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# Neuromodulation Using Computer-Altered Music to Treat a Ten-Year-Old Child Unresponsive to Standard Interventions for Functional Neurological Disorder

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## CASE HISTORY

Marie-Therese, known as MT by family and friends, was a ten-year-old girl in Year 5 of primary school referred to the Mind-Body Program by a pediatrician for treatment of functional somatic symptoms—unsteady gait, blurry vision, periods of confusion or appearing dazed, and persisting headache—that had been triggered in the context of a viral illness. MT lived with her parents, a younger sister, and her grandmother. Both parents worked full time as architects. The family history included rheumatoid arthritis (mother), epilepsy (uncle), and type 2 diabetes (grandfather) on the mother's side of the family, and colorectal cancer (grandfather) on the father's side. MT had been diagnosed with celiac disease at age 6, which was being managed with a gluten-free diet.

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### Presentation

In the three weeks prior to referral, MT had been ill with a viral infection: a runny nose, sneezing, nasal congestion, and frontal headaches. In the second week of this illness, she developed blurriness in the right eye, neck stiffness, pain on eye movement, facial pain, lethargy, and anorexia. With a working diagnosis of partially treated meningitis, she was admitted to hospital for intravenous antibiotics (five-day course). A swab returned rhinovirus positive. In the third week of this illness, her headache persisted, the blurred vision spread to both eyes, and she developed additional neurological symptoms: unsteady gait and difficulty speaking (mumbling). Some days later she became confused, appeared "dazed" and slow to respond to the pediatrician's questions, and developed slurred speech, right-hand weakness with an occasional tremor, right jaw twitching, and ongoing unsteadiness that required a walking frame for mobility. Routine bloods—full blood count, electrolytes, inflammatory markers, and thyroid function tests—were normal. A contrast-enhanced CT scan and an MRI were also normal, with an incidental finding of Chiari malformation (4 mm). A lumbar puncture was deemed potentially unsafe and therefore was not performed. A review by a neurologist yielded the diagnosis of functional neurological disorder (FND) and comorbid complex/chronic pain (see Text Box 1).*

### Psychological Medicine Assessment with MT and Her Family

The family assessment with our team—a child and adolescent psychiatrist, a clinical psychologist, and two pediatric trainees on their psychological medicine rotation—took place via

* For details about the neurology examination for children with FND, see Kozlowska and Mohammad (forthcoming).[1]

**Text Box 1**
**Summary of MT's Positive Rule-In Signs for Functional Neurological Disorder in the Neurology Examination**

Repeated neurology examinations with MT yielded positive rule-in signs—listed below—consistent with FND:

- A very dramatic, sudden onset of symptoms, occurring spontaneously or in the context of an identifiable stressor—in this case rhinovirus infection and incidental finding of a Chiari malformation on CT.
- Mixed neurological signs that were not clinically congruent in their origin. For example, MT's unsteady gait was subsequently complicated by right-hand weakness, which became a right-hand tremor, which then reverted back to right-hand weakness (back and forth, back and forth, back and forth).
- MT's leg and right-arm weakness varied with distraction.
- MT's tremor could be entrained (made to follow a particular frequency), and it increased with attention and decreased with distractibility.
- MT's symptoms varied with distractibility. They were better when she was engaged in an activity she liked—for example, coloring in—and worse when her parents focused on the symptoms.

telehealth in the midst of the COVID-19 pandemic. The family were seated in one clinic room, and each member of the team in a separate room.

### Developmental History: Summary of Key Issues

MT's early developmental history—in utero, delivery, developmental milestones in the first five years—were all unremarkable. MT had been an outgoing and happy preschooler. She underwent tonsillectomy and adenoidectomy when she was three years old and had been diagnosed with celiac disease at six years of age (Year 1 at school) after she had experienced persistent abdominal pain and was found to be anemic. MT also began to experience recurring headaches.

MT showed an aptitude for learning, and her school reports described her as a conscientious and bright student. There was a history of school stress, beginning in Year 1 of school and continuing into Year 5. MT reported that her years at school had been made very stressful because her class had been ongoingly disrupted by children with behavioral problems (confirmed by MT's school teacher). In this context MT also described her distress pertaining to a variety of issues: failing to receive acknowledgment from her teacher for working well (Year 1); the stress of a strict teacher constantly yelling at the class, making MT's ears hurt (Year 2); loss of a close friend (who left that school), feelings of loneliness and exclusion, and experiences of being bullied (Year 3); the loss of her teacher, who left due to stress and was followed by multiple substitute teachers (Year 4); and teasing and bullying by a group of girls (Year 5). MT and her parents described how her stress level had dropped substantially (from 9/10 to 4/10) during the two months—during the pandemic—that she did schoolwork from home and engaged in extra tuition in preparation for selective school tests. Her stress level rose again (to 8/10) on returning to school. She became more withdrawn and had stopped talking to her parents—in particular, her mother—about her difficulties relating to school. Her headaches became severe, and she was admitted to hospital for review by a neurologist (including an MRI).

In a parallel process, the family themselves had been stressed following the birth of MT's sister (for MT, Year 3) because the sister suffered from severe colic followed by night terrors.

### Formulation

The psychiatrist shared the team's formulation at the end of the family assessment. She highlighted that in 50% of cases, FND was triggered by a physical stressor—such as a viral illness—and that MT's presentation fit this pattern. She also acknowledged that MT had a long history of stress at school and that she had experienced stress-related headaches (see above). Using a visual metaphor the psychiatrist explained the current medical understanding of FND and comorbid pain (see Figure 1),[2,3] adding that changes in cognitive function were seen in approximately 10% of pediatric cases and were understood to be related to the release of brain stress hormones and to hyperventilation.[4] The psychiatrist noted that throughout the assessment, MT's breathing rate had ranged from 30–50 breaths per minute (≥99th percentile).[4,5] She also noted that MT had appeared very flat during the assessment (flat affect and slumped posture), and indicated that the team would further assess her mood and mental state more generally since comorbid depression and anxiety were common in FND.[3] The psychiatrist told the family that with treatment, most young children achieved a full recovery.[6] Finally, she discussed the treatment program in detail (see Text Box 2).[7] MT was offered admission into the Mind-Body Program following the two-week break for school holidays.

