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Impact of transcranial magnetic stimulation on motor function in children with acquired brain injury: a scoping review protocol

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ABSTRACT

Background Children with severe acquired brain injury (ABI) require early and effective neurorehabilitation provision to promote a good long-term functional outcome. Transcranial magnetic stimulation (TMS) has been used to improve motor skills for children with cerebral palsy but there is limited material supporting its use in children with ABI who have a motor disorder.

Objective To systematically answer what the TMS intervention effects are on motor function in children with ABI as reported in the literature.

Methods and analysis This scoping review will follow Arksey and O'Malley's scoping review methodological framework. A comprehensive computerised bibliographic databases search will be performed in MEDLINE, EMBASE, CINAHL, Allied and Complementary Medicine, BNI, Ovid Emcare, PsycINFO, Physiotherapy Evidence Database, Cochrane Central Register using keywords related to TMS and children with ABI. Studies that examine the effect of TMS intervention on motor function as either a primary or secondary objective will be included for this review. Study design and publication detail, participant demographic details, type and severity of ABI and other clinical information, TMS procedure, associated therapy intervention, comparator/control parameters and the outcome measure used data will be gathered.
The International Classification of Functioning, Disability and Health for Children and Youth framework will be used to report the TMS effect in children with ABI. A narrative synthesis of the findings describing the therapeutic effects of TMS intervention, limitations and adverse effects will be synthesised and reported. This review will help to summarise the existing knowledge base and to guide further research areas. This review outcome may help to evolve therapists' role to next-generation technology-based neurorehabilitation programmes.

Ethics and dissemination No ethical approval is required for this review as we will be collecting data from previously published studies. We will present the findings at scientific conferences and publish in a peer-review journal.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Transcranial magnetic stimulation (TMS) has been used to improve motor skills through neural plasticity in adults who have suffered from a stroke; and for children with cerebral palsy. There is limited evidence, however, of its use in improving motor function in children with acquired brain injury (ABI).

WHAT THIS STUDY ADDS

⇒ Evidence of the impact of TMS on motor function in children with ABI.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The outcome of the review will inform the existing evidence related to the therapeutic effect of TMS in children with ABI. This will help to identify any knowledge gaps, future research questions and to develop future clinical trials that will be able to assess the effectiveness of TMS in children with ABI rehabilitation.

BACKGROUND

Acquired brain injury (ABI) is the term used to describe traumatic and non-traumatic brain injuries that occur after birth and a period of typical development.[1] In the UK, ABI accounts for 35,000 childhood presentations to emergency departments annually. Of these, 5% have moderate to severe brain injury.[2] Children with severe ABI will often have movement difficulties caused by weakness, abnormal muscle tone, poor motor control, poor concentration, fatigue and other comorbidities.[3] They may also have difficulties with speech, swallowing and cognitive impairment. A subgroup of children with ABI present with a stroke like presentation limiting their activity, balance, gait and fine motor skills. They are likely to develop tightness and contractures in both the upper and lower limbs.[4] This impairment leads to functional difficulties including self-care, playing with and manipulating toys, socialising with and academic activities.[4] During the acute phase, children with moderate to severe ABI frequently require a period of demanding medical and rehabilitative care to optimise their long-term capabilities and quality of life

through neuroplasticity.[5] This acute care can last up to 12 months following the initial brain injury which often requires a wide range of neurorehabilitation measures from a multidisciplinary team.[6]

Early and effective neurorehabilitation provision promotes a good long-term functional outcome for children with ABI.[7] Active rehabilitation begins as soon as they are medically stable. The typical rehabilitation includes facilitation of movements, postural control, postural care management, constraint-induced movement therapy (CIMT), strength training, dysphagia and communication management; and tone medications to improve motor and functional skills through neuroplasticity.[6] Recent advances in technology enable clinicians to use functional electrical stimulation, virtual reality (VR)[4] and transcranial magnetic stimulation (TMS) to improve motor skills for children with central nervous system-related movement disorders.[8 9]

