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Effects of Translumbosacral Neuromodulation Therapy on Gut and Brain Interactions and Anorectal Neuropathy in Fecal Incontinence: A Randomized Study

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ABSTRACT

Objectives: Translumbosacral neuromodulation therapy (TNT) improves symptoms of fecal incontinence (FI), but its mechanism of action is unknown. We tested the hypothesis that TNT at one or more frequency will significantly improve underlying pathophysiology of FI through modulation of ascending and/or descending signaling pathways in the gut and brain axis and anorectal sensorimotor function.

Materials and Methods: We assessed afferent anorectal-cortical evoked potentials (CEP) following electrical stimulation of anorectum, efferent cortico-anorectal and lumbo-anorectal and sacro-anorectal motor evoked potentials (MEP) after transcranial and lumbosacral magnetic stimulations, and anorectal manometry before and after six weekly TNT sessions in FI subjects, randomized to 1, 5, or 15 Hz repetitive magnetic stimulations. Neurophysiology, anorectal sensorimotor function, and symptoms were compared to examine mechanistic effects. Co-primary measures were ano-cortical CEPs, cortico-anal MEPs, and lumbosacral-anal MEPs. Baseline and post-treatment data were compared with Wilcoxon signed-rank test and changes between the three frequencies with one-way ANOVA.

Results: Thirty-three FI patients participated. After TNT, the afferent anal CEP latencies significantly decreased in the 1 Hz group compared to baseline ($p = 0.0029$) and 5 Hz or 15 Hz groups ($p = 0.032$). Cortico-anal MEPs were unchanged in all three groups. Bilateral lumbo-anal and sacro-anal MEP latencies significantly decreased with 1 Hz, lumbo-anal with 15 Hz, and sacro-anal with 5 Hz compared to baseline but without group differences. The 1 Hz group showed significant increase in anal squeeze sphincter pressure ($p < 0.005$) and maximum tolerable volume ($p < 0.019$) and demonstrated higher FI responder rate ($p < 0.04$) compared to the other two groups. The MEP responders were significantly correlated with FI responders ($p = 0.006$) in 1 Hz group.

Conclusions: TNT significantly improves afferent ano-cortical signaling, efferent lumbo-anal and sacro-anal neuropathy and anorectal sensorimotor function. These neurobiologic effects were most prominent with 1 Hz frequency. TNT improves FI by modifying the underlying pathophysiology possibly through neuromodulation.

Keywords: Anorectal function, cortical evoked potential, fecal incontinence, lumbosacral neuropathy, neuromodulation therapy, neurophysiology

Conflict of Interest: All authors declare no conflicts of interests with this study.

INTRODUCTION

Fecal incontinence (FI) affects one in seven Americans (1), predominantly women, elderly, and nursing home residents (2,3) and significantly lowers quality of life (3). FI is caused by several mechanisms that include anorectal sensori-motor dysfunction, lumbosacral neuropathy, decreased rectosigmoid reservoir capacity and maladaptive pelvic floor-brain innervation and age-related neuronal degeneration (3–5).

Given the multifactorial nature of FI, treatments directed against a single dysfunction, for example, anal dextranomer injection or anal sphincteroplasty that help to reinforce the anal barrier are less likely to remedy this multidimensional problem (6). Likewise, although useful, how sacral nerve stimulation (SNS) works

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remains unknown, as anal sphincter function and rectal sensation remain mainly unchanged (7,8). Thus, there is scarce knowledge on how treatments work or affect the pathophysiological mechanisms of FI.

Recently, we found that both the peripheral lumbo-anorectal and sacro-anorectal nerve conduction pathways as measured by the motor evoked potentials (MEPs) were significantly delayed in FI patients (9,10). These findings suggest that anorectal neuropathy may play a significant role in the pathogenesis of FI (9,10). Rectal hyposensitivity has also been reported in FI patients (11), suggesting that the afferent signaling between the anorectum and brain may be delayed (12), although this has not been assessed. Another study found delayed conduction between the brain and anorectum in FI patients (10). Together, these studies suggest the possibility of abnormal bidirectional gut and brain interactions in FI patients, but each of these components has not been systematically assessed in the same individual. Furthermore, whether treatments directed at improving anorectal neuropathophysiology affect the bidirectional gut and brain interactions and may be useful in FI is unknown. Recently, we showed that translumbosacral neuromodulation therapy (TNT) at 1 Hz frequency was more effective than 5 Hz or 15 Hz frequency in decreasing the number of FI episodes, and the 1 Hz group showed a higher responder rate (13). However, the mechanistic basis for TNT remains unclear.

Therefore, we tested the hypothesis that TNT at one or more frequency will significantly improve the underlying pathophysiology of FI by modulation of ascending and/or descending signaling pathways in the gut and brain axis and anorectal sensorimotor function. Our aims were to investigate the mechanistic effects of TNT at 1, 5, and 15 Hz frequency, in FI patients, by examining: 1) the cortical evoked potentials (CEP) after anal and rectal stimulation (ascending), the cortico-rectal and cortico-anal MEPs after transcranial magnetic stimulation (TMS), and the lumbar and sacral plexus MEPs after translumbar and transsacral magnetic stimulations (descending) and 2) the anorectal sensorimotor function.

