Transcranial Magnetic Stimulation in Autism Spectrum Disorders: Neuropathological Underpinnings and Clinical Correlations

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Abstract

Despite growing knowledge about autism spectrum disorder (ASD), research findings have not been translated into curative treatment. At present, most therapeutic interventions provide for symptomatic treatment. Outcomes of interventions are judged by subjective endpoints (e.g., behavioral assessments) which alongside the highly heterogeneous nature of ASD account for wide variability in the effectiveness of treatments. Transcranial magnetic stimulation (TMS) is one of the first treatments that targets a putative core pathological feature of autism, specifically the cortical inhibitory imbalance that alters gamma frequency synchronization. Studies show that low frequency TMS over the dorsolateral prefrontal cortex (DLPC) of individuals with ASD decreases the power of gamma activity and increases the difference between gamma responses to target and non-target stimuli. TMS improves executive function skills related to self-monitoring behaviors and the ability to apply corrective actions. These improvements manifest themselves as a reduction of stimulus bound behaviors and diminished sympathetic arousal. Results become more significant with increasing number of sessions and bear synergism when used along with neurofeedback.

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When applied at low frequencies in individuals with ASD, TMS appears to be safe and to improve multiple patient-oriented outcomes. Future studies should be conducted in large populations to establish predictors of outcomes (e.g., genetic profiling), length of persistence of benefits, and utility of booster sessions.

Keywords

transcranial magnetic stimulation; autism spectrum disorder; minicolumns; gamma oscillations; executive functions

Introduction

Autism spectrum disorder (ASD) is a multifactorial disorder, associated with the combined effects of multiple genes and environmental factors. Diagnosis depends on behaviors including difficulty in social engagement and communication along with sensory abnormalities, restricted interests and repetitive behaviors. It is a pervasive and heterogeneous disorder whose symptom expression and natural history varies from patient to patient. Most cases are idiopathic with a specific etiology identified in only 5–10% of cases[1–2]. Gross examination of the brain tends to be normal but research studies point to an abundance of seemingly disparate microscopic findings[3].

John Darby is credited with having performed the first and most comprehensive analysis on the neuropathology of ASD[4]. In his pioneering study, Darby described how known conditions (e.g., tuberous sclerosis) could give rise to an ASD phenotype. Darby went on to conjecture that many organic disorders with varied clinical presentations could be funneled through a singular pathophysiological mechanism[5]. This supposition is similar to an earlier proposal by Bellak who claimed a "final common pathway" or *locus minoris resistentiae* to the nature of schizophrenia[3]. In modern times, the final common pathway for schizophrenia has been reconceptualized as the dopaminergic hypothesis[6]. Data derived from treatment trials and neuroimaging studies have led to the empirical validation of this hypothesis[7]. In common to both Darby and Bellak, Margaret Bauman has emphasized that researchers should "still be hunting for what is similar,…for some core, unifying feature of the brains of children with autism"[8].

In ASD, the presence of heterotopias, increased cellular density at both the grey-white matter junction and the molecular layer, minicolumnar abnormalities (minicolumnopathy), and focal cortical dysplasias are all suggestive of a neuronal migration disorder[9–14]. Indeed, abnormalities of germinal cell division and their subsequent progenitor migration are common in ASD. In a recent series, employing serial whole brain sections, Wegiel et al.[11] reported the presence of these neuropathological markers in 92% of cases. The findings are deemed to be sufficiently frequent commonalities for researchers to propose the use of *in vivo* correlates of a dysplastic process as a way of subtyping or stratifying ASD patients[15].

The excitatory/inhibitory bias of the cerebral cortex depends on the coordinated action of both pyramidal cells and interneurons. Abnormalities of brain development, wherein neurons are prevented from migrating to their proper location within the cerebral cortex

(e.g., focal cortical dysplasias), alter the integrative action of pyramidal cell-interneuron dyads[16.] Postmortem studies reveal that the anatomical compartment that contains the inhibitory circuits of the minicolumns, the peripheral neuropil space, is significantly reduced in ASD[17–18]. It is therefore unsurprising that ASD is associated with inhibitory GABA neurotransmission abnormalities including reduced $GABA_A$ and $GABA_B$ subunit expression[19]. The findings help explain the presence of seizures, sensory abnormalities, and cognitive deficits in ASD[12].

