



# Transcranial magnetic stimulation as a diagnostic and therapeutic tool in cerebral palsy

## Przezczaszkowa stymulacja magnetyczna jako diagnostyczne i terapeutyczne narzędzie w dziecięcym porażeniu mózgowym

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### Abstract

**Purpose:** Cerebral palsy (CP) is one of the leading causes of child disability, which profoundly affects the lives of whole families and contributes to the burden of health care. Despite the extensive rehabilitative, surgical and other therapeutic efforts of an array of specialists, a significant proportion of patients remain severely disabled. Transcranial magnetic stimulation (TMS) is a non-invasive diagnostic tool in various diseases of the cerebral cortex and cortico-spinal tract (CST). Repetitive TMS (rTMS) is able to induce a long-lasting cerebral plasticity, which is associated with a therapeutic effect in a number of psychiatric and neurological diseases. This article reviews the diagnostic findings gained with TMS in CP as well as therapeutic trials performed with rTMS.

**Views:** The absence of responses in the motor cortex in the first months of life, as revealed by TMS, may predict the development of CP in children at risk. In a proportion of children with the unilateral form of CP, TMS documents the pathological preservation of ipsilateral, cortico-spinal connections from the non-lesioned hemisphere, which is associated with poor outcome.

rTMS seems to be a safe method with significant therapeutic potential in CP. The data published so far reveals an almost unanimously significant therapeutic benefit in motor performance over placebo. However, the studies conducted to date have almost without exception involved children with unilateral palsy, and have focused nearly exclusively on therapy for motor symptoms.

**Conclusions:** Magnetic stimulation brings significant diagnostic and therapeutic effects in CP. However, more studies that go beyond the limits specified above are still awaited.

**Key words:** transcranial magnetic stimulation, cerebral palsy, ipsilateral connections, motor improvement.

### Streszczenie

**Cel:** Mózgowe porażenie dziecięce (MPD) to jedna z wiodących przyczyn niepełnosprawności wśród dzieci. Obecność MPD drastycznie zmienia ich życie oraz życie ich rodzin, a także jest znacznym obciążeniem dla opieki zdrowotnej. Pomimo zharmonizowanych wysiłków rehabilitacyjnych, chirurgicznych oraz innego rodzaju zabiegów terapeutycznych, przeprowadzanych przez wielu specjalistów, znaczna część dzieci pozostaje trwale i głęboko niepełnosprawna. Przezczaszkowa stymulacja magnetyczna (*transcranial magnetic stimulation* – TMS) jest nieinwazyjną metodą diagnostyczną w różnych schorzeniach kory mózgowej i dróg korowo-rdzeniowych. TMS serią bodźców (*repetitive TMS* – rTMS) jest metodą długotrwałej indukcji plastyczności mózgu i przynosi efekt terapeutyczny w wielu chorobach psychicznych i neurologicznych. W pracy omówiono wyniki diagnostycznego zastosowania TMS w MPD oraz badania nad terapeutycznym wykorzystaniem rTMS w MPD.

**Poglądy:** Brak odpowiedzi ruchowej po stymulacji nad korą ruchową w pierwszych miesiącach życia może mieć wartość predykcyjną co do rozwoju DPM u dzieci z czynnikami ryzyka. U części dzieci z połowiczą postacią MPD za pomocą TMS udokumentowano patologiczne przetrwanie ipsilateralnych połączeń korowo-rdzeniowych z półkuli niedotkniętej uszkodzeniem, które jest związane ze znaczną niesprawnością ruchową. Metoda rTMS wydaje się techniką bezpieczną, mającą istotny potencjał terapeutyczny w DPM. Dotychczas opublikowane dane niemal jednomyślnie potwierdzają istotne korzyści terapeutyczne dla sprawności ruchowej w porównaniu z placebo. Badania przeprowadzone do tej pory włączały jednak prawie wyłącznie dzieci z połowiczą formą porażenia oraz koncentrowały się prawie w całości na deficytach ruchowych.

**Wnioski:** Stymulacja magnetyczna z dużym prawdopodobieństwem przynosi diagnostyczne i terapeutyczne korzyści w DPM. Konieczne są jednak dodatkowe badania, wychodzące poza ograniczenia wymienione powyżej.

**Słowa kluczowe:** przeczaszkowa stymulacja magnetyczna, dziecięce porażenie mózgowe, połączenia tożstronne, poprawa deficytów ruchowych.

