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Original Research

Comprehensive behavioural intervention for tics: a neurophysiological intervention

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Abstract

Background: Gilles de la Tourette Syndrome (GTS) is a childhood-onset neuropsychiatric disorder characterised by motor and vocal tics. While Comprehensive Behavioural Intervention for Tics (CBIT) is an effective, non-pharmacological treatment for patients with GTS, the underlying neurophysiological basis of this intervention has not been investigated. **Methods**: To investigate the clinical effectiveness of CBIT in reducing tic severity in young people with GTS and explore neurophysiological mechanisms associated with clinical change. **Results**: There was a significant overall improvement in tic severity of large effect size. The Cortical Silent Period (CSP) to motor evoked potential (MEP) ratio (CSP/MEP ratio) increased after the intervention with a small effect size. Other neurophysiological measures of inhibition were not significantly related to the change in tic severity. **Conclusions**: Alongside significant clinical improvements, these results suggest a role for motor cortical Gamma-aminobutyric acid (GABA)-ergic inhibitory circuitry in the neurophysiological changes underlying CBIT treatment. These findings need to be replicated in larger studies using control samples.

Keywords: Comprehensive Behavioural Intervention for Tics (CBIT); Neurophysiology; Transcranial magnetic stimulation; Tourette Syndrome

1. Introduction

Gilles de la Tourette Syndrome (GTS), is a childhood-onset neuropsychiatric disorder, characterised by the presence of multiple motor and one or more vocal tics that persist for more than one year [1]. Once thought to be a rare disorder, the prevalence of GTS is now understood to be approximately 1% in the general population [2]. GTS is associated with social, emotional and academic problems, including poor social skills, low self-esteem, mood and anxiety disorders, and underperformance in school environments [3–5].

While pharmacotherapy, using alpha-2 adrenergic agonists and neuroleptics, remains the mainstay of treatment, these are often associated with notable side effects in children and are not uniformly effective for all patients [6]. Of the other approaches available to control tics, Comprehensive Behavioural Intervention for Tics (CBIT), which incorporates habit reversal training, relaxation training and function-based interventions, is significantly more effective than psychoeducation and supportive therapy in a randomised controlled trial where 87% of participants reported sustained tic improvements six months post-intervention [7]. Multiple practice guidelines now include CBIT as a first-line treatment [8–12].

While the specific underlying pathophysiology of GTS remains unknown, it is accepted that dysfunction of the cortico-striatal-thalamo-cortical (CSTC) pathway is involved in the pathogenesis of GTS [5,13]. Involuntary movements, including tics, have been hypothesised to result from reduced cortical inhibition of unwanted motor patterns originating from the basal ganglia [14,15]. Premonitory urges could result from deficient sensory gating, which prompts the performance of tics, and results in aberrant habits [15–17]. Cortical inhibition is influenced by n-methyl-d-aspartate (NMDA) receptors [18,19] as well as GABAergic interneurons producing inhibitory postsynaptic potentials on pyramidal neurons in the cortex [20–22]. Clinically, reduced motor cortical inhibition may result in reduced capacity to consciously suppress motor movement, as observed in GTS. Evidence for the existence of an imbalance between excitatory and inhibitory pathways is supported by post-mortem studies demonstrating a decreased number of parvalbulmin-positive GABAergic interneurons in the striatum and an increased number in the globus pallidus in GTS [22–24]. Furthermore, cortical expression of Gamma amino-butyric acid (GABA) in motor areas in GTS is abnormal [25].

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In humans, the potency of cortical inhibition can be investigated using transcranial magnetic stimulation (TMS). Short interval intracortical inhibition (SICI) and the cortical silent period (CSP), measures of motor cortical inhibition, are mediated by $GABA_A$ receptors and $GABA_B$ receptors, respectively [26]. Reduced SICI and a shortened CSP have been demonstrated in GTS patients [27,28]. CSP refers to the excitation of inhibitory interneurons acting upon pyramidal cells to decrease corticospinal neuronal firing, preventing excessive/repeated neuronal firing. Inhibition occurs immediately after initial stimulation of the motor cortex and is indexed by a period of silence in the background EMG of an activated muscle. Therefore, significantly reduced CSP duration might be an index for the reduced neurophysiological inhibitory mechanisms proposed to be responsible for 'breaking' cycles of repetitious tics [29].

