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MEDIAN NERVE STIMULATION AS A NON-INVASIVE TREATMENT METHOD FOR TOURETTE SYNDROME

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Keywords: Tourette syndrome, median nerve stimulation, non-invasive neuromodulation, tics, premonitory urge, neural oscillations, CSTC circuits.

Summary

Tourette syndrome (TS) is a chronic neuropsychiatric disorder characterized by motor and vocal tics and is increasingly understood as arising from impaired inhibitory control and dysfunctional sensorimotor integration within cortico-striato-thalamo-cortical (CSTC) networks. Abnormalities in GABAergic inhibition, heightened sensorimotor cortical excitability, and disrupted movement-related neural oscillations are thought to contribute to tic generation and premonitory urges. Current pharmacological and behavioural treatments are limited by incomplete efficacy, side effects, and accessibility, highlighting the need for alternative therapeutic approaches.

Median nerve stimulation (MNS) has recently emerged as a novel, non-invasive neuromodulation strategy for TS. Clinical studies demonstrate that rhythmic MNS produces short-term reductions in tic frequency, tic intensity, and premonitory urge with minimal adverse effects and high patient acceptability. Mechanistic work suggests that MNS may modulate sensorimotor cortical activity, initially proposed to act via entrainment of mu-band oscillations associated with motor inhibition. However, randomized controlled trials indicate that arrhythmic stimulation can yield comparable clinical benefits, suggesting that oscillatory entrainment may be sufficient but not necessary for tic reduction. This implies that MNS likely engages multiple mechanisms, including altered sensory afferent input and broader modulation of sensorimotor network excitability.

Importantly, MNS can be delivered via a wearable, wrist-worn device, enabling home-based use, and including potential applicability in paediatric populations. While short-term efficacy and tolerability are well supported, further longitudinal and mechanistic studies are required to determine optimal stimulation parameters and long-term clinical utility. Overall, MNS represents a promising, accessible, and physiologically grounded intervention for Tourette syndrome.

Introduction

Tourette syndrome (TS) is a chronic neuropsychiatric disorder characterized by the occurrence of vocal and motor tics that persisted for at least a year and are often repetitive, stereotypical, involuntary, and sometimes inappropriate [1-3]. TS is more prevalent in male population and the symptoms in male population tend to be more severe [2, 4]. Tics are often preceded by an urge to tic, called premonitory urge (PU) [3]. Patients describe this urge as an unpleasant sensory feeling of discomfort [3, 14]. Therefore, expressing tics results in a temporary relief [3, 5, 6].

TS is associated with a worse quality of life, with social, occupational and psychological well-being affected [2, 4, 7, 8]. Current treatment options for TS patients represent an area of unmet clinical needs. Medications are effective in only about half of the cases and therefore patients often decide to discontinue medication treatments due to associated side effects such as weight gain and sedation [7, 8]. Behavioural therapies require well-trained therapists, and patients must be able to attend to sessions regularly [7].

In response to the demand of non-pharmacological and non-invasive treatments, many studies have utilized non-invasive brain stimulation methods with an aim to address disrupted cortical excitability to reduce tics [8, 9]. Most of the work has been focusing on repetitive transcranial magnetic stimulation (rTMS) and direct current stimulation (tDCS). Both tDCS and rTMS have been shown to modulate cortical excitability during, and shortly after stimulation. Both tDCS and TMS require application of stimulation to the scalp to be able reach the cortical targets below. For targeting specified brain regions, an MRI might be necessary for current flow modelling and optimizing coil and/or electrode placement. This approach requires extensive resources for both partici-

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pants and researchers [8]. Thus, a smaller, wearable device would appear to be a valuable treatment option [1].

The aim of this study is to review the latest scientific literature on median nerve stimulation as a non-invasive treatment method for Tourette syndrome.

Research results

Neurophysiology. Neuroimaging studies have revealed structural as well as functional anomalies in brain areas such as basal ganglia, thalamus, cortex, and cerebellum. Though precise pathophysiologic mechanism of tic-related disorders remains unclear, such findings suggest that TS is associated with dysfunction within cortical-striatal-thalamic-cortical (CSTC) brain circuits [1-3, 5, 10]. The pathophysiological mechanism of TS has been associated with a lower number of inhibitory GABA-ergic interneurons in striatum and might lead to an increased neural noise within CSTC circuit [11]. As CSTC is involved in the selection of movements, impaired operation of GABA signalling within the striatum, and hyper-excitability of cortical sensorimotor regions might contribute to the occurrence of tics [1, 3]. In particular, it is hypothesized that dysfunction in CSTC results in striatum being overactive thus spontaneous neuronal firing in the striatum, which then releases the thalamus from tonic inhibition. This results in the increased excitability of the sensorimotor cortex and generation of tics [8].

