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A Comprehensive Review of Dorsomedial Prefrontal Cortex rTMS Utilizing a Double Cone Coil

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Background: Repetitive transcranial magnetic stimulation (rTMS) has become increasingly popular during the last decades mainly driven by the antidepressant effects of dorsolateral prefrontal cortex stimulation with "butterfly" coils. Only recently, alternative targets such as the dorsomedial prefrontal cortex (dmPFC) have been brought into focus and innovative coil designs such as the angled geometry of the double cone coil (DCC) have raised hope to reach even deeper located targets.

Objective: To provide a systematic and comprehensive review on the application of rTMS stimulation of the dmPFC using the DCC in neuropathological and healthy samples.

Methods: We systematically searched the MEDLINE® database (http://www.ncbi.nlm.nih.gov/pubmed/). Due to the heterogeneous naming of DCC stimulation over the dmPFC a variety of search terms was applied resulting in a numeral quantity of 340 hits.

Results: DCC stimulation over the dmPFC has been proven to be safe and feasible in various neuropsychiatric disorders and in healthy subjects. Clinical results are encouraging, but have to be considered as preliminary as data from sham-controlled clinical trials and knowledge about the neurobiological underpinnings are still scarce.

Conclusion: DCC stimulation over the dmPFC represents a promising approach in the fast evolving noninvasive brain stimulation techniques aiming at the functional modulation of brain areas vitally involved in affect, sensory autonomic, cognitive, and salience regulation. This may hold potential for both neuroscientific research and clinical applications in the treatment of psychiatric disorders.

Keywords: ACDC anterior cingulate cortex dm-PFC dorsomedial prefrontal cortex double cone coil repetitive transcranial magnetic stimulation

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INTRODUCTION

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is an emerging brain stimulation technique that has become increasingly popular thanks to its focal, noninvasive and clinically well-tolerated characteristics (1). A number of TMS techniques are nowadays used for routine diagnostic application (2) and over the last decade repetitive transcranial magnetic stimulation (rTMS) has received increasing attention as a therapeutic tool in the treatment of different neuropsychiatric conditions (for a comprehensive overview about the use of rTMS for the treatment of neuropsychiatric disorders see (3)). rTMS is regarded a safe intervention, with limited and transient side effects in most cases (4), and has proven suitable for both in- and out-patient treatment settings (5).

Limitations and Challenges

Although, an extensive literature supports the efficacy of rTMS in its most common application treating major depression (1,6,7), outcomes remain quite variable across individuals, and many studies have suggested at best moderate efficacy in clinical routine applications (3). Moreover, rTMS effects depend on stimulation related (e.g., coil form and position, intensity, frequency, number of stimuli, stimulation pattern) and patient related (e.g., age, medication, activities before, and during stimulation) factors and a complex interaction between them.

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Therefore, further research and development is strongly needed for better establishing the role of rTMS in the treatment of psychiatric disorders, and for improving treatment outcomes.

The Role of Coil Selection

Large "circular" coils (Cc) stimulate a wide region of cerebral tissue (for instance, when placed over the vertex they induce bilateral effects), which limits their use if focal stimulation is sought. Focality is improved with a "figure-of-eight" coil (F8c) (8), reducing the stimulation zone to a few square centimeters (9) and making it sensitive to coil handle orientation. However, the penetration depth of "conventional" TMS coils such as the figure-of-8-coil in brain tissue is limited to superficial cortical areas (10) leading to a variety of newly developed innovative coil types. One of these, the "double cone" angulated coil (DCC) consists of two large circular coils forming an obtuse angle. To our knowledge, this type of coil was first introduced by Magstim in the year 1999/2000; Magventure presented a similar coil type certified for medical use in 2004. At the expense of less focality, this type of coil is useful for reaching deeper targets such as the representation of the lower limbs in the primary motor cortex (M1) located within the interhemispheric fissure (11) allowing for the modulation of deeper located brain structures of interest. In particular, such coils may enable stimulation of limbic cortical regions such as the anterior cingulate cortex (ACC) (12). It should not be overlooked, that determined by the principles of physics existent TMS coils are limited in their precision of spatial targeting (focality) especially when aiming to reach deeper located brain structures. A certain trade-off between depth, focality and the energy required by the coil is inherent to the system (13).

The role of the ACC

The ACC consists of four different subregions within Brodmann areas 24 and 25 (14) and is involved in different emotional, cognitive, sensory, and autonomic functions (15,16). In a recent publication (17) on the functional role of the ACC in psychiatric disorders, it was proposed that the rostral ACC is involved in uncertainty processing (18–21), the dorsal ACC (dACC) in an urge for action (22), obtaining more information, the pregenual ACC (pgACC) in suppressing further input (17) and hedonia (23), and the subgenual ACC (sgACC) in autonomic processing (24). The sgACC plays a major role in the pathophysiology of depression (25,26). Ventral and dorsal subregions exist, with hyperactivity in ventral/subgenual ACC regions and hypoactivity of dorsal ACC regions commonly reported in major depression and several other disorders (25,26). Structural neuroimaging studies demonstrate volume reduction in ventral ACC in depressed patients (27), whereas functional neuroimaging studies have shown elevated resting-state-activity in the ventral ACC in depressed patients (28,29) and during experimental induction of sadness in healthy subjects (29). Importantly, both ventral and dorsal ACC activity has been demonstrated to represent a potential predictor of therapeutic response in unipolar depression (30) and have been closely linked to the therapeutic effects of TMS in depression (31–34).

Recently, increasing evidence has emerged to link the dorsal ACC in particular to the pathophysiology of a wide range of mental and neurological disorders. A recent meta-analysis based on 193 voxel-based-morphometry (VBM) studies looked for a common neuronal substrate across multiple psychiatric disorders (35). This study revealed that three regions, the left and right anterior insula and the dorsal ACC, showed significant gray matter loss across all psychiatric disorders (35). These three regions constitute the anterior cingulo-insular network, which has been designated as the "salience network" (36).

Table 1. Pubmed Search Terms and Hits Retrieved During the Systematic Literature Search on the Topic.

PubMed search terms	Number of hits
((dACC) AND TMS) OR ((dACC) AND rTMS)	12
((dorsalACC) AND TMS) OR ((dorsalACC) AND rTMS)	9
((anterior cingulate) AND TMS) OR ((anterior cingulate) AND rTMS)	136
((mPFC) AND TMS) OR ((mPFC) AND rTMS)	29
((medial PFC) AND TMS) OR ((medial PFC) AND rTMS)	12
((medial prefrontal cortex) AND TMS) OR ((medial prefrontal cortex)) AND rTMS)	95
((dmPFC) AND TMS) OR ((dmPFC) AND rTMS)	20
((dorsomedial PFC) AND TMS) OR ((dorsomedial PFC) AND rTMS)	2
((dorsomedial prefrontal cortex) AND TMS) OR ((dorsomedial prefrontal cortex) AND rTMS)	24
((acdc) AND TMS) OR ((acdc) AND rTMS)	1
Total of hits (including duplicates)	340

Deficiencies in self-regulation of emotions, thoughts, and behaviors are a core feature of psychiatric illness, and are also consistent with what is known about the functions of the dACC and anterior insula (37). The dACC stands midway along a hierarchy of medial prefrontal regions (ranging from the medial frontopolar cortex anteriorly, to supplementary motor area posteriorly) that guide goal selection, thought selection, and action selection based on internal drives, as opposed to external cues (38,39).

