



# Neuromodulation for the treatment of functional neurological disorder and somatic symptom disorder: a systematic review

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## ABSTRACT

Functional neurological disorder and somatic symptom disorder are complex neuropsychiatric conditions that have been linked to circuit-based dysfunction of brain networks. Neuromodulation is a novel therapeutic strategy capable of modulating relevant brain networks, making it a promising potential candidate for the treatment of these patient populations. We conducted a systematic review of Medline, Embase and PsycINFO up to 4 March 2021. Trials investigating neuromodulation devices for the treatment of functional neurological disorder or somatic symptom disorder were selected. Extracted variables included study design, demographic and clinical characteristics, psychiatric comorbidity, neurostimulation protocols, clinical outcome measures and results. 404 studies were identified with 12 meeting inclusion criteria. 221 patients were treated in the included studies with mean study sample size of 18 (4–70). Five studies were randomised clinical trials. Functional motor symptoms (six weakness, four movement disorders) were the most studied subpopulations. Transcranial magnetic stimulation (TMS) was the most frequently used device (10 studies), followed by electroconvulsive therapy (one study) and direct-current stimulation (one study). Treatment protocols varied in intended therapeutic mechanism(s): eight studies aimed to modulate underlying network dysfunction, five aimed to demonstrate movement (one also leveraged the former) and three boosted their primary mechanism with enhanced suggestion/expectation. All but one study reported positive results; however, methodological/outcome heterogeneity, mixed study quality and small sample sizes precluded quantitative meta-analysis. Neuromodulation, particularly TMS for the treatment of functional motor symptoms, shows preliminary promise in a growing line of research. Larger, sham-controlled studies are needed to further establish efficacy and better understand therapeutic mechanisms.

## INTRODUCTION

Functional neurological disorder (FND), also known as conversion disorder, and somatic symptom disorder (SSD) are complex conditions that lie at the intersection of neurology and psychiatry. Both FND and SSD are commonly encountered in medicine and it is estimated that functional neurological symptoms may account for approximately 30% of outpatient neurology visits.<sup>1</sup> These conditions also

have high rates of disability, substantial healthcare costs, and limited available evidence-based treatment options.<sup>2–6</sup> Though distinct Diagnostic and Statistical Manual-5 (DSM-5) diagnostic entities under the Somatic Symptom and Related Disorders umbrella,<sup>7</sup> they are frequently comorbid and lumping versus splitting approaches have been debated over time.<sup>8</sup> Broadly speaking, both represent symptom presentations that are incompatible with recognised medical/neurological conditions. FND also has ‘positive’ clinical signs (eg, Hoover’s sign, tremor entrainment, and tubular visual field) that aid in diagnosis beyond exclusion. Both FND and SSD have complex, incompletely understood etiologies but share a common pathophysiological substrates of brain network dysfunction.<sup>4,9,10</sup> Current best practices include appropriate delivery of the diagnosis and psychoeducation, cognitive behavioural therapy and physical therapy.<sup>4</sup> For patients who have symptoms refractory to the above management, there are very limited additional treatment options available.

With accumulating neuroimaging research demonstrating evidence of brain network dysfunction in these disorders,<sup>9–11</sup> neuromodulation interventions targeting implicated brain regions and networks could offer an optimal new treatment strategy.<sup>12</sup> Some technologies such as transcranial magnetic stimulation (TMS), a safe, well-tolerated and non-invasive device with Food and Drug Administration (FDA) approval for the treatment of depression, obsessive-compulsive disorder (OCD) and migraine, offer the potential for focal cortical stimulation.<sup>13</sup> Transcranial direct current stimulation (TDCS) can also stimulate cortical regions (with lower spatial resolution) by providing weak electrical stimulation (1–2 mA for 5–30 min) that may facilitate or inhibit spontaneous neural activity.<sup>14</sup> Other more invasive forms of neuromodulation, such as electroconvulsive therapy (ECT), with a long-standing history of use and efficacy for many treatment-resistant psychiatric disorders, provide more generalised effects. This study aims to systematically review and assess the quality of studies investigating neuromodulation device technologies for the treatment of FND and SSD.

## METHODS

A systematic review was performed using the following databases: MEDLINE, Embase and



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PsycINFO initially on 11 August 2020 and updated on 8 November 2020 and 4 March 2021. Search terms included: '(rTMS OR transcranial magnetic stimulation OR TMS OR ECT OR electroconvulsive therapy OR TDCS OR transcranial direct current stimulation OR neuromodulation OR neurostimulation OR DBS OR deep brain stimulation) AND (somatoform disorders OR conversion disorder) OR (astasia abasia OR functional neurological disorder OR somatic symptom disorder OR somatoform) OR (conversion disorder adj. Hysteria OR reaction)'. Studies were included if they were primary treatment studies using neuromodulation device technologies for FND or SSD. Studies were excluded if they were not focused primarily on FND or SSD, case reports or series ( $n < 3$ ), not original research (reviews, opinion articles), conference abstracts, not available in English text, or did not use neuromodulation (other treatments or technologies). Articles were reviewed for inclusion by two independent researchers (CO and AM). Any discrepancies were discussed and when a consensus was not achieved, a third independent reviewer was called on to resolve conflicts (MJB). This systematic review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (please see PRISMA checklist in online supplemental materials for further detail).

Data extraction was completed by CO and AM, and included the following variables: study design, sample size, patient group, duration of symptoms, target symptoms, mean age of participants, percent female, neuromodulation technique, neuromodulation protocol parameters, duration of treatment, primary and secondary outcome measures and follow-up data. We also collected detailed information on psychiatric comorbidities, including whether trials included patients with coexistent psychiatric disorders and preassessments/postassessments of mood-related symptoms.

Study quality was assessed by CO and AM using a validated protocol from the National Institute of Health (<https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>). 'Quality Assessment of Controlled Intervention Studies' was used for studies with control group design, where as 'Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group', and 'Quality Assessment Tool for Case Series Studies' were used for retrospective cohort and case-series studies, respectively. Studies were assigned either 'good' (least risk of bias with valid results), 'fair' (susceptible to some bias deemed not sufficient to invalidate the results), or 'poor' (significant risk of bias with low validity) ratings.

