VRIJE UNIVERSITEIT BRUSSEL

Proef ingediend met het oog op het behalen
van de graad van Master in de Geneeskunde

Evaluating the structural effects of High Frequency spinal cord stimulation over time in patients with Failed Back Surgery Syndrome:

A voxel-based morphometric study

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2019-2020

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1. Abstract

Background| Spinal cord stimulation is a neuro-modulatory technique used for the treatment chronic back pain. This system induces pain alleviation through an implantable device which delivers electrical stimuli to the spinal cord. The principal aim of this study was to explore the supra-spinal mechanisms of action of high-frequency (10kHz) spinal cord stimulation, which is a novel modality of this therapy. More specifically, by analysing the structural effects on the human brain occurring after treatment with 10kHz spinal cord stimulation.

Methods| A total number of 11 patients, diagnosed with failed back surgery syndrome (FBSS), were included in this study. Following clinical and neuroimaging (MRI imaging) evaluation, each patient was planned for surgery in order to implant a spinal cord stimulator. Clinical outcomes were measured with the visual analogue scale (VAS), central sensitisation inventory (CSI), pain catastrophizing scale (PCS), Pittsburgh subjective sleep quality index (PSQI) as well as actigraphy (Philips ActiWatch Spectrum Plus^{R}). Thereafter, pain alleviation was assessed by means of the VAS over a period of two weeks during a trial phase. If the amount of pain alleviation surpassed the threshold of 50%, a second intervention was carried out to implant the definitive spinal cord stimulator device. To assess the evolution of our subjects, patients would undergo neuroimaging as well as clinical assessment after, respectively, 1 and 3 months of treatment. The acquired raw MRI data was then pre-processed in SPM for subsequent voxel-based morphometrical analyses, necessary to detect volumetric alterations between the different timepoints. Similarly, statistical analyses were performed to determine if patients had undergone any statistically significant evolution in their clinical situation. Finally, a repeated measure correlation test was carried out to assess to what extent the cerebral structural alterations were associated to the clinical improvement. More importantly, this analysis provided important information about the temporal aspect of the morphological alterations.

Results| All patients successfully responded to the initial trial therapy. After just 1 month of 10kHz spinal cord stimulation, a statistically significant reduction in pain catastrophising was observed. Likewise, a statistically significant decrease of the pain intensity in back pain was seen after 1 and 3 months of treatment. In terms of leg pain however, a significant reduction in pain intensity was only observed after 3 months. In terms of structural alterations of the brain, significant decreases in volume were observed after 3 months of treatment. More precisely, in the left and right hippocampus. No volumetric changes were registered in white matter. The repeated correlations measure reported a significant correlation over time between the volumetric changes in the hippocampal formation (bilaterally) and the reduction in back pain.

Conclusions| This study reveals that 10kHz spinal cord stimulation can induce volumetric changes in brain regions involved in the modulation of pain after just 3 months of treatment. Moreover, our findings suggest these morphological alterations may relate to the pain-relieving effect of 10kHz SCS in patients suffering from FBSS.

Keywords| Spinal Cord Stimulation, High-frequency, Chronic Back Pain, Failed Back Surgery Syndrome, Neuroplasticity, Volume, Structural, Voxel-Based Morphometry

Financial support| This study was funded by Nevro, Inc.

2. Abbreviations

SCS: spinal cord stimulation, FBSS: failed back surgery syndrome, B: baseline, T1: 1st month after SCS implantation, T2: 3rd month after SCS implantation, VBM: voxel-based morphometry, DN4: douleur neuropathique en 4 questions, VAS: visual analogue scale, CNS: central sensitisation symptoms, PCS: pain catastrophizing scale, PSQI: pittsburg subjective sleep quality index, ROI: regions of interest, TGMV: total grey matter volume, TWMV: total white matter volume

3. Introduction

Chronic pain is a major problem in our society, affecting approximately 1-19% of the European adults. Patients are often greatly disabled and lack a descent quality of life(1-5) due to a loss of mobility, persistent pain, reduction of their social functioning and economic consequences(1, 5-7). With a prevalence ranging from 5 to 10%, chronic back pain is one of the most frequently occurring pain disorders, and is thought to be one of the leading causes of disability worldwide (4, 8-13). For this reason, there has been an increasing interest in topics relating to chronic pain disorders over the past years. One topic in particular, neuroplasticity, has been one of the more frequently discussed topics due to the everlasting search for biomarkers and/or mechanisms in various disorders(14-18).

In this context, research has already demonstrated the occurrence of both functional and structural neuroplasticity in the brain of patients suffering from chronic disorders such as Alzheimer, MS, depression etc(19-25). For instance, grey matter changes in fronto-limbic brain regions as well as the cerebellum have been observed in patients suffering from a major depression and multiple sclerosis respectively (19, 25). Similarly, when the brain of patients, suffering from a chronic pain disorder, is compared to healthy individuals significant alterations of cerebral morphology can be observed(4, 8, 26-39). In general, the brains of these patients display a reduction in grey matter volume(26). Furthermore, it appears that volumetric alterations are not randomly scattered over the brain but occur in very distinct brain areas(40). More specifically, regions that are part of the pain neuromatrix, a system involved in the modulation of pain on different levels, being sensory, cognitive and affective processing(4, 8, 10, 26-31, 34).

Certain authors believe that some of these structural alterations of the brain might be maladaptive and suggest that this neuroplasticity could incite the chronification of acute pain. Therefore, these changes could instigate a vulnerability for chronic pain disorders(10, 14, 16, 26, 27, 33, 38, 41). The idea behind this hypothesis is that the observed grey matter loss, occurring in brain areas involved in pain regulation, would lead to dysfunctionality of the pain modulation system. This could result in a higher

sensitivity to nociceptive input and flawed pain-coping mechanisms. Individuals would subsequently direct more attention to their symptoms, which could impede the treatment responsiveness(32).

The current approach to chronic pain treatment is primarily conservative, relying on oral analgesics such as non-steroidal anti-inflammatory drugs and opioids(7, 12, 42-48). After all, this is an accessible, cheap, and often relatively safe solution to pain(49). However, recent research suggests that this approach might not be the most appropriate choice for the treatment of chronic lower back pain(45, 47, 48, 50-52). A first issue of oral analgesics is the limited clinical efficacy, especially on a long-term basis(43, 45, 48, 49, 51, 53-56). In a study by Shaheed et al. for instance, meta-regression analysis indicates that clinically significant pain relief is unlikely to be achieved when using opioids at doses beneath 240mg. Increasing the dose beyond this recommended amount would moreover not guarantee further improvement of the clinical effectiveness(48). A second issue which restricts the clinical effectiveness of this treatment is its side-effects (gastro-intestinal toxicity, somnolence, etc), frequently associated with this type of medication(43, 45, 46, 48, 49, 56, 57). Finally, the use of opioid analgesics is accompanied by the risk of addiction, which can lead to drug overuse and/or death(54, 58).

In cases where pain symptoms are related to an organic or structural defect, a interventional treatment is often proposed as an alternative to medication(59). This consists of minimally invasive procedures, such as epidural drug injections, ablation of targeted nerves, and surgical techniques, such as discectomy and the implantation of intrathecal infusion pumps or spinal cord stimulators(60). The additional benefit of such interventions however appears to be variable(49, 50). It's role in the management of chronic pain disorders is therefore limited, especially when considering the cost and risk of complications associated with surgery(61).

Although considered an interventional therapy, spinal cord stimulation (SCS) often forms the next stage in the management of pain when the abovementioned methods fail to control the patient's complaints, as is the case for patients suffering from FBSS(6, 43, 59, 62-64). SCS is a neuro-modulatory technique, which consist of an implantable device that delivers electrical stimuli to the spinal cord (Fig. 3). The leads conducting the electrical pulses are fixated into the epidural space and connected to the pulse generator, which is implanted into a small subcutaneous pocket (ex. in the gluteal region). The required surgical intervention for SCS is minimally invasive, as it only requires two skin incisions and a partial laminectomy to provide an access to the spinal canal(65). By stimulating the spinal cord, SCS appears to modulate and subsequently reduce painful sensations. Moreover, evidence suggest that this treatment is more cost-effective than conservative treatment and surgical options(2, 6, 63, 64, 66). The initial idea behind this therapy is based upon the gate control theory of Melzack et al.(7, 12, 67). As

such, SCS is able to mask the painful area by inducing paresthesia. However, the downside of this therapy is that patients must endure a constant tingling sensation resulting from the supra-threshold stimulation (Fig. 1).

This limitation as well as other restraints, has encouraged the search for alternative waveforms as well as the improvement of device components over the past five decades(62). As such, ongoing research has led to the development of novel SCS modalities such as high-frequency (10kHz), burst and high dose SCS. In this study we focused on high-frequency stimulation only. This type of SCS induces a sub-threshold stimulation of the dorsal spinal cord by using a lower amplitude of electrical impulses compared to conventional SCS. In contrast, the frequency of the electrical pulses is much higher than conventional SCS (respectively 10kHz and 30-80 Hz)(68). This is necessary to deliver the same amount of energy to the spinal cord per second. The advantage of using lower pulse amplitudes is that they do not exceed the action potential threshold. As such, 10kHz SCS ensures a paresthesia-free pain alleviation, which is more comfortable than the conventional modalities(68, 69).

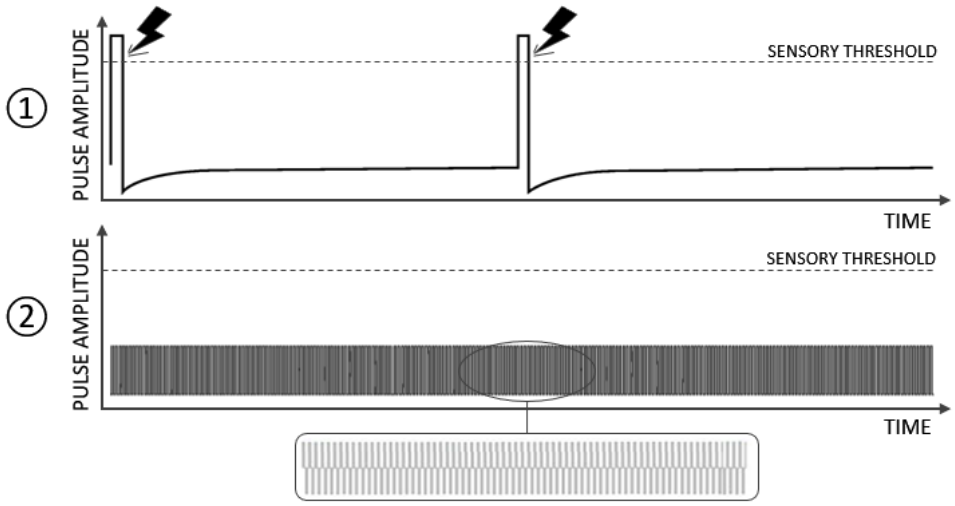

Figure 1: Comparison between conventional and 10kHz SCS. ①The electrical stimulation as seen in conventional supra-threshold SCS. ②Displays 10kHz SCS, in which electrical stimuli do not exceed the sensory threshold. Figure adapted from(70).