### Managing Parental Anxiety About the FND Diagnosis

MT made no improvement at home during the holiday break. Her headaches got worse as she tried to mobilize, and she had developed the new symptom of dizziness. In this context her parents and the family doctor became increasingly anxious that the diagnosis of FND was incorrect. Because the Mind-Body Program does not accept children whose diagnosis has not been clarified or whose parents do not accept the diagnosis—everyone has to be on the same page[2]—our team put the mind-body admission on hold and supported the family to seek re-review from the neurologist and second opinions from a second neurologist and a neurosurgeon. During the resulting four-week period—which included two additional presentations to the Emergency Department because of MT's symptoms of worsening gait, back pain, nausea, difficulty swallowing, and difficulties talking (visit 1) and a 40-minute functional seizure (visit 2)—the diagnosis of FND

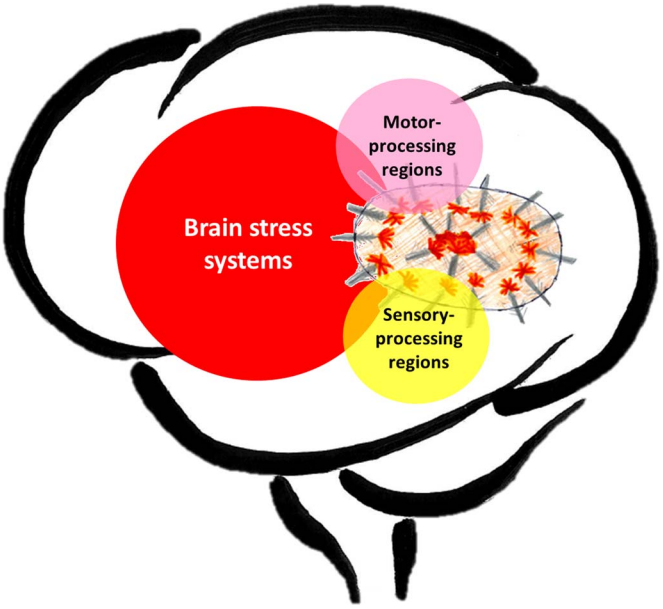


**Figure 1.** Visual representation of the formulation. In explaining the neurobiology of FND to MT and her parents, we used this visual metaphor alongside the following language: "The red ball represents the brain regions that underpin salience detection, arousal, and emotional states—the *brain stress systems,* for short. The pink ball represents brain areas involved in motor processing—*motor-processing regions,* for short. The yellow ball represents brain areas involved in sensory processing—*sensory-processing regions,* for short. The spikey ball represents pain-processing regions—*pain maps,* for short. When all is well, the brain stress systems get on with their job, as do the motor-, sensory-, and pain-processing regions, and they interact together in a balanced way. In FND the relationship between the brain stress systems and motor-, sensory, and pain- processing regions changes and becomes unbalanced. The brain stress systems become larger and stronger, and they disrupt motor and sensory processing and amplify pain." ©Kozlowska 2019.

was reaffirmed at all consultations. Additional investigations included MRI of the spine, video electroencephalogram, and nerve conduction studies.

### Mind-Body Rehabilitation Program

Six weeks after the family assessment interview, MT was admitted into the Mind-Body Program (see Text Box 2). MT was now very unwell (see Figure 2). The process of the admission was difficult for MT, her parents, and the team.

Unlike most children her age, MT struggled to engage in all components of the program. Individual therapy sessions were difficult for her. She was unable to talk (though sometimes spoke in a whisper), generally had to communicate in writing, intermittently lost her hearing or use of her hands, or was unable to open her eyes. By the same token, the therapist found it difficult to communicate with MT, to use visual representations, and to engage in regulation work. The therapist's attempts to help MT track her body state (including escalations of arousal that precede functional seizures[8]), to use hypnosis, to engage in slow-breath training using biofeedback,[9] and to use visualization and relaxation exercises, as well as grounding (weighted blanket) and sensory (clay, stress ball) strategies, all failed. MT remained in a state of high arousal that was reflected in an elevated respiratory rate and an inability, using any of the above-described regulation strategies, to achieve any increase in heart rate variability (restorative parasympathetic function) on the biofeedback device. Her high levels of anxiety and low mood became apparent to her psychologist (in session, where her tendency to ruminate and catastrophize was identified) and to the physiotherapist (in session, where the anxiety emerged as reluctance to play and to try new activities and games). MT functioned best in the setting of the school classroom—completing her work as requested—where the teacher, who was used to dealing with functional somatic symptoms, kept the focus away from the symptoms. The only therapeutic spaces that MT enjoyed were the art therapy sessions, where no demands were placed on her.

MT's parents found the process stressful. During the admission MT's symptoms continued to shift and change (see

**Text Box 2**
**Key Components of the Inpatient Mind-Body Program for FND**

| Treatment component | Interventions embedded in the daily timetable |
|---|---|
| Physical therapy (daily) | Broad range of physical interventions to normalize motor function and prevent secondary complications |
| Psychological therapy (daily, including art therapy sessions) | Broad range of mind-body interventions to help the child identify states of high arousal and distress, and to use strategies—including a change in the focus of attention—to downregulate arousal and manage distress<br>Interventions to help the child to build up her emotional capacity to manage pain and future stress<br>Interventions promoting a playful, relaxed body-brain state |
| Pharmacotherapy | Use of medication to regulate sleep, help with pain, switch off the brain stress systems, and manage comorbid anxiety and depression |
| Family work (weekly, with additional meetings if needed) | Identifying problems in family system that may be contributing to the activation and maintenance of the child's stress response (and therefore the FND)<br>Supporting the family in managing their anxiety and focus of attention, and in building parental capacity so that at discharge, parents are able to run the program independently<br>Addressing any other pertinent family issues |
| Hospital school (daily) | Maintaining normal daily function and normal age-appropriate activities |

