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The influence of High Dose Spinal Cord Stimulation on the descending pain modulatory system in patients with failed back surgery syndrome

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List of abbreviations

ACC = anterior cingulate cortex
AMY = amygdala
AI = anterior insula
BOLD = blood oxygen level-dependent
B.U.N. = Belgian unique number
CompCor = component based method
CONN toolbox = connectivity toolbox
CSF = cerebrospinal fluid
DN4 = douleur neuropathique 4
DNIC = diffuse noxious inhibitory control
DPMS = desecending pain modulatory system
EEG = electroencephalography
FBSS = failed back surgery syndrome
FC = functional connectivity
Fmri = functional magnetic resonance imaging
FOV = field of view
FSPGR = fast spoiled gradient echo
GM = gray matter
HD-SCS = High dose spinal cord stimulation
HySCO = Hyperelastic Susceptibility Artefact Correction
MCID = minimum clinically important difference
mFG = medial frontal gyrus
MOA = mechanism of action
MRS = magnetic resonance spectroscopy
NCT = national clinical trial
NRS = Numeric Rating Scale
PAG = periaqueductal gray
PCS = Pain Catastrophizing Scale
PET = positron emission tomography
PSQI = Pittsburgh Sleep Quality Index
Q1 = quartile 1
Q3 = quartile 3
ROI = region of interest
rsfMRI = resting state functional magnetic resonance imaging
RVM = rostral ventromedial medulla
SE-EPI = spin echo echo-planar imaging
SPECT = single photon emission computerized
SPM = statistical parametric mapping
SPSS = statistical package for the social sciences
TE = echo time
TFE = turbo field echo
tSNR = temporal signal-to-noise ratio
V1 = first visit
V2 = second visit
V3 = third visit
V4 = fourth visit
VNRS = verbal numeric rating scale
WM = white matter

Introduction

The descending pain modulatory system (DPMS) comprises a network of cortical and subcortical brain and brainstem regions that can inhibit nociceptive afferent brain input (Ossipov et al., 2010; Tracey, 2010; Zhuo and Gebhart, 1997). These pathways seem to be altered in several chronic pain syndromes such as knee osteoarthritis,

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fibromyalgia, painful diabetic neuropathy and low back pain (Brietzke et al., 2019; da Graca-Tarrago et al., 2019; Kong et al., 2018; Segerdahl et al., 2018). The DPMS network comprises the bilateral anterior insulae (AI), the anterior cingulate cortex (ACC), bilateral middle frontal gyri (mFG), both amygdalae (AMY), the rostral ventromedial medulla (RVM) and the periaqueductal gray (PAG) (Goksan et al., 2018; Schweinhardt and Bushnell, 2010).

In the past, it has been suggested that traditional, paresthesia-generating Spinal Cord Stimulation (SCS) induces several changes in modulation circuits located in the cerebrum and brainstem. An inhibitory effect of traditional SCS on somatosensory evoked potentials, and potential mediators like the thalamus and the anterior cingulate cortex (ACC), could play a role in the mechanism of action (MOA) of SCS as well (Bentley et al., 2016; De Ridder and Vanneste, 2016; Moens et al., 2013, 2012). Several studies have provided evidence of the impact of SCS on the DPMS resulting in this inhibitory supraspinal effect (Sankarasubramanian et al., 2018; Schuh-Hofer et al., 2018). More recently, researchers have hypothesized similar influences on the DPMS by other paradigms of SCS such as high frequency SCS at 10 kHz and Burst SCS, as well as by other forms of neurostimulation e.g. occipital nerve field stimulation (Ahmed et al., 2018a, 2018c).

Tonic SCS at sub-sensory threshold and at 500 Hz and pulse width 500μsec, so called *high density* or *high dose SCS* (HD-SCS), is a SCS form based on the impact of electrical charge delivery to the spinal cord (Chen et al., 2018; Linderoth and Foreman, 2017; Miller et al., 2016; Sweet et al., 2016; Wille et al., 2017). After some initial case series studies, researchers are still exploring the clinical effect and impact on chronic pain of HD-SCS (De Jaeger et al., 2017; Provenzano et al., 2017; Wille et al., 2017).

In the past, several researchers have investigated the supraspinal effects of SCS by examining human cerebral circuits via different neuroimaging techniques (e.g. MR Spectroscopy (MRS), single photon emission computerized tomography (SPECT), positron emission tomography (PET), electroencephalography (EEG) and, functional magnetic resonance imaging (fMRI)) to capture alterations in modulation circuits (De Ridder and Vanneste, 2016; Kishima et al., 2010; Moens et al., 2013, 2012; Nagamachi et al., 2006). fMRI is especially interesting due to the robustness and test-retest reliability of the functional connectivity (FC) method in clinical applications (Apkarian, 2015; Shehzad et al., 2009). Additionally, the introduction of MRI-conditioned SCS devices enables further exploration of MOA of SCS, not only during trial period but also on long-term implanted devices.

Based on this knowledge, we hypothesized, in this study, that HD-SCS may alter the DPMS and indirectly, might generate an inhibitory supraspinal effect. This hypothesis-driven pilot study aimed to investigate the influence of HD-SCS on FC within the DPMS, measured by resting state fMRI.