Such observations fit well with the notion that the ACC may contribute to individual differences in personality traits related to reward sensitivity and persistence. These traits in turn represent a neurocognitive construct, which, according to the Research Domain Criteria framework, express dimensionally across the population and give rise to multiple mental disorders, when expressed in a maladaptive way (40). Taken together these data suggest that the dorsal ACC is critically involved in the neurocognitive constructs of "cognitive control," and specifically the subconstruct of "response selection," and that deficiencies in these functions represent a common element across psychiatric disorders, notwithstanding their differences in other domains (37).

Targeting the dorsal ACC may therefore be a fruitful therapeutic approach across a variety of diagnostic entities, via a mechanism of action involving enhancements of cognitive control, impulse control, and affective stability.

Objective of This Review

Repetitive TMS using a double cone coil (DCC) has been shown to modulate the neural activity in the dorsal anterior cingulate (dACC) by placing the coil over the dorsomedial prefrontal cortex (dmPFC) (12). This stimulation procedure has been claimed as ACDC-stimulation (anterior-cingulate stimulation by DCC rTMS) (41). Unfortunately, no common "labeling" of this kind of stimulation has been consistently carried out impeding a detailed and quick overview of the available literature on the topic. This situation led to the authors' decision to integrate various targets when supposedly affecting the ACC by DCC rTMS (Table 1). ACDC-rTMS and dmPFC-DCC rTMS are regarded as synonyms in the context of this manuscript.

Table 2. Comprehensive Survey on Published Data Dealing With dmPFC-DCC Stimulation in I) Preclinical/Neuroscientific Populations and II) Clinical Conditions Ranked in a) Chronological and b) Alphabetical Order (dmPFC-Stimulation Applying Double-Cone-Coil rTMS to the Dorsomedial Prefrontal Cortex).

I. Preclinical and Neuroscientific Applications

Publication	Indication	Stimulated individuals	Sham control	Stimulation parameters	RMT parameters	Target	Outcome
Hayward 2007 (*Exp Brain Res*)	Healthy controls	7 (experiment 1 = pulse train study) and 8 (experiment 2 = factorial design with cognitive task);	No	Double-cone coil (P/N 9902–00; Magstim); short trains of four pulses given at an intensity of 110% of each participant's threshold and at a frequency of 10 Hz.	Participants' toes following stimulation of the midline Toe and leg area of primary motor cortex	mfTMS coil position was the same as the most anterior site used in Ref. (42), namely 1.5 cm anterior to 1 / 3 of the distance from the nasion to the inion.	In a whole-brain analysis, striking changes in rCBF were observed distal to the ACC following medial frontal TMS.
Klucharev 2011 (*J Neurosci*)	Research on social conformity	49 healthy subjects	No (control target parietal cortex and "sham" at 10% MSO)	Magstim DCC, 80% RMT, cTBS (40s train of 500 Hz stimulation, 600 pulses).	Midline toe/leg area	General target: pMFC / rostral cingulate = BA 24,32,6,9: neuronvigated MNI = [x,y,z = 8,16,52]; No individually neuronavigated TMS application; individual distance of pMFC from central sulcus determined by head size according to Klem 1999, Knoch 2009 (mean distance: 4,5 cm anterior cental sulcus).	pMFC downregulation reduced conformity as indicated by reduced conformal adjustments in line with group opinion compared to sham and control condition (parietal cortex stimulation).
Tzabazis 2013 (*Molecular Pain*)	Experimental pain (healthy adults), fibromyalgia patients	16 volunteers (induced pain) (crossover-design), 16 fibromyalgia patients	Yes	Multicoil rTMS (Cervel Neurotech, Foster City) with up to 4 simultaneously activated coils tailoring the magnetic field towards maximal effect on the dACC; different coil configurations assessed at different frequencies (1 and 10 Hz); 1 session in volunteers, 20 sessions in patients (1800 pulses each), max. 110% RMT.	Thumb		Single 30 min 1 Hz session produced robust reduction of evoked pain in volunteers. In patients, 20 rTMS sessions also produced significant pain inhibion but only when operated at 10 Hz, stable pain reduction maintained 4 weeks after last stimulation. No SAE's, relatively high incidence (sham vs. real) of scalp pain (11 vs. 2%), lightheadedness (22 vs. 2%), neck pain (0 vs. 13%), hot flashes (22 vs. 0%);
Schuwerk 2014 (*Behav Brain Res*)	Research on Theory of Mind	Healthy adults; 17 students	Yes (tilted figure-of-8-coil by 90°)	Cool-DB80 (Magventure, Denmark) DCC, tangentially along midline, 1 Hz, 2000 stimuli, 100% RMT.	M. abductor digiti minimi (accessed via figure-of-8-coil)	dACC (according to localisation of Ref. (12))	Intervention decreases the discrepancy between self and other in Theory of Mind reasoning.

Table 2. *Continued*

Cho 2015 (*Neuropsycho-pharma-cology*)	Effect of mPFC stimulation on discounting of delayed rewards	24 healthy subjects	No	1 session of 10 Hz-rTMS of the MePFC and 1 session of vertex stimulation (control condition) in 1 day (15 10-pulse trains of 1-s duration at 10 Hz, between-train interval of 10 s) (double-cone coil (P/N 9902–00; Magstim), 80% RMT), handle pointing backward). Thereafter, 11 subjects completed the PET study at rest using [11C]-(þ)-PHNO for striatal dopamine measurement. A total of 150 pulses were delivered for the behavior study and 750 pulses were delivered preceding the start of the PET acquisition.	Tibialis anterior muscle	Neuronavigation for mPFC target; coordinates selected for targeting the MePFC (BA 10; x¼40, y¼59, z¼12) are similar to those described in previous studies (Kable and Glimcher, 2007).	Modulation of the MePFC excitability influenced delayed rewards and interfered with synaptic dopamine level in the striatum. The present study yielded findings that might reconcile the role of these areas in inter-temporal decision making and dopamine modulation.
D'Agata 2015 (*PLoS One*)	Experimental pain	13 healthy volunteers	no	Stimulation after 5 min from the beginning of the painful stimulation. 5 single pulses, temporally spaced by 30 seconds, at 50%, 70%, 90%, 100%, and 100% power fraction of the maximum. TMS output (MAG&More, München), equipped with a double-cone coil;. biphasic, current traveling in the anterior–posterior direction first, coil placed on the scalp in a way so that the handle was kept perpendicular to the skull.	Not applicable (see left)	Each participant underwent 6 experimental sessions: a baseline session and five experimental ones. In each experimental session one of 5 equidistant points along the medial cortex in antero-posterior direction: AFz, Fz, FCz, Cz, CPz) was stimulated	TMS stimulation temporarily decreased the pain ratings, and pain adaptation was suppressed when applying the TMS over the FCz site on the scalp. No effect was found for distress ratings.
Christov-Moore 2016 (*Soc Neurosci*)	Research on generous behavior	Healthy subjects playing unregulated dictator game	Yes, active stimulation with a flat figure-of-eight coil over MT/V5	cTBS (600 pulses; 200 bursts, consisting of 3 pulses at 50 Hz repeated at 5 Hz for a total of 40s, 80% AMT) with Magstim angled coil.	*M. tibialis* anterior (assessed with the angled coil)	Right dmPFC neuronavigated	Increased generosity by disrupted prefrontal cortex (cTBS of DMFCS caused increased offers to players with low socioeconomic status).
Holbrook 2016 (*Soc Cogn Affect Neurosci*)	Research on religious beliefs	38 healthy subjects	Yes (10%MSO)	cTBS (600 pulses; 200 bursts, consisting of 3 pulses at 50 Hz repeated at 5 Hz for a total of 40s, 80% AMT) with Magstim angled coil.	M. tibialis anterior (assessed with the angled coil)	Right pMFC, BA 24, 32, 6, 9 as described in Ref. (46) (MNI coordinates (*x,y,z*) [8,16,52] mm, average distance 3.75 from target to motor hot spot (tibia).	Parameters of interest were group prejudice and religious belief; provides a proof-of-concept that adherence to high-level abstract beliefs can be experimentally neuromodulated.