MATERIALS AND METHODS

We recruited patients with FI between April 2015 and March 2018. Once eligible for screening, participants signed an informed consent approved by the human ethics board (No. 619411) and kept a two-week prospective stool diary that included number of incontinence episodes, stool consistency using Bristol Stool Form Scale (BSFS), and severity of leakage amount (1 = mild, 2 = moderate, and 3 = excessive) (14,15). The inclusion criteria were a history of recurrent episodes of FI for six months that was nonresponsive to fiber, antidiarrheals and Kegel exercise; and absence of colonic mucosal disease (colonoscopy + biopsy), and at least one episode of solid or liquid FI/week on stool diary. Exclusion criteria were severe diarrhea (≥6 liquid stools/day, Bristol scale ≥6), opioids, tricyclics (except on stable doses >3 months), severe depression, severe comorbid illnesses such as cardiac disease, COPD or chronic renal failure, previous gastrointestinal surgery, neurologic diseases (e.g., head injury, epilepsy, multiple sclerosis, strokes, spinal cord injury), impaired cognizance (mini mental score of <15/25), metal implants, pacemakers, radical hysterectomy, ulcerative and Crohn's colitis or rectal prolapse. Patients were allowed to continue their baseline antidiarrheals or fiber supplements throughout study. Registered at Clinical trials.gov no NCT02556151.

Study Protocol

Enrolled patients filled out FI questionnaires and underwent anorectal manometry, anal ultrasound and bidirectional neurophysiology assessments (see Flow Chart in the Supporting Information Fig. 1). High-resolution anorectal manometry (HRARM) was performed as described previously (16,17). Briefly, a circumferential, 12-sensor, solid-state probe (ManoScan AR Catheter, Medtronic, MN, USA) with a 4 cm long balloon was placed into the anorectum. Anal sphincter pressures at rest, and during squeeze were measured (16,17). The thresholds for first sensation, desire to defecate, urge to defecate, and the maximum tolerable volume were recorded (16,17). Rectal compliance was evaluated as described previously (17).

Bidirectional Gut and Brain Axis Assessments

The CEP study was performed by placing an anorectal probe with two pairs of bipolar steel ring electrodes, each 2 cm apart (Gaeltec Devices Ltd., Dunvegan, UK) into the anorectum and using previously published methodology. The active scalp electrode was positioned 2 cm posterior to the vertex (C p3) (Fig. 1) (18,19). Four runs of 50 stimuli at 0.2 Hz were performed. The order of rectal or anal electrical stimulation was randomized.

The TMS study was performed in a semi-reclined position. A double cone coil (The MAGSTIM Company Limited, Whiteland, Wales, UK) was positioned over the cranium's vertex and stimulations were performed as described previously (10,18,19). The translumbosacral anorectal magnetic stimulation (TAMS) test was performed by applying the Magstim Rapid (2) stimulator (The Magstim Company Limited) on each side at the L3 and the S3 levels, both about 4 cm lateral to the midline (Fig. 1) (9,10). The same anorectal probe used for CEP study also served as the recording probe for both anal and rectal MEP (10,18,19). The range for magnetic stimulation intensity was 50%–90%. Five MEP recordings with anal and rectal MEP responses of at least 10 μV were considered adequate for analysis.

TNT Therapy

The total duration of study was eight weeks that included two weeks of screening with stool diary and baseline neurophysiologic assessments, and a total of six treatment sessions, once a week. Patients were randomized to one of three frequencies (1, 5,or 15 Hz) of TNT therapy as described previously (13). The treatments were administered using a 70 mm air film self-cooling coil (MAGSTIM Rapid (2)) positioned randomly over the right or left lumbar or right or left sacral regions. Six hundred stimulations were delivered to each site, in two trains of 300 stimulations each with a wait time of 3 minutes between trains (total = 2400 stimulations/session) (Fig. 1). The duration of treatment at each site was variable and depended on the frequency. For the 1 Hz frequency, the duration of treatment at each site was 10 min with a total duration of 40 min, and for the 5 Hz, it was 2 min and 8 min, respectively, and for the 15 Hz, it was 40 sec at each site and 2 min and 40 sec in total. There was a 5-min wait time between each site. The magnetic stimulation intensity for each site was individually tailored and set at 50% above the minimum threshold intensity required to evoke an anal/rectal MEP response and contraction of the posterior tibialis muscle and varied between 40% and 100%. Following their last treatment session, CEP, TMS, TAMS, anorectal manometry, and FI symptoms (1 week stool diary) were re-assessed.

