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Changes in functional connectivity of brain regions associated with movement and awareness under the influence of cervical epidural spinal cord stimulation in chronic disorders of consciousness: a pilot study

Larisa Mayorova[1,2,a], Margarita Radutnaya[1,b], Ekaterina Bondar[1,c], Anastasia Kushnir[1,2,d], Vladimir Khorev[1,e], Semen Kurkin[1,f], Elena Pitsik[1,g], and Alexander Hramov[1,h]

[1] Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology, Lytkino, 777, Solnechnogorsk 141534, Russia
[2] Institute of Higher Nervous Activity and Neurophysiology of Russian Academy of Science, 5A Butlerova St., Moscow 117485, Russia

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Abstract Cervical epidural spinal cord stimulation has great potential for the correction of various neurologic deficits, but the efficacy and mechanism of such effects are not sufficiently studied. In this study, we examine the functional rearrangements of the brain under the influence of epidural spinal cord stimulation in patients with spasticity syndrome and chronic disorders of consciousness. We performed spinal cord stimulation in nine patients and compared the effect with a control group of nine patients. Resting-state functional MRI data were acquired using a 1.5 T system and processed using the statistical parametric mapping package. We tested the hypotheses that stimulation affects the sensorimotor system of the brain and the brain systems involved in the realization of consciousness function. Our results confirmed the effect of the procedure on the sensorimotor system of the brain; we found both intra- and crosshemispheric enhancements of functional connectivity of motor areas in the patients of the main group. It was also shown that the absence of stimulation leads to deconsolidation of connections in the network of motor areas. Also, due to spinal cord stimulation, a number of nonspecific enhancements of functional connectivity were observed, which are difficult to interpret at this stage of development of the issue. Our results extend the few available insights into the mechanisms of spinal cord stimulation effects on higher central nervous system compartments.

1 Introduction

Currently, there is a need to develop methods for both reducing spasticity within spastic syndrome of various etiologies and increasing the level of consciousness in patients with chronic disorders of consciousness. Given that these two conditions are often associated, the ideal option in such a case would be to have a method that in the background facilitates the processes of neuronal plasticity. Various brain stimulation techniques are promising means of restoring lost brain function. Cervical epidural spinal cord stimulation (SCS) is one of such techniques.

[a] e-mail: larimayor@gmail.com (corresponding author)
[b] e-mail: doctor.radutnaya@gmail.com
[c] e-mail: bondar@fnkcrr.ru
[d] e-mail: naya.kushnir@gmail.com
[e] e-mail: khorevvs@gmail.com
[f] e-mail: kurkinsa@gmail.com
[g] e-mail: pitsikelena@gmail.com
[h] e-mail: hramovae@gmail.com

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Physical brain stimulation techniques, in addition to a different mechanism of action, have a number of advantages over drugs: drugs always have side effects and cases of intolerance, as well as incompatibilities, and titration of the drug is much more complicated than calibration of the device [1]. Epidural spinal cord stimulation has analgesic effects [2], improves motor, sensory, and bladder function [3–8], may be effective for the treatment of spasticity [1, 9]. Anti-spasticity effects have been documented in a variety of neurological conditions ranging from multiple sclerosis to spinal cord injury [6, 10–18]. According to a review of studies on the use of spinal cord stimulation in patients in vegetative and minimally conscious states, the technique has yielded encouraging results in patients with impaired consciousness [19].

The mechanism of action of cervical epidural stimulation is currently poorly understood. In our opinion, the best way to clarify this issue is to objectify the effect, if any, using neuroimaging before and after the course of stimulation. In this case, the analysis of functional connectivity of the brain could provide at least a considerable amount of information about the mechanics of the effect of spinal cord stimulation on the overlying parts of the central nervous system. In addition to determining how the functional topography of the brain changes as a result of injury or stroke, functional connectivity analysis provides valuable insights into experience-dependent plasticity at the level of large-scale functional networks [20]. It has been experimentally shown that functional connectivity of the brain can be significantly altered by various, both very light exposures, such as a 5-minute massage [21], and various long-term trainings, such as 10 days of specific brain-computer interface exercises in a rehabilitation hospital [9]. Moreover, in our previous studies, the effect of short-term epidural spinal cord stimulation on functional brain connectivity in patients of other groups has been shown [22, 23].

With most devices available on the market, the installation of a permanent system at the level of the cervical spinal cord does not technically allow an fMRI study with mapping of functional changes after a course of treatments. For example, in two studies of the effects of spinal cord stimulation (for the treatment of neuropathic leg pain), the stimulator was turned off at the time of scanning and thus the preconditioning effect of SCS was not excluded [24, 25]. Such a methodological problem can be solved by using test stimulators and performing fMRI immediately before implantation and immediately after removal of the spinal cord stimulation system.