Afferent inhibition of cortical excitability can also be assessed with TMS. Typically, homotopic sensory inputs lead to a rapid reduction in motor cortex excitability. The immediate inhibition is referred to as the short-latency afferent inhibition (SAI), whereas long-latency afferent inhibition (LAI), a consistent longer-term inhibition, is measured at $>$100 ms post-stimulus. In GTS patients both SAI and LAI are reduced compared to control groups [30,31]. Since M1 receives input from the sensory cortex, this may reflect decreased access of sensory input to motor cortex, and therefore increased excitability of the motor cortex [27]. Reductions in GTS parameters are thought to manifest as reduced suppression of sensory influences and tics [30].

A proposed behavioural model of the presence of GTS symptoms is that repeated performance of tics to reduce or eliminate "premonitory urges" causes a long-term persistence of (and possible increase in) the severity of both urges and tics. Current research suggests that in over 90% of patients with GTS, the premonitory urge, usually described as "an itch" or "build-up of pressure", is only relieved by performing the motor or phonic tic. In 2005, Singer linked these preceding somatosensory urges with observable instances of neural excitation, accompanied by decreased cholinergic and GABA-mediated inhibition in the frontal cortices [5,29].

An explanation for the effectiveness of Habit Reversal Training (HRT), a core element of CBIT, is that the implementation of competing responses will interrupt this urge-to-tic cycle and reduce tics [32,33]. In addition, promoting habituation to premonitory urges by using a competing response may eventually reduce the presence of urges, which discontinues the reinforcement circle and improves symptoms [32,33]. It has also been suggested that frontal compensatory responses could be involved in the underlying mechanism of HRT in reducing tic severity [34]. It is possible that behavioural therapy could be associated with similar neuroplastic changes, which could be reflected in improvements in measures of cortical inhibition. However, we do not yet understand the neurophysiological basis of HRT and CBIT; further research is needed to confirm changes in neural circuits that may occur.

This study, the first of its type to the authors' knowledge, aimed to investigate the clinical and neurophysiological mechanisms of action of CBIT through examination of tic severity and sensorimotor and motor inhibition before and after intervention. It was hypothesised that HRT delivered in CBIT would reduce tic symptoms while concurrently enhancing CSP, SAI, and LAI as neurophysiological indicators of tic suppression.

2. Subjects and methods

Participants had a diagnosis of GTS as per diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV) and had moderate tics or worse at the time of study according to the Yale Global Tic Severity Scale (YGTSS). Participants volunteered to be involved in the study through the Tourette Syndrome Association of Australia, related conferences, and referrals. Sample size was determined based upon the expectation of large effect sizes [35], and also in recognition of the complexity and novelty of the research design. All participants who completed the study were right-handed. Exclusion criteria included a primary psychiatric diagnosis apart from Chronic Tic Disorder, or unacceptable risk factors for TMS-induced seizure (claustrophobia, seizure, stroke, previous head, or brain injury, implanted cranial devices, epilepsy, or drug abuse). Participants receiving psychotropic medications to manage tics were included in the study providing that their current dose had been stable for the previous six weeks and there were no planned medication changes to occur during the study.

Of the 24 participants interested in the study, 17 ultimately completed all phases (71% completion rate). Of the five non-completers, two participants moved from the area before completing the study and five were not available for post-CBIT neurophysiological assessment within the required time frames.

2.2 CBIT intervention

A clinical psychologist from the community administered the CBIT intervention as per the provided therapist guide, "Managing Tourette Syndrome: A Behavioural Intervention for Children and Adults" [36] and had access to a clinical psychologist skilled in the use of CBIT for peer consultation. Psychologists also completed a session-by-session log to allow monitoring of intervention fidelity, and all sessions were ultimately conducted with 84% or greater fidelity to the manualised intervention. Parents of the participant were given a companion parent workbook to use simultaneously with the intervention and were also contacted periodically to monitor the progress of intervention's progress.

