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Current Biology

Entraining Movement-Related Brain Oscillations to Suppress Tics in Tourette Syndrome

Highlights

- Rhythmic median nerve stimulation can entrain sensorimotor mu-band oscillations
- Mu-band entrainment has minimal effect on volitional movement or cognition
- Mu-band entrainment significantly reduces motor and vocal tics in Tourette syndrome
- Mu-band entrainment reduces the urge-to-tic in Tourette syndrome

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In Brief

Morera Maiquez et al. report that brain oscillations linked to movement suppression can be effectively entrained by using rhythmic pulse trains of median nerve stimulation (MNS) and demonstrate that rhythmic pulse trains of MNS are sufficient to significantly reduce the occurrence of tics and the urge-to-tic in individuals with Tourette syndrome.

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Entraining Movement-Related Brain Oscillations to Suppress Tics in Tourette Syndrome

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SUMMARY

Tourette syndrome (TS) is a neuropsychiatric disorder characterized by the occurrence of vocal and motor tics. Tics are involuntary, repetitive movements and vocalizations that occur in bouts, typically many times in a single day, and are often preceded by a strong urge-to-tic—referred to as a premonitory urge (PU). TS is associated with the following: dysfunction within cortical-striatal-thalamic-cortical (CSTC) brain circuits implicated in the selection of movements, impaired operation of GABA signaling within the striatum, and hyper-excitability of cortical sensorimotor regions that might contribute to the occurrence of tics. Non-invasive brain stimulation delivered to cortical motor areas can modulate cortical motor excitability, entrain brain oscillations, and reduce tics in TS. However, these techniques are not optimal for treatment outside of the clinic. We investigated whether rhythmic pulses of median nerve stimulation (MNS) could entrain brain oscillations linked to the suppression of movement and influence the initiation of tics in TS. We demonstrate that pulse trains of rhythmic MNS, delivered at 12 Hz, entrain sensorimotor mu-band oscillations, whereas pulse trains of arrhythmic MNS do not. Furthermore, we demonstrate that although rhythmic mu stimulation has statistically significant but small effects on the initiation of volitional movements and no discernable effect on performance of an attentionally demanding cognitive task, it nonetheless leads to a large reduction in tic frequency and tic intensity in individuals with TS. This approach has considerable potential, in our view, to be developed into a therapeutic device suitable for use outside of the clinic to suppress tics and PU in TS.

INTRODUCTION

Many neurodevelopmental disorders, including Tourette syndrome (TS), have been linked to alteration in the balance of excitatory and inhibitory influences within key brain networks [1, 2]. TS is a neurological disorder of childhood onset that is characterized by the occurrence of vocal and motor tics. Tics are involuntary, repetitive, stereotyped movements and vocalizations that occur in bouts, typically many times in a single day [3]. TS has been particularly associated with dysfunction within cortical-striatal-thalamic-cortical (CSTC) brain circuits that are implicated in the selection of movements [4], impaired operation of inhibitory (GABA-mediated) signaling within the striatum [5] and cortical motor areas [6], and hyper-excitability of limbic and sensorimotor regions of the brain, that might contribute to the occurrence of tics [4].

The majority (~90%) of individuals with TS report that their tics are often preceded by "premonitory sensory and urge phenomena" (PU) that are described as uncomfortable cognitive or bodily sensations that occur prior to the execution of a tic and experienced as a strong urge for motor discharge. Individuals who experience PU often report that these experiences are more bothersome than their tics, that expressing their tics gives them relief from and temporarily abolish their PU, and that they would not exhibit tics if they did not experience PU. For this reason, it has been proposed that PU should be considered as the driving force behind the occurrence of tics and that tics are a learnt response to the experience of PU. Furthermore, PU are of particular clinical importance because they form the core component of behavioral therapies that are currently used in the treatment of tic disorders [3].

Neural oscillations of the brain's electromagnetic activity reflect the synchronized firing of populations of neurons, and it is known that GABA-mediated interneurons play a critical role in coordinating the synchronized activity of populations of pyramidal neurons that give rise to brain oscillations [7]. Two frequency bands are particularly relevant to the occurrence of tics in TS: alpha or mu (8–14 Hz) and beta (15–30 Hz), which have long been associated with sensorimotor function [8], are linked to maintaining the current motor set [9], and become de-synchronized when a movement is initiated [8]. It is noteworthy that studies of electroencephalographic (EEG) signals that are thought to arise in the supplementary motor area (SMA) ahead of movement indicate that these signals are abnormal in individuals with TS ahead of tic execution [e.g., 10] and that real-time functional magnetic resonance imaging neurofeedback in

adolescents with TS indicates that neurofeedback of SMA activation might be effective in improving tic symptoms [11].

Non-invasive brain stimulation delivered to cortical motor areas has been shown to modulate cortical motor excitability [6], entrain brain oscillations [12], and reduce tics in TS [13–15]. However, these techniques are not optimal for treatment outside of the clinic or for use with young children. Our solution was to investigate the potential therapeutic use of peripheral somatosensory stimulation. Specifically, we investigated whether we could use median nerve stimulation (MNS) to entrain brain oscillations linked to the suppression of movement and as a result influence the initiation of movement. Our long-term objective is to develop a safe and effective non-drug therapy, suitable for administration by the individual outside of the clinic, that can contribute significantly to clinical intervention.

We adapted an approach reported by Thut et al. [16] in which they had demonstrated that rhythmic pulses of transcranial magnetic stimulation (TMS) could be used to entrain cortical alpha (8–14 Hz) oscillations. Thut et al. delivered five-pulse rhythmic trains of TMS at each individual's preferred alpha frequency (a-TMS) and demonstrated alpha entrainment (increased alpha power and phase synchrony in the alpha band). Importantly, this effect was not observed when five-pulse trains of TMS were delivered arrhythmically within the same time window.

In our study we combined EEG recording with rhythmic mu-band (12 Hz) versus arrhythmic 10-pulse trains of MNS, and we demonstrate that rhythmic but not arrhythmic trains of MNS lead to entrainment of 12 Hz oscillations (i.e., increased 12 Hz power and phase synchrony) contralateral to the site of peripheral stimulation. Second, in two further studies, we demonstrate that compared with *arrhythmic* MNS, *rhythmic* (12 Hz) MNS, delivered during the motor preparation phase of a manual choice reaction time (CRT) task, resulted in slowed manual responses (reaction times [RTs]) delivered within the same time window. Third, to investigate whether MNS would reduce the occurrence of tics in individuals with TS, we investigated the efficacy of rhythmic MNS versus no stimulation in a group of children and young adults with TS. We demonstrate that, compared with no stimulation, mu (10 Hz) MNS leads to a significant reduction in both tic frequency and tic intensity. Finally, to evaluate whether the beneficial effects of MNS in TS patients were simply due to the MNS distracting attention from their tics, we ran a further behavioral study in which we investigated the effects of rhythmic 12 Hz MNS on an attentionally demanding continuous performance task (CPT). Importantly, we demonstrate that rhythmic 12 Hz MNS delivered during the execution of a CPT does not significantly increase the number of errors or the mean RT for correct responses compared with in a no stimulation control condition.

RESULTS

We adopted the approach outlined by Thut et al. [16] to investigate whether rhythmic bursts (10 pulses) of MNS, delivered at 12 Hz to the right wrist, could entrain mu (12Hz) oscillations measured over the contralateral sensorimotor cortex. Thut et al. [16] had compared short bursts of rhythmic TMS against an arrhythmic TMS control condition and demonstrated that rhythmic TMS led to entrainment of cortical alpha (8–14 Hz) oscillations. In the current study, we compared pulse trains of 10 pulses of rhythmic 12 Hz MNS against an arrhythmic MNS control condition in which 10 pulses of MNS were delivered within the same 749 ms time window used for the rhythmic stimulation (see Figure 1A). Stimulation was delivered to the median nerve of the right wrist and 64-channel EEG data were recorded throughout.

In their TMS study, Thut et al. [16] had observed that rhythmic TMS produced two distinct phases of EEG response: an initial period of evoked activity (in response to pulses 1–2) that produced a large broadband response, followed by a more focused increase in power and phase synchrony at the target stimulation frequency (in response to pulses 3–5). Importantly, whereas this initial broadband activity was observed for both rhythmic and arrhythmic TMS and had a widespread, bilateral, and spatial topography, the later focused response at the targeted stimulation frequency was only observed at the TMS stimulation site. We therefore predicted that 12 Hz rhythmic MNS delivered to the right wrist would lead to an initial, bilateral, and broadband response increase in EEG power, which will be followed by a subsequent entrainment (i.e., increase in 12 Hz power and phase synchrony) measured at the contralateral scalp over the left sensorimotor cortex. Relevant data are presented in Figures 1B, 1C, and 2.

