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Burst and Tonic Spinal Cord Stimulation: Different and Common Brain Mechanisms

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Objective: Spinal cord stimulation is commonly used to treat medically intractable pain. Different stimulation designs are used to obtain pain suppression such as tonic stimulation, high frequency stimulation, and burst stimulation. Preliminary analysis of the same data used in this study demonstrated that burst stimulation likely modulates the medial pain pathways in contrast to tonic stimulation. The question arises what different and common supraspinal mechanisms burst and tonic stimulation use.

Materials and Methods: The clinical and electroencephalography (EEG) data of five patients undergoing tonic, burst, and sham stimulation were analyzed to look at the commonalities and differences between burst and tonic stimulation. A source-localized (sLORETA) EEG substraction and conjunction analysis is performed in each condition for both activity and functional connectivity. A ratio between the dorsal anterior cingulate cortex (dACC) and pregenual anterior cingulate cortex/ventromedial prefrontal cortex (pgACC/vmPFC) is calculated to reflect a balance between pain supporting and pain suppressing systems.

Results: Differences are noted in the dACC, dorsolateral prefrontal cortex, the primary somatosensory cortex, and the posterior cingulate cortex (PCC). Burst and tonic stimulation share activation in the pgACC, inferior parietal area, which encompasses the inferior secondary somatosensory cortex, PCC, and the parahippocampus. Burst suppression normalizes the pain supporting/pain suppressing balance in contrast to tonic stimulation.

Discussion and Conclusion: These data suggest that burst and tonic stimulation both modulate the descending pain inhibitory system (via pgACC), as well as a self-referential contextual (via PCC) aversive memory system (via parahippocampus). However, burst normalizes the pain supporting/suppressing balance in contrast to tonic mode by a greater effect on the dACC.

Keywords: Burst, cingulate, parahippocampal, posterior, pregenual cingulate, spinal cord, stimulation, tonic

Conflict of Interest: Dirk De Ridder has a patent for burst stimulation. Sven Vanneste has no conflicts of interest to declare.

INTRODUCTION

Pain has been defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage (1). It thus incorporates both a sensory and an affective component. Physiologically nociceptive pain can be considered as a protective sense, but loses this function and becomes independent of it in chronic neuropathic pain (2). Neuropathic pain is defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system (3). The unpleasantness of pain induces a motivational capacity to self-orient one's behavior to withdraw from the painful stimulus. Pain is usually an aversive signal processed by at least three pathways, two ascending pain-evoking pathways (4,5), and at least one descending pain-inhibitory pathway (6). The medial pain pathway encodes the motivational/affective component of pain (4,5) (i.e., the unpleasantness (5,7)), the lateral pathway encodes the discriminatory/sensory (5) component, and the descending pathway suppresses ongoing pain in a state-dependent manner (6). The medial and lateral pain pathways are processed in parallel (8) and can be individually modified without affecting the other pathway (5). The ascending medial system is activated by C-fibers and connects to the mediodorsal and ventral posterolateral nuclei of the thalamus. From there, each respectively reaches the anterior cingulate and anterior insula (4,9,10). The ascending lateral pain pathway is activated by C, Aδ and Aβ fibers, and connects to the ventralposterolateral (VPL) nuclei of the thalamus and then reaches the somatosensory cortex and parietal area (4,9). The descending pain inhibitory system involves the rostral and pregenual anterior cingulate cortex and connects to the periaqueductal gray. From there, the information is relayed further to the somatosensory periphery (9,11) (Fig. 1). It is clear that the ascending pain-evoking and descending pain-inhibitory pathways need to interact in some way, and it has been suggested that these interactions are dynamically changing (13) depending on the context (14). The exact anatomical and functional connectomics in pain have yet to be unraveled; however, both structural (=anatomical) and functional (=resting state) MRI studies in pain demonstrate complex interactions between somatosensory cortex, cingulate cortex, insula, amygdala, thalamus, and frontal cortex (15,16).

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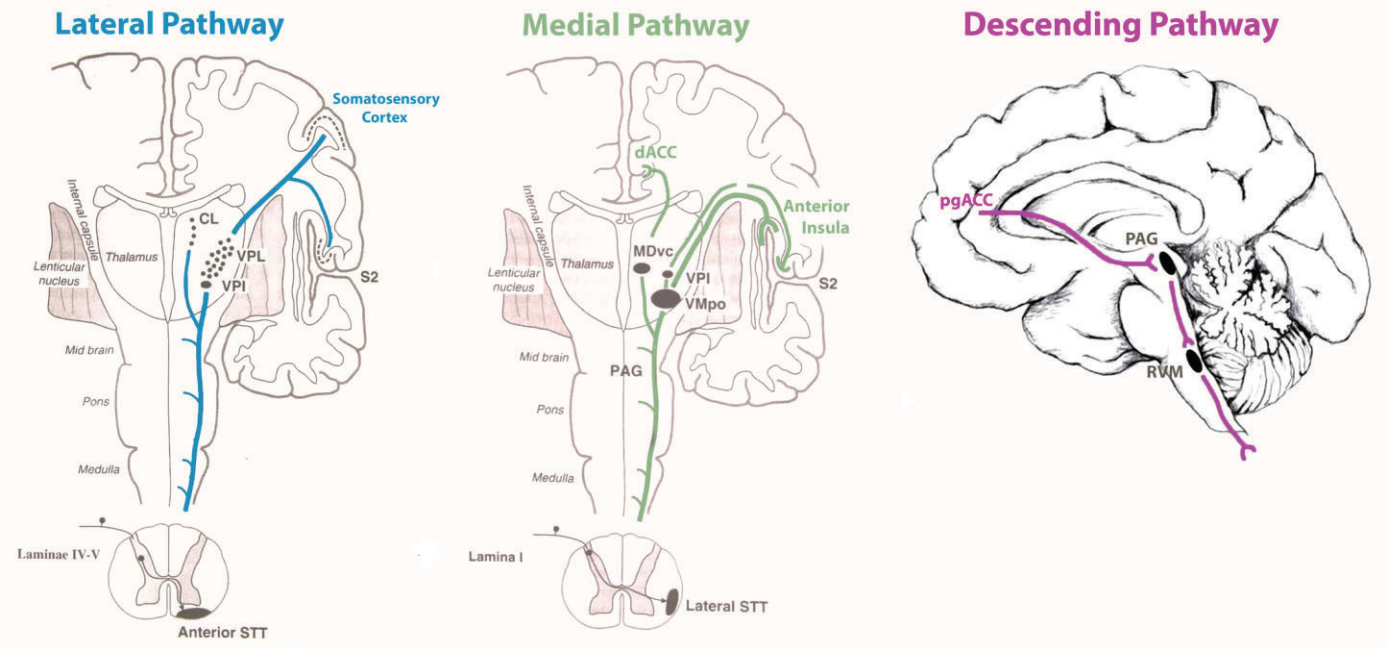

Figure 1. Ascending and descending pain pathways. Two ascending pain-supporting pathways have been described, and one pain-inhibitory descending pathway. The lateral ascending pathway processes the discriminatory components of pain, whereas the medial pathway processes the motivational, affective, attentional components of pain. The pain inhibitory pathway suppresses ongoing pain (figure modified and extended from Squire (12)).

Pain is context dependent (14), as exemplified by placebo analgesia (14), and the fact that pain can be unpleasant or pleasant depending on the context (17). Pleasant pain is mediated via activation of the antinociceptive system, whereas unpleasant pain is processed via the medial pain system (7,17).