In the CBIT intervention, the patient's tics are initially identified and ranked in a tic hierarchy, which sets out the order that tics are addressed in therapy. In the following sessions, awareness training and competing response training are put into practice for each tic, and patients are encouraged to use competing responses outside of sessions [7]. For the functional intervention, situations that influence tic severity are identified and then individualised behavioural strategies are implemented to reduce the impact of these factors. Parents are also instructed on managing their responses to tics and preventing tics from influencing family life. The therapist manual outlines eight sessions to be completed, with the option of two booster sessions. All participants completed a course of CBIT as determined by their clinician, with a mean of 8.6 sessions (Standard Deviation (SD): 1.6, range 5–10): Several participants did not undertake booster sessions and one was deemed to have completed the program after five longer appointments.

2.3 Clinical outcome measures

Demographic and GTS related information including the severity of tics, and other comorbidities and psychiatric/medical diagnoses, family history of GTS and related symptoms were ascertained using the brief version of the National Hospital Interview Schedule (NHIS) for the assessment of Gilles de la Tourette Syndrome [37] and the Yale Global Tic Severity Rating Scale (YGTSS).

The YGTSS is a clinician-rated instrument that assesses the nature of motor and vocal tics present in the past week across the following dimensions: number, frequency, intensity, complexity, and interference (scale of 0–5 each) [38]. Scores are added to give separate motor and vocal tic scores (range 0–25 each), which are then summed to give a combined tic severity score (range 0–50). A separate impairment rating is completed on tic-related disability with the overall impairment rating anchored by 0 (nil impairment) and 50 (severe impairment) [39]. The clinician delivering CBIT was given a pre- and post-intervention YGTSS to complete before and after delivering the intervention.

The Parent Tic Questionnaire (PTQ) is a parent-reported measure that assesses the presence, frequency, and intensity of tics in children [40]. Each of the 28 motor and vocal tics is marked as either present or absent in the past week, and a rating of the frequency and intensity is given for tics present. Psychometric data for the PTQ demonstrate internal consistency ($\alpha = 0.90$), excellent test-retest reliability over 1 and 2 weeks (ICC = 0.71 to 0.89), and acceptable concurrent validity when compared to the YGTSS subscale [40].

2.3 TMS/EMG

2.3.1 TMS/EMG testing

The protocol and settings used were based on past TMS studies investigating primary motor cortex (M1) neurophysiology in GTS [41,42]. Transcranial magnetic stimulation (TMS) is a non-invasive technique whereby an electric current applied to a 'figure-of-eight' stimulating coil generates a temporary high-intensity magnetic field at the focal point, which passes through the skull. Based on the principle of electromagnetic induction, neural pathways in the underlying cortex of the magnetic field are stimulated. When placed above the motor cortex, it is possible to induce a focal muscle twitch, or motor-evoked potential (MEP) [43] measured using the electromyogram (EMG) recorded from the target muscle. TMS studies of paediatric populations are not rare and it the literature suggests that there is no increased risk or reduced tolerance in that population [44].

2.3.2 TMS methods

Adhesive EMG electrodes (Medi-trace, 2 cm interelectrode distance) were affixed to the first dorsal interosseous (FDI) muscle of the participant's dominant hand, as established by the Edinburgh Handedness Questionnaire [45]. EMG was amplified (1k $\times$) and bandpass filtered (20–500 Hz). TMS was applied over the M1 hotspot for FDI on the contralateral hemisphere using a Magstim 200 stimulator (Magstim Company Limited, UK) and focal figure-of-eight stimulating coil (outer coil diameter 90 mm). In this position, active threshold (AMT) was assessed with the FDI muscle activated at 20% of the participant's maximal voluntary contraction (MVC) as measured by EMG, and also at rest (resting motor threshold; RMT).