In our pilot randomized controlled trial, we aimed to investigate whether cervical spinal cord epidural stimulation affects the functional connectivity of brain areas and which functional connections are most affected in a group of patients with disorders of consciousness (DoC). In this controlled study, we tested two hypotheses: (i) epidural spinal cord stimulation affects the functional interactions of motor areas implicated in the pathogenesis of spasticity development; (ii) epidural spinal cord stimulation affects the functional interactions of brain areas involved in providing the function of consciousness (arousal and awareness). In addition, we also performed a whole-brain connectivity analysis, i.e., using no hypothesis approach when analyzing functional connectivity.

2 Materials and methods

2.1 Subjects

Patients admitted to the hospital between January 2020 and September 2024 were included in the study. Patients were recruited by a group of neurosurgeons and anesthesiologists into two groups: main (SCS therapy, nine patients) and control (standard therapy, nine patients). Inclusion criteria were: (1) chronic impaired consciousness of various etiologies, (2) age from 19 to 80 years, (3) spasticity syndrome in one or both limbs. Exclusion criteria were (1) the presence of psychiatric or neurologic pathology in the premorbid history, (2) the presence of contraindications to MRI. Demographic, clinical, and intervention data in the two groups of patients are presented in Table 1.

Patients in the main and control groups did not differ statistically in age, disease duration, CRS-R and MAS scores. Group differences were observed in the time between the first and repeated fMRI; to eliminate the effect of this difference, we entered this index into the main analysis as a nonsense covariate. Comparative analysis of the groups is presented in Table 2.

2.2 Study design and SCS procedure

Trial epidural electrode placement was performed to evaluate the efficacy of this technique in reducing spasticity and the clinical rationale for further permanent stimulator placement (Fig. 1). The surgical aspects of the spinal cord stimulator placement procedure are described in detail in our previous article [22]. We used an eight-terminal monoaxial electrode (Octrode kit, St. Jude Medical, USA). After implantation, a test pulse generator (St. Jude Medical, USA: model 3599, https://fda.report/GUDID/05415067016553) was connected to the distal part of the electrode to check impedance. The stimulation mode for each patient was selected individually according to the presence of clinical effect and is shown in Table 1. The patients were provided with standard medical care and rehabilitation measures against the background of stimulation.

Table 1 Demographic, clinical and intervention data in study participants

N	Age	Gender	Group or disorder	Etiology	Disease duration (days)	CRS-R at admission	MAS at admission	Sedation at fMRI	Time between fMRIs (days)	SCS mode	SCS duration days (12 hours per day)
Main											
P1	40	F	MCS+	Anoxic	67	10	7	+	8	Burst	4
P2	74	M	MCS–	HS	40	4	0	_	5	Burst	5
P3	38	M	UWS	TBI	747	5	18	_	6	Burst	4
P4	45	M	UWS	Anoxic	80	5	14	_	17	Burst	9
P5	28	F	MCS+	TBI, anoxia	123	17	5	_	14	Burst	6
P6	37	F	UWS	TBI	48	5	14	_	7	Burst	4
P7	38	F	UWS	Anoxic/ toxic	12	9	9	_	56	Burst	4
P8	26	M	MCS–	TBI	40	22	4	_	39	Burst	7
P9	30	F	UWS	Anoxic	86	5	4	+	14	Burst	4
Control											
P10	20	M	UWS	TBI	66	5	10	_	15	_	_

Table 1 (continued)

N	Age	Gender	Group or disorder	Etiology	Disease duration (days)	CRS-R at admission	MAS at admission	Sedation at fMRI	Time between fMRIs (days)	SCS mode	SCS duration days (12 hours per day)
P11	82	M	CMC–	TBI	27	8	4	_	36	_	_
P12	44	F	CMC–	Anoxic	88	9	8	_	45	_	_
P13	44	M	UWS	TBI	85	4	8	_	56	_	_
P14	37	M	UWS/MCS–	Anoxic	290	5	20	_	43	_	_
P15	71	F	MCS+	HS	41	18	4	_	14	_	_
P16	55	F	UWS	Tissue+	48	5	1	_	25	_	_
P17	50	M	MCS–	IS	106	12	13	_	26	_	_
P18	30	M	UWS	TBI	28	3	1	_	87	_	_

\pg{\medskip} AS, Ashworth scale; C, cortical; CS, cortico-subcortical; F, female; IS, ischemic stroke; L, left; M, male; P, patient; R, right; S, subcortical; SCS, spinal cord stimulation; TBI, traumatic brain injury; HS, hemorrhagic stroke; IS, ischemic stroke; UWS, unresponsive wakefulness syndrome; MCS, minimal conscious state

Table 2 Median values of the subject groups, interquartile range, the value of the Mann–Whitney U-test comparing the groups of subjects