Cohen's  $d$  effect sizes were generated where applicable (ie, intervention and control comparison with mean and SD data available) by calculating the mean difference between groups and dividing by the pooled SD. A correction factor was implemented to account for overinflation of effect size since most studies had small ( $n < 50$ ) sample sizes.

Assessment of the presence and impact of psychiatric comorbidities within the studies was completed by CO and included the following variables: mood data collected at baseline, exclusion of patients with psychiatric illness, preintervention and postintervention data.

## RESULTS

### Included studies

A total of 404 studies were identified, and 390 were excluded after screening titles and abstracts (figure 1). One article was found after updated search on 8 November 2020.<sup>15</sup> No additional studies were found following an updated search on 4

March 2021. Fourteen progressed to full text assessment of eligibility. Two articles were excluded at full text review on the grounds of not being primary treatment studies of the target populations. Ultimately, 12 studies were included in the qualitative synthesis. Please see tables 1 and 2, as well as figure 2 for a summary of our systematic review results.

### Study design and characteristics

A total of 221 patients were recruited in the 12 studies included in our systematic review. Of these studies, 10 used TMS,<sup>15–24</sup> 1 used TDCS<sup>25</sup> and 1 used ECT.<sup>26</sup>

With respect to study design, five were randomised controlled trials (RCTs),<sup>15 19 21 24 25</sup> five were case series<sup>16 18 20 22 23</sup> and two were retrospective cohort studies.<sup>17 26</sup> Treatment protocols varied from one single stimulation session to 12 weeks of stimulation (see table 1).

Regarding recruited patient populations, six studies focused on functional weakness/paresis,<sup>15–17 19 21 25</sup> four on functional movement symptoms (FMS),<sup>18 20 24 25</sup> one on functional seizures,<sup>22</sup> one on SSD (DSM-IV somatoform pain),<sup>23</sup> and one on mixed FND and SSD symptom presentations.<sup>26</sup>

The mean study sample size was  $n=18$  (4–70). On average, women comprised approximately 2/3 (68%) of all study participants, with a mean age of 38.7 and an average illness duration range of 5 days to 30 years. We did not exclude any trials based on age; however, 40 of the 70 patients<sup>17</sup> were adolescents (aged 11–20). No other paediatric studies were identified.

Only four studies used a sham-controlled clinical trial design.<sup>15 19 24 25</sup> Most studies were not blinded; three studies were double-blinded,<sup>15 24 25</sup> and two were single-blinded.<sup>18 19</sup> Validity of blinding was documented in only three studies.<sup>15 19 25</sup> Of the ten TMS studies, only two used neuronavigation.<sup>19 22</sup>

Studies did not exclude patients with common comorbid mental health conditions such as depression or anxiety. However, three studies did exclude patients with select severe psychiatric disorders (eg, psychotic disorders).<sup>21 22 24</sup> There was limited assessment of pre/post outcomes on mental health or mood related measures. See online supplemental table 1 for further details.

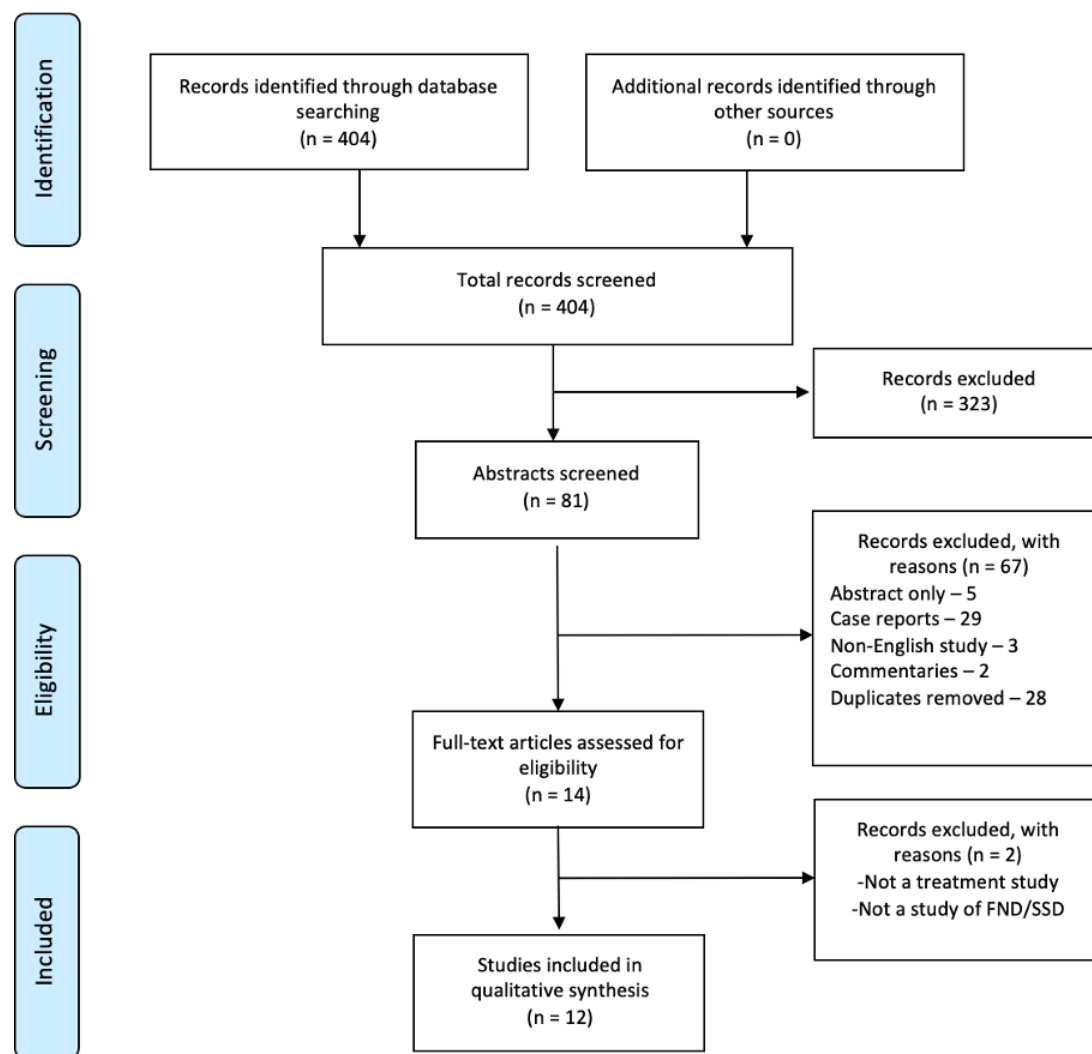
### Quality assessment

Of the five RCTs, two were rated as 'good' quality,<sup>15 24</sup> one was rated as 'fair' quality,<sup>25</sup> and two were rated as 'poor' quality.<sup>19 21</sup> Three of the case series included in this review received a 'good' quality rating,<sup>18 20 22</sup> and two were of 'fair' quality.<sup>16 23</sup> Lastly, for the retrospective cohort studies, both were rated as 'poor' quality.<sup>17 26</sup> See online supplemental table 2 for further details regarding quality assessment.