Table 2. *Continued*

II. Clinical Applications

Publication	Indication	Stimulated individuals	Sham control	Stimulation parameters	RMT parameters	Target	Outcome
de Ridder 2011 (*Neuro-science Letters*)	Alcohol craving	1 (case report)	No	1 Hz, 600 pulses (=10 min)	50% machine output	dACC	1 successful rTMS application, 1 unsuccessful with relapse; fMRI and rs-EEG performed, craving associated with with EEG beta activity and connectivity between the dACC and PCC in comparison to healthy population, disappearing after successful rTMS.
Vanneste 2011 (*BMJ*)	Chronic tinnitus	78 tinnitus patients	Yes	1, 3, 5, 10, and 20 Hz	50% machine output	dACC	results showed that 1 and 3 Hz of DCC frontal TMS can improve both tinnitus intensity and tinnitus distress, 5 Hz is equal to sham and 20 Hz is significantly worse than sham. Of the 78 tinnitus patients, 52 had no control response.
Downar 2012 (*Frontiers in Psych*)	Case report on refractory bulimia nervosa	1 case	No	20 sessions of neuronavigated rTMS, one session per weekday over 4 weeks, Cool-DB80coil (MagVenture) with 60 trains of 10 Hz stimulation at 120% of resting motor threshold in 5 strains with a 10-s inter-traininterval,for a total of 3000 pulses to each hemisphere, as per a previously published protocol (Hadley et al., 2011).	Contralateral hallux using previously published methods (Schutter and van Honk, 2006; Hayward et al.,2007).	Coordinate (x 0, y + 28, z + 45) in standard space (Talairach and Tournoux,1988), corresponding to DMPFC.	After rTMS session2 the episodes stopped entirely for 1 week; after session 10 there were no further recurrences. Depression scores improved more gradually to remission at session 10. Full remission from depression and binge eating/ purginge pisodes was sustained more than 2 months after treatment completion.
Vanneste 2013 (*Brain Stimul*)	Chronic tinnitus	73 tinnitus patients receiving single (n = 46) or repeated (n = 27) sessions of ACDC	Yes	1 Hz, 1500 pulses	50% machine output	dACC	Single sessions as well as multiple sessions (i.e. 8 sessions) of ACDC TMS suppress both tinnitus distress (respectively 7.60% vs. 26.19%) and tinnitus intensity (respectively 7.12% vs. 19.60%) transiently. It was further shown that multiple sessions of AC/DC TMS generate a higher suppression effect in comparison to a single session of AC/DC TMS and that more patients responded to repeated sessions of 1 Hz stimulation in comparison to a single session.

Table 2. *Continued*

Downar 2014 (*Biol Psych*)	Unipolar or bipolar major depression, resistant to medication	47 patients, open-label add-on study	No	DCC Cool-DB80 (MagVenture); 20 sessions, 120% RMT stimulation intensity, 10 Hz, 5 seconds on-10 seconds off, 3000 pulses in 60 trains per heimsphere per session, lateral coil localisation for preferential stimulation of each hemisphere (total of 6000 stimuli per sesssion).	M. extensor hallucis longus	Neuronavigated target localisation	24 of 47 patients achieved □50% symptom reduction according to HAMD-17-score and 20 patients achieved the remission criterion of HAMD-17 ≤ 7 posttreatment. The authors report various clinical and neuroimaging outcome predictors suggesting the existence of distinct depression subtypes (with or without preserved hedonic function) responsive or unresponsive to ACDC-stimulation. Noteably, stimulation was subsequently carried out with lateral coil orientation for subsequent stimulation of both hemispheres.
Salomons 2014 (*Neuro psycho pharma cology*)	MDD (treatment resistant)	25 patients	No	Cool- DB80 stimulation coil, 20 sessions, 10 Hz, at a duty cycle of 5 s on, 10 s off for a total of 3000 pulses in 60 trains per hemisphere per session.	M. extensor hallucis longus	according to Downar 2012, dmPFC under MRI neuronavigation	Mean HAMD17 score at baseline was 21.3 (±6.7). Following dmPFC-rTMS treatment, mean HAMD17 score had decreased Significantly to 12.0 (±8.2) (po0.05). successful treatment was associated with increased dmPFC-thalamic connectivity and decreased subgenual cingulate cortex-caudate connectivity.
Vanneste 2014 (*Neurocase*)	Medication resistant chronic depression	1 (case report)	No	P/N 9902–00 (Magstim); 10 Hz, 10 sessions, 2000 stimuli each, 40% stimulation intensity (65% RMT).	Not specified	SMA (Brodman 6/8) (Hayward 2007)	Along with the clinical improvement EEG resting state activity changed in the dACC and sgACC in this patient in comparison to a normative group.
Bakker 2015 (*Brain Stimul*)	Major depression	Chart review on 185 patients	No	30 min 10 Hz or 6 min iTBS in 20–30 sessions of DMPFC-rTMS; Cool D-B80 Coil (MagVenture, Farum, Denmark), 3000 stimuli per session for each hemisphere (total 6000) for 10 Hz; 600 stimuli per session for each hemisphere (total 1200) for iTBS. 120% RMT for both 10 Hz and for iTBS.	Extensor hallucis longus	According to Downar 2012	Overall response/remission rates: BDI-II: 41.8%/30.1%; HamD17: 49.7%/33.5%. No significant difference between groups in pre- or post-treatment BDI-II or HamD17.