Material and methods

Participants

A total of 11 consecutive patients, diagnosed with FBSS and eligible to HD-SCS, were recruited between January 2016 and July 2017 at the University Hospital Brussels. Pre-operative assessment included completing DN4, medication use and amount of previous surgeries. All participants provided written informed consent prior to participation. The study was approved by the ethics committee of the University Hospital Brussels (B.U.N. 143201526930) and registered at ClinicalTrials.gov (NCT02650349). This study was conducted according to the revised Declaration of Helsinki (1998).

Study protocol

This exploratory, prospective study consisted of four outpatient visits (Fig. 1). The first two visits took place before SCS implantation. The remaining two visits were scheduled after permanent implantation. The first (V1) and third (V3) visit were short appointments of about 20 min and were scheduled at least 2 weeks before the neuro-imaging visits (V2 and V4). Visit 4 was scheduled around 3 months (± 2 weeks) after permanent SCS. All patients were receiving HD-SCS. During visits V1 and V3, every patient received an Actiwatch spectrum plus (Phillips Respironics Inc., Murrysville, PA, USA) for the collection of sleep quality data and a Numeric Rating Scale (NRS) diary for measuring pain intensity (rating at 3 fixed points during the day). During V2 and V4 patients were asked to complete two questionnaires (Pain Catastrophizing Scale (PCS) and Pittsburgh Sleep Quality Index (PSQI)). Thereafter they underwent a neuroimaging fMRI-protocol. Between the second and third visit, patients underwent a trial implantation of SCS, followed by a permanent implantation of SCS. All patients received surgical paddle leads. The electrode was placed in the posterior spinal epidural space under radiographic control and was attached to either an external stimulator (during the trial phase) or a subcutaneously implanted IPG. Accordingly to the Belgian reimbursement rules (trial period of 4 weeks and pain reduction of 50%), all 11 patients included in this study were implanted with a Restore Sensor™ SureScan MRI neurostimulator system connected with a Specify™ 5–6–5 SureScan MRI surgical lead (IPG RestoreSensor, Medtronic, Inc., Minneapolis, MN, USA). Regarding the parameters for SCS, HD-SCS was defined as tonic stimulation with a pulsewidth of 500 μsec and a frequency of 500 Hz (= 25% pulse density, i.e. the percentage of time electricity is delivered during a full duty cycle (frequency x pulse width (Miller et al., 2016))). The stimulation parameters of the permanent implanted pulse generator remained the same and constant in the period between V3 and V4.

Questionnaires

All patients completed the NRS pain diary 3 times a day (morning, noon and evening) for a period of two weeks. The pain diary assessed pain intensity for back and leg pain separately. A score of 0 represented no pain at all, whereas a score of 10 represented the worst imaginable pain. The minimal clinically important difference for the NRS is estimated to be around 2 points (Farrar et al., 2001).

The PCS questionnaire was used to measure the level of pain catastrophizing. This questionnaire consists of 13 pain-related cognition items that needed to be scored on a 5-point Likert scale (0 = not at all, 4= all the time)(Sullivan et al., 1995). Scores ≥ 30/52 indicate a clinically relevant level of catastrophizing (Sullivan, 1995). The internal consistency, test-retest reliability and validity are acceptable for chronic pain patients (Lame et al., 2008; Osman et al., 1997).

Objective sleep quality was measured with the Actiwatch spectrum plus (Philips Respironics, Inc., Murrysville, PA, USA) for a period of two weeks. This electronic device is similar in size to a wristwatch and records physical movement with an accelerometer. It collects data for seven sleep quality parameters: wake after sleep onset percentage, sleep onset latency, actual sleep percentage, mean night-time activity, fragmentation index, number of wake bouts, and sleep efficiency. Actigraphy is validated in various patient populations and can reveal important changes in activity with treatment in low back pain patients (Alsaadi et al., 2013; Van de Water et al., 2011).

Subjective sleep quality was measured with the Pittsburgh Sleep Quality Index (PSQI). This questionnaire retrospectively asks patients about their sleep habits of the last month. This questionnaire consists of 19 self-rated questions and 5 questions for the partner, whereby only the self-rated questions are used to calculate the total score. The self-rated questions were combined to provide scores from 0 (no difficulties during the last month) to 3 (difficulties more than three times a week) on each of the seven subcomponents (sleep quality, sleep duration, sleep latency, use of sleep medication, daytime dysfunctioning, sleep disturbances, and habitual sleep efficiency) and combined into a total score with a range from 0 to 21. A recent meta-analysis concluded that