	Main Group ($n = 9$)	Control Group ($n = 9$)	p-value
Age, years	37.5 (29–41.5)	47 (40.5–63)	0.288
Female, %	55.55	33.33	–
Disease duration, days	64 (40–104.5)	66.5 (34.5–97)	0.965
CRS-R at adm.	5 (5–13)	6.5 (4.5–10.5)	0.649
MAS at adm.	7 (4–14)	6 (2.5–10.5)	0.790
Time between 1st and 2nd fMRI	14 (6.5–28)	39.5 (25.5–50.5)	0.0301

CRS-R, coma recovery scale revised; MAS, modified Ashworth scale; adm., admission

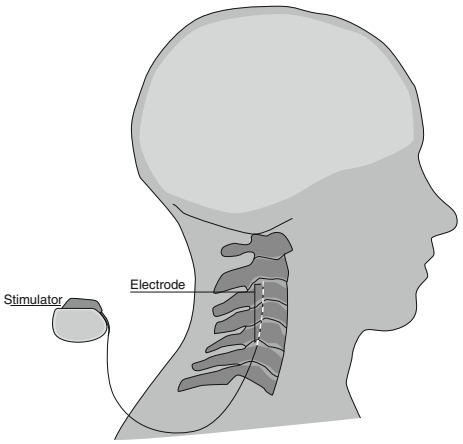

Fig. 1 Spinal cord stimulation system electrode placement

2.3 Clinical assessment

In accordance with the study design, all patients were evaluated for limb spasticity using the modified Ashworth scale (MAS). The presence of spasticity in each limb was assessed using a 5-point scale and then the values were added up, the total score is presented in Table 1. The level of consciousness was assessed using the revised coma recovery scale. The assessment was performed by two neurologists before and after placement of the temporary/test spinal cord stimulator on the same days as the pre- and postoperative fMRI. The neurologists were not specifically informed whether the patient belonged to the main or control group. Clinical scale data were analyzed using SPSS 23.0 software (IBM, Chicago, IL, USA). Wilcoxon Signed-Rank tests were performed to assess differences in repeated measures on the CRS-R and MAS scales. Given the small sample size, corrections for multiple comparisons were not used; results were considered significant at $p < 0.05$.

2.4 MRI data collection

Resting-state functional and anatomical images were acquired a day before SCS-system installation and right after removal using a 1.5 T Siemens Essenza (Siemens, Ltd., Germany) with an eight-channel head coil. Each resting state functional run consisted of 300 T2-weighted echoplanar images (EPIs). The imaging parameters were as follows: 3.9×3.9 mm in-plane voxel size, covering the whole brain volume 4.0-mm slices, interslice gap 0.8 mm, repetition time (TR) = 3670 ms, echo time (TE) = 70 ms, 64×64 matrix. In addition to the functional images, we collected a high-resolution T1-weighted anatomical scan for each participant (192 slices, resolution 1×1×1 mm, TR = 10 s, TE = 4.76 ms, 256×256 acquisition matrix).

2.5 Functional data preprocessing pipeline and statistical analysis

Data processing was performed using the CONN functional connectivity toolbox package (http://www.nitrc.org/projects/conn), version 19c and SPM12 (http://www.fil.ion.ucl.ac.uk/spm). The preprocessing procedure included standard steps for motion correction, slice timing, co-registration of functional and anatomical images, bringing them into MNI space, outlier cleaning (ART) (http://www.nitrc.org/projects/artifact_detect) and spatial smoothing with an 8 mm Gaussian kernel, and removal of the following confounders using linear regression: blood oxygen

level dependent (BOLD) signal from the white matter and CSF mask (5 principal components of each signal); cleaning (the number of regressors corresponded to the number of unreliable scans identified); and motion regression. The resulting signals were subjected to band-pass filtering at frequencies of 0.008-−0.12 Hz. Statistical analysis of fMRI data was performed to test 3 hypotheses: (i) SCS alters the functional state of the sensorimotor system of the brain, which was also obtained in our previous work performed on post-stroke patients with spasticity but without impaired consciousness; (ii) SCS may have a modulatory effect on brain regions associated with consciousness function; (iii) SCS may have a nonspecific modulatory effect on the functional connectome as a whole and lead to rearrangements of interactions between brain regions not directly involved in the pathogenesis of functional deficits in these patients. To test hypotheses (i) and (ii), we performed a Seed-based functional connectivity analysis using a mixed-design analysis of variance (RM-ANOVA 2×2) with one between-subjects factor (groups) and one within-subjects factor (therapy). As seeds we used brain regions associated with motor function hypothesis (i)) and areas, which are thought to be associated with two aspects of consciousness function, arousal and awareness (hypothesis (ii)). We performed a similar statistical test at the ROI-to-ROI level of the whole brain (165 pairs of functional connectivity) in a hypothesis-free analysis. Post-hoc analysis was performed to compare functional connectivity before and after SCS (contrast Post-SCS minus Pre-SCS) in the main and control groups. We entered the time between the first and repeat fMRI scans as nonsense covariates. Regions with significant differences ($p < 0.01$) were identified and adjusted for multiple comparisons (FDR) at the cluster level $p < 0.05$. For ROI-to-ROI analysis results were considered significant at $p < 0.05$ at the cluster level adjusted for multiple comparisons (FDR).

