

Sacral Neuromodulation for Fecal Incontinence A Review of the Central Mechanisms of Action

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Sacral Neuromodulation for Fecal Incontinence

A Review of the Central Mechanisms of Action

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Objective: Fecal incontinence (FI) has a devastating effect on the quality of life and results in social isolation. Sacral neuromodulation (SNM) is proven to be an effective, minimal invasive treatment modality for FI. Despite the increasing application of SNM, the exact mechanisms of action remain unclear. The initial assumption of peripheral motor neurostimulation is not supported by increasing evidence, which report effects of SNM outside the pelvic floor. A new hypothesis states that afferent signals to the brain are essential for a successful therapy. This study aimed to review relevant studies on the central mechanism of SNM in FI.

Methods: Clinical and experimental studies on the central mechanisms, both brain and spinal cord, of SNM for FI up to December 2015 were evaluated.

Results: In total, 8 studies were found describing original data on the central mechanism of SNM for FI. Four studies evaluated the central effects of SNM in a clinical setting and 4 studies evaluated the central effects of SNM in an experimental animal model. Results demonstrated a variety of (sub)cortical and spinal changes after induction of SNM.

Conclusion: Review of literature demonstrated evidence for a central mechanism of action of SNM for FI. The corticoanal pathways, brainstem, and specific parts of the spinal cord are involved.

Key Words: sacral neuromodulation, sacral nerve stimulation, fecal incontinence, mechanism of action, central nervous system

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Fecal incontinence (FI) is a devastating condition because of the great impact it has on quality of life, often leading to social isolation.¹ Reports of the prevalence and incidence of FI vary greatly, with up to 10% of adults experiencing some degree of involuntary loss of solid or liquid stool.² Sacral neuromodulation (SNM) is a minimal invasive treatment for intractable FI that involves chronic electrical stimulation of the third sacral nerve roots. SNM originated in the field of urinary incontinence (UI) and has been an effective treatment modality for UI for decades.^{3–5} Research

focused on the etiology of UI demonstrated a complex underlying neural mechanism. This mechanism consists of multiple micturition reflexes, which require activation of both the central and the peripheral nervous system.^{6,7} Because of the complexity of the micturition-reflex pathway, even subtle injuries to the peripheral nervous system can cause UI.⁸ Peripheral changes in the micturition pathway also induce changes in the central nervous system (CNS). This was demonstrated by imaging studies that reported changes in neural activity in the midbrain and the limbic cortical regions in both urinary incontinent and urinary retention patients compared with healthy volunteers using positron emission tomography (PET)-computed tomography scans.^{9–11} Application of SNM and stimulation of sacral somatic afferents to the brain have shown to restore the micturition reflex in patients with urinary retention.^{9,12,13} Activity was particularly restored in the anterior midbrain in a region encompassing the substantia nigra and at the junction of the pons and medulla.¹⁰

After modification of the original application for UI by Matzel et al,¹⁴ SNM has become the preferred treatment for FI as well as UI, with a success rate of 74% to 86%.^{15–19} However, unlike the micturition reflex, the mechanisms underlying the therapeutic effects of SNM in FI are poorly understood, despite the increasing application of this technique. In the beginning, the hypothesis was that SNM directly stimulated the anal sphincter, resulting in an increased resting and squeeze pressure.¹⁴ Later, it was believed that the effect of SNM is based on an increase of anal sphincter pressure and rectal sensory.²⁰ However, because of controversial results and imaging studies reporting brain changes after SNM in FI patients, it is now hypothesized that, like the micturition reflex, afferent effects to the CNS play an essential role.^{19,21,22}

The majority of clinical studies up to date have solely focused on the effects of SNM on the end organ(s)—for example, rectum and anal sphincter. The number of studies on the neurophysiological effect of SNM remain limited. However, considering the increasing number of studies on the neurophysiological effect of SNM, it is important to have an overview of the current knowledge regarding the central mechanisms of action of SNM in the treatment of FI to facilitate future research. In this review, we describe the central effects of SNM in the treatment of FI to increase the understanding of its working mechanisms.