It is known that alpha or mu (8–14 Hz) and beta (15–30 Hz) frequency bands are relevant to the occurrence of tics. When a movement is initiated, these bands become desynchronized. Studies of electroencephalographic (EEG) show that the signals are thought to arise in the supplementary motor area (SMA) ahead of movement and indicate that these signals are abnormal in individuals with TS ahead of tic execution [3].

Clinical evidence. Previous studies that included repetitive transcranial magnetic stimulation (TMS) showed that rhythmic TMS pulses entrained cortical oscillations (increased the amplitude and phase synchronization of oscillations at the frequency of stimulation) and reduced tics in TS. However, such non-invasive methods are unsatisfactory for treatment outside of the hospital or for use with children [14]. Morera Maiquez et al. from the University of Nottingham in 2020 proposed peripheral electrical stimulation of the median nerve (median nerve stimulation, MNS) as a treatment for TS [3]. MNS is thought to work by electrically stimulating the median nerve to entrain neural oscillations [9]. By combining the use of EEG sensors located over the contralateral sensorimotor area and therefore EEG recordings (n=16, mean age 22) with rhythmic mu-band versus arrhythmic 10-pulse trains of MNS to the right wrist (12 Hz), it was demonstrated that only rhythmic trains of MNS resulted in entrainment of 12 Hz oscillations and was sufficient to significantly reduce the occurrence of tics and the urge to tic in individuals with TS (compared to periods of no stimulation, p=0,03). Analyses using Pearson correlation and linear regression techniques revealed a positive correlation (r = 0,75, R2 = 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. Also, the study demonstrated that rhythmic mu stimulation had no significant effect on the performance of an attentionally demanding cognitive tasks (p = 0,65-0,72) and had no perceptible effect on the execution of volitional movements [3]. Though these results might suggest MNS as a promising potential treatment option for TS, the experiment had no control treatment group.

In a randomized, double-blind, controlled, crossover trial (n=32, age 15-64), Iverson et al. used arrhythmic MNS as a control arm. The study showed that 1-minute rhythmic MNS at 10 Hz improved tics (p<0,0001). What is more, rhythmic 12 Hz MNS improved tic frequency, intensity, and urge to tic similarly to arrhythmic 12 Hz MNS which does not entrain cortical EEG (the two methods did not differ significantly, p>0,5). This study provided no evidence that the positive effect on tic suppression by MNS persisted after stimulation ended. In this study, no other variations of MNS were assessed, therefore specificity of median nerve (versus any other peripheral nerve) or stimulation frequency was not addressed. The discomfort during procedures was minimal with discomfort rated by participants as none or minimal on 89% of the visits [7]. 31 out of 32 individuals (aged 15-64) who completed this study agreed to participate in an open-label follow up study that provided an opportunity to have and to use the device at home. The patients were provided with a transcutaneous electrical nerve stimulation (TENS) unit to put on the wrist, and to use as desired for 12 Hz MNS for 4 weeks. 27 participants completed the study, median device use was 1,5 days per week and 50 minutes per day. MNS was found to improve tic frequency and intensity with minimal side effects: mean tic frequency improvement was 1,0 on a 0–5 scale, p < 0,001, tic intensity mean improvement was 0,9, p < 0.001, mean discomfort was 1,2 (mild) according to a 3-point scale. Two participants reported skin irritation at the electrode site. In total, 78% of participants reported that they would continue using the device in the future [1].