Table 2. *Continued*

de Ridder 2015 (*J Neurosurgery*)	Chronic tinnitus	2 cases of prior rTMS of the dACC followed by ACC-implants	Yes	DCC; 1,5,10 Hz tonic and burst mode (50% machine output).	Not specified	Bold activity in dACC	In tonic mode at 1 Hz the tinnitus is improved to 5/10 on the right, 7/10 on the left, at 5 Hz 2/10 on the right and 6/10 on the left and at 10 Hz 3/10 on the right and 6/10 on the left. With theta burst TMS at 5 Hz the tinnitus is reduced to 2/10 on the right and 5/10 on the left.
Dunlop 2015a (*Neuropsychopharmacology*)	OCD	20–30 sessions of bilateral 10 Hz dmPFC-rTMS in 20 treatment-resistant OCD patients, with 40 healthy controls as baseline comparators	No	Cool-DB80 coil (MagVenture); neuronavigation; Lateral coil orientation for preferential stimulation (Harmer et al, 2001; Terao et al.., 2001) of the left then right dmPFC at 10 Hz, at 120% of RMT with a duty cycle of 5 s on, 10 s off, for 60 trains (3000 pulses per hemisphere per session) for 20 daily sessions on weekdays, with non-remitters offered extension to 30 sessions.	M. extensor hallucis longus	As previously published work on dmPFC-rTMS (Bakker et al....., 2014; Downar et al, 2014; Salomons et al, 2014). location corresponds to approximately 25% of the distance from nasion to inion	Ten of 20 patients met the response criteria; dmPFC-rTMS responders had higher dmPFC-ventral striatal connectivity at baseline; reductions in fronto-striatal hyperconnectivity were associated with treatment response to dmPFC-rTMS in OCD.
Dunlop 2015b (*J Vis Exp*)	Treatment-resistant major depression	Methods paper; describes a 20–30 session course of bilateral 10 Hz dmPFC-rTMS and presents sample results from Ref. (64)	No	DCC Cool-DB80 (MagVenture); 20–30 sessions, 120% RMT stimulation intensity, 10 Hz, 5 sec on-10 sec off, 3000 pulses in 60 trains per heimsphere per session, lateral coil localisation for preferential stimulation of each hemisphere (total of 6000 stimuli per session).	M. extensor hallucis longus	dmPFC (as Downar 2014, Salomons 2014) neuronavigated ($X = 30$; $Y = +30$; $Z = +30$)	Treatment-resistant MDD patients achieved significant improve ments on both HAMD-17 and BDI-II.
Dunlop 2015c (*Neuroimage Clin*)	Refractory binge/purge behaviors	28 patients (26 female)	No	Cool-DB80, 10 Hz, 120% RMT, 5 s on, 10 s off, 3000 pulse per hemisphere (procedure: Harmer et al. 2001), with left, then right lateralized coil orientation (Terao et al 2001), 20 (non-responders)-30 (responders) sessions.	M. extensor hallucis longus	dmPFC (as Refs. (62,64)) neuronavigated ($X = 30$; $Y = +30$; $Z = +30$)	16/28 responders (≥50% reduction in binge/purge frequency); enhanced frontostriatal connectivity associated with response to dmPFC rTMS for binge/purge behavior.

Table 2. *Continued*

Kreuzer 2015a (*Brain Stimul*)	Major depression	Three-armed study (15 F8c-rTMS to left DLPFC, 13 ACDC, 12 sham), add-on treatment to standard inpatient setting	Yes	Cool-DB80 (Magventure, Denmark) DCC at 10 Hz, 2000 stimuli per session, 15 sessions, 110% RMT.	M. abductor digiti minimi (accessed via figure-of-8-coil)	dACC (according to localization of Hayward 2007)	Significant group × time interaction effect regarding change in the 21-items HAMD (baseline vs. end of treatment), no severe adverse events, ACDC stimulation well tolerated by majority of patients similar to F8c-rTMS and sham.
Kreuzer 2015b (*Sci Rep*)	Chronic tinnitus	40 patients	No (active control condition)	Combined stimulation; mediofrontal stimulation with Cool-DB80, (2000 stimuli, 10 Hz) followed by left temporo-parietal stimulation with F8-coil (2000 stimuli, 1 Hz) to left dorsolateral-prefrontal-cortex stimulation with F8-coil (2000 stimuli, 10 Hz) followed by temporo-parietal stimulation F8-coil (2000 stimuli, 1 Hz).	Left thenar (accessed via figure-of-8-coil)	dACC (Hayward 2007) (as part of a combined treatment approach comprising temporoparietal areas)	Feasibility of a combined mediofrontal/temporoparietal-rTMS-stimulation with DCC in tinnitus patients; no better outcome compared to an actively rTMS treated control group.
Modirrousta 2015a (*BMC Neurosci*)	OCD	Open-label design, 10 OCD patients	No	8 trains of 150 pulses (=1200) of 1-Hz per session, (uncooled) double-cone coil (Magstim) (therefore 2 min intertrain-interval and 10 min break after 4th train), 110% RMT, for 10 days.	extensor hallucis brevis	mPFC (Brodmann areas 24 and 32), neuronavigation	All patients demonstrated improvement in their OCD symptoms after 10 rTMS sessions shown by a mean improvement in Y-BOCS score of 39% (SD = 15%; $p < 0.001$, $F = 62.95$). Stable improvement for 1 month follow-up.
Modirrousta 2015b (*Depress Anxiety*)	OCD	10 OCD patients (10 sessions) and 10 aged-matched controls (1 session); Flanker task testing before and after first rTMS (both groups) and after session 10 (patients)	-	Magstim DCC; 8 trains of 150 pulses (=1200 pulses per session) at 1 Hz, 2-min intervals between stimulation trains to avoid overheating of the uncooled coil; 10 rTMS sessions at 110% RMT.	M. hallucis brevis	Target area (BA 24 = ACC, 32), neuronavigated	Partial correction of error monitoring (conscious error report and post error slowing), all OCD patients responded to 2 weeks of rTMS with significant symptom reductions, persisting effect for 1 month following treatment.

