Neuromodulation and depression

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Chapter 2

Non-invasive neuromodulation as a new therapeutic strategy in the management of functional somatic symptoms

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Submitted.

Objective

A large proportion of medical symptoms remain unexplained and medical management of these symptoms is often inadequate. These unexplained symptoms include functional neurological motor symptoms, fibromyalgia and complex regional pain syndrome. Due to the absence of an aetiological framework there are currently no curing and disorder-specific treatments. Here we review the evidence on an upcoming therapeutic option, non-invasive neuromodulation, as a method of treatment for functional somatic symptoms.

Methods

A systematic search of the literature was performed: two independent readers screened the abstracts identified with specific search strings in the four databases. The resulting hits were screened on the inclusion criteria and after full text reading the Risk of Bias was applied to all included studies.

Results

Neuromodulation as a treatment option for functional somatic symptoms is under investigation in multiple medical disciplines. While in some symptom categories such as fibromyalgia and paresis placebo-controlled randomized controlled trials are available, case-studies or small groups are reported in other such as functional neurological symptom disorder. First results are promising but further research is warranted as is standardisation of treatment protocols.

Conclusions

The literature indicates that various forms of neuromodulation yield positive therapeutic results with very infrequent side effects. The involvement and relevance of a placebo effect is discussed.

1. Introduction

Currently there is no established etiological framework for Functional Somatic Symptoms (FSS). As a consequence, these symptoms constitute a significant clinical challenge in terms of therapeutic management. Non-invasive neuromodulation inspire new hope of finding an effective treatment for FSS in addition to behavioral therapies. The current review aims to provide an overview of the first studies on neuromodulation methods in FSS.

FSS concern a group of symptoms that affect motor or sensory functioning and cannot be adequately explained by any known physical pathology (DSM-5) (American Psychiatric Association 2013). This classification refers to a heterogeneous group (Barsky and Borus 1999; Fink and Schroder 2010) and includes sensory related phenomena such as chronic pain and tinnitus, motor related phenomena such as conversion paresis and more elaborate syndromes such as irritable bowel syndrome, fibromyalgia and complex regional pain syndrome type I (CRPS-1). Functional symptoms have to be distinguished from intentionally simulated symptoms in which the patient is in search of financial gain (malingering) or psychological support (factitious disorder). The prevalence of functional symptoms is high and reports vary between 22 – 50% of patients that present FSS in primary care, depending on the methodology used (e.g. inclusion criteria) and the clinical setting that reports the numbers (Escobar et al. 1998; Mergl et al. 2007; Nimnuan, Hotopf, Wessely 2001;

Olde Hartman et al. 2009; Roca et al. 2009).

Previously FSS were labeled as 'non-organic', 'psychogenic' or 'hysteric' referring to the assumed role of psychological factors in the etiology of these symptoms (Lipowski 1988) Whereas in former editions of the DSM the presence of a psychological conflict was mandatory for the diagnosis of FSS, the current diagnostic criteria no longer require this. This change in terminology is important as it reflects a shift in theory and clinical criteria for the diagnosis of FSS from the DSM-IV-TR to the DSM-5 (American Psychiatric Association 2013). Cognitive theories on FSS stress that symptoms are not intentionally produced but are the result of wrongfully activating cognitive schemata while inhibiting the relevant ones (Brown 2004). The physical symptom that is the result of this process is perceived by the patient but the underlying erroneous executive management of schemata is not within the patient's control.

In search of the etiological mechanisms of FSS neuroimaging methods increase understanding of brain mechanisms involved. Several studies report abnormal functional brain activity in patients with FSS compared to patients with a known pathology or healthy controls (Picarelli et al. 2010; van Beilen et al. 2011). The use of neuromodulation techniques that have the potential to bring about changes in cortical excitability and plasticity (Bilek et al. 2013; Hsieh et al. 2015) could be a promising treatment by influencing brain activity (Pollak et al. 2014). A new method of treatment is welcome, since current clinical therapeutic options are often insufficient. In addition, treatments commonly used such as Cognitive Behavioral Therapy (Kroenke 2007), physical therapy (Moene et al. 2002), and hypnosis (Zonneveld et al. 2012) require motivation for a behavioral approach of somatic symptoms. It can be difficult to motivate patients for a behavioral intervention when underlying mechanisms of the symptoms remain unexplained.

1.1. Cerebral involvement in Functional Somatic Symptoms

Neuromodulation as a treatment in FSS disorders implicates the existence of abnormal cerebral functioning in patients. Indeed, for a wide range of functional symptoms neuroimaging research has confirmed abnormal brain function (Aybek et al. 2014; Cagnie et al. 2014; Cojan et al. 2009; de Lange, Roelofs, Toni 2007; Di Pietro et al. 2013; Halligan et al. 2000; Jorge and Amaro 2012; Labate et al. 2012; Linnman, Becerra, Borsook 2013; Marshall et al. 1997; Nicholson et al. 2014; Pollak et al. 2014; Voon et al. 2010; Voon et al. 2011). This does not imply that abnormal brain function is the cause of the symptoms; it might just as well be the result of them. The mechanisms of the persistence of FSS are circular, and abnormal brain activation is taking part in that circle. Typically multi-causality is assumed and

the symptoms originate, perpetuate and sometimes vanish and point at a complex interaction between somatic, behavioral, medical, societal and cultural factors.