Increase in Spectral Power and Phase Locking after Rhythmic MNS

Time-frequency analysis revealed an increase in spectral power at the beginning of each MNS pulse train that involved several frequency bands including theta, mu, and beta bands (Figure 1B, window 1 [W1]). This initial broadband increase in power is only present in the initial 1–3 pulses of the train and can be observed for both the rhythmic condition and the arrhythmic stimulation. This initial broadband response is followed by an increase in mu-power in a narrow band that peaks at the targeted frequency of the stimulation (i.e., 12 Hz) (Figure 2B, W2) in response to pulses 4–10 and disappears shortly after the final pulse. This increase in power centered at 12 Hz and is absent in the arrhythmic condition. This difference becomes clearer when subtracting the arrhythmic condition from the rhythmic condition (Figure 1B, bottom). Importantly, the 12 Hz power event-related spectral perturbation (ERSP) for the rhythmic stimulation condition is significantly increased ($p < 0.05^{FDR\text{-}corrected}$) above that for the arrhythmic condition only during the period of stimulation (Figure 1C).

To examine whether rhythmic 12 Hz MNS entrained the targeted 12 Hz cortical oscillations, we analyzed inter-trial coherence by quantifying phase-locking values (PLVs). PLVs quantify the consistency with which oscillations fluctuate at the same phase and rhythm across trials and are used as a measure of phase alignment or phase synchrony; high PLV values correspond to high consistency. Relevant data are presented in Figure 2. PLVs increased substantially over the contralateral sensorimotor cortex coincident with the onset of MNS. Initially, this increase was equivalent for both rhythmic and arrhythmic stimulation (W1), but after the initial 1–2 pulses, PLVs decreased for arrhythmic MNS compared to rhythmic MNS and remained significantly different ($p < 0.05^{FDR\text{-}corrected}$) throughout the period of stimulation (Figures 2A and 2C). Immediately after stimulation

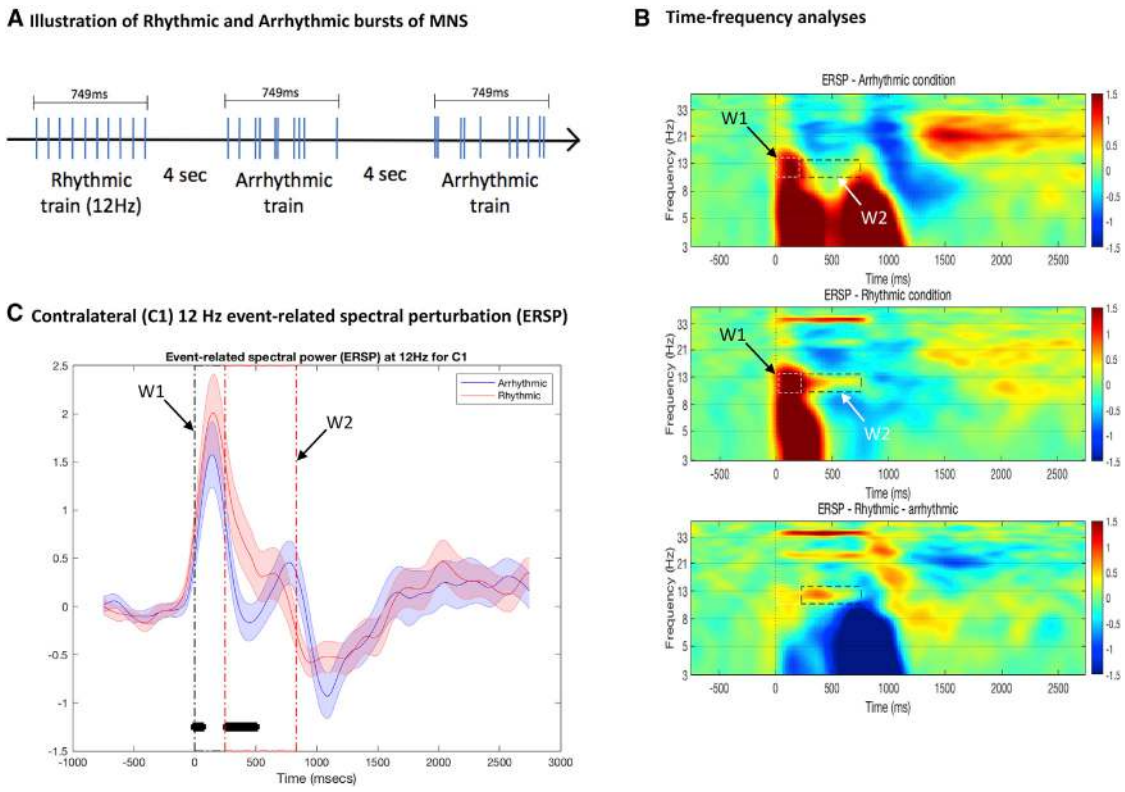

Figure 1. Study Design and Time-Frequency Plots of ERSP for Rhythmic and Arrhythmic MNS

(A) Illustration of rhythmic 12 Hz and arrhythmic bursts of MNS.

(B) Time-frequency plots of ERSP for arrhythmic (top) and rhythmic (middle) MNS and the rhythmic minus arrhythmic subtraction (bottom). The time course of the 12 Hz ERSP, measured over the left sensorimotor region (C1) and corresponding to the initial 3 MNS pulses, are contained within W1. The time course of the 12 Hz ERSP for the remaining MNS pulses (4–10) are contained within W2.

(C) Results of statistical comparison of ERSP values for arrhythmic and rhythmic 12 Hz measured at C1. Statistically significant values are indicated with * symbols ($p < 0.05$ FDR-corrected).

For further information please refer to Figure S2.

ceased, PLVs for both conditions decreased in magnitude and became equivalent to one another (Figures 2A and 2C). To examine whether entrainment in response to rhythmic 12 Hz MNS was spatially localized to the scalp over the sensorimotor cortex contralateral (left) to the site of MNS (the right wrist), we compared PLVs measured at the left and right sensorimotor cortex. Relevant data are presented in Figures 2B and 2D. PLVs increased substantially at both locations coincident with the onset of rhythmic 12 Hz MNS (W1), but after the initial 1–3 pulses, they decreased over the ipsilateral (right) sensorimotor cortex but were sustained over the contralateral (left) sensorimotor cortex (W2) until MNS ceased. The difference in PLVs measured at the left versus right scalp locations was only statistically significant ($p < 0.05^{FDR\text{-}corrected}$) during the latter period of MNS (W2).

Phase Resetting in Response to Each MNS Pulse

Thut et al. [16] demonstrated that the rhythmic TMS pulses delivered in their study led to a progressive synchronization of the targeted brain oscillation frequency and that enhanced synchronization was critically dependent on the existing, pre-TMS phase of the signal generator. Importantly, they demonstrated that each individual TMS pulse had the effect of resetting that phase. To determine whether MNS had a similar effect of resetting the phase of the targeted signal generator, we plotted the 12 Hz oscillations for each pulse for both rhythmic and arrhythmic stimulation (Figure 3). The results show that rhythmic MNS leads to the predicted resetting of the phase for every pulse of the train. By contrast, this phase reset is only seen for the first 3 pulses in the arrhythmic condition. This is consistent with our observation of an increase in power and PLVs that is observed only at the beginning of the train for arrhythmic MNS (pulses 1–3) and with the finding that there is a sustained increase in power and PLVs, centered at 12Hz, for pulses 4–10 only during rhythmic MNS.