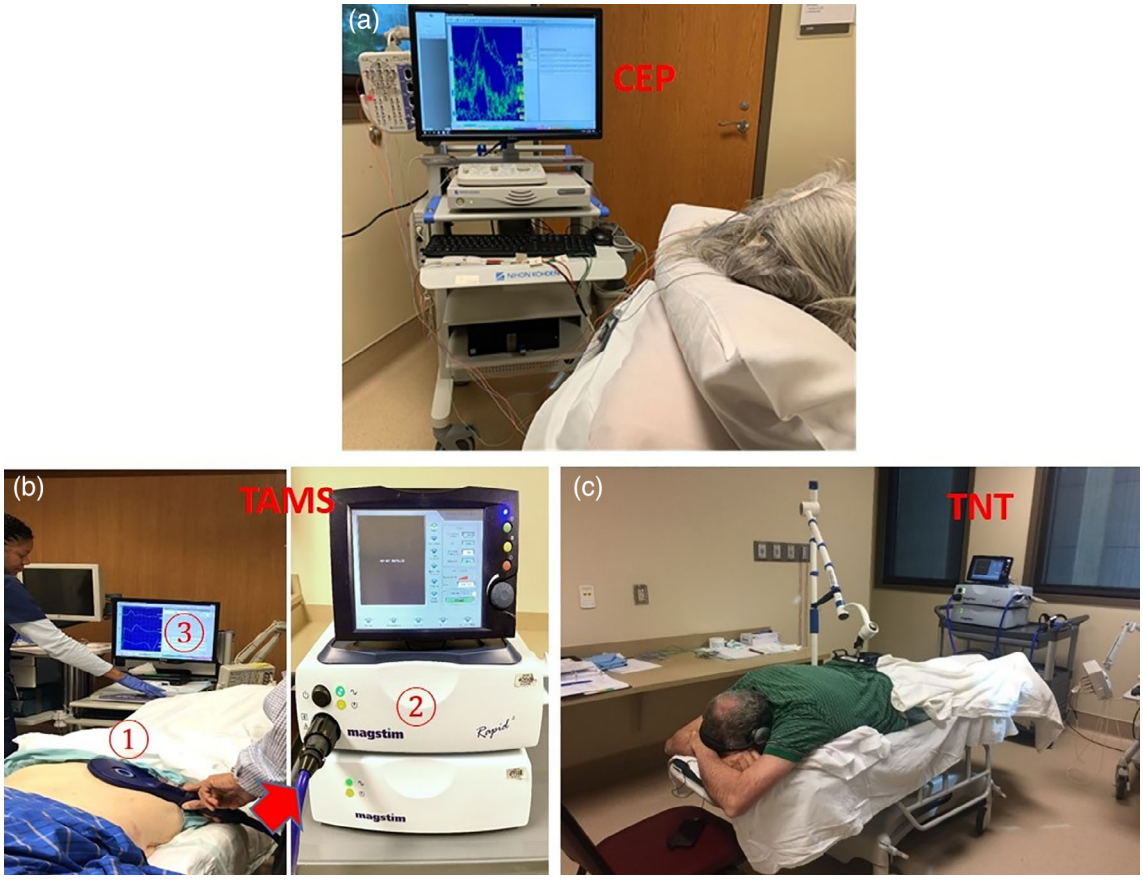

Figure 1. (a) Recording of cortical evoked potentials (CEPs) showing scalp electrodes connected to a neurophysiology recorder; (b) recording of translumbosacral anorectal magnetic stimulation (TAMS) study showing magnetic coil 1) located on the back of a subject which is connected to a magnetic energy generator, 2) (Magstim) and a neurophysiology recorder, 3) for assessing lumbosacral-anorectal motor evoked potentials (MEPs); (c) display of the equipment for performing translumbosacral neuromodulation therapy (TNT) with a repetitive coil located on the back of a subject. [Color figure can be viewed at wileyonlinelibrary.com]

Measurements and Analyses

Cortical Evoked Potential Measurements

The four runs of CEPs, following anal and rectal stimulation from each subject, were averaged. The latency was defined as the time interval (milliseconds) from triggering the stimulus to the onset of each CEP component (18,19). Positive CEP peaks were labeled P1 and P2, and negative peaks were labeled N1 and N2 (Fig. 2). Latency of the rectal and anal CEPs from each subject were determined separately and group means were calculated, and the data compared between the groups.

Motor Evoked Potential Measurements

The MEP data were analyzed manually using the Neuropack® (Nihon Kohden, Tokyo, Japan) software. The MEP latency was defined as the interval between the onset of stimulus and the onset of the first deflection of individual rectal or anal MEP waveforms and was expressed in milliseconds (10,19) (Fig. 3). The latencies of the cortico-rectal and cortico-anal MEPs, and the lumbo-rectal, lumbo-anal, sacro-rectal and sacro-anal MEPs bilaterally were calculated and compared between groups (10,19). Because peripheral lumbosacral neuropathy was recently described in FI patients (9,10), we also compared the lumbosacral MEP data with historical controls from our laboratory.

Cortico-Lumbar and Cortico-Sacral Spinal Cord Conduction. The cortico-spinal conduction time (CSCT) was calculated from the differences in MEP measurements obtained for the TMS and TAMS studies on the same side (left or right) and from the same site (anal or rectal) as described previously (10).

Because of different mechanistic assessments, multiple co-primary and secondary measures were used. The co-primary measure for afferent CEP was the latency of P1 and N1 ano-cortical response and for the efferent brain and anorectal signaling was the P1 latency of anal MEP response to TMS, and secondary measures were P1 latencies for rectal CEP and MEP. The co-primary measures for lumbosacral-anorectal assessments were the P1 latencies for lumbo-anal and sacro-anal MEPs, and secondary measures were lumbo-rectal and sacro-rectal MEPs. Symptomatic outcome measures included changes in weekly FI episodes and the responder rate (responder = ≥50% decrease in FI episodes) (13). We also assessed the correlation between the MEP outcomes and clinical outcomes. For this purpose, we defined a MEP responder as a subject who showed normalization of the nerve conduction time (MEP) in more than four of the eight lumbosacral MEPs (>50%). These data were compared with the FI responders for each of the three frequencies.

Power and Sample Size Calculations

Because the mechanistic study was part of the clinical trial evaluating TNT, the sample size was calculated on the assumption that the number of FI episodes within each of the three treatment arms has a coefficient of variation (ratio of standard deviation to mean) of 0.25 (1:4). To observe a 20% reduction in the number of

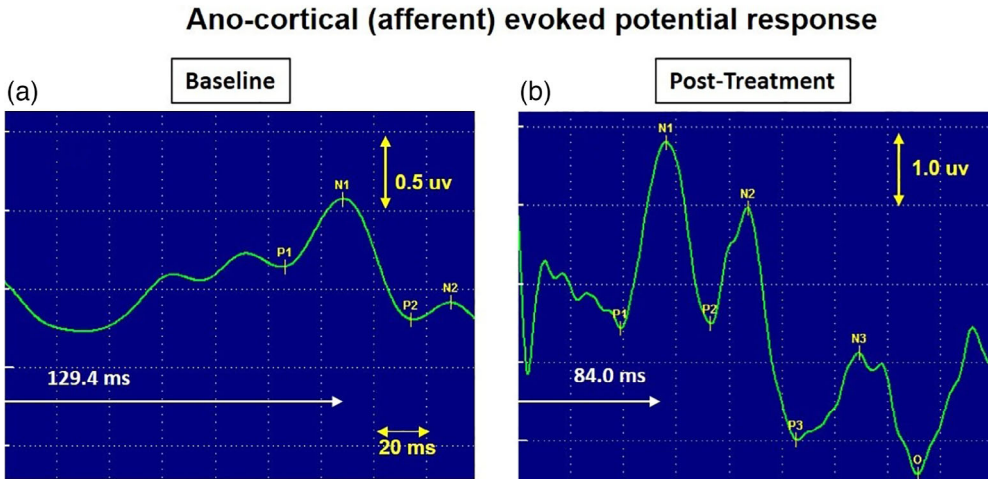

Figure 2. Typical ano-cortical (afferent) evoked potential (CEP) response in a FI patient at baseline (a) and post-TNT treatment (b), showing significant reduction in N1 latency time, as well as P1, P2, and N2 latencies. [Color figure can be viewed at wileyonlinelibrary.com]