## INTRODUCTION

Cerebral palsy (CP) is one of the leading causes of child disability, which often persists into adulthood [1]. CP can manifest as tetra-, hemi- or paraplegia, movement disorders, cerebellar syndrome and other forms of motor impairment. A significant proportion of patients suffer additionally from epilepsy, cognitive disabilities, language and learning problems and behavioural changes [2]. All these symptoms may vary in severity, though CP usually brings significant disability to the child, affecting their life and that of the whole family dramatically. With epidemiology reaching 2.08 per 1000 live births [3], CP is also a significant social and healthcare burden. The main causes of CP occur before and during prenatal life and include systemic diseases, the effects of intoxicants, infections, impaired fertility of the mother during preconception and pregnancy, vaginal bleeding, placental malfunction, tocolytic drugs, oligohydramnios, polyhydramnios, intrauterine suppression, and intrauterine hypoxia. Peri-, neo- and postnatal causes account for 10 to 18% of cases. The most common of these causes are premature rupture of membranes, premature birth, infections, metabolic changes, and convulsions during the neonatal period [4]. The most frequent direct mechanism of development of CP is stroke [5]. Comprehensive motor rehabilitation is the most important therapy for CP. It is based on the concept of neuroplasticity, i.e. the capability of the brain to induce long-lasting functional and structural changes in response to specific stimuli. Treatment of spasticity often requires physiotherapy and pharmacotherapy, with baclofen and benzodiazepines for generalized effect [6] and botulinum toxin administered focally [7]. In severe cases, surgical assistance may be necessary. Complications related to CP are frequent and are treated by an array of specialists and procedures. Orthopedic correction is often needed for the hip joint and for deformities in other locations, and bisphosphonates are often given to maintain bone density. Seizures, which affect over a half of patients with CP, require pharmacological control, frequently with several antiepileptic drugs [8-12]. Further management of CP also involves speech therapy, training of cognitive functions, psychotherapy for the child and family, and the management of bedsores and pain [13], as well as therapy for feeding difficulties [14]. Even in the populations and areas where access to comprehensive

therapy is well provided, the motor and other disabilities associated with CP are frequent and often severe. In general, 30% of patients with CP are wheelchair-bound. A similar proportion is severely intellectually impaired, 10% have severe visual impairment, 20% have active seizures [15] and over 50% have problems with speech [16]. Overall motor and other disability related to CP remains a significant burden for affected individuals, their families, and for the society.

One of the newer diagnostic and therapeutic options with the potential to improve CP outcomes is transcranial magnetic stimulation (TMS). This method belongs to the array of modalities of non-invasive brain stimulation, in which the brain is stimulated directly with physical forces but without the need for surgery or general anesthesia. In TMS, brief, time-varied magnetic field pulses, of an intensity up to 2T, are generated in a coil held directly over the scalp. The magnetic field passes through scalp and skull with negligible attenuation and reaches the cerebral cortex. Due to the relatively good electroconductivity of the cortex, the magnetic field induces the electric current which in turn depolarizes the neurons. Depolarization takes place only in the area of the cortex beneath the coil. The magnetic field abates exponentially with the distance from the coil and is too weak to induce a significant electric current in the subcortical structures, as well as the cortical areas located remotely from the coil [17]. A TMS stimulator may generate single- or paired pulses, or may elicit magnetic pulses in series. The first two of these modalities are used mainly for diagnostic purposes and the third, called repetitive transcranial magnetic stimulation (rTMS), is used mainly for therapy. Single pulses enable the assessment of cortical excitability and conduction in the corticospinal tract. The excitation of primary motor areas (PMA) induces volleys that descend down the central and peripheral motor pathways and finally results in the contraction of respective skeletal muscles, which can be recorded with superficial electrodes as motor evoked potential (MEP) with equipment and techniques similar to those used in nerve conduction studies. The recording of MEPs allows for the estimation of the motor threshold (MT), which is the lowest intensity of magnetic field capable of reliably inducing MEPs. TMS with single pulses also allows the assessment of intracortical inhibition by recording the cortical silent period (CSP). CSP is a brief involuntary relaxation of the con-

tracted muscle which directly follows the MEP. In normal individuals it should last between 100 and 200 milliseconds and it is thought to be mediated mainly by intracortical GABAergic transmission. Finally, performing TMS in a single pulse mode and coupled with a neuronavigation system enables the functional mapping of PMA [18].

