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Biomarkers obtained by transcranial magnetic stimulation in neurodevelopmental disorders

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Abstract

Transcranial magnetic stimulation (TMS) is a method for focal brain stimulation that is based on the principle of electromagnetic induction where small intracranial electric currents are generated by a powerful fluctuating magnetic field. Over the past three decades, TMS has shown promise in the diagnosis, monitoring, and treatment of neurological and psychiatric disorders in adults. Yet, the use of TMS in children has been more limited. We provide a brief introduction to the TMS technique, common TMS protocols including single-pulse TMS, paired-pulse TMS (ppTMS), paired associative stimulation (PAS), and repetitive TMS (rTMS), and relevant TMS-derived neurophysiological measurements including resting and active motor threshold, cortical silent period, ppTMS measures of intracortical inhibition and facilitation, and plasticity metrics following rTMS. We then discuss the biomarker applications of TMS in a few representative neurodevelopmental disorders including autism spectrum disorder, fragile X syndrome, attention-deficit hyperactivity disorder, Tourette syndrome, and developmental stuttering.

Keywords

transcranial magnetic stimulation; neurodevelopmental disorders; pediatrics; neurology; biomarkers

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Conflicts of Interest Statement

A.R. is a founder and advisor for Neuromotion, serves on the medical advisory board or has consulted for Cavion, Epihunter, Gamify, Neural Dynamics, NeuroRex, Roche, Otsuka, and is listed as inventor on a patent related to integration of TMS and EEG. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

1. Introduction

Transcranial magnetic stimulation (TMS) is a 30-year-old technique for focal, noninvasive, electrical cortical stimulation (see (1) for a comprehensive review). In contrast to many neurostimulation protocols, TMS has robust prospects in the diagnostic and biomarker space. Specifically, TMS-derived biomarkers have been obtained for a range of disease states that include epilepsy (2), migraine (3), and pain (4). Yet, most of these have been studies in adults. Reviews of TMS safety in children (5–11) indicate minimal risk associated with the technique. Accordingly, TMS may serve to further our understanding of the underlying pathophysiology of neurodevelopmental disorders such as autism spectrum disorder or fragile X syndrome, and help identify biomarkers to aid in early diagnosis, monitoring disease progression, and development of novel therapies.

2. Common TMS Protocols and TMS-EMG Measures of Cortical Excitability and Plasticity

TMS is based on Faraday's principle of electromagnetic induction where a powerful fluctuating magnetic field induces a small intracranial electrical current in the brain (12). The induced current depolarizes the nearby neuronal assemblies located underneath the coil and can generate neurophysiological and/or behavioral effects (1). The true biophysical dynamics of TMS and the exact neural elements are activated by TMS remain unclear, and may vary across different brain regions and individuals (13–16). Models of TMS (17–20) raise many of the relevant issues, but need to be tested further on cellular and molecular levels (21,22).

Applying TMS to the primary motor cortex (M1) can selectively activate the contralateral muscles that are controlled by the targeted M1 (23). The extent of this activation can be quantified via motor evoked potential (MEP) amplitudes using skin-surface electromyography (EMG), enabling TMS-derived measures of the cortical excitation and inhibition (6), two opposing forces that influence many cortical functions in the mammalian cerebral cortex (24,25). The extent of inhibition generated in cortical networks is typically proportional to local and/or incoming excitation through the recruitment of interneurons via feedforward and/or feedback excitatory projections (25). Such excitation:inhibition (E:I) balance, in which increases in excitation are accompanied by increases in inhibition, has been observed *in vitro* in several sensory cortical regions (26–28) as well as during spontaneous cortical activity (29–31).

The stimulation intensity in TMS protocols is typically adjusted based on normalized measures such as motor threshold, the intensity that elicits an MEP of ≥ 50 μV on 50% of the pulses applied over the cortical hot spot of a target muscle either at rest (*resting motor threshold*; rMT) (32) or during isometric contraction (*active motor threshold*; aMT).

The pattern of stimulation and outcome measures of TMS modalities can vary based on the number and intensity of the TMS pulses, inter-pulse/inter-train intervals, stimulation

frequency, TMS pulse waveform, and the direction of the induced current in the brain (13,33,34). The three main types of TMS protocols are as follows (Table 1):

a. Single-pulse TMS

Single-pulse TMS (spTMS) typically consists of single pulses delivered at 5–8 s intervals, to avoid cumulative effects of individual pulses over time. A standard TMS pulse is usually 150–300 μs in duration and can cause depolarization followed by a refractory period, after which neurons recover rapidly. spTMS is used to assess corticospinal integrity and maturity (35–39), for motor mapping (40), and to assess the aftereffects of repetitive TMS (rTMS) protocols (41,42).

The cortical silent period (cSP) is a period of EMG suppression following an MEP elicited by spTMS during the voluntary contraction of a given muscle that lasts between 100–300 ms (43). The early part of the cSP (up to the first 50 ms) is related to activation of spinal inhibitory interneurons by the fibers descending from M1 (44), whereas the later portion is due to the cortical inhibition originating from M1 (45). cSP duration is a reflection of $GABA_B$- and $GABA_A$-mediated motor-cortex inhibition (46). For example, several studies have found shortened cSP duration in the epileptic hemisphere in patients with focal motor epilepsy (47–49), which may indicate a disruption in cortical inhibitory mechanisms that results in epileptic EEG activity. Another study found bilaterally lengthened cSP, but less prominently in the epileptic hemisphere, in patients with focal epilepsy (50). The significance of such cSP increase is not certain, but it may reflect a compensatory increase in interictal cortical inhibition to prevent epileptic activity (43). Increased cSP duration has also been observed in patients with idiopathic generalized epilepsy (51,52).