METHODS

Articles containing information on the central mechanism of SNM in FI were reviewed. The reports were found by a literature search using the Medline (PubMed, Ovid), Embase (Ovid), and The Cochrane Library databases using

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any combination of the following text words and MESH items: sacral neuromodulation; sacral nerve stimulation; sacral nerve modulation; sacral nerve; “fecal incontinence” (MESH); faecal incontinence; anal incontinence; “brain” (MESH); “cerebral cortex” (MESH); cortical and central. All publications until December 2015 were reviewed without language restriction, both experimental and human studies. The references of the included papers were searched for relevant additional reports not found by this search. Studies were included if they reported any physiological data related to the central effects of SNM for FI. Studies were not excluded on the basis of study design or sample size. Moreover, the investigators were not blinded to the manuscript title, author’s name, or institution. No filters or limits were applied in the literature search. Studies were excluded if either no treatment or no physiological data were presented. Studies were also excluded if they presented only urology data or spinal cord injury models. Finally, all opinion and/or review articles were excluded. Two independent reviewers (P.T.J.J., N.K.) extracted data from the included studies. The recorded data were first author, year of publication, study design, and the described outcomes.

RESULTS

In total, 8 studies were found describing original data on the central mechanism of SNM for FI (Fig. 1). Four studies evaluated the central effects of SNM in a clinical setting; 4 studies evaluated the central effects of SNM in an experimental setting.

Clinical Studies

Thus far, 3 studies have evaluated the central effects of SNM in a clinical setting. One study investigated changes in brain activity after rapid-rate lumbosacral magnetic

stimulation (rLSMS), which is a very similar technique to SNM, and is also included in this review. The study by Harris et al²³ was included, as the results can help improve understanding the central effects of SNM. We will discuss the included clinical studies in chronologic order of publication, as they resemble no similarities in study methods and results. The results of the clinical studies are displayed in Figure 2.

Sheldon et al²¹ evaluated the effects of SNM on corticoanal motor pathways in 10 fecal incontinent women using transcranial magnetic stimulation (TMS). The resting and squeeze pressures of the anal sphincter were also measured before and during SNM but failed to show any difference. However, a trend was noticed toward increased rectal sensitivity during and after cessation of SNM. The corticoanal representation on the motor cortex was magnetically stimulated before SNM, 14 days after SNM, and after removing temporary SNM, that is, peripheral nerve evaluation (PNE). The size and amplitude of the anal electromyographic (EMG) response caused by TMS decreased after 14 days of SNM, although not significantly. Simultaneously, a significant reduction of the area associated with the cortical representation of the anal sphincter was seen after 14 days of SNM in these patients. After removal of SNM, a trend toward a rebound effect in increased EMG excitability was demonstrated. There also was an increase in the area associated with the cortical representation of the anal sphincter. The authors concluded that SNM induces inhibitory changes in the corticoanal excitability associated with clinical improvement of FI, without changes in anorectal manometry.

Another study using TMS to evaluate the changes in the corticoanal pathway in 8 healthy subjects was reported by Harris et al.²³ The anal sphincter motor cortex was stimulated using TMS and the anal EMG signal was

