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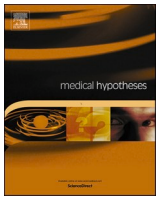

Research Article

Personalized repetitive transcranial magnetic stimulation guided by the spectral electroencephalogram may enhance and democratize therapy for autism spectrum disorder

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ABSTRACT

Autism spectrum disorder (ASD) is a genetically heterogeneous group of neurodevelopmental disorders that affect 1 in 36 children (CDC data) and have recognizable core deficits in common, including repetitive stereotyped behaviors and difficulties in social interaction and communication. Pharmacological interventions moderate some ASD comorbidities, but do not alleviate core deficits and have significant side effects. While many behavioral therapies are inadequate, a very intensive form called applied behavioral analysis (ABA) is demonstrably effective. ABA is based on graded progression and immediate feedback. ABA has raised concerns over its intensive nature and has triggered unease about being too harsh. One solution may derive from a widespread hypothesis of ASD pathogenesis, which posits that the brain in ASD is overexcited, i.e., excitation dominates over inhibition, and electroencephalographic (EEG) alpha band oscillatory activity is altered, which degrades sensory input and task management. This may also disrupt the brain mesolimbic dopaminergic reward cascade causing social interactions to be unrewarding, leading to deleterious social behavior and poor communication. We hypothesize that a comprehensive, personalized form of spectral EEG guided repetitive transcranial magnetic stimulation that we term PrTMS, can normalize alpha EEG oscillations, E/I balance, and dopaminergic reward signaling, to facilitate improved psychosocial behavior. The goal is for PrTMS to synergize with behavioral interventions, so that ABA for example, could be less intensive. This may hold the promise of making self-determination more readily attainable for ASD persons, and could also democratize ASD therapy by rendering it more affordable.

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Introduction

Autism spectrum disorder (ASD) affects 1 in 36 children (US Centers for Disease Control) and refers to an array of neurodevelopmental disorders that have recognizable core deficits in common, including the expression of repetitive stereotyped behaviors and difficulties in terms of social interaction and communication [1]. The pathogenesis of this disorder is highly complex and incompletely understood, and a plethora of advanced molecular biological, genetic, and epigenetic studies have not translated into any treatment modality or working biomarkers for guiding front-line therapy [2]. Moreover, it is not clear whether ASD is lifelong and enduring in all patients. ASD may be "acquired" and in some individuals an abatement of ASD manifestations may develop [3]. There is a diversity of thought in this regard, and recently it was found that a third of patients at age 6 don't meet the criteria for ASD despite early ASD diagnoses [4].

In any case somewhere between 1 and 2 % of the population has ASD, making it a significant public health concern [1]. While pharmacotherapy may reduce ASD comorbidities, such as irritability and aggression, it does not treat core ASD manifestations. ASD affects signaling in the brain mesolimbic system, which is exquisitely nuanced and involves multiple neurotransmitters and receptor subtypes. This is to an extent depicted by the schematic of Fig. 1. Despite the relatively simplified nature of this representation, it may nonetheless be appreciated that alterations of mesolimbic signaling in ASD are likely highly complex and have thus far defied ready targeting and resolution. Moreover, current pharmacological interventions induce adverse effects, such as weight gain and sedation [5]. Behavioral therapies such as sensory integration therapy, music therapy, and holding therapy are not supported by concrete evidence of efficacy [6].

In contrast to the aforementioned measures, applied behavioral analysis (ABA) is an intensive and effective intervention that teaches appropriate behaviors via graded steps and immediate feedback [6]. ABA is widely viewed as the gold standard for ASD therapy, and when applied comprehensively for 20–40 h per week over a number of years, it produces significant benefits in intellectual function, language, and social behavior [7,8]. Unfortunately, ABA is intensive and costly, and it has been criticized in some circles as being too harsh. Lower intensity ABA may only provide moderate improvement [9]. Therefore, there is a high demand for a treatment modality that synergizes with ABA to facilitate the mitigation of intensity and perceived harshness, thereby reducing cost and discomfort. Such an approach may provide patients with a well-tolerated combination therapy that markedly contributes to the stable neurobiological underpinnings needed for social interactions and individual self-determination.