TMS with paired pulses applies two pulses separated by a short time interval. The pulses differ in their intensity. The first is called the conditioning pulse and it modulates (i.e. decreases or increases) the amplitude of the MEP obtained after the second, i.e. the test impulse. The direction and the magnitude of this modulation depends on the time separating both stimuli, the intensity of the conditioning stimulus, and its location. There are many paradigms of the use of paired pulse simulation used for clinical purposes and in neuroscience. Patients with CP were investigated with three of them, namely with short interval cortical inhibition (SICI), intracortical facilitation (ICF), and with interhemispheric inhibition (IHI). In SICI the conditioning stimulus has subthreshold intensity and precedes the test stimulus by one- to-four milliseconds. The amplitude of MEP, evoked by the test stimulus, will decrease in a healthy subject up to 40% (with respect to the amplitude of MEP evoked by the same test stimulus but without the preceding conditioning stimulus). SICI is closely related to GABAergic transmission, involving mainly GABA-A neurons within the motor cortex [19]. The prolongation of the interstimulus interval over 7 ms and up to 20 ms will induce ICF, with an increase in the MEP amplitude which may even quadruple. ICF is related to glutaminergic transmission [20, 21]. Finally, interhemispheric inhibition (IHI) can be measured by applying the conditioning stimulus to the PMA contralateral to the PMA, stimulated by the test stimulus with an interval ranging from 6 to 50 ms, which will decrease the amplitude of MEP in healthy subjects [22].

### Repetitive transcranial magnetic stimulation

rTMS uses a series of magnetic stimuli which repetitively depolarize the targeted neurons. Repetitive depolarization induces synaptic plasticity: high frequencies of depolarization i.e.  $\geq 5$  Hz will predominantly induce long term facilitation (LTF) with an increase in local metabolic rate, synaptic transmission and enhancement of activity of the related brain circuits. On the contrary, low frequency rTMS i.e.  $\leq 1$  Hz will result mainly in long term depression (LTD) with a decrease in metabolic rate and transmission [23]. Magnetic stimuli can be also elicited in a more complex way than the constant frequency. The most frequently used excitatory pattern is called intermittent theta burst (iTBS), whereas the inhibitory pattern is the continuous theta burst (cTBS). These protocols usually need fewer stimuli and much less time to achieve similar neurophysiological and often also clinical effects than stimulation with constant frequency.

However, they still provide significantly less evidence of therapeutic efficacy [24]. A single rTMS session, which may consist of several hundred to several thousand stimuli, induces changes which outlast the stimulation for minutes, hours or, occasionally, days. Repeating the sessions, once daily or several times a day, will consolidate the effect, which may last for weeks or months. Such a long-lasting modification of brain activity may be associated with therapeutic benefits. In depression, enhancing the activity of the left dorsolateral prefrontal cortex (DLPFC) with high frequency, rTMS or decreasing the activity of the right DLPFC with low frequency rTMS, reinstalls the balance between the frontal areas and other regions, which improves mood and other symptoms, even in drug-resistant patients [25, 26]. High frequency stimulation over the frontal areas and over the precuneus helps to preserve and even to improve cognitive functions in various types of dementia and mild cognitive impairment [27-32]. Stimulation of the motor cortex can induce an analgesic effect in neuropathic pain due to its antidromic excitation of thalamocortical connections [33, 34]. Other evidenced therapeutic effects include improvement of spasticity in multiple sclerosis, suppression of epileptic activity of the epileptic foci, alleviation of tinnitus, alleviation of auditory hallucinations in schizophrenia, and others [24].

### Transcranial magnetic stimulation findings and therapy in adult stroke

In acute stroke MT is increased, reflecting the loss of a proportion of excitable motor neurons [35, 36]. MEPs are low or absent on the affected side. If present, they predict good recovery [37-40]. The contralateral MEPs from the unaffected hemisphere increase, representing overactivity [41-43]. SICI is reduced on the affected and possibly also on the unaffected side, reflecting disinhibition due to impairment of GABAergic transmission [44]. rTMS improves post-stroke weakness, neglect and aphasia [45]. Usually, rTMS is performed over the contralesional motor cortex at low frequency, which inhibits the pathologic overactivity of the non-lesioned hemisphere, which in turn creates more space for the lesioned cortex to reorganize its connections and renew its function. A number of trials have also used the high frequency in the lesioned PMA, which activated the neurons that survived the stroke and thus helped to restore function. Some used cTBS and iTBS over the non-lesioned and lesioned hemispheres respectively [24]. In CP, TMS findings and therapeutic protocols with rTMS will parallel to some degree those in adults with stroke. On the other hand, significant differences are present which should be considered when performing magnetic stimulation in a patient with CP. Moreover, as the TMS has been done in children for a markedly shorter period of time, the amount of evidence and number of findings are still low. These issues,

as well as other aspects of the current knowledge about diagnostic and therapeutic efficacy of magnetic stimulation in CP, are presented below.

