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# The potential of repetitive transcranial magnetic stimulation for addressing sleep difficulties in children with autism – A brief communication

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ABSTRACT

Sleep difficulties can co-occur with autistic traits and have been frequently reported in children diagnosed with autism. Thus, sleep difficulties may impact neural development, cognition, and behavioural functioning in children with autism. Interventions, such as repetitive transcranial magnetic stimulation (rTMS), that target aberrant neural structures underpinning autistic traits and sleep difficulties in children could have beneficial effects. The rTMS effects on the pathophysiological pathways hypothesised to underpin autism and sleep difficulties are well-established in the literature; however, clinical evidence of its potential to improve sleep difficulties in children with autism is limited. While the preliminary data is promising, further robust rTMS studies are warranted to encourage its use in clinical practices.

## 1. Sleep difficulties in children with autism

Sleep is a biological necessity for typical neural development and functioning. Sleep maintains and enhances synaptic processes and cortical plasticity, which are necessary for learning and memory consolidation [1]. Thus, sleep difficulties may impact neural development, cognition, and behavioural functioning [3]. Sleep difficulties can co-occur with autistic traits and have been frequently reported in children diagnosed with autism [4]. Autism and co-occurring sleep difficulties in children are strongly associated with concomitant parental stress and reduced quality of life. Consequently, the National Sleep Foundation identifies children with autism as one of the highest-priority populations for sleep research.

Sleep difficulties that can frequently co-occur in children with autism include difficulty falling asleep, sleep onset delay, bedtime resistance, sleep anxiety, daytime sleepiness, early waking, co-sleeping, shorter sleep duration, frequent and prolonged night waking, low sleep efficiency and parasomnias [4]. These sleep difficulties may be multifactorial in origin, with causes including synaptic protein abnormalities, sensory abnormalities and increased arousal, abnormal sleep-regulating hormones, and circadian sleep disruptions. For a full review, see Lorsung and colleagues (2021) [12]. One potential mechanism underpinning these aetiologies may include the role of the GABAergic system in sensory abnormalities and increased arousal in autism [5] and sleep difficulties [6].

Effectiveness of repetitive transcranial magnetic stimulation in children with autism with sleep difficulties.

Recommended first-line interventions for children with autism and sleep difficulties typically include behavioural sleep strategies such as sleep hygiene, faded bedtime, and chronotherapy [4]. Repetitive transcranial magnetic stimulation (rTMS) is an intervention of interest given that it employs a magnetic field generated from an electromagnetic coil placed on the scalp regions corresponding to specific brain areas, such as the dorsolateral prefrontal cortex (DLPFC), to modulate neural structures and functions implicated in the pathophysiology and neurochemistry underlying autism (For a full review, see Desarkar et al. [7] and Khaleghi et al. [8]). rTMS should be differentiated from single-pulse transcranial magnetic stimulation as the latter is solely used for explorative purposes [9].

The DLPFC is also a specific brain area involved in the

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pathophysiology of sleep difficulties [2]. rTMS of the DLPFC may be beneficial to sleep difficulties co-occurring in children with autism. Such hypotheses have been reported in several neurological conditions. For instance, a recent review by Babiloni and colleagues (2020) documented improved sleep difficulties co-occurring in depression, parkinsonism and chronic pain following rTMS of the DLPFC. However, multiple regulatory agencies have only approved rTMS for the treatment of depression, anxiety, obsessive-compulsive disorder, and substance use disorders [10]. Furthermore, there is a lack of evidence and data on its effectiveness on sleep difficulties co-occurring in children with autism. Currently, there are no recommended guidelines for rTMS in children with autism and sleep difficulties.

Table 1 summarises the characteristics of the two recent non-randomised controlled small sample size studies on the rTMS effect within the population. The open-label study by Gao et al. [11] recruited 41 children with autism (mean age 9.0 ± 4.4; male to female ratio 4:1) and an elevated (>41) Total Children's Sleep Habits Questionnaire (CSHQ) score. The authors delivered a combination of low (1 Hz) and high (5 Hz)-frequency rTMS to the left and right dorsolateral prefrontal cortex (DLPFC), five sessions per week for one week, in two courses four weeks apart. Thirty-nine children completed the study. There was a mean decrease in the Total CSHQ scores from 53.2 ± 6.1 to 47 ± 6.2 ($p < 0.01$) between the baseline (T0) to the 8th week (T2). The CSHQ subdomain scores were statistically insignificant between the 4th week (T1) and 8th week (T2).