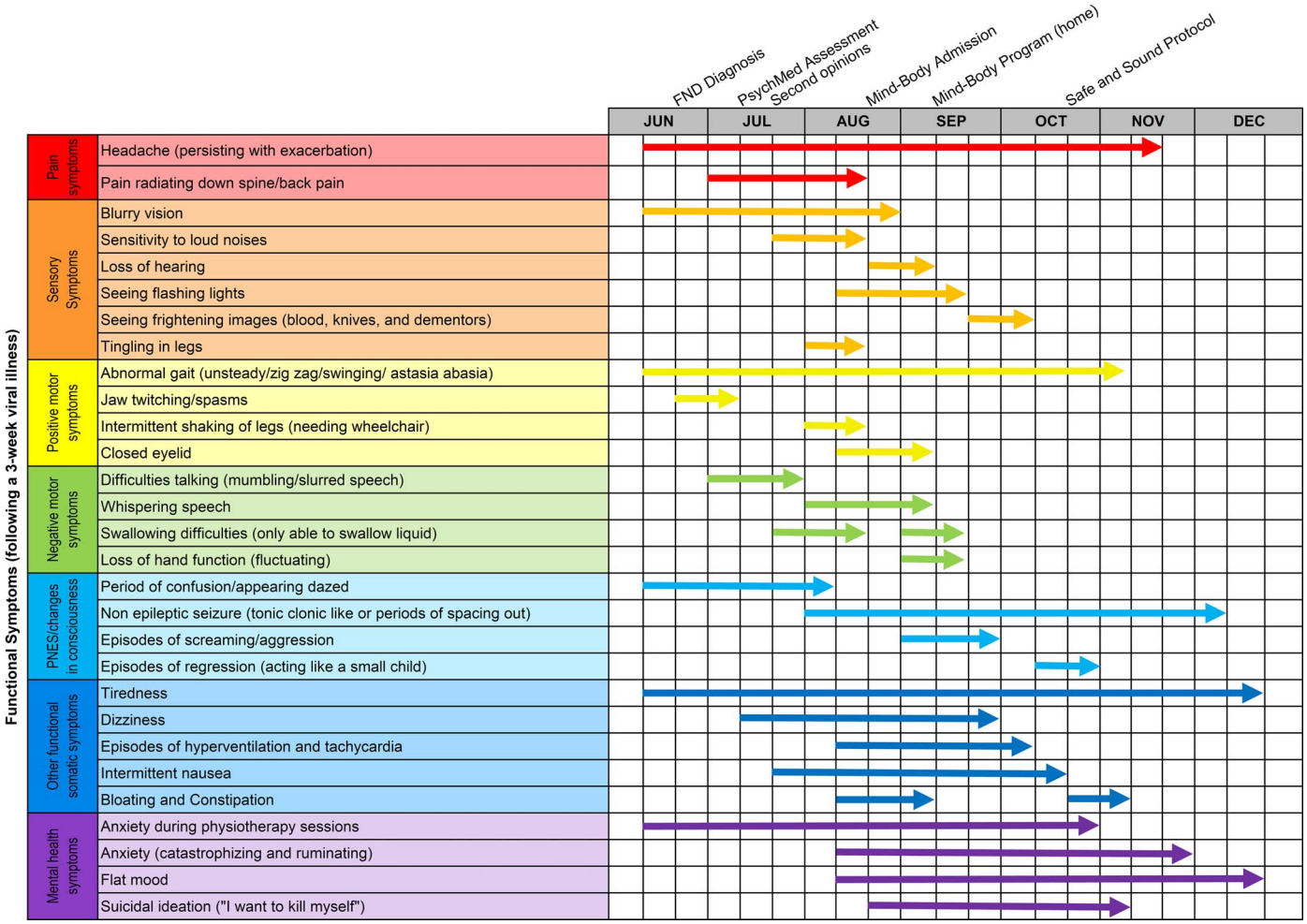


**Figure 2.** Visual representation of the time frame of MT's constantly changing functional symptoms during the six months of her illness. PNES, psychogenic non-epileptic seizures (current term: functional seizures).

Figure 2), and with each new metamorphosis, the parents experienced a new wave of panic and were unable to shift their focus of attention away from the new symptom(s). For example, when MT's blurry vision and swallowing difficulties resolved, they were replaced by increased nausea, loss of hearing, and a fluctuating inability to open her eyes. In the same way, MT's symptom of blurred vision morphed into seeing flashing lights, and then morphed into images of knives, blood, and dementors (spirit-like creatures in the Harry Potter books). MT's parents also struggled to tolerate her distress during exacerbations of headache, and they experienced anguish and disbelief when the team expected MT to continue on with the scheduled activities of the Mind-Body Program even with ongoing pain (headache).

It proved to be a challenge for the team to trial pharmacotherapy for arousal, pain, anxiety, and low mood. MT's parents were inclined toward natural therapies (e.g., herbal medicines, Chinese cupping, acupuncture) and disliked the idea of using medications, and it was difficult (for everyone) to distinguish new functional symptoms from potential medication side effects. During the admission a trial of quetiapine (6.25 mg before physiotherapy sessions to decrease arousal) was discontinued because MT's parents thought that it made MT more flat. A trial of gabapentin (300 mg a day) for headache was discontinued after two days when MT experienced an increase in nausea. A trial of fluvoxamine (titrating to 25 mg morning, 50 mg at night) for MT's ruminating, catastrophizing, anxiety, and mood was withdrawn—with no change in mental state—when MT's ruminations began to have suicidal content (see Text Box 3). Eventually, MT was stabilized on a regimen of amitriptyline (10 mg at bedtime), which resulted in substantial improvement in her headaches, and guanfacine (1 mg in the morning), which helped decrease her arousal and led to a decrease in the frequency and number of her functional seizures. Her other symptoms persisted unabated (see Figure 2).

Despite the challenging nature of the admission, six important goals were achieved. (1) MT's parents came to the realization that their anxious responses to MT's morphing symptoms were unhelpful. They began the hard task of working to stay calm and to manage their focus of attention away from symptoms and toward activities that promoted normal function. (2) When MT filled out the Depression, Anxiety, and Stress Scales (DASS) with her mother—and scored 48 of the

**Text Box 3**
**Examples of MT's Suicidal Ideation, Drawn from Texts to Her Mother**

"I hate life. I want to stab myself."

"Nothing helps. I try and try to distract myself and I do breathing but I still felt like dying."

"It is just that I keep on getting so so much BLUE AND RED [code for bad thoughts] that it is out of control, so feel like dying and going on the road and getting killed."

"Just I felt too bad."

"Why is life horrid? I kept on trying to calm down but it doesn't help. I want to die because there is so so so so much RED AND BLUE that is so unbearable that I want to go on a road and die and stab my left nostril right nostril. I am trying to do, trying to play with clay but doesn't work."

"I hate life. I hate you. I hate everyone."

"But I am such a horrible horrid person. I can't control myself."

"RED headache I just want to stab myself."