## VIEWS

This review was conducted following the Scale for the Assessment of Narrative Review Articles [46]. We included clinical studies regarding: (1) the use of TMS parameters to assess cortical excitability and motor pathways in CP, and (2) the use of repetitive TMS in the treatment of CP. We searched the electronic databases of MEDLINE through Pub-Med (United States National Library of Medicine, Bethesda, Maryland, USA) for relevant research articles published up to March 2021. The search strategy consisted of the following terms used in combination: “transcranial magnetic stimulation”, “TMS”, “cerebral palsy”, “perinatal stroke”. Additional searches of the references of the retrieved manuscripts were also conducted in order to collect information about additional relevant literature.

### Transcranial magnetic stimulation findings in patients with cerebral palsy

In general, studies using TMS and rTMS in CP reported a lack of serious adverse events and good tolerance [47], even in children in their first year of life [48]. One of the main findings is the preservation of short-latency and high amplitude ipsilateral MEPs after stimulation of the non-lesioned motor cortex in unilateral CP. According to studies on healthy infants, ipsilateral motor responses are present in the first months of life. They have comparable amplitudes and thresholds to the contralateral ones but significantly shorter latencies [49]. From the third month of life onwards ipsilateral corticospinal connections undergo withdrawal in competition with contralateral ones, so that in the second year ipsilateral MEPs should be significantly smaller and of longer latencies. Low amplitude MEPs of prolonged latency may be still evoked in normal adults as the small proportion (8 to 15%) of the fibers of the cortico-spinal tract remains uncrossed [50]. Withdrawal of ipsilateral connections neither occurs, nor is hampered, if the contralateral motor cortex has been damaged in the pre-, peri- or postnatal period [49, 51]. Moreover, persistent ipsilateral connections from the non-lesioned hemisphere seem to contribute to the gradual withdrawal of contralateral projections from the lesioned hemisphere which survived the perinatal damage, thus worsening the disability [52]. In accordance with these mechanisms, lack of contralateral MEPs after stimulation of lesioned PMA and well-preserved ipsilateral MEPs after stimulation of contralesional PMA, or the presence of both, predict poor motor outcome [53-61]. Moreover, the presence of ipsilateral MEPs of high am-

plitude may predict the development of mirror movements – a form of involuntary movement typical in some patients with CP [62]. This is in contrast with lesions of PMA acquired at a post-infant age, which does not result in the appearance of high-amplitude ipsilateral responses of normal latency [63, 64]. Studies using TMS and imaging suggest that the causes of the most severe abnormalities in MEPs are multicystic encephalomalacia as well as cortical and deep grey matter lesions [65, 66]. While the persistence of ipsilateral MEPs is generally not a favorable factor, it seems that it may be overcome with intensive motor training. Such a conclusion results from the recent studies which have reported a lack of differences in motor improvement gained during intensive constraint-induced movement therapy (CIMT) and bimanual training between children with contralateral, ipsilateral, or bilateral corticospinal connections [67-69]. In a study of Juenger *et al.* (2013), the ipsilateral MEPs to the paretic hand decreased, along with the motor improvement of this hand achieved with CIMT [70]. These results indicate that the relation between corticospinal tract organization and the outcome may be more complex, and that some not-yet-discovered capacities of brain plasticity may be mobilized with the proper intensive training. Furthermore, a study by Marneweck *et al.* (2018), which used a neuronavigation system, indicated that the magnitude of cortical area on the non-lesioned side, in which bilateral MEPs can be evoked, correlates positively with the dexterity of the paretic hand (but, at the same time it correlates with the occurrence of the mirror movements) [71]. This may be an indication that ipsilateral connections from the non-lesioned cortex may have a multidirectional effect on the ipsilateral body side. Other finding gained with TMS and navigation is the topographic, lateral shift of somatotopic areas of the examined muscles in a proportion of patients [72, 73]. The most likely interpretation of this finding is the recruitment of adjacent, spared cortical areas to overtake the motor control, which is a sign of high plastic capability of the developing brain. Of other relevant studies in patients with unilateral lesions, a number of clinical trials should be mentioned, which assessed the efficacy of motor rehabilitation – usually CIMT and bimanual training – and monitored its effect on the corticospinal tract along with changes in motor performance. These studies showed a constant reactivity of TMS parameters – usually in the form of an increase of the amplitude of contralateral MEP to motor rehabilitation [74-79]. Only a few studies applied TMS to infants in their first months of life [48, 80], yet the findings are probably of crucial importance: they revealed that the absence of contralateral MEPs after ipsilesional stimulation is associated with the development of atypical movements in the first year and a later diagnosis of CP. TMS may therefore be a useful tool with which to diagnose CP early; this would allow rehabilitation to be started in a timely manner, without

missing the period during which plasticity and therapeutic potential are at their peak.