Altogether, the data reported above indicate that there is an initial (W1, pulses 1–3), broad increase in power and PLVs in response to both rhythmic and arrhythmic MNS that is observed over the sensorimotor cortex in both hemispheres. However, this general effect is followed (W2, pulses 4–10) by a more specific increase in power and PLVs at the targeted 12 Hz frequency after rhythmic 12 Hz MNS, which is specific to the hemisphere contralateral to the site of MNS. Finally, examination of the response to each individual MNS pulse indicates that the sustained entrainment effect observed after rhythmic 12 Hz MNS might be a result

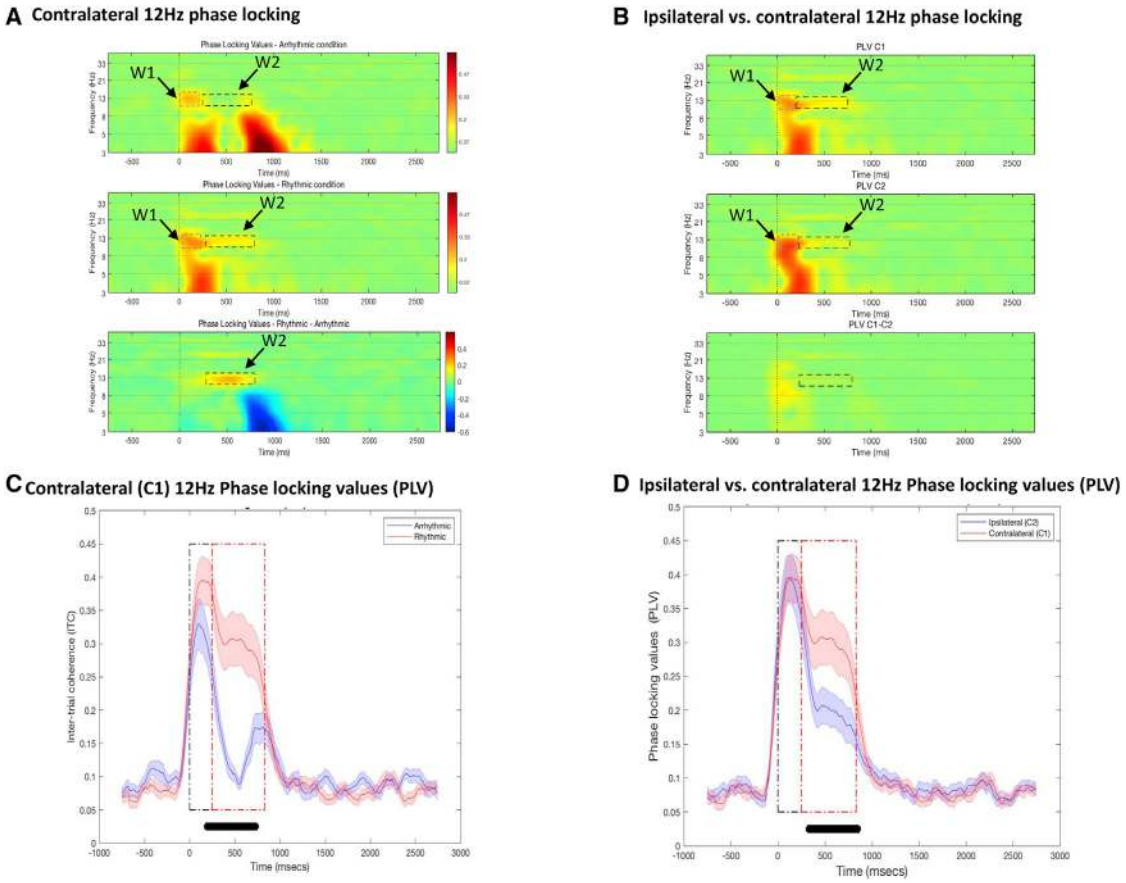

Figure 2. Time-Frequency Plots of Phase-Locking Values for Rhythmic and Arrhythmic MNS

(A) Time-frequency plots of PLVs for arrhythmic (top) and rhythmic (middle) MNS and the rhythmic minus arrhythmic subtraction (bttom). The time course of the 12 Hz PLVs, measured over the left sensorimotor region (C1) and corresponding to the initial 3 MNS pulses, are contained within W1. The time course of the 12 Hz PLVs for the remaining MNS pulses (4–10) are contained within W2.

(B) Time-frequency plots of PLVs for 12 Hz MNS measured over the contralateral sensorimotor (C1) (top) and ipsilateral sensorimotor (C2) and the C1 minus C2 subtraction (bottom).

(C) Statistical comparison of PLVs for arrhythmic and rhythmic 12 Hz measured at over the contralateral sensorimotor cortex (C1). Statistically significant values are indicated with * symbols ($p < 0.05$ FDR-corrected). (D) Statistical comparison of PLVs measured over the contralateral sensorimotor (C1) and ipsilateral sensorimotor (C2) for rhythmic 12 Hz MNS. Statistically significant values are indicated with * symbols ($p < 0.05$ FDR-corrected).

of phase resetting of the 12 Hz oscillation in response to each MNS pulse of the train. It is important to note, however, that the entrainment of brain oscillations associated with movement suppression is unlikely to be specific to any particular frequency within the mu- or beta-bands. Thut et al. reported that rhythmic TMS pulses across a range of alpha-band frequencies were effective in eliciting alpha-band entrainment [16], and we have demonstrated in our own unpublished studies that we observe beta-band entrainment after both rhythmic 19 Hz and 20 Hz MNS but do not observe this for appropriate arrhythmic control conditions.

After Effects of Rhythmic Mu-Band Stimulation

To investigate whether there were any aftereffects of rhythmic mu-band stimulation, we conducted further time-frequency analyses for the period after stimulation had ceased and for frequencies other than those directly stimulated. These results of these analyses are reported in Figure S1 of the Supplemental Information and demonstrate that there are significant differences in beta-band power after rhythmic mu-band stimulation compared with arrhythmic stimulation.

Effect of Rhythmic MNS on the Execution of Volitional Movements

To investigate whether delivering rhythmic trains of MNS had a significant effect on the execution of volitional movements, we conducted two separate CRT studies in which the effects of rhythmic versus arrhythmic MNS on RTs executed in response to visual stimuli were compared directly. In one study, the order of rhythmic and arrhythmic MNS trains was randomized, whereas in the other study, the order was blocked and counterbalanced across participants. The results were comparable in either case and are presented in Figure 4. Specifically, we found that mean RT for correct trials were significantly slowed by rhythmic MNS compared with arrhythmic MNS in both studies (randomized presentation: $t(19) = 2.01$, $p = 0.029$, effect-size [Hedges' g] = 0.23; blocked presentation: $t(19) = 2.56$, $p < 0.01$, effect-size [Hedges' g] = 0.08). It should be noted

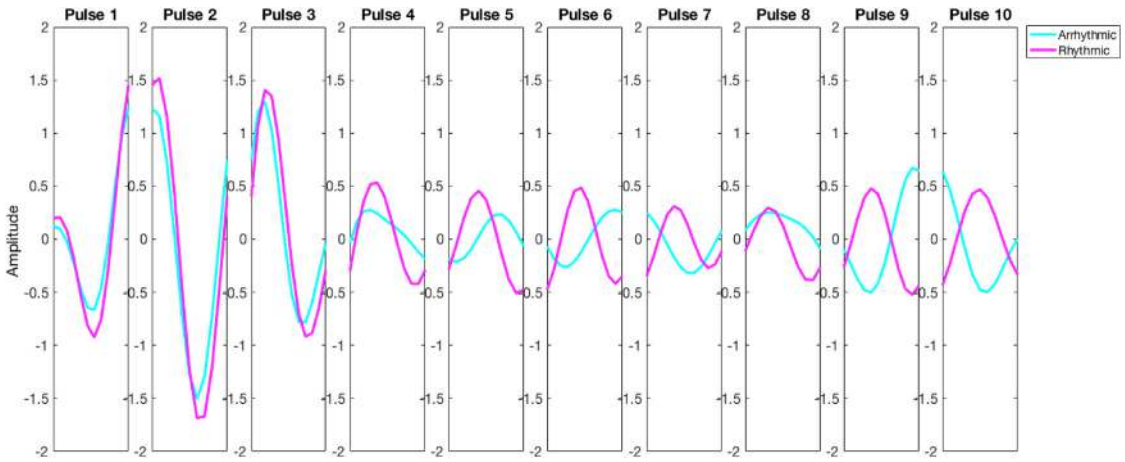

Figure 3. Evoked Activity in Response to Each Successive Pulse of MNS

Waveforms recorded from over the left sensorimotor region (C1) are shown for arrhythmic (cyan) and rhythmic (pink) MNS.

that although these results confirm that rhythmic MNS led a statistically significant slowing of average RT in relation to arrhythmic MNS, it is important to recognize that the magnitude of this effect is actually very small and in fact led to no material impairment in the execution of volitional movements. It is important to keep this in mind when reviewing the effects of rhythmic MNS on the occurrents of tics in TS outlined below.