The ipsilateral silent period (iSP), a variant of the cSP, is used to assess the functional integrity of the transcallosal projections between motor cortices in which spTMS to M1 causes a transient suppression of voluntary tonic muscle activity in the ipsilateral hand muscles.

Strength of corticospinal projections are reflected by the shape and slope of an input/output (I/O) curve, also known as the *recruitment curve*, which is obtained by measuring MEP amplitudes elicited by single TMS pulses delivered over a wide range of intensities (53). The I/O curve for the intrinsic hand muscles has a sigmoid shape (54), in which the main outcome measures are the slope of the curve and the intensity at which it reaches a plateau. The slope of the I/O curve is steeper for intrinsic hand muscles that have a lower activation threshold (i.e., a lower rMT) and becomes less steep following administration of sodium- and calcium-channel blockers (e.g., lamotrigine) and $GABA_A$ receptor agonists (e.g., lorazepam) (54). The finding that lorazepam has no effect on rMT but modulates the I/O curve, particularly at highest intensities (54), indicates that the I/O curve provides complementary information relative to rMT about the motor-system activity, including the GABAergic circuitry (13).

b. Paired-pulse TMS

In paired-pulse TMS (ppTMS), a conditioning stimulus (CS) is followed by a test stimulus (TS) after an interstimulus interval (ISI). PpTMS is used to assess intracortical inhibitory

or facilitatory mechanisms, most commonly local to M1. In most ppTMS protocols (except LICI, described below), CS and TS intensities are set at sub-rMT and supra-rMT intensities, respectively. In short-interval intracortical inhibition (SICI) (ISI = 1–6 ms), CS subliminally influences intracortical neurons, which will not resume their full responsiveness until they have had time to recover. Thus, a TS preceded by a CS can only activate a subset of neurons in the target region resulting in lower MEP amplitudes than the ones elicited by the TS alone. While the stimulation sequence utilized in the short-interval intracortical facilitation (SICF) protocol is similar to that in SICI, the two protocols differ in that CS and TS intensities in SICF are supra-rMT and sub-rMT, respectively (55), or both stimuli are close to rMT intensity (56). The TS in SICF is thought to excite directly the initial axon segments of the excitatory interneurons that were depolarized by excitatory post-synaptic potentials elicited by the CS but did not fire an action potential (57,58). In intracortical facilitation (ICF) (ISI = 8–30 ms), CS engages facilitatory intracortical neurons that enhance the output of response to TS, resulting in greater MEP amplitudes compared to those elicited by the TS alone (59). In long-interval intracortical inhibition (LICI) (ISI = 50–200+ ms), both CS and TS are suprathreshold, resulting in inhibition of the TS MEP (60,61). Epidural recordings of the descending corticospinal volley have found LICI likely engages intracortical neurons that inhibit the *I-waves* produced by indirect activation of layer-V pyramidal tract neurons (62). Table 1 details the stimulation parameters of common ppTMS protocols and their likely mechanisms.

Short-interval inhibitory effects are mainly mediated by gamma-aminobutyric acid (GABA) activity, whereas long-interval facilitatory effects are mainly mediated by glutamatergic activity (63–66). Specifically, SICI reflects $GABA_A$-mediated regional cortical inhibition, while ICF reflects glutamate [*N*-methyl-*D*-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor types]-mediated excitation, and LICI represents $GABA_B$-mediated inhibition and (likely) an aggregate inhibitory tone mediated by the $GABA_A$ receptor system (46,67). SICI represents fast inhibitory postsynaptic potentials (IPSPs) in corticospinal neurons mediated by $GABA_A$ receptors, whereas LICI additionally represents slow IPSPs that are mediated, at least in part, by $GABA_B$ receptors. Applying ppTMS to M1 can be used to assess abnormal states of low or high cortical excitability by measuring the cortical E:I ratio, e.g., by measuring the SICI/ICF ratio (68,69), which provides an estimate of the relative strength of local intracortical inhibitory and excitatory activities (38,70), whereas ppTMS, when applied to two cortical regions, can assess inter-regional connectivity and conduction time (71,72).

c. Repetitive TMS

rTMS typically consists of several pulses at 1–20 Hz frequency over long periods of stimulation (up to 30 minutes), at times including stimulation-free intervals (13). rTMS is commonly used to modulate regional cortical activity in neuropsychiatric disorders and, particularly when applied as long trains over consecutive daily visits, can induce long-lasting plastic aftereffects (73,74) by influencing the brain networks associated with the targeted region (1). Typically, low-frequency (≤ 1 Hz) rTMS with at least 300–900 pulses can induce sustained inhibition of cortical excitability, whereas high-frequency (≥ 5Hz) or discontinuous rTMS can induce long-lasting facilitation of cortical excitability (41,75). The

inhibitory and facilitatory aftereffects of low-frequency and high-frequency rTMS resemble use-dependent, long-term depression (LTD) and long-term potentiation (LTP) of excitatory (glutamatergic) synaptic strength – however, these aftereffects are in part also mediated by GABAergic mechanisms (76–78).