2.3.3 Motor threshold measurements

RMT was assessed with the patient completely relaxed. It was defined as the lowest intensity TMS pulse that produced a motor evoked potential (MEP) of 50 μV peak-to-peak amplitude in three out of five consecutive stimuli upon the EMG [46]. AMT was defined as the lowest TMS intensity that evoked a motor evoked potential (MEP) of 200 μV peak-to-peak amplitude, in three out of five consecutive stimuli [46]. All MEP paradigms used a randomly jittered interstimulus interval of 4–6 seconds interval during the initial test. MEPs were recorded using LabChart^{TM} 7.2 software (ADInstruments Inc., VIC, Australia) via an analogue-digital interface (PowerLab 8/30, ADInstruments Inc., VIC, Australia) at a sample rate of 4 kHz.

2.3.4 Afferent inhibition

Peripheral cutaneous electrical stimulation was applied to the lateral aspect of the second digit via a Digitimer constant-current stimulator (DS7A; Digitimer; Hertfordshire; UK) which delivered single pulses with a duration of 200 μs. Electrical stimulation was applied at 200% of perceptual threshold [47]. SAI and LAI were measured by conditioning the MEP with a preceding afferent electrical stimulus at either 20 ms or 200 ms, respectively, before a single TMS pulse at 120% RMT. Single TMS pulses were delivered randomly in a block of 66 trials with 22 SAI, LAI and control trials (no peripheral conditioning stimulus) randomly distributed throughout.

2.3.5 Cortical silent period

The cortical silent period (CSP) is a period of EMG silence following an MEP (elicited from a single TMS pulse) that occurs during voluntary muscle activation. CSP was assessed as subjects maintained an isometric contraction of FDI at 20% of MVC. It was defined as the time from stimulus onset (0 ms) to the time point after the MEP where the EMG amplitude first re-exceeded the average pre-stimulus EMG. Twenty-two stimulus pulses administered at 140% AMT were averaged to produce a mean CSP.

In this study, we also used the CSP/MEP ratio. It is well established that there is a strong correlation between CSP duration and the MEP area, or amplitude [48]. If repeated measures of CSP are being made there is a significant chance that any effects of an independent variable will be lost if the evoked MEP is not precisely the same between sessions. Given the likelihood that AMT estimation between sessions and also coil placement between sessions is likely not to be perfectly replicated (more so the case with a young GTS population for whom lengthy, very accurate estimations of AMT are not possible) there is a significant likelihood that the length of the raw CSP will be more a function of the MEP amplitude than the independent variable. The most well-established method of accounting for MEP/CSP covariance is by expressing CSP as a ratio of the MEP amplitude [49,50]. This approach has also been used in a comparable GTS study [27].

2.4 Neurophysiological data analysis

All EMG trial sets were cleaned prior to analysis. Traces showing muscle activation during the afferent-inhibition trials were discarded [27]. Special attention was paid to the region 5ms prior to the TMS pulse, as this could significantly affect MEP calculations.

3. Statistical analyses

Non-parametric statistical testing was used due to the relatively small sample size and non-normal distribution of some variables. Changes in neurophysiologic measures (CSP/MEP ratio, SAI, and LAI) were explored using the Wilcoxon Signed Ranks test. The Wilcoxon Signed-Rank Test was also applied to ascertain significance of intervention effectiveness based on each clinical parameter. Alpha was set at $p < 0.05$ for all comparisons, following recommendations by Saville [51], who argues for this per-comparison level rather than a family-wise approach when conducting research in novel areas. Effect sizes were also calculated using Cohen's d [52]. It is widely accepted that Cohen's d values $\geq$0.2 denote small effect size, $\geq$0.5 medium effect size and $\geq$0.8 denote large effect size.

4. Results

4.1 Clinical outcomes

Demographic details of the seventeen participants (13 males and 4 females) ranging in age from 8 to 21 years (mean = 11.5, SD = 3.3) are provided in Table 1.

Table 1. Baseline demographics and characteristics of the participants.