Other documented changes in cortical excitability and function of corticospinal tract in children with unilateral lesions resemble, in general, changes seen in adult stroke: The contralateral MEP from the non-lesioned PMA tends to have higher amplitude and shorter latency, reflecting the hyperexcitability of the non-lesioned hemisphere (Eyre *et al.*, 2001). SICI is decreased and ICF unaltered in CP [81]. The interhemispheric inhibition is altered or absent and MT is higher on the lesioned side [82-84].

Only two studies examined patients with spastic diplegia due to CP [72, 85]. In the first, the recording of MEP was limited to the right tibialis anterior and the shortening of CSP was the only difference to healthy volunteers. In the second, ipsilateral responses were found only in subjects who showed significant between-side differences of motor function.

### Repetitive transcranial magnetic stimulation as a therapeutic tool in cerebral palsy

The first trials of rTMS in CP paralleled the most commonly used therapeutic protocol in adult stroke, which is low frequency rTMS over the non-lesioned motor cortex aimed at the suppression of its inhibitory impact on the lesioned PMA. Consistently with protocol selection, only hemiparetic children, usually of school age, were recruited [55, 86]. Significantly, the studies revealed a better effect of rTMS on motor performance over placebo stimulation. Kirton *et al.* reported improved grip strength, and Gillick *et al.* on improvement in the Assisting Hand Assessment, a video recording based test in which 22 items evaluate the child's performance in tasks which require bimanual activity. The effect was, however, no more visible at six months follow up [87]. Importantly, Gillick *et al.* also measured sensory deficits with the 12-objects stereognosis test, in which children needed to recognize a maximal number out of 12 standardized objects, which were subsequently put into the affected hand; however, no improvement in the stereognosis was seen. The only partial effectiveness and lack of long-term effectivity shown in the study of Gillick *et al.* may be associated with the relatively low number of rTMS sessions involved (five), which in addition were administered every second day (on the alternate days, the CIMT was performed). The therapeutic advantage of a larger number of sessions was documented in the later study by Rajak *et al.*, where improvement in the gross motor function measure was more prominent after 40 rather than 30 or 20 sessions [88]. The PLASTIC CHAMPS study (Plastic Adaptation Stimulated by TMS and Induced Constraint for Congenital Hemiparesis After Perinatal Stroke) is distinguished from the others as it involved a significantly bigger group ( $n = 45$ ) receiving more intensive therapy: ten daily

rTMS sessions and the CIMT therapy covering 90% of waking time [89]. Children received one, both or neither of these therapies. Receiving both therapies brought long-lasting improvement in the form of learning new motor skills, which was still present during the six months follow-up. The study also documented the effect of neuromodulation on excitability parameters: after the therapy, the amplitude of the MEPs evoked from the paretic muscles after stimulation over the lesional hemisphere increased and the SICI decreased. No changes were seen in ICF and IHI [76, 84].

With the exception of the first study on rTMS efficacy [55], in almost all other studies patients underwent rTMS (or sham rTMS) concurrently with motor rehabilitation. Technically, rehabilitation was performed directly after the rTMS session. One study compared the effect of rTMS alone vs. rTMS with occupational therapy. Two therapies combined brought significantly better improvement than rTMS alone [90].