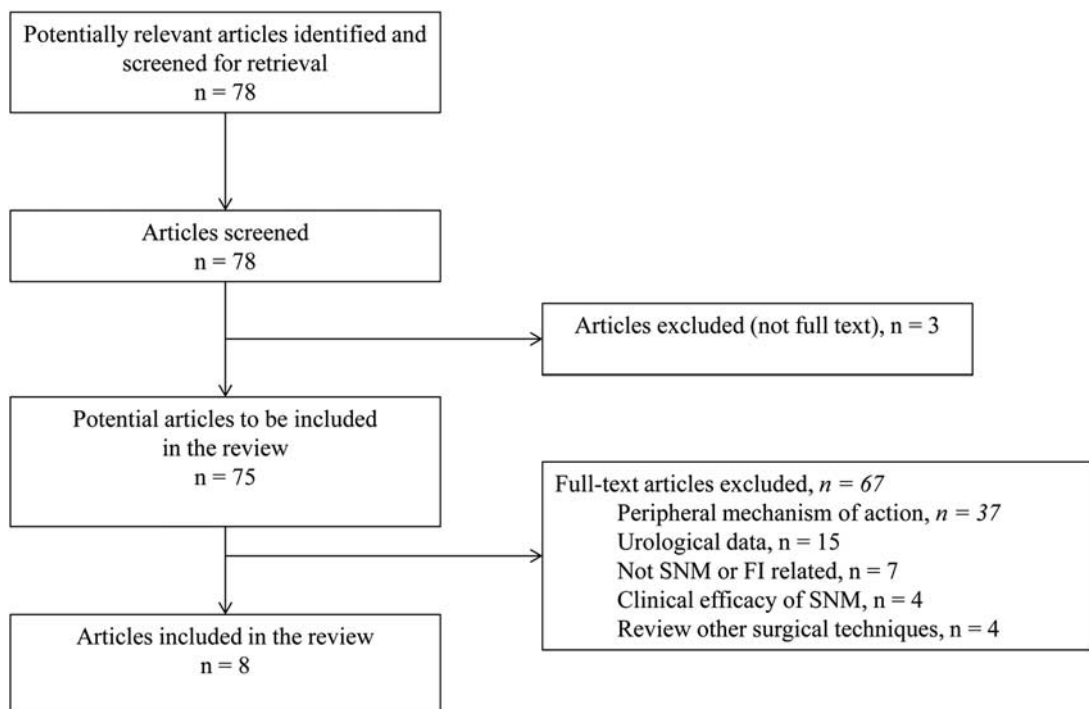


FIGURE 1. Flow diagram illustrating manuscript selection for this review. FI indicates fecal incontinence; SNM, sacral neuromodulation.

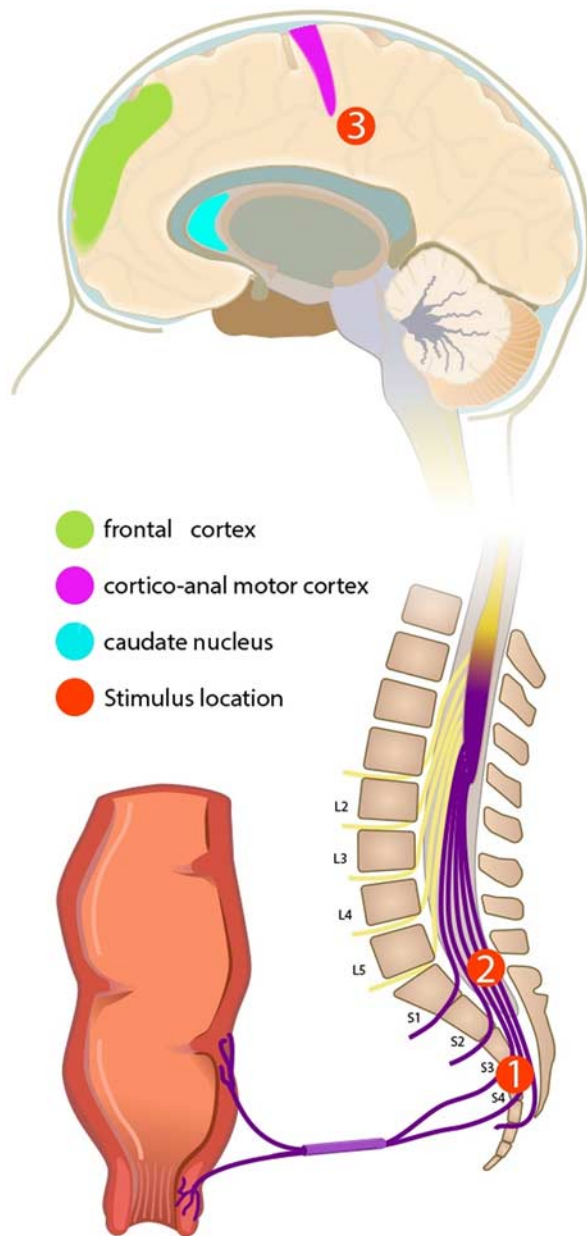


FIGURE 2. Activation of the different areas of the central nervous system by sacral neuromodulation (Giani et al²⁴; Lundby et al²⁵), rLMS (Harris et al²³), and TMS (Sheldon et al²¹) as described in the different clinical studies.

recorded. The sacral roots (S2-S3) were stimulated by rLSMS, which is comparable with the technique of SNM, at 5 and 15 Hz or sham stimulation. Comparable to the study by Sheldon et al,²¹ the anal EMG signal was recorded and compared with the baseline. Moreover, changes in anal sphincter resting and squeeze pressure and rectal sensitivity threshold before and during rLSMS were compared. Equal to the results of Sheldon and colleagues, no differences in anal sphincter resting or squeeze pressure were found. Moreover, rectal sensory and pain threshold remained unchanged following stimulation. However in contrast with the results of Sheldon and colleagues, a significant increase in corticoanal EMG response was demonstrated at 1 hour

after 15 Hz rLSMS. This is suggestive for an excitability effect of the anal sphincter motor cortex. Stimulation at 5 Hz or sham stimulation did not evoke this significant increase in corticoanal EMG response. The results suggest that the changes in cortical excitability after high frequency rLSMS appear to be of central origin and may be associated with synaptic cortical/neuronal plasticity. The latter term refers to changes in neural pathways and synapses due to changes in behavior, environment, neural processes, thinking, and emotions, as well as to changes resulting from bodily injury.²⁶