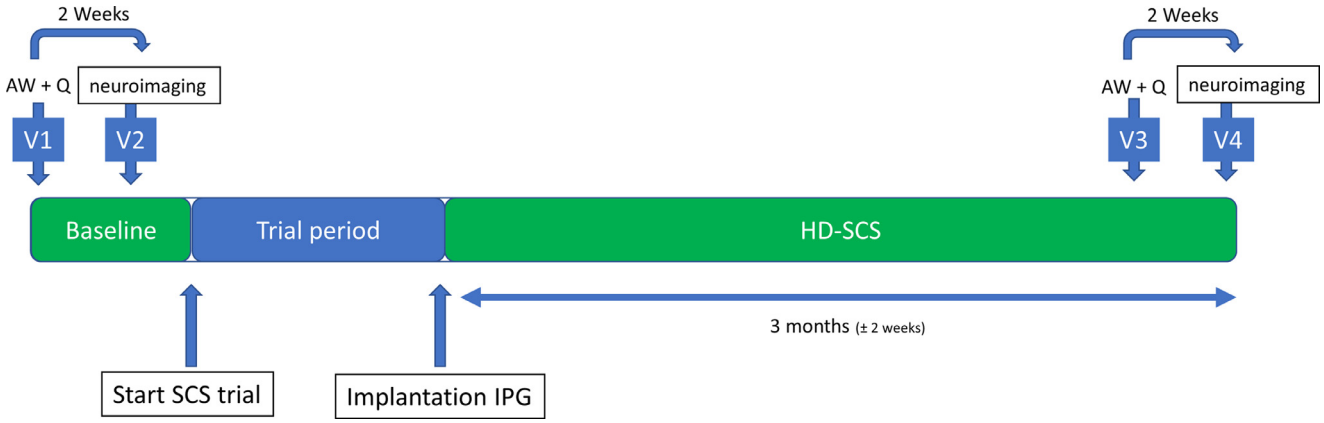

Fig. 1. Study protocol. Patients with FBSS were enrolled 1 month before SCS trial implantation and were followed up for 3 months after permanent implantation. Every patient underwent a neuroimaging protocol at baseline and during HD-SCS. Abbreviations. AW: Actiwatch, HD-SCS: High Dose Spinal Cord Stimulation, Q:questionnaires, V: visit.

the PSQI has a strong reliability and validity (Mollayeva et al., 2016).

MRI data acquisition

MRI scans were performed on a GE MR 750 w Discovery 3T using a 24-channel head coil. Total acquisition time for each MRI session is 8 min 20 s. A high-resolution anatomical image was acquired using an axial fast spoiled gradient echo (FSPGR) bravo scan, consisting of 124 axial slices with slice thickness 1 mm, no inter-slice gap, TR = 7.74 ms, TE = 3.75 ms, flip angle = 12°, scan matrix = 256 × 256 and FOV = 240 × 240 mm^2. Functional imaging data consisted of 250 resting state (rs)fMRI volumes using a spin echo echo-planar imaging sequence. The following scan parameters were selected: 23 axial slices covering the whole brain with slice thickness of 4 mm and a 1 mm inter-slice gap, TR = 2 s, TE = 55 ms, flip angle = 90°, matrix size = 128 × 128 and FOV = 240 × 240 mm^2. Patients were instructed to stay awake and to immediately inform the investigators in case any unusual sensation was felt at the implantation site, because SCS was left on during imaging.

Imaging processing

Resting state fMRI preprocessing and data analysis

The resting state fMRI data were pre-processed and analyzed using Statistical Parametric Mapping (SPM) software version 12 (Wellcome Trust Center for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm/) and a functional connectivity toolbox (CONN, version 17.C, MATLAB-based cross-platform software, freely available from NITRC at https://www.nitrc.org/projects/conn). First, all data were transformed to NIFTI files and previewed with ArtRepair (see https://www.nitrc.org/projects/art_repair/) to detect the global mean intensity and motion outliers in fMRI data. Additionally, ArtRepair detected and repaired bad slices (slices with artifacts due to radiofrequency (RF)-coil fluctuations) in the raw images, whereby the default threshold (outslice = 18) was selected.

Blood oxygen level-dependent (BOLD) fMRI time series preprocessing steps included the removal of the first three volumes for signal stabilization, realignment to remove movement artefacts and HySCO 2.0 (using Artefact correction in diffusion MRI toolbox) for susceptibility artifact correction of epi images. In addition, phase swap fMRI series were co-registered to the mean of the functional time series. Furthermore, differences in acquisition time between slices were corrected, the fMRI series were normalized using normalization parameters of the co-registered anatomical scan and normalized image volumes were smoothed using a Gaussian kernel with a FWHM of 8 mm. Then, outlier volumes were repaired with Artrepair. Therefore, the default threshold of 1.5% variation in standard deviation away from the global brain mean as a function of time and a default threshold at 0.5 mm/Repetition Time variation were selected. Finally, the temporal signal-to-noise ratio, in which the mean signal over time is taken into account, was used to determine the SNR of fMRI time series. After performing the resting state fMRI preprocessing, an age-covariate was added. During the normalization step of the preprocessing protocol, the MRI data were transformed into a common 3D brain space (MNI space).

The denoising procedures in CONN included 1) linear regression of CSF and WM following the Compor method 2) linear regression of the 6 motion realignment parameters 3) identification and interpolation of inconsistent frames due to time courses and movement time courses 4) bandpass filtering between 0.008 and 0.09 Hz. To avoid the introduction of false negative correlations, the global signal was not regressed out (Behzadi et al., 2007; Power et al., 2012). To assess region of interest (ROI) functional connectivity matrices, the Pearson correlation coefficient between the mean signal intensity BOLD time courses within all ROI-pairs of each network was calculated with CONN. A Fisher's r-to-z transformation was applied to each correlation map to allow statistical group-level analysis (Whitfield-Gabrieli and Nieto-Castanon, 2012). Thereafter, a second-level analysis was performed using a paired *t*-test to identify coherent functional connectivity patterns of paired ROIs between both time points (V2 vs V4) in patients with covariate age. ROIs were considered significant if $p < 0.05$ after permutation testing.