Table 2. *Continued*

Naro 2015 (*J Pain*)	Pain processing detection in chronic disorders of consciousness	10 healthy controls, 10 minimally conscious state patients, 10 unresponsive wakefulness syndrome (UWS)	Yes	Magstim DCC; 600 stimuli at 1 Hz; 110% RMT coil loops put lateral to midline; stimulation site individually set according to MRI approx. 2 cm anterior to one-third of distance nasion-inion.	M. tibialis anterior	ACC	In all the healthy controls and minimally conscious state and in 2 of the UWS subjects, rTMS increased γ-band oscillatory activity and reduced the cortical nociceptive potentials evoked by transcutaneous EEP amplitude, whereas pain-rating assessment scoring improved in the healthy controls.
Schulze 2016 *(Eur Neuro Psycho-pharmacol.)*	MDD (treatment resistant)	21 patients	No	DCC Cool-DB80 (MagVenture); 20 sessions, 120% RMT stimulation intensity, 10 Hz, 5 seconds on-10 seconds off, 3000 pulses in 60 trains per heimsphere per session, lateral coil localisation for preferential stimulation of each hemisphere (total of 6000 stimuli per session).	M. extensor hallucis longus	dmPFC (as Downar 2014, Salomons 2014) neuronavigated ($X = 30$; $Y = +30$; $Z = +30$)	No deterioration in cognitive performance on any measures, significant improvement on Stroop Inhibition/Switching and Trails B independently from improvement of depressive symptoms.
Schulze 2018 (*Brain Stimul*)	MDD	130 patients	No	DCC Cool-DB80 (MagVenture), once daily 10 Hz vs. twice-daily 20 Hz dmPFC-rTMS; same number of pulses in each group (6000 per day) divided into 1 vs. 2 fractions. Stimulation intensity 120% RMT.	M. extensor hallucis longus	dmPFC (cpil vertex was positioned over dmPFC at position 25% of the distance posteriorly along midline from nasion to inion following heuristic approach validated against MRI-guidance in 232 patients	Safety, tolerability and degree of final improvement did not differ between groups.
Hara 2017 (*Neuro-report*)	Brain injury after motorcycle accident	Case report	No	DCC (Cool-DB80; 10 Hz, 12 sessions (24 sets of 10s train (100 pulses/train) and 50 s intertrain-interval (2400 pulses per session and day).	90% RMT (first dorsal interosseous muscle of unaffected side)	Anterior cingulate gyrus, neuronavigation by Localite	Additional TMS to intensive rehabilitation therapy, no significant side effects, improvement of Mini-Mental-State-Score remained stable during 3-months-follow-up (no change in Wechsler Memory Scale and Rivermeda Behvioural Memory Test).
Sasaki 2017 (*Euro* Stroke *Neurol*)		13 patients	Sham group (7 verum vs. 6 sham utilizing an unconnected pseudo-coil)	DCC (Cool-DB80; 10 Hz, 5 sessions (20 sets of 10s train (100 pulses/train) and 50 s inter-train-interval (2000 pulses per session and day); 80% RMT.	RMT of the intact leg motor area for each subject (visible dorsiflex movement of the intact ankle).	MRI guided navigation to the "upper-midle of the forehead extending from the external auditory meatus to 30° above the orbitomeatal line, vertical placement of the coil over the midsagittal plane).	Heterogenous effects indicating that high frequency rTMS over the dACC and mPFC may be a useful intervention for apathy due to stroke.

Table 2. *Continued*

Zack 2016 (Brain Stimul)	Pathological gambling	9 community-recruited, nontreatment-seeking men with pathological gambling	Yes (vertex with f8-coil oriented perpendicularly)	DCC (P/N 9902–00; Magstim); 10 Hz stimulation, 450 pulses in total; stimulation intensity 80% of active motor threshold (AMT).	AMT was defined from the tibialis anterior muscle	mPFC (BA 10; $x = 0$, $y = 59$, $z = 12$)	Medial prefrontal cortex (PFC) transcranial magnetic stimulation and right dorsolateral PFC continuous theta burst stimulation reduced gambling reinforcement in pathological gamblers. Relative to sham, neither active treatment reduced impulsive choice on a delayed discounting task, and cTBS impaired Stroop performance.

MDD = major depression disorders; OCD = obsessive compulsive disorders; dmPFC = dorsomedial prefrontal cortex; mf = mediofrontal; dACC = dorsal anterior cingulate cortex; RMT = resting motor threshold; MRI = magnetic resonance imaging; TMS = transcranial magnetic stimulation; DCC = double cone coil; F8c = Figure-of-8-coil = butterfly coil.

Taken together the two factors of a) the vital role of the dACC not only in depression but as part of the hypothetical "common core" network of psychiatric disorders in general and b) the technical reachability of the dACC as a target of DCC rTMS strongly deserve further research. As a basis, the present manuscript aims to provide a systematic and comprehensive overview on the current knowledge about dmPFC-DCC-rTMS in the available clinical and neuroscientific literature to date.

METHODS

We systematically searched the MEDLINE® database (http://www.ncbi.nlm.nih.gov/pubmed/; accession date April 3, 2018). Due to the heterogeneous naming of dmPFC-DCC-stimulation, we applied a variety of search terms listed in detail in Table 1. We also searched the reference lists of articles identified in this search strategy and selected relevant articles. We excluded articles using the H-coil even if it shares some similarities with the double-cone coil also aiming at a stimulation of deeper brain areas. However, the H-coil clearly differs from the DCC with respect to the geometry of the produced magnetic field allowing a broader and even deeper (but less focal) stimulation of brain areas.

RESULTS

Only 30 of the initially identified 340 hits (Table 1) were fitting to the issue of the review. Remarkably, these manuscripts cover a broad range of applications in both healthy volunteers and members of clinical populations. We provide a comprehensive overview of the reviewed manuscripts, the indication for stimulation, the number and characteristics of stimulated individuals, the presence and type of a sham control condition, the applied stimulation parameters, equipment, the exact target and the main outcomes in Table 2.

Neuroscientific and Preclinical Studies

In 2004, Hayward and colleagues demonstrated that the Stroop interference effect can be abolished through rTMS over the anterior cingulate (42). The same group then used H2 (15)O PET to explore the physiological effects of double-cone coil TMS over the medial frontal cortex (12) when rTMS was administered at 10 Hz by means of a Magstim DCC located 1.5 cm anterior to 1/3 of the distance from the nasion to the inion. SPM99 analyses, using the ACC as a region of interest, revealed clusters of increased regional cerebral blood flow (rCBF) during medial frontal TMS in Brodmann area (BA) 24 and reduced rCBF in more ventral ACC (12). A whole-brain analysis revealed striking rCBF changes distal to the ACC (12).

The inhibition of the posterior medial prefrontal cortex (pMPFC) by 1 Hz dmPFC stimulation and its effects on theory of mind (TOM) reasoning has been investigated in 17 healthy students. The discrepancy in reaction times between judging another's and one's own belief was decreased by one single session of 2000 pulses of dmPFC-DCC–stimulation at 1 Hz (43). This result was interpreted as support for pMPFC's causal role in establishing perspective differences.

Moore et al. reported increasing generosity after stimulating the prefrontal cortex with continuous theta burst stimulation applying DCC TMS in healthy subjects playing an unregulated dictator game (44). Colin Holbrook reported the modulation of group

prejudice and religious beliefs by dmPFC-DCC–stimulation providing a proof-of-concept that adherence to high-level abstract beliefs can be experimentally modulated by dmPFC rTMS (45).

Klucharev and colleagues demonstrated in 2011 that the transient down-regulation of the posterior medial frontal cortex by theta-burst TMS reduces social conformity thus providing the first interventional evidence of the critical role of the dmPFC in social influence on human behavior (46).

Another study was conducted focusing on experimental pain was published by D'Agata and colleagues in 2015 (47). Superficial electrical stimulation was used to induce continuous pain on the dominant hand. TMS (five single pulses at increasing intensities) was applied on five equidistant points (one per session) over the medial line of the scalp in 13 healthy volunteers using a double-cone coil. TMS stimulation temporarily decreased the pain ratings, and pain adaptation was suppressed when applying the TMS over the FCz site on the scalp. No effect was found for distress ratings (47).