Research suggests that 10kHz SCS is more effective than the initial conventional SCS(6, 68, 71). However, regardless of its clinical effectiveness, little is known about the working mechanism of this modality. Initially, the effect of SCS was thought to rely solely upon segmental effects. This working hypothesis was primarily based upon the gate control theory of Melzack et al.(72-74). In this framework, Shealy et al believed that electrical stimulation of the dorsal column in the spine could inhibit the transmission of nociceptive stimuli through Aδ and C fibres which would ultimately reduce pain by induction of paraesthesia(11, 12, 58, 62, 67-70, 75-82). Although the gate control mechanism has been widely accepted throughout the past, there are still certain clinical aspects associated to SCS which cannot be explained by this theory. For instance, SCS is unable to reduce acute nociceptive

pain(62, 77). Moreover, the rise of new (sub-threshold) stimulation modalities has proven that the pain relief does not rely upon the paraesthesia (68, 70, 82).

These observations have led authors to believe that the SCS-associated effects cannot be attributed to segmental mechanisms alone(62, 68, 69, 77, 80, 82). Instead, research suggests the involvement of supra-spinal mechanisms, established through orthodromic stimulation of brain regions, might contribute to the pain alleviation(12, 62, 68, 70, 77, 80, 82-90). This idea is endorsed by different studies which have demonstrated the effectiveness of SCS in other neurological disorders resulting from cerebral dysfunction/deterioration(19-25, 62, 91-93). Overall, there are two possible supraspinal mode of actions by which SCS might exert its effect. On one hand, the observation of significantly altered concentrations of neurotransmitters, such as serotonin, norepinephrine, gamma-aminobutyric acid (GABA), in patients responding to SCS, imply the involvement of descending neuro-humoral pathways(62, 70, 80, 82, 94). On the other hand, observations from neuroimaging studies also reveal functional and metabolic changes in brain regions involved in cognitive, affective or sensory processing of pain(83, 85, 94-100). These findings suggest that, aside from reducing the transmission of nociceptive input on a segmental level, SCS might also influence the way pain is experienced.

Although a substantial amount of research has been performed on the topic of cerebral neuroplasticity in the context of pain disorders, no studies have yet investigated the structural short- and long-term treatment effects on the cerebral morphology. Thus, the goal of this study was to objectify the impact of 10kHz SCS on the brain from a structural perspective. Insight into these supra-spinal effects is key as they may improve our understanding of the underlying mechanism of action of 10kHz SCS. In turn, this could result in the improvement of the long-term efficacy of the treatment and optimisation of its pain relieving effects(18, 62, 77, 80, 81).

Earlier on, we mentioned the occurrence of structural changes in distinct brain areas as result of chronic pain, which are thought to be maladaptive of nature(4, 8, 26-39, 101). In regard to this aspect, we asked ourselves if treatment could also induce neuroplastic changes. Based on results of recent studies we hypothesised that 10kHz SCS could induce volumetric cerebral alterations, which would be related to the pain reduction(6, 82, 83, 95, 96, 98, 102, 103). Moreover, we believed that these volumetric changes would most likely occur in brain regions involved in the modulation of pain.

4. Methods & materials

4.1 Participants

Our patients were recruited at the University Hospital of Brussels between September 2015 and May 2017 and consisted of 11 patients suffering from FBSS. This is a type of chronic lower back pain, occurring in approximately 10 to 40% of patients who have undergone back surgery(2, 11, 67). More precisely, it is defined as a "lumbar spinal pain of unknown origin either persisting despite surgical intervention or appearing after surgical intervention for spinal pain originally in the same topographical location"(104). Prior to participation, all patients signed an informed consent. Thereupon, the douleur neuropathique en 4 questions (DN4) questionnaire was applied to assess the neuropathic component of the patients' complaints(105). For this test, a score ≥ 4 suggested a neuropathic component of the pain, which patients were suffering from(106). The in- and exclusion criteria which we applied for our patient recruitment are listed in Table 1. Our exclusion criteria were chosen in such manner to reduce the occurrence of any morphological or functional alteration of the brain by factors other than SCS.

Table 1: In -and exclusion criteria	
Inclusion criteria:	Exclusion criteria:
1. Chronic back pain	1. Medical history of neuropsychological disorders
2. Life expectancy > 6 months	2. Neurological disorders (MS, seizures,…)
	3. History of head trauma's
	4. History of alcohol or drug abuse
	5. History of treatment with psychotropic medication
	6. Contra-indication for MRI scanning
	7. Fear for entering an MRI

Table 1: In -and exclusion criteria for patient recruitment.

4.2 Ethical approval

This study was approved by the ethics committee of the University Hospital Brussels (B.U.N. 143201526931) and conducted following the ethical Principles for Medical Research of the WMA(107).

4.3 Study protocol

In this longitudinal prospective study patients were followed over a period of approximately 4 months. During this period, data was collected on 6 occasions (Fig. 2: A1-A6). During the first, third and fifth appointment clinical data was acquired by means of 4 questionnaires and an ActiWatch-spectrum plus wristwatch (Philips Respironics Inc, Murrysville, PA, USA). As such, five parameters were assessed; [1] pain intensity, [2] central sensitisation symptoms, [3] pain catastrophizing, [4] subjective sleep quality and [5] objective sleep quality (cfr. 4.2.3). This data served as a (subjective) measurement for the clinical

effectiveness of the treatment. All three clinical appointments (A1, A3, A5) took place 2 weeks in advance of, respectively, the second, fourth and sixth appointment (A2, A4, A6), during which neuroimaging was performed. The aim of these neuroimaging sessions was to assess the cerebral morphology, respectively, prior to implantation, 1 month and 3 months after implantation of the SCS.

Prior to implantation of the definitive SCS, a trial version of the SCS was implanted (S1). Subsequently, clinical improvement was assessed 4 weeks later (S1-S2). Patients who were satisfied with the pain alleviation (i.e. ≥50% decrease in pain) were scheduled a second time for surgery in order to implant the definitive SCS (S2). The final SCS consisted of a 10kHz spinal cord stimulator (Senza rechargeable system: Nevro Corp., Redwood City, CA, USA). During the first surgical intervention two leads were placed percutaneously in the posterior spinal epidural space under radiographic imaging and subsequentially attached to an external stimulator. On the other hand, the leads were attached to a subcutaneously implanted pulse generator (IPG) in the definitive intervention. In both trial and definitive interventions, the distal tip of the electronic leads was positioned at T8 and T9, near anatomical midline (Fig. 3). Stimulation was configured bipolarly in all patients and could be adjusted during the trial phase in terms of impulse amplitude. During the definitive 10kHz SCS treatment however, stimulation parameters were held constant. The impulse amplitude was set at 1.5 to 2.5 mA, depending on the patient's preferences, and the pulse width was set at 30 μs.

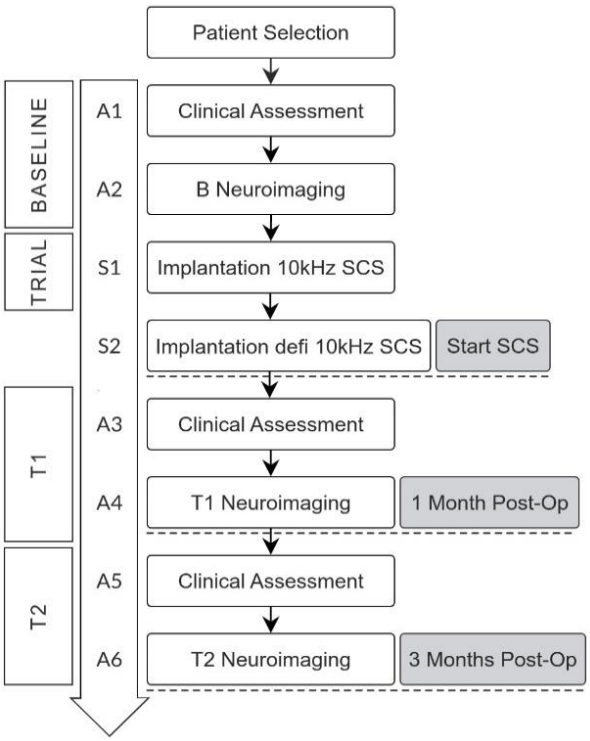

Figure 2: The timeline of study consists of 3 periods (Baseline, T1, T2), during which patients had 6 appointments (A1-A6) for clinical evaluation and neuroimaging. Prior to definitive implantation of the SCS (S2), a trial phase (S1) was implemented to assess the treatment response rate in our patients.