Giani et al²⁴ evaluated the afferent effect of SNM using cerebral somatosensory-evoked potentials (SEPs), measured by EEG and induced by bilateral stimulation of the dorsal nerve of the clitoris or penis (pudendal stimulation). SEPs are a series of electrical potentials generated in sensory pathways at the peripheral, spinal, subcortical, and cortical levels of the nervous system. They can be elicited by electrical or other stimuli including tactile, mechanical, and thermal stimuli. Clinical SEPs are elicited most effectively by electrical stimulation of a peripheral nerve, which preferentially activates the faster conducting fibers from proprioceptors and mechanoreceptors destined for the dorsal column-lemniscal (or “lemniscal”) pathway.²⁷ Two different stimulation frequencies (21 and 40 Hz) were compared with no stimulation in 23 patients with FI. The latency before the first positive deflection (P40 latency), the first negative deflection (N50), and the amplitude of the SEP were used as outcome measures. Patients were stimulated before SNM and after 1 month of SNM, that is, PNE. All FI patients responded well to PNE and received a permanent implantation. After 6 months, 16 patients were still successfully treated with SNM. The authors found a significantly higher P40 latency before SNM in the 16 patients who were treated successfully, as opposed to the 7 patients in whom SNM was not successful. In addition they found a significant fall in P40 latencies in patients who were treated successfully after 1 month of SNM with a stimulation frequency of 40 Hz. These results are equivalent to the results of Malaguti et al,²⁸ in a study on patients with urinary symptoms. The authors conclude that P40 latency over the somatosensory cortex can predict the outcome of SNM when stimulation lasts at least 1 month.

Lundby et al²⁵ hypothesized that SNM acts by stimulating afferent projections mediated by the vagus nerve. This hypothesis was based upon literature showing therapeutic effects of vagal nerve stimulation (VNS) in patients with different neurological pathologies.^{29,30} As previous imaging studies have shown increased regional cerebral blood flow (rCBF) in the frontal cortex after VNS, they also hypothesized that SNM is associated with increased frontal cortex activity.^{31,32} Cerebral activity measured by rCBF was evaluated using PET and MRI imaging immediately after implantation of the electrode without stimulation and after 30 minutes of stimulation. After 2 weeks of continuous stimulation the scan was performed again and repeated 30 minutes after stopping the stimulation. The scans showed a significant increased rCBF in the contralateral frontal cortex after the initial 30-minute stimulation, a change similar to the VNS change. After continuous stimulation for 2 weeks, the increase in rCBF had shifted to the dorsal part of the caput of the ipsilateral caudate nucleus, a region involved in learning and reward processing. According to the authors, the study design did not permit correlation of these results to the clinical results of the individual patients.

This is unfortunate, as the finding of the region of increased activity therefore cannot be validated.

Experimental Studies

Four experimental studies focused on the effect of SNM on neuronal plasticity of the CNS. The results of the experimental studies are presented in Figure 3.

Griffin et al³³ evaluated the sensory activation of the cerebral cortex after stimulation of the left sacral root in 44 rats. An increase of cerebral excitability over the cortical representation of the anal canal, measured by SEPs, was assessed after SNM, posterior tibial nerve stimulation (PTNS), or sham stimulation. A molecular marker of neuronal plasticity [polysialylated neuronal cell adhesion molecule (PSA-NCAM)] was quantified in a biopsy of the sensory area of the cerebral cortex. PSA-NCAM is of crucial importance for the induction of neuroplasticity, which was demonstrated by multiple experimental studies.^{34,35} In rats the dorsal root ganglia from L6-S2 contribute to the inferior rectal nerve (IRN) and most afferents originate from S1. For SNM stimulation in rats, a needle is placed in the S1 foramen and correct positioning of the electrode yields a tail twitch. In this study, the electrode was placed in the left S1 foramen and the left IRN was stimulated. The posterior tibial nerve (PTNS) was stimulated after placement of an electrode in the left hindpaw. Stimulation was applied for a total of 1 hour and the same stimulation parameters were used for both SNM and PTNS (frequency 15 Hz, pulse duration 1 ms, amplitude 6 V). A single burst of SNM produced significant rapid and long-lasting SEPs over the cortical representation of the anal sphincter. However, there were no changes in latency or duration of the cortical-evoked potentials. Besides the central effects of SNM, this study also evaluated the anal canal compliance. There was no change in anal canal resistance before and after SNM. The mean density of PSA-NCAM-positive cells after 1 hour of SNM was significantly increased in the contralateral sensory cortex compared with the sham group and the ipsilateral hemisphere after SNM in postmortem histology. Increase of PSA-NCAM is of importance for induction of long-lasting activity of the somatosensory cortex, which was previously demonstrated by multiple experimental studies.^{34–36} Moreover, the speed at which PSA-NCAM was expressed after 1 hour of SNM was striking compared with the expression of PSA-NCAM in rodent learning and memory studies, which followed only after 6 and 12 hours of training.^{37,38} These results suggest that a learning-component can be of great significance for the success rate of SNM, which was also suggested by Lundy et al.²⁵ Another feature of this study was investigation of the type of nerve fiber, which was recruited by SNM. For this, the IRN was evaluated. At the voltage used in SNM (maximum, 6 V), all myelinated fibers were recruited and only 7% to 12% of the total amount of unmyelinated C-fibers. All C-fibers were recruited at a voltage of 20 V.