TMS is a non-invasive treatment technique.[10] It is safe to use for children and adolescents with neurological conditions.[11] It delivers repetitive magnetic pulses directly to specifically targeted brain areas through electromagnetic induction. TMS is applied over the scalp either on the same or opposite side to modulate cortical excitability through electromagnetic induction. In TMS, an electric charge is applied to a small coil and this produces a magnetic field perpendicular to the coil. This magnetic field creates an electrical current in the brain tissue parallel to the coil. This activates the localised neurons through cortical excitation.[12] Low frequency TMS reduces cortical excitability but the high frequency increases it, thereby producing the desired therapeutic effect.[13] Navigated repetitive TMS is delivered to a targeted brain area to change polarisation and it has been shown to influence cortical excitability many minutes after initial stimulation.[14] This will help to facilitate, inhibit or interrupt the cortical network depending on the frequency and intensity of the stimulus, thus promoting a cortical function change through neuroplasticity.[15]

TMS has been widely used in adult stroke rehabilitation to facilitate cortical excitability and to promote neuroplasticity.[16] Early application of TMS (from 2 weeks to 2 months, 5–15 sessions; 1–10 Hz) coupled with other rehabilitation therapy intervention has been shown to result in decreased motor impairment, improved activity and participation level in the stroke population.[14] TMS has been used to treat children with neuropsychiatric disorders including children on the autistic spectrum, those with attention deficit hyperactivity disorder, obsessive–compulsive disorder and also tics.[8] A systematic review investigated the effectiveness of non-invasive brain stimulation for rehabilitation of children with cerebral palsy (CP).[17] This review identified 4 studies that used repetitive TMS (5–10 sessions, with each session lasting between 10 and 20 min). Three studies used inhibitory low frequency repetitive TMS over the contralateral motor cortex and one study used both high and low frequency repetitive TMS over the primary motor area. A meta-analysis of the outcome measure indicated improved upper limb function following repetitive TMS.[17]

It is worth noting that some literature includes children with CP as ABI. An injury to the brain occurs in very early life in CP, whereas in ABI the injury is sustained after a period of normal development.[18] It could be argued that the description and presentation of CP is markedly different from those who sustained moderate to severe ABI at a later time in their childhood. Enhanced neuroplasticity in the developing brain may prove to be advantageous in rehabilitation following ABI. Structural and functional neural plasticity is attributed to change in regional volumes in brain cells or formation of neural pathways through synaptogenesis, axonal or dendritic sprouting and the creation of new neurons.[19] Synaptic and intrinsic mechanism regulates neural excitability which influences neural plasticity.[20] Metaplasticity, an activity-dependent modulation of synaptic plasticity was induced by TMS in adult neurological disorders such as stroke and Parkinson's disease. TMS can be an effective tool to treat brain disorders through inducing metaplasticity.[21] TMS coupled with regular rehabilitation could provide improved outcomes through neural plasticity[22] and metaplasticity. If this is the case, TMS combined with intensive rehabilitation appears to be a promising new intervention approach with wider future applications for children with ABI. There is, however, limited material supporting its use in children with ABI who have a motor disorder.

The intervention effect in rehabilitation research has been widely reported using the International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY) framework.[23] The ICF-CY domain consists of body structures and function, activity, participation and contextual factors (environment and personal) which can be used to classify the level of functioning in childhood.[6] This model can be applied to report the functional outcome of children and young people (CYP) with ABI who have impaired physical, cognitive and emotional difficulties and the impact on activity limitation and participation restriction following an intervention.[6]

The overall objective of this scoping review will be to examine the literature relating to the therapeutic effect of TMS in children with ABI. The outcome of this review will be categorised according to the ICF-CY dimensions. This review will help to summarise the existing knowledge base and to identify areas requiring further research.

METHODS

This review protocol will follow both the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist[24] and Arksey and O'Malley's scoping review approach.[25] In addition, the PRISMA protocol guidelines will be followed to ensure scientific rigour[26] (see online supplemental file).

Identifying the research question

The primary aim of this scoping review will be to characterise TMS intervention. We will specifically answer the question 'what are the effects of TMS interventions on motor function in children with ABI as reported in the literature?'.

Identifying relevant studies

Search strategy

A copy of the full search strategy as run in Ovid Medline is provided in online supplemental appendix 1. This search will be modified as necessary to be completed in the following databases.