The current review aims to provide an overview of the first literature currently available on neuromodulation methods in a variety of FSS. FSS include a heterogeneous group of symptoms and hence differences in related brain function is assumed. In this review the focus is on those symptoms in which some evidence is reported for abnormal neuroimaging results or the symptoms are of a neurological behavioral nature. These syndromes include sensory related phenomena such as fibromyalgia and CRPS-1 and motor related phenomena such as conversion paresis. Before providing an overview of the available literature on non-invasive neuromodulation in FSS, we briefly describe the current neuromodulation techniques.

1.2. Subtypes of non-invasive neuromodulation

1.2.1. (Repetitive) Transcranial Magnetic Stimulation (TMS and rTMS)

Transcranial Magnetic Stimulation is a non-invasive technique used to stimulate nerve cells in the superficial areas of the brain. It is based on the principle of electromagnetic induction. A TMS pulse is produced by generating a large, rapidly changing electrical current that is passed through a coil. This pulse generates a fluctuating magnetic field, which induces a small current in the brain. For example, the hand muscles of a patient with functional paresis can be activated with the use of TMS. In repetitive Transcranial Magnetic Stimulation (rTMS) series of pulses (up to 100 Hz) can be applied. These pulses alter brain functioning and the duration of the effect exceeds the duration of the stimulation. A pulse delivered at a frequency below 1 Hz inhibits cortical excitability and above 5 Hz increases the cortical excitability (Fitzgerald, Fountain, Daskalakis 2006).

1.2.2. Pulsed electromagnetic fields (PEMF)

PEMF is an intervention in which physical principles similar to TMS are applied. However, in PEMF the field strength is much weaker (< 10 mT). The stimulation fits the physiological signals better than the pulses used by TMS. The frequency content of the signals is generally in the extremely low frequency band (ELF - 3 Hz to 3 kHz) and even 0.1 Hz. PEMF can effectively induce acute (minutes) and sustained (days) changes in cell cultures (Atalay et al. 2013), whole animals (Elmusharaf et al. 2007; Martin, Koren, Persinger 2004), and humans (Kortekaas et al. 2013; Persinger, Hoang, Baker-Price 2009).

1.2.3. Transcranial Direct Current Stimulation (tDCS)

In tDCS a non-invasive direct current is applied to the head. In the simplest form, two sponge electrodes are attached to the head and a small (1-2 mA) electrical current is applied. The positive or anodal electrode is thought to stimulate the underlying brain area while the negative or cathodal electrode is thought to have an inhibitory effect (Stagg and Nitsche 2011). tDCS can modulate neurotransmitter release, leading to changed neuronal activity, cerebral blood flow, oscillatory brain activity and functional connectivity in the brain (Hansen 2012).

2. Methods

2.1. Search protocol

The database search was updated last in April 2017. Databases searched: PubMed, PsycINFO, Cochrane and Embase.

2.2. Search terms

For each category of disorders, symptoms or syndromes a specific search string was used, see supplemental digital content for details.

2.3. Inclusion criteria studies

All abstracts were screened and selected by two independent observers (EK; SvB). After the initial selection based on the abstract, the full text of the articles was screened and the Risk of Bias was applied to all included articles to get an indication of the quality of the studies included. Of the papers identified by the search string further selection was based on the following criteria:

- General information: year, first author, disorder, N.
- Methodology: type of neuromodulation, location of stimulation, duration of stimulation, intensity of stimulation, RCT, placebo device, type of control group/ treatment.
- Clinical outcome measures: symptom reduction, other outcome measurements, and additional effects neuromodulation.

2.4. Functional symptom categories

The focus in this review is on symptoms that generally warrant a referral to the neurologist. Subtypes of Functional Somatic Syndrome Disorders and other MU Symptoms included are:

1. Sensory and specifically pain related:

- Complex Regional Pain Syndrome (CRPS I)
- Fibromyalgia

2. Movement related:

- Paresis (reduced movement)
- Movement disorders (excessive movement, such as tremor)

3. Results

For an overview of the quality of the randomized controlled trials (RCTs), see Figures 2.1 and 2.2. The risk of bias shows that most of the information reported in this review comes from studies with a low or unclear risk of bias. See table 2.1 for an overview of the methodology used and results presented in the included papers.

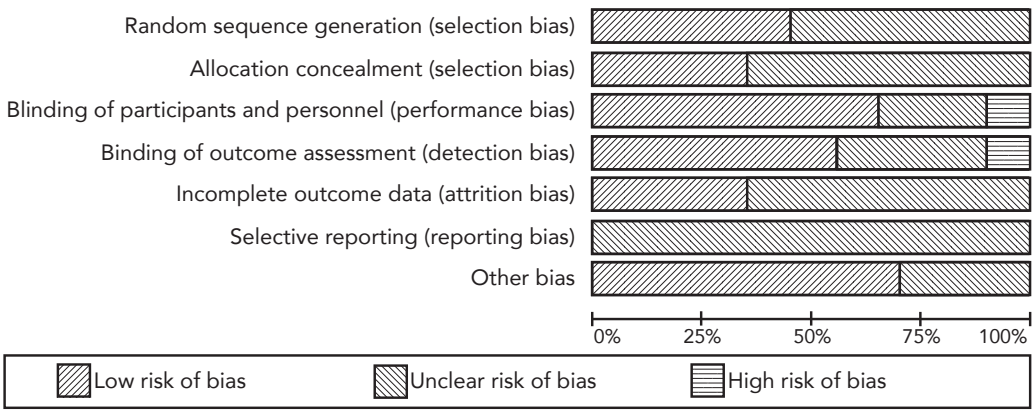

Figure 2.1: Risk of Bias of all investigated RCTs.