A form of patterned rTMS known as theta-burst stimulation (TBS) consists of 50 Hz bursts of three TMS pulses repeated every 200 ms (i.e., at 5 Hz), for a total of 600 pulses, in one of two protocols: (1) a 2-s on, 8-s off intermittent TBS (iTBS) for 190 s that can increase MEP amplitude by ~35% for up to 60 min, or (2) a continuous TBS (cTBS) for 40 s that can reduce MEP amplitude by ~25% for up to 50 min (79). Facilitation and suppression of MEPs by iTBS and cTBS are considered indices of LTP- and LTD-like mechanisms of synaptic plasticity, respectively (77,80). The time necessary for post-TBS MEPs to return to pre-TBS baseline and the pattern of post-TBS aftereffects are considered neurophysiologic indices of the mechanisms of cortical plasticity (79,81,82), albeit with considerable inter- and intra-individual variability in responses (83–86). Physiologic and pharmacologic TBS studies in humans indicate the involvement of glutamatergic and GABAergic mediators consistent with LTP and LTD, respectively, and the pattern and time course of their aftereffects (77,78,87,88).

d. Paired Associative Stimulation (PAS)

PAS is an electrophysiological technique that involves repeated pairing of two stimuli, e.g., a peripheral electrical pulse delivered to a nerve of the hand, usually the median nerve (median-nerve stimulation; MNS), that activates the primary sensory cortex (S1) and a TMS pulse over the corresponding hand representation in the contralateral M1 (89). Through this S1-M1 coupling, PAS is able to modulate corticospinal excitability as indicated by the change in MEP amplitudes (89,90). PAS-induced modulation of MEPs reflects the propensity of the nervous system to adapt, i.e., plasticity. This plasticity is presumed to rely on the principles of Hebbian synaptic plasticity (91) such that the modulation of MEP amplitude depends on the interstimulus interval (ISI) between the sensory stimulus and the TMS pulse applied to M1. Specifically, based on a temporally asymmetric Hebbian rule (92), a shorter interval (ISI = 10 ms) produces a decrease in the MEP amplitude, whereas a longer interval (ISI = 25 ms) induces an increase in the MEP amplitude (89,90,92,93). These interventions have been termed PAS10 and PAS25, respectively (93). PAS aftereffects develop rapidly (within 30 min), are long-lasting (at least 60 min), reversible, and cortically generated (89,90,94). PAS25 aftereffects depend on NMDA glutamatergic receptors, and are thought to be mediated by an LTP-like mechanism (89,92). In a variant referred to as PAS_{N20+2}, stimulation consists of 225 pairs (rate, 0.25 Hz) of MNS followed at an interval equal to the individual N20 latency of the median nerve somatosensory-evoked cortical potential plus 2 ms by applying spTMS to the hand area of the contralateral M1 (90,95).

3. TMS biomarkers in neurodevelopmental disorders

a. Autism Spectrum Disorder (ASD)

ASD is a lifelong developmental syndrome that affects ~1 of 59 children (96) and is characterized by difficulties with interpersonal relationships and communication,

and presence of restrictive and repetitive behaviors, interests, or activities (97). There are currently no FDA-approved treatments for core ASD symptoms. Development of novel therapeutics will require reliable biomarkers and improved understanding of ASD pathophysiology (98).

Among many mechanistic ASD models are those reliant on imbalance of cortical excitation and inhibition (99–101). However, most spTMS and ppTMS measures of cortical excitability such as rMT, MEP amplitude, LICI, or ICF show no clear difference between patients with ASD and neurotypical (NT) individuals (81,102–104). In the 2013 study by Enticott and colleagues (103), SICI in cognitively normal patients with ASD was shortened compared to their NT counterparts, and the $GABA_A$ergic activity, as indexed by SICI, was associated with the extent of developmental delay in language acquisition in patients with ASD. This suggests that some of the heterogeneity in ASD symptomatology may be associated with interindividual variability of $GABA_A$ergic activity. Two other studies, however, found SICI in ASD patients to be normal as compared to NT controls (105,106).

Pedapati and colleagues (107) recently reported findings from the largest sample of ASD youth to undergo ppTMS to date (n=59), and found normal SICI and cSP in ASD youth compared to typically developing children. However, enhanced SICI (greater inhibition) and prolonged cSP were highly correlated with clinical history and standardized measures reflecting academic struggles in reading, spelling, and/or math. Moreover, across all ASD youth, ICF was inversely correlated with worse inattention, and lack of ICF was associated with inattention and executive dysfunction (107).

In contrast to spTMS and ppTMS measures, Oberman et al. (81) identified a reliable distinction between the ASD and NT groups using TBS. The investigators used cTBS and iTBS paradigms to evaluate LTD- and LTP-like plasticity, respectively, in 20 cognitively normal adults with ASD and found greater and longer-lasting modulation of M1 reactivity following both TBS paradigms compared to age-, gender-, and IQ-matched NT controls. These results were confirmed in a separate cohort of 15 adults with ASD (81) as well as in a follow-up study by Oberman and colleagues on 10 adults with ASD (108). The longer-lasting iTBS aftereffects in the ASD group are consistent with the hypothesis that a lack of inhibitory tone would lead to a greater propensity for LTP. Similarly, the longer-lasting cTBS aftereffects among subjects with ASD are consistent with the Bienenstock, Cooper, and Munro (BCM) model (109) that predicts an already-potentiated synapse will have a lower threshold for LTD, and, thus, will exhibit a stronger LTD-like response than a depressed or neutral synapse (110). The greater potential for both LTP and LTD, coupled with the finding that measures of baseline cortical excitability such as rMT and baseline MEP amplitude were comparable between the ASD and NT groups (81), indicated an unstable state of synaptic plasticity in ASD, which results in exaggerated, *hyperplastic*, response to TBS. In a subsequent study of children and adolescents with ASD, Oberman and colleagues (111) found a positive relationship between age and the extent of cTBS-induced modulation, suggesting a maturational trajectory for LTD-like plasticity during childhood and adolescence in ASD.

Recently, we extended those findings by comparing M1 cTBS aftereffects between 11 children and adolescents with ASD and 18 of their age-, gender-, and IQ-matched controls (112). We found cTBS aftereffects differentiated between the ASD and control groups due to more-facilitatory cTBS aftereffects in the ASD group relative to the control group. Notably, the difference in cTBS responses between ASD and control groups remained after participants with ADHD were excluded from the ASD group. We also found an age-related increase in the maximum cTBS-induced suppression of MEPs in the ASD group only, suggesting a dysmaturity in the LTD-like plasticity in ASD youth (112).