Spinal cord stimulation (SCS) is an efficacious way to suppress chronic pain related to complex regional pain syndrome and failed back surgery syndrome (FBSS) (18). SCS not only reduces pain but also improves quality of life, reduces analgesic consumption, and allows some patients to return to work with minimal side-effects apart from paresthesia (19). Furthermore, other meta-analytic studies have shown that SCS is beneficial in refractory angina (20) as well as in chronic critical limb ischemia (21).

Recently, burst stimulation has been developed which permits paresthesia-free stimulation (22,23) analogous to what has been claimed for high-frequency stimulation (24) permitting placebo-controlled studies (22,25). In burst stimulation 5 pulses are delivered per burst at a frequency of 500 Hz, and 40 bursts are applied per second (23). The cumulative charge of the five monophasic 1 ms spikes is balanced during 5 ms following the spikes, and charge balancing is not completely performed after each individual spike. In order to avoid electrode dissolution or tissue destruction, the stimulator system has to ensure that no residual charge remains at the electrode-electrolyte interface. Therefore, the charge injected in the tissue and the charge removed from the tissue should be equal or in other words balanced.

Burst stimulation, in contrast to tonic stimulation, seems to exert a different effect on the attention paid to pain and pain changes (22,23). A preliminary small functional neuroimaging study using source-localized electroencephalography (EEG) in five patients demonstrated that burst stimulation in contrast to tonic stimulation directly or indirectly changed activity in the anterior cingulate cortex (22), which is involved in processing the attention paid to pain (26,27) as well as the unpleasantness (5,7). Thus, it was hypothesized that burst stimulation not only modulates the lateral discriminatory pain system but also the medial affective/attentional pain system (22).

The pain-improving effect of SCS is related to a combination of spinal and supraspinal mechanisms (28,29). The spinal mechanism involves antidromic activation of ascending dorsal column fibers, but SCS might also interact via orthodromic ascending fibers with the descending pain-inhibitory pathway (30). The direct effects of burst stimulation on the spinal cord locally have only been investigated in animals. Using the same stimulation parameters in animals as the ones used in humans, both for burst and tonic stimulation, it was shown that burst SCS is more efficacious than tonic SCS in attenuating visceral nociception (31). Both burst and tonic SCS suppress responses in lumbosacral neurons to noxious somatic and visceral stimuli. However, burst SCS has a greater inhibitory effect on noxious somatic stimuli in comparison with noxious visceral stimuli (32). Multiple stimulation parameters influence the amount of inhibition of neuronal activity, including pulse number, pulse width, and amplitude (33). Pulse frequency and amplitude, on the other hand, influences the amount of responsive neurons (33). The charge per burst is correlated both to a reduction of firing rate in wide dynamic range neurons, as well as on the amount of neurons responding to burst SCS (33). Of interest, burst SCS in contrast to tonic SCS does not increase spontaneous activity of neurons in the gracile nucleus (31). In other words, it does not seem to exert its effect via the posterior funiculus/lemniscal pathways. Furthermore, it has been shown that in contrast to tonic stimulation, burst stimulation does not exert its effect by local γ-amino butyric acid (GABA) release (34). This suggests that burst stimulation might exert its effect by a different neurotransmitter system, which theoretically opens the perspective of combining tonic and burst stimulation to verify whether the two stimulation designs could be complementary.

Table 1. Patient Characteristics.

Patient	Age	Gender	Indication	Surgeries	Electrode used	Electrode position
1	46	M	FBSS	5	Lamitrode tripole	Thoracic
2	53	F	FBSS	3	Lamitrode penta	Thoracic
3	52	M	FBSS	5	Lamitrode penta	Thoracic
4	57	F	FBSS	4	Lamitrode penta	Thoracic
5	51	M	FBSS	5	Lamitrode tripole	Thoracic

FBSS, failed back surgery syndrome.

Therefore, due to of the absence of differences on the lateral pain pathway, the question can be raised whether burst and tonic stimulation do in fact also share a common anti-nociceptive supraspinal mechanism and whether this can also be seen on a source-localized EEG. EEG measures spontaneous resting state electrical brain activity and functional connectivity, rather than indirect measures of brain activity such as positron emission tomography (PET) or functional magnetic resonance imaging (fMRI), which measure glucose or oxygen consumption associated with brain activity. As pain is related to changes in brain activity, EEG has the capacity to record these changes directly in contrast to PET and fMRI. Furthermore, additional analyses can be performed to explore whether more differences exist between burst and tonic stimulation, which might guide decision-making to select one or the other stimulation design.

MATERIALS AND METHODS

Participants

Five patients (1 man and 4 women) between 39 and 46 years old, with a mean of 42.30 years, were included in this study. The data are of the same patients from an earlier publication (22) and were re-analyzed by performing a conjunction analysis and a functional connectivity analysis looking for a common activation and functional connectivity patterns associated with burst and tonic SCS. Furthermore, a placebo-controlled subtraction analysis is performed to look at the differences between tonic and burst stimulation and a ratio of the current densities between the dorsal anterior cingulate cortex (dACC) and pregenual anterior cingulate cortex/ventromedial prefrontal cortex (pgACC/vmPFC) is calculated to reflect a balance between pain-supporting and pain-suppressing systems.

The study has been approved by the Antwerp University Hospital Institutional review board ("Comité voor medische ethiek") and registered on Clinical Trials NCT01486108. The patients were investigated using an amendment on the above-mentioned study.

Implantation and Programming

All patients underwent implantation of a lamitrode (SJMedical neurodivision, Plano, TX, USA) via laminectomy under general anesthesia (see patient overview. Tables 1 and 2). During the mandatory period of external stimulation, which is minimally 28 days according to Belgian healthcare requirements for reimbursement, every individual patient was trialed applying three different stimulation designs. For classical tonic stimulation, 40 Hz tonic mode with 330 μsec pulse width was programmed in such a way as to obtain paresthesia coverage of the painful area. For burst stimulation, 40 Hz burst mode and 500 Hz spike mode with 1000 μsec pulse width were selected at 90% of paresthesia threshold with the same electrode configuration as for tonic mode. Placebo stimulation was performed by turning off the stimulator after paresthesia were shortly induced. The EEG recordings were performed on separate days to prevent a carry-over effect.

Table 2. Individual and Average Scores for Baseline, Tonic, and Burst Stimulation for Back Pain, Limb Pain, and General Pain.

		Baseline	Sham	Tonic	Burst
Back pain	1	7.2	6.8	2.7	1.2
	2	5.8	6.7	4.4	7.0
	3	8.9	2.7	1.3	0.9
	4	8.8	6.4	8.7	5.5
	5	8.6	8.4	7.2	6.8
	Mean	7.9	6.2	4.9	4.3
Limb pain	1	6.8	5.7	5.1	1.1
	2	7.0	7.1	4.3	7.4
	3	9.3	6.2	2.2	1.8
	4	6.5	6.1	8.7	5.7
	5	8.8	2.1	4.2	0.7
	Mean	7.7	5.4	4.9	3.3
General pain	1	7.3	6.3	3.7	0.9
	2	7.0	7.3	4.3	7.5
	3	9.2	4.3	1.5	1.1
	4	8.9	5.2	8.5	5.7
	5	8.9	5	6.5	3.7
	Mean	8.3	5.6	4.9	3.8

Patients were told they would receive three stimulation designs, some of which they might feel the paresthesia, some of which they might not feel the paresthesia.