ROI identification

The descending pain modulatory system (DPMS) constitutes a network of cortical and subcortical brain regions who are responsible for modulation of afferent sensory input and the accompanying pain behavior. The ROIs of the DPMS network comprised the anterior cingulate cortices (ACC), the amygdala (AMY), the rostral ventromedial medulla (RVM), the periaqueductal gray (PAG), the bilateral anterior insula (AI), and the anterior-ventral part of bilateral middle frontal gyri (mFG) (Baeken et al., 2014; Brooks et al., 2017; Goksan and Baxter, 2018; Koyama et al., 2017; Linnman et al., 2012). The center of each ROI was defined in CONN and showed in Table 1. Each ROI had a spherical radius of 10 mm and consisted of average BOLD signal time series within the ROI voxels.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences software (IBM SPSS for windows, version 25, SPSS Inc., Chicago, Illinois, USA). Wilcoxon tests were calculated to analyze differences in FC and differences in questionnaires, between the two

Table 1
Region of Interest identification. The x, y and z Montreal Neurological Institute peak coordinates of each region of interest are provided (in millimeter).

DPMS coordinates Region of interest	Abbreviation	Side	x	Y	z
Middle frontal gyrus	MFG	Left	−30	46	33
		Right	42	38	30
Anterior insula	AI	Left	−44	13	1
		Right	47	14	0
Amygdala	AMY	Left	−20	−4	−15
		Right	22	−2	−15
Anterior cingulate cortex	ACC		0	22	35
Periaquaductal gray	PAG		1	−29	−12
Rostral ventromedial medulla	RVM		2	−36	−42

visits. Besides questionnaires with statistically significant differences in scores over time, also minimum clinically important difference (MCID) and clinical cut-off values were used to estimate SCS response rate. For NRS and PSQI scores, MCID values (NRS: ≥2 points difference and PSQI: ≥3 points of difference) were considered (Eadie et al., 2013; Farrar et al., 2001; Hughes et al., 2009). For the PCS questionnaire cut-off scores (PCS: ≤30) were considered (Neblett et al., 2013; Osman et al., 1997). Relative differences between V2 and V4 were calculated as ((V2-V4)/V2) * 100.

To calculate the Spearman correlation between FC and clinical questionnaires, the differences in relative scores on the questionnaires and the absolute connectivity values of ROI analyses between the two time points were used.

Results

Patient characteristics

A total of eleven patients with FBSS (8 females, 3 males) and median age of 55 y (Q1:50 – Q3: 65), were included in this study (Table 2). All patients reported predominant leg pain and all but one patient were experiencing pain more than 1 year. All patients had undergone, per definition, at least once spinal surgery, however 4 patients had been submitted to 3 or more surgeries. Ten patients experienced a neuropathic component (scored at least 4/10 on the Douleur Neuropathique 4 [DN4] questionnaire). All but two patients used opioids on a regular basis, two of them in combination with pregabalin. All patients were compliant with the neuroimaging protocols.

Clinical results

The NRS score for back pain was not significantly decreased during HD-SCS (before SCS: 4.79 (Q1-Q3:2.36–5.9), HD-SCS: 3.68 (Q1-Q3:2.09–4.48)) ($Z = -0.8$, $p = 0.424$). The median NRS score for leg pain significantly decreased during HD-SCS (before SCS: 5.81 (Q1-Q3:3.45–7.39), HD-SCS: 3.14(Q1-Q3:3–5.14)) ($Z = -2.49$, $p = 0.013$) (Fig. 2). Applying the MCID of 2 points out of 10, after HD-SCS, 7(3) patients improved for leg (back) pain. The median PCS score before SCS (37 (Q1-Q3: 21–43)) was not statistically significant from the median PCS score during HD-SCS (27.5 (Q1-Q3: 11.75–38.25)) ($Z = -1.326$, $p = 0.185$). At baseline, 4 out of 11 patients reached the threshold of 30 on the PCS. Five of them still had significant levels of catastrophizing during HD-SCS. No difference was found in median PSQI score before SCS (10 (Q1-Q3:9–11)) and during HD-SCS (12(Q1-Q3(9–13)) ($Z = -0.361$, $p = 0.718$). Using the MCID of the PSQI (≥3points of difference between two time points), 36% of the patients improved during HD-SCS. Sleep latency, measured by the Actiwatch spectrum plus, significantly decreased from 24.3 min (Q1-Q3:16.5–41.3 min) before SCS to 10.6 min (Q1-Q3: 8.6–20.4 min) during HD-SCS ($Z = -2.701$, $p = 0.007$). There were no other statistically significant differences for objective sleep parameters measured by the Actiwatch spectrum plus.

Table 2
Individual patient characteristics. Individual patient characteristics of the 11 included patients before SCS implantation. Abbreviation. F: female; M: male.

Patient	Sex	Age	Previous surgeries	DN4 score	Pain medication pre-SCS
1	F	64	1	4	Paracetamol + opioids + pregabaline
2	M	46	5	5	NSAIDs
3	F	55	3	4	Paracetamol
4	F	77	2	4	Opioids
5	M	55	2	6	Paracetamol + opioids + pregabaline
6	F	71	5	5	NSAIDs + opioids + gabapentine
7	F	50	2	6	NSAIDs + opioids
8	F	48	1	5	Opioids
9	M	65	3	6	Paracetamol + opioids
10	F	53	1	3	NSAIDs + opioids
11	F	52	1	5	Opioids

Functional connectivity results

Connectivity strength matrices between all ROI-pairs were calculated between both time points (before SCS versus HD-SCS). Subsequently, a comparison of FC differences between baseline and HD-SCS in the DPMS was calculated as a connectivity strength matrix and visualized on a 3D anatomical template (Fig. 3).