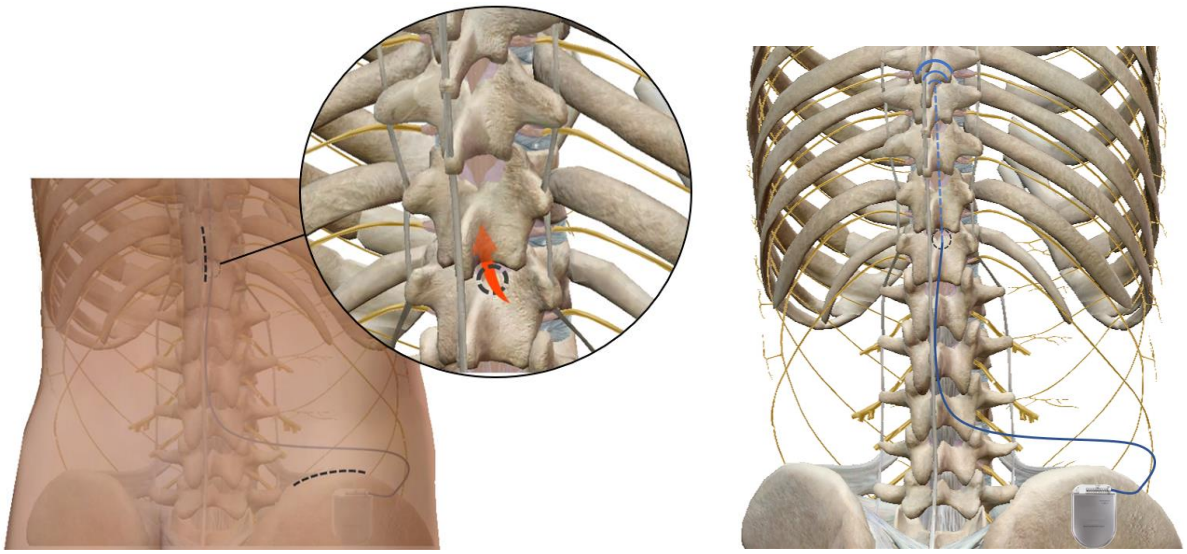

Figure 3: An overview demonstrating the placement of the spinal cord stimulator. The dotted lines on the skin illustrate the skin incisions through which the device components are inserted. In our study the IPG was implanted in the gluteal region. However, this may also be implanted on other locations such as the flank, lower abdomen or pectoral area(108). In the area delineated by the dotted circle, a laminectomy is performed to provide access to the spinal canal.

4.4 Outcome measures

The primary endpoint of this study was the pre- and post-operative assessment of the structural effects in the brain under influence of 10kHz SCS therapy. The secondary endpoint was the evaluation of the clinical progression of patients as well as its correlation with structural alterations in the brain.

4.4.1 Structural brain alterations

Changes in brain morphology were assessed on T1 weighted anatomical MRI images, acquired through neuroimaging at A2, A4 and A6. The voxel-based morphometry (VBM) toolbox, within the Statistical Parametric Mapping (SPM12) program, was applied to specifically determine the location and size of these alterations(23, 109, 110). VBM is an MRI-based neuroimaging technique which allows the calculation of the global brain size as well as the volume of local regions(111). The utility of VBM has already been demonstrated in chronic pain disorders such as chronic lower back pain as well as other disorders such as epilepsy(112, 113), schizophrenia(114, 115), dementia(116, 117) and headache-related pain disorders(118, 119). This provided us key information on the optimal settings necessary for VBM analyses as well as potential caveats that needed to be avoided. Contrary to other approaches such as resting-state fMRI, EEG, PET-CT and others, VBM examines the brain from a structural perspective (Fig. 4). More specifically, on a voxel-base level. Each of these voxels represent a small rectangular portion of our brain which consists of one or more tissue types (white matter, grey matter and/or cerebrospinal fluid)(120). Essentially, alterations of the human brain can be analysed in terms of either volumetric or density changes (23, 109, 111). Density is the concentration of a tissue type within voxels of a certain brain region, whereas the volume indicates the amount of voxels (expressed in ml or mm^3) from which a tissue type is composed of(23, 32, 120, 121).

In VBM, the principal aim is the identification of regional differences in the concentration (density) of a particular tissue(23). The drawback of analysing density however, is that we cannot determine which tissue type has in- or decreased, in brain regions which show an altered density. Hence, our principal point of interest was the identification of global and focal volumetric changes, rather than density changes. A modulation procedure was therefore performed upon the MRI data (cfr. 4.6), allowing the calculation of absolute volumetric changes(23, 111, 121, 122).

4.4.2 Clinical status

Pain intensity

The extent of the pain was quantified with the visual analogue scale (VAS), which is sensitive to treatment effects(123). Over a period of two weeks, three times per day, patients were asked to indicate the amount of pain they experienced on a 10cm long line which was scaled from 0 to 100. Cut-off values were interpreted as following: [0-4 mm] no pain; [5-44 mm] mild pain; [45-74 mm] moderate pain; [75-100 mm] severe pain(124). The drawback of the VAS is that it is unable to provide a complete overview of the pain experience (loss of function, pain tolerance, emotional burden etc.)(125-127). However, research indicates that VAS is a reliable and sensitive tool to asses treatment outcomes on the severity of pain, especially in chronic pain disorders (125, 126, 128-130).

Central sensitisation symptoms

Central sensitisation is a phenomenon in which neurons of our central nervous system become hyperactive, which leads to a higher sensitivity to noxious and non-noxious nociceptive stimuli. As result, pain tends to occur faster, due to a lower pain threshold, and last longer(131). Central sensitisation symptoms were measured by means of the central sensitisation inventory (CSI), which has a sensitivity of 81% and specificity of 75%. The questionnaire consists of 35 questions, divided into two parts. The first, contains 25 questions scaled from 0 (never present) to 4 (always present). The second, consists of 10, yes or no, questions. The cut-off value for clinically significant central sensitisation symptoms is a score of ≥30. Symptom severity can further be divided into a mild (30-39), moderate (40-49) and severe category(60-100) (132).

Pain catastrophizing

Pain catastrophizing is a psychological phenomenon associated with the aggravation of pain as result of an impaired coping mechanism(133, 134). This is instigated by magnification of the experienced pain, rumination and feelings of helplessness(133, 135). These factors were assessed with the Pain Catastrophizing scale (PCS), which consists of 13 self-rated questions. Each answer quantifies a reaction to pain on a scale of 0 (not at all) to 4 (all the time). The resulting total score ranges from 0 to 52 and the cut-off value for pain catastrophizing is set on ≥30. In terms of accuracy, it is suggested that the PCS

has a “moderately acceptable reliability”. However, the validity of the questionnaire is considered good, with an internal consistency ranging from 0.6 to 0.87(136-138).

Subjective sleep quality

Using the Pittsburgh Subjective Sleep Quality Index (PSQI), 7 aspects of sleep were assessed over a period of 1 month. More precisely, the subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction (139). A total of 19 questions, scaled from 0 to 3, were distributed over all 7 domains. With a sensitivity of 89.6% and specificity of 86.5%, questionnaire is considered very reliable. A cut-off value of ≥5 determines a poor sleep quality(139).

Objective sleep quality

Objective sleep quality was assessed on 5 different levels using an ActiWatch-spectrum Plus wristwatch (Philips Respironics Inc, Murrysville, PA, USA) which measures ambient light intensity and movement at night(140). The following parameters were analysed; [1] total sleep, [2] sleep onset latency, [3] sleep efficiency, [4] sleep fragmentation and [5] number of wake bouts. The sleep fragmentation was defined by defined by the periods of wakefulness after a sleep onset(141). In our case we did not analyse the sleep percentage and fragmentation index. The sleep data was collected over a period of 2 weeks during the baseline, T1 and T2 period. The reliability of the Actiwatch-spectrum was confirmed in a study by Mantua et al. that compared the ActiWatch-spectrum with conventional polysomnography(142).

4.5 Image acquisition & scanning protocol

Neuroimaging was performed at the University Hospital of Brussels. In the past decade, the safety of MRI scanning on patients with SCS implants has only been assessed by a few studies. Overall, research suggests that MRI examinations are only safe in some SCS systems under strict implementation of specific protocols(143-147). These protocols, which vary among the various brands of SCS, describe which parameters are permitted for scanning. Currently however, there is not a single MRI compatible SCS device on the market. This issue is related to the magnetic fields of the MRI, which can exert forces and result in displacement of metallic objects. Patients may also suffer important nerve damage to the spinal cord during neuroimaging, due to an increase in temperature at the tip of the SCS lead. Such changes in temperature are caused by fluctuations in electrical current, generated by the emitted radiofrequency-waves of the scanner. Prior to MRI imaging it is thus strongly advised to check the SCS compatibility(148, 149). In our case, the manufacturer’s manual stated that our device was “MRI conditional”(150). Specific imaging guidelines were therefore followed to minimize the risk of complications(149). For safety reasons, our patients were advised to notify the investigators in case of unusual sensations at the implantation site, as the spinal cord stimulator was left on during image

acquisition (151). They were also instructed to remain motionless and awake throughout the procedure to optimise the accuracy of the acquired data.

MRI data was obtained following the same scanning protocol as described in the study of De Groote et al.(152). Anatomical images were acquired using an axial fast spoiled gradient echo (FSPGR) bravo scan obtained from a GE MR 750w Discovery 3T^{TM} MRI scanner. These images consisted of 124 axial slices with slice thickness 1 mm, no inter-slice gap, repetition time = 7.74 ms, echo time = 3.75 ms, flip angle = 12°, scan matrix = 256 x 256 and FOV = 240 x 240 mm2.

4.6 Image processing

For our morphometrical analysis a voxel based morphometrical (VBM) technique was applied. Although its application is complex, the idea behind this technique is simple. Essentially, VBM conceives the brain as a collection of thousands of little boxes. These so-called voxels may contain grey matter, white matter, and/or cerebrospinal fluid(120). After a series of image processing steps (Fig. 4), the compositions (amount of each tissue type) of each of those voxels is calculated and subsequently compared between the first, second and third measurement. As such in- or decreases in volume of a certain tissue type are mapped out and calculated(109).