Programming started with an initial tonic programming session to define which electrodes needed activation to obtain paresthesia coverage. This was performed while patients were lying down. Subsequently, therapeutic SCS was initiated, with three different stimulation designs: burst stimulation, tonic stimulation, and placebo stimulation, each for one week and the sequence of stimulation patterns were randomized. The patients were discharged home on the second postoperative day and were instructed not to change the stimulation parameters during the next week. They were only allowed to use a magnet for forcefully stopping stimulation in case of emergency; however none of the patients activated a forced stop with the magnet for an extended period of time. At the end of each week, the patients returned to the outpatient clinics where they were interviewed and brought with them a written report delivered by the blinded evaluator, after which they were reprogrammed for the next stimulation week by the programmer. Reprogramming consisted of first turning off the stimulator and when the patient mentioned the pain had recurred to its prestimulation level, the new

stimulation set was applied. The limb pain area was covered in all patients with paresthesia and paresthesia was not perceived as uncomfortable. The stimulation intensity for tonic and burst mode during randomized stimulation was selected based on the maximal pain suppression as determined by the patient for tonic stimulation and at 90% of paresthesia threshold for burst stimulation.

The burst mode was programmed using custom software and programming devices. Typically, burst stimulation is characterized by a lower amplitude, but a larger pulse width, resulting in a similar energy delivery per pulse (23). In burst mode, the amplitude was increased up to the moment that paresthesia was elicited. Subsequently, the amplitude was decreased to a level below (90%) paresthesia threshold.

Measurements

Primary outcome measures were the EEG correlates of shared activity and functional connectivity between tonic and burst stimulation. Secondary outcome was a ratio of current density in dACC/pgACC (pain activating/pain inhibiting activity) as a measure of perceived global pain.

EEG Data Collection and Processing

EEG recordings (Mitsar-201, NovaTech http://www.novatecheeg.com/) were obtained in a quiet and dimly lighted room, with each participant sitting upright on a small but comfortable chair. The duration of the EEG recording was five min so at least two min of clean data could be obtained for further processing. The EEGs are performed at baseline, i.e., prior to stimulation in the painful state, and the end of each week tonic and burst stimulation in five of the investigated patients. Average Fourier cross-spectral matrices were computed for bands delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz), and gamma (30.5–44 Hz). Standardized low-resolution brain electromagnetic tomography (sLORETA) was used to estimate the intracerebral electrical sources that generated the scalp-recorded activity in each of the eight frequency bands (35).

The log-transformed electrical current density was averaged across all voxels belonging to the regions of interest. Regions of interest were the pregenual anterior cingulate cortex and the dACC. To calculate the ratio, we divide the log-transformed current density from the pgACC by the DACC for each frequency band separately.

The methodology used on the source localization EEG data is non-parametric. It is based on estimating, randomization, the empirical probability distribution for the max-statistic, and under the null hypothesis comparisons (36). This methodology corrects for multiple testing (i.e., for the collection of tests performed for all voxels, and for all frequency bands). Due to the non-parametric nature of the method, its validity does not rely on any assumption of Gaussianity (36). sLORETA statistical contrast maps were calculated through multiple voxel-by-voxel comparisons in a logarithm of F-ratio. The significance threshold was based on a permutation test with 5000 permutations. A comparison was made between the baseline, tonic, and burst stimulation. In addition, we conducted a conjunction analysis between tonic and burst stimulation after subtracting the baseline measures (37–40) in both groups. A conjunction analysis identifies a "common processing component" for two or more tasks/situations by finding areas activated in independent subtractions (37–40). We opted to subtract images of the baseline from both the tonic and burst stimulation so that only stimulation-related activity (activity that differed from the baseline activity) remained for both tonic and burst stimulation separately.

Lagged phase coherence between two sources can be interpreted as the amount of cross-talk between the regions contributing to the source activity (41). As the two sources oscillate coherently with a phase lag, the cross-talk can be interpreted as information sharing by axonal transmission. More precisely, the discrete Fourier transform decomposes the signal in a finite series of cosine and sine waves (in-phase and out-of-phase carrier waves, forming the real and imaginary part of the Fourier decomposition) at the Fourier frequencies. The lag of the cosine waves with respect to their sine counterparts is inversely proportional to their frequency and amounts to a quarter of the period; for example, the period of a sinusoidal wave at 10 Hz is 100 ms. The sine is shifted a quarter of a cycle (25 ms) with respect to the cosine. Then the lagged phase coherence at 10 Hz indicates coherent oscillations with a 25 ms delay, while at 20 Hz the delay is 12.5 ms, etc. The threshold of significance for a given lagged phase coherence value according to asymptotic results can be found as described by Pascual-Marqui et al. (42), where the definition of lagged phase coherence can be found as well. This analysis was corrected for the amount of pairwise comparisons using a Bonferroni correction. Time-series of current density were extracted for all region of interests using sLORETA for all the frequency bands delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz), and gamma (30.5–44 Hz). Power in all 6239 voxels was normalized to a power of 1 and log transformed at each time point. Region of interest values reflect the log-transformed fraction of total power across all voxels separately for specific frequencies. We included the dACC, pgACC, posterior cingulate cortex (PCC), the left and right parahippocampus, left and right insula, the dorsal lateral prefrontal cortex, and the left and right somatosensory cortex.

RESULTS

Clinical Outcomes

For back pain, an average reduction was obtained for tonic stimulation of 38% and for burst stimulation of 46% in comparison with baseline (Table 2). A comparison between tonic and burst stimulation revealed a further pain reduction of 12% for burst stimulation. For limb pain, a reduction of 36% was demonstrated for tonic stimulation and 57% for burst stimulation in comparison with the baseline measurement, while between tonic and burst stimulation a further pain reduction of 33% was obtained for burst stimulation. For general pain, a pain reduction was obtained for tonic stimulation of 41% and burst stimulation of 54%. Comparing both measures revealed a further pain reduction of 22% for burst stimulation. Overall, patients had a larger pain reduction on burst stimulation, with exception of one patient. Statistical analysis demonstrated a significant effect for burst stimulation only in comparison with sham stimulation for both back ($W = -1.75$, $p = 0.04$) and limb pain ($W = -1.75$, $p = 0.04$), but not for general pain ($W = -1.21$, $p = 0.11$). For tonic stimulation, no improvement could be obtained. The individual and average scores for baseline, tonic and burst stimulation for back pain, limb pain and general pain can be found in Table 1.

Electrical Neuroimaging

A comparison between tonic stimulation vs. burst stimulation shows a significant ($p < 0.05$) increase in synchronized activity in the left and right dACC extending into the dorsomedial prefrontal cortex as well as the primary somatosensory cortex for the alpha1 frequency band for burst stimulation in comparison with tonic

stimulation. A difference was also noted in left dorsolateral prefrontal cortex for the beta2 and beta3 frequency bands, with more activity associated with burst stimulation in comparison with tonic stimulation (Fig. 2).

Comparing burst stimulation with the baseline revealed an increase ($p < 0.05$) of alpha1 activity at the edge of the primary and secondary somatosensory cortex, the rostral to pgACC and the precuneus (Fig. 3).

For tonic stimulation, a comparison with baseline showed a significant ($p < 0.05$) decrease in beta3 activity in the PCC and decrease of gamma activity in the parahippocampus (Fig. 4).

A conjunction analysis revealed a significant effect for the theta ($z = 2.57$, $p < 0.05$) and gamma ($z = 7.41$, $p < 0.001$) frequency band common to tonic and burst stimulation (Fig. 5). For the theta frequency, band tonic and burst stimulation commonly change activity in the primary somatosensory cortex, the inferior parietal area, and the multisensory supramarginal gyrus extending into the secondary somatosensory cortex as well as the PCC and the parahippocampal area. For the gamma frequency band, the pgACC extending into the vmPFC is commonly activated for both tonic and burst stimulation. No significant effects were obtained for the delta, alpha1, alpha2, beta1, beta2, and beta3 frequency bands.