### Neuromodulation for functional limb weakness

Six studies explored the use of neurostimulation for functional paresis/weakness ( $n=128$  patients).<sup>15–17 19 21 25</sup> Five studies investigated the use of TMS on functional paresis,<sup>15–17 19 21</sup> while one used TDCS.<sup>25</sup> Studies varied considerably in terms of size, structure, stimulation protocols, outcome measures and overall quality (see table 1).

Two studies specifically explored paresis localised to the upper limb.<sup>19 21</sup> Schönfeldt-Lecuona *et al*<sup>16</sup> and Chastan and Parain<sup>17</sup> explored functional paraparesis, while Pick *et al*<sup>15</sup> included patients with monoparesis, paraparesis, tetraparesis and/or hemiparesis. Demartini *et al*<sup>25</sup> mostly explored non-specific functional weakness and also included patients with other FMS presentations (eg, tremor and dystonia) ( $n=4$ ). Stimulation



**Figure 1** PRISMA flow diagram for the selection of neuromodulation FND and SSD treatment studies. FND, functional neurological disorder; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SSD, somatic symptom disorder.

targets included contralateral motor cortex,<sup>15–17 19 21</sup> and right posterior parietal cortex (PPC).<sup>25</sup>

Primary outcomes included: subjective improvement,<sup>15</sup> disability and self-reported symptom severity,<sup>21</sup> objective change in muscle strength,<sup>16 19</sup> clinician-rated muscle power,<sup>17</sup> and interoceptive sensitivity and spatial attention.<sup>25</sup> Secondary outcomes were reported by two studies, including hand grip strength and tapping frequency<sup>21</sup> and subjective change in muscle strength.<sup>19</sup>

Positive results were reported by all studies with the exception of McWhirter *et al.*<sup>21</sup> Demartini *et al.*<sup>25</sup> (n=16) reported significant improvement in interoceptive sensitivity when comparing active vs sham TDCS ( $p=0.001$ ), and a corrected Cohen's  $d$  of 0.72 was calculated indicating a large effect size. Pick *et al.*<sup>15</sup> (n=21) found small-moderate effect sizes (Cliff's  $\delta=-0.1-0.3$ , 95% CI  $-0.79$  to  $0.28$ ) for the active treatment group (67% improved after the second stimulation session vs only 20% in sham group). Both Broersma *et al.*<sup>19</sup> (n=12) and Schönfeldt-Lecuona *et al.*<sup>16</sup> (n=4) reported objective improvements in muscle strength post-TMS treatment: Broersma *et al.* reported statistical significance versus sham (median increase of 25%;  $p=0.004$ ) while Schönfeldt-Lecuona *et al.* reported improvement in three of four patients. Chastan and Parain<sup>17</sup> (n=70) found that rTMS was effective for 89% of participants

(13% with dramatic recovery and 76% with complete recovery), with treatment being more effective for acute versus subacute symptoms ( $p=0.009$ ). Lastly, McWhirter *et al.*<sup>21</sup> did not find significant improvement in disability or symptom severity at the 3-month follow-up post-TMS ( $p=0.1$ ). However, the study was categorised as 'poor' on quality rating, only used a single stimulation session and was discontinued early due to low enrolment.

### Neuromodulation for FMS

Four studies explored the efficacy of neurostimulation for FMS (n=92).<sup>18 20 24 25</sup> There was considerable heterogeneity in protocols used, sample size, functional movement disorder subtype, outcome measures and reported efficacy (see tables 1 and 2). Three studies utilised TMS.<sup>18 20 24</sup> Both Garcin *et al.*<sup>18</sup> and Shah *et al.*<sup>20</sup> explored the use of TMS for a variety of FMS including fixed dystonia, myoclonus, tremor, jerky dystonia, Parkinsonism and stereotypies. Taib *et al.*<sup>24</sup> looked specifically at functional tremor in the upper and lower limbs of patients. Demartini *et al.*<sup>25</sup> used TDCS and they recruited a variety of FMS presentations (tremor, dystonia, myoclonus and gait disturbance).

Site of stimulation included the right PPC,<sup>25</sup> primary motor cortex (PMC)<sup>18 24</sup> and PMC and premotor cortex.<sup>20</sup> Three studies reported statistically significant improvement in their