Balance between brain excitation versus inhibition and ASD

A pertinent, widely held construct which forms the central theme of the present article is that ASD initially arises from any of a large and complex array of developmental, genetic, and epigenetic alterations, which converge to common neurophysiological pathways [10]. Within this general context, a dominant theory is that ASD derives from dysregulated excitatory (E) versus inhibitory (I) circuits in the brain which adversely impacts oscillatory neuronal activity and mesolimbic dopamine mediated brain reward signaling. Gao and Penzes (2015) in their excellent review observed that information processing in the brain is modulated by the E/I balance, which at the level of individual neurons is determined by the ratio of excitatory versus inhibitory synaptic inputs [1,11]. The neurotransmitter glutamate activates neurons while gamma-aminobutyric acid (GABA) is inhibitory, and the ratio of glutamate versus GABA synaptic inputs for each cell defines the cells E/I behavior. Compensatory mechanisms modulate this effective ratio [12].

The main consequence of E/I dysregulation is altered oscillatory activity and its associated cognitive processes [13]. Studies have suggested that ASD brains are more excitatory than normal, which affects oscillatory patterns and dopaminergic reward centers [14–16]. Dysregulated reward signaling renders social interactions unrewarding, which degrades social motivation, resulting in significant socio-behavioral deficits. Stavropoulos and Carver (2018) reported that children with ASD exhibit dysregulated alpha oscillatory activity in response to social stimuli. Repetitive transcranial magnetic stimulation (rTMS) is thought to restore cortical E/I balance and the synchrony of brain cortical alpha frequency oscillations [15,16].

This foregoing is of great interest because the alpha band is the dominant spectral EEG band in awake individuals [17–19], and alpha activity may filter sensory input and be especially pronounced in ASD individuals [20,21]. Heiken and coworkers reported that increased calcarine brain region resting state alpha oscillatory power was associated with lower social responsiveness scale scores [22]. Nonetheless,

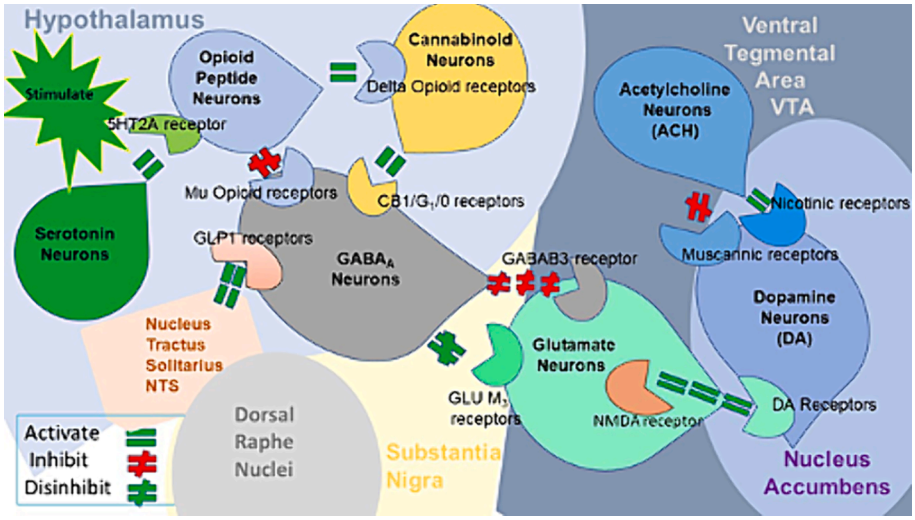

Fig. 1. Dopaminergic brain reward system cascade. The schematic is partitioned into major reward system anatomical structures and the general flow of activation is from left to right, involving at least seven neurotransmitter classes to ultimately stimulate the nucleus accumbens (NAc). The NAc essentially comprises the ventral striatum, a critical reward system structure, to effect reward sensation. The NAc has a reciprocal interaction with the brain cortex, which is not depicted, via afferent and efferent anatomical linkages. The intent of this schematic is to illustrate the complexity of reward signaling, and how dysfunction at any point might conceivably lead to dysregulated reward neurophysiology, a lack of reward sensation from social interactions, and resultant social behavioral deficits. (With permission, Blum et al. [76]).

how the E/I balance may operate in ASD is not well delineated and some authors dispute the E/I theory in ASD [23].