Cell fate specification studies have shown that a variety of interneurons develop at specific laminar locations at different times during neurodevelopment. These cells migrate to the cortical plate during the entire period of corticogenesis using multiple tangential routes in order to reach their final destination[20]. The large variety of interneurons, in terms of their topography, timing of origination, and postsynaptic targeting, necessitates their subtyping whenever researchers assess their role in the pathophysiology of any given disorder.

In ASD, a recent postmortem study immunolabelled interneurons according to their expression of calcium-binding proteins. In this study, the number of parvalbumin+ (PV) interneurons was significantly reduced in all cortical areas examined (BA46, BA47, BA9)[21]. Studies of animal models add significance to these findings as decreased PV expression levels have been correlated to some behavioral deficits that are shared with ASD[22–23]. According to some researchers, downregulation of PV represents one point of convergence that provides a "common link between apparently unrelated ASD-associated synapse structure/function phenotypes"[23].

Parvalbumin-positive GABAergic interneurons are fast-spiking cells that synchronize the activity of pyramidal cells. These cells help generate cortical gamma oscillations (30–80 Hz) that modulate our attention focus, while also playing an important role in those cognitive paradigms of relevance to executive functions[24–25]. Knockout (PV–/–) mice display a reduction in social behaviors, deficits in prepulse inhibition, and abnormalities in auditory phase-locked gamma oscillations[26–27]. It is therefore unsurprising that gamma band abnormalities are associated with the perceptual and cognitive functions that are compromised in ASD[28]. Furthermore, some gamma band deficits are also observed in unaffected first degree-relatives suggesting the hereditability of the findings[28]. The seeming universality of gamma related abnormalities in ASD has therefore been proposed as a potential biomarker for the condition[29–30].

The cortical dysplasia described in ASD can be found in all lobes examined but appear in overabundance within the prefrontal lobes[12]. Stereological analysis of dysplastic foci has revealed the presence of smaller pyramidal cells (suggesting shorter projections or less efficient longer ones) and a concomitant reduction in the total number of interneurons[12]. The varied topography of the neuropathological abnormalities may help explain EEG lateralization findings in ASD that are regionally and functionally specific[31]. The electrophysiological findings may predispose affected individuals to abnormalities in social reasoning[32], dispositional mood (positive and negative affect)[33], risk for depression[34], and verbal abilities[35].

A large number of studies within the medical literature attest to a correlation between the activity of parvalbumin cells, gamma oscillations, and social deficits. Modulation of gamma oscillations, especially over the dorsolateral prefrontal cortex (DLPC), has been associated with improvements in cognitive performance[36], alterations in the excitatory inhibitory balance of the cortex, and normalization of social behavior deficits in animal models of ASD[37]. Similarly, pharmacological interventions that rescue parvalbumin-immunoreactive neurons ameliorate deficits in prepulse inhibition, relieve the reduction in phase-locked gamma oscillations, and ameliorate social behavioral deficits[27].

In humans, transcranial magnetic stimulation (TMS) is a reliable method for modulating gamma band activity. TMS therapy over the DLPC of schizophrenic patients normalizes gamma oscillations as well as cognitive performance[26]. These effects are selective for the gamma bandwidth[38] and are probably mediated by cortical changes that increase the levels of GABA[39]. These considerations led us to study the use of TMS in ASD with the idea of rescuing gamma band abnormalities, and improving both cognitive functions and attendant social behaviors[40,41].

Transcranial Magnetic Stimulation (TMS)

Although the biological effects by which TMS exerts its physiological actions are still being investigated, the physical effects of the technique on tissue can readily be inferred from our knowledge of electromagnetic induction. According to Faraday's law, induction makes reference to an electromagnetic force (or voltage) that is created in a closed circuit due to the influence of a nearby magnetic field. Induction happens when there is relative movement between a conductor and a magnetic field. In the case of TMS, a burst of current passing along a conductor creates a rapidly expanding, and then collapsing, magnetic field. Winding the wire into an insulated coil and increasing the current intensifies the strength of the magnetic field while the shape of the coil allows convergence of the magnetic flux over a specific location. The magnetic field produced induces its effect on anatomical elements wherein membrane bound anatomical elements filled with electrolyte fluids act as the conductors.