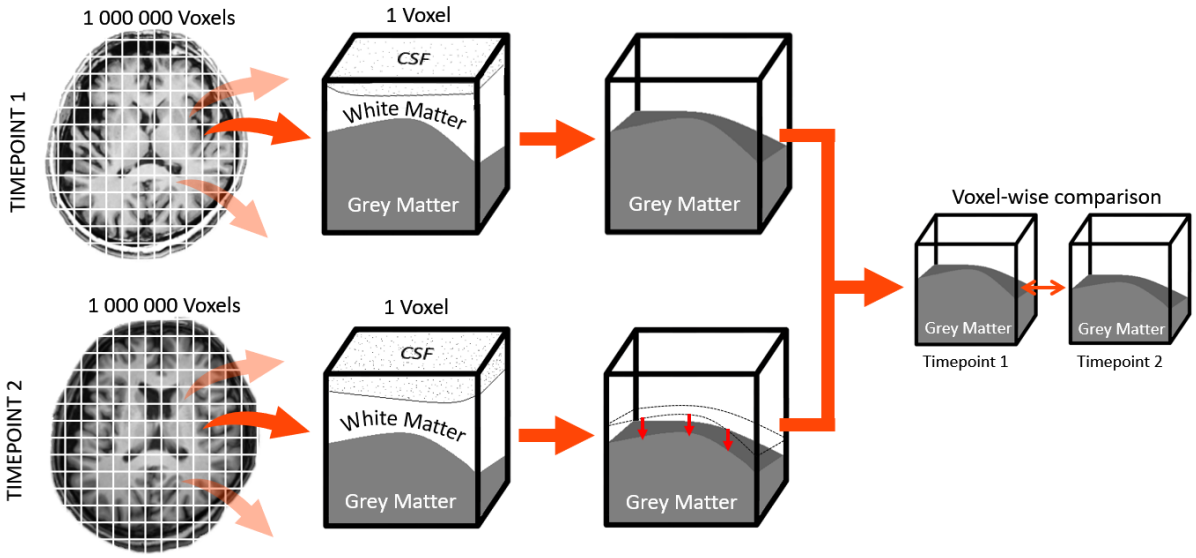

Figure 4: A simplified overview of the mechanism by which volumetric alterations are determined by VBM. After a series of image processing steps, the composition of each voxels is computed per tissue type and subsequently compared with the same voxel from a previous MRI scan. This step is repeated for all other voxels.

Naturally, our patients possessed different brain sizes and shapes(111, 153). In order to compare structural aspects of an individual's brains between different occasions as well as patients, a voxel-wise correspondence between the different MRI scans was imperative. If we consider three non-normalised brains A – B – C for instance (Fig. 5), as well as one voxel in each of them. A precise comparison of their composition would be impossible since they do not represent the same anatomical region within the brain, even if they share the same location in space.

The acquired raw MRI data was therefore pre-processed prior to morphometrical analyses. This image preparation ensured that identical voxels of different scans could be equitably compared, which allowed us to calculate volumetric changes over the course of time(154). This implied that voxels are located on identical coordinates within a 3D/stereotactic space. Pre-processing was performed using the twelfth version of SPM software (Wellcome Department of Cognitive Neurology, London, UK) following a DARTEL-based protocol (Fig. 6), developed by Ashburner et al.(110).

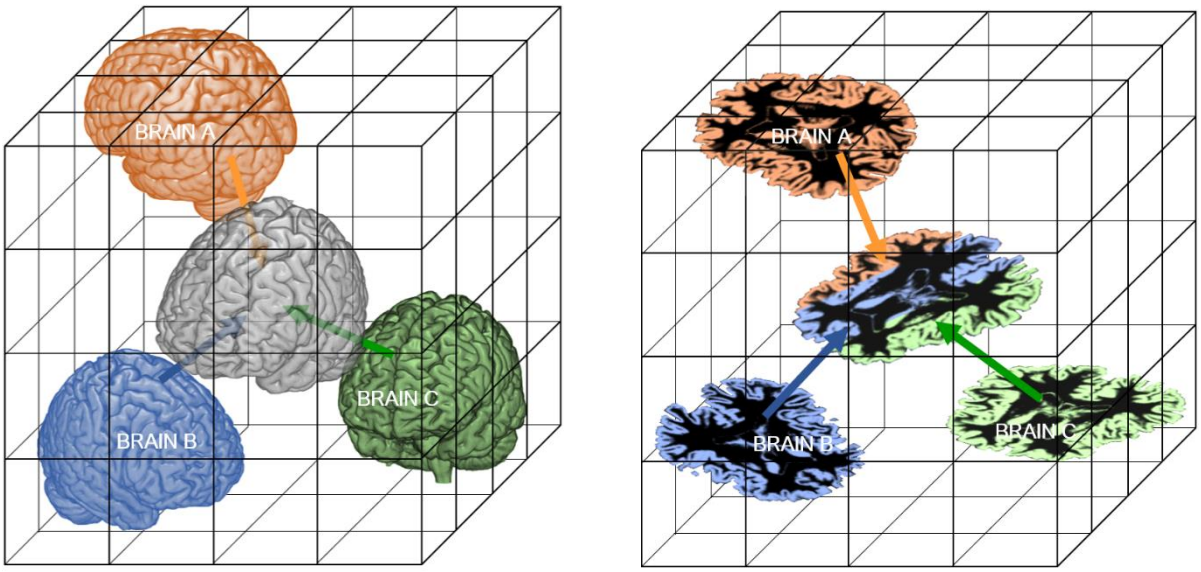

Figure 5: During pre-processing mismatched brains are brought together to a common point in a 3D space to ensure a voxel-wise correspondence between the tissue specific images. The right image displays the segmented equivalents of the brain models shown in the left image.

Pre-processing consisted of 5 stages (Fig. 6). First, we converted raw data (1 Tesla MRI scans) from DICOM format to a NIFTI format, which enabled further image editing. Thereupon, a segmentation was performed to separate MRI images into three tissue-specific images. More precisely, [1] grey matter, [2] white matter and [3] cerebrospinal fluid (CSF). Because segmentation did not change the coordinates of the brain, tissue specific images still could not be compared. A normalisation procedure was therefore applied, in which the segmented data of all patients were then co-registered to a mutual template. As such, our data was warped into a common stereotactic space (Fig. 5) (122). This space can be pictured as a group of voxels organised within a 3D space by means of a specific set of coordinates.

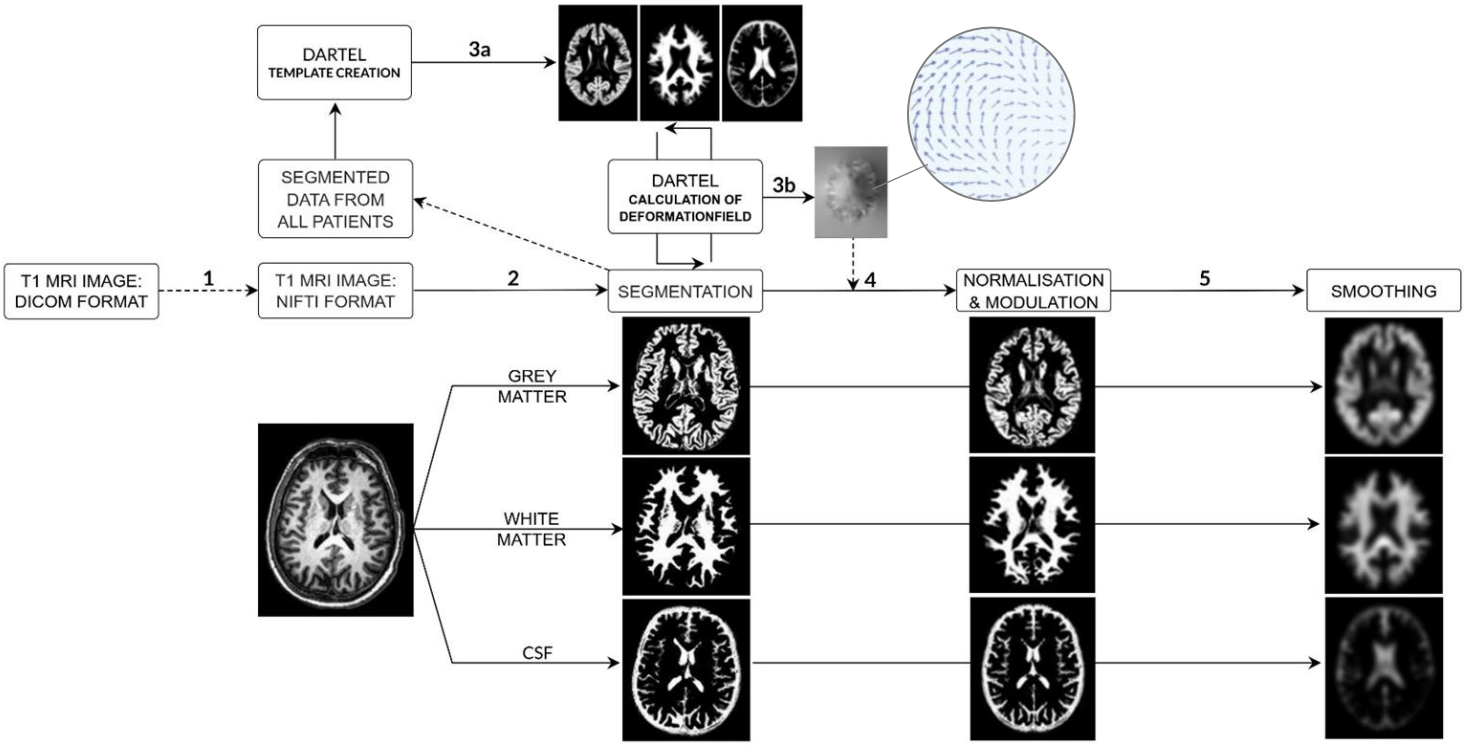

Figure 6: Summary of image processing steps:

Step 1: Format transformation

Step 2: Segmentation

Step 3: DARTEL procedure: Template creation (a) & Calculation of deformation fields (b)

Step 4: Normalisation & Modulation

Step 5: Smoothing

Prior to spatial normalisation, a DARTEL procedure was executed to create template images of grey matter, white matter and CSF, which were generated by averaging our patients' segmented images(110). During the second stage of the DARTEL procedure, deformations were applied onto the tissue-specific templates to reproduce each of the segmented images. The inverse deformation was then again applied to re-create the templates. As such deformation fields were calculated. These images describe the manner in which a patient's brain need to be displaced in space, in order for it to fit into the same stereotactic space as our templates(109, 121). This back and forth process is repeated multiple times, with each iteration using slightly different warping parameters. The DARTEL algorithm typically applied so-called small diffeomorphic deformations, which were easily calculated and reverted (110). As result, the program can repeatedly calculate deformation fields through a loop mechanism on a short notice. After several loops, the algorithm then selects the values that ensure the best transformation. Following on the DARTEL procedure, segmented images were normalised by means of the deformation fields and warped into to the common stereotactic space. Our space was based upon the MNI (Montreal Neurological Institute) coordinate system which is frequently used in VBM-studies(155).