**Table 1** Overview of published studies for neuromodulation treatment of FND/SSD

Study	Design	Blinding	Patients	Symptom	Treatment duration	Target	Treatment protocol	Comparator group
<b>TMS</b>								
Schönfeldt-Lecuona <i>et al</i> 2006 <sup>16</sup>	Case series	No blinding	Active=4 Age=38.75±18 SD=5 weeks to 5 years 50% Female	Functional weakness	5–12 weeks	PMC	15 Hz (4000 pulses) 110% RMT Daily sessions for at least 2 weeks	N/A
Chastan and Parain 2010 <sup>17</sup>	Retrospective	N/A	Active=70 Age=24.7 (8–79) SD=1 day to 3 years 63% Female	Functional weakness	Single session +booster session	PMC	'30 stimuli at low frequency with a 2.5 T coil'	N/A
Garcin <i>et al</i> 2013 <sup>18</sup>	Case series	Single-blind (raters). Blinding effectiveness not assessed.	Active=24 Age=44.5±13.2 SD=6 months - 30 years 66% Female	Functional dystonia (n=14) myoclonus (n=5) tremor (n=3) parkinsonism (n=1)	Single session (n=12 received anywhere from 1 to 4 booster sessions)	PMC	0.25 Hz (20 pulses) 110% RMT	N/A
Broersma <i>et al</i> 2015 <sup>19</sup>	Clinical Control Trial (crossover)	Single-blind (patients). Blinding effectiveness assessed.	Active=11 Sham=8 Age=34–65 SD=3 years 64% Female	Functional weakness	2 weeks	PMC	15 Hz (pulses not reported) 80% RMT 10 sessions total (30 mins each)	Sham coil
Shah <i>et al</i> 2015 <sup>20</sup>	2 Phase Case Series	No blinding for primary outcome or intervention. 1 secondary outcome measure was blinded.	Active=6 Age=43 (32–56) SD=3–16 years 83% Female	Functional tremor (n=3) myoclonus (n=3) gait disturbance (n=3) pain (n=1)	Phase 1: 1 week Phase 2: 1 week	Phase 1: PMC Phase 2: dorsal preMC	0.33 Hz (50 pulses) 90% RMT Phase 1: 5 sessions Phase 2: 5 sessions	N/A
McWhirter <i>et al</i> 2016 <sup>21</sup>	RCT	No blinding	Active=10* Age=23–52 SD=2.3 years 60% Female	Functional weakness	Single session	PMC	0.3 Hz (46–70 single pulses) 120%–150% RMT	Delayed start (standard of care)
Peterson <i>et al</i> 2018 <sup>22</sup>	Case Series	No blinding	Active=7 Age=43.1±8.8 SD=14.5±13.8 years 86% Female	Functional seizures	3 weeks	Right TPJ	10 Hz (3000 pulses) 110% RMT 30 sessions total (two per day)	N/A
Singh <i>et al</i> 2018 <sup>23</sup>	Case Series	No blinding	Active=5 Age=40.6 (32–50) SD=10 years (2–18 years) 80% Female	Somatoform pain disorder	3 weeks	Left dlPFC	10 Hz (1200 pulses) 100% RMT 18 sessions total	N/A
Taib <i>et al</i> 2019 <sup>24</sup>	2 Phase RCT†	Double-blind. Blinding effectiveness not assessed.	Phase 1: active (n=9) vs sham rTMS (n=9) Phase 2: active rTMS +hypnosis (n=18) Age=49 (24–64) SD=4 months - 16 years 55% Female	Functional tremor	Phase 1: 1 week Phase 2: 3 weeks	PMC	1 Hz (800×2 biphasic pulses) 90% RMT Phase 1: 5 sessions Phase 2: 1 session per week for 3 weeks	Sham coil
Pick <i>et al</i> 2020 <sup>15</sup>	RCT	Double-blind. Blinding effectiveness assessed.	Active=10 Sham=11 Age=40 (median), 32.5–51 (range) SD=3.5 years (median), 1.2–8.9 years (range) 85.7% Female	Functional weakness	4 weeks	PMC	Single pulse TMS 120 pulses 120% RMT two sessions total	Real coil with stimulation set at 80% RMT

TDCS

Continued



Table 1 Continued

Study	Design	Blinding	Patients	Symptom	Treatment duration	Target	Treatment protocol	Comparator group
Demartini <i>et al</i> 2019 <sup>25</sup>	RCT (crossover)	Double-blind. Blinding effectiveness assessed.	Patients=9 HC=7 Age=48.22 ± 17.548 SD=not reported 87.5% Female	Functional weakness (n=5) myoclonus (n=2) dystonia (n=1) tremor (n=1)	two sessions (one active, 1 sham)	Right PPC	Type: Constant current Intensity: 1.5 mA Single 20 min session	TDCS stimulator switched to 'study mode'
ECT								
Leong <i>et al</i> 2015 <sup>26</sup>	Retrospective	N/A	Active=28 Age=48.7 ± 12.0 SD=1–28 years (mean, 7 years) 57% Female	Somatoform pain (n=15) Functional weakness (n=11) gait disturbance (n=8) paresis (n=6) Functional seizure (n=6) cognitive dysfunction (n=4) myoclonus (n=4) tremor (n=3)	Length of hospitalisation in days (mean, range): 90, 25–274	RUL (n=21) Bifrontal (n=6) Bitemporal (n=1)	No of treatments (mean, range): 11.5, 3–22 Energy (mean, SD): 48.7±15.1 J Pulse width (fixed): 0.5 ms (brief) Seizure duration (seconds; mean, SD): 34.1±11.6	N/A

\*10 patients randomised to either immediate (n=7) or delayed (n=3, 3 months) active stimulation groups.

†Phase 1=randomised, double-blind, two-arm, prospective, parallel, controlled trial with outcomes assessments at 1 and 2 months. Phase 2=starting 3 months after inclusion, was open-label conditions, with outcome measurements at months 6 and 12.

dIPFC, Dorsolateral prefrontal cortex; ECT, electroconvulsive therapy; FND, functional neurological disorder; HC, healthy controls; J, joules; N/A, not available; PC, prospective cohort; PMC, primary motor cortex; PPC, posterior parietal cortex; preMC, premotor cortex; RCTs, randomised controlled trials; RMT, resting motor threshold; RUL, right unilateral; SD, symptom duration (median); SSD, somatic symptom disorder; TDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation; TPJ, temporal-parietal junction.

primary outcome. Taib *et al*<sup>24</sup> (n=18) demonstrated an improvement in psychogenic movement disorder rating at 1-month follow-up for active rTMS versus sham TMS ( $p<0.001$ ). Shah *et al*<sup>20</sup> (n=6) reported a significant improvement in physical domain scores pre vs post stimulation ( $p=0.04$ ). However, they also reported worsening psychological well-being ( $p=0.05$ ) and no significant improvement in quality of life. Garcin *et al*<sup>18</sup> (n=24) reported 86% clinical improvement in their open-label case series. Cohen's d effect sizes were calculated for Taib *et al*<sup>24</sup> and Shah *et al*<sup>20</sup> and were 1.16 (large effect size) and 0.11 (small effect size) respectively. Demartini *et al*<sup>25</sup> (n=16) found significant improvement as described in the previous section.

### Neuromodulation for functional seizures

One study investigated the effects of TMS on functional seizures (n=7).<sup>22</sup> Following high-frequency repetitive stimulation of the right temporoparietal junction for 30 sessions over 3 weeks, all patients experienced a significant decrease in weekly seizure frequency. Seizure remission was sustained in four out of seven subjects at 3 months follow-up. A variety of secondary outcome measures were also collected relating to overall somatic symptoms, comorbid psychiatric symptoms and disability. They reported significant decreases in the post-treatment vs baseline reporting of dissociative and functional neurological symptoms.