3.1. Complex Regional Pain Syndrome type I

CRPS-I is a chronic condition characterized by severe pain, sensory abnormalities (e.g. hyperalgesia and allodynia), vasomotor instability (e.g. temperature and skin colour changes), sudomotor abnormalities (e.g. oedema or sweating), motor changes (decreased range of motion or motor dysfunction) and trophic changes (e.g. hair, nail and skin) (Harden et al. 2007). Symptoms frequently emerge following traumatic injury, or a clinical condition such as a heart attack, stroke, cancer, infection, spinal cord injury, arthritis, or polymyalgia. Symptoms can arise in the absence of a triggering injury or illness as well. A striking feature is that the symptoms are disproportional to the severity of the trauma. The International Association for the Study of Pain distinguishes between two types of CRPS (1986). In CRPS-I no evident nerve injury is present, whereas in CRPS-II the cause can be ascribed to a definable major nerve injury, like a lesion or a tumor.

The pathophysiology of CRPS-I is yet to be defined, but appears to be associated with dysregulation of the central nervous system and autonomic nervous system . The available literature describes the various potential mechanisms for CRPS symptoms such as trauma-related cytokine release, exaggerated neurogenic inflammation, sympathetically maintained pain and cortical reorganization (Birklein 2005).

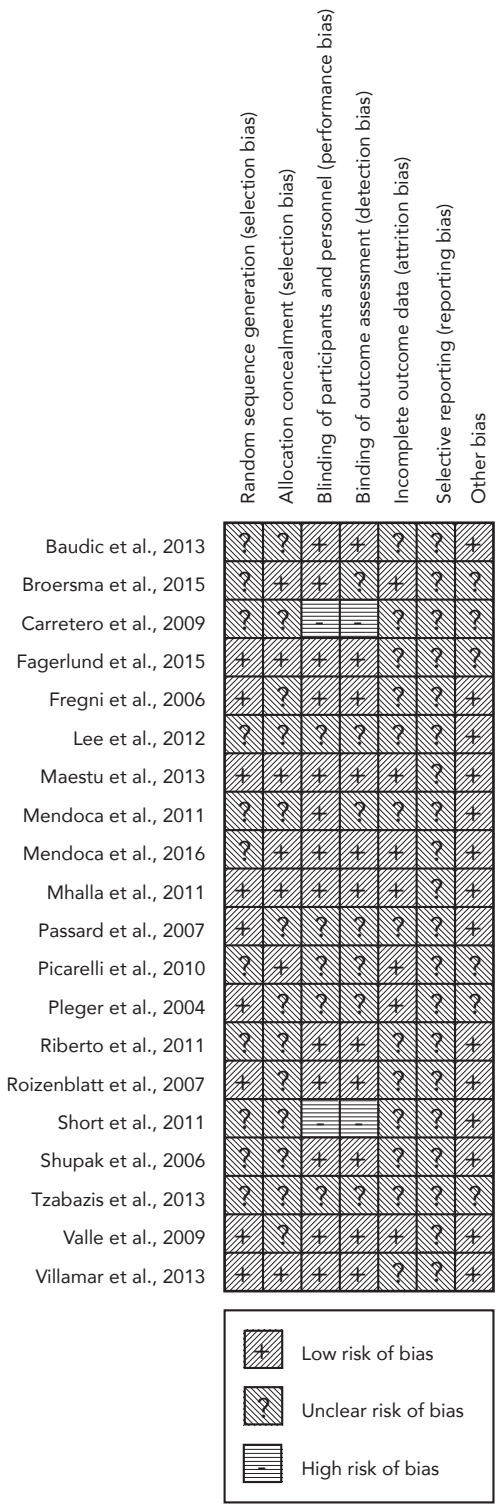

Figure 2.2: Risk of Bias per RCT.

3.1.1. Neuroimaging

Studies that focus on brain imaging indicate that patients with CRPS-I exhibit alterations in the parietal lobes, mid-insula, mid-cingulate gyrus, superior medial frontal gyrus and the primary somatosensory cortex (S1) (Linnman, Becerra, Borsook 2013). A systematic review of the latter area revealed a smaller S1 representation of the affected hand in patients compared to controls (Di Pietro et al. 2013). There is evidence that sensory and motor hyper excitability correspond to regions in the brain involved with the central nervous system of patients with well-localized CRPS-I (Eisenberg et al. 2005). The presence of abnormal brain activity may suggest that cortically directed treatments could have a positive effect on pain perception in CRPS-I patients.