Significant increases in connectivity strength between mFG left – mFG right (mean difference −0.358 (95% CI −0.612 to −0.104), $t(10) = 2.69$, $p = 0.02$), mFG left – RVM (mean difference −0.148 (95% CI −0.223 to −0.073), $t(10) = 2.3$, $p = 0.04$), mFG right – AI left (mean difference −0.129 (95% CI −0.232 to −0.026), $t(10) = 2.87$, $p = 0.02$) were found during HD-SCS. A significant decrease in connectivity strength during HD-SCS, compared to before SCS was found in ROI-pair ACC – AI right (mean difference 0.126 (95% CI 0.007 to 0.246), $t(10) = -2.61$, $p = 0.03$) (Fig. 4).

When evaluating individual differences in effect size of FC strength during HD-SCS, an increase in FC strength was assessed in 9 patients for mFG left – mFG right, 10 patients for mFG left – RVM and 9 patients for mFG right – AI left. A decrease in FC strength was measured in 8 patients for ROI-pair ACC – AI right.

Correlation between functional connectivity and clinical results

As mentioned above, only NRS leg scores ($Z = -2.49$, $p = 0.013$) and sleep latency ($Z = -2.701$, $p = 0.007$) measured with AW were statistically different between both study visits and were considered for the correlation analysis with the functional connectivity ROI-pairs. However, no statistically significant differences were revealed.

Discussion

The current study is the first report exploring functional connectivity changes in the DPMS during HD-SCS, with fMRI as measurement tool. The DPMS is an anatomical network, regulating nociceptive processing in favor of facilitation or inhibition, depending on the circumstances (Tracey and Mantyh, 2007). It is for example known that the pain inhibiting circuit contributes to the “fight-or-flight response”, a form of environmental analgesia. In healthy persons, the descending pain facilitatory and inhibitory systems are in balance (You et al., 2010). In chronic pain patients, the balance of this system is often disturbed with an attenuation of descending inhibition, leading to a dysregulation of DPMS (De Felice et al., 2011). In patients with chronic low back pain, signs of enhanced PAG – mPFC coupling were revealed as compared to healthy volunteers (Yu et al., 2014). The implication of this dysregulation or decreased activation of the endogenous inhibitory system is a higher likelihood of developing chronic pain (Ossipov et al.,

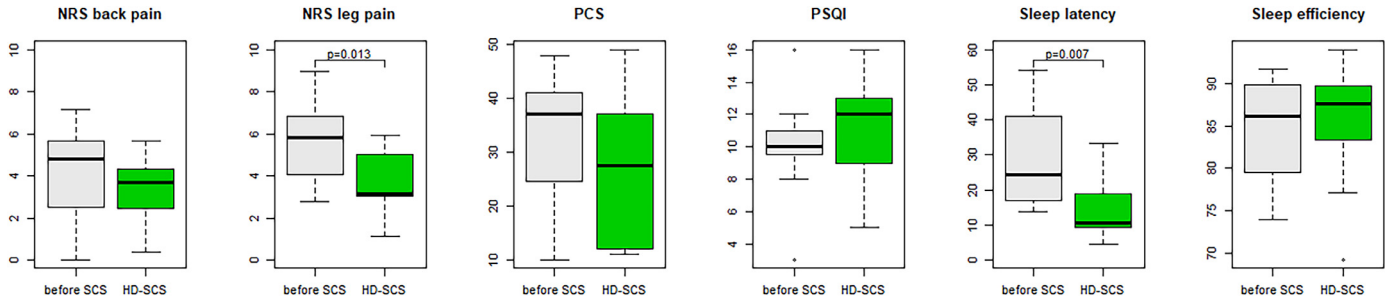

Fig. 2. Boxplots of the clinical results of NRS, PCS and PSQI scores and actigraphy variables of all patients. Gray and green boxes are representing respectively baseline data and data after 3 months of SCS. Abbreviations: NRS: numeric rating scale, PCS: pain catastrophizing scale, PSQI: Pittsburgh sleep quality index.

2014). Animal studies revealed that the engagement of the descending inhibitory pathway is a protective factor against the development of experimental neuropathic pain (De Felice et al., 2011).

Several authors already reported promising results of HD-SCS to reduce pain intensity scores (Hamm-Faber et al., 2019; Provenzano et al., 2017; Sweet et al., 2016). This statement was confirmed in the current study due to statistically significant reduced pain intensity scores for the leg pain component. Regarding back pain intensity, a large variance in back pain scores before SCS was revealed, wherefore it was rather unlikely that the decrease in back pain scores