While the study of Gillick *et al.* excluded patients in whom stimulation of ipsilesional PMA could not elicit MEP, the other studies did not. Their favorable results indicate that the lack of electrophysiologic confirmation of preserved integrity of lesioned motor pathways does not preclude a therapeutic response. In addition, the PLASTIC CHAMPS study revealed a lack of association of preserved MEP with the therapeutic efficacy of rTMS [89]. Only one trial included exclusively children with bilateral CP. It investigated the influence of rTMS on the disruption of the structural brain network, however, no effect on clinical signs was reported [91]. In another trial, children with bilateral CP along with unilateral paresis were recruited. In this study, rTMS with angulated coil, which probably covered the entire bilateral motor cortex, resulted in a decrease of spasticity [92]. While most of the studies measured only motor performance as the outcome, the study by Dadashi *et al.* also documented improvement in balance control [93]. One case report and one controlled trial assessed the effect of rTMS on cognitive performance in CP [94, 95]. In the first, the right DLPFC was stimulated with low – 0.5 Hz, and in the second the left DLPFC with high – 10 Hz, frequency. The case report was a six-year-old boy, who improved in the Gesell developmental diagnosis scales after eight months of rTMS administered once daily on all working days. Along with cognitive improvement, the repetitively and extensively studied fMRI showed a gradual increase in functional brain connectivity, especially within the precuneus and hippocampus, as well as between the default mode network, dorsal attention network, and insula network. In the second study, the effect of four weeks of stimulation on learning ability was compared with that of the standard rehabilitation for daily living activities with 15 children in each group. rTMS improved learning abilities, along with an increase

in EEG alpha power and other electroencephalographic changes. However, no detailed comparison with the other group and no information regarding randomization and blinding were provided in the article.

## LIMITATIONS

This review is not systematic and the quantification of the available data is not provided.

## CONCLUSIONS

TMS provided insight into the organization of central motor pathways in patients with CP, which is characterized by the preservation of ipsilateral projections from the non-lesioned PMA. Moreover, it documented the possibility that ipsilateral projections may competitively weaken contralateral ones, which may further worsen paresis. Ipsilateral connections are also related to the development of pathologic mirror movements. On the other hand, a domination of ipsilateral responses should not discourage rehabilitative efforts as such children may also gain significant functional improvement. Of particular significance for the management of CP are the few studies which have investigated infants in their first year of life and which documented the association of the absence of MEP with the later development of paresis. Performing TMS in the first months of life may therefore contribute to the early diagnosis of CP and to a timely initiation of rehabilitation.

An important conclusion resulting from the clinical trials with rTMS conducted to date is the general safety and good tolerance of this method among children with CP. This should encourage professionals in child neurology to introduce TMS into their practice and research. The general paucity of studies indicates that some lack of confidence regarding safety may persist even in academic centers. On the other hand, rTMS in children may bring particularly great benefits as the degree of plasticity is higher in the developing brain, especially during the first year of life [96]. In this light, most desperately lacking are trials on infants, which have not yet been done at all. The existing data were collected mainly on children in school and preschool age,

and it seems to convincingly support the use of rTMS in CP in further research, and probably already in practice. Even if the number and heterogeneity of the available studies does not allow us to conduct a systematic review or meta-analysis of therapeutic efficacy, the results are moderately favorable in the majority of the trials. No study reported negative results, i.e. a lack of efficacy of rTMS, which is in striking contrast to the research made on adults. Further studies should certainly include more populations with bilateral palsy or paraparesis, which in terms of incidence exceed the patients with hemiplegic phenotype [97]. In connection with this remark, future clinical trials should also target the lesioned hemisphere with high frequencies or with other protocols inducing, mainly, long-term potentiation, such as iTBS. Experiences of work with adult patients with stroke indicate that the effects may be favorable [24]. In lesioned PMA, eliciting MEPs may be difficult or impossible and therefore in such trials the use of neuro-navigation systems is advocated. This also concerns the use of rTMS for purposes other than motor rehabilitation, such as stimulation outside PMA. The few attempts that have been made indicate that rTMS may have potential in cognitive rehabilitation. No data exist on therapy for speech impairment, ataxia, or behavioural complications related to CP. Another possibility to extend the therapeutic potential of rTMS in CP is the simultaneous application of rTMS and motor rehabilitation, e.g. in form of virtual reality. Such a trial has already been successfully conducted with transcranial direct current stimulation – another modality of non-invasive brain stimulation [98]. The relatively strong sounds and sensory sensations which are associated with rTMS make simultaneous rehabilitation difficult, but the first studies in adults with dementia showed that such an approach is possible [99].

In summary, the work completed to date indicates TMS as a valuable tool for gaining insight into the pathophysiology of motor pathways in CP, and for predicting early development of CP in children at risk. rTMS is a safe method of modulation of brain plasticity with promising results regarding its therapeutic efficacy in CP. Future studies should provide data that will help with the optimization of therapy, extend its application to not-yet investigated symptoms, and tailor the site and protocol of stimulation to particular phenotypic subgroups of CP.

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### Conflict of interest/Konflikt interesu

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