Age in years (mean; SD; range)	11.5; 3.3; 8–21
Sex (male; female)	13; 4
Cultural background	15 Australian 1 Chinese 1 Australian Aboriginal
On Medication (no. of participants)	8[1]
Other Diagnoses (no. of participants)	13
OCD	7
ADHD	9
Mean AMT (SD; range)	
Before CBIT	41; 10; 27–75
After CBIT	40; 10; 28–57
Mean RMT (SD; range)	
Before CBIT	62; 13; 43–90
After CBIT	63; 12; 42–85

*Note: AMT, Active Motor Threshold; RMT, Resting Motor Threshold.

1. Two participants took Atomoxetine only; two took Clonidine only; one took Clonidine and Tetrabenazine; one took Fluvoxamine only; one took Risperidone only, and one took Risperidone and Clomipramine.

The correlation between clinician YGTSS and parent PTQ ratings at pre-test was $r = 0.71$, $p = 0.007$ and at post-test was $r = 0.82$, $p = 0.001$; suggesting consistency amongst ratings made.

The YGTSS total tic score was significantly reduced after the CBIT treatment protocol ($z = –2.56$; $p = 0.011$, Cohen's $d = 0.95$). This result was supported by clinicians rating 80% of participants as having a >10% reduction in tic frequency from pre- to post-intervention, and the same percentage as having a > 10% reduction in tic intensity.

PTQ total tic severity score was found to be significantly lower after CBIT ($z = –2.34$; $p = 0.019$; Cohen's $d = 0.71$). Similar results were observed in total motor tic severity ratings ($z = –2.48$; $p = 0.013$; Cohen's $d = 0.79$) yet interestingly, not in total vocal tic severity, which was not found to be statistically significant ($z = –1.59$; $p > 0.05$; Cohen's $d = 0.49$).

4.2 Neurophysiological outcomes

Contrary to our hypothesis, CSP was not found to be significantly increased after the intervention, ($z = –1.41$; $p > 0.05$; Cohen's d effect size = 0.48). However, a more

robust transformation of this measure, the CSP/MEP ratio [48], was found to be marginally increased after CBIT (z = –1.98; p = 0.048; Cohen's d effect size = 0.38).

Neither SAI nor LAI were found to be significantly changed after the intervention ($p > 0.05$ and Cohen's d = –0.02 and 0.30, respectively). See Table 2.

Table 2. Neurophysiological parameter values pre- and post-CBIT.

Parameter	Pre-CBIT [Mean (SD)]	Post-CBIT [Mean (SD)]
CSP	112.1 (57.8)	89.1 (34.6)
CSP/MEP	53.3 (28.5)	64.7 (31.4)*
LAI	0.8 (0.3)	0.8 (0.4)
SAI	1.0 (0.8)	0.8 (0.4)

* $p \leq 0.05$.

Note: CSP, Cortical Silent Period; CSP/MEP, Cortical Silent Period/Motor Evoked Potential ratio; LAI, long-latency afferent inhibition; SAI, short-latency afferent inhibition.

Given it was hypothesised that the degree of clinical improvement (identified by the YGTSS and PTQ instruments) would be associated with corresponding changes in neurophysiological outcomes, an alternative way to analyse these data is via correlations between change scores (i.e., post data minus pre-data) across the key clinical and neurophysiological measures. No significant associations were observed, aside from that between YGTSS and PTQ change scores. While not statistically significant, we would observe that the largest correlation coefficient of r = 0.41 was for the association between PTQ and CSP/MEP change scores, suggesting a moderate-sized positive association between change to the CSP/MEP ratio and change to PTQ scores pre- to post-intervention. See Table 3.

Table 3. Correlations between clinical outcomes and neurophysiological measure change scores.