In line with the previously discussed study by Griffin et al,³³ more research on neuronal plasticity of SNM in the somatosensory cortex was conducted by Evers et al.³⁹ SEPs of the anal canal were recorded over the primary somatosensory cortex, after SNM in anesthetized rats. An electrode was inserted in the first sacral foramen, and SNM was applied using different stimulation frequencies (0.1, 1, 10, 100 Hz). SNM was applied for 1.8 to 180 seconds, and changes in SEPs were evaluated at 3 and 30 minutes after

stimulation. A lower stimulation frequency was associated with a maximum increase of SEP amplitude. Further analysis demonstrated a maximum increase of SEPs' amplitude using a frequency of 2 Hz (1.7 to 2.1 Hz). Moreover, the effect of stimulus amplitude on the maximum increase of SEP amplitude was calculated at 100%, 75%, 50%, and 25% of the motor threshold. There were no differences between stimulation at 100%, 75%, and 50% of motor threshold. This suggests that the voltage used for an effective treatment of SNM is based on an "all or nothing" phenomenon with a minimum voltage of half the motor threshold. Duration of stimulation was not associated with a significant increase of SEP amplitude. However, stimulation for 180 seconds was sufficient for evoking SEPs and stimulation for 18 seconds was not. Stimulation longer than 180 seconds showed no difference in evoking SEPs. Therefore, it appears that a low stimulation frequency (2 Hz) with stimulus amplitude at half the motor threshold and an intermittent pattern of stimulation are the most effective stimulation parameters. Notably, these conclusions are in contrast to the common clinical parameters of a continuous stimulation at a higher frequency of 14 to 31 Hz and a voltage at sensory threshold.⁴⁰ Comparable to the experimental study of Griffin et al,³³ SNM seems to induce an increase of evoked potentials over the somatosensory cortex. These results are comparable to 2 previously discussed clinical studies reporting an increase in SEPs recorded by EEG.^{23,24}

The effect of SNM on neuronal plasticity in the spinal cord was evaluated by 1 study.⁴¹ This study focused on whether the central effect of SNM is similar to a phenomenon known as diffuse noxious inhibitory controls (DNIC).⁴² In short, a noxious stimulus applied to 1 part of the body can reduce the response to a subsequent noxious stimulus elsewhere in the body.⁴³ Pathophysiological afferent information from both the bladder and the anal canal to the dorsal horn neurons were considered as noxious stimuli in the case of urinary and FI, respectively. Electrical stimulation of peripheral nerves at intensities sufficient to excite nociceptive afferents is proven to be sufficient for inhibition of nociceptive-activated dorsal horn neurons.⁴⁴ *C-Fos* protein expression can be used as a high-resolution metabolic marker for polysynaptic pathway tracing in the CNS^{45–47} and as a functional marker for the population of nociceptive cells.⁴⁸ DNIC can be expressed as a change in expression of *c-Fos* protein and it seems possible that SNM can induce *c-Fos* expression within the CNS. To reduce an increase of *c-Fos* induced by surgery, an electrode was implanted 1 week before stimulation in the foramen of S1 on the right side only. For stimulation, SNM was applied continuously for 2 hours with the animals under general anesthesia. SNM significantly increased the number of *c-Fos*-positive cells in segments L5 to S3, but especially in sections of L6-S1 that specifically innervate the anorectum in rats. The density of *c-Fos*-positive cells was highest in the ipsilateral side of electrical stimulation and specifically in the dorsal commissure and the sacral parasympathetic nucleus. These regions are suggested to be primarily involved in the concept of DNIC.⁴⁵ On the basis of these results, the authors suggested that the concept of DNIC can be applied to SNM.