RTMS and the spectral electroencephalogram (EEG) in ASD form a key part of our proposed approach to ASD

Importantly, the clinical outcomes of ABA are evaluated by subjective endpoints, i.e., behavioral assessments, which are limited. Hence, there is an emerging, widespread recognition of the need for a non-subjective and non-invasive neurophysiological ASD status measure, such as the electroencephalogram (EEG), that can help stage ASD severity and chronicle treatment progress [14]. For example, Cao and coworkers suggest more solidly based and less subjective disease status indices in ASD and other neuropsychiatric disorders [24]. They advocate the application of rTMS concurrently with EEG assessment, and discuss deviations from normal in neural patterns, particularly cortical excitability, plasticity, and connectivity, and they identify studies predicting treatment responses and clinical states, using TMS-EEG.

A recent metanalysis of 12 studies on rTMS in ASD by Smith and colleagues [25] revealed that, in aggregate, the data incorporated in their multivariate *meta*-analysis suggested improvement in cognitive outcomes with low-frequency rTMS in the dorsolateral prefrontal cortex (DLPFC). Based on this comparatively small *meta*-analysis, the authors concluded that rTMS may be beneficial for young ASD patients. Moreover, Bejenaru et al. also recently conducted a metanalysis of the English language literature addressing ASD and rTMS, and found that rTMS was safe, and induced improvement in social indices, cognition, eye-hand performance, and irritability [26]. Moreover, some of the studies cited by Bejenaru et al. suggested that rTMS was associated with a reduction in cortical excitability [26].

Hypothesis

"Personalized repetitive transcranial magnetic stimulation (PrTMS) guided by the spectral EEG may enhance and democratize therapy for autism spectrum disorder (ASD)"

The above hypothesis is based on the literature and on an expanded and dynamic form of rTMS that we term PrTMS. Our proposed use of PrTMS is novel and differs from all other approaches for ASD and from standard rTMS, as it involves the following: **(1)** frequent updating of cortical stimulation sites throughout the treatment course which could range from months to years, **(2)** continuous updating of the stimulation frequency, and **(3)** multiple stimulated cortical sites which are targeted according to the regional spectral EEG and via neurocognitive tests. The spectral EEG may be a non-invasive indication of E/I balance, and imbalance of cortical E/I activity is believed to be due to widespread dysregulation of GABA, which is implicated in ASD [27,28]. Other neurotransmitters are almost certainly dysregulated, such as endorphins [17], serotonin [29], cannabinoids [30], glutamate [31], acetylcholine [32], and dopamine [33]. Various explanations have been formulated to explain these findings based on known correlates of neurotransmitter interactions within the brain reward circuitry, as depicted in Fig. 1.

Importantly, within the context of the ratio of E/I balance and cortical preparedness and ASD, individual intrinsic alpha band peak EEG frequency (IAPF) and the synchronicity of alpha oscillations in the cortex may be key indicators [34]. The IAPF increases with age and normal maturation in children. Reduced alpha oscillatory activity in the frontal lobes and reduced connectivity between the frontal lobes and other brain areas have been associated with ASD, and Kang et al. suggested that alpha band properties may be ASD markers [18]. Alpha band coherence between brain cortical regions is crucial for brain connectivity, and a core feature of ASD is atypical oscillatory coherence and disturbed functional brain connectivity [35,36]. Importantly, in the case of the EEG alpha band center frequency, patient to patient variability is not a medical misnomer as it may be for various other physiologic measures, and its potential importance is not overstated. There is considerable between subject variability as multiple studies suggest that each patient's IAPF is different, and we have measured this with our own patients [37,38].