Effect of Rhythmic MNS on the Occurrence of Tics and the Urge-to-Tic in TS

To investigate whether delivering rhythmic trains of mu-band (10 Hz) MNS to the right wrist had a significant effect on the occurrence of tics and the experience of the urge-to-tic in TS, we conducted a lengthy series of case studies in which 19 individuals with TS were video recorded while receiving randomly interleaved 1-min periods of MNS versus no stimulation. Throughout this period, participants were required to continuously report their self-estimated urge-to-tic by using a slider device reported previously [17]. Three patients withdrew from the study because they found the MNS uncomfortable, and a further three participants required a reduction in stimulation intensity (80% of threshold) to continue. In general, these were the youngest individuals in the sample or those who appeared particularly anxious about participating. Video recordings from the remaining 16 cases (9 males, aged 14–51, mean age = 22) were subject to a carefully conducted, blind, analysis of tic frequency and tic intensity during each 1-min epoch of MNS or no stimulation, and self-estimated urge-to-tic ratings were similarly computed for MNS and no stimulation epochs. Relevant data are presented in Figure 5, and representative video clips are presented in the Supplemental Information. Inspection of Figure 5 indicates that the effect of stimulation on urge intensity, tic frequency, and tic intensity was quite variable across individuals. To investigate which individuals benefitted most from stimulation, we ran additional multiple regression analyses. These results are presented in Figure S2 of the Supplemental Information. The results of these analyses indicated that those individuals who exhibited the most severe clinical symptoms showed the most benefit from the rhythmic MNS stimulation.

All participants were asked to comment on their experience of the stimulation and any spontaneous comments were recorded. All participants reported that the stimulation had been effective and that it had influenced their TS symptoms. Some reported that the stimulation had reduced their tics, and others reported that the stimulation had primarily removed or reduced their urge-to-tic. Others stated that the stimulation had affected both their tics and their urge-to-tic. For example, individual participants stated that muscles that never relax did so on the during MNS, that stimulation definitely decreased their urges, that MNS stopped them from wanting to tic. that with the stimulation they didn't need to tic as much, and that during MNS their urges were reduced and their tics weren't on their mind. Three others reported that stimulation made them calmer. Interestingly, one participant said that the stimulation reduced their urges a great deal but not their tics, and so with the stimulation they could no longer tell when their tics were going to happen. Two sets of comments are particularly worthy of note. First, several participants wondered whether the reduction of tics they experienced was due to the distracting nature of the stimulation. Second, three participants stated that the effects of the stimulation lasted for some time after it had ceased. This latter point was confirmed in the video analysis.

Quantitative analysis revealed that compared with comparable time periods of no stimulation, rhythmic MNS significantly reduced both tic frequency (i.e., total number of tics recorded over a total period of 4 min) and tic intensity (i.e., the independently, blind, rated intensity of each tic) (means for tic frequency: no stimulation = 87.6 ± 71.4, rhythmic MNS = 126.3 ± 94.5; $t(15) = 2.36$, $p = 0.03$, Figure 5 left; means for tic intensity: no stimulation = 3.0 ± 0.6, rhythmic MNS = 2.8 ± 0.6; $t(15) = 2.41$, $p = 0.03$, Figure 5 middle). By contrast, although all participants stated that the effects of MNS were to reduce their perceived urge-to-tic and that quantitative analysis of the continuous self-estimated urge-to-tic data showed an overall reduction in the self-estimated urge-to-tic during MNS of ~33%, the difference between rhythmic MNS and no stimulation was only marginally significant (means for self-estimated tic-to-tic intensity: no stimulation = 41.3 ± 31.7, rhythmic MNS = 29.1 ± 20.7;

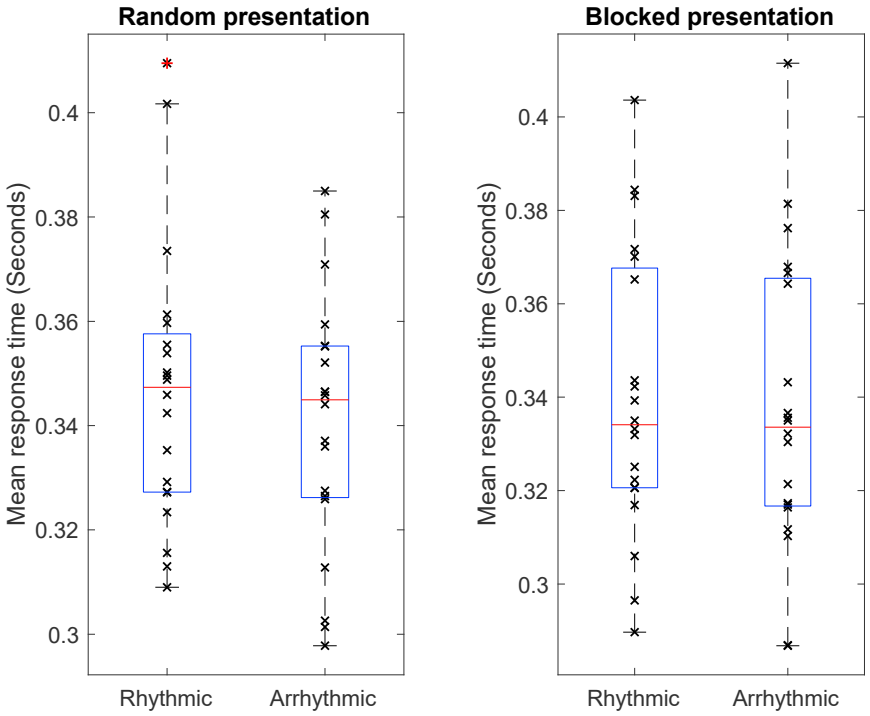

Figure 4. Effects of Rhythmic 12 Hz Versus Arrhythmic MNS on the Initiation of Choice-RTs

Choice-RT data for correct trials for rhythmic 12Hz versus arrhythmic MNS. Shown the left are data for random presentation of rhythmic and arrhythmic MNS pulse trains, and on the right is a blocked presentation of rhythmic and arrhythmic MNS. The boxplot shows the median values (red line), inter-quartile ranges (blue box), and individual data points (x) in each case. Red "*" symbols represent outliers. In both cases, the difference between means for rhythmic and arrhythmic MNS was statistically significant ($p < 0.05$).

t(15) = 1.83, p = 0.09, Figure 5 right). It is likely, in our view, that this result stems from two potential factors that will be discussed below. First, it is clear from our video analyses and the subjective reports from the patients that individuals might vary on when and for how long the benefits of MNS occur. For some individuals the effects of MNS are only observed and experienced during stimulation (see also Video S1). By contrast, others report that the beneficial effects of MNS can outlast the period of stimulation for some time. This might lead to a potential under-estimation of the beneficial effects of MNS when we compare interleaved periods of MNS with no stimulation. Second, the relationship between PU and tics in TS is not entirely clear. Some studies report a positive correlation between tic severity and questionnaire measures of PU in TS [e.g., 18], whereas others report no correlation [e.g., 10]. Furthermore, as was noted above, those individuals who experience PU often report that expressing their tics give them relief from, and temporarily abolishes, their PU. For this reason, it is of particular interest in the current study to investigate how MNS-induced changes in tic frequency are associated with alterations in self-estimated urge-to-tic. To examine this, we used Pearson correlation and linear regression techniques. These analyses revealed a positive correlation ($r = 0.75$, $R^2 = 0.56$, $F = 12.74$, $p = 0.005$), indicating that a reduction in tic frequency was associated with a reduction in self-estimated urge-to-tic experiences and demonstrated that the observed MNS-induced reduction in tic frequency accounted for approximately 56% of the variance in the self-estimated urge-to-tic.

In this study, we investigated whether providing rhythmic mu-band MNS would lead to a clinically relevant reduction in tic severity and the urge-to-tic in individuals with TS, and our results indicate that this might be the case. However, it is important to acknowledge what can and cannot be concluded from this observation. We suggest that our results indicate that rhythmic mu-band MNS is sufficient to bring about a significant reduction in tic frequency and tic intensity, but we acknowledge that it might not be a necessary condition. Thus, it might be that other types of stimulation, including other frequency bands, could prove equally effective in suppressing tics. Furthermore, although the EEG results of study 1 indicate that rhythmic mu-band MNS leads to entrainment of mu-band brain oscillations and arrhythmic stimulation does not, it is important to note that in study 3 we have not reported the effects (if any) of arrhythmic MNS on tic severity. It therefore remains to be determined whether arrhythmic MNS might also lead to a reduction in tics.