Based on the involvement of GABAergic synaptic transmission in cTBS aftereffects (78,113), the more-facilitatory responses to cTBS in the ASD group than in the TD group lends further support to the notion of GABAergic dysfunction in ASD (114–116). Thus, quantification of M1 cTBS aftereffects may serve as a physiologic biomarker for children and adolescents with ASD, which can improve the classification of clinical endophenotype and understanding of ASD pathophysiology, and be used to assess target engagement and monitor response to experimental pharmacologic or neuromodulatory therapies for ASD (98,117).

However, the findings of hyper-plasticity on ASD are not consistent with the results of one study that compared PAS plasticity measures between ASD and control groups; Jung and colleagues (105) found that, unlike healthy controls, patients with ASD did not show the expected PAS25-induced facilitation of MEPs. The authors found similar results with PAS_{N20+2} in a small subgroup of ASD patients. The results suggested reduced LTP-like plasticity and deficits in sensorimotor integration in ASD (105).

Notably, as the majority of the participants in the aforementioned studies (summarized in Table 2) are children or adolescents with ASD who are cognitively and linguistically normal, it remains unclear whether these results extend to adults or children with ASD who have cognitive or language deficits.

b. Fragile X Syndrome (FXS)

FXS is the most common cause of inherited intellectual disability (118), with a prevalence estimated at 1.4 and 0.9 per 10,000 males and females, respectively (119), and the most common genetic cause of autism, with 30% of children with FXS diagnosed with autism and 2–5% of autistic children having FXS (120). FXS is caused by the expansion of the trinucleotide sequence CGG located in the 5’ untranslated region (UTR) of the X-linked *FMR1* gene that results in hypermethylation and consequent silencing of the *FMR1* gene. The silencing of the *FMR1* gene prevents the encoding of the fragile X mental retardation protein (FMRP) and forms the basis for the FXS phenotype (121). FMRP is an inhibitory regulator of translation of metabotropic glutamate receptor 5 (mGluR5), which is involved in formation of new synaptic connections, stabilizing LTD, and inducing LTP. Absence of FRMP results in excess mGluR5 activity and subsequent abnormalities in synaptic plasticity, as observed in animal FXS models (122,123).

rTMS protocols in subjects with FXS have also demonstrated evidence for abnormal neural plasticity. In a study by Oberman and colleagues (124), FXS patients showed a lack of

response to cTBS, an enhanced response to iTBS, and a complete blocking of iTBS response on the subsequent day, suggesting abnormalities in plasticity and *metaplasticity*. Metaplasticity refers to a change in the state of the synapse that alters its ability to make subsequent plastic changes, involves many of the same mechanisms as conventional LTP and LTD, and likely serves as a homeostatic function to maintain plasticity within a normal working range (124).

In a follow-up study, Oberman and colleagues (108) found that six adults with FXS showed abnormal TBS-induced plasticity and metaplasticity; the duration of the cTBS response in the FXS group in the first visit was significantly shorter than that in the control group, and they showed paradoxical facilitation of MEPs following cTBS in their second visit. The results from both ASD and FXS subjects provide evidence for aberrant TMS-induced plasticity and metaplasticity at the level of cortical circuits, which are consistent with the theories proposed to explain these processes at the synaptic level, e.g., the BCM model that predicts a lower-than-normal LTD threshold, and thus, a stronger LTD-like response than a depressed or neutral synapse (109).

c. Attention-Deficit Hyperactivity Disorder (ADHD)

ADHD is one of the most common neurodevelopmental disorders affecting 2–7.5% of school-aged children, with core symptoms of inattention, hyperactivity, and impulsivity (125). The pathophysiology of ADHD remains unclear, and there is currently no widely accepted biomarker or diagnostic test for ADHD. Thus, an ADHD diagnosis is typically based on parent- and teacher-reported behavioral rating scales combined with a physician's clinical impression. An influential theory of ADHD pathophysiology posits that executive dysfunction in ADHD is due to deficient inhibitory control (126,127), the neural substrate of which involves basal ganglia-thalamocortical circuits (128). Impulse-control deficit and hyperactivity in ADHD have been associated with dysfunction of frontostriatal circuits including underactivity of ventrolateral prefrontal cortex, dorsolateral prefrontal cortex, and anterior cingulate cortex. The negative association between inhibitory control and hyperactivity in ADHD is paralleled by abnormally reduced SICI (129), an inverse correlation between SICI and symptom severity in most patients with ADHD (127,130), and, interestingly, paradoxical facilitation following SICI in a few cases (127). SICI is normalized following administration of methylphenidate (131) indicating that SICI may function as an index of therapeutic response to methylphenidate, and, therefore, may play a role in dosing of stimulants, and future drug development for treatment of children with ADHD. Future studies on the effect of other stimulants on SICI are needed to investigate its utility for drug selection in patients with ADHD.

Prolonged latency and duration of the ipsilateral silent period (iSP) found in ADHD suggests deficient transcallosal-mediated inhibition in ADHD (132). Interestingly, the iSP duration is correlated with the degree of hyperactivity and restlessness in ADHD, and is also normalized with a single dose of methylphenidate. This indicates the prominent role of abnormal cortical excitability, rather than structural abnormalities of the corpus callosum, in the pathophysiology of ADHD. This view is supported by the finding that iSP duration in ADHD is inversely correlated with the magnitude of SICI (133,134). In contrast to children

with ADHD, the iSP in adults with ADHD is abnormally shortened but has a normal onset-latency (135). The difference in iSP between children and adults with ADHD could be due to developmental differences in inhibitory intracortical circuits (125).

The findings that SICI is correlated to hyperactivity severity in ADHD, and methylphenidate normalizes SICI while reducing hyperactivity, indicate that SICI could function as an index of therapeutic response to methylphenidate, and, therefore, guide drug selection, dosing of stimulants, and future drug development for treatment of children with ADHD.