3 Results

3.1 Clinical effects of SCS

In the studied groups, we did not observe a statistically significant change in the distribution of CRS-R scores, i.e. the level of consciousness, according to the score, remained unchanged. A tendency to decrease spasticity was observed in the group after spinal cord stimulation according to the MAS scale, but we did not observe a statistically significant effect.

3.2 Seed-based functional connectivity analysis

In the analysis of variance between connectivity scores after and before therapy, we examined two groups of seeds: (i) a group of seeds related to motor function; (ii) a group of seeds related to consciousness function. In the third case, we did not use hypotheses at all; we analyzed all brain areas at once. A significant group effect ($p_{FDR} < 0.05$) was found in a number of seed brain areas from both groups. A list of these structures is given in Table 3.

For motor seeds, the largest significant effect in the number of connections was observed in the area of the right precentral gyrus. It changed its crosshemispheric connections with supramarginal gyrus, postcentral gyrus, Occipital Pole Left, as well as intrahemispheric connections: with the area of precuneus and lingual gyrus. Overall, there were a significant number of cases of changes in cross-hemispheric connections. But intra-hemispheric connections also changed, both in the right and left hemisphere. It is worth noting separately the presence of an effect for connectivity between the postcentral and supplementary motor cortex within the left hemisphere.

For seeds associated with consciousness function we observed effects for the medial prefrontal cortex (the default network node) and its connections to the left agranular retrolimbic area and left temporal pole. Also in the nodes of the salience network (right rostral prefrontal cortex and bilateral supramarginal gyrus) we observed changes in cross- and intrahemispheric functional connectivity with the right frontal cortex and right temporal cortex (Table 3). Subsequent pairwise comparisons in the main and control groups showed that after SCS therapy in the main group there was an increase in functional connectivity of the right pre- and postcentral gyrus, in the right and left sensorimotor network ($T(14)>4.14$, $p_{FDR} <0.05$). There were no changes in the other motor areas. In the control group, on the contrary, there was only a decrease in functional connectivity in all motor areas, except for the right postcentral cortex and right sensorimotor network nodes—there were no changes in them ($T(14)>4.14$, $p_{FDR} <0.05$). That is, the main group showed only an increase in functional connectivity, while the control group showed only a decrease.

A posteriori pairwise comparisons for the hypothesis with the seeds involved in the realization of the function of consciousness in the main group showed an increase in functional connectivity only in the pair right rostral prefrontal cortex (salience network)—frontal pole right, and no changes were observed in the other areas. In the control group, growth of functional connectivity was observed in the pair left parietal lobule (default network)—temporal pole left, and there was also a decrease in functional connectivity in the pair right supraorbital gyrus (salience network)—middle temporal gyrus and right inferior frontal gyrus ($T(14)>4.14$, $p_{FDR} < 0.05$).