"I am too horrible. I can't calm myself down but I am trying trying a lot."

possible score of 63 (very high)—her mother understood that MT perceived the cumulative stressors that she had experienced as very substantial.[†] (3) MT's parents—and the team—realized that MT's recovery process would take longer than was typical for young children and that they needed to prepare for the long haul. (4) By the end of the two-week admission, MT's parents felt capable of running the program from home, with MT attending physiotherapy and psychotherapy sessions as an outpatient and returning to her home school with a safety plan and in a wheelchair. (5) The therapeutic relationship now established between MT's parents and the team would enable the team to support the parents via weekly telehealth meetings. And (6) it was clear that MT was unable to benefit from any of the active regulation interventions—whether bottom-up and top-down[2,10–12]—that helped most children.

### The Quest for a Passive Regulation Strategy

Our team had come across difficult-to-treat cases before where the children seemed to be unable to use any of our standard interventions and where their state of arousal remained elevated despite all our efforts. Six years previously, we had unsuccessfully tried to obtain a topical (via the tongue) noninvasive neuromodulation device that had been safely used in children with posterior fossa syndrome—the Portable Neuromodulation Stimulator (PoNS)—which was reported both to induce a relaxation response and to facilitate motor rehabilitation.[13,14] Subsequently, other neurostimulation methodologies—which used the ear, rather than the tongue, as a portal to the brain—had been developed. For example, in 2014, Stephen Porges developed a five-hour modified-music intervention—the Safe and Sound Protocol—whose aim was to decrease auditory hypersensitivity and chronic autonomic arousal in children with autism.[15,16] More recently, Kovacic and colleagues[17] used Neuro-Stim—a means of auricular neurostimulation developed by Innovative Health Solutions, which delivers percutaneous electrical nerve field stimulation in the external ear—to treat children with functional abdominal pain. They found that the intervention improved pain scores and overall well-being[17,18] and that children with more substantial autonomic dysregulation—measured by vagal efficiency—experienced better responses to the auricular neurostimulation.[19] Our team trained in the Safe and Sound Protocol because it was available in Australia and because we thought that a passive music intervention would be a good addition to our Mind-Body Program.[2,7]

### Safe and Sound Protocol with MT

The Safe and Sound Protocol was added to MT's outpatient treatment program seven weeks after her discharge. During the intervening period her symptoms had persisted (see Figure 2). The five-hour intervention was delivered in nine sessions (over six weeks), starting with a 15-minute block and building up to 30 minutes.

During her first session, MT reported that the music made her ears feel funny. She settled after a five-minute break.

In the next six sessions (resulting in a total of three hours of music), MT became chatty during the sessions, engaged in "mindfulness coloring-in" exercises,[20] but would move restlessly in her wheelchair toward the end of the sessions. At this point in the treatment, MT's parents reported that she had started walking around the house utilizing the walls as support, something that she had previously been too anxious to try. Her physical therapist, outside psychologist, and schoolteacher all reported that she had become more engaged in her therapies and in school. MT also begun to actively use the regulation strategies she had previously learned—for example, slow breathing and managing catastrophic thoughts—to settle herself when she felt her body activating.

During the period of the next two sessions (the fourth hour of music, overall), MT showed substantial improvement in her gait: she was now able to walk without the support of a parent or a wall; she began to climb onto play equipment; and she came to her session pushing her wheelchair (rather than sitting in it). During the sessions themselves, her previously ceaseless chatter abated, and she was now content to sink into a soft chair to listen to the music. She appeared deeply relaxed while she did so.

During the period of the next two sessions (the fifth hour of music, overall) MT began to walk normally, her suicidal thoughts settled, and her functional seizures decreased to once a day for seconds at a time. She and her parents were now able to identify the warning signs of an impending functional seizure, which enabled MT, in turn, to practice implementing active strategies to avert it.[21] Physiotherapy was replaced by engagement in exercise appropriate to MT's age.

[†] The total DASS score just prior to commencement of the Safe and Sound Protocol seven weeks later was even higher (see Table 1 toward the end of the case history).

**Table 1**

**Pre- and Posttreatment Measures on the Depression, Anxiety, and Stress Scales (DASS) and on the Body Perception Questionnaire (BPQ)[a]**

| Measure and domain | Pretreatment with Safe and Sound Protocol (baseline) | Posttreatment with Safe and Sound Protocol (one month after completion of protocol) | Healthy control comparison (n = 155) |
|---|---|---|---|
| **Depression, Anxiety, and Stress Scales** | | | |
| Depression scale | 18 | 2 | Mean = 6.25 (range, 0–12) |
| Anxiety scale | 21 | 1 | Mean = 1.38 (range, 0–12) |
| Stress scale | 17 | 8 | Mean = 2.84 (range, 0–7) |
| Total DASS score[c] | 56 (clinical range) | 11 (normative range) | Mean = 5.63 (range, 0–37) |
| **Body Perception Questionnaire** | | | |
| Body Awareness (percentile) | 91.0% (clinical range) | 21.3% (normative range) | |
| Body Awareness (T-score) | 63.4 (clinical range) | 42 (normative range) | |
| Supradiaphragmatic (heart/chest/throat) reactivity (percentile) | 98.0% (clinical range) | 26.3% (normative range) | |
| Supradiaphragmatic reactivity (T-Score) | 70.6 (clinical range) | 43.7 (normative range) | |
| Subdiaphragmatic (gut) reactivity (percentile) | 98.9% (clinical range) | 9.0% (normative range) | |
| Subdiaphragmatic (gut) reactivity (T-Score) | 72.8 (clinical range) | 36.6 (normative range) | |

[a] The Body Perception Questionnaire is a measure of autonomic activation.

[b] For comparison, DASS scores for 155 healthy children who had taken part in a research program for FND are reported for the DASS 21 (as reported in Hilton et al. [2022]).[22]

[c] The maximum total DASS score is 63.

MT continued therapy sessions with her outside psychologist. The amitriptyline for headache was ceased one week after completion of Safe and Sound. She remained on the guanfacine because her parents had noticed that when she missed a dose, MT's functional seizures increased.

Autonomic measures on the biofeedback device—HeartMath—were taken before, during, and at the completion of the Safe and Sound intervention. While HeartMath is promoted as delivering research-level heart rate variability data, it was unable to handle signals from the highly dysregulated MT, even though she was compliant and still during testing. The situation may have been complicated by the bronze tone of MT's skin—which, a HeartMath scientist later informed us, might have affected the acquisition of data. In any case, because HeartMath failed to give reliable, valid heart rate variability metrics, they are not included in the current report.