Pedapati and colleagues (107) found ICF was significantly reduced in ASD children with ADHD comorbidity (ASD+) compared to ASD children without ADHD comorbidity (ASD–) and typically developing children. This reduction in ICF, together with the reported functional abnormalities in the temporal lobe and amygdala in ASD− and ASD+ youth (136), suggests that ICF may represent the combined effects of several aberrant cortical and subcortical circuits specifically relevant to the presence of ADHD symptoms in the ASD population (107).

d. Tourette Syndrome (TS)

Tourette syndrome (TS) is a chronic, childhood-onset neuropsychiatric disorder characterized by more than 1 year of motor and vocal tics. Tics are repetitive, stereotypical but nonrhythmic, involuntary, or compulsive movements that occur at irregular intervals, usually between purposeful movements. TS affects 1–3% of Western school-aged children, with the age of onset ranging from 2 to 21 years (137). Chronic tic disorders, characterized by either motor or vocal tics, but not both, occur in 5% of school-aged children (137). Common comorbidities include ADHD, obsessive-compulsive disorder (OCD), learning disabilities, conduct disorders, self-injury, and sleep disturbances (138,139). The pathophysiology of tics in TS likely involves dysfunctional integration of information with motor output from many sources via basal ganglia-thalamocortical circuits that results in incomplete suppression of unwanted behaviors (140).

Adults with TS have normal rMT and aMT (141,142) but, according to Orth et al. (143), recruit significantly fewer corticospinal neurons at higher stimulation intensities as indexed by shallower I/O curve slopes compared to healthy controls. This pattern of results suggest that while the most excitable connections (i.e., those recruited at rMT) are in a comparable state in TS patients and healthy controls (141–144), the difference between the most and the least excitable corticospinal neurons is greater in TS than in healthy controls (143). In a subsequent study by Heise et al. (144), no such difference in the I/O curve slopes was found, perhaps due to the less-severe symptoms of TS patients compared to the cohort studied by Orth et al. (143).

Several ppTMS studies have found abnormally reduced SICI at rest in TS patients (141–144). While TS patients have normal thresholds for SICI (the stimulation intensity needed to produce SICI), their recruitment of inhibition at suprathreshold intensities is abnormally reduced (142,143). The reduced SICI in TS patients correlates with greater motor tic severity, especially in patients who are not under treatment with dopamine antagonists and those patients who have comorbid ADHD (145,146). Interestingly, the ability to normalize

SICI during movement preparation is associated with fewer tics and lower tic severity (144), suggesting that control over tic movements depends on the ability to reduce the excitability of motor neurons in line with increased intracortical inhibition (140).

One study (147) identified greater ICF in patients with TS and comorbid ADHD compared to healthy controls, individuals with TS alone, or individuals with TS and comorbid OCD. This result suggested that comorbid conditions like ADHD may also independently affect TMS measures of cortical excitability or inhibition. Other studies, however, did not find such a difference in ICF between TS and control groups (141,146,148), a discrepancy that may be due to the well-established interindividual variability in ICF (149).

cSP duration in TS patients has been found to be abnormally shortened (141,142) or normal when cSP measurements are corrected for differences in MEP amplitude between TS and control groups (143). These results indicate that the relationship between corticospinal excitability and the intracortical inhibitory mechanism reflected in the cSP, possibly via corticospinal motor-neuron recurrent collaterals (150), is comparable in TS patients and controls (140).

There is a reduction in MEP amplitude elicited by suprathreshold spTMS in individuals with TS during the period immediately preceding volitional movements compared to the expected increase in MEP amplitude in control subjects during the same timeframe (151,152). Ganos and colleagues found that voluntary tic suppression in adults with TS also reduced corticospinal excitability, as indexed by reduced MEP amplitude following spTMS and a shallower I/O curve, the extent of which was associated with the ability to control tics (153). These findings suggest that cortical excitability is reduced in the period immediately preceding volitional movement or that individuals with TS have impaired ability to modulate motor cortical excitability prior to tics. However, unlike adults with TS (141,142), rMT was found to be higher in adolescents and young adults compared to age-matched controls, with the differences being more pronounced in the younger age groups (154). MEP variability is also larger in TS patients, although the degree of variability decreases with age both in individuals with and without TS. Similar to results seen in adults with TS, adolescents (<18 years old) with TS also exhibited reduced motor excitability during the period immediately prior to volitional movements. rMT depends upon recruitment of corticospinal neurons that project to a target muscle, and increases in motor excitability and decreases in MEP variability result from consistent firing patterns of a given group of motor cortical neurons recruited during movement preparation. Therefore, this age-related difference in rMT and MEP variability may be related to a delay in the formation of cortical-cortical and corticospinal motor networks in TS that leads to a reduced number of neurons recruited by a TMS pulse or inconsistent firing of recruited motor cortical neurons (154).

Plasticity induced by TBS protocols has also been studied in TS patients, specifically to test whether abnormal thalamo-cortical motor inputs in TS influence M1 plasticity by eliciting aberrant activity in cortical layers responsible for the measured TBS aftereffects (155–157). Wu and Gilbert (156) found TS patients showed greater iTBS-induced facilitation of MEPs at 1 and 10 minutes post-iTBS than healthy controls. In contrast, Suppa and colleagues (157) found that TS patients, with and without psychiatric comorbidity, showed reduced

responses to both iTBS and cTBS compared to healthy controls. The authors suggested that the lack of correlations between tics and neurophysiological measures could be due to the involvement of nonprimary motor cortices, basal ganglia and cerebellum, in addition to M1 and brainstem, in the generation of tics (157). It has been suggested that alterations of synaptic plasticity in TS may arise from metaplasticity effects occurring as a consequence of tics (155,156).