Evaluation of the hypothesis

Autism Behavior Checklist (ABC) scores were significantly improved with rTMS by Kang and colleagues, who also demonstrated that rTMS increased IAPF and coherence over the left DLPFC [18]. Coldea and colleagues in a small study reported that the IAPF may correlate with perceptual sensitivity, possibly through the speed of sensory sampling-which is thought to be disrupted in ASD [39]. Importantly, these authors stated that they found that the difference between IAPF and a fixed 10 Hz rTMS stimulus regime determined whether subject performance improved or worsened, suggesting that rTMS stimulation frequency should be individualized [39]. In other words, the greater the difference between the fixed 10 Hz stimulation and the patients actual IAPF, the worse the outcome in terms of the patient's performance. On the other hand, however, the alpha band peak center frequency may be difficult to discern in ASD as a discrete alpha peak may not be apparent [40]. In this context, a robust regression of the spectral EEG, as described by Donoghue et al., Waschke et al., and Alnes et al., may be a key EEG measure related to E/I balance and oscillatory synchrony, and possibly E/I balance in ASD [41,42]. The results obtained thus far suggest that a systematic, blinded sham-controlled study assessing the change in the E/I indicated by the spectral EEG along with improvement in ASD scores during and after PrTMS in ASD patients may yield important validating data.

A key element of the perspective we proffer is that PrTMS intentionally avoids potentially ineffective or even deleterious 'one size fits all" rTMS regimens, and thus will be less disruptive and more effective. The use of PrTMS as an adjunct therapy may help to mitigate and enhance ABA to achieve therapeutic improvement in a better tolerated way, and thus, ultimately, lead to empowerment of ASD patients as individuals. This is highlighted by the findings of Lin and Fang, who personalized the rTMS stimulus frequency over the frontal cortex of patients by using alpha power and connectivity as guides, in a single patient with ASD, who exhibited improved scores on the childhood autism rating scale (CARS) and the autism spectrum quotient (ASQ) [43]. In this study, the level of alpha coherence increased between the frontal and parietal and frontal and temporal lobes. Similarly, in a larger study of 28 ASD patients by Ezedinma et al., the individual peak alpha frequency was used to guide rTMS stimulus frequency, and this approach increased individual alpha frequency and significantly improved CARS and PedsQLTM 4.0 autism survey scores [44].

Potential clinical implementation of the hypothesis

Importantly, ASD typically involves multiple brain cortices, so simply treating the DLPFC alone or with one other site may be insufficient. A key premise of PrTMS is the treatment of multiple cortical sites at reduced rTMS machine power, as suggested by Zmeykina et al. [45]. Lower machine power allows for the targeting of multiple treatment sites along with sensory, premotor, and motor sites with far less risk of seizure and other potentially adverse effects [45,46]. Hence, we are proposing that patients presenting with ASD be evaluated via physiological and genetic tests to determine the presence and extent of their ASD. First, we suggest that patients provide a cheek swab to identify known reward gene polymorphisms (DNA) and known antecedents with the validated Genetic Addiction Risk Severity (GARS) test [47–53].

Second, the spectral EEG may be a useful, noninvasive ASD biomarker, and here it is noteworthy that recently Makale et al. showed clinical improvement with spectral EEG-guided PrTMS treatment of a large cohort of military veterans with post-traumatic stress disorder (PTSD) [37]. PTSD is a neuropsychiatric syndrome that has indeed been associated with ASD [37,54], and ASD may predispose individuals to