Self-report (see Table 1) was consistent with MT's observed functional improvement.

### Follow-Up and Outcome

Following the two-month summer break, MT returned to school full time with no functional symptoms (see Figure 2). A year and a half later, her sense of well-being was ongoing.

## QUESTIONS TO THE CONSULTANTS

- What is the potential value of neuromodulation for treating functional neurological symptoms? (Dr. Pick)
- Children and teenagers with severe functional neurological symptoms often struggle with maintaining emotional and behavioral regulation to allow for participation in treatment. Against that background, what are the rationale and underlying mechanisms for the use of modulated music in the care of this patient? (Prof. Porges)
- Complex FND presentations in a young child can often be a challenge requiring multimodal treatment approaches. Against that background, what are the role of behavioral and pharmacological approaches in treating children and teenagers with FND and overlapping pain? (Dr. Torbey)

### Susannah Pick, PhD

Neuromodulation broadly refers to the use of external (i.e., electrical, magnetic, chemical) stimuli to modulate functioning in targeted regions or circuits in the peripheral or central nervous system. Depending on the stimulation device and protocol used, neuromodulation can inhibit or facilitate neural activity in a given region, with effects that last from seconds to months.

Well-established neuromodulation approaches with reasonable evidence bases for treatment efficacy include surgical (invasive) approaches such as deep brain and vagus nerve stimulation, and noninvasive techniques such as transcranial magnetic stimulation (TMS), transcutaneous direct current stimulation (tDCS), and transcranial focused ultrasound.[23] Existing neuromodulatory treatments have been applied in a range of neurological, psychiatric, and neurodevelopmental disorders, including chronic pain, Parkinson's disease, epilepsy, multiple sclerosis, obsessive-compulsive disorder, major depression, and autism.[23–26]

Emerging noninvasive topical approaches include the following: Portable Neuromodulation Stimulator (PONs), delivering low-grade rhythmic electrical signals to the mucosa of the tongue;[27–30] Safe and Sound Protocol, delivering sound waves to the middle ear in the form of modified music;[31] IB-STIM (previously Neuro-Stim), delivering percutaneous electrical nerve field stimulation via the external ear;[17–19,32] NeuroSigma, delivering low-level electrical pulses to the forehead region innervated by the trigeminal nerve;[33–36] and other forms of transcutaneous vagus nerve stimulation (tVNS).[37] Topical approaches aim to stimulate homeostatic afferents, including the afferent component of the vagal nerve,[38,39] to modulate neural networks and facilitate induction of neuroplastic changes.[14,40–42] Evidence pertaining to topical approaches is in the process of being established.[‡,15,17–19,27–29,37,43] The present case report highlights the potential value of auricular neurostimulation as a treatment for comorbid chronic pain and functional neurological symptoms.

Functional neurological symptoms (FNS) refer to any type of neurological symptoms that are not explained by, or consistent with, identifiable neurological disease. They include seizures, motor disturbances (weakness, tremor, dystonia, jerks), and sensory disturbances. FNS cause significant disability and are often associated with additional physical symptoms (e.g., pain, fatigue, swallowing/speech dysfunction) and psychological distress (e.g., anxiety, depression, dissociation, posttraumatic symptoms)[44] that further exacerbate impairments in functioning and quality of life.

Contemporary explanations of FNS suggest that they are manifestations of disturbed motor and cognitive control, elevated affective reactivity and autonomic arousal, and impaired awareness of the bodily self.[45,46] Neuromodulatory treatments have considerable potential for modifying these disordered processes by targeting underlying neurocircuitry, possibly resulting in improvements in both FNS and associated symptoms (e.g., depression, pain, anxiety).

Several randomized, controlled trials have tested the feasibility or efficacy of TMS for treating functional motor symptoms in adults. Most studies thus far have targeted primary motor cortex with TMS, showing some benefits in subjective or objective functional motor symptom measures. Potential mechanisms of action include the following: changes in the patient's higher-level beliefs (effecting top-down modulation via expectations because TMS has demonstrated the limb's capacity for function),[47–49] motor retraining, and modulation of motor cortex excitability.[50,51] In addition to treating functional motor symptoms, neuromodulation could potentially be harnessed to target other FNS or, indeed, disturbed neurocognitive processes that cut across FNS presentations. For example, stimulation of sensory cortical regions may be a valuable approach for treating functional sensory deficits (e.g., functional numbness, visual or auditory impairments). Neuromodulation could also be used to facilitate improvements in emotion regulation and cognitive control, and to regulate autonomic arousal. The dorsolateral prefrontal cortex may be an optimal target for excitatory neuromodulation in patients with FNS, given its known involvement in these core processes and existing evidence that repetitive TMS (rTMS) to the dorsolateral prefrontal cortex can successfully treat mood disturbance.

The current case report, however, suggests that a minimal, auricular, neuromodulatory treatment may be of value in treating FNS. The Safe and Sound Protocol was developed to noninvasively stimulate parasympathetic nervous system activation via the vagus nerve, thus promoting regulation of autonomic arousal. As suggested above, it has been proposed that a key mechanism underlying FNS symptoms is excessive autonomic responsivity combined with diminished bodily awareness (interoception) and dissociation.[46] The Safe and Sound Protocol and other similar treatments might therefore be valuable tools for regulating autonomic reactivity, enhancing bodily awareness, and self-regulating affect in people with FNS.

A key advantage of the Safe and Sound Protocol is that, rather than targeting a specific symptom, it has potential to act on core mechanisms that span the full range of FNS presentations (e.g., functional seizures, motor symptoms, sensory symptoms). The approach is also likely to be acceptable to patients with FND for several reasons. First, it assumes a brain-based mechanism, which minimizes the stigma that can be associated with purely psychological explanations and treatments. Second, the Safe and Sound Protocol can potentially be delivered in a wide range of settings, thus maximizing convenience for patients and their carers. Nevertheless, because the protocol is designed to modulate the autonomic nervous system, it can, in the short term, be associated with various low-grade (and usually temporary) adverse events, including the following: increased auditory or other sensory sensitivities; ear discomfort or pressure; "ringing" in the ears; emotion dysregulation (changes in arousal); gastrointestinal discomfort; fatigue; and headache (personal communication, 1 March 2022, from Rebecca Knowles);[§] The adverse side effects with the Safe and Sound Protocol (headaches and discomfort are also common side effects with other neuromodulatory treatments) are managed by titrating sessions according to what the patient's nervous

[‡] Kaczmarek (2017)[27] summarizes all preliminary studies using the PONs published prior to 2017.