- Electronic database search: A comprehensive computerised bibliographic databases search will be performed in the following databases:
  - MEDLINE (1946–current).
  - EMBASE (1974 to current).
  - Cumulative Index to Nursing and Allied Health Literature.
  - Allied and Complementary Medicine (1985 to present).
  - British Nursing Index (1992–present).
  - Ovid Emcare (1994 to current).
  - PsycINFO (1806–current).
  - Physiotherapy Evidence Database.
  - Cochrane Central Register.
- Trial registers: The unpublished and ongoing clinical trial information will be gathered by searching www.clinicaltrial.gov, www.who.int/trialsearch and www.controlled-trials.com.
- Contacting the corresponding authors of the included articles and asking them to provide the details of any other TMS-related research studies in ABI either by their team or by their associates and research group.
- Citation Searching from the included individual studies.
- Other sources
  - The references included in the list of papers selected from the electronic database.
  - A handsearch will be carried out in specific key journals that have published the maximum number of relevant articles selected for this review. This option will only be carried out if there are more than three articles selected from a particular journal.
- Searching Dissertation Abstracts (using ProQuest), conference proceedings and abstracts related to TMS and contacting the researchers to provide any additional information.
- The following TMS equipment manufacturers/distributors will be contacted via email and asked for the details of any trials related to TMS in paediatric ABI population (Axilum Robotics, Brainbox, Brainsway, DEYMED Diagnostic' EB Neuro, eNeura, Jiangsu Aegean Technology, MAG & more, Magstim, MagVenture, Neuronetics, Neurosoft, Nexstim, NIBBOT International, Remed, Sebers Medical, Shenzhen Yingchi Technology, Soterix Medical, Syneika, Xuzhou Kejian).

Eligibility criteria

The searches will be confined to children under 18 years old with ABI only. Some studies include the adolescent population (15–25 years) and the review team will contact the authors to seek data for the children under 18 years old only. If no response is received, the article will be excluded and this will be documented. All the subgroups of ABI including traumatic, non-traumatic and brain tumour will be included but children with CP will be excluded. If a study has children with CP along with the ABI population, the review team will exclude data related to the CP population. If such information is not clearly available, the review team will contact the authors to seek clarification. If no response is received, the article will be excluded and this will be documented.

Studies that examine the effect of TMS intervention on motor function as either a primary or secondary objective will be included. Research studies that include TMS for diagnostic purposes will be excluded.

All type of studies such as reviews, clinical trials, cohort studies, case series, case reports and technical reports will be included. No exclusion criteria will be set for language or publication years, and these studies will be considered if the title and abstracts have been written in English. The review team will contact the corresponding authors and request the information in English within 2 weeks. If no response is received, those studies will be excluded and this will be documented.

Study screening and selection

An electronic database search will be completed by the professional librarian and uploaded in the Ryaan software after removing duplicated studies. The collected titles and structured abstracts from the electronic database will be scrutinised independently by two reviewers by following the set inclusion and exclusion criteria. The excluded studies will be classified as irrelevant and the reasons will be documented. Grey literature and the trial database will be searched by two reviewers independently.

Full articles that meet the selection criteria from the above source will be collected from the NHS library services and the University of Birmingham library services. Two reviewers will decide which articles will be suitable for the final review and any disagreement will be managed after discussing with the third reviewer.

The selection process will be piloting 20% of the collected electronic and grey literature at the beginning to ensure reliable interpretation and agreement between the reviewers. Disagreement will be resolved with a consensus meeting. If no consensus reached, a third reviewer will be consulted. A PRISMA flow chart will be used to inform the selection process.

Charting the data/data extraction

After the screening, two reviewers will independently extract the data (CR and VM) in an Excel spreadsheet

data extraction tool. Data extraction protocol will be piloted on the first five articles. This will help to maintain consistency in data extraction and to make the required changes in the data extraction tool. The above process will be documented. One of the reviewers will extract the data (CR) in an excel spreadsheet from the remaining included studies and the second reviewer (VM) will independently check the collected data.