Cho et al. (48) examined the effects of mPFC stimulation by DCC on discounting of delayed rewards applying one session of 10 Hz-rTMS of the mPFC and 1 session of vertex stimulation (control condition) in 1 day (15 10-pulse trains of 1-sec duration at 10 Hz). Thereafter, a subgroup of the participants were involved in a PET study using [11C]-(þ)-PHNO for striatal dopamine measurement. Modulation of the mPFC excitability influenced delayed rewards and interfered with synaptic dopamine level in the striatum (48).

Tzabazis and colleagues conducted a technically elaborate study on shaped magnetic field pulses by multicoil rTMS consisting of up to four simultaneously activated coils tailoring the magnetic field towards maximal effect on the dACC in healthy controls as well as patients suffering from fibromyalgia (49) substantially differing from the technical setup of all studies on dmPFC-DCC-rTMS reported above. Results showed that a single 30 min session using one of three tested rTMS coil configurations operated at 1 Hz produced robust reductions in evoked pain in volunteers. In fibromyalgia patients, 20 rTMS sessions also produced a significant pain inhibition, but only when operated at 10 Hz. This degree of pain control was maintained for at least 4 weeks after the final session (49).

Clinical Studies

One of the very first clinical applications of dmPFC-DCC-rTMS was reported by de Ridder et al. in 2011 (50) treating a patient with alcohol craving. One rTMS treatment was successful, another resulted in a relapse; however, fMRI and resting-state EEG were performed and demonstrated, that craving related EEG beta activity and connectivity between the dACC and posterior cingulate disappeared after successful dmPFC-DCC-rTMS (50). Another case report was published by the same group reporting clinical improvement of a patient with medication-resistant chronic depression after 10 sessions of 10 Hz dmPFC-DCC-stimulation that was accompanied by resting-state EEG changes in the dorsal and subgenual ACC (51).

Further, Vanneste published a manuscript in which the effects of single sessions of dmPFC-DCC-stimulation at different frequencies on tinnitus were reported. In a first study in 78 tinnitus patients was demonstrated that 1 and 3 Hz dmPFC-DCC-rTMS were able to improve both tinnitus intensity and distress, whereas 5 Hz stimulation equaled sham and 20 Hz was significantly worse than sham (52). In a second study patients received either single sessions of 1 Hz dmPFC-DCC-rTMS or repeated treatments (53): single sessions as well as multiple sessions suppressed tinnitus distress and intensity transiently with a higher suppression effect and enhanced responder rates when applying multiple sessions (53). De Ridder also proposed dmPFC-DCC-stimulation for predicting clinical effects of ACC-implants: In two patients with chronic tinnitus, who had a transient response after dmPFC-DCC-stimulation, long lasting tinnitus suppression could be achieved by implantation of epidural electrodes over the ACC (54).

A case report by Downar et al. in 2012 laid the groundwork for later studies on dmPFC stimulation in binge-purge-behaviors. In a woman suffering from refractory bulimia nervosa and receiving high-dose dmPFC stimulation for the treatment of her comorbid depression an unanticipated rapid remission of her bulimia nervosa was observed (55).

In a subsequent study (56), the effects of 20–30 sessions of bilateral 10 Hz dmPFC-rTMS in treatment-resistant patients suffering from obsessive compulsive disorder (OCD) were investigated. Fifty percent of the treated patients met response criteria and reductions in fronto-striatal hyperconnectivity were associated with treatment response to dmPFC-rTMS (56). The same research group reported results of an open-label-study on patients with treatment-resistant major depression. In this study, patients were treated by neuronavigated dmPFC stimulation and showed significant improvements on two common clinical scales for depression (HAMD-17 and BDI-II) after 20 sessions (57). A further study dealt with the treatment of 28 patients suffering from refractory anorexia nervosa, binge-purge subtype or bulimia nervosa. Patients were treated by 10 Hz dmPFC-rTMS stimulation in 20–30 sessions and 16 out of 28 patients reported a reduction of binge-purge-frequency by at least 50% (58).

The same group contributed several more manuscripts: Schulze et al. (59) had a close look on cognitive safety of dmPFC stimulation in major depression. In 21 patients who underwent 20 rTMS sessions no deterioration in cognitive performance was detected in any measures. However, a significant improvement on Stroop Inhibition/Switching and Trails B testing was noted independently from the improvement of depressive symptoms (59). In 2018, Schulze et al. published a manuscript reporting results of an open-label study for once- vs. twice-daily dorsomedial prefrontal rTMS in major depression involving 130 patients retrospectively (60). Coil positioning followed a heuristic model validated against MRI-guidance in 232 patients priorily (61). Overall, treatment was well tolerated, no treatment-limiting adverse events occurred in any of the 130 participants. No significant difference in rates of response and BDI-score-changes were detected. Salomons (62) reported a significant decrease of mean HAMD-17 score from 21.3 ($\pm$6.7) at baseline to 12.0 ($\pm$8.2) after 4 weeks of dmPFC stimulation in depressive patients. Successful treatment was associated with increased dmPFC-thalamic connectivity and decreased subgenual cingulate cortex-caudate connectivity (62). Bakker et al. (63) did a retrospective chart review on safety, tolerability, effectiveness, and outcome predictors for 10 Hz vs. intermittent theta-burst stimulation of the dmPFC in medication-resistant depressive patients (10 Hz, n = 98; iTBS, n = 87) and reported no seizures or serious adverse events in both groups. The effectiveness of 6 min iTBS and 30 min 10 Hz protocols appeared comparable with outcomes not differing significantly between groups after 20–30 TMS sessions (Response/remission rates: Beck Depression Inventory-II: 10 Hz, 40.6%/29.2%; iTBS, 43.0%/31.0%. 17-item Hamilton Rating Scale for Depression: 10 Hz, 50.6%/38.5%; iTBS, 48.5%/27.9%). Downar et al. published a manuscript on the possibility to distinguish nonresponders from responders to dmPFC stimulation in major depression both

clinically and neurobiologically by anhedonia and reward-circuit connectivity, respectively (64). Clinically, they reported a strongly bimodal distribution of clinical effects after 20 sessions of 6000 stimuli of dmPFC-DCC-stimulation at 10 Hz with a lateral coil orientation facilitating a preferential hemispheric stimulation of the ACC (subsequent stimulation of left and right hemisphere with 3000 stimuli each): patients were either showing minimal or marked improvement, nonresponders showed lower connectivity through a reward pathway comprising the ventral tegmental area, striatum, and ventromedial prefrontal cortex at baseline (64). In a further large study, it has been shown that clustering of patients based on resting state fMRI measurements reveals neurophysiologically distinct subtypes of depression which differ in their response to both 10 Hz rTMS and iTBS of the dorsomedial prefrontal cortex (65). fMRI based connectivity features predicted individual differences in the rTMS responsiveness with 78.3% accuracy (65).

Modirrousta et al. published two manuscripts dealing with dmPFC-DCC-stimulation of patients suffering from OCD in 2015: the first (Ref. 66 in Table 2) reported results of an open-label study in ten OCD patients. All patients showed an improvement of their OCD symptoms after ten sessions of 1 Hz rTMS (1200 pulses) and remained stable during the 1 month follow-up period (66). The second study (Ref. 67, Table 2) focused on the improvement of impaired trial-by-trial adjustment of cognitive control in the same ten patients "after deep repetitive transcranial magnetic stimulation" by DCC rTMS targeting the anterior cingulate (BA 24 and 32) with 1200 pulses/session of 1 Hz stimulation (66). OCD patients in this experiment showed abnormally slow response times (RTs) following correct responses. Patients symptoms and slowed RTs following correct responses improved after ten sessions of 1 Hz rTMS, 1200 pulses/session (67).

