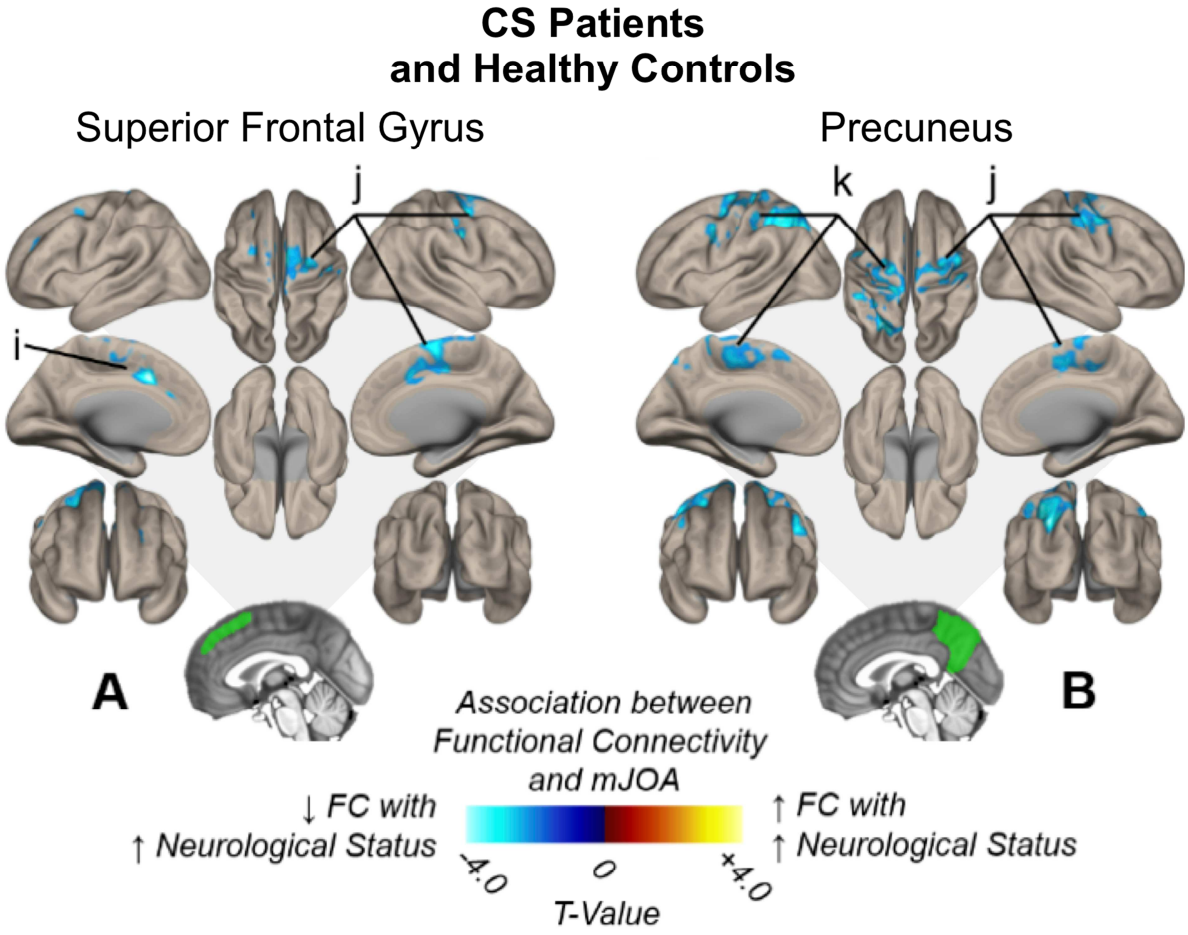

CS Patients and Healthy Controls
CS Patients Only
i
j
A
Precentral
D
B
Postcentral
E
k
l
m
n
C
SMA
F
Association between Functional Connectivity and mJOA
↓ FC with ↑ Neurological Status
↑ FC with ↑ Neurological Status
-4.0
0
+4.0
T-Value


CS Patients and Healthy Controls
CS Patients Only
m
n
i
k
j
l
A
Thalamus
D
o
p
B
Putamen
E
C
Cerebellum
F
Association between Functional Connectivity and mJOA
↓ FC with ↑ Neurological Status
↑ FC with ↑ Neurological Status
-4.0
0
+4.0
T-Value


CS Patients
and Healthy Controls
Superior Frontal Gyrus
Precuneus
j
i
k
j
A
B
Association between
Functional Connectivity
and mJOA
↓ FC with
↑ Neurological Status
↑ FC with
↑ Neurological Status
-4.0
0
+4.0
T-Value

HIGHLIGHTS

- Patients with cervical spondylosis exhibiting neurological impairment demonstrate an increased functional connectivity within sensorimotor areas.
- Patients with cervical spondylosis exhibit increased functional connectivity between the anterior cingulate and SMA, thalamus, and cerebellum with increasing neurological function.
- Areas of the thalamus, cerebellum, and putamen present increasing functional connectivity with the bilateral precuneous and posterior cingulate with increasing mJOA score in patients with cervical spondylosis.

ABBREVIATIONS:

AAL = automated anatomic labeling

AC = anterior cingulate

ART = artifacts detection tool

BOLD = blood oxygen level dependent

CAIPIRINHA = controlled aliasing in parallel imaging results in higher acceleration

CS = cervical spondylosis

CSF = cerebrospinal fluid

CSM = cervical spondylotic myelopathy

FC = functional connectivity

fMRI = functional magnetic resonance imaging

FOV = field of view

FWHM = full width half maximum

GLM = general linear model

GM = gray matter

HC = healthy control

HIPAA = Health Insurance Portability and Accountability Act

IC = insular cortex

IRB = institutional review board

MFG = middle frontal gyrus

mJOA = modified Japanese Orthopedic Association score

MNI = Montreal Neurological Institute

MPRAGE = magnetization prepared rapid gradient echo

PC = posterior cingulate

rs-fMRI = resting-state functional magnetic resonance imaging

ROI = region of interest

SPM = statistical parameter mapping

SPL = superior parietal lobule

SMA = supplementary motor area

SFG = superior frontal gyrus

TR = repetition time

TE = echo time

WM = white matter

CONFLICTS OF INTEREST

The authors do not have any conflicts of interest pertaining to the subject matter in this research study.