### Neuromodulation for SSD or mixed SSD/FND

Only one neuromodulation study was identified specifically for the treatment of SSD or related somatoform disorders.<sup>23</sup> They focused on chronic somatoform pain (10-year mean duration of illness) and the protocol involved high-frequency rTMS (10 Hz, 1200 pulses at 100% resting motor threshold) of the left dorso-lateral prefrontal cortex (dlPFC). They reported that all patients

in their case series had an improvement in their pain, ranging from 25% to 77% after 18 stimulation sessions over a period of 3 weeks.

A retrospective cohort study by Leong *et al*<sup>26</sup> (n=28) evaluated the effects of right unilateral, bifrontal, or bitemporal ECT for somatoform pain syndromes (n=15), functional motor symptoms, such as weakness (n=11), gait and balance disturbance (n=8), tremor (n=3) and myoclonus (n=4), and on functional seizures (n=6). The number of treatments varied between 3 and 22 sessions (mean=11.5), with an average energy of 48.7 Joules delivered in a brief pulse-width of 0.5 ms and average seizure duration of 34.1 s (SD±11.6 s). Overall, 86% of patients reported marked subjective improvement in their symptoms. Of the patients with somatoform pain (n=15), 79% had significant subjective improvement while 21% experienced worsening pain.

### Therapeutic mechanisms

Multiple intended therapeutic mechanisms were used across different FND/SSD symptom presentations. This included: (1) network-level neuromodulation of circuits implicated in underlying pathophysiology,<sup>16 19 20 22–26</sup> (2) using stimulation to offer a behavioural demonstration of normal movement<sup>15–18 21</sup> and (3) enhanced placebo effects/suggestion.<sup>18 20 21</sup> These mechanisms were not mutually exclusive and some protocols leveraged multiple approaches. Please see figure 3 for further details on therapeutic mechanism.

### DISCUSSION

To the best of our knowledge, this is the first systematic review to synthesise data across the spectrum of neuromodulation technologies that have been used in the treatment of patients with FND and/or SSD. In a field where treatment options are

**Table 2** Outcome data for neuromodulation treatment studies of FND/SSD

Study	Outcome (measure)	Active Pre-Score	Active Post-Score	Sham Pre-Score	Sham Post-Score	Reported results	Follow-up
<b>TMS</b>							
Schonfeldt-Lecuona <i>et al</i> 2006 <sup>16</sup>	Motor power (Neurologic exam)	N/A	N/A	N/A	N/A	Marked improvement in 3/4 patients	6 months to 1 year. Improvements retained in 3/4 patients.
Chastan and Parain 2010 <sup>17</sup>	Motor power (specific measure not reported)	N/A	N/A	N/A	N/A	89% with 'total or dramatic recovery'; predominantly for patients with acute-onset paralysis. (p=0.009)	Offered to patients with ongoing symptoms (longest was 160 days post-treatment)
Garcin <i>et al</i> 2013 <sup>18</sup>	Custom made scale for movement disorders	N/A	N/A	N/A	N/A	75% improved by ≥50% with a third achieving complete symptom resolution immediately after TMS administration	1 year. 71% had sustained improvement
Broersma <i>et al</i> 2015 <sup>19</sup>	Muscle strength % change (dynamometer)	N/A	25%, increase (median) –1% to 264% (range)	N/A	10% increase (median) –77% to 71% (range)	Change in hand muscle strength was larger after active rTMS (p=0.004)	No follow-up
Shah <i>et al</i> 2015 <sup>20</sup>	Quality of Life (WHOLQOL-BREF at 2 weeks post treatment (four domains))	Domain I: physical 54.3±8.6 Domain II: psychological 56.3±16.4 Domain III: social relationships 70.8±19.6 Domain IV: environment 62.8±4.1	Domain I: P1: 55.3±10.7 P2: 75.2±10.3 Domain II: P1: 59.3±16.7 P2: 45.8±8.5 Domain III: P1: 81.3±17.3 P2: 79.3±16.8 Domain IV: P1: 66.0±5.0 P2: 67.8±8.3	N/A	N/A	Significant improvement only in physical domain following treatment to preMC (phase 2, p=0.04) (Cohen d=0.11, small effect size)	No follow-up
McWhirter <i>et al</i> 2016 <sup>21</sup>	Disability (SF-12 and MRS) SRSS (5-point Likert Scale)	SF-12 34.9±11.4 MRS 45.3±11.2 SRSS 3.4±0.8	SF-12 29.2±12.8 MRS 44.8±10.5 SRSS 3.0±0.8	N/A	N/A	Small reduction in symptom severity immediately after treatment. No improvement in grip strength, tapping frequency, or disability.	3 months. No improvement reported.
Peterson <i>et al</i> 2018 <sup>22</sup>	Weekly seizure frequency (diary)	7.3±5.3 events	1.0±1.3 events	N/A	N/A	Significant improvement in seizure frequency following treatment (p=0.001)	1, 2, and 3 months. 4/7 participants remaining seizure free at 3 months.
Singh <i>et al</i> 2018 <sup>23</sup>	Pain (VAS score)	8.2	3.6	N/A	N/A	Marked improvement in 4/5 patients (62.5%–77% reduction in symptoms). 1 patient experienced 25% reduction in symptoms.	No follow-up
Taib <i>et al</i> 2019 <sup>24</sup>	Psychogenic movements (PMDRS score at 1 month post treatment)	P1: 29.5±17.6 P2: 15.3±13.0	P1: 17.7±15.3 P2: 15.0±16.2	P1: 28.2±16.4 P2: 24.1±14.5	P1: 23.3±13.6 P2: 24.9±18.1	P1: Significant improvement following active rTMS group (p<0.001, Cohen d=1.16, large effect size) P2: No significant changes within or between groups	P1: 1- and 2 months post treatment P2: 6- and 12 months post-rTMS. Improvement following active rTMS maintained.