A novel approach to study the effect of SNM on neuronal plasticity in the spinal cord and brainstem was described in a recent study by Langlois et al.⁴⁹ The study investigated the effect of SNM on neuroplasticity in the

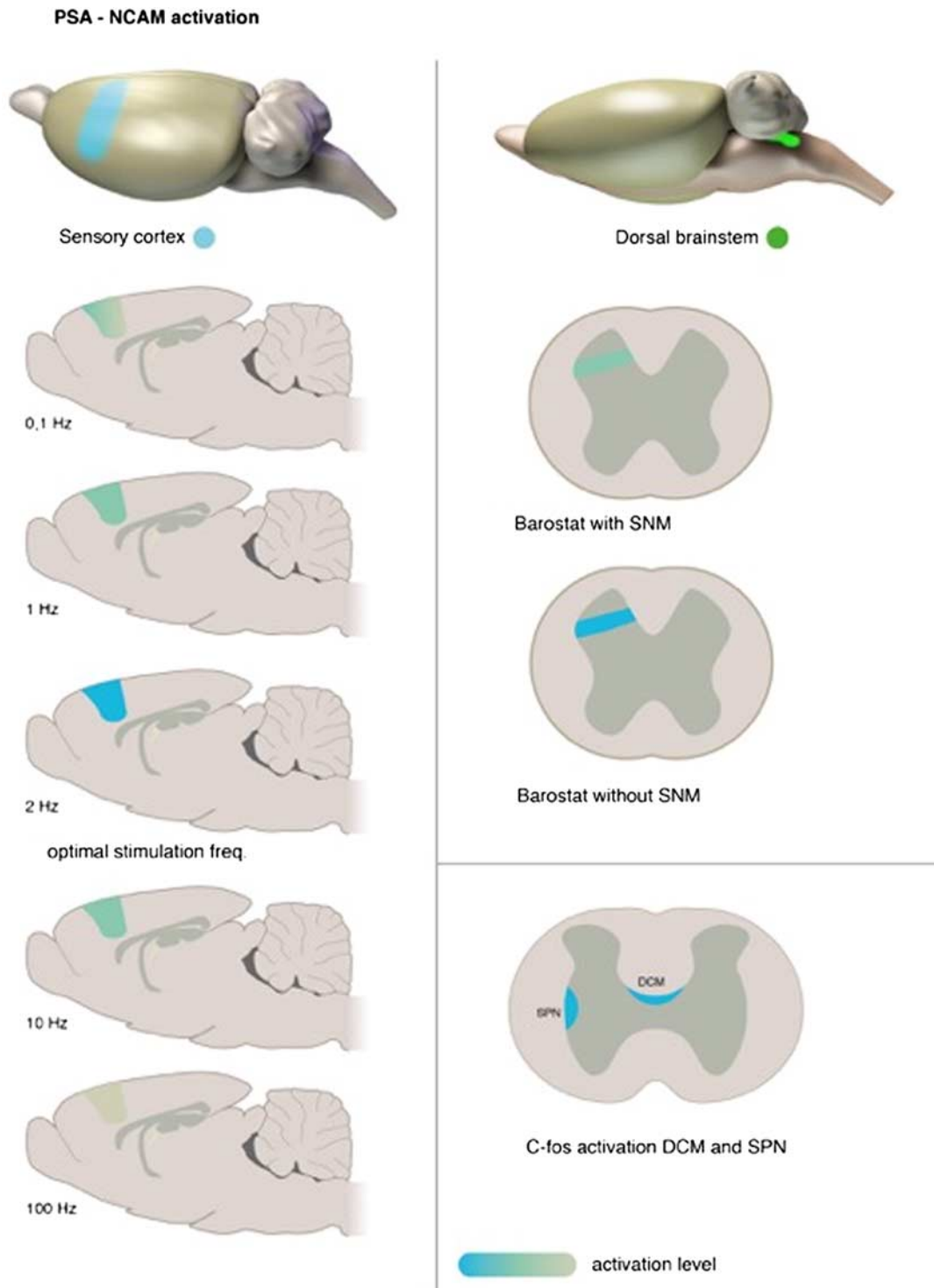


FIGURE 3. Activation of different areas of the central nervous system of the rat by sacral neuromodulation as described by the different experimental studies. DCM indicates dorsal commissure; SNM, sacral neuromodulation; SPN, sacral parasympathetic nucleus.