We calculated the ratio of the current density between the pgACC/vmPFC and the dACC, which revealed a significant effect for the gamma frequency band (Fig. 6a). Our results indicate that the pgACC/dACC ratio was reduced after burst stimulation in comparison with tonic stimulation and the baseline measure (Fig. 6a). No significant ratio effects were obtained for the delta, alpha1, alpha2, beta1, beta2, and beta3 frequency bands. In addition, we compared the pgACC/dACC ratio for burst stimulation and healthy controls. No effect was obtained.

A connectivity analysis comparing baseline vs. burst stimulation revealed a significant reduced connection ($p < 0.05$) between the dACC and the right parahippocampus for burst stimulation (Fig. 7). No significant connectivity effects were obtained for the delta, alpha1, alpha2, beta1, beta2, beta3, and gamma frequency bands. A comparison between baseline and tonic stimulation as well as between tonic and burst revealed no significant effects.

DISCUSSION

The aim of this study was to look for commonalities and differences in supraspinal mechanisms associated with tonic and burst stimulation by means of EEG. Quantitative (=digital) EEG permits to separate the EEG activity in different frequency bands, which follow a linear progression on the natural logarithmic scale (43). The different frequency bands follow a power law($1/f^a$), suggesting a scale-free structure (44). This means that the EEG is built up of a lot of low-frequency activity, with progressively decreasing power for higher frequencies. The different frequency bands are interrelated by cross-frequency coupling, with the lower frequency bands (delta, theta, and alpha) proposed to be carrier waves on which higher frequency bands (beta and gamma) are nested. The different frequency bands have possibly a different fundamental function. Delta activity (1–3 Hz) has been associated with reward/motivational and autonomic nervous system/basic homeostatic processing (45), theta activity(4–7 Hz) has predominantly been linked to memory-related processing (46), and alpha activity (8–12 Hz) to attentional processes (47). Beta activity (13–30 Hz) is related to a status quo of ongoing activity (48) and gamma activity (>30 Hz) to changes or prediction errors in the environment (49).

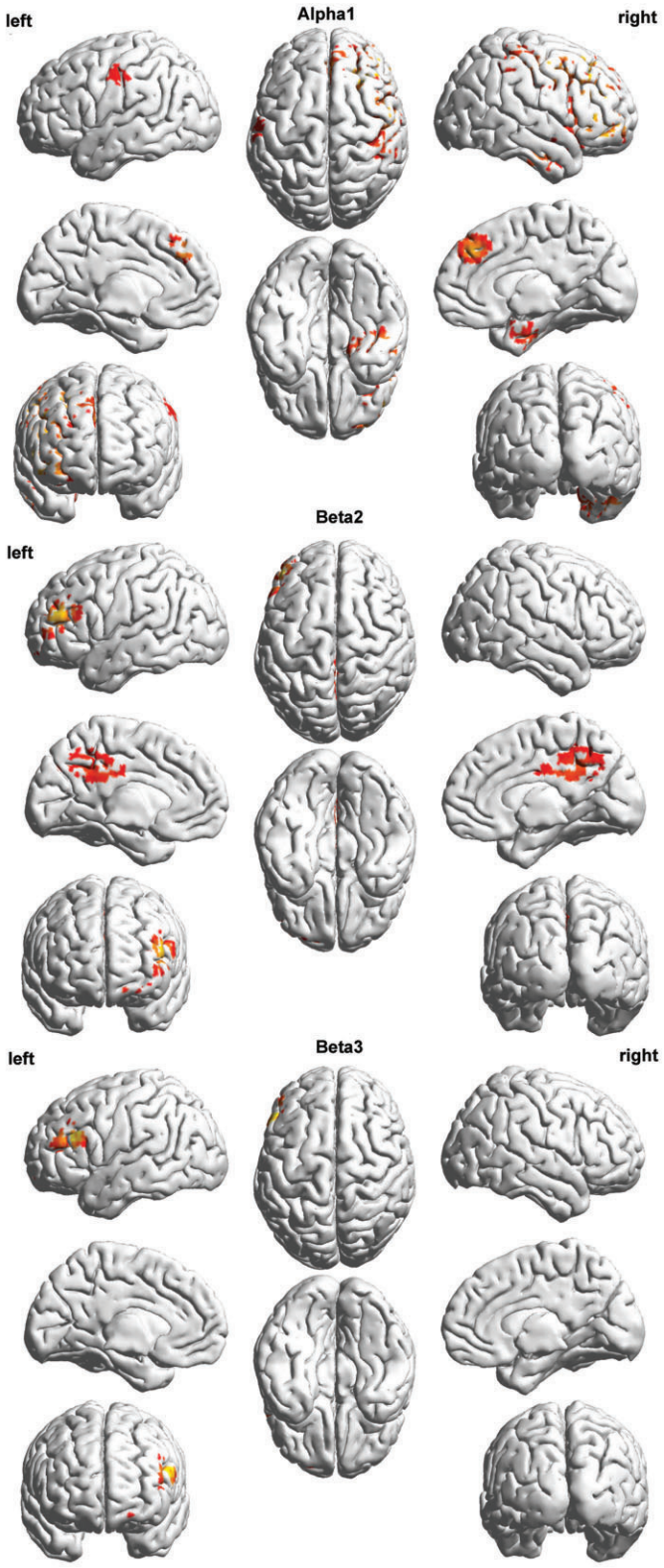

Figure 2. A comparison between tonic and burst stimulation on the source-localized EEG recording data revealed a significant ($p < 0.05$) increase in synchronized activity (yellow to red colored areas) in the left and right dorsal anterior cingulate cortex extending to the dorsomedial prefrontal cortex, as well as the primary somatosensory cortex for the alpha 1 frequency band and the left dorsal lateral prefrontal cortex (DLPFC) and posterior cingulate cortex for beta2 and DLPFC for beta3 frequency bands for burst stimulation in comparison with tonic stimulation.

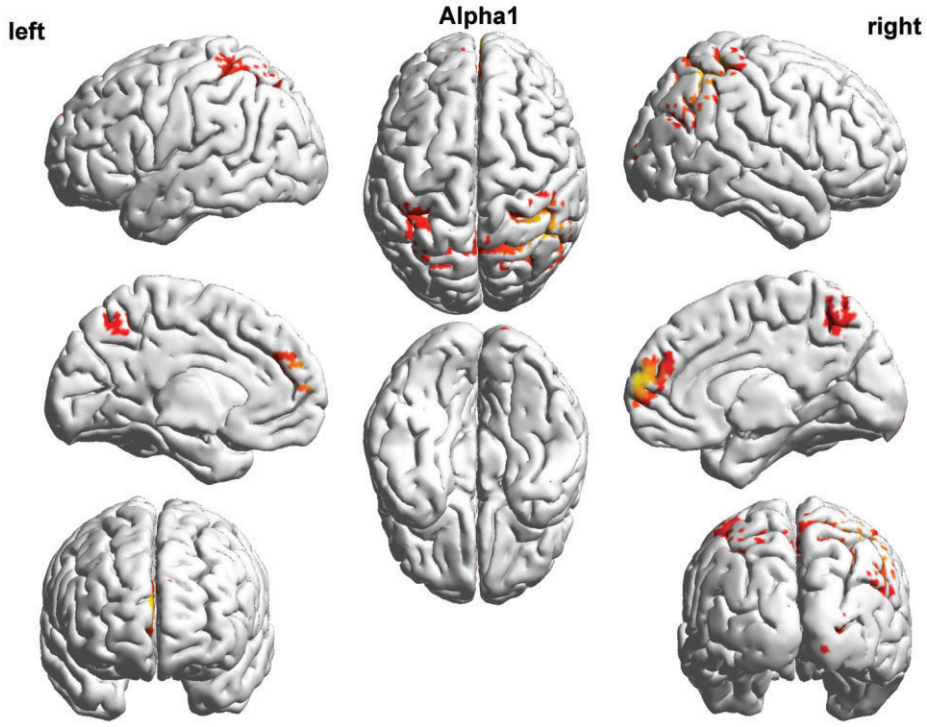

Figure 3. A comparison between baseline and burst stimulation on the source-localized EEG recording data revealed a significant ($p < 0.05$) increase in synchronized activity (yellow to red colored areas) for alpha 1 activity of rostral anterior cingulate cortex extending to the dorsomedial prefrontal cortex as well as an increase in the precuneus and somatosensory cortex.