As such we normalised the disparity in brain shape and size between different patients(23, 24). This process is known to enhance and/or suppress local volumes in certain brain areas in function of the deformation field due to the stretching and squeezing of images. The normalised data was therefore modulated to preserve absolute volumes by multiplying the normalised data with the Jacobian determinant, obtained from the deformation field themselves(109). Finally, images were smoothed using an 8 mm FWHM (Full Width Half Maximum) isotropic Gaussian kernel. This ensured the normality of our data and compensated for inaccuracies produced by the normalisation(23, 24).

4.7 Data analysis

To assess if 10kHz SCS could induce supra-spinal effects, we performed a VBM analysis to determine if our patients' brains had endured structural changes after SCS (Fig. 6). In our case, we were only interested in grey and white matter.

All calculations were implemented in the statistical parametric mapping (SPM12) software which ran on Matlab 2018b (Mathworks^{TM} Boston). The voxel-based morphometrical analyses were performed using a general linear model approach(109). First, a factorial design was executed by means of a one-way ANCOVA test. Grey and white matter were analysed separately. The analysis included three factor groups, each containing pre-processed images of, respectively, baseline, T1 and T2. In both grey and white matter analyses, age was added as a covariate to our analysis to correct any unwanted morphological changes related to this factor. Furthermore, an absolute threshold of 0.2 was applied, rather than the default 0.1, to minimise the partial-volume effect. The absolute threshold determined how much of grey or white matter a voxel should contain in order to be included in the morphometrical analysis. Lowering the threshold increases the number of voxels that was included in the analysis. As most of those voxels only contain minor ("partial") volumes of grey (or white) matter however, the specificity of the obtained results will decrease. Therefore, volumetric alterations in these brain regions are incorrectly identified. In other words, the observed alteration in volume of a certain tissue type will in fact result from changes in other matters. This partial volume effect is most pronounced near the borders between grey and white matter(156, 157).

Following the factorial design, we then used the SPM contrast manager to exactly locate focal alterations in grey or white matter between the different timepoints. This tool uses contrasts to determine if any in- or decreases in volume of certain brain regions had taken place throughout the treatment with 10kHz SCS (Table 2). In essence, the program conceives pre-processed images from one timepoint as a "condition", which can then be subtracted by another condition (from another timepoint) to create a contrast. For example, by subtracting grey matter images of T2 from those of Baseline we can determine if grey matter volume has decreased after 3 months of treatment. In other

words, the equation B – T2 implies that images from baseline show a higher grey matter volume than those taken after three months of treatment. If this is the case, the program will subsequently locate voxels on the MRI images from T2 which show a significant reduction in grey matter. Results are then rendered in a statistical parametric t map, which displays where and to which extent brain regions decreased in volume. The t map also provides information on the size (in number of voxels) and the exact coordinates of the altered brain regions. To assess the structural evolution of the brain from baseline to T1 or T2, two contrast were constructed (Table 2). For these contrast-analyses, a significance threshold of p (uncorrected) < 0.001 and a cluster threshold (K_E) of 25 were selected.

Table 2: Summary of applied conditions for the design of different contrasts

	☐ ↓ Baseline	☐ ↓ T1	☐ ↓ T2	Where: 1 = include -1 = subtract 0 = do not include
1. Baseline > T1	1	-1	0	Baseline - T1
2. Baseline < T1	-1	1	0	T1 - Baseline
3. Baseline > T2	1	0	-1	Baseline - T2
4. Baseline < T2	-1	0	1	T2 - Baseline

Table 2: Summary of the conditions applied for the design of different contrasts to identify possible structural changes of the brain throughout the treatment. The abovementioned contrasts were constructed to examine whether grey or white matter volume: [1] Decreased after 1 month of treatment, [2] Increased after 1 month of treatment, [3] Decreased after 3 months of treatment or [4] Increased after 3 months of treatment.

Thereafter, regions of interest (ROI) were defined based on the MNI coordinates of the cluster regions which demonstrated significant volumetric changes. This was performed by means of Marsbar (0.44 version) toolbox (158). An attempt was then undertaken to determine the anatomical location of the ROI using the build-in SPM viewing options (Display > Labels > Neuromorphometrics). However, due to the lacking resolution of our template image upon which results were displayed, findings of this descriptive analysis were unreliable. This issue could be attributed to our pre-processing method, in which we constructed population-based templates, to normalise the different brains, rather than using the default MNI template. Though this approach contributed to a more specific localisation of brain regions(121), image sharpness was undoubtedly compromised. Consequently, further analysis was performed by means of the third version of automated anatomical labelling Atlas toolbox(159). Using a digital atlas, this software generates a list of anatomical structures which can be found in the 3 dimensional space that is delineated by our specific ROI(155). These structures were manually controlled in MRIcron by overlaying the ROIs onto the same digital atlas(160, 161).

Finally, structural alterations were determined using the "get_totals" algorithm, which extracted absolute volumes separately from all segmented MRI images. This was performed to assess volume on whole-brain level, for grey and white matter, as well as on a regional level for our ROIs(152, 162). Grey and white matter volumes were calculated separately for baseline, T1 and T2. Increases or decreases in volume were then identified by subtracting the average baseline volume by the average T1 or T2 volume. Whole-brain volumes were calculated by summation of the total grey and white matter volumes. In order to estimate the regional volumetric alterations, the Marsbar toolbox was applied to create a mask of the brain regions which showed structural changes. This image is a 3-dimensional outline of a ROI, which conceals the brain regions outside this domain. Grey matter volumes of ROIs were subsequently calculated by selecting the pre-processed grey matter images in addition to one of the masks we just created. In this manner, the algorithm would exclusively extract the volume from the region which was delineated by the mask. Just like whole brain volumes, the procedure was performed for baseline, T1 and T2 separately. Structural changes were then quantified by subtracting the average baseline volume of our ROI's from the average volumes of T1 or T2.

4.8 Statistical analysis

The evolution of the brain volume and clinical status were assessed by means of the statistical package for the social sciences software (IBM SPSS for Windows, version 25, SPSS Inc., Chicago, Illinois, USA). Given that our patient population was small-scaled, a non-parametrical statistical approach was adopted for the following analyses(163). In first instance, a Friedmann test was executed on the total volume of grey and white matter, whole-brain volumes and subsequently on our ROI's. As such, we assessed if any significant volumetric changes had occurred on global or focal scale. Thereafter, post-hoc testing (Wilcoxon Signed Ranks test) was performed upon the brain volumes which showed a significant evolution. The same procedure was applied for the clinical parameters.

A third point of focus was the correlation between the (significant) morphological alterations and the clinical evolution of the patient. This relationship was computed in R Studio(164) by means of the rmcorr package (165) for repeated measures correlation(166). This calculated the within-person association of paired variables, which had been simultaneously measured on two or more occasions for multiple subjects(166). As this approach assesses how variables evolve together over the course of time, a temporal aspect is integrated within the correlation factor (r_{rm})(167). A Bonferroni correction was applied for multiple testing in the repeated measures analysis.

5. Results

5.1 Participants

As mentioned earlier, 11 patients with a median age of 54.7 [Interquartile range (Q1-Q3) 51.5-57] were recruited for this study, all of which were suffering from FBSS (Table 3). The median number of years of pain sufferance prior to the implantation was 3 years [Q1-Q3: 2-5.5]. Patients explicitly designated their back pain as the principle source of burden. Based on the DN4 questionnaire, we found that in 9 out of 11 cases a neuropathic component was involved in the chronic pain syndrome. All patients had already undergone at least 1 surgical intervention of the spine. The median number of previous operations in our population was 2 [Q1-Q3: 1-2.5], none of which had provided significant long-term pain relief. Following the 4-week trial therapy, all patients reported a pain reduction of at least 50%. Consequently, patients were re-scheduled for operation to implant the definitive 10kHz SCS (Senza rechargeable system, Nevro Corp., RedwoodCity, CA, USA).

Table 3: Patient characteristics

Patient	Sex	Age at implantation	Pain duration (years)	N° surgeries	DN4 score
1	F	57	14	3	6
2	F	56	5	2	4
3	M	67	1	1	5
4	M	57	1	1	6
5	F	46	5	3	4
6	F	53	3	1	5
7	F	46	3	1	8
8	F	56	3	2	5
9	F	59	6	5	2
10	F	50	1	1	8
11	F	55	8	2	2
Median		54.7	3	2	5
Q1-Q3:		51.5 – 57	2 – 5.5	1 – 2.5	4 – 6

Table 3: Patient characteristics; Pain duration is expressed in number of years. The douleur neuropathique en 4 questions (DN4) was applied to measure the neuropathic component of the lower back pain.

5.2 Clinical Results

In response to the definitive 10kHz SCS treatment, the patients' reported outcome measurements displayed a progressive clinical improvement over the course of time. More specifically, the PCS (χ^2=6.00, p=0.05) as well as the average back (χ^2=9.53, p=0.009) and leg pain (χ^2=6.20, p=0.045) intensity score appeared to have significantly improved. In contrast, no significant improvement was

observed in central sensitisations symptoms. We did also not observe any significant changes in subjective reporting nor in the objective measurement of our patient's sleep quality.

In terms of the PCS score (Fig. 7), a statistically significant decrease was observed after 1 month of treatment (Z=-2.62, p=0.009) compared to baseline. At baseline the median score consisted of 36/52 [Q1-Q3: 20-43.5], which then decreased to 17/52 [Q1-Q3: 13-33] after 1 month of 10kHz SCS. No further significant improvement was seen in the following two months of treatment however, where the median score increased to 31/52 [Q1-Q3: 14-37.75]. In terms of pain intensity, a statistically significant decrease was observed in the VAS for both back and leg pain (Fig. 7) after 1 and 3 months of SCS. The greatest improvement was seen in back pain (B-T1: Z = -2.6, p = 0.009 | B-T2: Z = -2.6, p = 0.009). At baseline the median VAS score was 5.98 [Q1-Q3: 5.13-7.12], 4.27 [Q1-Q3: 3.37-4.38] after 1 month of SCS and 3.42 [Q1-Q3: 2.74-4.29] after 3 months of SCS. As for leg pain, the intensity mostly decreased after 1 month (B-T2: Z = -2.09, p = 0.037). At baseline the median score was 5.85 [Q1-Q3: 3.82-6.75], 3.5 [Q1-Q3: 2.46-5.16] after 1 month of SCS and 4.21 [Q1-Q3: 3.63-5] after 3 months of SCS.