spinal cord and brainstem areas activated by colorectal distension (CRD). A compliant distension balloon was inserted in the distal colon of anesthetized rats, an electrode was placed in the foramen of S1, and acute SNM was applied using clinical parameters (14 Hz, 33 ms) at a stimulation 20% below the motor threshold. *C-Fos*-positive

cells were counted in the brainstem (parabrachial nucleus and nucleus of solitary tract) and in the lamina I of S1. An increase in *c-Fos* expression in the dorsal horn of the spinal cord and the brainstem was found after CRD. SNM reduced the increase of *c-Fos* expression in both the spinal cord and brainstem areas compared with sham. Another

TABLE 1. Results of Human Studies

References	Subjects (N)	Study Design	Stimulation Parameters	Results
Sheldon et al ²¹	Patients (10)	TMS motor cortex before and after SNM	TMS (2.2 T); SNM (15 Hz, pulse width 210 μ s, amplitude 1-3 mA)	Reduction in corticoanal area SNM (2 wk SNM)
Harris et al ²³	Healthy (8)	rLSMS after TMS (15 vs. 40 Hz)	rLSMS at 5, 15 Hz and sham stimulation	Increased corticoanal EMG response (15 Hz, 1 h rLSMS)
Giani et al ²⁴	Patients (23)	Stimulated pudendal nerve SEP before and after SNM	Pudendal nerve stimulation at 21 and 40 Hz	Higher P40 latency before SNM; fall in P40 latencies after SNM (40 Hz)
Lundby et al ²⁵	Patients (8)	MR imaging and PET: acute vs. 2 wk SNM	SNM (14 Hz, pulse width 210 μ s, amplitude 0.5-4.5 V)	Increase in rCBF frontal cortex (acute SNM); shift in rCBF to caudate nucleus (2 wk)

EMG indicates electromyography; MR, magnetic resonance; PET, positron emission tomography; rCBF, regional cerebral blood flow; rLSMS, rapid-rate lumbosacral magnetic stimulation; SEP, somatosensory-evoked potentials; SNM, sacral neuromodulation, TMS, transcranial magnetic stimulation.

feature of this study was the impact of SNM on gastrointestinal mechanosensitivity threshold to CRD using cardiovascular changes. The mechanosensitivity threshold in this study was defined as the change in mean arterial pressure (MAP) in response to CRD. MAP was quantified using a perfused catheter placed in the right carotid artery. MAP variation in response to CRD has been established as a reliable marker for visceral mechanosensitivity.⁵⁰ SNM reduced MAP variation induced by CRD compared with baseline and sham stimulation. Injection of a nonspecific opioid receptor antagonist prevented the SNM-induced decrease in MAP variation. The combined results of this study suggest that SNM decreases colonic mechanosensitivity induced by CRD through involving an opioidergic pathway. On the basis of reduced *c-Fos* expression in the spinal cord and brainstem after SNM, it was suggested that SNM increases the colorectal threshold through a spino-bulbar loop involving an opioidergic pathway. This is in agreement with previous studies demonstrating a decrease in rectal hypersensitivity after SNM.^{51,52}

DISCUSSION

The majority of the included clinical studies have evaluated the neurophysiological effect of SNM on the cortical presentation of the anal sphincter pathway. Only 1 study used imaging techniques to identify involvement of deeper brain structures (Table 1), despite the evidence of multiple experimental studies that demonstrate the involvement of

multiple CNS structures (Table 2). Most studies identified the somatosensory cortex as an important structure related to the effect of SNM.^{21,23-25,33,39} However, results regarding the effects of SNM on the cortical excitability seem rather conflicting. Acute rLSMS (< 30 s) leads to a significant increase of corticoanal EMG response, and the authors concluded that this was due to an increased excitability of the anal sphincter motor cortex.²³ This finding is in agreement with the increase of SEP over the cortical representation of the anal sphincter and the increase of PSA-NCAM in the sensory cortex after acute SNM.³³ This excitability effect of acute SNM was also suggested by an increase of *c-Fos* expression in the spinal cord (L6-S1) and brainstem.^{41,49} However, the studies by Sheldon et al²¹ and Giani et al²⁴ both reported a significant reduction in excitability of the corticoanal and somatosensory cortex after 2 weeks of SNM. Although these data regarding cortex excitability seem conflicting, the same time effect was reported by Lundby et al.²⁵ Their PET imaging study demonstrated a shift of increased rCBF from the frontal cortex (acute SNM) to the caudate nucleus after 2 weeks of SNM (short-term SNM). Unfortunately, results of this last study could not be correlated to the clinical effect because of the study design, and results must therefore be interpreted with caution.