Burst stimulation was conceived as a novel stimulation design to mimic burst firing in the brain, and as such be a physiological stimulation mode (50). Burst firing in the brain is considered a wake-up call from the brain (51), exerting both a stronger inhibitory and excitatory postsynaptic potential due to its nonlinear built-up and its higher signal-to-noise ratio (51). It has furthermore been suggested that burst firing is involved in rerouting information (52), permitting parallel processing, and is involved in synchronizing network activity (52). Copying burst firing in an electronic version might capture some of these characteristics, which could be beneficial as a stimulation design (50). As mentioned for SCS, the patient's internal pulse generator is routinely programmed at 40 Hz burst mode with 500 Hz spike mode, using spikes at 1000 µsec pulse width (22,23), similar to what was used for subcutaneous C2 nerve field stimulation for FBSS (53). On the other hand, for somatosensory cortex stimulation to treat neuropathic pain, 4 to 8 Hz burst mode with 500 Hz spike mode is used (54). For the auditory cortex stimulation in the treatment of tinnitus, different burst frequencies are being used (55,56), whereas for dorsolateral prefrontal cortex stimulation in the treatment of tinnitus, 22 Hz (harmonics of 11 Hz, which was the patient's individual alpha frequency) empirically yielded the best result (57). Ultimately, the goal is to mimic natural and physiological burst firing by adjusting programming to the target tissue. Our clinical outcome measures confirm previous findings that burst stimulation can generate a larger pain suppression effect than tonic stimulation (22,23,25,53,58,59). The difference suggests that burst stimulation might differ from tonic stimulation in its supraspinal mechanism, but both stimulation designs have a pain-suppression effect, which could be due to a common final pathway.

When comparing burst and tonic stimulation (Fig. 1), differences are noted between burst and tonic SCS with more alpha1 activity related to burst stimulation in the dACC, dorsolateral prefrontal cortex, primary somatosensory cortex, and PCC. This suggests that burst stimulation has a statistically more profound effect on both the medial and lateral pathways. However, that does not exclude tonic stimulation to also influence these pathways, albeit in a lesser way. Burst stimulation activates alpha activity in the pgACC, primary and secondary somatosensory cortex, and precuneus (i.e., it might normalize activity in the antinociceptive pathway), the lateral pain pathway, and the default mode network (Fig. 3). Tonic stimulation seems to decrease gamma band activity in the parahippocampus and the PCC (Fig. 4). In other words, both stimulation designs seem to modify brain activity differentially.

The conjunction analysis demonstrates that both stimulation designs also have a common mechanism related to the theta and gamma frequency band. Theta activity is commonly modulated in the somatosensory cortex, i.e., the main component of the lateral pathway, as well as the PCC and in the inferior parietal area, which encompasses the inferior secondary somatosensory cortex, PCC, and the parahippocampus. The pgACC is commonly modulated for gamma (Fig. 5).

An fMRI study performed during tonic SCS has demonstrated that tonic stimulation modulates predominantly the lateral pain pathways due to blood oxygen level dependent (BOLD) changes that are noted in the somatosensory cortices (60). This was confirmed by a more recent study showing changes in the thalamus, primary sensorimotor area, posterior insula, and secondary somatosensory cortex (61). However, the amount of pain suppression resulting from SCS is related to the amount of activation in the pgACC (61), i.e., how much the anti-nociceptive pathway was activated. Furthermore, evoked potentials elicited by painful stimulation measured with and without SCS demonstrate consistent attenuation of evoked potentials in primary and secondary somatosensory cortex but less so in the dACC (62), suggesting that tonic stimulation predominantly

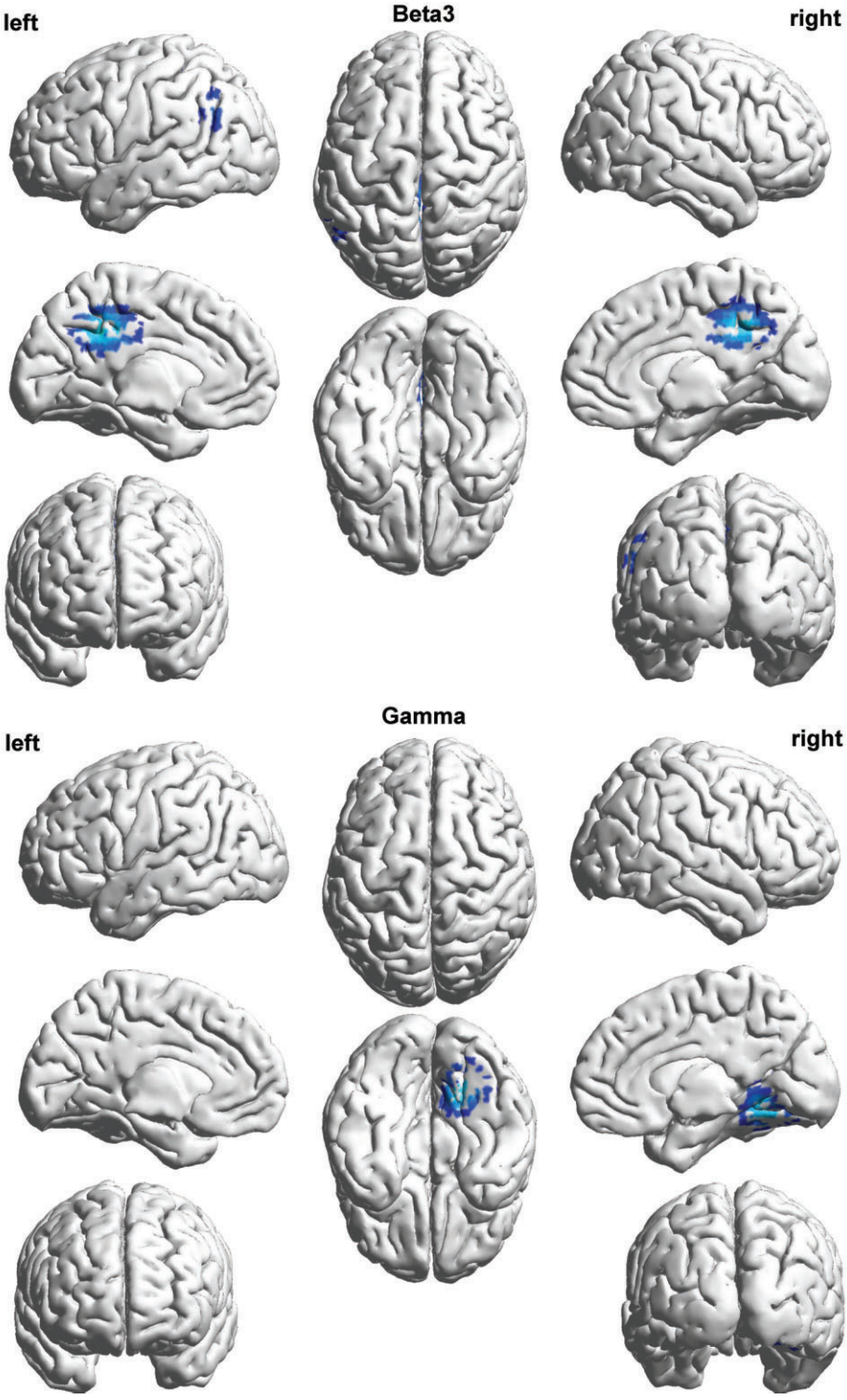

Figure 4. A comparison between baseline and tonic stimulation on the source-localized EEG recording data revealed a significant ($p < 0.05$) decrease in synchronized activity (blue colored areas) in beta3 activity in the posterior cingulate cortex and decrease (blue colored areas) of gamma activity in the parahippocampus after tonic stimulation.