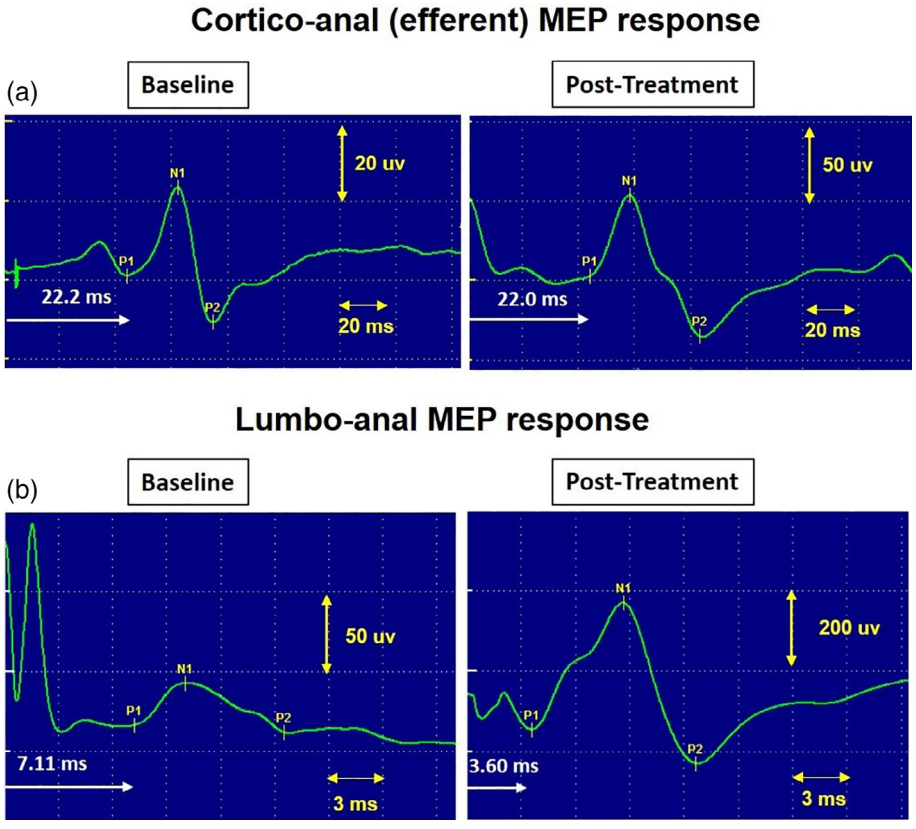

Figure 3. (a) Typical cortico-anal (efferent) motor evoked potential (MEP) response at baseline and post TNT treatment in a FI patient showing no change in P1 latencies; (b) typical lumbo-anal (efferent) MEP response at baseline and post-TNT treatment in a FI patient showing significant decrease in P1 latency time. [Color figure can be viewed at wileyonlinelibrary.com]

FI episodes with an 80% power, at 5% significance level, a sample of 12 subjects will be needed in each treatment arm, that is, a total of 36 subjects.

Randomization Procedures

Subjects were randomly assigned to one of three treatment arms; 1, 5, or 15 Hz. The randomization schedule was generated by biostatistician using the permuted blocks of three method. Also, to assign the combination of testing conditions for each subject, we used a 2 × 2 factorial design—two sides of lumbar (left/right) and two sides of sacral (left/right). Serially numbered, opaque, sealed envelopes containing the frequency dose assignments and the testing condition assignments were developed by the biostatistician, and included a unique, site specific randomization number, and this information was used by the research

assistant who performed the tests and/or TNT study. The research assistants performing tests/treatment (X.X., T.P.) were not involved with data and statistical analysis.

Statistical Analysis

We used nonparametric tests to assess changes because of the small sample sizes across the three groups, and the observations failed the Shapiro–Wilk normality test. The baseline and post-treatment measures within each of the three frequencies were compared using a Wilcoxon signed-rank test. To compare the changes (delta) between the three frequencies, a Kruskal–Wallis one-way ANOVA was used with the frequencies as factors. We also performed a correlational analysis between the MEP and the FI responder data using the phi coefficient, a correlational measure for dichotomous variables that is calculated from the Pearson chi-squared test statistic, and assessed its significance with the chi-squared association test. All the *p*-values were adjusted for multiple testing using Benjamin–Hochberg false discovery rate correction. An intention to treat analysis was performed and for missing data the last observation was carried forward.

RESULTS

Demographics

Thirty-five patients were enrolled, of whom two were withdrawn, one because of severe diarrhea and another because of personal reasons and diarrhea, prior to randomization (Supporting Information Fig. 1). Thirty-three FI patients (21 females) were randomized. We found no differences in the demographic variables including bowel symptoms, severity or type of FI and proportion of patients with anal sphincter defects or neuropathy, between the three groups as published previously (13).