Moreover, comparable data regarding a time effect on cortical excitability were also seen in studies reporting on SNM for UI. Research regarding the central mechanism of action of SNM for UI is more advanced compared with

TABLE 2. Results of Experimental Studies

References	Subjects (N)	Study Design	Stimulation Parameters	Results
Ishigooka et al ⁴¹	Rats (12)	<i>C-Fos</i> in spinal cord and brainstem after SNM	SNM: 10 Hz, pulse width 200 μ s, amplitude 1.1 (0.2) mA; 2 h	Increased expression of <i>c-Fos</i> L6-S1 (DCM, SPN)
Griffin et al ³³	Rats (44)	Acute SNM on SEP and neuronal plasticity	SNM: 15 Hz, pulse width 1 ms, amplitude 6 V; maximum 1 h	Increase in SEP over cortical area anal sphincter; PSA-NCAM increased in sensory cortex
Evers et al ³⁹	Rats (72)	Different stimulation SNM frequencies on SEP amplitude	SNM: 1.8-100 Hz, pulse width 1 ms, amplitude 15 V; 1.8-180 s	SEP amplitude associated with stimulation frequency; minimum is 50% motor threshold
Langlois et al ⁴⁹	Rats (40)	Neuronal plasticity in spinal cord and brainstem after SNM	SNM: 14 Hz, pulse width 330 μ s, amplitude 20% < MT	SNM limits CRD-related increase in <i>c-Fos</i> in S1 and brainstem

CRD indicates colorectal distention; DCM, dorsal commissure; MT, motor threshold; SEP, somatosensory-evoked potential; SNM, sacral neuromodulation; SPN, sacral parasympathetic nucleus.

research regarding SNM for FI. PET imaging studies in the field of urology demonstrated increased cortical activity during acute SNM and a reduction of cortical activity after chronic SNM in patients suffering from UI compared with unstimulated controls.¹¹ These results are in line with previous studies that have suggested a comparable mechanism of action for SNM for both urinary and FI.⁵³

Blok et al¹¹ showed with his PET study that activity of the periaqueductal gray, amygdala, and thalamus was reduced by SNM in patients with UI compared with unstimulated controls. These results suggest that SNM deactivates the reticulothalamic system back to baseline, resulting in a decreased sensation of urge. Deactivation of these areas leads to a block of afferent signal from the bladder to the pontine micturition center.⁵³

Most neurophysiological research suggests that SNM has an effect outside the suggested pelvic end organs. Placement of the lead in the S2-S4 region induces stimulation of afferent (sensoric) fibers from the anal sphincter, rectum, and pelvic floor. Somatic fibers (pudendal nerve) are also stimulated. Most likely, low-level stimulation of pelvic and rectal afferents (S2-S4), as described in the Gate Theory, reduces activation of C-fibers in the dorsal horn during rectal filling, which blocks inputs from the rectum to the pontine center.^{53,54} This leads to a reduction of reflex inhibition of the sphincter function and rectal contractility through Onuf nucleus.

However, despite the increasing amount of data regarding the mechanism of action of SNM for FI, the exact mechanism of action remains poorly understood. One consequence of this poor understanding is that SNM is applied to the patient by a trial-and-error approach. After implantation of an electrode, the clinical response during the test period determines whether a final internal pulse generator will be implanted or not. The test period usually varies between 2 and 4 weeks, but implantation of a final internal pulse generator can take much longer.⁵⁵ In addition to the trial-and-error approach, the lack of understanding of the full mechanism is also illustrated by the uncertainty of whether motor response or sensory response is the best predictor for success during lead placement.⁵⁶

In conclusion, an increasing body of evidence shows that SNM has an effect on the CNS. This review stresses that although a general hypothesis regarding the mechanism of action of SNM is known, most data underlying the current hypothesis are derived from research in the field of SNM for UI. Therefore, to improve our understanding of the central mechanism of action of SNM for FI, studies focusing on a correlation between changes in cerebral activity and the individual clinical outcome are necessary. Furthermore, more experimental animal studies evaluating neuroplasticity after SNM are essential to understand the exact central mechanism of action. Recent studies as reported by Evers et al⁵⁷ contribute vital data in understanding the mechanism of action. These studies correlate changes in anal-evoked potentials over the somatosensory cortex with immunohistochemical changes in the cortex and spinal cord to evaluate brain plasticity due to SNM for FI. A better understanding of the central mechanism of action of SNM for FI may lead to improved inclusion criteria, identification, and application of the most optimal stimulation parameters and improve the treatment of late clinical failures.

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