3.1.2. Neuromodulation

Neuromodulation may be effective in altering pain perception in CRPS-I according to two RCTs applying neuromodulation to the motor cortex. A randomized controlled trial (RCT) on single-session rTMS as an add-on therapy to regular treatment applied to the motor cortex found a decrease in pain intensity in 7 out of 10 patients with CRPS-I whereas placebo treatment did not (Pleger et al. 2004). Another RCT with repetitive sessions of high-frequency TMS stimulation of the motor cortex found a decrease in pain intensity in 51% of 23 patients with CRPS-I, whereas pain intensity decreased in 25% of patients in the placebo condition (Picarelli et al. 2010). At the 10th session

58% (n=7) of patients had achieved a reduction in VAS-score of more than 40% whereas only 25% (n=2) in the sham group showed a similar improvement. Adverse effects reported such as headache, neck pain and dizziness were also reported in the sham groups. The number of studies is however very limited, and both the placebo effect and the treatment effect were considerable.

3.2. Fibromyalgia syndrome

Fibromyalgia syndrome (FMS) is characterized by widespread musculoskeletal pain with diffuse tenderness at multiple tender points (Wolfe et al. 2010). Other symptoms of FMS are distress, fatigue, unrefreshing sleep, and cognitive and somatic problems (Fitzcharles et al. 2013). It is estimated that point-prevalence is around 2-8%, depending on the diagnostic criteria (Clauw 2014). The pathophysiology of FMS is still unclear. Although widespread pain is felt peripheral, there is no evidence for peripheral tissue pathology, structural abnormalities, or otherwise chronic stimulation of pain afferents (Meeus and Nijs 2007). It has been thought that physical or emotional stressors, such as emotional or physical trauma, can trigger symptoms (Schmidt-Wilcke and Clauw 2011), especially when there is a genetic vulnerability (Fitzcharles et al. 2013). However, there is evidence for pain-related pathophysiological changes in the central nervous system (Schmidt-Wilcke and Clauw 2011).

3.2.1. Neuroimaging

Neuroimaging findings in FMS are plentiful and include grey matter atrophy mainly in the anterior cingulate cortex (ACC), prefrontal cortex (PFC) and insula, altered functional connectivity, and an increased activation of the pain matrix (thalamus, insula, ACC, S1 and PFC) (Cagnie et al. 2014; Jorge and Amaro 2012). It is hypothesized that this increased activation amplifies nociceptive signals, which in turn explains exaggerated pain in the presence of minimal and undetectable tissue damage as seen in FMS (Meeus and Nijs 2007).

3.2.2. Neuromodulation

Twenty-seven eligible studies were identified for FMS. Eight sham controlled FMS studies applied rTMS to various brain areas (M1, DLPFC, dACC). Six studies reported pain scores as measured by numeric rating scale (NRS) or visual analogue scale (VAS), one study reported effect of rTMS on cognition, and one study described the effects on quality of life and pain. Most studies showed an improvement of pain scores over time; however, in three of the six studies there was no statistically significant difference between active and sham (Carretero et al. 2009; Lee et al. 2012; Tzabazis et al. 2013).

Others did show a significant greater improvement over time in the active condition: NRS 62 to 50 (Mhalla et al. 2011), NRS 66 to 50 (Passard et al. 2007), and NRS 67 to 40 (Short et al. 2011). With regard to cognition no improvement was seen (Baudic et al. 2013). When rTMS was applied to study the effects on Quality of Life (QoL) and pain, it became clear that it has effect on QoL but not on pain (Boyer et al. 2014). Two meta-analyses dedicated to the effect of rTMS for FMS found that there is no evidence for a clinically significant effect of rTMS (Saltychev and Laimi 2017) and that rTMS is not superior to sham (Knijnik et al. 2016). So, rTMS does not seem to be effective for treatment of FMS.

Seven randomized sham controlled studies used tDCS as an experimental treatment for FMS patients (Fagerlund, Hansen, Aslaksen 2015; Fregni et al. 2006; Mendonca et al. 2011; Mendonca et al. 2016; Riberto et al. 2011; Valle et al. 2009; Villamar et al. 2013). One study reported the add-on effects on aerobic exercise of tDCS compared to sham (Mendonca et al. 2016). One study used a crossover design (Villamar et al. 2013), the others a parallel design. All had the left primary motor cortex (M1) as stimulation site; two targeted in addition the left Dorsal Lateral Prefrontal cortex (DLPFC) (Fregni et al. 2006; Valle et al. 2009) and one the frontal pole (FP) (Mendonca et al. 2011). All studies reported anodal effects over the stimulation site; two reported additional cathodal stimulation (Mendonca et al. 2011; Villamar et al. 2013).