Gao et al. [11] reported sleep outcomes to be partially mediated by improved sensory abnormalities, such as tactile and auditory abnormalities, emotional conduct, and social problems. Within this cohort, it could be suggested that reported sleep difficulties are underpinned by sensory abnormalities and increased arousal [12], potentially due to disruptions in the GABAergic system [6]. Another aetiological pathway worth mentioning is orexin disruption, given its association with the GABAergic system in regulating the sleep-wake cycle [13]. However, evidence that improved sensory abnormalities partially mediate sleep outcomes via both aetiologies remains scarce [2].

As mentioned previously, the GABAergic system is also implicated in increased arousal in autism [5] and sleep difficulties [6]. Gao et al. [11] may have opted for a low-frequency stimulation protocol to dampen the increased arousal of the GABAergic system implicated in sleep difficulties [13]. Although the author's use of low stimulation intensity output, compared to other rTMS studies [8], may suggest limited modulatory effect of underlying GABAergic systems. Therefore, in the absence of an established standard rTMS protocol, such as stimulation site, frequency, and intensity output, the lack of a control group to adjust for a potential placebo effect or primary caregiver's response bias on the CSHQ survey is significant [14].

In a retrospective study, Ezedinma et al. [14] reviewed the clinical charts of 28 children with autism (mean age 6.1 ± 1.8; male to female ratio 13:1) with caregiver-reported history of *sleep problems* (n = 17, 60 %). Subjects received 19 sessions (one session per weekday) of high-frequency (8–13 Hz) rTMS to the dorsomedial prefrontal cortex (dmPFC) and or medial parietal cortex (mPC). Clinical notes of the 17 patients with *sleep problems* showed 8 (improved), 3 (had no change) and 6 (had missing data). From the Paediatric Quality of Life Inventory survey (PedsQLTM 4.0), which included a question on *sleep troubles,* scored on a Likert scale, analysis of pre-post treatment data (not included in the original publication) showed that 9 (improved), 13 (had no change) and 6 (worsened) with a mean decrease of 1.79 ± 1.5 to 1.46 ± 1.3 ($p = 0.1$).

The mixed caregiver-reported sleep outcomes (i.e., improvement, no change and worsening) may be due to the subjectivity in PedsQLTM 4.0 and the fact that this is not a validated sleep measure. Mixed outcomes were also documented alongside improved alpha rhythms. Alpha rhythms are the most salient electroencephalogram (EEG) event and may be fundamental to neural development, cognition and behavioural functioning [15]. Given that sleep difficulties impact these fundamental processes [3], an improvement in alpha rhythms may correlate with improved sleep difficulties [16]. Thus, electroencephalographic measures of alpha rhythms during awake and sleep states, following rTMS, are needed to demonstrate such correlation.

Importantly, Sandyk [17] hypothesise that alpha rhythm could be an electrophysiological marker for pineal gland activity in individuals with autism. Evidence suggests a potential link between the expression of alpha rhythm and pineal gland melatonin secretion [18]. rTMS effect on

**Table 1**
Characteristics of rTMS studies.

| Authors | Sample size (Age range, mean age± standard deviation in years) | Sex | Study design | rTMS protocol | | | | Assessment measures | Outcomes | Side effects |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Stimulation site(s) | Stimulation frequency | Number of Sessions | Resting motor threshold (%) | | | |
| Gao et al. [11] | 39 (2–18; 9.0 ± 4.4) | 31 Males, 8 Females | Open-label | L and R-DLPFC | 1 Hz and 10 Hz | 40 | 25 | CARS, CSHQ, RBQ-2, SSP, SDQ, PPVT | Significant improvement in sensory abnormalities, such as tactile and auditory abnormalities, and emotional conduct and social problems of autism and sleep problems. | Not reported |
| Ezedinma et al. [14] | 28 (3–9; 6.1 ± 1.8) | 26 Males, 2 Females | Retrospective Case series | DmPFC/ mPFC | 8–13 Hz | 19 | 80 | CARS, PedsQLTM 4.0, EEG, clinical evaluation | Improvement in autism symptoms, quality of life, alpha rhythms, and mixed findings on sleep outcomes. | Transient hyperactivity, tantrums, crying, screaming, and a rare case of hypersalivation were reported. |