In TMS, depending on the circuitry design, the voltage produced by the power supply may be biphasic (sinusoidal) or rectified to a monophasic waveform whose amplitude and polarity may be controlled. The power supply charges a bank of capacitors which can then be discharged using a switch that creates a pathway leading to a coil. These capacitors are passive electronic component that store energy in an electrical field. Capacitors can discharge more rapidly than batteries as the latter have a latency associated with the chemical reaction that provides for the transfer of energy. The rate of the charge/discharge cycle of the capacitor can be selected by the user in order to provide for single or multiple pulses at selected frequencies. The lack of significant resistance offered by the wire and other components in the circuit allows for its rapid charge and discharge in a small fraction of a second. However, rapid rate stimulation is often limited in sustained operations by coil heating. The end result of the TMS circuitry is a large magnetic field of up to several Tesla being produced with a current flow of several kiloamperes.

The skull is largely invisible to magnetic fields. In the case of TMS, the influence of the magnetic field is limited to about 3 cm from the coil with an intensity that falls exponentially with distance. By convention, repetitive TMS of less than 1 Hz is considered low frequency stimulation. Models on long-term potentiation suggest that low frequency TMS is inhibitory while faster stimulation (5 Hz) is excitatory[42]. The difference in threshold may be due to the orientation selectivity of the cerebral cortex to magnetic stimulation[43]. Lower frequencies stimulation may preferentially induce currents along longitudinally oriented elements; that is, along axons rather than across the axons[43]. Accordingly, the position of interneurons and their projections in the minicolumns make them especially susceptible to low frequency TMS stimulation. Indeed, Mountcastle described the arrangement of interneurons in minicolumns as a strong vertical flow of inhibition, while other researchers have coined the more descriptive appellation of a shower curtain of inhibition[44,45].

Topographical analysis of minicolumnar abnormalities in ASD have shown salient deficits within the prefrontal lobe46,47. Since TMS is capable of affecting brain regions interconnected to the stimulated site, we decided on targeting the DLPC48,49. For the purpose of our studies it was thought that modulating the output of the DLPC would procreate a beneficial cascade through many of its interconnected brain regions. The high density of reciprocal cortico-cortical and cortico-subcortical connections enables the DLPC to assume an organizing role for those behaviors that allow an individual to respond to stimuli by matching previous experiences to existing environmental circumstances50. Researchers believe that the metacognitive functions of the DLPC permits an individual to navigate the challenges of environmental exigencies with context appropriate and goal-oriented behavior that denote planning, self-regulation, and self-monitoring51. Many of these supervisory mental processes appear to be dysfunctional in ASD, leaving affected individuals prone to stimulus bound behaviors52.

Gamma Oscillations

Electrophysiological monitoring of the brain reveals the presence of oscillatory patterns of activity measured as voltage fluctuations. The amount of information carried by these oscillations depends on both frequency and bandwidth. For brain oscillations, the highest frequency and largest bandwidth correspond to gamma oscillations (30–80 Hz). This frequency is directly associated with entrainment of local networks and the binding of perceptual features (i.e., seeing organized structures as wholes rather than as their individual constituent parts). Gamma band activity can be analyzed within specific time windows that denote event related rhythmic responses that persist after stimulus onset. Responses in gamma band activity are classified into either evoked or induced, depending on latency after stimulus onset. It is believed that the phase-locked initial evoked activity (latency of around 100 ms after stimulus) represents early sensory processing and the binding of perceptual information within the same cortical field[53]. The induced gamma band activity (latency of around 250 ms) is not phase-locked to the stimulus. The induced component is thought to represent the binding of feedforward and feedback processing among networks of cortical regions[53]. For a review on gamma oscillations and ASD see Casanova et al.[53–54] and Rippon[55]

Results of electrophysiological research have shown that gamma activity is an indicator of the co-activation of cortical cells involved in visual processing[56]. The onset of a visual stimulus gives rise to a burst of gamma activity over occipital sites. When more complex tasks are performed, discrete bursts of activity are observed in additional brain regions thought to be involved in that undertaking[57]. Kanizsa illusory figures have been shown to produce gamma oscillations during visual cognitive tasks[58]. EEG recordings, while trying to identify the presence or absence of an illusory figure, have shown an overall increase in gamma activity in ASD as compared to controls[57]. The authors of the latter study interpreted the findings as consistent with decreased signal to noise ratio due to reduced inhibitory processing. Weak signals boosted by the presence of white noise gives rise to stochastic resonance, a phenomenon capable of explaining both the hypo- and hyper-sensitivities observed in ASD[54].