Effects of TNT on Ano-Cortical and Recto-Cortical CEPs (Afferent Gut–Brain)

A typical ano-cortical CEP response before and after TNT is shown in Fig. 2. The mean ano-cortical latencies for the P1, N1, P2, and N2 responses of the CEP were all significantly decreased when compared to baseline in the 1 Hz group but not in the 5 Hz or 15 Hz groups (Table 1). Also, in the 1 Hz group, the P1, N1, and N2 latencies were significantly decreased when compared to the 5 Hz and 15 Hz frequency groups after treatment (Table 1). The mean recto-cortical latencies for P1, N1, P2, and N2 responses were unchanged in all three groups compared to baseline (Table 1).

Effects of TNT on Cortico-Anal, Cortico-Rectal, Cortico-Spinal, and Lumbosacral-Anorectal MEPs (Efferent Brain–Gut)

A typical cortico-anal and lumbo-anal MEP response is shown in Fig. 3. The baseline MEP latencies were similar between the three groups. The cortico-anal and cortico-rectal MEPs as well as the cortico-lumbar and cortico-sacral MEPs, that is, cortico-spinal MEPs were mostly unchanged after TNT (Table 2). The baseline data for all eight peripheral spino-anorectal MEPs were abnormal when compared to historical control data previously reported from our laboratory (10). After TNT, the bilateral lumbo-anal and sacro-anal MEP latencies were significantly shortened in the 1 Hz group ($p < 0.025$) compared to baseline. In contrast, only the right side sacro-anal MEP was shortened in the 5 Hz group, whereas bilateral lumbo-anal latencies were shortened in the 15 Hz group

Table 1. Effects of Three Different TNT Frequencies on the Anal CEP and Rectal CEP Responses and on the Rectal Sensory Thresholds During Rectal Balloon Distension (Mean ± SEM).

		1 Hz			5 Hz			15 Hz			Overall *p*
		Baseline	Post-treatment	*p*	Baseline	Post-treatment	*p*	Baseline	Post-treatment	*p*	
Anal CEP	P1 latency (msec)	86.6 ± 10.3	69.8 ± 7.5	0.013	78.9 ± 9.2	89.3 ± 5.4	0.406	82.9 ± 8.0	79.2 ± 10.7	0.838	0.045
	N1 latency (msec)	115.0 ± 13.5	91.7 ± 10.3	0.002	107.3 ± 10.9	117.3 ± 9.5	0.343	105.7 ± 9.8	107.7 ± 11.8	0.683	0.032
	P2 latency (msec)	169.2 ± 16.6	141.0 ± 13.7	0.024	158.8 ± 15.3	169.2 ± 14.3	0.722	162.2 ± 20.2	154.2 ± 20.5	0.540	0.155
	N2 latency (msec)	197.7 ± 19.0	152.6 ± 14.7	0.003	176.2 ± 15.2	198.9 ± 16.8	0.406	195.9 ± 25.8	185.5 ± 28.6	0.475	0.021
Rectal CEP	P1 latency (msec)	72.8 ± 6.3	64.5 ± 4.4	0.147	79.9 ± 9.8	78.1 ± 10.9	0.918	71.8 ± 10.7	63.9 ± 5.3	0.921	0.658
	N1 latency (msec)	103.5 ± 5.8	97.1 ± 5.4	0.101	105.8 ± 10.7	108.4 ± 12.3	0.838	101.6 ± 15.1	93.7 ± 7.5	0.798	0.370
	P2 latency (msec)	159.4 ± 11.8	152.8 ± 9.2	0.637	156.1 ± 12.2	153.4 ± 15.4	0.475	161.2 ± 22.4	153.6 ± 16.6	0.375	0.520
	N2 latency (msec)	194.4 ± 16.2	177.9 ± 13.6	0.413	172.1 ± 12.9	177.2 ± 16.3	0.918	201.5 ± 31.3	183.9 ± 24.9	0.625	0.794
Rectal sensory thresholds	First sensation (mL)	15.5 ± 2.1	18.2 ± 2.3	0.204	20.0 ± 2.7	25.4 ± 5.3	0.261	14.6 ± 2.1	13.6 ± 1.5	0.425	0.495
	Constant sensation (mL)	31.8 ± 4.4	64.6 ± 6.3	0.024	36.4 ± 4.9	52.7 ± 8.1	0.055	28.2 ± 5.5	36.4 ± 4.3	0.134	0.678
	Desire to defecate (mL)	98.2 ± 27.1	125.5 ± 20.2	0.135	74.6 ± 9.3	81.8 ± 11.5	0.361	60.9 ± 11.2	55.5 ± 5.3	0.528	0.277
	Urge (mL)	143.6 ± 28.6	189.1 ± 19.9	0.038	102 ± 11.4	131.8 ± 17.4	0.082	90.9 ± 14.8	85.5 ± 8.4	0.316	0.143
	MTV (mL)	162.3 ± 27.0	225.3 ± 19.1	0.019	107 ± 12.3	163.6 ± 23.4	0.014	96.7 ± 14.0	103.6 ± 10.2	0.110	0.189

CEP, cortical evoked potential; MTV, maximal tolerable volume.

Table 2. Effects of Three Different TNT Frequencies on Cortico-Rectal and Cortico-Anal MEP After TMS and Spino-Anorectal MEP After TAMS (Mean ± SEM).