Effects of MNS on Attention

One potentially straightforward explanation for the reduction of tics observed in individuals with TS during MNS is that MNS is simply distracting and that by distracting attention from the urge-to-tic, or from the tics themselves, MNS might reduce the propensity to tic or the experience of the urge-to-tic in TS. Although the basis for any reduction induced by MNS might not actually matter a great deal if it can be shown that MNS is both well tolerated and clinically effective in suppressing tics or the urge-to-tic, it might nonetheless be important in refining the approach to determine what mechanisms underlie the effect. To examine this issue more directly, we investigated the effects of rhythmic MNS on an attentionally demanding CPT in which twenty young adults had to make a speeded manual response to any 1 of a set of 13 target letters (selected pseudorandomly from the alphabet) and withhold a response to any one of 2 non-target letters, selected from the remaining 13 non-target letters of the alphabet. To make the CPT particularly demanding, we set the ratio of target to non-target letters to 70:30. The results of this study demonstrated that MNS had no significant distracting effect on participants performance in the CPT. Specifically, there was no effect of MNS on the number of errors made during MNS compared with the no stimulation condition (total error means: no stimulation = 11.9 ± 5.1, rhythmic 12 Hz MNS = 12.3 ± 4.9, p = 0.65; commission errors: no stimulation = 10.34 ± 4.5, rhythmic 12 Hz MNS = 10.6 ± 4.4, p = 0.72; omission

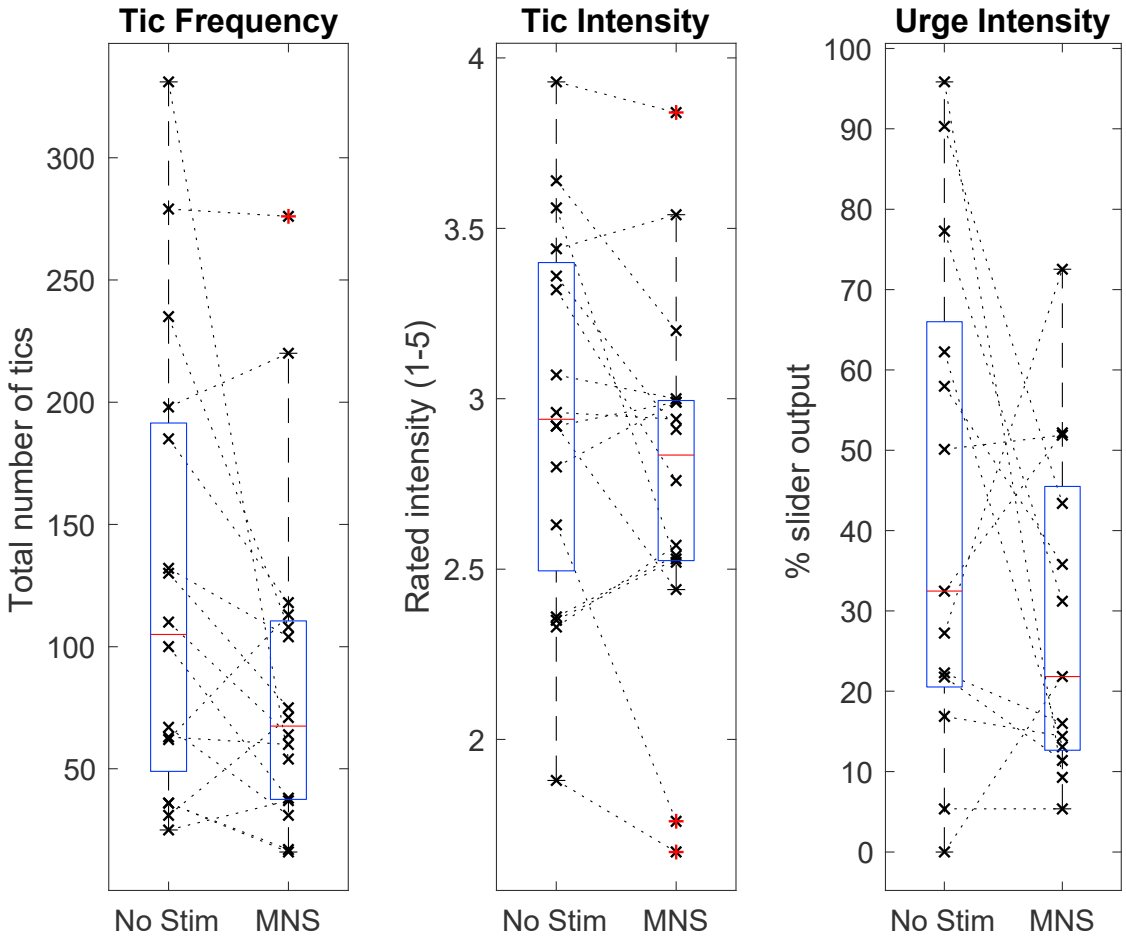

Figure 5. Effects of Rhythmic 10 Hz MNS versus No Stimulation on Tic Frequency and Intensity, and the Urge-to-Tic, in Tourette syndrome
Illustrates the effects of rhythmic 10 Hz MNS compared to a no-stimulation control condition. Shown on the top left are data for tic frequency as measured by the total number of tics recorded in each condition ($p < 0.05$). In the middle are data for tic intensity ($p < 0.05$). Shown on the right are data for urge-to-tic intensity ($p = 0.09$). The red * symbols represent individual data points that are statistical outliers. For further information please refer to Videos S1–S3, Table S1, and Figure S2.

errors: no stimulation = 1.56 ± 1.3, rhythmic 12 Hz MNS = 1.68 ± 1.8, $p = 0.72$; and no effect of MNS on mean RTs for correct trials during MNS compared with no stimulation, $p = 0.35$). Given the importance of a null result in this context, we conducted an additional Bayesian analysis to evaluate the likelihood of the null. This analysis confirmed the non-significant alternative hypothesis for both errors (BF10 = 0.26) and correct RTs (BF10 = 0.39) and revealed that strong evidence in favor of the null hypothesis for both errors (BF01 = 3.9) and correct RTs (BF01 = 2.86).

DISCUSSION

In the current study, we began by investigating whether rhythmic 12 Hz MNS could be used to entrain the cortical mu-band oscillations linked to the suppression of movement and as a result influence the initiation of movement. Our objective was to determine whether rhythmic mu-band MNS might be effective in reducing the likelihood of unwanted movements and vocalizations (tics) being initiated in TS. We delivered rhythmic 12 Hz MNS to the right wrist and compared this to an arrhythmic MNS control condition. Our EEG data demonstrated that rhythmic mu (12 Hz) stimulation (10 pulses) produced a sustained increase in 12 Hz power and phase synchrony that was localized to EEG sensors located over the contralateral sensorimotor area and was not observed for the arrhythmic control condition. Our results indicated that rhythmic MNS led to a resetting of the 12 Hz oscillatory phase for every pulse of the MNS pulse train. By contrast, this phase-reset was not sustained beyond the initial three pulses in the arrhythmic condition. These results are highly similar to, and consistent with, the results reported by Thut et al. [16], who had demonstrated robust alpha-band entrainment after five pulses of rhythmic alpha-band TMS, which was not observed after five pulses of arrhythmic TMS. For a detailed discussion and mechanistic account of phase-locking after rhythmic stimulation, readers should consult the paper by Thut et al. [16].

We then examined, in two separate studies, whether rhythmic 12 Hz MNS could influence the initiation of volitional movement by using a simple CRT task. Our results indicated that rhythmic 12 Hz MNS leads to a small but statistically significant slowing

of movement initiation (RTs) in relation to the arrhythmic control condition in both studies. This finding is consistent with a previous study, which demonstrated that entrainment of 20 Hz cortical activity by using transcranial alternating-current electrical stimulation (tACS) was sufficient to slow voluntary movement [12]. However, although statistically significant, the size of the observed effect in both of the current studies was of the order of a few milliseconds and did not affect the execution of voluntary movements in any meaningful way. This was also the case for the previous study in which the effect of 20 Hz entrainment by using tACS was a small reduction in movement velocity.