Table 3 Resting-state functional connectivity, RM-ANOVA 2×2

Seed	Region	MNI (x, y, z)	Cluster size	$F(2,14)$	p-FDR
Motor hypothesis					
Brainstem	No significant effect				
Precentral g. r	Precuneus cortex right (r–r)	+ 04 – 64 + 10	122	> 11.78	0.003371
	Supramarginal gyrus, anterior division left (r–l)	– 62 – 22 + 30	93	> 11.78	0.008586
	Lingual gyrus left (r–r)	– 24 – 48 – 08	81	> 11.78	0.010646
	Precuneus cortex right (r–r)	+ 12 – 76 + 42	78	> 11.78	0.010646
	Postcentral gyrus left (r–l)	– 36 – 40 + 64	69	> 11.78	0.015103
	Occipital pole left (r–l)	– 08 – 88 + 14	59	> 11.78	0.024515
Precentral g. l	Supplementary motor cortex-right	+ 10 – 02 + 62	198	> 11.78	0.000072
Postcentral g. r	Supramarginal gyrus, anterior division left	– 60 – 36 + 34	120	> 11.78	0.003880
Postcentral g. l	Supplementary motor cortex-left	+ 02 – 12 + 50	216	> 11.78	0.000013
	Precentral gyrus right	+ 46 – 12 + 54	63	> 11.78	0.036815
Supplementary motor cortex r	Postcentral gyrus left	– 60 – 14 + 26	168	> 11.78	0.000175
	Precentral gyrus left	– 30 – 26 + 66	75	> 11.78	0.021771
Supplementary motor cortex l	Superior frontal gyrus left	+ 02 + 28 + 38	72	> 11.78	0.039145
	Frontal pole right	+ 18 + 38 + 44	60	> 11.78	0.046343
Sensori-motor network (L lateral)	Precentral gyrus left	– 06 – 20 + 50	196	> 11.78	0.000032
	Middle temporal gyrus, posterior division Left	– 54 – 22 – 20	127	> 11.78	0.000599
	Postcentral gyrus left	– 18 – 38 + 66	89	> 11.78	0.003875
Sensori-motor network (R lateral)	Central opercular cortex left	– 62 – 24 + 26	145	> 11.78	0.000739
	Temporal occipital fusiform cortex left	– 32 – 44 – 14	65	> 11.78	0.035775
Sensori-motor network (superior)	No significant effect				
Consciousness hypothesis (arousal and awareness hubs)					
Brainstem	No significant effect				
Thalamus L/R	No significant effect				
DMN (PCC)	No significant results				
DMN (MPFC)	Agranular retrolimbic area Left	– 10 – 44 + 14	64	> 11.78	0.048465
DMN (LP l)	Temporal pole left	– 50 + 18 – 08	60	> 11.78	0.001035
DMN (LP r)	No significant results				
FPN (LPFC r)	No significant results				
FPN (LPFC l)	No significant results				
FPN (PPC l)	No significant results				

Table 3 (continued)

Seed	Region	MNI (x, y, z)	Cluster size	$F(2,14)$	p-FDR
FPN (PPC r)	No significant results				
Salience (ACC)	No significant results				
Salience (RPFC l)	No significant results				
Salience (RPFC r)	Frontal pole right	+ 40 + 34 – 12	74	> 11.78	0.034035
Salience (SMG l)	Frontal pole right	+ 40 + 34 + 10	66	> 11.78	0.031289
Salience insula r	No significant results				
Salience insula l	No significant results				
Salience (SMG r)	Middle temporal gyrus, temporooccipital part right	+ 64 – 56 – 02	82	> 11.78	0.013079
	Inferior frontal gyrus, pars triangularis right	+ 52 + 32 + 00	60	> 11.78	0.029426

L, left; r, right; g., gyrus; DMN, default mode network; PCC, posterior cingulate cortex; MPFC, medial prefrontal cortex; LP, lateral parietal; LPFC, lateral prefrontal cortex; PPC, posterior parietal cortex; ACC, anterior cingulate cortex; RPFC, rostral prefrontal cortex; SMG, supramarginal gyrus

3.3 ROI-to-ROI analysis

Analysis of the data within the ROI-to-ROI approach, where we tested three hypotheses regarding possible changes in functional connectivity of the brain under the influence of spinal cord stimulation, showed that the hypothesis of an effect on the motor system of the brain was generally confirmed. In addition, in the analysis without hypothesis we found changes in brain regions associated with higher mental functions, such as speech and attention functions (Table 4).

For the motor hypothesis, subsequent a posteriori comparisons showed that the observed effect is due to the fact that in the control group the functional connectivity between the indicated connections (Table 4) decreases from the first to the second fMRI study ($T(2,14)<$ - 1.97 (p_{FDR} <0.05). A map of the decrease in functional connectivity in the control group is shown in Fig. 2.

A posteriori comparisons for the whole-brain analysis revealed that functional connectivity of brain areas in cluster 1 (predominantly cross-hemispheric connections of motor areas) increased in the main group by the second study, whereas it decreased in the control group. In cluster 2 (predominantly intrahemispheric connections of nodes of the dorsal attention network, salience and speech network), functional connectivity in the main group remained without statistically significant changes, whereas in the control group it decreased again.

4 Discussion

In this pilot study, we examined changes in functional connectivity of the brain under the influence of cervical epidural spinal cord stimulation. We were interested in whether there was a functional reorganization of the motor system and the system supporting consciousness as a result of electrical stimulation. We found a number of functional reorganizations both within the motor system and within brain networks involved, according to the literature, in the maintenance of conscious activity. The effect was more pronounced for the motor system (Fig. 3.).

4.1 Clinical effects of SCS

We did not observe an increase in the level of consciousness after completion of the course of cervical epidural spinal cord stimulation. In almost half of the cases, we observed a decrease in spasticity, but we could not find statistically significant differences in MAS scores before and after stimulation. This does not mean that the procedure has no clinical effect, especially since in our and other studies such an effect was shown; rather, it is due to the methodological peculiarities of this particular study, which will be summarized in the limitations chapter.