Continued

Table 2 Continued

Study	Outcome (measure)	Active Pre-Score	Active Post-Score	Sham Pre-Score	Sham Post-Score	Reported results	Follow-up
Pick <i>et al</i> 2020 <sup>15</sup>	Subjective Improvement (CGI-I)	Session 1 90% 'no change, worse, or much worse' 10% 'minimally improved' 0% 'much improved' Session 2 33% 'worse or much worse' 0% 'minimally improved' 67% 'much improved'	Session 1 No change Session 2 No change	Session 1 73% 'no change, worse, or much worse' 18% 'minimally improved' 9% (n=1) 'much improved' Session 2 70% 'no change, worse, or much worse' 10% 'minimally improved' 20% 'much improved'	Session 1 No change Session 2 No change	Small-moderate effect sizes (Cliff's delta=-0.1-0.3, 95% CI -0.79 to 0.28) reflecting a more positive outcome for the active treatment (67% at session 2 vs 20% in sham group).	3 month follow-up. 44% in active group retained 'much improved' status vs 20% in the sham group.
TDCS							
Demartini <i>et al</i> 2019 <sup>25</sup>	Interoceptive sensitivity (IS) (heartbeat detection test) Spatial attention (SA) (Posner paradigm)	N/A	IS FMS: 0.672±0.151 HS: 0.810±0.072 SA Reaction times FMS: 121.38±67.15 HS: 45.18±32.37 Accuracy FMS: -0.05±0.071 HS: -0.01±0.030	N/A	IS FMS 0.466±0.132 HS: 0.697±0.078 SA Reaction times FMS: 143.70±68.72 HS: 41.81±48.61 Accuracy FMS: -0.04±0.081 HS: -0.04±0.062	Significant improvement in IS for FMS group after active stimulation (p=0.001) (Cohen d=0.72 large effect size). No significant changes for measures of SA	No follow-up
ECT							
Leong <i>et al</i> 2015 <sup>26</sup>	Participants' subjective change in clinical symptoms 1 month post-treatment (improved, unchanged, or worse)	N/A	Improved (22/28) Unchanged (4/28) Worsened (2/28)	N/A	N/A	86% marked improvement in subjective symptoms. 79% with pain had significant subjective improvement 21% had worsening of their pain.	No follow-up

Values provided are SD.

CGI-I, Clinical Global Impression-Improvement scale; FMS, functional movement symptoms; FND, functional neurological disorder; MRS, Modified Rankin Scale; N/A, not available; PMDRS, Psychogenic Movement Disorders Rating Scale; PreMC, premotor cortex; SRSS, self-reported symptom severity; SSD, somatic symptom disorder; TDCS, transcranial direct current stimulation; VAS, Visual Analog Scale; WHOLQOL-BREF, WHO Quality of Life brief scale; WSR, Willcoxon signed-rank test.

limited, this synthesis suggests that neuromodulation may be a promising emerging treatment strategy for these complex and challenging to manage patient populations. Individuals with functional motor symptoms were the most commonly studied subpopulation and largely positive results were reported across trials. Limited but promising data for functional seizures and somatoform pain/symptom disorders were also identified. The vast majority of studies used TMS, followed by ECT and TDCS. The overall strength of evidence was limited by methodological heterogeneity between studies, mixed study quality (including only three double-blind, sham-controlled RCTs) and small sample sizes (n<30) for most studies. These factors precluded quantitative meta-analysis and thus caution is needed in the interpretation and application of this synthesis.

Ongoing research is demonstrating that disruption of functional brain networks may be central to the pathophysiology of FND and SSD.<sup>49-11</sup> This includes fronto-limbic emotional/threat processing, salience and attentional networks, circuits implicated in self-agency and pathways specific to a given symptom presentation (eg, motor control and output networks in those with functional motor symptoms). While the underlying aetiology driving such dysfunction and the interactions between circuits remain incompletely understood, it makes intuitive

sense that devices capable of targeted modulation of these relevant networks could offer an optimal treatment strategy for FND and SSD. Many of the protocols reviewed aimed to achieve such a therapeutic mechanism by using repetitive pulse trains of brain stimulation (eg, rTMS) to modulate the excitability and plasticity of relevant brain circuits. Targets for these studies included: PMC for functional weakness<sup>16 19</sup>; PMC,<sup>20 24</sup> premotor cortex<sup>20</sup> and PPC/temporal parietal junction (TPJ) for FMS<sup>25</sup>; PPC/TPJ for functional seizures<sup>22</sup>; and dlPFC for SSD.<sup>23</sup> All studies leveraging this intended mechanism, though variable in their methodological rigour and study quality, reported beneficial therapeutic responses. As mentioned above, the dlPFC is a critical node in executive control/attentional and emotional processing networks<sup>10</sup> and the PPC/TPJ is a critical node for multi-sensory integration and self-agency.<sup>27</sup> It is also important to note that many important structures potentially implicated in FND/SSD network dysfunction, including the amygdala and cingulo-insular areas, were not targeted in the studies reviewed. This is likely because traditional non-invasive neuromodulation devices such as TMS and TDCS cannot reliably stimulate such deep structures due to a depth/focality trade-off.<sup>13</sup> New TMS devices and other targeted neuromodulation devices (such as focused ultrasound or DBS) may be capable of stimulating such

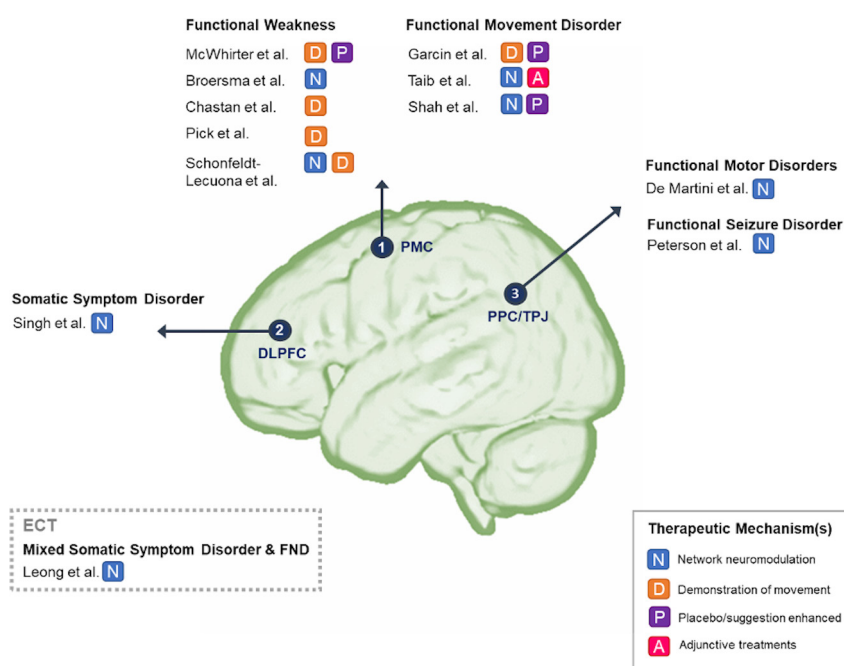
Summary of Neuromodulation Studies					
Transcranial Magnetic Stimulation			Transcranial Direct Current Stimulation	Electroconvulsive Therapy	
Design	5 Case Series	4 Randomized Control Trials	1 Retrospective Chart Review	1 Randomized Control Trial	1 Retrospective Chart Review
Quality & Results	5/5 with positive results	3/4 with significant improvement and small effect size	89% with significant improvement	Significant improvement with large effect size	86% with marked improvement
	3 Good Quality* 2 Fair Quality	2 Good Quality 2 Poor Quality	Poor Quality	Fair Quality	Poor Quality