In the first study of TMS reported in ASD (n = 8 children with ASD, n = 5 wait-list participants, n = 13 age-matched controls, ADOS and ADI-R diagnosed) our group measured the power of the EEG gamma band during a Kanizsa visual attention task[40] (a summary of published TMS studies in ASD is provided in Table1). TMS was delivered at 0.5 Hz, 2 times per week, for 3 weeks. At baseline, the power of the gamma activity in our control group increased during the presentation of target-stimuli as compared to non-target stimuli. By contrast, the power of the gamma oscillations was higher and had a shorter latency in our ASD group. After six TMS sessions the power of gamma activity in our ASD group decreased over the frontal and parietal locations (on the same side of the stimulation), and there was an increased difference between gamma responses to target and non-target stimuli. These findings were reproduced in later studies using different patient populations and number of sessions[51–53]. The latter studies also noted topographical differences in evoked gamma power between frontal and parietal regions (frontal>parietal) to all stimuli which was lacking in the ASD group. The findings suggest that anatomical and physiological measures of anatomical regions taken in isolation may be of little significance in helping us to understand the pathophysiology of ASD; rather, this complex condition involves multiple local abnormalities along with downstream effects on interconnected brain regions.

Our group has also examined the effects of bilateral DLPC TMS in both event-related potential (ERP) and gamma phase coherence. One study consisted of 18 sessions with 54 participants using two groups of children with ASD (TMS and wait list as controls, 27 individuals per group). Results indicated a significant posttreatment increase in latency and reduction in amplitude of frontal and fronto-central N100, N200 and P3a ERP components to non-targets in the treatment group as compared to the wait-list control group[53]. In another study, 18 sessions of bilateral DLPC TMS was used to examine EEG gamma phase coherence between frontal and parietal sites[59] in 32 participants (TMS and wait list controls, 16 per group). TMS had its most significant effect on induced gamma in the frontal region of our active treatment group as suggested by increased gamma phase coherence in response to target stimuli. In addition, TMS also increased induced gamma phase coherence between ispi- and contra-lateral frontal and parietal regions.

Similar to our previously reported gamma findings (*vide supra*), ERP studies during a visual novelty processing tasks have indicated that ASD individuals lack stimulus discrimination between target and non-target stimuli as compared to controls. This is manifested as significantly prolonged and augmented ERP components to irrelevant distracters over frontal and parietal recording sites[40,55]. The reported changes are especially salient for early ERP components peaking within the first 100 milliseconds (e.g., P100, N100). These early components are labelled as "sensory" or "exogenous" as they depend on the physical parameters of the stimulus. These findings are similar to those reported by Grice et al.[60] where autistic individuals did not show significant differences in frontal gamma activity during the processing of upright and inverted faces (the latter acting as "physical parameters" of the stimuli) as opposed to clear increases in control subjects.

We should stress that the evoked gamma component in our studies were measured at the same time and over the same cortical regions as the previously reported ERP components. The findings support the idea of a disturbance in the activation of task relevant neuronal assemblies and the perceptual control of attention in ASD[53]. In a neural system that appears to be overactivated[61,62] local cortical connectivity may be enhanced at the expense of long-range connections, thus making it difficult for ASD individuals to either direct their attention or to activate specific perceptual systems based on the relevance of the stimuli (e.g., target *vs.* non-target)[53].