[§] Rebecca Knowles, OTD, OTR/L, RYT, is Training and Research Manager at Unyte Health. She reviewed data on adverse events through the Unyte Health case consultation process and put together a risk statement on the Safe and Sound Protocol. The statement was reviewed by the Clinical Advisory Board for Unyte Health.

system can manage (e.g., MT's sessions began with a 15-minute block) and by implementing regulation strategies (e.g., MT used mindfulness coloring-in exercises) or activities that involve co-regulation with the therapist (e.g., a joint activity that helps to regulate the child).

Larger, controlled studies, as well as feedback from patients, families, and others, are needed to determine the extent of the Safe and Sound Protocol's adverse effects, patient and carer views on tolerability, and whether the adverse effects result in withdrawal from treatment. It should also be noted that the efficacy and acceptability of the Safe and Sound Protocol for treating FND is not yet established and that, more broadly, the evidence base for polyvagal theory—the approach's scientific rationale—is still limited and emerging. Larger trials are therefore also needed to test more stringently this novel, but promising, treatment, ideally alongside investigations of its mechanism(s) of action.

**Stephen Porges, PhD**

As a consultant in this Clinical Challenge, I see my role as twofold: (1) to explain the core mechanisms that would manifest in a subset of symptoms experienced by MT, and (2) to explain how modulated vocalizations/music would function as a neuromodulator to optimize neurophysiological regulation and reduce MT's symptoms.

This case study of a child with FND—complicated by other functional somatic symptoms—documents that the child's clinical course improved following the use of computer-altered music as a neuromodulator. The neuromodulator in question—the Safe and Sound Protocol—is one that I developed as part of a long-term research and clinical endeavor to understand the workings of the vagal nerve and how that knowledge may be used, in turn, to improve clinical care. The *polyvagal theory*, which I first articulated in the mid-1990s, continues to serve as the main intellectual framework for my research and clinical efforts.**[52,53]

My work is consistent with important advances in neuroscience—in particular, those of A. D. (Bud) Craig—pertaining to the neuroanatomy of homeostatic afferents (including vagal afferents) and their major role in modulating important neural networks.[38,39] The work is also consistent with advances in the field of medicine, where a range of surgically implanted devices—and transcutaneous devices in the more recent past—were developed to modulate spinal cord afferents or the vagal nerve itself in cases of intractible pain, refractory epilepsy, or depression.[37] Likewise, recent advances in neuroscience have confirmed that breathing interventions used for upregulating vagal function and for promoting states of well-being[54–56] rest on a solid evidence base. That is, though the history and effective use within Eastern traditions date back thousands of years, it is only very recently that the neuroanatomy, including the close anatomical proximity of the respiratory rhythm generator and vagal nuclei in the brain stem—which facilitates the functional coupling between them—has been clearly delineated.[57] Prior to that, research identifying a common cardiopulmonary oscillator was published in 1990,[58] which was then incorporated into the original, 1995 description of the polyvagal theory. The upshot result has been a burgening range of portable biofeedback devices.[59,60]

Coming back to the Safe and Sound Protocol, preliminary research using an earlier version (Listening Project Protocol) with children with autism spectrum disorders showed that the intervention improved sociality, vagal regulation of the heart, and auditory processing, while reducing hyperacusis.[15,43] Studies—currently in progress with other clinical populations of children (e.g., autism spectrum, Ehlers-Danlos syndrome, Prader-Willi syndrome)—are expected to provide a further evidence base.

The use of modulated vocalizations/music as a neuromodulator may appear distinct to both the clinical features and the neurophysiological mechanisms assumed to underlie the patient's clinical status. However, if the clinical features are viewed through a different theoretical perspective, then the features and the clinical success of neuromodulation through an acoustic portal are explainable. Polyvagal theory (1995, 2007, 2011) provides a science-based theoretical orientation to reorganize expressed symptoms and succinctly explain why and how the intervention would be helpful.[52,53,61] On that theory, several of MT's symptoms can be understood as the product of a destabilized autonomic nervous system—in particular, a disruption in the ventral vagal circuit involving a brain stem area known as the ventral vagal complex. This brain stem area provides the neuroanatomical and neurophysiological substrate for both spontaneous social engagement behaviors and the vagal regulation necessary to promote calmness and optimize homeostatic function.

An inspection of MT's symptom profile (see Figure 2) suggests common neural mechanisms involving the ventral vagal complex. Specifically, dampening vagal influences from this area would result in tachycardia and atypical breathing, a general feeling of threat reflected in anxiety, and gastrointestinal issues including nausea, bloating, and constipation. In concert with this autonomic backdrop, decreased neural tone via special visceral efferent pathways to the striated muscles of the face and head (taken together, the substrate of the *social engagement system*) would result in hyperacusis and hyposensitivity to voice, eyelid dropping, flat facial affect, atypical intonation of speech, and dysregulation of the coordination of sucking, swallowing, and breathing.

Passive listening to modulated vocalizations/music within a specific frequency band associated with positive social communication (e.g., a mother's prosodic voice or lullaby) is an

** As with any new theory, polyvagal theory has its critics and remains a matter of scientific controversy. That said, and looking toward a Kuhnian horizon (see Thomas Kuhn, *The Structure of Scientific Revolutions*), based on supporting empirical science (with the foundational papers of the theory being cited in about 14,000 peer-reviewed studies), I anticipate that polyvagal theory will find a place in next-generation discussions about the nervous system.

efficient portal to the ventral vagal complex and becomes the basis for how music can be composed to calm the autonomic nervous system. All social mammals have a frequency band in which modulation of vocalizations serves to signal safety. This frequency band is determined by the physics of the middle-ear structures of the species and forms a mechanism through which mammals communicate that they are safe enough to approach or to be approached.[62,63] A recent study has documented that the degree of vocal intonation of the mother has an almost linear impact on calming her infant following a stressing disruption. The more prosodic the mother's voice, the more effective she was in reducing behavioral features of distress and in lowering heart rate.[64] In essence, the mother's voice was functioning as a neuromodulator increasing both vagal regulation of the heart and calming behavior.