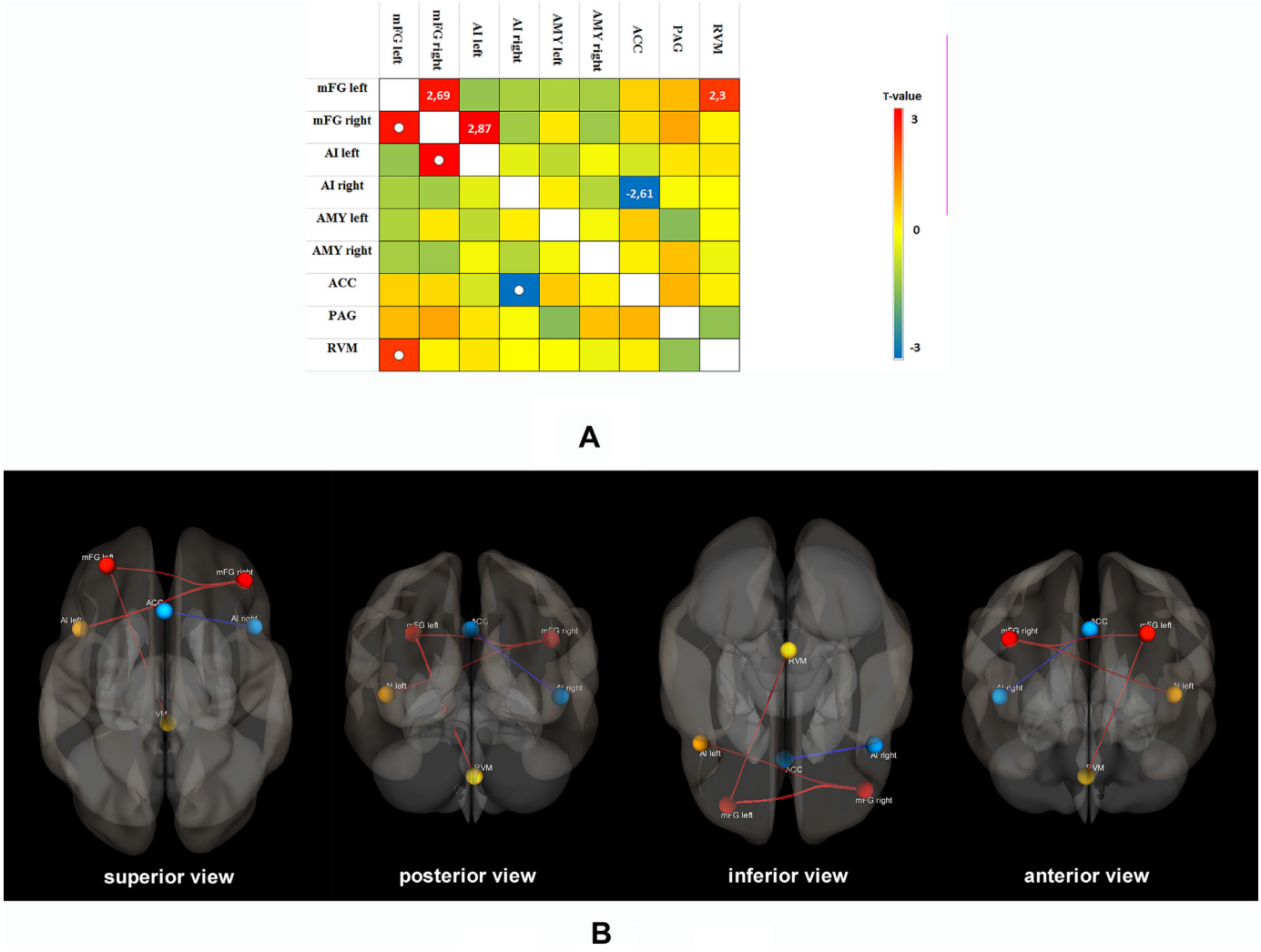

Fig. 3. ROI-ROI matrices, visualization of functional connectivity in resting state networks. A) Differences of the functional connectivity strength in ROI-pairs between HD-SCS vs baseline in all 11 patients are shown in the ROI-ROI matrices. B) The significant results ($p < 0.05$ with permutation testing) were visualized by colored circles projected on a 3D anatomical brain template (superior/posterior view). The red lines indicate increased connectivity after HD-SCS vs baseline while blue lines indicate decreased connectivity, and their thickness varies as a function of the associated T-value. In the ROI-ROI matrices, the color scale represents the T-value of connectivity strength between two brain regions (ROIs) of the selected resting state networks. Blue colors indicate a negative decreased connectivity while the red colors indicate a positive increased connectivity between two ROIs. Significant connectivity links are symbolized with a white dot and their coherent T-value. Each square corresponds to a specific resting-state network and uses predefined regions of interest. Abbreviations. ACC: anterior cingulate cortex, Al: anterior insula, mFG: middle frontal gyrus, RVM: rostro ventromedial medulla.