TMS studies have also investigated LTP-like plasticity response induced by the PAS protocol in TS patients. Brand and colleagues (158) found that while most healthy controls showed the expected LTP-like response following PAS_{N20+2}, TS patients were more likely to show a paradoxical, LTD-like response, the extent of which was correlated with less-severe urges and fewer tics. Their results also suggested that aberrant PAS-induced facilitation of MEPs in TS could be related to reduced long-term consolidation of motor skills in a rotary pursuit task (158).

e. Developmental Stuttering (DS)

DS is a disruption in the normal speech rhythm characterized by repetitions, prolongations, and tense pauses manifesting speech blocks (159). Secondary, associated symptoms of DS include movements/spasms, most commonly in facial muscles (160,161). The prevalence of DS, with various degrees of severity, is ~5% in children and ~1% in adults (162).

In the first TMS study in DS, Sommer and colleagues (163) investigated the abnormalities in intracortical inhibition and facilitation of hand-muscle MEPs at 1–30 ms ISIs. The rMT and aMT were both abnormally high in DS patients, indicating lower corticospinal excitability in DS. Consistent with this finding, Busan and colleagues (164) found lower MEP recruitment in DS patients, especially in DS males, at higher intensities (e.g., 150% of rMT), indicating abnormally low cortical excitability in DS. Interestingly, cSP durations were negatively correlated with stuttering severity in males, perhaps due to a compensatory mechanism by intracortical circuits (164). Another piece of evidence for lower corticospinal excitability was obtained by Alm and colleagues (165) who found higher rMT in the left hemisphere of DS patients, both relative to their right hemisphere and to the left hemisphere of fluent speakers, indicating lower excitability of corticospinal pathways in DS originating from the left M1. The authors interpreted this finding as reflecting difficulty in the initiation of movement in DS patients (165).

rTMS studies have also revealed abnormalities in motor-control networks in DS. Neef and colleagues (166) used subthreshold 1Hz rTMS to investigate the roles of right and left premotor cortices on motor output in DS. They found performance in a timed motor task was more influenced by applying rTMS to the right premotor cortex in DS patients but to the left premotor cortex in fluent speakers. This result suggested a possible compensatory mechanism by motor circuits related to the control of timed movements in the right hemisphere of DS patients due to dysfunction of the corresponding circuits in the left hemisphere (166).

TMS has also been used to investigate the motor representation of speech muscles in DS. In the first TMS study of corticobulbar pathways in DS, Neef and colleagues (167) found

a steeper I/O curve as well as reduced SICI (at 2ms ISI) and ICF among DS patients. These results suggested alterations in intracortical networks in DS, possibly mediated by altered GABAergic activity. More recently, Neef and colleagues (168) examined the change in MEP amplitudes elicited by spTMS over M1 during transition between a fixed labiodental articulatory configuration and immediately following articulatory configurations in adults with DS and healthy controls. Interestingly, adults with DS exhibited a lack of left-hemisphere facilitation during the transition phase, the extent of which was negatively correlated with objective measurements of stuttering severity (168). These results suggested a deficit in controlling speech motor plans in DS, likely in the left M1. Consistent with these results, Busan and colleagues (169) found an abnormally prolonged cSP in the left M1 representation of tongue, as well as significantly higher aMT in the left hemisphere of DS patients relative to their right hemisphere, the extent of which correlated with stuttering severity (169). Abnormalities of TMS measures in DS, especially in the left hemisphere, including reduced corticospinal and corticobulbar excitability, as well as reduced ICF and prolonged cSP can indicate a decreased tonic excitation of afferent inputs to M1 (170), possibly as a result of the white-matter abnormalities reported in DS, involving the left superior longitudinal fasciculus and the white-matter fibers between the left frontal and premotor cortices (171,172). Table 2 details the common TMS-based biomarkers in the disorders included in this review.

4. Adoption of TMS-based biomarkers in the clinic

Several TMS devices have received FDA approval for treatment of medication-resistant major depressive disorder (173–179). Additional devices have also been FDA-approved for acute and prophylactic treatment of migraine headache (180), presurgical motor and language mapping (181,182), and adjunct treatment of obsessive compulsive disorder (183). While TMS-derived biomarkers can be generated with these devices in the clinical setting, there remain a few barriers to wide adoption of their clinical use. We briefly summarize these below.

a. Education

Compared to other clinical protocols, TMS is relatively new, and thus, does not receive adequate coverage in medical educational curricula (184–186). Notably, while “rigorous training” for all physicians administering TMS for clinical purposes is advised by consensus statements (187), licensing and training requirements for clinicians to use TMS are largely absent. Intensive educational courses have been developed that partially address the need for organized TMS training programs (186), but the more-common incomplete training in TMS techniques among neurologists and psychiatrists remains one of the greatest barriers to the widespread adoption of TMS in the clinic.

b. Safety concerns

When application guidelines (32,188) are followed, TMS has an excellent safety profile in adults (188–190) and in children and adolescents (8–11). Still, concerns about an extremely rare, but potentially serious, side effect of rTMS, i.e., seizures, might dampen the motivation of physicians to use TMS in the clinic. However, while rare instances of rTMS-induced

seizure have been reported in adults (188), there has been no reported case of seizure induced by spTMS and ppTMS, among patients without epilepsy, which form the basis of the majority of TMS-based biomarkers. A measure of TMS safety in the pediatric population is provided in a recent study, in which no seizures or any other serious adverse events were reported after near 3 million rTMS stimulations in 119 children and adolescents, of whom 59 participants had perinatal stroke or mild traumatic brain injury and another 43 participants had major depression or Tourette's syndrome (10). These results underscore that TMS protocols, including rTMS, are safe and well-tolerated in children and adolescents, and can be considered minimal risk (8,10). Improving knowledge about the TMS safety profile among physicians can ease their potential safety concerns and set the stage for the more widespread use of TMS techniques in the clinic.