In a randomized controlled study add-on treatment of depression by dmPFC-DCC-stimulation at 10 Hz has been compared to sham and conventional stimulation of the left dorsolateral prefrontal cortex (DLPFC) using a figure-of-eight coil (68). In this study, there was a significant group *x* time interaction effect regarding the HAMD-21-score; post hoc *t*-tests revealed a significant superior effect for dmPFC-DCC vs. DLPFC-F8c stimulation at week 3/end of treatment. In a second study from this group a combined stimulation paradigm comprising dmPFC-DCC-stimulation was applied in patients with chronic tinnitus which failed to show superiority of ACDC-stimulation and low-frequency stimulation of the temporoparietal junction area (TPJ). In comparison to an active TMS-control-condition consisting of 10 Hz-stimulation of the left DLPFC followed by 1 Hz-stimulation of the TPJ (69) lacking a sham-controlled study arm.

Naro and colleagues conducted a study on pain processing detection in chronic disorders of consciousness (DOC) and enrolled ten healthy controls, ten MCS (minimally conscious state) patients, and ten UWS patients (unresponsive wakefulness syndrome). In all healthy controls and MCS patients and in two of the UWS subjects, 600 stimuli of 1 Hz-rTMS increased γ-band oscillatory activity and reduced the amplitude of cortical nociceptive potentials evoked by transcutaneous electric sinusoidal stimuli (EEP) (70).

Hara and colleagues reported two cases of patients with severe brain injury treated with TMS (Cool-DB80-coil), the first one targeting the ACC as single-photon emission computed tomography excaminations had shown reduced perfusion at this location. The patient received 12 sessions of 10-Hz TMS (total of 2400 pulses per day and session) resulting in an improvement of Mini-Mental-State Scores remaining stable over the 3-month follow-up period. However, no change in Wechsler Memory Scale and Rivermeda Behvioural Memory Test was observed (71).

Sasaki and colleagues presented another manuscript examining the efficacy of anterior-cingulate-cortex TMS utilizing a Cool-DB-80 coil in 13 patients with chronic stroke (72). They were assigned randomly to two groups: rTMS group (n = 7) and sham stimulation group (n = 6). The patients received five sessions of either high-frequency rTMS over the region spanning from the dorsal anterior cingulate cortex (dACC) to medial prefrontal cortex (mPFC) or sham stimulation for 5 days. The severity of apathy was evaluated using the Apathy Scale (AS) and the severity of depression was evaluated using the Quick Inventory of Depressive Symptomatology (QIDS) serially before and after the 5-day protocol (2000 pulses per session). The AS and QIDS scores were significantly improved in the rTMS group, although they were not changed in the sham stimulation group.

Zack et al. (73) reported that rTMS and cTBS can reduce gambling reinforcement in nine noncomorbid men with pathological gambling. The authors used a P/N 9902–00 DCC by Magstim to stimulate the mPFC (neuronavigated target positioning). Interestingly, stimulation intensities were set at 80% of the active motor threshold (AMT) of the tibialis anterior muscle. The experiment was set up in a repeated-measure, Latin square design applying TMS shortly before a slot machine game, stroop task, delay discounting task and several psychometric assessment scores.

DISCUSSION

Variability in Terminology and Methodology

One of the major findings of our literature search was the fact that DCC stimulation of the ACC by placement of the coil over the dmPFC was conducted by both researchers and clinicians in a broad range of indications and conditions reaching from basic research in healthy subjects to a variety of clinical applications. Unfortunately, no common nomenclature of this kind of stimulation has been consistently conducted impeding a detailed and quick overview of the available literature on the topic. In some cases, the dmPFC has been stated as primary target without mentioning the ACC at all, other manuscripts only focused on the ACC as target of the stimulation. Moreover, differences in the application of dmPFC-DCC–rTMS are not limited to terminological conventions. In addition, we found a large variability in several aspects such as coil positioning, stimulation intensity, number of pulses, number of sessions, stimulation frequency, and intertrain intervals. Most studies used high (>5 Hz) and low (<5 Hz) stimulation frequencies according to the "rule of thumb" that high-frequency stimulation should exert excitatory and low-frequency stimulation should exert inhibitory effects on neural activity. This "rule of thumb" has been derived from rTMS of the motor cortex and assessment of cortical excitability by magnetically evoked motor potentials (MEPs) (74–76). However, the question remains open whether this basic rule may be easily transferred to other cortical areas in an unmodified way especially with regard to the ACC.

The ACC contains several subregions, at least the dACC and the subgenual ACC (sgACC). The former is closely connected to the prefrontal cortex and plays a critical role in cognitive-emotional processing (77), the latter seems to be closely involved in emotion recognition (78). The activity of the dACC and the sgACC seem to be functionally anticorrelated, what has been shown in different conditions such as depressive states and experimentally induced

sadness, and on the contrary during antidepressant treatment (cognitive behavioral therapy, antidepressant medication, deep brain stimulation, etc.) (30). This interaction of dACC and sgACC has also been found in the only study that investigated the effects of dmPFC-DCC-stimulation by neuroimaging (12). This study revealed that cerebral blood flow was increased in the dACC and reduced in sgACC after 10 Hz dmPFC-DCC-stimulation. Thus, more research investigating the effects of different stimulation parameters on the activity of the different subdivisions of the ACC is needed. In addition to the relevance of the stimulation frequency also the effect of stimulation intensity should be further explored. This is particularly important for the comparison of effects observed in different studies, as our literature search revealed that even basic principles, such as the recommendation to adapt the individual stimulation intensity according to the participant's/patient's resting motor threshold, was not conducted in the same manner in all studies: some groups referred to the detection of the individual motor threshold by means of a conventional figure-of-8-coil M1-stimulation of the arms transferring this parameter 1:1 to the double-cone-coil-stimulation, others implemented the M1-stimulation of the legs (in most cases the tibialis-anterior-muscle) as basic parameter for the determination of the final stimulation intensity (see Table 2 for details). This is based on the assumption that the M1-region of the lower extremities is located in a similar distance from the surface of the brain (practically: the scull) as the ACC target. Different positioning methods (neuronavigated positioning following anatomic landmarks vs. target-based landmarks vs. 10-20-EEG-system based positioning without the use of neuronavigation tools) have been applied and some groups (e.g., Downar and colleagues) conducted the stimulation with the handle of the coil pointing toward the ear according to Terao (79,80) following the procedure described by Harmer (81), others (e.g., Langguth, de Ridder) conducted the stimulation with the coil handle pointing backward following the concept of Hayward et al. (12).