	YGTSS change score	PTQ change score
PTQ change score	0.80 **	–
CSP length change score	–0.37	–0.36
CSP/MEP change score	0.38	0.41
LAI change score	0.31	0.40
SAI change score	–0.33	–0.26

** $p \leq 0.01$.

Note: All change scores were calculated by subtracting post scores from pre scores. YGTSS, Yale Global Tic Severity Scale total score; PTQ, Parent Tic Questionnaire; CSP, Cortical Silent Period; CSP/MEP, Cortical Silent Period/Motor Evoked Potential ratio; LAI, long-latency afferent inhibition; SAI, short-latency afferent inhibition.

5. Discussion

This study supports the previous findings of Piacentini *et al.* [7] that CBIT effectively reduces tic severity in young people with GTS. The significant decrease in YGTSS and PTQ total scores indicates that CBIT is effective in reducing tic severity, frequency and intensity when delivered in a community setting using the available therapeutic manuals with relatively minimal supportive peer consultation.

In neurophysiological terms, it is accepted that the CSP is a result of spinal inhibitory mechanisms for up to the first 50 ms, and the later part is from inhibition from the motor cortex [53]. When the motor cortex is stimulated using TMS, inhibitory interneurons that project onto pyramidal cells (likely to be Golgi II cells with long axons) are activated and inhibit activation of corticospinal neurons [54]. The increase in the CSP/MEP after CBIT reflected a small effect (Cohen's d = 0.38) providing initial support for our hypothesis that neurophysiologic measures of cortical inhibition would improve with CBIT. With replication, this finding would support the hypothesis that reducing tic severity via CBIT intervention stems from an improvement in inhibitory interneuronal control in the motor, possibly through the potentiation of GABAergic receptor-mediated inhibitory neurotransmission [26]. The CSP/MEP ratio is an effective indicator of cortical inhibitory capacity [55], and has shown strong test-retest reliability (coefficient of variance <10%) [48]. We note that reciprocal significant effects were not observed with the raw CSP modulation in this study. However, between-subject variation in CSP duration is thought to be high [56] and the typical reason for calculating the ratio of CSP duration/MEP amplitude or CSP duration/MEP area is to reduce intersubject variability [48].

These results are reflective of earlier studies. For example, using functional magnetic resonance imaging (fMRI), Deckersbach *et al.* [57] observed a significant decrease in striatal (putamen) activation following CBIT intervention. They suggested that this may be due to normalization of aberrant cortico-striato-thalamo-cortical associative and motor pathways in individuals with GTS following CBIT. Moreover, increased EEG coherence between sensorimotor areas and the prefrontal and mesial frontal cortex during voluntary tic suppression also suggests that increased frontal cortex activity compensates for abnormal subcortical input to achieve motor inhibition [58]. It has been previously demonstrated that patients with GTS have a significantly reduced SAI and LAI [41]. Afferent inhibition is caused by peripheral sensory input reducing corticospinal excitability, either through directly projecting to the motor cortex, or indirectly via the sensory cortex and then cortico-cortical pathways to the motor cortex [31]. Deficits in afferent inhibition in patients with GTS due to less efficient gating of sensory input is hypothesised to contribute to the experience of premonitory urges, as sensory gating is impaired in GTS. However, no significant change in SAI or

LAI was found in participants after the intervention.

The lack of any effect in LAI or SAI likely reflects the distinct neurophysiologies of inhibition that are expressed in these measures (for review see [59]). Methodological choices might also have contributed to reduced affects in the measures of afferent inhibition, that is, the use of 200% of perceptual threshold [60,61] as an intensity for peripheral conditioning rather than 300% [62] which is also often used, might mean that the measures were too close to floor in the first testing session. However, for now this remains an unanswerable empirical question.

Utilising TMS, we investigated the proposed emergence of neurophysiological changes occurring in conjunction with clinical improvement, thereby evidencing the notion that tic expression is intrinsically linked to inhibitory neuron deficits, and the capacity for neuroplastic change in response to effective behavioural therapy. In particular, the main positive finding of significant CSP/MEP ratio improvement supports cortical inhibitory development as a factor in observed clinical benefits. The results achieved lend preliminary support, however, future studies are necessary to illustrate these concepts comprehensively.