modulates the lateral pathway. A PET study was performed in nine patients with neuropathic pain related to different causes compared with baseline painful state (SCS off for 12 hours) with a pain-reduced state after tonic SCS (pain reduction from 76.1 ± 25.2 to 40.6 ± 4.5). This study demonstrates that activity increases in the thalamus contralateral to the painful limb and in the bilateral parietal association area, as well as in the anterior cingulate cortex and prefrontal areas. It was assumed that activity changes induced by SCS in the contralateral thalamus and parietal association area would regulate the pain threshold, whereas anterior cingulate cortex and prefrontal areas would control the emotional aspects of intractable pain, resulting in the reduction of neuropathic pain after SCS (63). An MRI

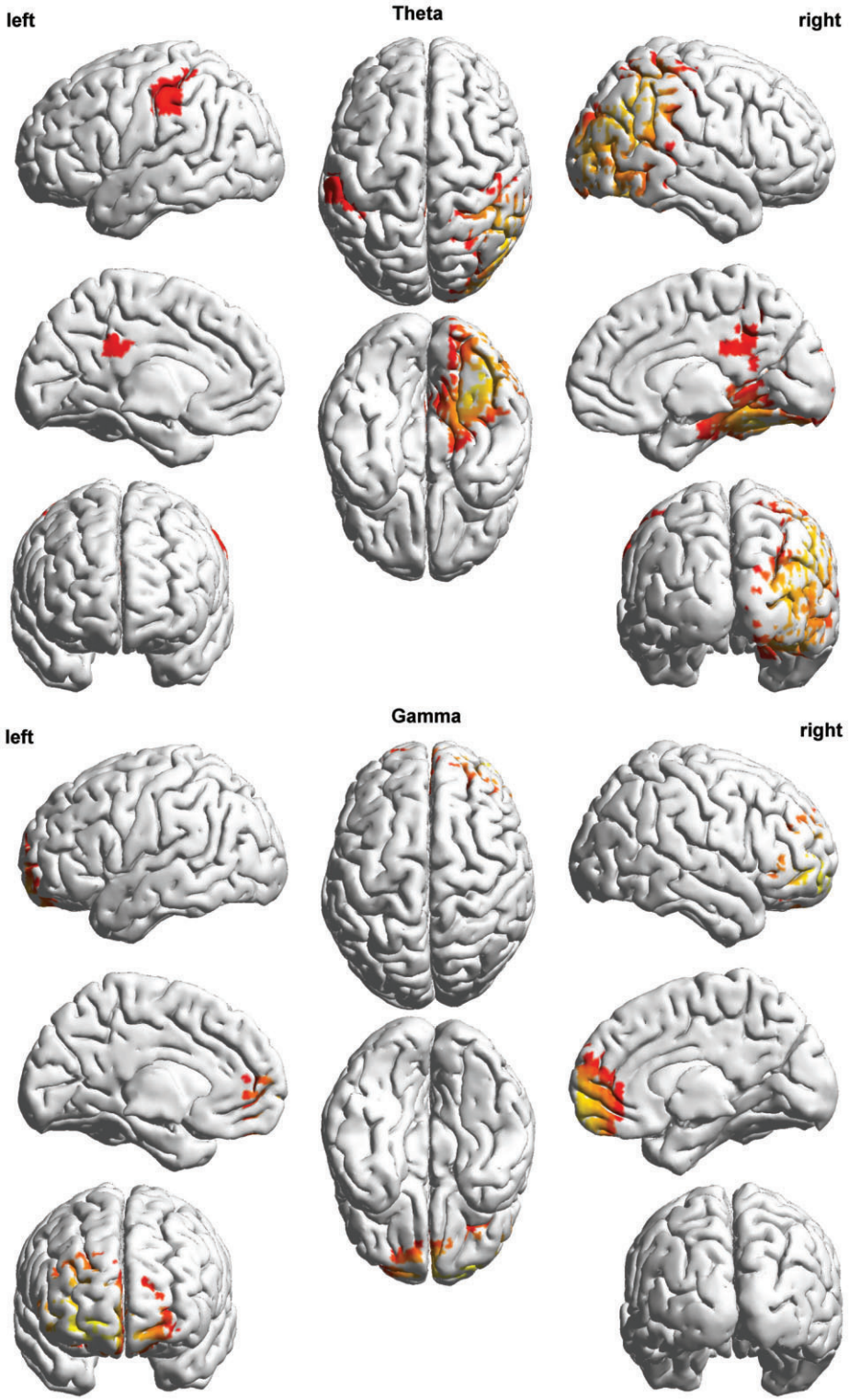

Figure 5. Conjunction analysis between tonic and burst stimulation corrected for baseline measures for the theta and the gamma frequency bands. Activation in tonic and burst stimulation goes in the same direction (yellow to red areas) for theta activity in the somatosensory cortex, posterior cingulate cortex, parahippocampal area, and inferior parietal area. For gamma activity, similar activation patterns are noted in the pregenual anterior cingulate cortex extending into the ventromedial prefrontal cortex bilaterally.

spectroscopy study with thalamus and rostral anterior cingulate cortex as regions of interest demonstrated changes in GABA in the thalamus, which was explained by modulation of the medial pain pathway (64). However, the voxel size in this study precludes to differentiate between the dorsomedial nucleus and posterior part of the ventral medial nucleus (VMpo) nucleus, related to the medial pain pathway, from the ventral posterolateral nucleus (VPL) and ventral posteromedial nucleus (VPM) of the lateral pain pathway. In