Table 4 Resting-state functional connectivity, RM-ANOVA 2×2

Cluster	Connection	F	p	p-FDR	Hemispheric interactions
Motor hypothesis					
_	PostCG l–PostCG r	14.35	0.000	0.002	l–r
_	PostCG l–PreCG l	5.10	0.022	0.028	l–l
_	PostCG l–SensoriMotor.Lateral r	6.86	0.008	0.013	l–r
_	PostCG l–SensoriMotor.Superior	8.28	0.004	0.013	l–c
_	PostCG l–SMA l	4.10	0.040	0.045	l–l
_	PostCG l–SMA r	7.69	0.006	0.013	l–r
_	PostCG r–SensoriMotor.Lateral l	13.46	0.001	0.002	l–r
_	PreCG l–PostCG r	4.50	0.031	0.040	l–r
_	PreCG l–PreCG r	7.87	0.005	0.015	l–r
_	PreCG l–SensoriMotor.Superior	5.32	0.019	0.033	l–c
_	PreCG l–SMA r	10.62	0.002	0.007	l–r
_	PreCG r–PostCG l	21.79	0.000	0.000	l–r
_	SensoriMotor.Lateral l–PostCG l	6.87	0.008	0.011	l–l
_	SensoriMotor.Lateral l–PreCG l	10.59	0.002	0.006	l–l
_	SensoriMotor.Lateral l–PreCG r	7.86	0.005	0.009	l–r
_	SensoriMotor.Lateral l–SensoriMotor.Lateral r	8.14	0.005	0.009	l–r
_	SensoriMotor.Lateral l–SensoriMotor.Superior	7.31	0.007	0.010	l–c
_	SensoriMotor.Lateral l–SMA l	6.50	0.010	0.011	l–l
_	SensoriMotor.Lateral l–SMA r	9.92	0.002	0.006	l–r
_	SensoriMotor.Lateral r–SMA l	6.88	0.008	0.019	l–r
_	SMA r–SensoriMotor.Lateral r	6.98	0.008	0.018	r–r

Table 4 (continued)

Cluster	Connection	F	p	p-FDR	Hemispheric interactions
_	PreCG l–SensoriMotor.Lateral r	5.15	0.021	0.033	l–r
Consciousness hypothesis (arousal and awareness hubs)					
No significant results					
No hypothesis (whole brain areas)					
1	PreCG r–SPL l	3.89	0.045	0.045	l–r
1	SensoriMotor.Lateral r–DorsalAttention.IPS l	4.23	0.037	0.040	l–r
1	PreCG l–PostCG r	4.5	0.031	0.037	l–r
1	PostCG r–SPL l	4.57	0.030	0.037	l–r
1	SensoriMotor.Lateral r–PreCG l	5.15	0.021	0.030	l–r
1	PreCG l–SensoriMotor.Superior	5.32	0.019	0.030	l–c
1	PreCG r–DorsalAttention.IPS l	5.68	0.016	0.027	l–r
1	SensoriMotor.Superior–DorsalAttention.IPS l	5.93	0.014	0.025	l–c
1	PostCG l–SensoriMotor.Lateral r	6.86	0.008	0.018	l–r
1	SensoriMotor.Lateral l–SensoriMotor.Superior	7.31	0.007	0.016	l–c
1	SensoriMotor.Lateral l–PreCG r	7.86	0.005	0.014	l–r
1	PreCG r–PreCG l	7.87	0.005	0.014	l–r
1	SensoriMotor.Lateral l–SensoriMotor.Lateral r	8.14	0.005	0.014	l–r
1	PostCG l–SensoriMotor.Superior	8.28	0.004	0.014	l–c
1	PostCG r–DorsalAttention.IPS l	9.5	0.002	0.013	l–r
1	PostCG r–SensoriMotor.Lateral l	13.46	0.001	0.005	l–r
1	PostCG l–PostCG r	14.35	0.000	0.005	l–r
1	PreCG r–PostCG l	21.79	0.000	0.001	l–r
2	DorsalAttention.FEF l–toMTG l	4.11	0.039	0.041	l–l
2	Language.pSTG l–DorsalAttention.FEF r	4.31	0.035	0.039	l–r
2	Salience.SMG l–aSTG l	4.48	0.031	0.037	l–l
2	pSMG l–SMA r	4.74	0.027	0.037	l–r
2	Salience.SMG l–pMTG l	5.23	0.020	0.030	l–l
2	pSMG l–SMA l	6.4	0.011	0.021	l–l
2	SMA r–Language.pSTG l	7.73	0.005	0.014	l–r
2	aSMG l–toMTG l	10.43	0.002	0.011	l–l

l, left; r, right; g., gyrus; DMN, default mode network; FEF, frontal eye field; CG, central gyrus; SMG, supramarginal gyrus; STG, superior temporal gyrus; MTG, middle temporal gyrus; SMA, supplementary motor area; SPL, superior parietal lobule; IPS, intraparietal sulcus