Listening to modulated vocalizations/music is potentially an efficient strategy for neuromodulation of the autonomic nervous system. Passive listening may enhance vagal regulation and reduce symptoms. Consistent with this explanation, the technology embedded in the Safe and Sound Protocol received a patent that included a claim for its application as an acoustic vagal nerve stimulator.[31] In addition, as noted earlier, two previous studies documented beneficial effects of the protocol with children on the autism spectrum.[15,43]

Since polyvagal theory is based on a complex literature at the interface of several disciplines (including evolutionary biology, comparative neuroanatomy, developmental neurophysiology, psychophysiology, speech and hearing sciences), specific features of the theory as it relates to this clinical case are summarized below.

- Autonomic state influences behavior and mental process by functioning as an "intervening" variable influencing behavioral and physiological reactivity (e.g., calming or arousing) to environmental cues.
- Ventral vagal pathways enable mammals to experience physiological calmness and sociality while also supporting homeostatic processes leading to optimized health, growth, and restoration.
- The ventral vagal pathways originate in a brain stem area known as the ventral vagal complex, which includes the origin of both ventral vagal efferent pathways regulating the heart and bronchi, and special visceral efferent pathways regulating the striated muscles of the face and head traveling through several cranial nerves (i.e., CN V, VII, IX, X, XI).[65]
- Acoustic cues of safety (e.g., prosodic vocalizations) influence the ventral vagal complex and function like an acoustic vagal nerve stimulator that potentially can downregulate threat reactions by slowing heart rate, signaling safety to the enteric nervous system,[42,64,66,67] and hypothetically increasing neural tone to the muscles of the middle ear (reducing hyperacusis and improving auditory processing), face (increasing facial expressivity), and larynx and pharynx (enhancing intonation of voice).

If we look at MT's symptoms, do they converge with a disrupted social engagement system? When we look at the clinical trajectory following the Safe and Sound Protocol, is the outcome profile consistent with a "re-instatement" of that system? The organizing principles of the polyvagal theory provide the rationale to cluster many of MT's symptoms as a depressed or dysfunctional social engagement system. This system becomes dormant when the autonomic nervous system is retuned to support defense. When that occurs, it compromises sociality and accessibility, which would require a downregulation of defenses to enable proximity. An autonomic pattern of chronic defense is frequently observed in several psychiatric disorders (e.g., anxiety, autism, depression, posttraumatic stress disorder).[68]

A review of the clinical material suggests that MT's feedback is consistent with the model. For example, MT reported during the first session that her "ears feel funny." This is a frequently reported response to the Safe and Sound Protocol and appears to reflect a tensing of the eardrum as the middle-ear muscles become more active and the ossicle chain becomes more rigid. Similarly, "her previously ceaseless chatter abated" reflects a calmer autonomic state. In addition, her self-report on the Body Perception Questionnaire (see Table 1) emphasizes that her subjective feelings of autonomic state have profoundly moved from an autonomic state of defense to a state of calmness. These subjective responses are convergent with a more regulated autonomic nervous system.

Polyvagal theory identifies the hypothetical mechanisms through which modulated music works as a "neuromodulator." Intuitively, we know the calming power of a mother's lullaby, which is supported by a recent study documenting the potency of prosodic features in calming distress and shifting autonomic state.[64] Similarly, we are aware of the calming effect of melodic music. There is a science beneath these familiar observations.[69] Our own research has documented that prosodic maternal voices are effective in calming their infants' heart rate following a social disruptor,[70] and computer-modulated vocal music, similar to the Safe and Sound Protocol, has been documented to improve sociality, vagal regulation of the heart, and auditory processing, while reducing hyperacusis in children with autism spectrum disorders.[15,43] With this knowledge we can reconceptualize the calming effect of the prosodic voice/modulated music as an efficient and effective neuromodulator to "retune" the autonomic nervous system—an intervention that can potentially be used broadly in the clinical treatment of extreme states of anxiety and, in this case, FND.

When we understand the role of the bidirectional communication between specific brain stem structures (i.e., ventral vagal complex) and the autonomic nervous system—as well as the role of vagal afferents in the modulation of brain systems mediating arousal[38,42]—then we are in a position to understand, too, the link between MT's symptoms and the effectiveness of the intervention. Functionally, this neurally informed understanding links several of the symptoms

expressed by MT to a destabilized autonomic nervous system coupled with the neural network changes that characterize FND.[71] This understanding also directs the clinician to an effective intervention strategy.

**Souraya Torbey, MD**

Patients with FND have unique presentations and needs that are affected by distinctive biological, psychological, and social factors—predisposing, precipitating, and perpetuating. Given the range of possible co-occurring factors, however, any single modality of treatment is unlikely to be effective for all patients. For example, upon presentation, MT was unable to communicate verbally and had heightened levels of arousal, difficulty with her vision, and chronic pain. Her parents' behaviors also reinforced MT's FND. Given her presenting symptoms, traditional therapeutic modalities such as cognitive-behavioral therapy (CBT) could not be successfully implemented at that initial stage. The team therefore devised an individualized plan involving pharmacotherapy and other treatment modalities to target her needs. Given the unique challenges of every FND case, the gold standard is to conceptualize a patient's presentation through a biopsychosocial approach and to provide holistic, integrated, multidisciplinary treatment involving a diverse range of professionals focused on developing different skill sets and coping strategies.

It is common for patients with FND to have comorbid neurological and medical conditions, chronic pain, a history of trauma, and comorbid psychiatric disorders. Notably, patients with FND are at risk of being misdiagnosed as having an organic condition, with data showing that accurate diagnosis may be delayed by more than seven years and that patients are often treated with unnecessary interventions.[72] This is especially concerning because early diagnosis and treatment are associated with positive prognoses—especially in youth (such as MT), who have higher rates of remission than adults. Early diagnosis can also help to prevent overmedicalization, excessive health care utilization, and the functional deconditioning often seen in this patient population.

As noted above, the biopsychosocial approach is commonly used to describe predisposing, precipitating, and perpetuating factors for FND and chronic pain.[73] MT's case presents a good example of the importance of identifying these factors, which play a critical role in guiding medical decision making and creating an individualized behavioral approach and treatment plan. MT presented with several predisposing risk factors for FND, including female sex, history of bullying, loss of friendships, chronic pain, celiac disease, and family history of epilepsy and chronic medical illness (rheumatoid arthritis). Common predisposing factors for FND also include genetics, temperament, illness exposure, early childhood trauma, dissociative symptoms, and neurological illness.