c. Proof-of-principle and confirmatory evidence

A fundamental obstacle to the more-common use of TMS-based biomarkers in the clinic is lack of adequate proof-of-principle studies that establish feasibility and provide preliminary evidence for TMS-derived biomarker utility in clinical pediatric populations. A lack of large confirmatory studies that can accommodate the variability of TMS responses observed in adult participants (83–86,191,192) similarly raises questions of feasibility and TMS-derived biomarker utility. Such studies, ideally followed by FDA approval of the relevant applications, are needed before widespread and evidence-based use of TMS biomarkers for pediatric populations can take place in the clinic.

d. Individualized TMS measures

The vast majority of the TMS measures discussed in the present review represent differences at the group level. At the individual level, responses to TMS protocols show large inter- and intra-individual variability, even in healthy populations (83–86,191,192). Such variability indicates the need for multivariate modeling of TMS measures that yields optimally adjusted TMS "scores" that incorporate relevant demographic, genetic, neurophysiological, neuroimaging, and state-dependent factors. These composite scores can assist clinical decision-making by placing more precisely an individual patient's baseline and post-intervention neurophysiological responses within his/her clinical cohort. Depending on the TMS protocol, obtaining a reliable TMS measure for optimal clinical use may involve considering age (36,193,194), gender (195–197), genetic polymorphisms (198–202), the TMS device, pulse waveform, and induced current direction (33,34,194), stimulation intensity and baseline neurophysiological measures, e.g., rMT, aMT, and baseline MEP amplitude (83,85,194,203), the target muscle (194,204), the time of day (84,194,205), use of neuronavigation (206) and robotic arms (207), amount and quality of sleep the night before the TMS visit (208,209), blood glucose level and caffeine intake before and during the TMS visit (210–212), intensity and duration of physical activity before each visit (213,214), phase of the menstrual cycle (215,216), and the use of closed-loop systems that deliver TMS pulses timed to real-time, EEG indices of brain states (217,218).

The current state-of-the-art individualized methods for TMS target localization or prediction of response to rTMS treatment rely on measuring the baseline or induced changes in resting-state functional connectivity between relevant brain regions at the level of the Human

Connectome (219–221) or the individual patient (220,222–225), or the local/distributed changes in cortical excitability as measured by TMS-evoked EEG potentials (TEPs) (224). It is thus likely that the next generation of individualized TMS biomarkers for "precision medicine" will also need to leverage individual patient data obtained from neuroimaging modalities, whether structural (to determine cortical thickness, scalp-to-cortex distance, sulcal/gyral geometry, or diffusion weighted imaging), functional (task- or resting-state fMRI to identify target regions or networks, or to determine functional connectivity between relevant regions), or neurophysiological (e.g., TEPs).

5. Conclusion

Neurophysiological measures obtained with noninvasive stimulation of the motor cortex can provide practical and feasible biomarkers for neurodevelopmental disorders. Such TMS-derived metrics of cortical excitability, E:I imbalance, and plasticity in the motor cortex can help elucidate the underlying pathophysiology of a range of neurodevelopmental disorders.

Several established single-pulse, paired-pulse, and repetitive TMS protocols are available that can be utilized to assess disease severity, measure and predict therapeutic response to existing therapeutic approaches in neurodevelopmental disorders, and enable novel measures of target engagement in the treatment of those disorders. Due to the substantial overlap in clinical presentations of disorders such as ASD, ADHD, and Tourette's syndrome, it is important to consider the commonalities in TMS measures across such disorders in order to avoid potential confounding due to comorbidities. As more-comprehensive TMS evidence from larger populations of patients with such disorders becomes available, it becomes important to leverage the contrasting TMS findings in subgroups of these disorders, e.g., ASD with ADHD and ASD without ADHD, to enable more-refined classification and monitoring of patients in such subgroups based on the most-relevant TMS measure or combination of different TMS measures. Considering demographic, neurophysiological, genetic, and neuroimaging data may enable more-granular TMS biomarkers, approaching individualized measures.

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Table 1.

Neurophysiological measures derived from transcranial magnetic stimulation-electromyography (TMS-EMG).