With regard to anodal stimulation over the left M1, no significant improvement was seen in three studies (Mendonca et al. 2011; Mendonca et al. 2016; Riberto et al. 2011). The most recent of these three studies investigated tDCS as an add-on therapy in combination with aerobic exercise (Mendonca et al. 2016). They showed an improvement of 29 points on the NRS when tDCS was combined with aerobic exercise. Subjects treated with only tDCS improved least compared to exercise and sham or to exercise and active tDCS (Mendonca et al. 2016). Significant greater improvement of pain scores over time in the active condition was seen in the other four studies: VAS difference 40 (Fregni et al. 2006), VAS difference 20 (Valle et al. 2009), VAS difference 14 (Villamar et al. 2013), and NRS difference 7 (Fagerlund, Hansen, Aslaksen 2015). Active anodal stimulation over the left M1 did result in higher improvement of sleep efficiency compared to sham (Roizenblatt et al. 2007), in the same study population as described in an earlier study (Fregni et al. 2006). Three studies had additional anodal stimulation sites. The effects of left DLPFC-stimulation are mixed. One study did find significant more improvement of about 20 on the VAS after DLPFC-stimulation (Valle et al. 2009); the other did not find a significant improvement of pain (Fregni et al. 2006). One study reported the effect of frontal pole stimulation; they showed a significant improvement of about 50 on the VAS (Mendonca et al. 2011). Cathodal stimulation over the left M1 showed no

improvement in one study (Mendonca et al. 2011) versus a VAS difference of 14 in another study (Villamar et al. 2013). Cathodal tDCS-stimulation over the frontal pole, however, did result in an improvement of 20 on the VAS (Mendonca et al. 2011). One meta-analysis dedicated to the effect of tDCS for FMS found that anodal tDCS over the left M1 might relieve pain in FMS. No effect for cathodal stimulation over the left M1 or anodal stimulation over the DLPFC was found (Zhu et al. 2017). Thus, with regard to tDCS for FMS we can conclude that there is some positive effect on pain when anodal stimulation is applied to the left M1.

Two sham controlled studies tested efficacy of transcranial applied PEMF against FMS in an RCT. A single session of 30 minutes significantly improved pain compared to sham (Shupak et al. 2006). Another study reported an increase in pain thresholds when tested with an algometer over tender points, after 8 weeks of 1 day per week active PEMF-stimulation compared to a decrease in the sham condition (Maestu et al. 2013).

In short, based on the previous meta-analyses and on the individual studies, it seems that rTMS is not as effective in reducing reported pain intensity in fibromyalgia. There is some more evidence for an effect of tDCS on pain intensity in FMS. Also PEMF does appear to have a small positive effect.

3.3. Functional Neurological Symptom Disorder - Movement Disorder

Functional Neurological Symptom Disorder (FNSD) with abnormal movement as the core symptom (Movement disorders; FNSD-MD), also referred to as psychogenic movement disorder (PMD), describes a subclass of disorders with positive motor symptoms that cannot be attributed to anatomical or neurochemical disturbances (F44.4 (American Psychiatric Association 2013)). The symptoms often resemble organic diseases like Parkinson's disease, or symptoms such as tics, tremor, dystonia, myocloni, spasms and gait disorders (Jankovic, Vuong, Thomas 2006). The most frequently encountered symptoms are tremor and dystonia (Gupta and Lang 2009; Hallett, Weiner, Kompoliti 2012; Jankovic, Vuong, Thomas 2006). Other descriptions of the same condition are 'conversion tremor', 'non-organic movement disorders', 'functional movement disorder' and 'functional motor disorder'. In present days, the diagnosis is based on positive neurological criteria (e.g. abrupt onset or distractibility) (Stone and Carson 2011) and neurophysiological measurements (e.g. EEG, fMRI) are used to rule out organic causes. Current treatment options include psychotherapy, placebo therapy, pharmacotherapy (antidepressants) and physical therapy (Gupta and Lang 2009; Nowak and Fink 2009; Peckham and Hallett 2009).

3.3.1. Neuroimaging

Neuroimaging studies in patients with FNSD- tremor and FNSD-myoclonus dystonia reveal abnormal activity in various brain regions. In FNSD-tremor, studies report decreased activation in the right temporoparietal junction (TPJ) and the left supplementary motor area (SMA). Increased activation is reported in the right amygdala, the left anterior insula and bilateral posterior cingulate. In addition, lower connectivity between TPJ and sensorimotor regions and between the left SMA and bilateral dorsolateral prefrontal regions is reported (Voon et al. 2010; Voon et al. 2011).

3.3.2. Neuromodulation

Four eligible studies in which rTMS was used were identified for FNSD (Chastan and Parain 2010; Dafotakis et al. 2011; Garcin et al. 2013; Shah et al. 2015). FNSD-MD (tremor, myoclonia, dystonia, parkinsonism or stereotypies) were reduced in more than 70% of patients, with a total remission rate of symptoms ranging from 36% (Dafotakis et al. 2011) to 79% (Chastan and Parain 2010). One study on patients with various FNSD-MD reported improved physical but decreased psychological Quality of Life, after premotor cortex rTMS (Shah et al. 2015). This study included 6 patients with a longer illness duration (3-16 years) and stimulation intensity was below motor threshold. Overall, adverse effects reported were headaches and temporary worsening of symptoms (Shah et al. 2015), and one patient developed a presyncope with a feeling of faintness immediately after treatment (Dafotakis et al. 2011). No adverse effects were persistent.

In conclusion, a positive effect of neuromodulation above motor threshold is reported in patients with FNSD. This finding is highly relevant in clinical perspective as no other intervention is associated with recovery rates this high. However, RCTs have yet to be conducted.