4.2 Motor hypothesis

The seed-based analysis revealed that spinal cord stimulation affects the functional connectivity of many areas related to motor function. There is an increase in functional connectivity both locally: the right pre- and postcentral gyrus, and at the level of the sensorimotor network, its right- and left-hemispheric hubs. At the same time, the picture is intriguing when in the main group, unlike the control group, there is no decrease in functional connectivity in any of the seeds. This result in line with our previous study conducted on a group of conscious patients with upper motor neuron syndrome [22]. In Deogaonkar with co-authors study [24], significant changes in somatosensory cortex were also observed between on and off modes of spinal cord stimulation used to reduce pain syndrome. Moreover, according to a recently published review with EEG data monitoring the effects of SCS, this procedure is quite often accompanied by modulation of somatosensory cortex activity [26]. The decrease in functional connectivity in the control group is noteworthy, which again confirms the need for active work with patients. ROI-to-ROI analysis of the motor system of the brain also showed that a short course of test spinal cord stimulation allows functional

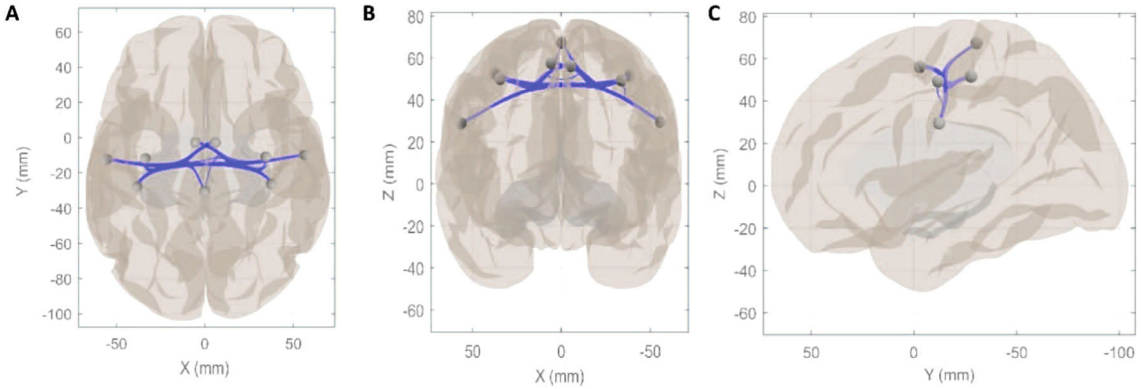

Fig. 2 Illustration of the decrease in functional connectivity from the first to the second fMRI study in the control group. Connections between pairs of areas (motor areas) are indicated in blue (T(2,14)< - 1.97 (p_{FDR} <0.05). A, top view; B, front view; C, left view

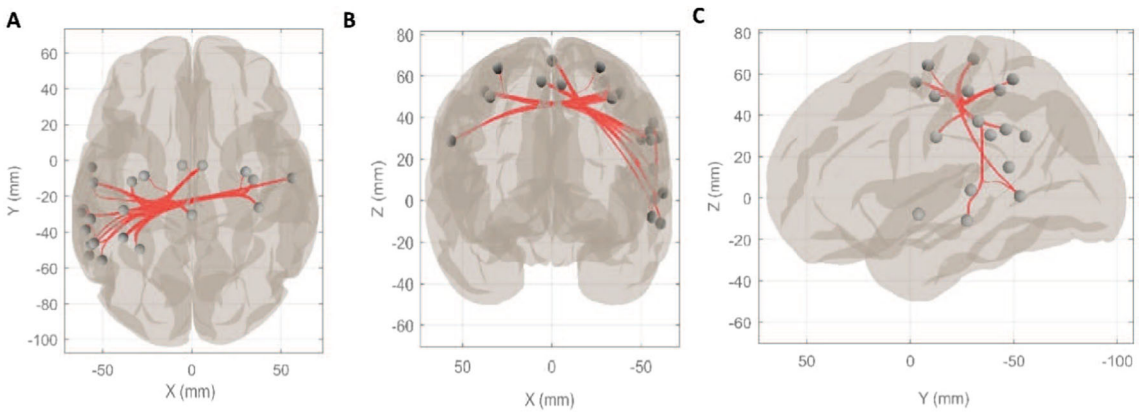

Fig. 3 Illustration of the localization of functional connectivity changes from the first to the second fMRI examination for the contrast "main group > control group". Connections between pairs of regions are indicated in red ($F(2,14)$> 7.39 (p_{FDR} <0.05). A, top view; B, anterior view; C, left side view

connectivity within the motor system to be maintained at a certain level. Moreover, these results were confirmed in the analysis of whole-brain areas, which demonstrated increased connectivity between motor areas. This result within the analysis of all 165 areas of interest also suggests a significant effect size. Overall, this result suggests the potential effectiveness of epidural spinal cord stimulation in terms of its effect on the motor system of the brain, whereas the absence of stimulation leads to a decrease in both inter- and intra-hemispheric connectivity in the brain.