TMS-EMG measure	Protocol	Likely mechanism(s)
Resting motor threshold (rMT)	spTMS: measure of minimum stimulus intensity necessary for a motor response at rest (recorded either by visual inspection or EMG) on 5 / 10 trials	Cortical motor neuron voltage-gated sodium channel-mediated membrane excitability
Active motor threshold (aMT)	spTMS: measure of minimum stimulus strength necessary for ≥ 200 μV MEP during isometric contraction on 5 / 10 trials	Cortical motor neuron voltage-gated sodium channel-mediated membrane excitability + spinal contributions
MEP amplitude	spTMS: average peak-to-peak amplitude of MEP over 15–30 single pulses at 5–8 s ITI	Cortical motor neuron voltage-gated sodium channel-mediated membrane excitability
Cortical silent period (cSP)	spTMS: measure of EMG suppression following MEP during voluntary contraction of a contralateral muscle	$GABA_B$-mediated and $GABA_A$-mediated motor cortex inhibition
Ipsilateral silent period (iSP)	spTMS: measure of EMG suppression following MEP during voluntary contraciton of an ipsilateral muscle	$GABA_B$-mediated and $GABA_A$-mediated motor cortex inhibition
Input / Output (I/O) curve	spTMS: measure of slope and plateau of the sigmoid curve of MEP amplitudes obtained at a wide range of stimulus intensities	Cortical motor neuron sodium- and calcium channel- mediated membrane excitability and $GABA_A$-mediated motor cortex inhibition
Short-interval intracortical inhibition (SICI)	ppTMS: CS = 50–90% rMT | < 100% aMT TS = 1 mV | 100–120% rMT ISI = 1–6 ms	$GABA_A$-mediated regional cortical inhibition
Long-interval intracortical inhibition (LICI)	ppTMS: CS = 100–130% rMT | TS 1 mV TS = 1 mV | 120% rMT ISI = 50–200+ ms	$GABA_B$-mediated inhibition and (likely) $GABA_A$-mediated network inhibition
Intracortical facilitation (ICF)	ppTMS: CS = 90+ % rMT | > 80% aMT TS = 0.5–1.5 mV ISI = 8–30 ms	Glutamate (NMDA and AMPA receptor types)-mediated excitation
Short-interval intracortical facilitation (SICF)	ppTMS: CS = 100–130% RMT | TS 1mV TS = < rMT | 90% rMT ISI = 1–5 ms	Glutamate (non-NMDA receptor type)-mediated excitation
Intermittent theta-burst stimulation (iTBS)	rTMS: 50 Hz bursts of three TMS pulses repeated every 200 ms in a 2-s on, 8-s off pattern for 190 s (a total of 600 pulses)	Glutamate- and GABA-mediated mechanisms
Continuous theta-burst stimulation (cTBS)	rTMS: 50 Hz bursts of three TMS pulses repeated every 200 ms for 40 s (a total of 600 pulses)	Glutamate- and GABA-mediated mechanisms
Paired associative stimulation (PAS)	spTMS + MNS: 90–200+ pairs of median nerve stimulation (MNS) at the wrist and spTMS to contralateral M1 at 7–10 ITI; ISI = 25 ms (PAS_{25}) | 10 ms (PAS_{10}) | N20 latency of MNS-evoked SSEP + 2 ms (PAS_{N20+2})	Glutamate (NMDA receptor type)-mediated excitation

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CS, conditioning stimulus; EMG, electromyography; GABA, γ-aminobutyric acid; ICF, intracortical facilitation; ISI, interstimulus interval; ITI, intertrial interval; M1, primary motor cortex; MEP, motor evoked potential; NMDA; *N*-methyl-*D*-aspartate; ppTMS, paired-pulse TMS; rTMS, repetitive TMS; SICF, short-interval intracortical

facilitation; SICI, short-interval intracortical inhibition; SSEP, somatosensory evoked potential; spTMS, single-pulse TMS; TS, test stimulus; TS #.# mV stimulator intensity required to elicit MEPs with peak-to-peak amplitudes of #.# mV.

Table 2.

TMS biomarkers in neurodevelopmental disorders.

Disorder	MT	MEP amplitude	cSP	I/O curve slope	SICI	ICF	LICI	TBS	PAS	Clinical correlates	Comments
Autism spectrum disorder	–	–	–		↓, –	↓, –	–	↑ cTBS/ iTBS duration in adults and children; ⊥cTBS-induced facilitation in children	↓	• greater SICI and prolonged cSP negatively correlated w/ academic performance; • ICF inversely correlated w/ inattention and executive dysfunction • reduced SICI correlated w/ developmental delay in language acquisition	• positive correlation between age and cTBS-induced modulation or maximum cTBS-induced inhibition
Fragile X syndrome					–		–	↓ cTBS response; ↑ iTBS response; ↓ cTBS duration; ⊥cTBS-induced facilitation on 2nd visit			• complete blocking of iTBS response on 2nd visit • normal SICI and LICI could be due to unaffected X chromosome / non-optimal ISI
Attention-deficit hyperactivity disorder	↑, –		–, ↓		↓, ⊥ SICI-induced facilitation in a few cases	↓, ↑, –	↓			• SICI inversely correlated w/ symptom severity • ISP duration correlated w/ hyperactivity and restlessness • SICI index of response to MPH	• SICI inversely correlated w/ ISP duration ↑ iSP latency in children ↑ iSP duration in children ↓ iSP latency in adults • ICF greater in ASD children w/ ADHD than in ASD children w/o ADHD

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Disorder	MT	MEP amplitude	cSP	I/O curve slope	SICI	ICF	LICI	TBS	PAS	Clinical correlates	Comments
Tourette syndrome	–, ↑	↓ during movement preparation and volunatry tic inhibition	↓, –	↓, –	↓	↑, –		↑, ↓ iTBS response ↓ cTBS response	⊥ PAS-induced inhibition	• reduced SICI positively correlated w/ motor tic severity • SICI normalization during movement preparation correlated w/ fewer tics and lower tic severity • PAS-induced inhibition correlated with less severe urges and fewer tics	↑ MEP variability ↓ I/O curve slope during voluntary tic inhibition
Developmental stuttering	↑		↑ for tongue	↓ for hand; ↑ for tongue	↓ for tongue	↓ for tongue				• cSP duration negatively correlated w/ stuttering severity in males • extent of higher aMT for tongue in left M1 relative to right M1 correlated with stuttering severity	• aMT for tongue in left M1 higher than in right M1

ADHD, attention-deficit hyperactivity disorder; aMT, active motor threshold; ASD, autism spectrum disorder; cSP, cortical silent period; cTBS, continuous theta-burst stimulation; ICF, intracortical facilitation; I/O, input/output; ISI, inter-stimulus interval; iSP, ipsilateral silent period; iTBS, intermittent theta-burst stimulation; LICI, long-interval intracortical inhibition; M1, primary motor cortex; MEP, motor evoked potential; MPH, methylphenidate; MT, motor threshold; nTMS, neuronavigated transcranial magnetic stimulation; PAS, paired associative stimulation; SICF, short-interval intracortical facilitation; SICI, short-interval intracortical inhibition; TBS, theta-burst stimulation; w/, with; w/o, without; ↑ increase; ↓ decrease; – no change; ⊥ paradoxical; blank cells, not tested;, conflicting results.