Similarly, in the current study we investigated whether concurrent rhythmic 12 Hz MNS led to a measurable distraction effect on the performance of an attentionally demanding cognitive task (CPT). Our results demonstrated that concurrent rhythmic 12 Hz MNS did not lead to an increase in either errors or in RT in relation to a no stimulation control condition. Together, these findings are particularly important because they demonstrate that entrainment of movement-related brain oscillations does not materially impair or impede the execution of volitional movements or materially impair cognitive function, as indexed by an attentionally demanding cognitive task. This is a necessary requirement for any potential clinical intervention that is aimed at suppressing tics or the urge-to-tic in TS.

Finally, we investigated the potential of rhythmic peripheral nerve stimulation as the basis for a therapeutic intervention for the suppression of tics and the urge-to-tic in TS. Specifically, we compared, in a case series of 16 patients, epochs of rhythmic mu-band (10 Hz) MNS against epochs of no stimulation, and we quantified any effects of MNS on tic expression through a careful, blind analysis of video recordings. This quantitative analysis clearly demonstrated that both tic frequency and tic intensity were significantly reduced by rhythmic 10 Hz MNS compared with no stimulation, and this analysis corresponded closely with patients' subjective reports in which they all reported that the MNS had reduced their tics, their urge-to-tic, or both. We also recorded, for each patient, a continuous self-estimated record of their urge-to-tic by using a slider device that we had used previously to record self-estimated urge experiences [17]. Despite of the fact that most participants spontaneously reported that they perceived their urge-to-tic to have been substantially reduced, and in many cases completely removed, by MNS, the quantitative analysis of the urge-to-tic intensity scores did not reach conventional levels of statistical significance. Nonetheless, our combined correlation and regression analysis demonstrated that the magnitude of any MNS-induced reduction in tic frequency was a significant predictor of, and positively correlated with, the reduction in the self-rated urge-to-tic experience.

One important observation is that during our video analysis of tics, and from the subjective reports of the patients, it became apparent that the effects of MNS might differ across participants. Importantly, although some patients clearly seem to benefit from MNS only while it was being delivered (see also Video S1), others report that MNS produced longer-lasting effects on their tics and their urge-to-tic, that persisted after the stimulation had ceased. Clearly, further investigation is needed to better understand the effect of rhythmic MNS on the experience of the urge-to-tic in TS. It should be noted that our current research is addressing this by investigating the aftereffects of MNS, including whether multiple sessions of MNS lead to a sustained reduction in tic frequency, tic severity, and the experience of urge-to-tic phenomena.

CONCLUSION

Consistent with our long-term objective to develop a safe and effective non-drug therapy for TS, suitable for administration by the child outside of the clinic, that can contribute to early clinical intervention, we investigated the feasibility of using MNS to entrain brain oscillations linked to the suppression of movement, and as a result influence the initiation of movements, in particular the propensity for unwanted movements (tics) in individuals with TS. We demonstrated that rhythmic mu-band (12 Hz) MNS can be used to entrain mu brain oscillations linked to movement suppression, that rhythmic 12 Hz MNS leads to no material impairment in the initiation of volitional movements or interferes with cognitive function, as indexed by an attentionally demanding task. By contrast, we demonstrated that rhythmic mu-band (10 Hz) MNS was sufficient to significantly reduce both tic frequency and tic intensity in individuals with TS. These findings suggest that this approach has considerable potential for development as a safe and clinically effective therapeutic device that could be utilized outside of the clinical or laboratory environment.

STAR★METHODS

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SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.cub.2020.04.044.

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AUTHOR CONTRIBUTIONS

Conceptualization: B.M.M., G.M.J., and S.R.J.: Methodology: B.M.M., H.P.S., K.D., and S.R.J.; Investigation: B.M.M., H.P.S., E.C., P.M., M.P., and A.R.;

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DECLARATION OF INTEREST

The authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and Algorithms		
MATLAB (multiple versions)	[19]	RRID: SCR_001622
EEGLAB toolbox	[20]	RRID: SCR_007292
Psychophysics toolbox (PTB3)	[21]	RRID: SCR_002881
Other		
Digitimer DS7A HV Current Stimulator	[22]	N/A

RESOURCE AVAILABILITY

Lead Contact

Further information and requests for should be directed to and will be fulfilled by the Lead Contact, Stephen Jackson (Stephen.jackson@nottingham.ac.uk).

Materials Availability

This study did not generate unique reagents

Data and Code Availability

- The EEG datasets reported in Study 1 are available on request. EEG data were analyzed using the MATLAB EEGlab toolbox. MATLAB code is available on OSF (https://osf.io/zw93x/).
- The behavioral data reported in Study 2 are available on OSF (https://osf.io/zw93x/). MATLAB code is available on OSF (https://osf.io/zw93x/).
- The video data reported in Study 3 cannot be made available as in most cases we do not have the agreement of the research participants to share this data beyond the research team. We obtained individual permissions solely to share the three video segments that we have reported in Supplemental Information. Processed data of tic frequencies, tic intensities, and urge intensities are available on OSF (https://osf.io/zw93x/).
- The behavioral data reported in Study 4, and the experiment code are available on OSF (https://osf.io/zw93x/).

METHOD DETAILS

Median nerve stimulation (MNS)

In each study, a Digitimer DS7A HV Current Stimulator was used to deliver square wave electrical pulses via a bar electrode placed over the median nerve of the right wrist. The bar electrode consisted of two stainless steel disks, each with a diameter of 8mm, and separated by 30mm. Following the application of conductive gel, the anode was placed most proximal to the hand and the cathode was placed most proximal to the arm. The intensity of stimulation was set as the minimum intensity that elicited a visible thumb twitch. Stimulation was delivered in pulse trains (for details see individual study descriptions below) and the duration of each single pulse was 200 μs.

Study 1: EEG entrainment effects of MNS

Participants

Twenty healthy adults (7 males, mean age = 24.2, range 18–38 years) participated in the study which was approved by an appropriate University of Nottingham ethical review committee.

Study 1: MNS

Pulse trains of 10 pulses of rhythmic 12Hz MNS were compared to a control condition of 10-pulse trains of arrhythmic MNS. Rhythmic and arrhythmic MNS were delivered within the same 749 ms time window. Rhythmic pulses were delivered every 83ms; whereas in the arrhythmic condition, pulses were delivered during the same time-window as the rhythmic condition but arrhythmically (see Figure 1A). Each participant received a total of 300 pulse trains consisting of 150 rhythmic and 150 arrhythmic stimulation. The order of rhythmic and arrhythmic trains was randomized for each participant. Pulse trains were delivered once every 4 s.

EEG recording

EEG data were recorded from 64 electrodes using a BioSemi Active Two System. Data were recorded with a sampling rate of 1,024 Hz which was later down-sampled to 128 Hz. The impedance of the electrodes was kept under 30 μV for all participants. Reference electrodes were placed on the left and right mastoids. Bipolar vertical and horizontal EOG was also recorded.

Data were low-pass filtered at 45 Hz and high-pass filtered at 1 Hz. Channels showing aberrant behavior were deleted, noisy channels were interpolated. No more than 3 channels were deleted from participants. Automatic Artifact Removal (AAR) was used to remove EOG artifacts using recursive least-squares regression. Time-windows of −1 to 3 s, time-locked to the first pulse of the train were extracted. The entire second before the start of each MNS train was used as baseline. Epochs showing abnormal trends or excessive noise were rejected. The average number of epochs between participants was 125 in the rhythmic condition and 123 in the arrhythmic condition. Independent components were found using Independent Component Analysis (ICA). Artifacts were rejected with the use of Multiple Artifact Rejection Algorithm (MARA) and visual inspection.

ERSP and PLV were divided into window 1 (W1) and window 2 (W2) at frequency 11–13 Hz. W1 corresponds to time 0 to 249, which includes pulses 1–3; and W2 corresponds to time 250 to 832, which includes pulses 4–10. Mu-waves were plotted for every pulse of stimulation from data low-pass filtered at 13 Hz and high-pass filtered at 8Hz.