Most important of all, a comprehensive review of the available literature revealed that these parameters of stimulation have not even been stated clearly in each single manuscript. Therefore, we would strongly suggest that each kind of manuscript reporting effects derived from double cone rTMS of the dmPFC/ACC should contain 1) at least the keywords: "dmPFC; ACC; rTMS; DCC) for easy identification of manuscripts dealing with the topic and enhanced accessibility of knowledge, 2) a detailed description of the stimulation equipment, namely the manufacturer and exact coil type applied in the trial, 3) a detailed description of the coil positioning procedures (e.g., neuro-navigation according to anatomical landmarks or functional data; coil positioning based on anatomical landmarks without neuro-navigation according to 10-20-EEG-system or another algorithm), detailed clarification of coil orientation (such as "handle pointing backwards or turned in a 90° angle to the left or the right"), 4) the detailed stimulation parameters (stimulation intensity, frequency, number of sessions, scheduling of sessions (sequential workdays; 2 days per week, etc.), number of x trains consisting of *y* stimuli with and intertrain interval of *z* sec (*x***y* = number of pulses per session, 5) procedures to assess the individual motor threshold (RMT; upper or lower extremity? Figure-of-eight-coil or DCC used to determine the RMT?), 6) detailed assessment and reports of adverse effects regarding the stimulation (e.g., many reports and clinical experiences indicate reduced tolerability of dmPFC-DCC-rTMS stimulation compared to conventional rTMS with figure-of-eight-coils leading to a (in relation to the RMT) reduced stimulation intensity of dmPFC-DCC-stimulation to assure compliance of participants).

Safety

Safety data from conventional rTMS applications (4) cannot be directly applied to the use of the DCC over the medial prefrontal cortex. From a safety perspective both the deeper and the broader effect of dmPFC-DCC-stimulation require a specific assessment of its safety. Also with respect to safety several methodological uncertainties and differences across studies have to be kept in mind. Even if available studies have not provided any hint for severe side effects, it has to be considered that the total number of investigated cases is still small and the largest study is based on a retrospective chart review, which bears the risk of underreporting of side effects. In our own experience, patients report the sensory sensation during stimulation as being more inconvenient than those in standard rTMS, particularly at higher stimulation intensities and frequencies. Similar observations are also reported by others. For example, Vanneste and colleagues (51) suggested dmPFC-DCC-stimulation as a treatment approach in affective disorders in 2014 and reported the successful treatment of a single patient suffering from treatment resistant depression. However, the patient was—although showing a relatively high RMT of 65% MSO—treated with a stimulation intensity of only 40% MSO because higher intensities were not well tolerated in this case.

In one study (59), cognitive function was systematically assessed in 21 depressive patients that underwent ten sessions of dmPFC-rTMS. The study demonstrated an improvement of cognitive function that was unrelated to improvement of depressive symptoms. Even if results of this open label study have to be interpreted with care, they at least suggest that this kind of rTMS might not worsen cognitive function. Taken together, the available data do not suggest any particular risk of dmPFC-DCC-rTMS, but the systematic assessment of safety data is strongly encouraged in future studies.

The Impact of Stimulation Protocols

The effects of single sessions of dmPFC-DCC-rTMS were assessed in patients with chronic tinnitus (52–54) and in healthy controls. In tinnitus patients a transient reduction of tinnitus after rTMS was observed for low frequencies of rTMS (1, 3 Hz) whereas higher frequencies (5, 20 Hz) did not yield better results than sham stimulation (52). Positive effects of single sessions could be prolonged by repeated sessions (53) and by epidural cortical implants (54).

One study in healthy controls combined TMS with neuroimaging (12) and revealed an increase of cerebral blood flow in the dACC and a decrease in the sgACC after 10 Hz dmPFC-DCC-stimulation. All other single session studies focused on the induction of transient behavioral effects in healthy controls. Based on the assumed ability to interfere with the ACC, effects on social interactions and theory of mind functions were investigated. In a theory-of-mind task of 1 Hz dmPFC-DCC-rTMS increased reaction times for answers about another's beliefs and reduced reaction times for answers about own beliefs. This result confirms the assumption that the medial prefrontal cortex is causally involved in perspective change and that its activity can be decreased by low frequency dmPFC-DCC-rTMS. The inhibitory effect of 1 Hz dmPFC-DCC-rTMS on ACC activity was confirmed by other studies in which single sessions of this protocol reduced electrophysiological and perceptual aspects of pain (49,70).

Behavioral data also suggest that continuous theta burst stimulation over the mPFC transiently reduces mPFC function resulting in reduced inhibitory control on prosocial behavior (44) or reduced adjustment following perceived conflicts between either own and group behavior (46) or between expected and perceived conditions (45).

In contrast to the single session studies, in which mostly inhibitory protocols (1 Hz, cTBS) were used, most clinical applications of dmPFC-DCC-stimulation were performed at a frequency of 10 Hz. 10 Hz rTMS with the DCC over the mPFC has been shown to increase cerebral blood flow in the dACC (12). Based on this finding 10 Hz dmPFC-DCC-rTMS has mainly been applied for the treatment of depression (57,62,63,68). Practically all available studies suggest an antidepressant effect (57,62,63,68), although only one study has been sham-controlled (68). Moreover, imaging studies revealed brain connectivity changes in treatment responders without a clear pattern across studies. In OCD both treatment with 10 Hz (56) and 1 Hz (66,67) resulted in symptom improvement. Further indications in which dmPFC-DCC-rTMS was explored include binge/purge behavior, bulimia, alcohol craving, tinnitus, and fibromyalgia (49,50,52–55,58,69).

CONCLUSION

Taken together the available clinical results indicate the potential of dmPFC-DCC-rTMS. However, both preclinical parameter studies combining TMS with neuroimaging and controlled clinical studies are urgently needed for further development of this promising new TMS approach.

Take Home Message

Taken together, DCC rTMS of the dmPFC/ACC region represents a promising and innovative neuromodulatory approach both with regard to a) theoretical backgrounds (such as the "common core hypothesis" of all psychiatric disorders of Goodkind (35), and Downar and colleagues (37)), b) basic research (e.g., the PET-based studies by Hayward and colleagues (12)) and c) clinical research (e.g. (41,51,57)). However, during the literature search for this review the authors were challenged by the enormous heterogeneity of terminology and the great variability of the applied stimulation paradigms. Most important of all, in the majority of the reviewed manuscripts (even our own ones), especially those from clinical research, crucial pieces of information (e.g., the coil orientation with the handle pointing backwards or twisted in a 90° angle) were consistently missing. Available data support the notion, that the ACC can be stimulated by DCC rTMS. To further exploit this potential basic research involving fMRI, PET, and EEG-methods as well as computational engineering and magnetic field simulations might help to clarify the underlying neurobiological mechanisms and the exact spatial extension of the magnetic field. Moreover, the research field would greatly benefit from a uniform nomenclature and detailed reporting of all relevant details of the stimulation procedure.

Authorship Statements

Peter M. Kreuzer and Berthold Langguth were responsible for data acquisition, interpretation and initial drafting of manuscript. Dirk de Ridder, Jonathan Downar, Jens Schwarzbach and Martin Schecklmann were responsible for data interpretation and manuscript correction. All authors have approved the final version of the manuscript.

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