		1 Hz			5 Hz			15 Hz			Overall *p*
		Baseline	Post-treatment	*p*	Baseline	Post-treatment	*p*	Baseline	Post-treatment	*p*	
Transcranial-anorectal MEP latencies											
Left	Cortico-anal (msec)	21.7 ± 1.1	23.6 ± 1.3	0.278	23.3 ± 1.3	20.0 ± 0.9	0.083	22.3 ± 1.4	22.4 ± 1.0	0.966	0.110
	Cortico-rectal (msec)	22.1 ± 1.3	23.3 ± 1.3	0.577	21.7 ± 1.4	20.5 ± 1.0	0.308	22.6 ± 1.4	20.7 ± 1.3	0.109	0.121
Right	Cortico-anal (msec)	22.6 ± 1.6	22.2 ± 1.1	0.831	24.4 ± 1.2	23.2 ± 1.4	0.414	22.9 ± 1.7	22.9 ± 0.9	0.966	0.798
	Cortico-rectal (msec)	21.3 ± 1.1	20.8 ± 0.7	0.646	26.1 ± 3.6	22.3 ± 1.7	0.154	22.2 ± 1.5	21.9 ± 0.9	0.878	0.462
Corticolumbar and corticosacral latencies (msec)											
Left	Corticolumbar (anal)	16.7 ± 1.2	19.8 ± 1.3	0.05	17.3 ± 1.6	14.4 ± 1.0	0.139	16.9 ± 1.1	18.4 ± 1.1	0.131	0.019
	Coticosacral (anal)	17.0 ± 1.1	19.8 ± 1.2	0.062	17.3 ± 1.5	15.0 ± 0.9	0.169	17.4 ± 1.6	18.0 ± 1.2	0.859	0.084
	Corticolumbar (rectal)	19.1 ± 1.4	20.7 ± 1.3	0.328	17.1 ± 1.5	17.1 ± 0.9	0.721	18.8 ± 1.4	16.7 ± 1.4	0.062	0.158
	Coticosacral (rectal)	18.9 ± 1.4	20.3 ± 1.3	0.398	16.4 ± 1.6	16.5 ± 1.1	0.959	18.6 ± 1.6	16.9 ± 1.5	0.11	0.206
Right	Corticolumbar (anal)	17.2 ± 1.3	18.4 ± 1.2	0.131	18.3 ± 1.4	18.0 ± 1.4	0.799	17.0 ± 2.0	18.5 ± 1.1	0.328	0.714
	Coticosacral (anal)	17.3 ± 1.5	18.5 ± 1.3	0.213	18.7 ± 1.4	18.6 ± 1.6	0.959	17.2 ± 1.6	18.3 ± 1.2	0.859	0.847
	Corticolumbar (rectal)	17.4 ± 1.3	17.8 ± 0.7	0.859	21.6 ± 3.6	18.4 ± 1.6	0.221	18.5 ± 1.6	18.0 ± 1.1	1.0	0.426
	Coticosacral (rectal)	17.5 ± 1.3	17.5 ± 0.7	0.929	21.2 ± 3.7	18.9 ± 1.7	0.575	17.6 ± 1.5	18.3 ± 1.0	0.534	0.512
Spino-anorectal MEP latencies											
Lumbar	Left-lumbar anal (msec)	5.1 ± 0.5	3.8 ± 0.3	0.021	6.1 ± 0.6	5.6 ± 0.6	0.192	5.4 ± 0.8	4.0 ± 0.6	0.010	0.559
	Right-lumbar anal (msec)	5.3 ± 0.4	3.9 ± 0.3	0.007	6.1 ± 0.5	5.2 ± 0.5	0.075	5.9 ± 0.7	4.4 ± 0.4	0.024	0.531
	Left-lumbar rectal (msec)	3.1 ± 0.3	2.7 ± 0.2	0.343	4.5 ± 0.5	3.4 ± 0.3	0.076	3.8 ± 0.4	4.0 ± 0.3	0.965	0.335
	Right-lumbar rectal (msec)	3.9 ± 0.4	3.0 ± 0.2	0.025	4.6 ± 0.7	3.9 ± 0.3	0.722	3.7 ± 0.3	3.8 ± 0.3	0.765	0.269
Sacral	Left-sacral anal (msec)	4.8 ± 0.4	3.8 ± 0.3	0.009	6.0 ± 0.5	5.0 ± 0.4	0.058	4.9 ± 0.6	4.4 ± 0.7	0.541	0.698
	Right-sacral anal (msec)	5.3 ± 0.5	3.7 ± 0.4	0.025	5.7 ± 0.6	4.5 ± 0.4	0.024	5.7 ± 0.6	4.7 ± 0.5	0.119	0.832
	Left-sacral rectal (msec)	3.3 ± 0.3	3.0 ± 0.2	0.154	5.3 ± 0.5	4.1 ± 0.4	0.097	4.0 ± 0.4	3.7 ± 0.5	0.083	0.614
	Right-sacral rectal (msec)	3.8 ± 0.3	3.3 ± 0.2	0.092	5.0 ± 0.8	3.4 ± 0.2	0.044	4.7 ± 0.5	3.6 ± 0.4	0.083	0.634

ms, milliseconds; MEP, motor evoked potential; TAMS, translumbosacral anorectal magnetic stimulation; TMS, transcranial magnetic stimulation.

Table 3. Effects of TNT on FI Episodes, Anal Sphincter Function, and Rectal Compliance (Mean ± SEM).