PTSD. ASD symptoms may be exacerbated by PTSD, and PTSD and ASD are thought to share common mechanisms [54]. So, in terms of diagnostics, Makale et al. reported that following PrTMS treatment in PTSD, the 1/f robust regression of the spectral EEG became steeper, denoting less cortical excitation and increased inhibition, with greater synchrony and less neural noise (Fig. 2) [37,55]. It is noteworthy that a prior individualized rTMS study by Taghva et al. in 16 patients also found clinical improvements on a PTSD questionnaire (PCL-M) and the relative global EEG alpha-band (8–13 Hz) exhibited increased power, going from 32.0 to 38.5 percent (P = 0.013) [56]. We predict that for ASD subjects a 1/f regression may be steeper after PrTMS, denoting less excitation in the brain cortex. Of course ASD is complex and the actual change in slope needs to be revealed experimentally, but in any case the spectral EEG regression slope may be a key biomarker.

In this paper we have hypothesized that by incorporating a more individualized or personalized approach, especially as it relates to neuromodulation of the reward circuitry, PrTMS may have enhanced heuristic value over and beyond current existing data acquired via simple non-EEG TMS in a moderate ASD cohort [57–60]. Fig. 3 provides a schematic of our proposed ASD treatment model. The spectral EEG may serve as a nonsubjective, noninvasive neurophysiological marker for ASD and may relate to ASD mechanisms. For example, the spectral 1/f robust regression is postulated to indicate the balance between excitation and inhibition, to provide an index of underlying cortical "noise", and that it may reflect the dominant neurotransmitter profile [55]. Currently there is an ongoing clinical trial being conducting by Lawrence Fung and colleagues at Stanford University using functional magnetic resonance imaging (fMRI) personalization of intermittent theta-burst TMS stimulation to target irritability in adults with ASD (ClinicalTrials.gov NCT04316338). The outcome of this personalized approach will be most interesting, especially when analyzed in the light of the concepts discussed in the present paper.

ASD related syndromes that may also respond to PrTMS

Post-Traumatic Stress Disorder (PTSD) – As mentioned earlier, Makale and coworkers (2023) demonstrated that PrTMS is effective for treating the manifestations of PTSD [37]. When contemplating the pathogenesis and salient features of ASD and PTSD, and the applicability of PrTMS, it may be worthwhile to explore the polyvagal theory and examine whether these two syndromes share pathophysiological mechanisms. According to the polyvagal theory, efferent and afferent fibers in the vagal nerves that are associated with autonomic cardiac and

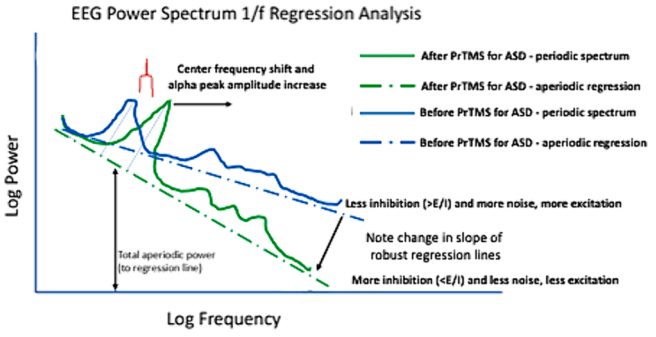

Fig. 2. Hypothesized $1/f^{a}$ spectral EEG before and after PrTMS for ASD. The periodic spectral EEG components include the alpha peak, which contains the center frequency, also called the individual peak alpha frequency (IAPF). A robust regression line indicates the aperiodic component, where $1/f^{a}$ is indicated, with a = slope, and is held to be reflective of relative excitation versus inhibition, i.e., E/I. A steeper regression, E≪I, indicates greater cortical inhibition relative to excitation. In ASD there is held to be greater excitation (E≫I) and the spectral EEG regression line should be relatively shallow, while PrTMS might steepen the line by alleviating the degree of excitation, e.g., E≪I. Adapted from Donoghue et al., Nature Neurosci (2020) [41].