Study 2: Effects of MNS on volitional action

Participants

40 healthy adults participated in this study (20 females, mean age = 20.75 ± 1.5 years). Participants were randomly divided into two groups, Study 2A (14 females, mean age = 20.81 ± 1.44 years, mean starting intensity of MNS pulses was 11.62 mA ± 4.18): participants completed a version of the task in which the rhythmic and arrhythmic pulses were delivered in blocks using an ABBA design, the order of which was counterbalanced across participants. Study 2B (6 females, mean age = 20.67 ± 1.56 years, mean starting intensity of MNS pulses was 9.75 mA ± 3.68): participants completed a version of the task in which the rhythmic and arrhythmic pulse trains were presented randomly with equal probability.

MNS

Participants completed 300 trials in each study, 150 trials were accompanied by rhythmic 12 Hz MNS trains and 150 trials by arrhythmic trains. Each pulse train consisted of 8 MNS pulses of with a pulse width of 200 μs. The minimum interval between pulses in the arrhythmic condition was 10ms.

Behavioral task

Participants completed a choice-RT task in which they made speeded manual responses to visual stimuli (blue or yellow circles) presented in the center of a visual display. Manual responses were made using the index and middle fingers of their right hand. Each response (i.e., index finger and middle finger) received the same amount of rhythmic and arrhythmic trains. Once MNS threshold had been established for each participant, and they had practiced the behavioral task (10 trials without stimulation and 10 trials with stimulation), they completed 4 blocks of 75 trials. For Study 2A each block resulted in a change in stimulation (i.e., rhythmic or arrhythmic). On each trial a fixation cross appeared in the center of the display for 550 ms. After a 300 ms delay, the MNS pulse train (of 583 ms duration) commences. 250 ms after the onset of the MNS pulse train (corresponding to the initial 3 MNS pulses), a blue or yellow target appears and participants respond by releasing either the left or right response key. The inter-trial interval is 4 s.

Study 3: Effects of Rhythmic MNS on the occurrence of tics in Tourette syndrome

Participants

19 individuals with TS participated (11 males, mean age = 21 years, range 12–51 years). All had a confirmed clinical diagnosis of TS. All participants (or a parent) gave informed consent and the study was approved by a University of Nottingham ethical review committee. Participants with comorbidities or taking medication were not excluded. A criterion for recruitment was that participants typically experienced very frequent tics, as defined as at least one tic every minute. Three of the youngest participants (aged 12–14 years) found the stimulation uncomfortable and asked to withdraw from the study. We therefore tested 16 participants (9 males, mean age = 22 years, range = 14–51 years). Details of these patients are provided in Table S1 in the supplementary Information.

MNS

MNS was delivered to the right wrist in one-minute epochs randomly interleaved with one-minute epochs of no stimulation. During rhythmic stimulation, 1-min MNS pulse trains were delivered at 10 Hz resulting in a total of 600 pulses in each pulse train. Participants completed 6 epochs of 10 Hz MNS and 6 epochs of no stimulation. Video of the participants' faces and their upper bodies was recorded throughout for offline analysis of tics. Continuous recording of participants' self-estimated urge-to-tic was accomplished using a slider device that participants operated using their left hand (see [17] for details).

Video analysis

Motor and vocal tics were counted, and their timing recorded. Each tic was scored for its intensity based upon the YGTSS scale. Minimal tics, were tics that are usually not noticed as they involve subtle movements of muscles, scored 1; mild tics, were tics that are usually not noticed but are more forceful than minimal tics, scored 2; moderate tics, were tics that are not outside the range of normal expression, scored 3; marked tics, were tics that are on an exaggerated character, scored 4; and severe tics, scored 5. Tic counting and scoring was undertaken independently by a very experienced researcher who were each blind to the order of conditions and did not know whether the participant was receiving stimulation or not. For reliability, tic counting and tic scoring was carried out for 12 of the 16 participants by a second additional experienced researcher who was also blind to the order of conditions. The ratings of both researchers were in excellent agreement (> 80%). Finally, to ensure that any reduction in tic frequency or tic intensity was not due to any distraction caused changing from one stimulation condition to another, we restricted our video analysis to the final 40 s period of each 60 s epoch. It is important to note that this cautionary procedure did not change the effects observed.

Study 4: Effects of MNS on attention

Participants

20 healthy adults (10 females, mean age = 19.9 years, range = 18–21 years) participated. All participants gave informed consent and the study was approved by a University of Nottingham ethical review committee.

Design and procedure

Thirteen letters of the English alphabet were selected at random to be the set of target letters and the remaining 13 letters were assigned to be the set of non-target letters. Target and non-target letter sets were selected at random for each participant. Trials consisted of a single capital letter (1 cm) appearing in the center of the screen for 250 ms. 70% of trials were Target trials and 30% non-target trials. The participant's task was to execute a manual keypress as fast as possible whenever they saw any letter from the target set but withhold their response to any non-targets. Trials were separated by an interval of 500 ms, 750 ms or 1,000 ms from the time a response was made. If no response was made the next trial appeared after 1 s. Following a period of practice on the task, participants completed a total of 8 blocks, each block containing 72 trials. Importantly, for each block, two non-target letters were selected at random from the set of 13 non-target letters, and these two letters comprised the non-targets for that particular block. Participants were informed of these two non-target letters ahead of each block. Non-target letters could be repeated between blocks, but a non-target letter was never repeated consecutively between blocks. In 50% of blocks participants received continuous MNS while in the other 50% they received no stimulation. The order of the blocks was determined using an ABBAABBA design that was counterbalanced across participants.

MNS

During stimulation blocks, rhythmic 12Hz MNS was delivered throughout the block.

QUANTIFICATION AND STATISTICAL ANALYSIS

All statistical analyses were performed with MATLAB.

Given that the data met the assumptions of normality necessary for parametric statistics, the analyses were performed using parametric tests. In all four studies, statistical analyses were performed using one-tailed paired-samples t tests. In study 1, analyses were extended by correcting for multiple comparisons using the False Discovery Rate (FDR) [23]. For correlations, Pearson's correlation was used. Statistical significance was defined by p value below 0.05. The central tendency was defined by the mean and the dispersion measure was defined by standard deviation. Statistical details, including statistical tests used and exact number of participants, can be found in the Results and the Methods details sections, respectively.

Possible initial behavioral effects of MNS (i.e., initial effects before getting used to the stimulation) were avoided by excluding the first 20 s of each condition in study 3; and excluding the first 20 s of each block in study 4. In Study 2 and Study 4, all RT with a bigger or lower than the average plus standard deviation of 2.5 were excluded.

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Supplemental Information

Entraining Movement-Related Brain Oscillations to Suppress Tics in Tourette Syndrome

Barbara Morera Maiquez, Hilmar P. Sigurdsson, Katherine Dyke, Eleri Clarke, Polly McGrath, Matthew Pasche, Anupriya Rajendran, Georgina M. Jackson, and Stephen R. Jackson