The above-mentioned studies have emphasized various temporal and spatial scales of neural oscillations in the gamma frequency band of autistic individuals. Current analysis methods assume that these oscillations are sinusoidal and that descriptive features of these waveforms are associated to physiological processes and behaviors[63]. In our studies, we have observed that the ringing of gamma oscillations, at a fading or decaying rate, is somewhat similar to what is experienced after a bell is struck or when water sloshes in a tub[64]. In transmission lines this phenomenon happens when a non-oscillating input travels through an inductive environment. Ringing in this context usually represents reflected energy due to faulty impedance matching. Impedance is a measure of resistance that varies with frequency. The anatomical equivalent of this restraining or resistive force is the inhibitory stimuli offered by interneurons within the cerebral cortex. This consideration is in agreement with studies claiming an inhibitory deficit in ASD. We believe that the observed ringing or "decay profile" at gamma frequencies is a direct reflection of the inhibitory deficit in ASD as: 1) it is accompanied by an output that takes a higher value before an amplitude decay followed by the stabilized response or steady level, 2) the ringing frequency and time constant is the same as that of the initial response suggesting it is not due to outside interference or parasitic properties of the system, 3) it is patent at the highest frequency of the brain's bandwidth (gamma), and 4) there are multiple studies with different techniques that support the presence of inhibitory deficits in ASD and help explain the genesis of the gamma oscillatory abnormalities (e.g., loss of parvalbumin neurons).

Executive function and repetitive behaviors

Phasic synchronization of local oscillations may provide the basis for functional integration across distant cortical networks[65–67]. In ASD, features of visual and auditory processing

abnormalities, as well as executive function, may be attributed to a reduced gamma synchronization and decreased temporal binding of activity between networks processing local features[53]. The large intra- and inter-regional connectivity of the prefrontal cortex enables it to orchestrate the oscillatory dynamics of these large-scale networks that are involved in those higher-order process that provide for goal-directed action. TMS treatment targeting the prefrontal lobes could help normalize gamma oscillations and improve a broad array of skills related to executive function.

Executive control involves mental skills that help regulate other brain processes. These functions include, among others, task monitoring, response inhibition, error detection, and compensatory behavior. Impairment of these functions contributes to poor cognitive and social function that ultimately impedes adaptation to novel, complex, or ambiguous situations[68]. Failure of these functions could result in excessive or repetitive motor activity, and stimulus-bound behaviors of the type typically seen in schizophrenia, obsessive compulsive disorder, and ASD.

Several of our studies have investigated whether TMS can change some of the core deficits of ASD, more specifically, those impairments in self-monitoring which comprise part of our supervisory attentional system[53,69–71]. In this regard we examined error sensitivity by measuring event-related potentials associated with responses to errors, i.e., error related negativity (ERN) and positivity (Pe), reaction time (RT), error rate, and post-error reaction time change. Baseline measures in our ASD population showed a reduced ERN and altered Pe along with a lack of post-error RT slowing. In the TMS treatment group, ERN became significantly more negative and the number of omission errors decreased. The RT did not change, but post-error RT became slower. There were no changes in RT, error rate, post-error RT slowing, nor in ERN/Pe measures in the wait-list group. The baseline results suggest that individuals with ASD have a reduced sensitivity for detecting or monitoring errors and executing corrective actions. This deficit might manifest itself as those perseverative behaviors that are commonly described as symptoms of ASD. The results of the current study also indicate that TMS may have facilitated attention and target discrimination by improving conflict resolution during the sorting of task-relevant from task-irrelevant stimuli.

TMS to the DLPC provides for improvement in behaviors as noted in caregivers' reports. The most notable change was a decrease of *T*-score of the Repetitive Behavior Scale-Revised[72], along with decreased irritability, lethargy/social withdrawal and hyperactivity rating scores of the Aberrant Behavior Checklist questionnaire[73]. It should be noted that we found significant reductions in irritability as a result of 12 sessions of bilateral stimulation[51], whereas reductions in repetitive behavior acquired significance after only six sessions of stimulation to the left DLPC[55,74]. These differences increased with the total number of treatment sessions. These improvements in measures of aberrant behavior and repetitive/ stereotyped behaviors have been reproduced in several of our studies where similar parameters and length of TMS intervention were used in children and adolescents with ASD[71,75].