Limitations and future research

A key limitation of this study was the relatively small sample. There are substantial resourcing implications in studies of this type, with clinical intervention and pre- and post-intervention neurophysiological study. However, given the promising results of this study, future studies with an increased sample, and therefore increased power to detect small effects, are indicated. Future studies may also consider incorporating a control group, which would improve the interpretability of shifts in the neurophysiological function of treated GTS patients. Narrowing the age range might also reduce the variability in neurophysiological parameters. A possible source of bias in this study was volunteer bias, as participants volunteered to be involved in the study mainly through the Tourette Syndrome Association of Australia. However, the presence of a relatively wide range of tic severity scores makes it unlikely for this source of bias to have a significant impact on results. Expectations of improvement with the treatment may have caused parents and or clinicians to underestimate tic severity in the post-testing session after the CBIT intervention was completed. Blind rating would have been preferable. However, it is unlikely that the self-report aspect had a substantial effect, as parent-rated PTQ, and clinician-rated YGTSS scores of total tic severity were correlated significantly and with large effect sizes at pre-test ($r = 0.71$ at pre-test and $r = 0.82$ at post-test). Eight of 17 participants were taking psychotropic medication during the study period. Given this was stable in the six weeks before to study commencement and did not change during the study, the clinical and neurophysiological changes observed are unlikely to have arisen due to the effect of medication, including with respect to the GABA system; however, future studies are required to confirm this with sub-group analyses or samples not prescribed medication.

6. Conclusions

This study has yielded data that suggest the CBIT intervention is an effective intervention for managing tics, including when delivered in the community. The small increase in the CSP/MEP ratio following intervention observed in the sample raises the possibility that neurophysiologic changes in cortical inhibition are involved in the underlying mechanism of CBIT in reducing tic severity. While these data may be considered pilot in nature, they point to a methodology for future studies seeking to replicate and extend upon the findings. This study has furthered our understanding of approaches for studying the neurobiological mechanism of HRT, but it also highlights the need for further investigation of other neurophysiologic measures. In addition, it raises questions about the effect of age, gender, medication use and presence of comorbid diagnoses on the delivery of CBIT and the associated clinical improvement. The small sample size of this study did not allow sub-group analysis to explore these factors.

Although the increase in the CSP/MEP ratio suggests that CBIT may enhance cortical inhibition in participants, the mechanisms by which such changes occur remain unknown. Future confirmatory research could investigate structural neuroplastic changes with the CBIT intervention using diffusion tensor imaging (DTI) to measure white matter integrity and/or magnetic resonance spectroscopy to measure changes in GABA profiles.

Abbreviations

GTS, Gilles de la Tourette Syndrome; CBIT, Comprehensive Behavioural Intervention for Tics; PTQ, Parent Tic Questionnaire; YGTSS, Yale Global Tic Severity Scale; CSP, Cortical Silent Period; AI, Afferent Inhibition; TMS, Transcranial Magnetic Stimulation; CSTC, Cortico-Striatal-Thalamo-Cortical; SICI, Short Interval Intracortical Inhibition; SAI, Short-Latency Afferent Inhibition; LAI, Long-Latency Afferent Inhibition; HRT, Habit Reversal Training; YGTSS, Yale Global Tic Severity Scale; MEP, Motor-Evoked Potential; EMG, electromyogram; FDI, First Dorsal Interosseous; AMT, Active Threshold; MVC, Maximal Voluntary Contraction; RMT, Resting Motor Threshold; DTI, Diffusion Tensor Imaging.

Author contributions

VE conceptualized the study and designed it with PFS and RČ. Authors AXP, OT, RL and JL contributed to the data collection and analysis. All authors assisted in the drafting of the manuscript.

Ethics approval and consent to participate

The study was approved by the Human Research Ethics Committee of the University of New South Wales approval HREC 10391. The study was approved by the Human Research Ethics Committees of the two Institutions where the study was conducted. Written informed consent was obtained from the participant or from the parent/guardian if aged below 18 years.

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Conflict of interest

The authors declare no conflict of interest.

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