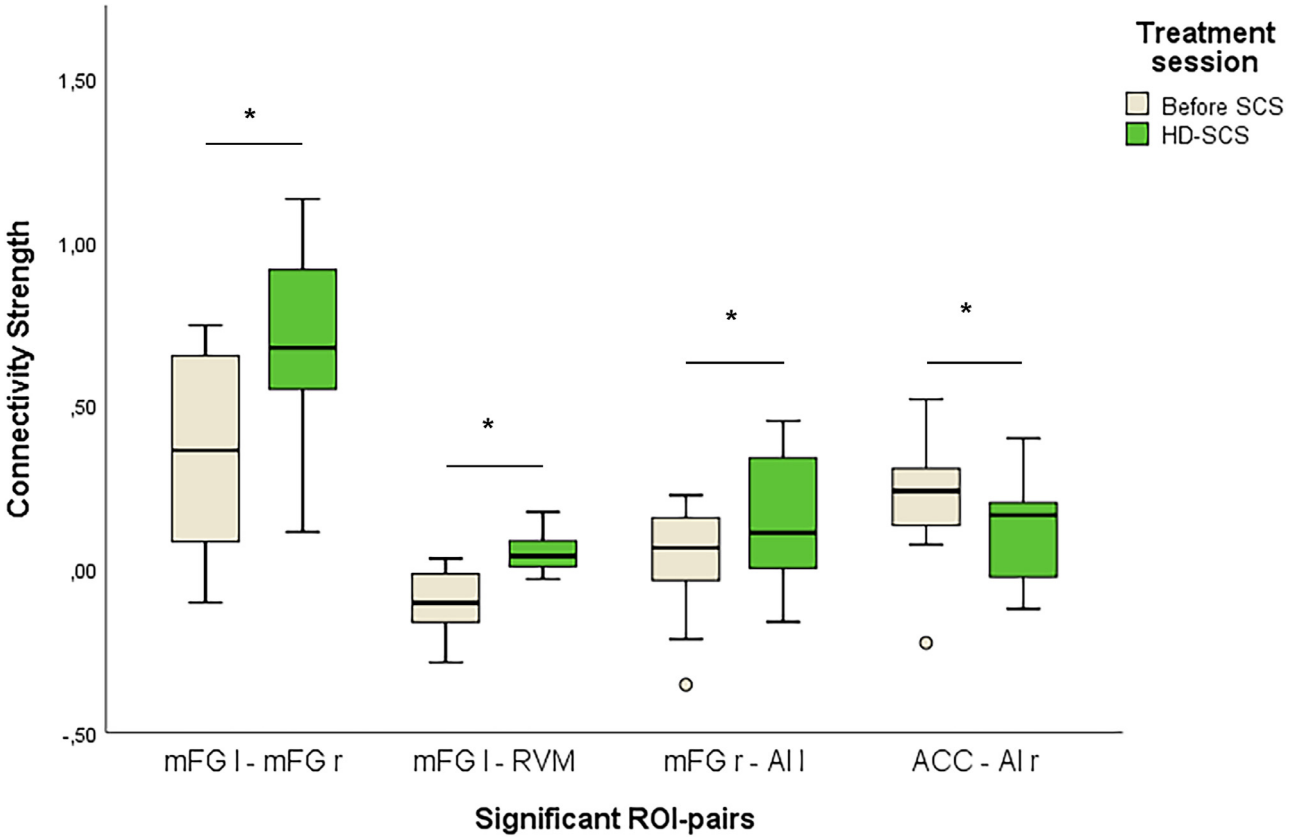

Fig. 4. Effect size of functional connectivity in ROI-pairs before SCS and during HD-SCS. During HD-SCS, there is a significant increase in functional connectivity strength in 3 ROI-pairs (mFG left – mFG right, mFG left – RVM, mFG right – AI left) and a decrease in ACC – AI right strength. *: $p < 0.05$. Abbreviations. ACC: anterior cingulate cortex, Al: anterior insula, mFG: middle frontal gyrus, RVM: rostro ventromedial medulla.

during SCS could reach a statistically and clinically significant difference. This study also demonstrated a significant decrease in sleep latency from 24.3 min (Q1-Q3:16.5–41.3 min) before SCS to 10.6 min (Q1-Q3: 8.6–20.4 min) during HD-SCS. Alsaadi et al. (2014) found that patients with chronic low back pain have a significantly higher sleep latency, compared to healthy controls (Alsaadi et al., 2014). Previously, it was already stated that SCS is able to influence sleep patterns in a positive way (Ramineni et al., 2016). This study specifically revealed improvements in sleep latency during HD-SCS, a benefit of HD-SCS that should be further explored in future studies.

Neuroimaging has been used in the past to investigate the cerebral response to pain and in particularly the descending inhibitory supraspinal influences. Studies with noxious stimulation have led to the identification of brain regions, involved in nociceptive processing. The somatosensory cortices are encoding sensory features of pain such as the quality, location and the duration of pain (Bushnell et al., 2013). The ACC, amygdala and insula are encoding emotional and motivational processes, providing the affective dimension of pain (Bushnell et al., 2013; Denk et al., 2014). It should be noted that activation of these higher brain regions is not exclusive in the context of nociceptive processes, but rather a functional connection in the context of nociception, enabling interactions between emotional factors and the experience of pain through the DPMS (Denk et al., 2014). The PAG receives input from those higher cortical sites and has reciprocal connections with the amygdala and ascending input from the spinal cord by the parabrachial nuclei (Gauriau and Bernard, 2002; Helmstetter et al., 1998). Through the reciprocal connections with the RVM, the PAG is capable of influencing descending nociceptive modulation (Ossipov et al., 2014). The RVM in its turn, is also receiving input from the thalamus, the parabrachial region and the locus coeruleus and serves as final relay in the descending modulation of pain (Ossipov et al., 2010, 2014).