	1 Hz			5 Hz			15 Hz			Overall *p*
	Baseline	Post-treatment	*p*	Baseline	Post-treatment	*p*	Baseline	Post-treatment	*p*	
FI Responder rate	90.9%			36.4%			54.5%			0.0441
No. of FI episodes/week	7.1 ± 2.2	2.9 ± 1.3	0.010	11.1 ± 3.4	9.1 ± 3.0	0.022	6.1 ± 1.3	2.7 ± 0.8	0.007	0.239
Resting Pressure (mm Hg)	54.7 ± 6.5	68.4 ± 9.0	0.041	65.5 ± 10.2	71.5 ± 11.1	0.120	55.3 ± 23.5	58.9 ± 18.4	0.312	0.573
Maximal Squeeze Pressure (mm Hg)	113.2 ± 8.4	176.7 ± 16.8	0.002	156.7 ± 38.7	172.7 ± 34.8	0.067	111.4 ± 18.2	141.2 ± 35.2	0.061	0.041
Sustained Squeeze Pressure (mm Hg)	66.5 ± 7.7	87.2 ± 9.1	0.005	100 ± 28.3	94.2 ± 20.6	0.379	67.3 ± 10.5	71.4 ± 10.1	0.206	0.037
Rectal distending volume	Rectal pressure (mm Hg)									
20 mL	20.6 ± 4.7	10.4 ± 3.7	0.018	19.8 ± 3.3	20.6 ± 6.8	0.540	27.0 ± 7.0	22.7 ± 7.1	0.336	0.374
40 mL	33.3 ± 4.3	22.9 ± 3.5	0.009	33.4 ± 4.6	30.7 ± 4.5	0.287	41.7 ± 4.7	31.3 ± 3.1	0.080	0.414
70 mL	33.8 ± 3.9	22.7 ± 3.5	0.012	38.7 ± 6.1	33.3 ± 7.7	0.285	49.5 ± 9.1	36.3 ± 3.9	0.500	0.764
100 mL	40.8 ± 4.0	24.6 ± 4.9	0.004	35.9 ± 4.7	25.2 ± 5.4	0.015	45.0 ± 5.8	42.8 ± 7.3	0.605	0.180

Responder= ≥50% reduction in FI episodes compared to baseline.

Table 4. Correlation of Lumbosacral-Anal and Lumbosacral-Rectal MEP Responder With Fecal Incontinence Responder.

TNT Frequency	Phi coefficient	*p*
Overall FI groups	0.41	0.0179
1 Hz	0.67	0.0067
5 Hz	0.069	0.819
15 Hz	0.516	0.087

compared to baseline (Table 2). TNT also decreased the right side lumbo-rectal MEP latency in the 1 Hz and right side sacro-rectal in the 5 Hz group, but there were no changes in the 15 Hz group and at other rectal sites, and there were no intergroup differences (Table 2).

Effects of TNT on Anorectal Sensorimotor Properties and Compliance

The anal resting pressure, maximal squeeze, and sustained squeeze pressures increased significantly in the 1 Hz group when compared to baseline ($p < 0.04$). Also, post-treatment, both squeeze pressure measurements were higher in 1 Hz compared to 5 or 15 Hz groups ($p = 0.04$) (Table 3). There were no changes in the 5 Hz and 15 Hz groups (Table 3). Also, the rectal sensory thresholds in the 1 Hz group for constant sensation, urge to defecate, and the maximal tolerable volume increased ($p < 0.05$) when compared to baseline, but there were no changes within the 5 Hz or 15 Hz or between the three groups (Table 1). The rectal compliance (dv/dp) improved ($p < 0.05$) in the 1 Hz group when compared to baseline, but not within the 5 Hz and 15 Hz groups or between groups (Table 3).

FI Symptoms

The number of FI episodes per week significantly decreased (1 Hz, $p = 0.01$; 5 Hz, $p = 0.022$ and 15 Hz, $p = 0.007$) after TNT treatment when compared to baseline, without intergroup differences (Table 3). The percentage of responders (90.9%) was significantly higher ($p = 0.04$) in the 1 Hz group when compared to 5 Hz group (36.4%) and 15 Hz group (54.4%), and between 1 Hz and 5 Hz groups ($p = 0.023$). These observations and other symptom profiles have been reported elsewhere (13).

Correlation of Lumbosacral MEPs With Clinical Outcome

There was moderate degree of overall positive correlation (0.41) between the MEP responders and the FI responders, and this was significant ($p = 0.017$; Table 4). Further, in the 1 Hz group, the MEP responders were also highly correlated (0.67) with the FI responders, and this was statistically significant ($p = 0.006$; Table 4). The 5 Hz and 15 Hz frequency groups showed no significant correlation.

DISCUSSION

Although fecal incontinence is caused by multiple pathophysiological mechanisms (3–5), there is sparse knowledge on how current treatments improve symptoms or how they modify the underlying mechanisms (5,6). In this first bi-directional gut and brain interactions study in FI, we found that the afferent nerve conduction time as measured by the latencies for the ano-cortical evoked potentials (P1, N1, P2, and N2) were significantly decreased after TNT treatment with the 1 Hz frequency when compared to its baseline values or those seen with the 5 Hz and 15 Hz frequencies. This finding of a shortened CEP latency time suggests that TNT improves signaling time between the anorectum and brain. Clinically, this could translate into enhanced awareness of stool perception, and thereby provide more warning time for FI patients to reach the restroom and prevent leakage.

The afferent recto-cortical evoked potentials, however, showed no differences when compared to baseline or between the three frequencies, suggesting that TNT may not affect the rectal sensory pathways. Another study recently showed no changes in recto-cortical representation after anal electrical stimulation but shortening of P1 latency and increased ano-cortical representation, especially cingulate gyrus (20). Together these findings suggest that peripheral stimulation improves the afferent ano-cortical neurobiologic axis.

The efferent signaling as assessed by the cortico-spinal MEP latencies (cortico-lumbar and cortico-sacral) inform how efficiently do messages from the brain reach the spinal cord in FI patients. These

values were mostly unchanged, suggesting that TNT does not affect descending pathways between the brain and spinal cord. Peripherally, the bilateral, lumbar and sacral plexus MEPs provide a comprehensive assessment of the overall nerve function from its origin in the lumbar and/or sacral plexus to their innervation in the anal and rectal muscles (10,18). At baseline these MEP values in FI patients were abnormal when compared to healthy controls (10,18), reaffirming that FI patients exhibit significant lumbar and sacral plexus neuropathy (9,10). Importantly, after TNT, the bilateral lumbar and sacral anal nerve conduction significantly improved as evidenced by the significant shortening of all anal MEP latencies in the 1 Hz frequency group, and to a lesser degree with the 5 Hz and 15 Hz groups. The lumbo-rectal and sacro-rectal MEPs were mostly unchanged in all three frequency groups. These observations suggest that TNT improves the efferent peripheral spino-anorectal neuropathy but does not affect the efferent function between the brain and spinal cord. Furthermore, we found an overall significant correlation between MEP responders and FI responders, and in particular a high degree of significant correlation only in FI patients who were treated with the 1 Hz frequency. These findings suggest that following TNT the mechanistic improvements in nerve conduction time and the underlying neuropathy correlate well with the clinical improvements seen in FI patients.