The onset of FND symptoms is often precipitated by multiple factors, and in this case the triggers included recent viral illness, return to school, and loss of friends and supportive teacher, along with worsening anxious distress and mood.

Functional seizures can be maintained and perpetuated by multiple biological factors, including destabilization of the autonomic nervous system, neural network deficits in limbic sensorimotor and prefrontal areas, and psychological factors. The latter include maladaptive coping skills, catastrophizing,[74] increased attention to physical symptoms, loss of sense of agency,[75] and secondary gains,[76] which are themselves maintained by operant conditioning through both positive and negative reinforcement, such as avoidance of stress associated with school or increased attention from family or friends.[77] These psychological factors are best addressed through behavior modification and parent-training interventions (often one of the most challenging aspects of addressing FND). In the initial process, parents often become distressed when asked to refrain from attending to their child during an episode; consistent support is therefore required early on. As expected, MT's symptoms improved when parents and teachers minimized attention to her symptoms

The multidisciplinary approach involves intervening in patients' illness beliefs, reducing maladaptive behaviors,[78] minimizing and normalizing functional symptoms, addressing problematic family dynamics, and emphasizing the importance of restoring functioning, along with psychoeducation.[79] This approach was paramount in achieving a positive outcome in MT's case. Once the diagnosis of FND is made, the first step is to effectively communicate and provide psychoeducation about the disorder, thus promoting a constructive relationship between the patient and the treatment team. The second step is to develop a plan to reassess the need for certain medications and to discontinue certain unnecessary medications, such as anti-epileptic medications for functional seizures and opiates for chronic pain.[80] Given the paucity of research on pharmacological treatment of FND in youth, the recommended approach is to minimize medication administration except in cases where comorbid psychiatric disorders or other medical problems are present.[80] For patients with comorbid anxiety, depression, ruminative thoughts, or obsessive-compulsive disorder, antidepressants such as selective serotonin and serotonin-norepinephrine reuptake inhibitors may be helpful in select cases. In MT's case, guanfacine was used to curb arousal and facilitate her capacity to engage in treatment.

If antidepressants are prescribed, close monitoring for response and tolerability is warranted, especially given the low, but existing, risk of suicidal ideation—as happened with MT when fluvoxamine was trialed. One randomized, clinical trial demonstrated a significant, 59% reduction of functional seizure frequency for patients treated with both CBT and sertraline, and a 51% reduction with CBT alone.[81] The sertraline-only group did not significantly reduce seizure frequency, whereas the CBT-only group experienced a greater improvement of secondary outcomes such as quality of life, depression, and anxiety. In an open-label, uncontrolled, prospective study of the effect of venlafaxine on patients with functional seizures and comorbid depression or anxiety, the frequency and

intensity of episodes decreased over five months.[82] Generally, serotonin-norepinephrine reuptake inhibitors are rarely used in younger school-age children such as MT. They can be considered in older youth who have failed trials with selective serotonin reuptake inhibitors or have comorbid chronic pain. Their use should also be considered carefully as they can worsen arousal and consequently functional seizures. Tricyclic antidepressants such as amitriptyline have been showed to be beneficial for pain and sleep, and are often used for headaches, as was the case with MT. It is important to note, however, that analgesia is achieved at lower doses than those needed to address depression[83] and that tricyclics are ineffective for depression in youth.[84]

As was evident in MT's case, patients with functional seizures often present in a high state of physiological arousal.[85] Given that alpha agonist medications, such as the guanfacine used with MT, often decrease sympathetic arousal, they may be helpful with FND symptoms.[86,87] Anticonvulsants are also often prescribed for patients with FND. Some studies have found that anticonvulsants can potentially reduce the frequency of episodes, but this finding is thought to reflect a placebo or anti-anxiety effect.[88] Unless the patients have comorbid conditions, such as chronic pain, for which anticonvulsants may be helpful, it is generally recommended to discontinue these medications once the diagnosis is confirmed.

Similarly, patients with FND are often prescribed benzodiazepines, but no research supports their use except in the presence of comorbid acute anxiety.

MT had several medication trials. Eventually, her hyperarousal symptoms responded favorably to quetiapine (which is supported by the literature) and subsequently to guanfacine (after MT's parents perceived that the quetiapine left her feeling too flat). Nevertheless, the use of neuroleptics should be carefully considered, especially in younger youth, and the benefits should outweigh the non-negligible risk of extrapyramidal symptoms and metabolic syndrome.[89]

Larger clinical trials are needed to fully assess the clinical impact of pharmacological treatment on functional symptoms, particularly in youth. At present, the use of pharmacological treatments for FND in youth is mostly extrapolated from adult data. Psychotherapeutic approaches are also critical. These can be classified into two groups: bottom-up and top-down modalities. Bottom-up approaches are body-based interventions that work with the felt sense of the body (homeostatic feelings) and that use interventions that target the body: mindful attention to the body, slow-paced breathing, grounding techniques, regulating movement, therapeutic touch, and biofeedback approaches. These interventions facilitate the individual's capacity to track body state, tolerate states of activation, and facilitate states of calm.[2,11,12]

Top-down approaches—in particular, CBT—have been shown to have a high level of efficacy, with the majority of the data being in adults. To facilitate behavioral modifications in older patients with FND, motivational interviewing may reduce ambivalence about treatment.[90] Other top-down psychotherapies include hypnosis,[91] retraining and control therapy (ReACT),[92] psychoeducation group interventions, psychodynamic psychotherapy, and mindfulness-based therapy.[12] Most of these therapies engage in psychoeducation using the biopsychosocial approach, which in itself is a key intervention in FND.[93] Neuromodulation approaches are also showing promise.

In summary, FND is an unmapped clinical entity that mimics various conditions and may overlap with organic disorders. While we cannot identify one treatment approach to manage all the symptoms, the use of multimodal treatment approaches that target functional recovery while also addressing medical and psychiatric comorbidities appears to be the most effective way of supporting patients and families. As shown with MT, novel approaches—in particular, noninvasive neuromodulating modalities that facilitate engagement in adaptive coping strategies—can have an important role in improving outcomes and should be further explored through clinical and research activities.

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