Many children and adolescents with ASD exhibit symptoms of an imbalanced autonomic nervous system[76,77]. Researchers believe that, in some cases, the abnormal autonomic

balance propitiates the expression of autistic symptoms, i.e., low psychophysiological flexibility, rigid social communication abilities, and the autonomic arousal typical of anxiety[78,79]. Our laboratory has used time and frequency domain analysis of heart rate variability (HRV), skin conductance level (SCL), and rTMS to study autonomic control in ASD[80–82]. Following 12–18 sessions of low frequency rTMS treatment, time-domain analysis of heart rate variability showed a significant increase in R-R cardio-interval length and a higher standard deviation of R-R intervals. Frequency-domain HRV results in our ASD subjects showed an increase of high frequency (HF) power in HRV, and a decrease in the LF/HF ratio (LF; low frequency). Electrodermal activity also showed a decrease in the form of lower tonic skin conductance level. The results indicate that in ASD normalization of autonomic parameters by TMS is mediated by concomitant changes in both the parasympathetic (enhancement) and sympathetic (diminution) tone. Normalization of autonomic parameters may prove an important therapeutic intervention in ASD directed at preventing sudden cardiac death associated with diminished heart rate variability and treating the excessive sympathetic arousal associated with anxiety.

TMS has been used along with EEG-based gamma neurofeedback to examine the possibility of therapeutic synergism. Results of 18 sessions of integrated neuromodulation treatment (N=20 active group, n=22 waitlist controls) improved ERP indices of attention to targets, reduce over-reactivity to non-targets, significantly reduced motor response errors to target stimuli, enhanced response-locked potentials reflective of error monitoring and correction (e.g., ERN, post-error RT slowing), and reduced both repetitive and stereotypic behaviors[75]. These results show the usefulness of gamma band oscillations for neurofeedback application and the added benefit when used in conjunction to TMS.

In summary, the cerebral cortex's inherent excitatory/inhibitory bias demands the presence of dampening mechanisms to maintain a proper set point when acquiring and processing stimuli. This bias is altered in ASD individuals and manifested as gamma oscillation abnormalities, deficits in executive function, and stimulus bound behaviors. TMS is a non-invasive therapeutic intervention capable of modulating evoked and induced gamma oscillations and altering maladaptive behaviors[83]. Recent reviews of the literature suggest that TMS is safe and effective when used in ASD[54,84–91]. Selecting appropriate outcome measures is of importance due to limitations in presently available sham procedures that help define differences between active and control populations[92]. It is therefore of importance that the selection process for outcome measures extends beyond subjective methods, such as behavioral screening, and into unbiased electrophysiological measures that maximize both internal and statistical validity. In addition, objective measures of quality care should be instituted and analyzed by themselves rather than being considered surrogate measures of outcomes. We have found that autonomic measures, themselves related to behavior problems and emotional regulation, help define functional changes associated with ASD while simultaneously monitoring adverse experiences[80,81]. At present, efforts should focus on developing large sample clinical trials with targeted inclusionary/exclusionary criteria and longitudinal follow-up. This will allow testing critical questions regarding possible predictors of outcome (e.g., genetic profiling), length of persistence of benefits, assessing outcome according to severity of phenotypic presentation, and utility of booster sessions.