In 2022 Morera Maiquez et al. conducted another study (n=121) to evaluate the efficacy of a home-administered rhythmic pulse trains of MNS delivered via a wearable watch-like device. These devices were lightweight, wireless, easy to use and were pre-programmed for each participant. An important notice is that the device was restricted to once-

a-day (10 minutes) usage and the device only operated if it was placed and attached correctly. In this double-blind, sham-controlled trial three groups were formed: 10 Hz active stimulation, 10 Hz sham stimulation at 50% of threshold, and waitlist group consisting of individuals who receive their usual medical treatment. It was shown that after 4-week rhythmic stimulation tic severity had reduced 35% for the active stimulation group and the reduction was statistically significant compared to both sham stimulation, and waitlist control groups (p=0,02). Also, tic frequency reduced substantially (>25%) during active stimulation (compared to sham stimulation, p<0,03). It was noted that while entrainment of alpha-band oscillations during rhythmic alpha-band MNS may be sufficient to produce a substantial reduction in tic frequency in TS, it may not be a necessary condition for reducing tics using MNS [8]. The method of MNS reported in this study (as well as in Morera Maiquez et al. 2020 study) was said to be suitable for use among children and young adult populations. What is more, the treatment using MNS could be delivered by a watch-like device and may be used outside the home [3, 8].

Discussion

Tourette syndrome is increasingly understood as a disorder of dysfunctional sensorimotor integration arising from impaired inhibitory control within CSTC circuits [1, 2, 12]. Disinhibition of the sensorimotor cortex, likely driven by altered inhibitory mechanisms and increased neural noise within striatal circuits, results in abnormal motor selection and the emergence of tics [1, 2, 5]. Against this neurophysiological background, median nerve stimulation (MNS) represents a novel and mechanistically plausible therapeutic approach that operates outside the traditional framework of central neuromodulation [7, 9].

Clinical studies of MNS consistently demonstrate short-term reductions in tic frequency, intensity, and premonitory urge, with minimal adverse effects and high acceptability [1, 7, 8]. Importantly, MNS can be delivered through a wearable, wrist-worn device, making it suitable for use outside of clinical settings and potentially applicable to paediatric populations [1, 8]. These features distinguish MNS from other neuromodulation methods such as rTMS and tDCS, which require specialized equipment and trained personnel [3, 4].

Initial mechanistic work suggested that rhythmic MNS reduces tics by entraining movement-related oscillations within the sensorimotor cortex, thereby restoring inhibitory control over movement execution [12]. This hypothesis is supported by EEG evidence demonstrating frequency-specific modulation of sensorimotor oscillatory activity during stimulation, alongside reductions in tic expression and urge severity [10, 12). Given that sensorimotor oscillations are known to be abnormal in Tourette syndrome and play a key role in motor inhibition, modulation of these rhythms represents a compelling neurophysiological target [10, 11].

However, subsequent randomized controlled trials revealed that arrhythmic MNS can produce comparable clinical improvements despite failing to entrain cortical oscillations, indicating that oscillatory entrainment may be sufficient but not necessary for tic reduction [7, 8]. This finding suggests that MNS likely engages multiple mechanisms, potentially including altered afferent sensory input, modulation of sensorimotor gain, changes in thalamocortical excitability, or broader network-level effects on motor readiness and urge processing [2, 5, 11]. Peripheral nerve stimulation may therefore act as a form of sensory neuromodulation that indirectly stabilizes motor output in Tourette syndrome [2, 4].

Another clinically relevant observation is the tight coupling between reductions in tic frequency and reductions in premonitory urge [1, 7]. This supports the notion that MNS influences not only motor execution but also the sensory phenomena preceding tics, reinforcing models that conceptualize tics as the resolution of abnormal sensory urges rather than purely involuntary motor events [5, 6].

Despite promising findings, several limitations remain. The durability of MNS effects beyond short treatment periods is unknown, and optimal stimulation parameters—including frequency, duration, and dosing schedules—have yet to be established [8, 9]. Additionally, while MNS is well tolerated, long-term adherence and effectiveness in diverse real-world environments require further investigation [1]. Future studies incorporating neurophysiological and neurochemical measures may help clarify the mechanisms through which MNS modulates inhibitory control in Tourette syndrome [2, 11].

In conclusion, median nerve stimulation represents a feasible, non-invasive, and well-tolerated intervention for Tourette syndrome that aligns with contemporary neurophysiological models of tic generation [2, 5, 10-12]. Its potential for wearable, home-based use positions MNS as a promising adjunct or alternative to existing treatments [1, 4, 7, 8]. Further mechanistic and longitudinal studies are warranted to refine stimulation protocols and determine long-term clinical utility [4, 8].