3.4. Functional Neurological Symptom Disorder – Paresis

Paresis is a common form of FNSD. It is characterized by a loss of voluntary muscle strength and movement. Patients appear to no longer automatize muscle function, as part of an attentional deficit (Stins et al. 2015). FNSD paresis is diagnosed by a neurologist based on intact neurophysiological measures and positive diagnostic neurological signs such as the Hoover's sign (Shahar et al. 2012).

3.4.1. Neuroimaging

Abnormal brain functioning in FNSD paresis is better studied than other functional neurological symptoms (Voon 2014), as patients with paresis are well suited candidates for neuroimaging research due to the absence of motion artifacts. Abnormal brain functioning appears to be present in FSND paresis. The first theory about the underlying mechanisms involved is described as active inhibition of intact motor function, with associated over-activation of the anterior cingulated gyrus (Halligan et al. 2000; Marshall et al. 1997). After this, the idea of increased self-monitoring of symptoms was related to abnormal activity in the temporal cortex (de Lange, Roelofs, Toni 2007). Recently, involvement of parietal regions such as the precuneus and the supramarginal gyrus is discussed (Cojan et al. 2009; van Beilen et al. 2011). These regions play a role in the early stages of motor initiation, such as the cognitive planning of intentional movement. Parietal regions are also associated with psychological functions such as level of consciousness, episodic memory, self-agency and self-reflection (van Beilen et al. 2011). Finally, anatomical abnormalities in the premotor cortex and the SMA are also reported (Aybek et al. 2014; Nicholson et al. 2014). In conclusion, FS paresis is related to varying abnormal brain activity, depending on the methodology, control groups and task used in the MRI scanner.

3.4.2. Neuromodulation

Three rTMS studies on the symptoms of conversion paralysis were identified. In the first study, four patients were treated with rTMS for the duration of 5 - 12 weeks, applied to the contralateral motor cortex in combination with therapies other than psychotherapy such as sports therapy or relaxation exercises (Schonfeldt-Lecuona et al. 2006). In three out of four patients the motor functions improved markedly. The patient that did not improve was later diagnosed as malingering. In the first two weeks stimulation above motor threshold was used, i.e. the patient could actually see and feel the paralyzed limb move. Second, in seventy patients, rTMS was applied to the contralateral motor cortex of the affected limb at a maximal intensity of 2.5 Tesla. In 89% the rTMS treatment appeared to improve motor symptoms, more improvement was observed in patients with recently acquired symptoms (Chastan and Parain 2010). Third, in 12 patients rTMS was applied to the motor cortex in a placebo-controlled cross-over design. This study showed that active rTMS increased muscle strength while placebo rTMS did not (Broersma et al. 2015). Interestingly, an effect of rTMS was found when applied below the motor threshold. Patients did not see or feel their thumb move during treatment. No adverse effects were reported for any of the studies. A first placebo-controlled study confirms that neuromodulation in paresis below motor threshold is a promising therapeutic option.

Table 2.1: Overview of the methodology used and results presented in the included papers.

Author	Method	Duration	Stimulation site	n	Outcome scores	Result
			CRPS-I			
Pleger et al., 2004	rTMS: 10 Hz	Single session	Contralateral M1	10	VAS	Significant reduction in VAS score: in 7 of 10 patients. Biggest reduction after 45 minutes (contrary to what they report at 15).
Picarelli et al., 2010	rTMS: 10 Hz	10 daily sessions	Bilateral M1	23	VAS, MPQ, SF-36, HDRS	Significant reduction in VAS scores: 50.9% (4.65) in treatment group vs 24.7% (2.18) in sham group.
			Fibromyalgia			
Fregni et al., 2006	tDCS	5 days	M1 Left, DLPFC Left	32	Visual numeric scale pain (1-10)	Small difference but statistically significant difference of 4 points improved in tDCS group vs 3 points in the sham group.
Passard et al, 2007	rTMS: 10 Hz	2 weeks; 5 days per week	M1 Left	30	Numeric rating scale pain (1-10)	Significant improvement in pain in rTMS group: 1.8 points improvement vs 0.1 in sham group.
Carretero et al., 2009	rTMS: 10 Hz	4 weeks; 5 days per week	Right DLPFC	26	Likert scale pain (0-10)	No significant improvement.
Valle et al., 2009	tDCS	10 sessions, 2 weeks of 5 days	M1 Left, DLPFC Left	41	Visual analogue scale pain (1-10)	Significant improvement M1 and DLPFC tDCS group compared to sham (2 vs 0.5 points).
Mhalla et al, 2011	rTMS: 10 Hz	14 sessions; over 21 weeks	M1 Left	40	Numeric rating scale pain (1-10)	Significant improvement in pain in rTMS group: 1 point vs 0.5 in sham group.
Mendonca et al., 2011	tDCS	Single session	M1 Left; supraorbital	30	Visual numeric scale pain (1-10)	Significant improvement supraorbital stimulation (2-5 points), no significant improvement in M1 stimulation.
Riberto et al., 2011	tDCS	Daily for 10 weeks	M1 Left	23	Visual numeric scale pain (1-10)	No significant improvement.
Short et al., 2011	rTMS: 10 Hz	2 weeks; 5 days per week	DLPFC Left	20	Numeric rating scale pain (1-10)	Significant improvement in pain, 1.6 in rTMS group vs 0.3 in sham group.