Acknowledgements

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Table 1

Authors	Design	N Intervention	N Control	Coil Placement	Frequency	MT	Duration	Montage	# of sessions
(year)	Control	(mean age)	(mean age)		(Hz)	(%)	(min)		
Enticott et al. [93]	-	1(20)	–	mPFC	5	1500	15	Bilateral	9
Niederhofer[94]	-	1(42)	–	SMA	1	1200	60	–	5
Cristancho et al. [95]	-	1(15)	–	DLPC	1	150–300	Not reported	Unilateral	36 (10 Right; 26 Left)
Avirame et al. [96]	-	2 (27.5±2.5)	–	mPFC	5	110	30	Bilateral	27; 29
Sokhadze et al. [74]	No	13 (15.6±5.8)	–	Left DLPC	0.5	90	Not reported	Unilateral	6
Casanova et al. [80]	No	18 (13.1±2.2)	–	DLPC	0.5	90	10–12	Unilateral/ Bilateral	18 (6 left; 6 right;6 bilateral)
Wang et al. [81]	No	33 (12.88±3.76)	–	DLPC	0.5	90	Not reported	Unilateral	12 (6 left; 6 right)
Sokhadze et al. [82]	No	32 (12.52±2.85)	–	DLPC	0.5	90	Not reported	Unilateral/ Bilateral	18 (6 left; 6 right; 6 bilateral)
Abujadi et al. [97]	No	10 (9–17)	–	Right DLPC	50	100	5	Unilateral	15
Sokhadze et al. [40]	Waiting list	8 (18.3±4.8)	5 (18.3±4.8)	Left DLPC	0.5	90	Not reported	Unilateral	6
Sokhadze et al. [70]	Waiting list	20 (13.5±2.5)	20 (14.1±2.4)	DLPC	1	90	Not reported	Unilateral	12 (6 left; 6 right_
Sokhadze et al. [75]	Waiting list	20 (14.7±3.3)	22 (14.2±2.8)	DLPC	1	90	60	Unilateral/ Bilateral	18 (6 left; 6 right;6 bilateral)
Sokhadze et al. [98]	Waiting list	27 (14.8±3.2)	27 (14.1±2.6)	DLPC	1	90	Not reported	Unilateral/ Bilateral	18 (6 left; 6 right; 6 bilateral)
Sokhadze et al. [83]	Heal thy controls	25 (13.6±3.22)	21 (14.9±4.3)	DLPC	1	90	Not reported	Unilateral/ Bilateral	18 (6 left; 6 right; 6 bilateral)
Sokhadze et al. [99]	Waiting list	25 (12.5±1.47) 30 (12.8±1.57) 31 (13.5±2.30)	26 (13.3±1.78)	DLPC	1	90	Not reported	Unilateral/ Bilateral	6;12;18
Baruth et al. [100]	Waiting list	16 (13.9±5.3)	9 (13.5±2)	DLPC	1	90	Not reported	Unilateral	12 (6 left; 6 right)
Casanova et al. [101]	Waiting list	25 (12.9±3.1)	20 (13.1±2.2)	DLPC	1	90	10	Unilateral	12 (6 left; 6 right)
Kang et al. [102]	Waiting list	16 (7.8±2.1)	16 (7.2±1.6)	DLPC	1	90	Not reported	Unilateral/ Bilateral	18
Fecteau et al. [103]	Sham	10 (36.6±16)	10 (36.6±16)	Left and right pars triangul aris; left and right pars	1	70	30	Unilateral	5 (1 per target; 1 sham)

Authors	Design	N Intervention	N Control	Coil Placement	Frequency	MT	Duration	Montage	# of sessions
(year)	Control	(mean age)	(mean age)		(Hz)	(%)	(min)		
				opercul aris					
Enticott et al. [104]	Sham	11 (17.55±4.06)	11 (17.55±4.06)	Left M1; SMA	1	100	5	Unilateral	3 (1 per target; 1 sham)
Enticott et al. [105]	Sham	15 (33.87±13.07)	13 (30.54±9.83)	dmPFC	5	100	Not reported	Bilateral	10
Panerai et al. [106]	Sham	9 (13.56±1.83) 6 (13.7±1.96) 6 (13.33±1.88) 6 (16.13±3.11)	9 (13.56±1.83) 5 (13.24±2.95) 5 (14.17±4.24) 4 (13.75±5.18)	PrMC	1; 8	90	15(1Hz); 30 (8Hz)	Unilateral/ Bilateral	Single and multisession
Anninos et al. [107]	Sham	10 (8.3+2.1)	10 (8.3+2.1)	Frontal cortex, vertex, bilateral temporal areas, bilateral parietal areas and occipital cortex	8–13	–	2	–	One crossover sesión with active or sham pT-TMS, then daily for one month
Ni et al.[108]	Sham	19 (20.8+1.4)	19 (20.8+1.4)	DLPC; pSTS	50	80 for active and 60 for sham iT BS	4	Bilateral	1 per target
Desarkar et al.[109]	Sham	7 (16–35)	7 (16–35)	DLPC	20	90	30–45	Bilateral	1
Gòmez et al. [110]	No	24 (12.2)	–	Left DLPC	1	90	20	Unilateral	20