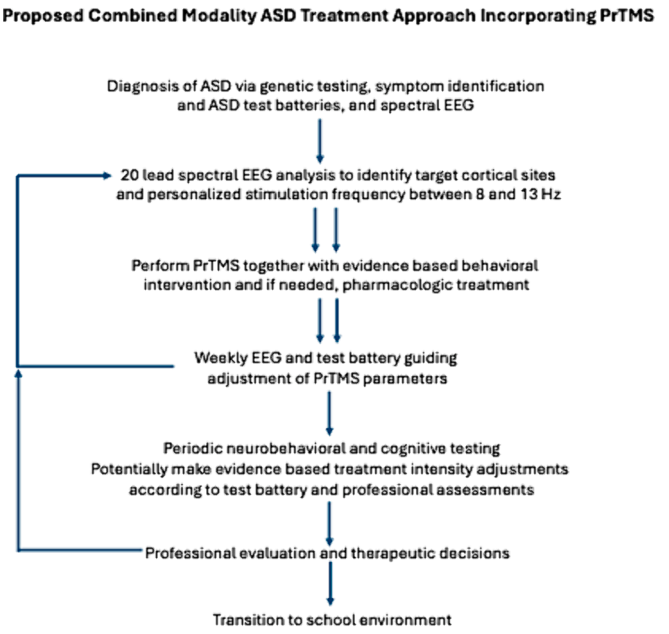

Fig. 3. Proposed ASD treatment scheme including PrTMS and evidence based behavioral therapy. The flow diagram indicates that initial assessment would also include the spectral EEG to guide selection of stimulation frequencies and the specific cortical territories that would be targeted for stimulation. After periodic assessment the patient would either continue the treatment with reduced intensity or transition to a school environment based on appropriate training.

respiratory activity have a reciprocal relationship with centers in the brain [61]. In the pig, which is physiologically comparable to humans, each vagal nerve contains roughly 360,000 fibers, of which about 80 % are afferents. In humans these afferent fibers via various brain anatomic linkages communicate with forebrain areas that are thought to be involved in a number of psychiatric disorders [62,63].

Physiologic states mediated by vagal nerves support different classes of behavior, such as behavioral shut-down and spontaneous social engagement [61]. The polyvagal theory proposes that the autonomic nervous system, of which the vagal nerves are key elements, is the substrate for emotional experiences and affective processes that comprise social behavior [61]. ASD individuals have disturbances in this autonomic cybernetic apparatus which are reflected in somatomotor and visceromotor elements of the social engagement system, and these subjects have altered connectivity between the autonomic nervous system and brain subregions [61,64–66]. ASD and PTSD include hyperactivity or hypervigilance, difficulty with social interactions with others, and difficulty with sleep and concentration [54,67]. These similarities and the high rate of co-occurrence between ASD and PTSD warrant a closer examination of related autonomic underpinnings and in that context, the E/I balance and the relative applicability of PrTMS for these two disorders [68].

Parkinson's Disease (PD) - Dopamine signaling alterations are involved in both ASD and Parkinson's Disease (PD) and systematic studies have shown that persons with ASD have a higher incidence of PD than the general population and matched controls. The pathophysiology of PD involves the selective loss of dopaminergic neurons in the substantia nigra along with other central nervous system structures [69]. Dopaminergic pathways are implicated in the pathogenesis of ASD since dopamine is responsible for social behavior and movement, and a key social reward locus is the striatum and the substantia nigra. Various genes such as *PARK2* are associated with both ASD and PD. Moreover, motor deficits are prevalent in ASD and PD [70]. Several publications have reported that rTMS may be beneficial in PD. Zhang and coworkers conducted a *meta*-analysis of the literature between 1988 and 2022, and

concluded that rTMS could be used as a possible adjuvant therapy for PD in terms of motor deficits and depression [71]. Jiang and colleagues performed a *meta*-analysis on 14 studies and concluded that multiple sessions of high frequency rTMS over the dorsolateral prefrontal cortex (DLPFC) may have positive effects on executive function in PD patients [72].