The review team will gather data about

- Study design and publication detail (reviews, RCT, comparative study, case reports, technical reports, authors detail, year of publication, study location).
- Participants demographical, type of ABI and other clinical information.
- TMS procedure (technique, equipment specification, stimulation parameters such as coil placement, intensity, duration, frequency, adverse effects).
- Any associated therapy intervention (physiotherapy, occupational therapy, VR and other therapy techniques such as CIMT, bimanual therapy, gait training, etc) with or without TMS intervention.
- Comparator/control parameters.
- Outcome measures used in the individual studies and the relevant observation relating to ICF-CY domains.

This review will be aimed at identifying the changes in motor function of children with ABI. All of the motor function-related outcomes reported in the selected articles will be classified under ICF-CY domains. Additional details explaining how these outcomes were measures and at what time points these were collected will be reported. This review will not assess the risk of bias on the included studies but will report their level of evidence.

Collating, summarising and reporting the results

This review is expected to find heterogeneity across the studies, therefore, a narrative synthesis of the findings describing the therapeutic effects of TMS intervention, limitations, adverse effects and the gaps will be synthesised and reported. A table summarising ICF-CY domain for each study will be presented along with the narrative results.

Patient and public involvement

The review team consulted two parents of children with ABI in the design of this protocol. The review team will contact the Child Brain Injury Trust (CBIT), a national charity organisation for children with ABI (UK), when conducting the review and seek their help interpreting the findings and dissemination. Any recommendations made by the CBIT will be implemented.

DISCUSSION

Our protocol explains the methodology to guide our review. The outcome of the review is carefully planned and documented to ensure transparency and research integrity to allow replication.[26]

From this scoping review, the review team will provide a descriptive analysis of TMS for children with ABI and how this has been delivered. This review will help to understand the range of TMS dose which includes frequency, intensity, duration, stimulation site, motor function outcome and the corresponding actual or proposed mechanism. Due to the known variation in neuroplastic ability in the developing brain, it will be important to understand the TMS influence on functional motor recovery across different age groups within our overall age range.

This scoping review will also provide some insight related to the factors influencing TMS outcome. Age, gender, duration of illness, concordance with the treatment plan, associated comorbidities such as increased tone, tightness/contracture in joints and concurrence with the treatment may be some of the patient-related factors that influence the TMS outcome. Anatomical variations such as skull size, previous neurosurgeries and structural changes in brain will be a challenge to apply TMS.[27] These procedure-related factors associated with the illness-related factors such as children with a high level of motor disability, medications to manage tone, seizure activity and other conditions may have an impact of the therapeutic outcome. Stimulation factors such as site of stimulation, intensity, frequency, duration and the number of stimulation episode will be other factors determining the outcome strength. The above factors will be observed and reported in our review.

This information will guide future trial development with TMS treatment components that are being commonly used and how they are being delivered. Such treatment information can be organised in the Template for Intervention Description and Replication checklist to assist future research work to plan and report[28] TMS intervention. This review will help to conduct high-quality patient and public involvement for future studies, designing feasibility studies, and may guide to identify eligible CYP with ABI for TMS intervention.

Our scoping review has certain limitations. The majority of the studies on ABI included children with CP and the review team is not intending to include this population. Any related studies will be excluded and the associated knowledge will be missed. It may be possible that there are a very limited number of studies related to TMS in ABI and this may lead to inconclusiveness about the predicted motor response. This could be because of small sample size, duration and techniques of TMS, and also the associated comorbidities such as mental health issues, fatigue, cognitive and memory problems. Observed limitations will be reported and mitigated in our future systematic review.

This review outcome may help to develop therapists' role from conventional hands-on therapy provision to next-generation technology-based neurorehabilitation programmes. It is also likely to have an impact on CYP access to advanced technology during their acute phase

to aid enhanced recovery and help improve their patient experience.

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Contributors CR, VM and JP: involved in study conceptualisation. CR, VM, JP, PB and RG: responsible for study design and protocol development. CR and VM: responsible for screening, selecting articles and data entry. CR, VM, JP, PB and RG: responsible for data interpreting and reporting. DY: responsible for constructing search strategy and conducting searches. CR, VM, PB, RG and JP: responsible for preparing final manuscript. CR: guarantor of the review. All authors will read, provide feedback and approve the final manuscript.

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