Author	Method	Duration	Stimulation site	n	Outcome scores	Result
Baudic et al., 2013	rTMS: 10 Hz	14 sessions; over 21 weeks	M1 Left	38	Cognitive test	No significant improvement in cognition.
Lee et al., 2013	rTMS: 10 Hz	2 weeks; 5 days per week	Right DLPFC	22	VAS pain	No significant improvement.
Tzabazis et al., 2013	rTMS: 10 Hz	4 weeks; 5 days per week	dACC	16	Numeric rating scale pain (1-10)	No significant improvement.
Villamar et al., 2013	tDCS	Single session	M1 Left	18	Visual numeric scale pain (1-10)	Significant improvement after 30 minutes: 1.38 - 1.41 points improvement in active vs 0.69 in sham group.
Boyer et al., 2014	rTMS: High freq	10 weeks; 14 sessions	M1 Left	38	QOL; FIQ	Significant improvement on QoL in rTMS group (10 points) vs sham (2 points worsening), no effect on pain.
Fagerlund et al., 2015	tDCS	5 days	M1 Left	48	Numeric rating scale pain (1-10)	Small significant improvement in pain intensity in tDCS group 0.66 points improved vs. 0.09 in sham.
Mendonca et al., 2016	tDCS	4 weeks; 3 days a week	M1 Left	45	Visual numeric scale pain (1-10)	No significant improvement tDCS only, combination with aerobic exercises superior.
					Paresis	
Schönfeldt-Lecuona et al., 2006	rTMS: 15 Hz	5-12 weeks	M1 contralateral	4	?	Improved motor function in 3 out of 4 patients. The latter one diagnosed as malingerer.
Chastan & Parain, 2010	rTMS 0.2-0.25 Hz	30 stimuli	M1 contralateral	70	?	Effective in 89% of patients, total recovery in 43 patients immediately after stimulation, 2 after a few days.
Broersma et al., 2015	rTMS: 15 Hz	10 days	M1 contralateral	12	Dynamometer to assess hand strength	Significant increase in hand strength in treatment group. Increase of at least 20% in 8 patients.

Author	Method	Duration	Stimulation site	n	Outcome scores	Result
			Movement/tremor			
Dafotakis et al.,	rTMS: 0.2 Hz	30 pulses	Contralateral M1 of hand area	11	?	Symptom relief transient in 7 patients, 4 patients lasting relief.
Chastan et al., 2012	rTMS: 0.2 Hz	30 pulses	Contralateral M1	19	?	Total recovery in 15 patients, no effect in 1. Symptoms recurred in 4 patients.
Garcin et al., 2013	rTMS: 0.25 Hz	?	Contralateral M1	24	Severity score by 2 physicians; Self-report after 1 year	6 absolute resolution of symptoms, 12 patients who improved >50% still improved at last follow-up. 2 felt worse. 10 relapsed, 4 returned to work.
Shah et al., 2015	rTMS: 0.33 Hz	5 days, 50 pulses	Dominant M1, Premotor	6	CGI patietrated global impression of change; WHO-QOL-BREF	Significant improvement in physical domain forpremotor cortex rTMS (20.9 points on WHO-QOL-BREF).

4. Discussion & conclusion

First results of non-invasive neuromodulation are promising in terms of symptom relief and larger studies with better methodological standards should be the next step. Underlying brain mechanisms are not yet investigated. In general, neuromodulation has the potential to bring about changes in cortical excitability and plasticity (Bilek et al. 2013; Hsieh et al. 2015). It is a promising treatment option to target the functional activation differences present in patients with FSS (Pollak et al. 2014).

The use of neuromodulation in FSS is most thoroughly studied in fibromyalgia by means of placebo RCTs. Non-invasive neuromodulation (rTMS, tDCS and PEMF) significantly reduced pain levels in eleven out of eighteen fibromyalgia studies. tDCS and PEMF provide the most positive results, although for the latter the number of studies are still limited. In addition, two studies performed on CRPS-I were also placebo-controlled and report that rTMS is able to alter pain perception.

In FNSD with paresis first results suggest that rTMS may be able to increase muscle strength compared to placebo, even when the stimulation applied is below motor threshold. Stimulation above threshold elicits movement of the affected limb and this approach shows promising results in terms of recovery rates. In FNSD movement disorders symptoms were reduced in the majority of patients and total remission ranged from 36 – 79%. Case-studies on symptoms such as headaches or aphonia suggest neuromodulation is a promising therapeutic tool in FNSD. A RCT in FNSD with sufficient power and follow-up measurements is currently not available.

4.1. Clinical advantage of neuromodulation

In clinical settings the focus is nowadays on cognitive and behavioral changes that the patient is required to make. The advantage of neuromodulation is the addition of a somatic approach on the symptoms without decreasing the behavioral and psychological responsibility of patients in the management of their symptoms.