4.3 Consciousness hypothesis

For the areas associated with the function of consciousness, the pattern of the effect of spinal cord stimulation was less pronounced than for motor areas. The presence of the effect was shown by areas of the medial prefrontal cortex, left lateral parietal cortex (DMN); right rostral prefrontal cortex, supraorbital gyrus bilaterally (Salience network). In the main group, only increased connectivity in the right rostral prefrontal cortex was observed. At the same time, in the control group there was both an increase in functional connectivity (in the left lateral parietal cortex) and its decrease (in the right supraorbital gyrus). It should be noted that there are very few studies on the effect of spinal cord stimulation on the level of consciousness, and even less on the accompanying functional reorganizations of the brain. Cases have been described in which the level of consciousness increased in such patients under the influence of electrical stimulation of cervical spinal cord segments [27, 28]. Authors agree that this therapeutic technique can be considered as a promising one for the treatment of disorders of consciousness [29–31]. However, since the first publications on this topic have appeared, it is still unclear whether the effect is due to a direct effect on neural transmission or to an improvement in hemodynamics. The case study we found of a patient emerging from a state of minimal consciousness after spinal cord stimulation (with appropriate monitoring

with EEG and fMRI) provides evidence that the DMN areas—the anterior medial prefrontal cortex and posterior cingulate cortex, as well as the dorsal medial prefrontal cortex in the network of control functions, approached normal [32].

In our work, we observed increased connectivity of the right rostral prefrontal cortex. Despite numerous evidences in favor of the involvement of this area in the realization of higher cognitive functions [33], there is insufficient data on the direct involvement of this area in the realization of consciousness function. Therefore, we cannot, with a high degree of unambiguity, attribute this result to a positive effect of SCS. The decrease in functional connectivity in the right supracortical gyrus in the control group also cannot indirectly testify in favor of spinal cord stimulation. Because the area of the supraorbital gyrus, although in close proximity to the right temporoparietal junction [34], is not interpreted as an area directly related to the maintenance of a certain level of awareness. Also rather nonspecific neuroplastic changes reflect the established increase in the strength of functional connectivity in the areas: left intraparietal sulcus cortex of the dorsal attention network—motor areas; oculomotor field of the dorsal attention network—left middle temporal gyrus and left posterior superior temporal gyrus (speech network), respectively; left supraorbital gyrus (salience network)—left posterior middle temporal gyrus; right supplementary motor area—left posterior superior temporal gyrus (speech network). Thus, the results obtained by us to a greater extent testify in favor of the positive effect of spinal cord stimulation on the sensorimotor system of the brain of patients.

4.4 Limitations

This study has several limitations. First, the relatively small sample size, a consequence of the challenges inherent in patient selection, may have limited the statistical power to detect a clinical effect. Furthermore, the assessment of this effect relied on scales with acknowledged limitations. Second, the absence of a sham stimulation control group prevents definitive conclusions regarding the specificity of the observed effects. Finally, the lack of an observed effect on brainstem structures, noted in our previous study, may be attributable to several factors: the small sample size, the specific patient pathologies, and the extreme sensitivity of these structures to magnetic field inhomogeneities and motion artifacts (including those resulting from arterial pulsation, respiration, and oropharyngeal movements).

5 Conclusion

The results obtained allow us to understand the mechanisms of influence of spinal cord stimulation on functional interactions of suffering brain sections due to neurological diseases. The effect on the brain compartments directly involved in the development of spasticity syndrome was revealed. Nonspecific functional rearrangements of the brain under the influence of spinal cord stimulation were also observed. These rearrangements were both local, intrahemispheric, and large-scale interhemispheric rearrangements. We found that for motor areas, spinal cord stimulation had only a consolidating effect, whereas in its absence, deconsolidation of connections was observed. For areas related to the function of consciousness a less pronounced effect was observed—changes in the main group occurred only in the rostral prefrontal cortex (salience network)—frontal pole right. In the control group, both strengthening and weakening were observed in two pairs of connections in the default and salience networks, respectively. It was also found that spinal cord stimulation also leads to a nonspecific increase in functional connectivity, which is subject to further investigation. Our findings have implications for understanding the mechanisms of neuroplastic remodeling under the influence of simulation techniques. Further studies are necessary to increase the statistical reliability of the obtained data.

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Data Availability The data presented in this study are available on request from the corresponding author.

Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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