**Figure 2** Summary of neuromodulation treatment studies for functional neurological disorder and somatic symptom disorder. For additional details regarding study size, functional symptoms targeted, neurostimulation protocols, and treatment duration, please see [table 1](#). Detailed summary of outcome measures, results, and follow-up can be found in [table 2](#). Figure 3 contains additional information on specific site of stimulation and therapeutic mechanisms. \*Case series are overall low level of evidence, and the rating of 'good' or 'fair' study quality was assigned based on 'Quality Assessment Tool for Case Series Studies' from the National Institute of Health.

regions in the future. A recent case report of an 18-year-old woman with severe/refractory functional seizures and catatonia used DBS to stimulate the bilateral subgenual anterior cingulate (in regions that were observed to be hyperactivated on PET). They reported immediate resolution of symptoms post-op; however, at 3 months catatonic episodes recurred and DBS settings were adjusted yielding 'acceptable control of functional seizures and catatonia'.<sup>28</sup> No larger or controlled studies using the latter technologies have been conducted to date. We did identify one ECT study for mixed presentations of SSD/FND symptoms that reported marked clinical improvement but was a retrospective study. ECT's broad-sweeping 'network reset'

mechanism, in contrast to targeted stimulation devices, likely alters activity in many deep and superficial structures relevant to FND/SSD.<sup>29</sup> Though ECT may have higher potential side effects than non-invasive devices, it certainly merits further investigation in FND/SSD patient populations and could be a particularly useful tool for treatment-refractory patients or those with severe psychiatric comorbidities.

The second major therapeutic mechanism for neuromodulatory devices is more cognitive-behavioural/demonstration based and is best evidenced by studies of functional weakness.<sup>15–17 19 21 25</sup> Single pulses of TMS applied to the motor cortex at an intensity above motor threshold yield observable jerks in the targeted



**Figure 3** Therapeutic mechanism of neuromodulation. Shah *et al*<sup>20</sup> stimulated PMC in phase 1 and premotor cortex in phase 2 of their trial; The adjunctive treatment in Taib *et al*<sup>24</sup> was hypnosis. This is an original image developed by one of our coauthors and we have permission to reuse the image for resubmission. DLPFC, dorsolateral prefrontal cortex; ECT, electroconvulsive therapy; PMC, primary motor cortex; PPC, posterior parietal cortex; TPJ, temporal-parietal junction.



muscle(s).<sup>30</sup> This can effectively demonstrate to a patient with functional paralysis that their limb 'can' move and potentially modify their cognitive beliefs surrounding the nature of their weakness. This can be likened as an extension of the clinical assessment akin to demonstrating and explaining to a patient Hoover's sign.<sup>31</sup> Unlike neuromodulation protocols that involve repetitive trains of stimulation (eg, rTMS), single pulses are generally not considered to yield circuit-level neuromodulatory changes that persist beyond the stimulation session.<sup>13</sup> However, in this context, the cognitive/behavioural demonstration combined with extrinsic activation of a functionally suppressed circuit, could potentially trigger indirect downstream changes in relevant motor networks. Indeed, the two potential mechanisms may overlap and are not necessarily mutually exclusive.<sup>32</sup>

Treatment of functional weakness using this cognitive-behavioural/demonstration-based approach reported favourable results in most studies except for McWhirter *et al.*<sup>15–17 21</sup> The latter group posited that one plausible explanation for this may be that their chronic FND study population may not be amenable to this type of protocol. However, Pick *et al.*<sup>15</sup> reported that chronic presentations (average symptom duration of 3.5 years) could still potentially benefit. We should also note that Schönfeldt-Lecuona *et al.* applied high frequency repetitive stimulation at supra-threshold intensities (resulting in limb jerks) and thus leveraged both mechanisms previously described.<sup>16</sup> This study was a case series but reported marked improvements in three in four patients that was sustained at 6–12 months. Finally, one FMS study delivered single pulses to the motor cortex with a behavioural mechanism to demonstrate modification of abnormal functional movements.<sup>18</sup> Similar to Schönfeldt-Lecuona *et al.*, this study was also a very promising case series and both of these protocols warrant further investigation with randomised/sham-controlled methodology.

It is critical to examine the potential role of placebo effects in the results reported by the studies reviewed. Placebo effects can be defined as therapeutic benefits derived from the context surrounding administration of a treatment rather than the treatment itself.<sup>33</sup> While the factors that drive placebo effect magnitude remain a topic of ongoing research, intensive and innovative procedure-based treatments such as brain stimulation may generate particularly large placebo effects.<sup>13</sup> Furthermore, some FND and SSD patient populations have been posited to be particularly placebo responsive and there is evolving research demonstrating that placebo effects could result in changes to brain regions that are relevantly implicated in FND/SSD pathophysiology.<sup>34</sup> These two factors highlight the critical importance for delineating potential treatment-specific effects from placebo effects in this field. In the multiple open-label studies and case series reviewed, these effect sources are conflated and there have been only three double-blind, RCT, placebo-controlled trials to date.<sup>15 24 25</sup> These trials were also relatively small and generally focused on feasibility rather than efficacy. Interestingly, study protocols in Garcin *et al.*,<sup>18</sup> Shah *et al.*<sup>20</sup> and McWhirter *et al.*<sup>21</sup> made efforts to potentially harness placebo effects with pretreatment phrasing and/or suggestion to boost patients' therapeutic expectations. Some may argue that if placebo effects can meaningfully help patients with FND/SSD that this should indeed be leveraged and may offer synergies with other therapeutic mechanisms. Further commentary on practical and ethical issues surrounding harnessing placebo effects for therapeutic purposes is beyond the scope of the present review and has been discussed elsewhere.<sup>34</sup>