Conclusion

1. As the precise pathophysiological mechanism of TS is still unclear, more research in the field is necessary. However, the sensorimotor cortices are known to be disinhibited in TS patients, and mu-alpha as well as beta frequency oscillations within this region, which are known to desynchronize before and during movement, were found to be abnormal. When

delivered at mu-alpha frequency, rhythmic MNS results in a reduction in tic frequency and intensity as well as the urge-to-tic in TS patients.

2. This is thought to be due to frequency specific entrainment of oscillations within the sensorimotor cortex. Rhythmic MNS has the potential to be developed into a wearable therapeutic device. In addition to a watch-like MNS device, a phone application would provide an opportunity to track patients‘ symptoms and patient-specific fluctuations longitudinally in their naturalistic environments as well as satisfy the need of a non-pharmacological and non-invasive treatment method for individuals with TS. MNS pulses evoke an uncomfortable but not painful sensation to some patients. However, this stimulation does not slow down the initiation of movement and does not affect cognitive performance therefore making it suitable for use outside of clinic (at work, school etc.).

3. Ultimately, these findings indicate that outside-of-clinic-administered rhythmic MNS delivered through a wearable wrist-worn device has the potential to be an effective treatment for TS.

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VIDURINIO NERVO STIMULIACIJA KAIP NEINVAZINIS TOURETTE SINDROMO GYDYMO METODAS: LITERATŪROS APŽVALGA

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Raktažodžiai: Tourette sindromas, vidurinio nervo stimuliacija, neinvazinė neuromoduliacija, tikai, įspėjamasis potraukis, neuronų virpesiai, KSTK grandinė.

Santrauka

Šio tyrimo tikslas - apžvelgti naujausią mokslinę literatūrą apie vidurinio nervo stimuliaciją kaip neinvazinį Tourette sindromo gydymo metodą.

Tourette sindromas (TS) yra lėtinis neuropsichiatrinis sutrikimas, kuriam būdingi motoriniai ir vokaliniai tikai. Vis dažniau pripažįstama, kad TS sukelia sutrikusi slopinimo kontrolė ir disfunkcinė sensomotorinė integracija kortiko–striato–talamo–kortikinėje (KSTK) grandinėje. Manoma, kad tikų ir įspėjamųjų potraukių (angl. premonitory urges) susiformavimą lemia GABA-erginės sistemos slopinamosios funkcijos pokyčiai, padidėjęs sensomotorinės žievės jaudrumas bei sutrikę su judesiais susiję neuronų virpesiai. Dabartiniai gydymo metodai pasižymi ribotu veiksmingumu, nepageidaujamu poveikiu ir ribotu prieinamumu, todėl išryškėja alternatyvių gydymo strategijų poreikis.

Vidurinio nervo stimuliacija (VNS) – nauja ir perspektyvi neinvazinė neuromoduliacijos strategija Tourette sindromui gydyti. Klinikiniai tyrimai rodo, kad ritminė VNS trumpam sumažina tikų dažnį, intensyvumą ir įspėjamuosius potraukius, pacientai ją gerai toleruoja, o nepageidaujamas poveikis būna minimalus. Remiantis tyrimais, teigiama, kad VNS gali reguliuoti sensomotorinės žievės aktyvumą. Manoma, jog šis poveikis pasireiškia dėl su judesių slopinimu susijusio miu dažnio neuronų virpesių susivienodinimo (angl. entrainment). Tačiau atsitiktinių imčių kontroliuojami tyrimai rodo, kad aritminė stimuliacija gali suteikti panašią klinikinę naudą, leidžiančią daryti išvadą, jog neuronų virpesių dažnio suvienodinimas gali būti pakankama, bet nebūtina tikų slopinimo sąlyga. Tai leidžia manyti, kad VNS greičiausiai veikia keliais mechanizmais, įskaitant pakitusį aferentinės sensorinės informacijos apdorojimą ir platesnį sensomotorinių tinklų jaudrumo moduliavimą.

Svarbu tai, kad VNS galima namų sąlygomis, naudojant prie riešo tvirtinamą prietaisą. Taip pat neatmetama galimybė metodą pritaikyti vaikų populiacijoje. Nors trumpalaikis veiksmingumas ir gera procedūros tolerancija yra pagrįsti, reikalingi tolesni ilgalaikiai išsamūs tyrimai, siekiant nustatyti optimalius stimuliacijos parametrus ir klinikinę naudą. Apibendrinant, VNS yra perspektyvi, prieinama ir fiziologiškai pagrįsta intervencija Tourette sindromui gydyti.

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