Consequences of the hypothesis and discussion

Individuals with autism spectrum disorder (ASD) have deficits in sensory processing, cognition, and social communication and interaction, together with restricted and repetitive patterns of stereotyped, ritualistic behaviors and rumination. Today, ASD occurs in 1 to 2 % of the population, and is not only disruptive in nature but also very costly [1]. Proposed underlying mechanisms of ASD include immune inflammation, gene transcription, epigenetic post-translational modifications, abnormal synaptic signaling pathways, inclusion as a subtype in reward deficiency syndrome, RNA and non-coding RNA translation, the brain-gut axis, and neural loop abnormalities [73].

In truth the pathophysiology of ASD is not known, and the disordered behavioral states that seem to persist, but do not do so in all ASD patients, present a challenge which can require effort to resolve. Our hypothesis addresses a possible convergent pathway in ASD. This is potentially very important in ASD treatment, because it may lead to PrTMS based therapy to help significantly lessen dysfunctional cortical relationships and activity patterns, and to reduce the acquisition of maladaptive stereotypical behaviors and reward deficiency addictive-like behaviors.

Limitations and conclusions

Here, it is imperative to understand that as scientists and clinicians we are not wishing to convey the idea of PrTMS neuromodulation by itself as a standalone therapy, or so called “cure” for ASD. We believe that by personalizing TMS stimulation frequency based on spectral EEG we can avoid negative effects and indeed can render PrTMS a useful orthogonal adjunct to ABA by positively affecting the E/I cortical balance, i.e., moving the center frequency of affected cortical territories in ASD toward the subject’s intrinsic IAPF which is retained in the visual cortex (occipital cortical area). The aim is reduction of cortical over-excitation that seems to be present with ASD. This form of adjunct therapy may help make the patient more responsive to less intensive and less uncomfortable ABA.

Some clinicians believe that behavioral interventions linked to ABA do help with behavioral aberrations, and we are suggesting a combined treatment approach consisting of two orthogonal therapeutic modalities [74]. However, despite our goal of decreasing the intensity and increasing the tolerability of ABA by coupling it with PrTMS, it is important to recognize that PrTMS may also conceivably be combined with other, evidence-based interventions, as many ASD rights and neodiversity thinkers have expressed significant reservations and concerns about ABA [75].

We also advocate neurophysiologically based assessments, specifically the spectral EEG analyzed via robust regression. These should be pursued as part of a novel, optimized treatment strategy to chronicle patient ASD status, and to guide the normalization of brain signaling patterns via PrTMS, administered together with evidence based behavioral therapies, to alleviate a range of disabling ASD manifestations.

Author contributions

KB and MM wrote the initial draft of the manuscript, AB, KS, reviewed and edited, MRM assisted with literature searches, analyses, and references, MSG edited for conceptual underpinnings, IE analysed concept and edited, CAD assisted with literature searches and organization, and KTM guided conceptualization and description of proposed PrTMS application.

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CRediT authorship contribution statement

Milan T. Makale: Conceptualization, Writing – original draft, Writing – review & editing. **Kenneth Blum:** Conceptualization, Writing – original draft. **Abdalla Bowirrat:** Writing – original draft. **Keerthy Sunder:** Conceptualization. **Miles R. Makale:** Writing – review & editing. **Mark S. Gold:** Writing – review & editing. **Igor Elman:** Writing – review & editing. **Catherine A. Dennen:** Writing – review & editing. **Kevin T. Murphy:** Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Blum is the inventor of GARS and KB220 patented in the USA and foreign domains. Dr. Blum is a paid consultant at the Sunder Foundation and PeakLogic. Dr. Makale is a paid collaborator at PeakLogic. Dr. Kevin Murphy is the inventor of PrTMS and owns PeakLogic. There are no other potential conflicts to report. Both the Sunder Foundation and PeakLogic honor persons with ASD and acknowledge the difficulties that led to its inclusion as a disorder in the DSM 5TR, and while all might not agree, the Sunder Foundation and PeakLogic fund research aimed at resolving the challenges experienced with ASD, for the improvement of quality of life (QOL) and to help attain self-determination.

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