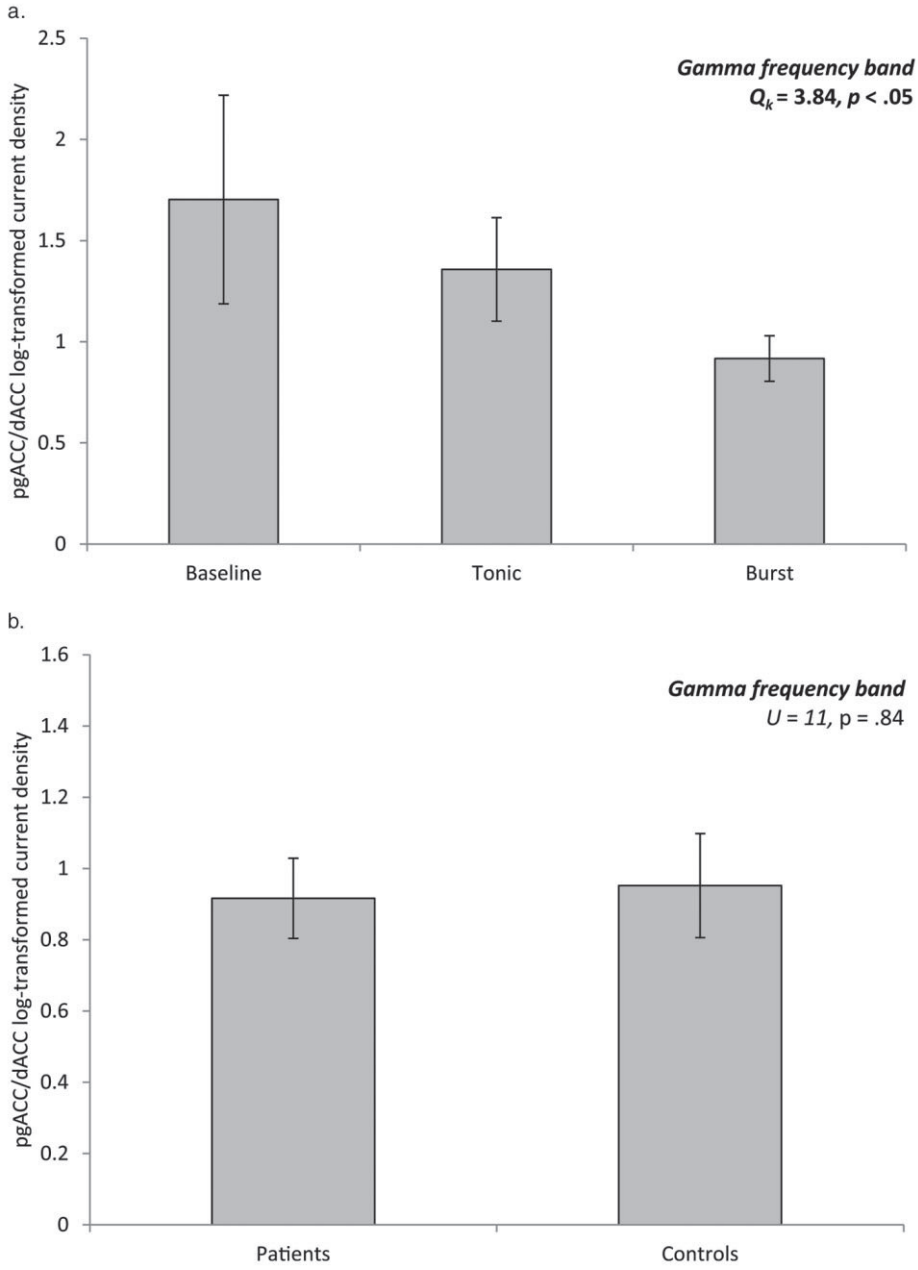

Figure 6. a. A comparison between the pregenual anterior cingulate cortex (pgACC)/dorsal anterior cingulate cortex (dACC) ratio for baseline, tonic, and burst stimulation reveals a significant reduction for burst stimulation for the gamma frequency band. b. A comparison for the pgACC/dACC ratio between burst stimulation and healthy controls revealed no significant difference.

summary, tonic stimulation seems to exert an effect predominantly on the lateral pathway but also somewhat on the medial pathway, and the fMRI study showed that the amount of pain suppression obtained by tonic stimulation seems to depend on the antinociceptive pathway (i.e. starting at the pgACC). Burst stimulation seems to exert a more important effect on the dACC, i.e. the medial pain system (22) (65–68).

The pgACC is part of the descending pain-modulating antinociceptive system, which also involves other areas such as the periaqueductal gray, the parahippocampal area, anterior insula, hypothalamus and rostral ventromedial brainstem (6,11,69). This system is involved in stress-mediated pain inhibition (70), placebo analgesia (69), and is deficient in pain syndromes such as fibromyalgia (71) which is characterized by spontaneous widespread pain. Furthermore, greater functional connectivity between the nucleus accumbens and the pgACC predicts pain persistence, i.e., the development of chronic pain by more than 80% (71). This fits with the concept that the transition to and continuation of chronic pain are dependent on the state of motivational/learning and reward mesolimbic-prefrontal circuitry of the brain (72–74). In other words, the reward system modulates the descending pain inhibitory system (72–74) and chronic pain can be seen as an imbalance between the two (medial and lateral (4,75)) ascending pain pathways and the descending pain inhibitory pathway which is presumably caused by a dysfunctional reward system. The reward system is dysfunctional in chronic pain states such as fibromyalgia (76), with

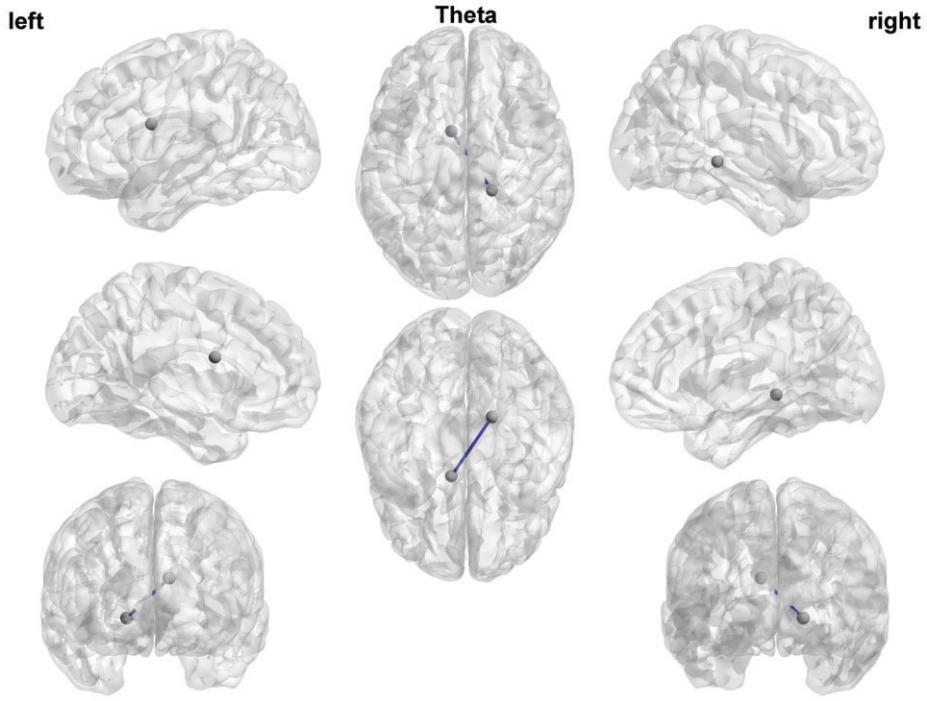

Figure 7. A functional connectivity analysis comparing baseline vs. burst stimulation revealed a significantly reduced lagged phase synchronization ($p < 0.05$) between the dorsal anterior cingulate cortex and the right parahippocampus for burst stimulation.

an associated dysfunctional descending pain inhibitory system more specifically in the pgACC (71). Our data confirm this, as pain correlates with the balance between the ascending medial system and the descending pain inhibitory system (Fig. 5).

This suggests that the supraspinal mechanism that decreases pain perception common to both tonic and burst stimulation is activation of the descending pain inhibitory system, mediated by both the pgACC and the parahippocampal area as well as modulation of the primary somatosensory cortex.

The parahippocampal area is the only area in the brain that is associated with an increase in gray matter volume in chronic pain (77). It is known to be associated with contextual processing (78–82) and is important in pain processing (83–85). It might be involved in a more general aversive network encompassing the cerebellum, parahippocampaus, hypothalamus, and subgenual anterior cingulate cortex (86). The parahippocampal involvement in pain might involve contextual memory, which could modulate pain by its influence on the descending pain inhibitory pathway (11,87), thereby encoding aversive pain memory traces (88–90). The importance of the absence of contextual pain suppression is seen by its dysfunction in fibromyalgia, in which emotional contextual pain suppression is dysfunctional (91). Even though the parahippocampal area might encode the contextual aversive memory trace, the effect on pain is mediated via modulation of the medial pain system, i.e., by the dACC and insula (91). Thus, the parahippocampal area can be envisioned to be a contextual control switch between activation of the ascending medial pain pathways and the descending pain inhibitory system. Our data lend some support to the concept that the parahippocampal area modulates the dACC, as functional connectivity is altered by burst stimulation (Fig. 6).