**Key:** NR – *Not reported, left (L), right I, bilateral (B), Dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (mPFC), dorsomedial prefrontal cortex (dmPFC), Electroencephalography (EEG), Childhood Autism Rating Scale (CARS) Paediatric Quality of Life Inventory 4.0 (PedsQLTM 4.0), Repetitive Behaviour Questionnaire (RBQ-2); Short Sensory Profile (SSP), Strengths and Difficulties Questionnaire (SDQ), Peabody Picture Vocabulary Test (PPVT), Child's Sleep Habits Questionnaire (CSHQ), Repetitive Transcranial Magnetic Stimulation (rTMS).*

pineal gland melatonin production [19] may be due to the widespread interconnectivity and potential exertion of integrated responses on distal and subcortical brain regions via dopaminergic pathway following stimulation of the frontal cortex [13]. Both studies stimulated the frontal cortex, suggesting that this frequently stimulated brain area may underscore the positive sleep outcomes as reported in other neurological conditions [13].

Given that rTMS modulates widespread neural structures, its safety in children is of great importance, especially when applying high-frequency stimulation. High-frequency rTMS (HF-rTMS) increases cortical arousal [13], which should be expected to worsen autistic traits [5] and sleep difficulties [6] via the GABAergic system. Despite delivering over 19 to 40 sessions of HF-rTMS, Ezedinma et al. [14] and Gao et al. [11] did not report any adverse events, such as seizures. Seizures are very rare, less than 0.01 %, and their absence in both studies is consistent with findings on the safety and tolerability of rTMS in children with autism [20]. It is important to note that both studies used a lower stimulation intensity that may have dampened the potential for increased cortical arousal during HF-rTMS.

## 2. Limitations and recommendations

The effect of rTMS on the pathophysiological pathways hypothesised to underpin autism and sleep difficulties are well described in the literature. However, evidence on the clinical benefits of rTMS to sleep difficulties co-occurring in children with autism is sparse and preliminary and should be interpreted cautiously due to several limitations such as small sample size, lack of randomised control groups and objective sleep measures, and multiple studies [11,14]. To address current limitations, a larger sample size, multisite, double-masked RCTs using standardised rTMS protocols (stimulation location, frequency and intensity), objective sleep measures (polysomnography or actigraphy) and long-term study follow-ups are needed to rigorously evaluate the potential of rTMS in sleep difficulties in children with autism in order to provide a solid evidence base for adoption into clinical practice.

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## CRediT authorship contribution statement

**Uchenna Ezedinma:** Writing – review & editing, Writing – original draft, Validation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Scott Burgess:** Writing – review & editing, Writing – original draft, Validation, Supervision, Formal analysis, Data curation, Conceptualization. **Jane Nikles:** Writing – review & editing, Writing – original draft, Validation, Supervision. **Terri Downer:** Writing – review & editing, Writing – original draft, Validation, Supervision. **Evan Jones:** Writing – review & editing, Validation, Supervision, Resources, Funding acquisition, Conceptualization. **Alexandra Metse:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology. **Shauna Fjaagesund:** Writing – review & editing, Writing – original draft, Resources, Project administration, Funding acquisition. **Florin Oprescu:** Writing – review & editing, Writing – original draft, Validation, Supervision, Formal analysis, Data curation, Conceptualization.

## Declaration of competing interest

UCHENNA EZEDINMA reports financial support was provided by TMS IP, an affiliated entity of the Brain Treatment Centre Australia. Evan Jones reports a relationship with TMS IP, an affiliated entity of the Brain Treatment Centre Australia that includes: board membership. Uchenna Ezedinma reports a relationship with TMS IP, an affiliated entity of the Brain Treatment Centre Australia that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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