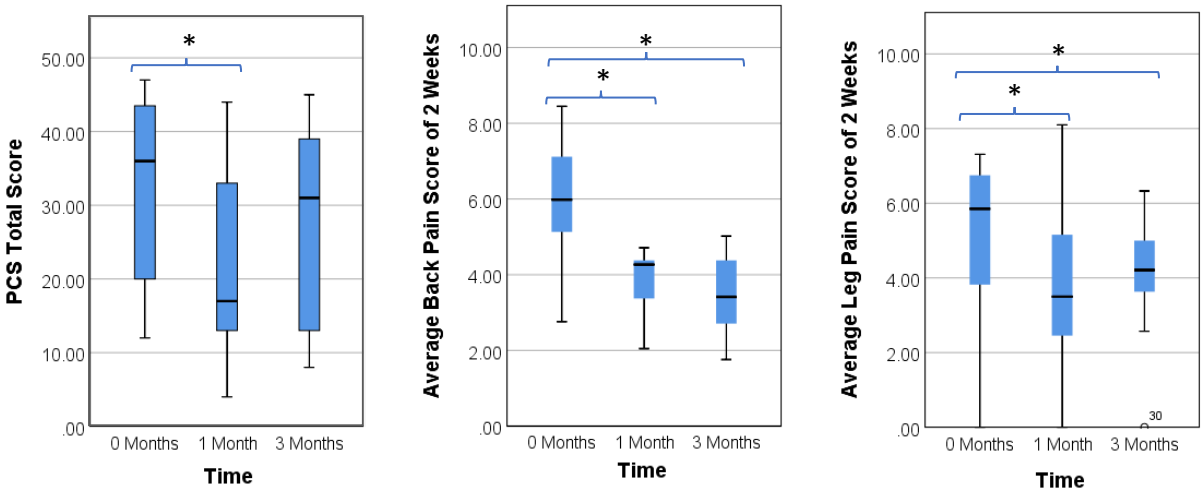

Figure 7: Boxplots display the evolution of, respectively, the PCS, the average VAS score for back and leg pain. The average was calculated from the VAS score which was repeatedly collected over periods of 2 weeks. (*) Indicates a statistically significant decrease in the PCS or VAS score relative to the baseline measurement. The black line within the blue beam indicates the median PCS score and the median of the average VAS score at respectively baseline, T1 and T2.

5.3 VBM Results

In terms of global volumetric measurements, no significant changes were observed in total grey matter (p = 0.178), white matter (p = 0.529) nor in whole brain volume (p = 0.148) after 1 and 3 months of treatment with 10kHz SCS. On a regional level, no significant in- or decrease was seen in white matter. In terms of grey matter however, a significant decrease in volume was observed after 3 months of treatment compared to baseline (Table 5). The highest voxel changes (Table 4) were located in the left and right hippocampus (Fig. 8), which respectively comprised 43,56% and 55,77% of our ROI according to the aal3 labelling procedure. The volume of our left ROI consisted of 0.133mL (Q1-Q3: 0.127-

0.137mL) at baseline, 0.122mL (Q1-Q3: 0.114-0.127mL) at T1 and 0.120mL (Q1-Q3: 0.117-0.126mL) at T2. The right ROI consisted of 0.055mL (Q1-Q3: 0.051-0.057mL) at baseline, 0.052mL (Q1-Q3: 0.048-0.055mL) at T1 and 0.049mL (Q1-Q3: 0.047-0.052mL) at T2.

Table 4: Summary of global volumetric changes

	B	T1	T2
Median TGMV:	611.28mL	616.01mL	611.87mL
Q1-Q3:	586.61– 655.52 mL	594.52-656.86 mL	586.37-657.89 mL
Median TWMV:	420.34mL	411.55mL	427.44mL
Q1-Q3:	397.45-440.43 mL	392.35-449.5 mL	395.19-463.23 mL
Median WBV:	1022mL	1026.53mL	1031.58mL
Q1-Q3:	1001.57–1083.79 mL	986.42-1135.62 mL	999.5-1129.26 mL

Table 4: Summary of the evolution of the median total grey matter volume (TGMV), total white matter volume (TWMV) and median whole brain volume (WBV). The latter one is the sum of TGM and TWM. For each variable the corresponding interquartile range of the measurements from that specific timepoint are specified. No significant changes in global brain volumes were observed after 1 and 3 months of SCS.

Table 5: VBM results

Brain region	Hemisphere	MNI coordinates (mm)			Number of voxels	T-value	P-value (uncorrected)
		X	Y	Z			
Baseline >T1	-	-	-	-	-	-	-
Baseline < T1	-	-	-	-	-	-	-
Baseline > T2							
Hippocampus	Left	-12	-38	-2	101	4.40	P<0.001
Hippocampus	Right	20	-36	6	52	3.83	P<0.001
Baseline < T2	-	-	-	-	-	-	-

Table 5: Results of VBM analysis for grey matter. Displayed above are two clusters of voxels which significantly decreased in volume from B to T2. More precisely, the left and right hippocampus.

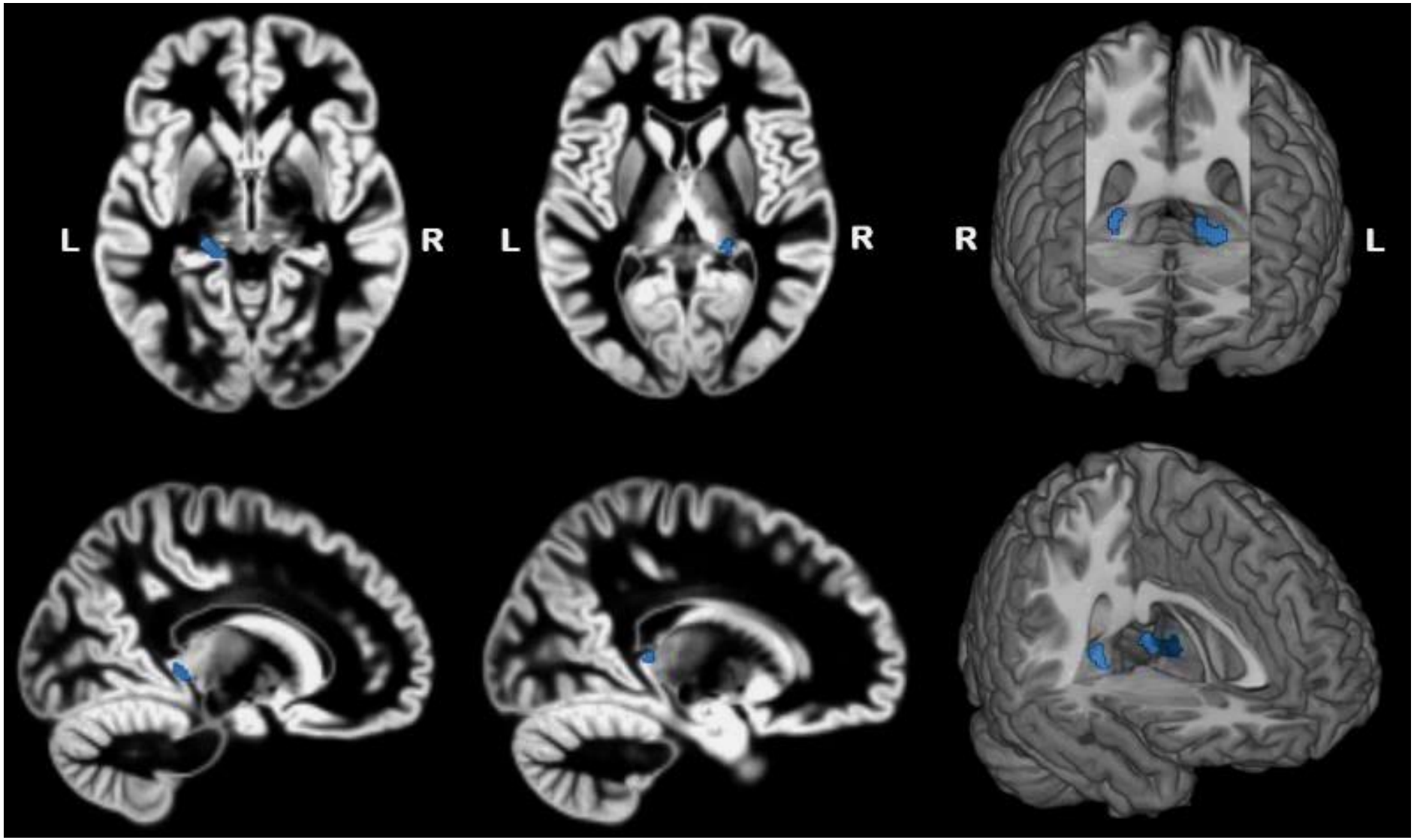

Figure 8: A combined 2D & 3D model of the brain showing grey matter decrease in the left and right hippocampus cluster, indicated in blue. Left axial and sagittal slice illustrate the left hippocampal cluster, whereas the right axial and sagittal slices illustrate the right hippocampal cluster. On the right side, both clusters can be visualised simultaneously in a 3D model of the brain.

5.4 Correlation between structural & clinical data

A significant correlation was observed over time between the volumetric change in our patient's left and right ROI and the improvement in back pain score. For the former, the correlation consisted of r_{rm}= 0.749 (p = 0.0000604) (Fig. 9A, left) whereas the latter consisted of r_{rm} = 0.652 (p = 0.001) (Fig. 9B, left). Similarly, when looking at the evolution of, respectively, the left (Fig. 9A, right) and right (Fig. 9B, right) ROI and the back pain score, a similar trend is observed in both parameters.