A complication in clinical practice is that the somatic nature of neuromodulation might not conform to the current referral protocol of medical professionals. In recent years, the therapeutic approach has been to guide patients away from a somatic interpretation of symptoms and to stop them seeking medical assessment. From this perspective, concerns might be raised of further medicalization, increased healthcare consumption and diminished motivation for behavioral interventions after referral to neuromodulation therapy. The presence of abnormal brain function does not diminish the importance of behavioral management of symptoms however. Neuroimaging results can educate patients about the interaction between body and behavior with

the brain as the mediating entity. Brain function is a close correlate of both behavior and bodily sensations and should be explained to patients as part of a behavioral-cerebral-somatic circular process. Neuromodulation can easily be combined with existing behavioral and somatic interventions.

4.2. Adverse effects or side-effects

No major adverse events or negative side-effects are reported in the literature. Neuromodulation appears to be a safe method in FS symptoms. Minor non-persistent side-effects were reported. Although these were transient, one patient discontinued the trial (Dafotakis et al. 2011). Patients with CRPS-I reported headache, neck pain and dizziness, but so did the participants in the placebo group.

A potential negative side effect could relate to neuromodulation being an extensive somatic treatment involving multiple contacts. This might result in aggravation of symptoms in reaction to a medical public, and decreased employment of self-management and behavioral coping strategies, or even to a lack of symptom improvement to secure sustained medical attention.

Unexpected additional positive effects are also reported. In functional neurological paresis rTMS on the hand area of the motor cortex did also improve motor function of the leg. In fibromyalgia, improved quality of life in absence of improvement of pain and improvement of sleep was reported after neuromodulation, and in another two patients headaches and migraine improved.

4.3. Limitations

It is a well-known phenomenon that studies with a new method tend to report larger effect sizes than later studies do. This is partly due to the smaller sample size seen in pilot studies. A publication bias may play a role since positive studies are more readily published than negative studies. It should also be noted that behavioral adverse events or changes in medical consumption were not taken into consideration in most studies, control conditions are usually explained symptom categories while care as usual will be an interesting comparison. Follow-up studies are scarce and behavioral outcome measures are not included.

4.4. Conclusion

Non-invasive brain modulation appears to be a treatment option worth exploring for a wide range of functional somatic symptoms including pain and various neurological symptoms. Few adverse events are reported. Consensus on the optimal stimulus

parameters (e.g. intensity, duration or stimulation site) or neuromodulation techniques is absent. Further research on behavioral side-effects and the duration of the effect is needed in comparison to care as usual. The use of neuromodulation may be most valuable as a clinical tool when it is used in combination with behavioral interventions.

5. Acknowledgements

The authors thank Natasha Maurits and Judith Rosmalen for their supervision and Ymke Groenendijk for her part in the data collection.

Source of funding: Authors were funded by the University Medical Center Groningen Innovation Fund (projects 689900, U-11-214, U-11-221), Zon-MW (project 85500032) and (nr 171101006) and NutsOhra (project 1103-068).

6. Disclosure

Conflicts of interest: None.

Supplemental - search terms

Pubmed

CRPS

("complex regional pain syndrome" OR (CRPS AND pain) OR dystroph*) AND (picotesla OR nanotesla OR micro tesla OR magnetic field* OR "pulsed magnetic field" OR "pulsed electromagnetic field" OR "extremely low frequency magnetic field" OR "extremely low frequency electromagnetic field" OR "pulsed magnetic fields" OR "pulsed electromagnetic fields" OR "extremely low frequency magnetic fields" OR "extremely low frequency electromagnetic fields" OR tDCS OR "transcranial direct current" OR "transcranial electric stimulation" OR "transcranial electrical stimulation" OR tSOS OR tACS OR TBS OR "theta burst stimulation" OR TMS OR sTMS OR rTMS OR "transcranial magneti*")

Fibromyalgia

("fibromyalgia") AND (picotesla OR nanotesla OR micro tesla OR magnetic field* OR "pulsed magnetic field" OR "pulsed electromagnetic field" OR "extremely low frequency magnetic field" OR "extremely low frequency electromagnetic field" OR "pulsed magnetic fields" OR "pulsed electromagnetic fields" OR "extremely low frequency magnetic fields" OR "extremely low frequency electromagnetic fields" OR tdcs OR "transcranial direct current" OR "transcranial electric stimulation" OR "transcranial electrical stimulation" OR tsos OR tacs OR TBS OR "theta burst stimulation" OR TMS OR stms OR rtms OR "transcranial magneti*") NOT ("Reflex Sympathetic Dystrophy"(Mesh) OR "Complex Regional Pain Syndromes"(Mesh))

FNSD movement

(("tremor" OR "psychogenic movement disorder") AND (Conversion OR nonorganic OR non- organic OR psychogenic OR unexplained)) AND (picotesla OR nanotesla OR micro tesla OR magnetic field* OR "pulsed magnetic field" OR "pulsed electromagnetic field" OR "extremely low frequency magnetic field" OR "extremely low frequency electromagnetic field" OR "pulsed magnetic fields" OR "pulsed electromagnetic fields" OR "extremely low frequency magnetic fields" OR "extremely low frequency electromagnetic fields" OR tdcs OR "transcranial direct current" OR "transcranial electric stimulation" OR "transcranial electrical stimulation" OR tsos OR tacs OR TBS OR "theta burst stimulation" OR TMS OR stms OR rtms OR "transcranial magneti*")

FNSD paresis

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Cochrane

CRPS

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Embase

CRPS

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