The neuromodulatory effects of improved signaling in the afferent ano-cortical and peripheral lumbo-anal and sacro-anal MEPs, especially at 1 Hz frequency imply that TNT may bring about these changes by inducing neuroplasticity, that is, the inherent ability of neurons to adapt and change, and thereby alter the excitability in the motor neurons of the spinal cord and improve nerve conduction (21). A previous animal model study showed that repetitive neural stimulation of sacral and posterior tibial nerves induced central neuroplasticity as evidenced by increased peak amplitude of somatosensory CEP and the density of polysialylated neural cell adhesion molecules (PSA-NCAM)—a neuroplasticity marker (22). Also, acute sacral neuromodulation at 2 Hz was superior to 14 Hz in increasing both CEP amplitude and PSA-NCAM expression suggesting neuroplasticity in rodents (23). These intriguing findings merit further validation in humans.

The anal squeeze sphincter pressure, and sustained squeeze pressure significantly improved as well as rectal sensory thresholds for constant sensation of fullness, urge to defecate and the maximum tolerable volume and rectal compliance after treatment with 1 Hz frequency only. Thus, TNT may improve anal sphincter strength, rectal sensory dysfunction and rectal reservoir function; all important mechanisms in the pathophysiology of FI possibly through neuromodulation.

Previously we showed that temporary SNS (frequencies > 14 Hz) decreased corticoanal excitability alongside improvements in FI symptoms but without changes in anorectal manometry (24). However, unlike SNS that typically uses electrical stimulation at 15 Hz (7,8,23), here we showed significant improvements in afferent excitability and peripheral spino-anal signaling and anorectal sensorimotor function with magnetic stimulation at 1 Hz frequency and not with other frequencies, suggesting greater efficacy for lower frequencies in peripheral neural stimulation. However, in the CNS, previous studies have suggested that higher frequency magnetic stimulation is more effective for delayed conduction and neuropathies (25). Also, one lumbosacral study showed that the 15 Hz frequency increased cortical excitability compared to 5 Hz, but 1 Hz was not tested, so that might explain a difference (26). In contrast, another study showed that the 1 Hz lumbosacral stimulation did alter spinal responses (27). Also 1 and 2 Hz was associated with greater potentiation of anorectal inputs into the somatosensory cortex than 14 Hz in rats (28). Another rodent study showed that SNS at 5 Hz was more effective than 15 Hz in improving rectal compliance and colonic transit in loperamide-induced constipation (29). These observations suggest that lower frequencies of repetitive stimulation may be more effective in improving peripheral neural dysfunction than higher frequencies. In addition to the frequency, the duration of TNT therapy may also affect outcome, as it required 40 min to deliver 2400 stimulations at 1 Hz, whereas it required 8 min for the 5 Hz and about 3 min for the 15 Hz frequency, respectively.

The limitations include the small number of subjects in each arm and the lack of sham controlled studies. This possibly led to a type II error with some of our analysis limiting the significance of our observations. However, this was an exploratory study to evaluate both the feasibility of TNT and underlying plausible mechanisms. Thus, despite the smaller sample size, TNT produced significant changes in most primary measures especially in the 1 Hz group, demonstrating its usefulness when compared to higher frequencies. However, these observations require confirmation in larger, sham-controlled studies to validate these mechanistic underpinnings. Also, the potential benefits of other paradigms including more frequent sessions, fixed duration, and longer trains of stimulation merit further study.

In conclusion this study shows that TNT appears to have a multidimensional effect on the pathophysiological mechanisms of FI, especially when applied at 1 Hz frequency, alongside improvements in bowel function suggesting that TNT could be a useful treatment for FI. These afferent gut and brain and peripheral neurobiologic, sensory and anal sphincter mechanistic effects are possibly mediated by neuromodulation and offer the real promise of a new noninvasive therapeutic approach.

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Authorship Statements

Satish Rao served as the Project Director and Principal investigator-Augusta site. Dr. Rao was responsible for the study concept and design, grant support, data analysis and interpretation, Translumbosacral neuromodulation therapy supervision, manuscript preparation, overall supervision and critical revision. Xuelian Xiang was responsible for administering TNT therapy, conducting neurophysiology tests and conducting anorectal physiology test. Amol Sharma was responsible for the study conduct and recruitment as well as manuscript preparation. Yun Yan was responsible for the data analysis, tables and figures. Deepak Ayyala was responsible for statistical design, statistical methods and data analysis. Shaheen Hamdy served as the Principal investigator-Manchester site. Dr. Hamdy was also responsible for the study design, grant writing, manuscript preparation, and critical revision. All authors have approved the final version of the manuscript submitted.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the supporting information tab for this article.

COMMENT

This is a randomized, controlled trial in which patients were randomized to 1, 5, or 15 Hz of repetitive magnetic stimulation in the translumbar space for fecal incontinence with measurement of motor evoked potentials (MAPs). The authors find that TNT significantly improves afferent ano-cortical signaling, efferent lumbo-anal and sacro-anal neuropathy and anorectal sensorimotor function, which has basis in possible reasoning for the mechanism of this treatment. While this study is underpowered and not designed to detect between-group differences, this exploratory work points the way to proper stimulation parameters and can be a future direction in fecal incontinence therapy.

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