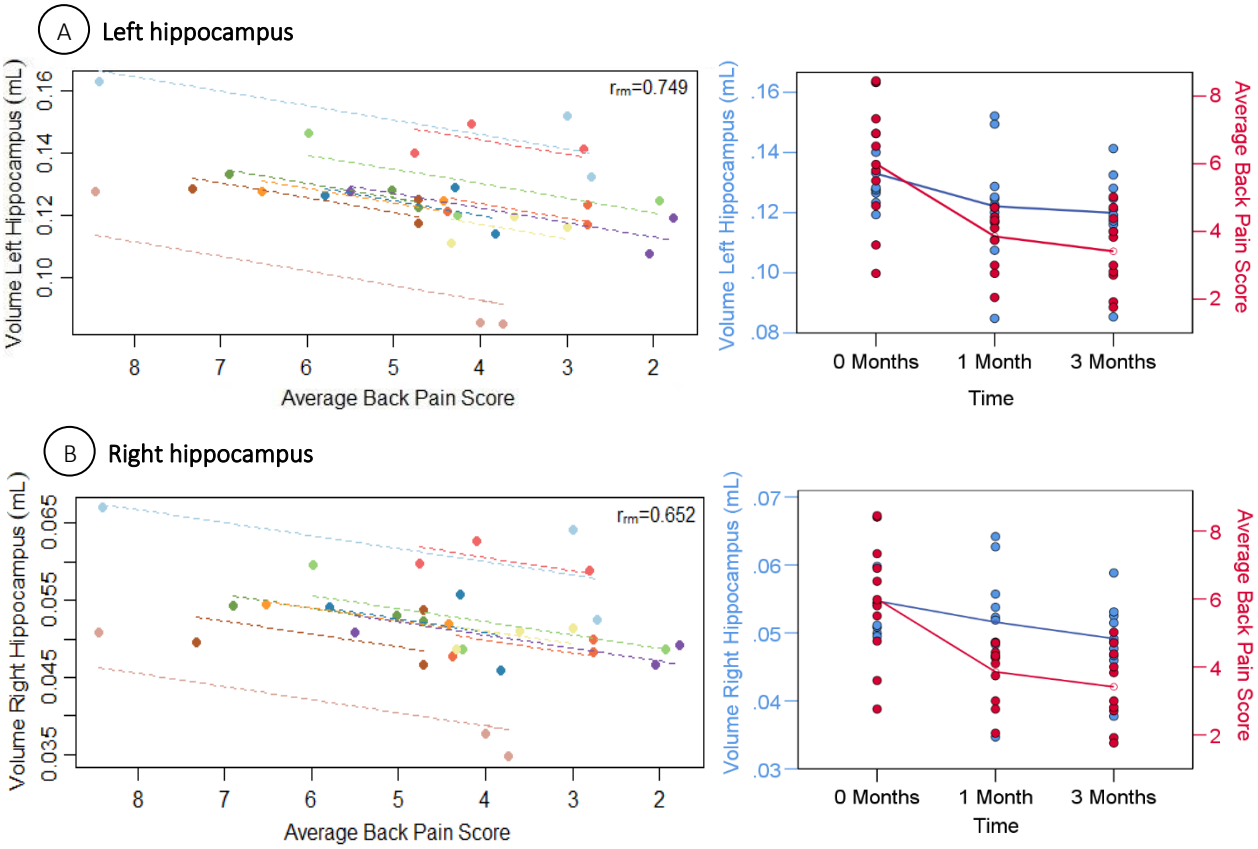

Figure 9: The left diagram displays the repeated measures correlation between the hippocampal volume and the average score for back pain over two weeks. Each colour corresponds to one of the eleven patients and contains three coordinates [1] $Volume_B$; Average VAS_B [2] $Volume_{T1}$; Average VAS_{T1} [3] $Volume_{T2}$; Average VAS_{T2}. Each dotted line represents the interpolation line of the variables of that patient. The right pane shows the evolution of the hippocampal volume and VAS score for back pain. Blue dots represent hippocampal volumes of all 11 patients, whereas red dots represent the average back pain score. The blue and red line are the interpolation line of, respectively, the hippocampal volume and average back pain score.

6. Discussion

High-Frequency Spinal Cord Stimulation

Spinal cord stimulation was developed in 1967 by Shealy et al. to treat refractive pain resulting from cancer(72, 73). The idea behind this novel therapy was primarily based upon the gate control theory of Melzack et al. (7, 12, 67, 72). This innovation offered an important improvement of patient's quality of life compared to previous treatment options (primarily oral analgesics)(7). However, the downside of the therapy was that patients had to endure a constant tingling sensation resulting from the paraesthesia, necessary to mask the pain. Moreover, a diminishing efficacy was observed over time in certain patients due to factors such as a poor maintenance of the therapeutic levels and inconsistent delivery of paraesthesia(69, 168). These limitations led to the development of newer technologies and modalities of SCS over the past decades.

As a result, sub-threshold SCS emerged on the market. Although multiple modalities are available in this matter, all share the same principle, being paraesthesia-free pain alleviation. In this study we analysed 10kHz SCS. Although the focus was primarily set on the supra-spinal effects of this treatment, clinical effects did remain an important factor in order to explore and clarify effects of 10kHz SCS. Our clinical findings support the idea that 10kHz SCS can reduce pain in patients suffering from FBSS. Patients showed high response rates on short notice in terms of pain reduction in which they displayed a statistically significant reduction in back and leg pain intensity. These findings are in accordance with recent studies by Kapural et al., Al-kaisy et al., Di Benedetto et al. and De Andres et al., which imply that 10kHz SCS can effectively reduce chronic back pain in patients suffering from failed back surgery syndrome(66, 169). Interestingly, leg pain intensity as well as the pain catastrophizing score display an increase after the initial significant reduction. In both cases however, values remain lower than those prior to treatment with 10kHz SCS. Moreover, we cannot exclude the possibility that pain intensity as well as pain-related psychological phenomena, such as pain catastrophizing, will gradually decline of time. The treatment of chronic low back pain is after all a life-long process.

Despite that a pain-free condition is unattainable, even after several years of SCS, much progress has been made in this treatment. Several studies comparing patients receiving 10kHz SCS to patients receiving conventional SCS, suggest that the former is associated with higher response rates for back and leg pain as well as a higher decrease in the usage of opioid analgesics(7, 11, 66, 67, 69, 75, 168). These observations stand in line with the SENZA RCT and its follow-up study, which suggest that the 10kHz modality delivers superior results compared to conventional SCS(170, 171). The suggested benefit of 10kHz SCS has recently been supported by a study of Strauss et al., which performed a real-world multicentre retrospective review on the efficacy of 10kHz SCS in 1660 patients(172). However,

studies by De Andres et al. and Russo et al. were unable to find significant differences in clinical effectiveness between 10kHz and conventional SCS(66, 77). Although opinions regarding the added benefit of 10kHz over conventional SCS remain variable, it appears that 10kHz SCS could have the benefit of improving general life quality. This is due to a higher sleep quality, lower functional impediment and higher satisfaction resulting from the absence of paraesthesia(7, 11, 169, 172, 173).

Down below or high up there? The spinal & supra-spinal effects

The gate control theory, upon which the first SCS therapy was based, describes the existence of an endogenous mechanism involving inhibitory interneurons located in the dorsal horn of the spinal cord, which could block the transmission of nociceptive signalling to the brain. These interneurons make synaptic connections with large diameter αβ fibres, which stimulate the interneurons and convey vibratory sensation. Synaptic connections are also made with small diameter Aδ and C fibres, which both inhibit the interneuron and convey nociceptive stimuli(74). Based on this theory, Shea et al. believed it was possible to reduce pain by electrically stimulating the dorsal horn of the spine. As such, the subsequent activation of large diameter Aβ fibres would result in the inhibition of pain transmission to the brain via small-diameter Aδ and C fibres and simultaneously the induction of paraesthesia(11, 12, 58, 62, 67-70, 75-82).

Presently, this mechanism of action is challenged with the rise of new devices and stimulation modalities, such as 10kHz SCS. These innovations present function and limitations which cannot be attributed to the gate control theory(12, 70, 77, 78, 80). 10kHz SCS for instance, does not produce paraesthesia, which implies that pain alleviation is not related to the size of the area covered by paraesthesia. Furthermore, when the electrical stimulation is ceased, a temporary continuation of pain alleviation can be observed. 10kHz SCS, nor any other type of SCS is unable to reduce acute nociceptive pain. For these reasons, it is believed that the pain-relieving mechanism of 10kHz SCS, as well as other modalities, rely upon different (more complex) mechanisms.

An initial working hypothesis was postulated at the 2016 Neuromodulation scientific congress in San Fransisco(68, 70), which suggested 10kHz SCS: [1] induces a fast-acting reversible blockage of the neural depolarisation, thus impeding the nerve conduction. [2] disrupts signalling patterns of neural clusters which fire simultaneously. [3] induces individual nerve cell signalling through temporal summation of electrical stimuli. Similarly, in a study by Arle et al., a differential blockade theory is brought forward as potential mechanism of action. Authors suggest that like so, 10kHz SCS preferentially inhibits large diameter fibres, yet activates medium and small diameter fibres in such manner to inhibit signalling from wide dynamic range neurons(78). However, both hypotheses have been challenged by a study of Song et al., which suggests 10kHz stimulation is unable to alter neural activity of the dorsal horn and

therefore unable to generate any conduction block(174). However, it should be noted that this study presents an important pitfall. Namely, 10kHz SCS of the dorsal horn was only maintained for a period of 2 hours. We believe this could have important implications on the measured effects at the level of the dorsal horn. After all, research indicates that the maximal effectiveness of 10kHz stimulation is only reached after several days(69, 70, 174). Moreover, a study by McMahon et al. observed a significant reduction in C fibre induced evoked potentials after sub-threshold 10kHz SCS(62, 70, 175). This suggest that 10kHz SCS could modulate the activity of dorsal horn fibres, independently of action potentials.