The PCC is the central hub of the self-referential (92,93) default mode network (92,94,95) and links the default mode network to the (pain) memory system via the parahipppocampal area (96). Meta-analytic functional imaging studies demonstrate that the PCC is activated in physical (97) and psychological (98) pain processing and inactivated in (placebo) analgesia (99). It has been shown that the salience network (dACC—insula (100)), i.e., the medial pain pathway, is activated when attending to pain (13), which signifies that pain is behaviorally important. Furthermore, the default mode network is suppressed when attending to pain (13), and the antinociceptive system is activated when mind wandering (by activating the default mode network) (101) away from pain (13). In chronic pain, whether osteoarthritic, complex regional pain syndrome, or chronic back pain, the default mode network seems to exhibit decreased connectivity of medial prefrontal cortex/pgACC to the PCC component of the default mode network, and increased connectivity to the insular cortex and links the default mode network to the (pain) memory system via the parahipppocampal area (96). In other words, in chronic pain the default mode network becomes connected to the salience network and disconnected from the antinociceptive network, and these abnormal connectivities are in proportion to the intensity of pain (102).

The inferior parietal area, encompassing the inferior secondary somatosensory cortex and the multisensory supramarginal gyrus, is involved in pain processing as demonstrated by multiple functional imaging studies such as meta-analytic studies analyzing pain persistence (103), by use of support vector machine classifiers (pain vs. no pain) (104), and also by structural (105) and functional connectivity (106) analyses. Pain also changes functioning of the default mode network (107) and default mode network functional connectivity (106). Chronic pain patients demonstrate increased default mode network connectivity to the pgACC, left inferior parietal lobule, and right insula (106), i.e., the default mode network is connected to the pain inhibitory pathways (pgACC and PCC), and salience network (right insula) (100,108,109). The left inferior parietal area processes both perceptual and memory-related informa-

tion (110–112) and is functionally connected to the parahippocampal area (113,114). Burst and tonic SCS modulates both left parahippocampal and left inferior parietal theta activity, likely modulating aversive contextual pain memory traces. Even though pain is commonly considered an aversive signal, in specific contexts (usually erotic) pain can be perceived as pleasurable. When pain is aversive, the dACC and insula are activated; however, when pain is perceived as pleasurable, the antinociceptive system is activated, including the nucleus accumbens, pgACC/vmPFC, and caudate nucleus (17). Due to its contextual processing, it can be hypothesized that the parahippocampal area is involved in the aversive vs. pleasurable perception of a painful stimulus, and is possibly mediated via a changing functional connectivity between parahippocampus and dACC.

The conjunction analysis thus suggests that burst and tonic stimulation both modulate the lateral pain pathways and the descending pain inhibitory system (via pgACC), as well as a self-referential contextual (via PCC) aversive memory system (via parahippocampus).

The pain suppression is correlated with a balance between activity in the medial pain pathway and descending pain inhibitory system as our data show. Both burst and tonic stimulations seem to have a similar effect on increased pain-related brain activity, but whereas for tonic stimulation there is only a trend to normalization, for burst stimulation, the pathological brain activity is completely normalized (Fig. 5a,b). This is clearly demonstrated by the fact that the pain-related imbalance between increased pain input and decreased pain suppression is decreased due to burst SCS and not different from the normal balance in people without pain in contrast to tonic stimulation.

The limitations of this study lie predominantly in the small size of the number of patients included in this study. Thus, larger randomized, preferably multicenter studies need to be performed to validate the results of this study. A second limitation is related to the use of source reconstruction EEG which cannot reliably record activity form deep nuclei such as the thalamus. Therefore, investigations using other functional imaging techniques such as PET or fMRI need to be performed to determine subcortical structures that are shared or different in tonic and burst stimulation and to get consilience or convergence of the data.

An intriguing but important question to ponder is how does the burst SCS reach the brain as burst stimulation does not alter firing rates in the gracile nucleus which processes information from the dorsal column proprioceptive input as well as touch, pressure, and vibration sense. In view of its connectivity to the dACC, it can be hypothesized that burst SCS must modulate the medial pain pathway directly (9) via C-fiber activation (115) ending in lamina 1 (4), connecting to the dorsomedial nucleus of the thalamus (9) and from there to the dACC (9). Thus, a local effect on the spinal cord might be further relayed to the brain, resulting in the supratentorial changes seen in this study. This could explain the absence of firing changes in the gracile nucleus. How this effect is exactly induced is still unknown. It can be hypothesized that burst stimulation disrupts synchronous burst firing of the high threshold C-fibers, which is the activity that is related to pain perception (65–67). This could be caused by reducing the synchrony or by generating inhibitory postsynaptic potentials, which are maximal at the applied 500 Hz bursts (68).

Future research should also look at differential network (default mode network, salience, antinociceptive) activation/deactivation in different SCS designs, as well as differential neurotransmitter engagement. These investigations will further help to elucidate the different mechanisms involved in burst vs. tonic stimulation.

CONCLUSION

In conclusion, it appears that burst and tonic SCS modulate the ascending lateral pathway and descending pain inhibitory pathway. The burst stimulation adds by also modulating the medial pain pathway, possibly by a direct modulation of the spinothalamic pathways as indirectly suggested by animal research. This normalizes an imbalance between ascending pain input via the medial system and descending pain inhibitory activity which could explain the superior results described by burst SCS in comparison with tonic stimulation (22,23,25,50,53,58,59,116,117). Further functional imaging studies should be performed, evaluating these findings on a larger sample and with other techniques.

Authorship Statements

Both authors were responsible for collecting and analyzing the data, as well as drafting the manuscript. Both authors approved the final version of the manuscript.

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COMMENTS

This is a very interesting discussion on the pathways involved in pain as well as how it is affected by different forms of stimulation of the spinal cord. Innovations in the use of waveforms have led to a paradigm shift from the previous notions on mechanisms and utility of spinal cord stimulation. This article serves to highlight the changes that are occurring in the brain and nervous system in response to these differing waveforms.

PET scan imaging, as well as functional MRI imaging is an indirect measure of brain activity. This is in comparison to the measurement of functional connectively that is achieved with EEG. Interestingly, the authors have a unique way of interpreting EEG data to determine changes in brain patterns that can be directly correlated with the stimulation. This is important as it quantifies the changes in the brain related to pain and its treatment with Burst and tonic stimulation. The authors discuss the goal of Burst stimulation mimicking natural and physiologic firing of the brain with the data demonstrating that although there is overlap on the descending pain pathways for both Burst and tonic stimulation there is a balancing effect experienced by Burst stimulation that is not seen with tonic stimulation.

The data analyzed and presented is well suited for the literature and an asset when looking at the differences associated with Burst and tonic stimulation. It highlights the importance of not only treating pain, but also treating the emotional and physiologic interpretation of pain in our nervous system.

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The search for the Holy Grail has begun. Since the 80's, several distinguished authors and researches over the world tried to unravel the mystery of the mechanisms of action (MOA) of spinal cord stimulation (SCS). The best among us succeeded with rodent models to determine local, segmental and even supraspinal effects by SCS.

However, the complexity of chronic pain in humans requires also MOA-studies on patients. This exploratory study is already the start for Burst stimulation in generating a hypothesis and determining the mode of its action. The authors used EEG as preferred measurement technique, with excellent temporal resolution. The only drawback is the spatial resolution. Electrical changes can only be detected at the cortical regions and not at deep or subcortical levels. Besides this drawback, they were able to postulate the hypothesis of the influence of the paleospinothalamic pathway during Burst stimulation. This hypothesis opens more doors to further research projects using techniques with superior spatial resolution in larger study populations.

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Comments not included in the Early View version of this paper.