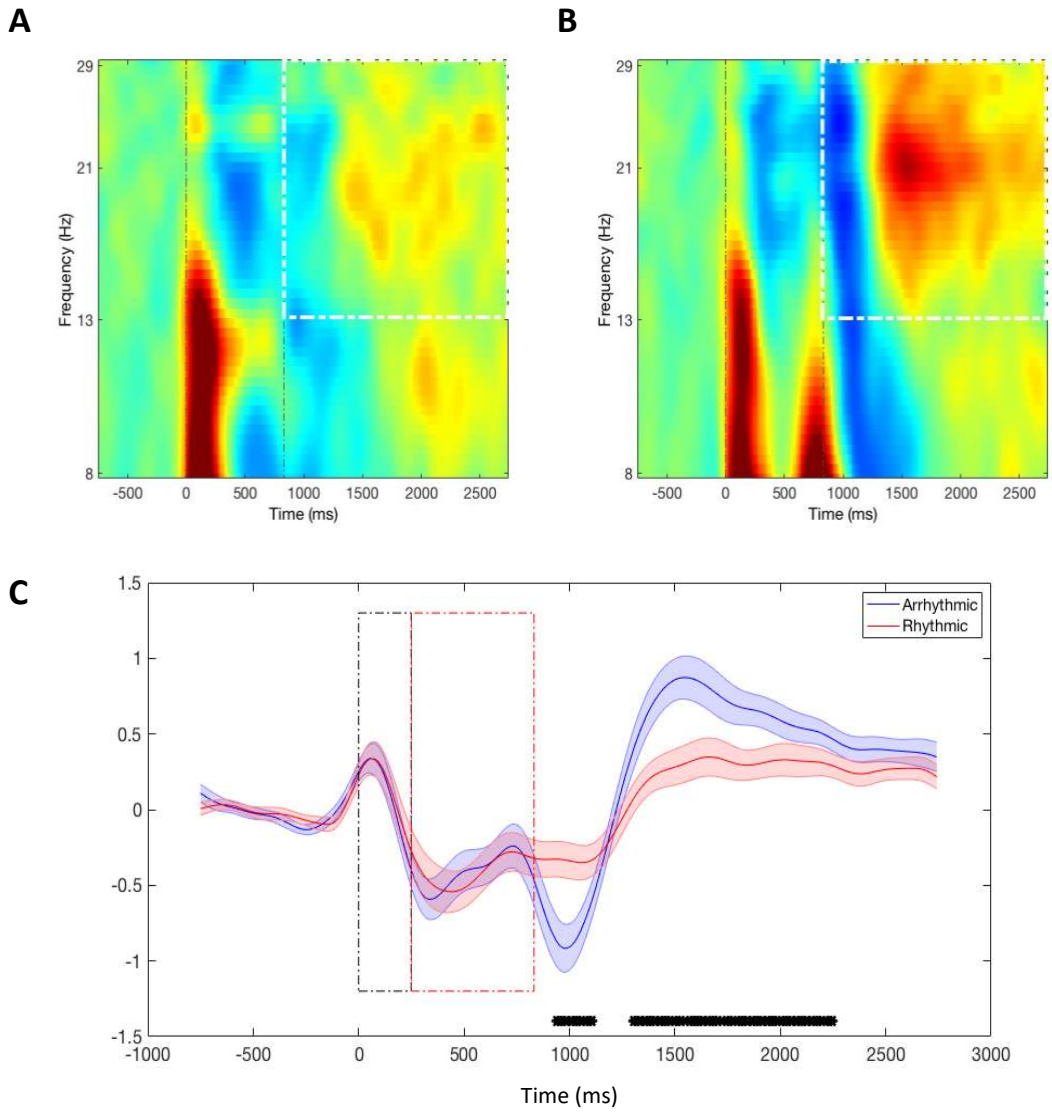

Figure S1: After effects of rhythmic Mu-band stimulation. Related to Figure 1. A. Time frequency analyses of event-related spectral perturbation (ERSP) recorded at electrode C1 for rhythmic 12Hz MNS. **B**. Time frequency analyses of event-related spectral perturbation (ERSP) recorded at electrode C1 for arrhythmic MNS. In each case 0 on the x-axis indicates the onset of the first pulse of the train. The vertical dotted line indicates the end of the train. Importantly, the white rectangle indicates alterations in ERSP within the beta-band (13-30Hz) after stimulation has ceased. **C**. A time-frequency plot for ERSP values for the average frequency of beta-band (13-30 Hz) for the rhythmic 12 Hz MNS (red) and arrhythmic MNS (blue) conditions recorded at electrode C1. Black * symbols indicate individual time points where the ERSP values between conditions was significantly different ($p < .05$ FDR-corrected). The black rectangle indicates W1 and the red rectangle indicates W2. This illustrates that while beta-band ERSP for rhythmic and arrhythmic MNS did not differ from one another during stimulation, there was nonetheless a significant beta-band aftereffect of rhythmic Mu-band stimulation. Specifically, the beta-band desynchronization and subsequent beta-rebound effect were significantly reduced following rhythmic Mu-stimulation.

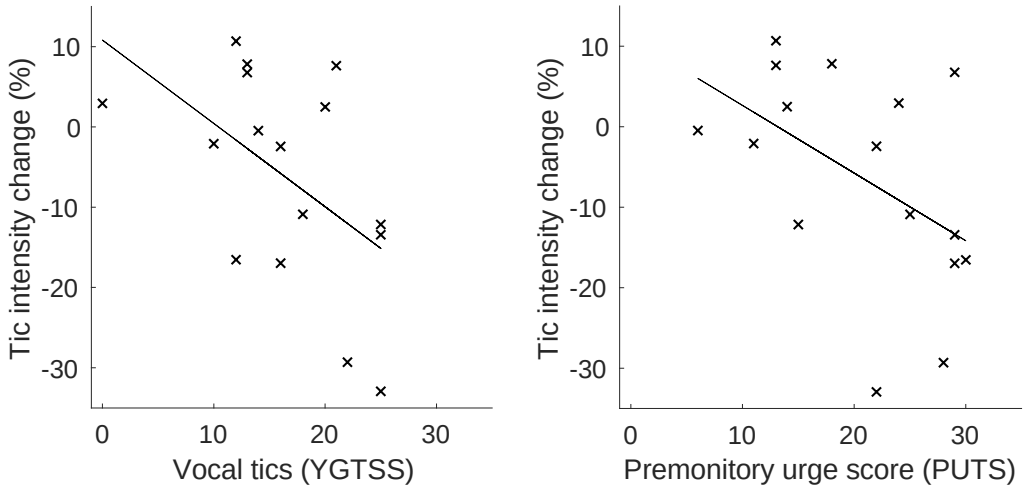

Figure S2: Clinical measures predict change in tic intensity. Related to Figure 5. To investigate which participants might benefit most from rhythmic MNS, we ran separate stepwise multiple regression analyses in which the following variables: Age, Sex, IQ, PUTS, Impairment, Motor, Vocal, and Global YGTSS scores were used to predict the magnitude of the effects of MNS on (a) MNS induced change in tic frequency, (b) MNS induced change in tic intensity, and (c) MNS induced change in urge intensity. The results of these analyses indicated that those individuals who exhibited the most severe clinical symptoms showed the most benefit from the rhythmic MNS stimulation. Specifically, vocal tic (YGTSS) and premonitory urge (PUTS) scores were significant predictors of the MNS induced change in tic intensity (Vocal tics = $t(15) = -2.52$, $p < 0.26$; Puts = $t(15) = -2.34$, $p < 0.36$; $F = 6.19$, Adj-Rsq = 0.41, $p < 0.013$). Scatter plots illustrating this relationship are shown. In each case, negative values on the y-axis indicate a reduction in clinical symptoms while positive values on the x-axis indicates increase in clinical symptoms.

TS ID	Age	Gender	Medication	Comorbidity	WASI	PUTS (/32)	Impairment (/50)	Motor (/25)	Vocal (/25)	Global (/100)
TS062	22.82	M	None	None	131	14	17	18	20	55
TS184	20.25	M	Sulpiride 400mg daily	None	82	29	50	25	25	100
TS196	37.30	F	None	None	120	22	25	25	25	75
TS061	15.00	M	None	None	99	29	0	18	16	34
TS204	32.95	M	Clonidine 50 micrograms	None	130	11	5	17	10	32
TS205	17.46	M	None	None	96	24	0	21	0	21
TS203	16.88	M	None	None	95	15	25	25	25	75
TS207	14.70	M	None	None	97	13	15	14	12	41
TS209	19.66	F	Mirtazapine 30mg	Depression, anxiety, BPD	111	30	25	19	12	56
TS198	25.13	F	Co-codamol 30mg/500mg (6x)	Depression	84	28	50	22	22	94
TS212	15.44	F	None	Ehler Danlos syndrome	110	29	49	19	13	81
TS213	21.39	F	Citalapran 20mg/day	None	109	22	45	22	16	83
TS230	20.16	F	None	None	108	18	40	22	13	75
TS231	19.36	F	None	None	84	6	50	22	14	86
TS233	13.57	M	Clonidine 50microgramsx2/day, Sertraline 25mg per day	None	81	13	35	22	21	78
TS234	51.39	M	Fluoxetine 60mg, Lorazepam 1.5mg	None	90	25	35	18	18	71
Mean	22.72	-	-	-	101.69	20.50	29.13	20.56	16.38	66.06

*WASI: Wechsler's Abbreviated Scale of Intelligence. PUTS: Premonitory Urge for Tics Scale (max score is 32). BPD: Borderline Personality Disorder. *Score taken from YGTSS: Yale Global Tic Severity Scale.*

Table S1. Details of TS group. Related to Figure 5. Relevant details of the TS patients who participated in Study 3 are presented in below. Inspection of this table confirms that most of the TS patients recruited did not present with a relevant co-occurring condition. Specifically, two patients had depression/anxiety conditions and one a physical condition unlikely to be related to TS (Ehler Danlos syndrome). Interestingly, none of the patients presented with co-occurring attention-deficit/hyperactivity disorder (ADHD) or obsessive-compulsive disorder (OCD). The majority of the patients were unmedicated.