Finally, it is important to note that neuromodulation studies of chronic pain and related functional somatic disorders

(ie, fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, etc) were not included in our review. There is ongoing debate regarding the operational and clinical definitions of these disorders and how to classify them in relation to FND or SSD.<sup>35</sup> However, emerging models reveal important overlapping symptom domains between FND, fibromyalgia, and chronic fatigue and thus it is important to contextualise our review with this broader literature.<sup>36</sup> A recent systematic review of TDCS for fibromyalgia by Zhu *et al.*<sup>37</sup> found that anodal stimulation over the PMC improved pain and functioning, but not with stimulation over the dlPFC or cathode stimulation over PMC. Results of rTMS for fibromyalgia have been more mixed, with a recent systematic review reporting overall positive results on pain and depression scores after dlPFC stimulation,<sup>38</sup> while three recent sham-controlled RCTs that delivered rTMS to PMC<sup>39</sup> and left dlPFC<sup>40 41</sup> did not improve pain scores. In a recent systematic review of neuromodulation for fatigue, only 2 of 15 studies focused specifically on chronic fatigue syndrome (one case series (n=7) and one sham-controlled RCT (n=24)) and both reported positive findings after dlPFC stimulation.<sup>42</sup> Neuromodulation for irritable bowel syndrome is relatively limited but has been explored by Algladi *et al.*<sup>43</sup> In their study, 16 patients with IBS were randomised to receive in sequential order repetitive lumbosacral magnetic stimulation (rLSMS) to spinal targets, rTMS over the anorectal motor cortex, and sham stimulation. Both 1 Hz rLSMS and 10 Hz rTMS increased rectal pain thresholds compared with sham stimulation. Lastly, for mal de débarquement syndrome, one sham-controlled cross-over RCT (n=8) of dlPFC stimulation and one pilot trial of continuous theta burst stimulation over the occipital cortex or cerebellar vermis (n=26) both reported positive results on measures of dizziness.<sup>44 45</sup> Taken together, these studies highlight a growing interest in applying neuromodulation techniques to complex functional somatic/chronic pain disorders that are commonly comorbid and could exist on a spectrum with FND and SSD.

### Future directions

Given the high preponderance of mixed/overlapping symptom presentations and relapses of different symptoms longitudinally in FND/SSD patient populations, more neuromodulation trials that target common underlying circuitry (rather than a specific symptom) may be particularly valuable moving forward. Regions such as the TPJ or dlPFC represent nodes of networks that may be implicated across different FND and SSD presentations and their cortical localisations are readily accessible with current non-invasive brain stimulation devices. For the latter, there are well-established treatment protocols that can be leveraged from depression and other psychiatric disorders.<sup>46</sup> Overall, such studies were relatively under-represented in the existing FND/SSD literature. Advancing developments of neuromodulatory technologies such as focused ultrasound and DBS in severely ill/treatment refractory patients will potentially offer future opportunities for stimulation of deeper structures (eg, the amygdala and anterior cingulate) also critically implicated in core FND and SSD pathogenesis.<sup>47</sup>

To date, there have been no neuromodulation studies with pre/post treatment neuroimaging. Including such methods in future studies will be critical for exploring and potentially demonstrating target engagement. For example, whether the connectivity and/or activity in the targeted networks is meaningfully changed after stimulation and if so, how this may correlate with symptom improvement. Ideally, advances in neuromodulation will parallel advances in FND/SSD neuroimaging with an

ultimate goal of identifying patient-specific network dysfunction and then modulating that network with a patient-specific stimulation protocol. Another important line of work will be to combine existing evidence-based treatments such as psychotherapy<sup>48</sup> or physical therapy<sup>49</sup> with neuromodulatory treatment. There is increasing research uncovering the importance of state dependency for neuromodulation and such combinations could effectively 'prime' the networks being stimulated.<sup>13</sup> Finally, with respect to non-targeted neuromodulation, prospective trials of ECT for FND/SSD treatment are clearly needed to build on the promising retrospective data. Given the existing availability of ECT at most academic health centres, ECT could offer a valuable tool for severe, treatment-refractory cases.

### Limitations

This systematic review has a number of limitations. Most notably, the methodological heterogeneity, mixed study quality and small sample sizes precluded quantitative meta-analysis. There is a clear need for more RCTs with larger sample sizes and high-quality designs to further investigate the potential efficacy of neuromodulation for FND and SSD. Similar to other treatment studies of these patients, improved consistency in outcome measurement is needed to facilitate better comparison of effects across studies and symptom types.<sup>50</sup> There is also a need for more comprehensive data on psychiatric comorbidity and whether or not mood-related symptoms may change after neuromodulation. With the limited data captured by the included studies (summarised in online supplemental table 1), we cannot delineate if clinical improvement in FND/SSD symptoms covaried or was independent of improvements in depression and anxiety. Potential for publication bias in the synthesised studies was also not assessed. This is an important issue given our small number of identified published studies with non-positive trials being less likely to be published. A future area of work could be to quantify publication bias by reviewing clinical trial registry databases to identify trials and then a systematic review of MEDLINE to determine what percentage were published. Previous reviews on this topic are limited. Finally, we attempted to identify, organise and group data in ways reflective of our current understanding of this field. However, we are mindful that topics of FND, SSD, functional somatic syndrome and chronic pain (eg, overlapping pathophysiology, grouping vs splitting) and mechanisms of neuromodulation are rapidly evolving and thus the optimal way to synthesise this data may change over time.

### CONCLUSION

Neuromodulation offers a promising new approach for complex and challenging FND/SSD patient populations who currently have limited evidence-based treatment options. We highlight the potential value and opportunities for different treatment protocols but emphasise the relative infancy of this field. Further studies are needed to further quantify efficacy and understand underlying therapeutic mechanisms.

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