Although studies have mainly focused on segmental effects of 10kHz SCS, little is known about the supra-spinal mechanisms. Considering the experience of pain is (in part) modulated on cerebral level(10, 14, 16, 18, 35, 176) it seems unlikely that the pain reduction, resulting from 10kHz SCS, can be attributed to segmental effects alone(69, 70, 77, 80, 151). Moreover, research suggests that the development of chronic pain might partly result from dysregulation of cerebral processes involved in sensory, emotional and cognitive processing of pain(10, 14, 16, 26, 27, 33, 38, 41). Therefore, we have reason to believe that the proposed spinal effects of 10kHz SCS might be complemented by supra-spinal mechanisms to induce the observed pain reduction. This idea is supported by different neuroradiological studies, which observed changes in neural activity of the brain in patients receiving SCS(83, 85, 94-100). For instance, a study by Moens et al. found that the thalamic activity as well as its functional connectivity with the rostral & caudal cingulate cortex and the insula had decreased(96). Interestingly, in a study by De Groote et al., increased functional connectivity was seen between structures of the salience network and the fronto-parietal network as well as the central executive network in patients receiving 10kHz SCS(85). These findings suggest that SCS may exert its function by modulation of networks which connect brain regions involved in the cognitive, affective or sensory processing of pain(70, 99). Up until present however, no other studies have evaluated the pre- and postoperative supra-spinal effects of 10kHz SCS. To our knowledge, this is the first MRI-based study to have explored the morphological effects on a supra-spinal level of 10kHz SCS treatment in patients suffering from failed back surgery syndrome. Our study therefore offers new information which could help further clarification of current hypothesises and/or identification of new mechanisms of action.

The second potential supraspinal mechanism by which SCS may contribute to pain reduction is thought to engage through action of descending neurohumoral pathways upon the dorsal horn. This has been suggested by studies which observed significant changes in the concentration of stimulating and inhibiting neurotransmitter such as serotonine, norepinephrine or aminobutyric acid (GABA), in patients responding to SCS(62, 70, 80, 82, 94). This was however not further analysed in this study.

Does our brain forget the pain?

As mentioned earlier, there has been a growing amount of research in the field of neuroplasticity over the past years, especially in the context of chronic pain disorders. Like so, studies have provided evidence showing that the brain endures structural and functional changes as result of a prolonged exposure to pain. However, there is an important inconsistency in reported findings between different studies. For instance some studies reported an increase in grey matter volume of the thalamus in patients suffering from chronic pain, whereas others have observed the opposite(4, 29, 30, 32). Furthermore, there is an important heterogeneity in the reported brain regions that show an altered morphometry or structure. This inter-study variability is likely due to sample size differences, clinical or demographic variability, and differences in image acquisition or processing (22, 26, 30, 177). Nonetheless, neuroplastic changes of certain brain regions are consistent across different studies. The hippocampus for instance appears to be one of the few regions that tends to increase in volume due to chronic pain(3, 36, 40, 101, 176, 178). Other brain areas which endure structural alterations as result of chronic low back pain include regions such as the pre-frontal cortex, pre- and post-central gyrus, middle cingulate gyrus, insula and thalamus(4, 8, 26-29, 32).

On the other hand, our study observed decreases of the grey matter volume in the hippocampus bilaterally in patients receiving spinal cord treatment after just 3 months. This stands in line with the study by Luchtmann et al. which observed a decreased hippocampal volume after microsurgical lumbar discectomy in patients suffering from chronic low back pain(156). These findings suggest that chronic pain treatment could reverse the previously occurred neuroplastic changes resulting from an altered cerebral function(85, 102, 156). Moreover, this emphasizes the importance of the hippocampal formation in the modulation of pain. This suspicion is supported by other research which has shown important similarities between chronic pain and the learning mechanism that is coordinated by the hippocampus(36, 179-188). Essentially, chronic pain is believed to be associated with maladaptive plasticity of the hippocampus which gives rise to the persistence of pain-related memories and/or inability of their extinction(3, 26, 27, 31, 36, 101, 156, 176, 182-185). Ultimately, structural and functional alterations would result in the common comorbidities seen in chronic pain disorders such as cognitive impairment, deterioration of long-and short term-memory and the inability to extinct pain memories(179, 182, 184, 186, 187).

Other than its function in learning mechanisms and memory, recent studies also suggest that the hippocampal formation could be involved in the modulation of pain(178, 179, 184, 185, 189). One way of doing so is by influencing our behavioural response to pain, together with the amygdala, by amplifying certain nociceptive aversive signals(101, 182, 189, 190). As such, our brain would be able to

favour behaviour that incites withdrawal from an aversive stimulus(3, 189). Functional magnetic resonance studies also revealed the involvement of the hippocampus in the contextual and emotional processing of pain(17, 183-185, 187, 189). In this manner, the hippocampus could affect the pain perception as well as the consolidation of the pain memory(179, 182, 187, 189, 190). Lastly, the experience of an aversive event as well as sensitivity to pain appears to be influenced by the anticipation on pain via the hippocampus(182, 184, 189-192).

Based on these findings, it is possible that the observed decrease in grey matter volume in our patient´s brain could be associated with the eradication of certain pain-related memories. As such we believe 10kHz SCS could stimulate the normalisation of the neurophysiological functioning of the pain neuromatrix. By means of this mechanism, the reduction in central sensitisation could allow segmental effects to reduce pain more effectively. Moreover, as proposed in a study by De Groote et al., pain reduction might result from a decline in the affective component of pain processing(85, 156).

Strengths & limitations

One of the strengths of this study is the usage of the DARTEL protocol for the normalisation of our anatomical images. The application of this algorithm yields a higher accuracy in pre-processing than the standard protocol in terms of inter-subject registration because deformations fields, necessary for spatial normalisation are re-calculated multiple times(110, 121, 193-195). Moreover, DARTEL-normalised images ensure a higher specificity for volumetric analysis, as templates are based upon study-specific data(196). On the contrary, the default MNI template is based on an average image of 152 MRI scans of healthy subjects(197). Thus, if we had used the default settings for the normalisation procedure, the calculated deformation field would have likely concealed volumetric alterations. This results from the fact that patients who suffer from chronic pain disorders often endure structural cerebral changes. The DARTEL template already included such morphological characteristics. Therefore, our patient's MRI images only necessitated smaller deformations for normalisation into the common stereotactic space. As such, important structural features could be preserved. Summarised, these factors have contributed to the validity of the VBM results, which are therefore less likely to have resulted from machine imperfections or detection flaws. We also believe that the short-term assessment on multiple occasions ensured a more elaborate insight into the supra-spinal effects. Likewise, this has also helped us to obtain more information about the temporal aspect of the neuroplasticity occurring after 10kHz SCS.

Some might argue that an important limitation of this study was the small sample size as well as its short time frame. However, no studies have yet been published, which evaluated the structural effects of 10kHz SCS treatment in FBSS patients. Therefore, our study can be considered a pilot study, which

sets the foundation for future, larger, studies. A second limitation of our study is that the identified ROI's were not FWE (family-wise error rate) corrected, which implies that there is a higher chance of obtaining significant results by chance due to multiple testing rather than actual alteration of volume(198). Hence, strict p values were applied to our SPM results to minimize this risk. Another limitation was that the automated labelling procedure was unable to label 15 to 19% of our ROI´s. This is likely related to the fact that the labelling procedure uses an atlas which is based upon a normalized high-resolution T1 MRI image of a single (healthy) individual(199). Therefore, there might be a discrete mismatch in the anatomical location of our clusters between the digital atlas and our patients' brain. Ideally, this labelling procedure should have been performed by means of a digital atlas which was developed with images from our own subjects. This would determine the anatomical location of our ROI in a much more precise way than our current approach. However, this would demand much more time and expertise, which was unattainable for this sort of work. Thus, to ensure an optimal accuracy of the labelling procedure, we controlled the anatomical location on MRIcron (with the same atlas) as well as an Sectional Anatomical Atlas of Depreitere et al.(200). Lastly, an important limitation of this study is that we are unable to determine whether the observed supra-spinal effects result from either direct or indirect treatment effects. In other words, we cannot exclude the possibility that morphological alterations are the consequence and not the cause of the pain alleviation. (34). Moreover, the associated reduction of pain medication might also have influenced our findings. However, it would be senseless to oblige patients to maintain the usage of oral analgesics during treatment in order to try and neutralise this effect.

7. Conclusion

Chronic back pain is a complex cognitive-affective syndrome, which drastically affects a patient's quality of life as result of the physical and psychological deterioration they endure. Today, the most common approach to chronic pain treatment is the application of oral analgesics. Interventional treatments may also be carried out in some instances, if the underlying cause of the back pain is thought to be related to an organic or structural defect. However, both therapeutic approaches only provide a limited amount of pain relief and often fail to guarantee a substantial improvement of the patient's quality of life on a long-term basis. As a result, the management of chronic pain remains a challenging task for clinicians as well as for the patients themselves.

Spinal cord stimulation has proven to be an interesting alternative to the former options for treating refractive pain. This is particularly true for novel SCS modalities such as 10kHz SCS, which has significantly contributed to the quality of this therapy by the establishment of paraesthesia-free stimulation. Despite its success however, we still do not fully comprehend the exact mechanisms by which this treatment relieves pain. Although studies have mainly focused on segmental effects of 10kHz SCS, little is known about the supra-spinal mechanisms. Thus, the goal of this study was to objectify the impact of 10kHz SCS on the brain from a structural perspective.

In summary, our findings demonstrate that 10kHz spinal cord stimulation in patients suffering from FBSS can induce significant structural alterations to the brain after just 3 months of treatment. More precisely, a decrease in the left and right hippocampal volume. Statistical analysis further revealed a negative correlation between the observed volumetric decrease and the experienced back pain intensity. This suggest that these supra-spinal effects might contribute to the pain-relieving effect of 10kHz SCS. However, such assumption should not be taken for granted, as our findings do not provide the necessary evidence allowing to determine the nature of this correlation. In other words, the observed alteration of the hippocampal volume might be the cause of pain alleviation after delivery of sub-threshold electrical impulses to the spine. On the other hand, the reduction of the hippocampal volume may also be the consequence of the clinical effect itself.

Quite evidently, further research is required to estimate the role of this supra-spinal mechanism in the clinical effects of spinal cord stimulation on chronic back pain. Moreover, future studies will also need to explore the existence of other potential supra-spinal sites of action. Regarding the latter, suggestions include structures such as the thalamus, insula, cingulate gyrus etc. These brain areas have frequently been discussed in functional imaging studies and may potentially unveil novel paths upon which we may act to treat chronic back pain.

8. Acknowledgement

I would like to thank Prof. Moens as well as Dr. Lisa Goudman and Sander De Groote for their constructive judgement. Their support and guidance during my work were indispensable. I also express my sincere appreciation towards my family for reviewing my work and their endless encouragement.

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