Besides the well-known segmental mechanisms of action of SCS, the contribution of supraspinal loops is widely accepted (Linderoth and Foreman, 2017). Through the descending pathways, SCS is able to promote the release of serotonin and norepinephrine at the spinal dorsal horn (Saade et al., 1984). Neurotransmitters, released from those descending pathways, exert an inhibitory effect via GABA-B-receptors in the spinal cord (Linderoth and Foreman, 1999; Vallejo et al., 2017). Additionally, a decrease in GABA release in the PAG and an activation of the serotonergic system in the RVM are among the indications for a descending pain modulatory system originating from the brainstem, partly involved in the pain-relieving effect of SCS and complementary to the segmental effects (Linderoth et al., 1992; Song et al., 2009; Stiller et al., 1995). Recent studies supported this inhibitory supraspinal effect by revealing modulation of the descending nociceptive inhibitory system (DNIS) by SCS (Sankarasubramanian et al., 2018; Schuh-Hofer et al., 2018). Transcranial direct current stimulation in combination with intramuscular electrical stimulation is able to improve DPMS function in patients with knee osteoarthritis (da Graca-Tarrago et al., 2019). Additionally, occipital nerve field stimulation can reverse the malfunctioning of the descending antinociceptive pathway (Ahmed et al., 2018b). Therefore, we presumed that also SCS is able to alter the functioning of DPMS, in patients with FBSS.

This study, investigating the hypothesis of the influence of SCS on the DPMS, revealed significant differences in ROI-pairs of the DPMS before SCS versus during HD-SCS. An increase was found in three ROI-pairs (mFG left – mFG right, mFG left – RVM and mFG right – AI left) whereby the mFG was involved in each connection. A decrease was revealed in the ROI-pair ACC – AI right. These changes confirm our predetermined hypothesis that SCS is able to alter brain regions of the DPMS, in a direct or indirect way. The decrease in functional

connectivity between ACC and AI right could be associated with the results of Hsieh et al. (1995). They reported an increased baseline activity in ACC when experiencing chronic neuropathic pain. Additionally, a previous study reported a positive correlation between increased activity in pain-related areas during expectation of painful stimuli and higher pain scores during subsequent painful stimulation (Hsieh et al., 1995). This indicated that persons with a high receptivity to nociception have high cerebral activity in the ACC and insula before noxious stimulation, which makes it more likely that they will process later nociceptive stimuli as painful (Boly et al., 2007). The decrease in this connection in our study, suggests that patients have a lower receptivity to nociception during HD-SCS. The increase in the ROI-pair mFG left – RVM could be associated with the increase in number of patients that revealed a CPM-effect (Goudman et al., 2019). The experimental manifestation of a CPM-effect is expected to involve at least the activation of the PAG, RVM, subnucleus reticularis dorsalis and locus coeruleus as critical brainstem structures, also involving higher order brain structures (Millan, 2002; Youssef et al., 2016). The increased connection with the RVM during HD-SCS, is in line with studies reporting an influence of SCS on the DNIS, which provides an output under the form of an increased number of patients with a CPM-effects (Goudman et al., 2019). Finally, the increased connectivity between left and right middle frontal gyrus during HD-SCS could be related to the increased connectivity between bilateral dorsolateral prefrontal cortices, which has previously been linked to individual pain sensitivity, such that stronger interhemispheric connectivity was associated with greater pain tolerance (Sevel et al., 2016). Based on the absence of correlations between clinical outcomes and functional connectivities, this study cannot confirm that fMRI connectivity strengths might serve as a biomarker of treatment effects based on clinical variables.

In this study we only focused on MOA of HD-SCS. Future studies could explore the possible differences in strength of the influence on the DPMS between different SCS stimulation parameters. This hypothesis-driven study also has some limitations. It may be difficult to directly compare the clinical effects in our study to previous studies because of the different outcome parameters: Visual Analogue Scale versus NRS, outpatient time stamp pain intensity versus pain intensity diary and mean versus median pain intensity reporting. Patients were not asked to refrain from their daily medication. Potentially, this could have influenced our measurements. Besides the limitation of a relatively small sample size, we also need to acknowledge the issues raised in the literature regarding fMRI of the brainstem. Brainstem nuclei have a smaller size than cortical or subcortical structures, meaning applying fMRI to the brainstem entails working at the spatial resolution limit (Beissner, 2015). Additionally, different sources of physiological noise for example fluctuations by changing the volume of the chest cavity during respiration and/or pulsations of large arteries could have affected the results (Beissner, 2015). Also, we need to acknowledge the restrictions of MRI-conditioned devices on the investigated MRI sequences. Finally, this study only demonstrated the influence of SCS on the descending pathway, however the “weight” of this influence in the total explanation of HD-SCS mechanisms of action remains to be determined.

Conclusion

Our results provide indications that HD-SCS may modulate brain and brainstem regions of the DPMS in humans with FBSS, resulting in inhibitory supraspinal effects.

Declaration of Competing Interest

S. De Groote PT: no conflicts of interest to disclose L. Goudman MSc PhD: no conflicts of interest to disclose R. Peeters MSc PhD: no conflicts of interest to disclose B. Linderorth MD PhD: Bengt Linderoth serves as a consultant to Medtronic, St Jude, Boston Sci and Elekta AB. P. Vanschuerbeek MSc PhD: no conflicts of interest to disclose S. Sunaert MD PhD: no conflicts of interest to disclose M. De Jaeger PT: no conflicts of interest to disclose A. De Smedt MD PhD: no conflicts of interest to disclose J. De Andrés MD PhD FIPP EDRA EDPM: no conflicts of interest to disclose M. Moens MD PhD: Maarten Moens has received speaker fees from Medtronic and Nevro Corp. There is no other conflict of interests to declare.

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