# rTMS and tDCS for the treatment of catatonia: A systematic review

Maximilian Hansbauer<sup>a,\*</sup>, Elias Wagner<sup>a</sup>, Wolfgang Strube<sup>a</sup>, Astrid Röh<sup>a</sup>, Frank Padberg<sup>a</sup>, Daniel Keeser<sup>a</sup>, Peter Falkai<sup>a</sup>, Alkomiet Hasan<sup>a,b</sup>

<sup>a</sup> Department of Psychiatry and Psychotherapy, University Hospital Munich, Nußbaumstraße 7, 80336 München, Germany

<sup>b</sup> Department of Psychiatry, Psychotherapy and Psychosomatics of the University Augsburg, Bezirkskrankenhaus Augsburg, University of Augsburg, Medical Faculty, Augsburg, Germany

# 1. Introduction

Catatonia is a severe psychomotor syndrome that may occur in numerous psychiatric disorders, affecting up to 10% of psychiatric inpatients (Francis et al., 2010; Pommepuy and Januel, 2002), whereas the prevalence of full-blown catatonia is lower. Although catatonia is mainly perceived as a subtype of schizophrenia, only about 30% of the patients with catatonia suffer from schizophrenia, whereas the majority suffers from an affective disorder (Pommepuy and Januel, 2002; Rosebush and Mazurek, 2010). It also occurs in other mental disorders such as post-traumatic stress disorder, obsessive-compulsive disorder or autism spectrum disorder (Sienaert et al., 2014). Up to 25% of cases are discussed as related to general medical or neurological conditions such as anti-NMDA-receptor encephalitis (Dalmau et al., 2008: Sienaert et al., 2014). Based on these observations DSM-5 operationalizes catatonia as a specifier to mental disorders (schizophrenia, affective disorders, autism) or medical conditions or as sole syndrome of catatonia (Tandon et al., 2013). According to the DSM-5, "Catatonia Associated with Another Mental Disorder (Catatonia Specifier)" is diagnosed if the clinical picture is dominated by at least three of the following: stupor, negativism, posturing, mannerisms, catalepsy, mutism, waxy flexibility, stereotypy, agitation, grimacing, echolalia or echopraxia. In addition, three clinical subtypes (stupor, catatonic excitement and malignant catatonia) are known, which derive from the prevailing symptoms. Recent reviews highlight a hyperactivity of premotor areas as important pathophysiological feature of catatonia (Walther et al., 2019) underlying the importance of addressing motor system pathology in schizophrenia. The origin of this hyperactivity is not yet fully understood, but impairments in the neural maturation during the development of schizophrenia, impairments in inhibitory

<sup>\*</sup> Corresponding author at: Department of Psychiatry and Psychotherapy, University Hospital Munich, Nussbaumstr. 7, D-80336 Munich, Germany.

E-mail address: Maximilian.Hansbauer@med.uni-muenchen.de (M. Hansbauer).

cortico-cortical networks and excess activity within inhibitory projections between cortical areas and basal ganglia are discussed as potential pathophysiological pathways (Walther and Mittal, 2017; Walther et al., 2019).

Benzodiazepines and electroconvulsive therapy (ECT) are usually the first choice of treatment (Madigand et al., 2016) as recommended in national and international guidelines (DGPPN - Deutsche Gesellschaft für Psychiatrie und Psychotherapie, 2019; Hasan et al., 2012). Catatonia related to schizophrenia can also be treated with antipsychotics when neuroleptic malignant syndrome is excluded (DGPPN - Deutsche Gesellschaft für Psychiatrie und Psychotherapie, 2019; Hasan et al., 2012). However, benzodiazepines and antipsychotics are often not effective and ECT is not generally available or sometimes medically contraindicated due to the necessary anaesthesia. Non-invasive transcranial brain stimulation (NTBS) techniques such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) interacting with brain functions by modulating neuronal activity and network connectivity (e.g. by increasing interneuronal activity or membrane activity) are discussed to be potential new treatment options for various neuropsychiatric disorders.

One systematic review of alternative treatment strategies for catatonia (Beach et al., 2017) included different NTBS techniques, but the authors only identified four articles for rTMS (Grisaru et al., 1998; Kate et al., 2011; Saba et al., 2002; Takamiya et al., 2015) and one article for tDCS (Shiozawa et al., 2013). However, due to this sparse data source, authors did not perform an in-depth analysis. Stip et al. (2018) addressed this topic in more detail, but did not perform a systematic literature research and excluded tDCS due to lack of sufficient data. Thus, a systematic evaluation of the efficacy and safety using rTMS or tDCS for the treatment of catatonia is lacking. Therefore, we performed a systematic review regarding the current data on rTMS and tDCS for the treatment of catatonia to evaluate the findings regarding their clinical efficacy and applicability. In the literature, several reviews regarding the pathophysiology and treatment of catatonia are available, but we could not identify any systematic reviews on alternative treatment strategies like NTBS. Since systematic reviews are a crucial first step for new treatment strategies, this work can provide a better basis for the design of future clinical studies and guide clinicians in cases of difficult-to-treat catatonia.

#### 2. Method

For this systematic review, we applied the criteria outlined in the Methodology Checklist 1: Systematic Reviews and Meta-analyses of the Scottish Intercollegiate Guidelines Network (SIGN) (SIGN, 2013) as well as the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline (Moher et al., 2015; Zang et al., 2006). In October 2019, we performed a systematic literature search in the following electronic databases: PubMed, Cochrane Library, Embase, PsycINFO and Web of Science. We then searched the WHO International Clinical Trials Registry Platform (ICTRP) and the ClinicalTrials.gov database for registered, but yet unpublished studies. In each database we searched for cataton<sup>\*</sup> (to capture catatonia and catatonic) in combination with the key words rTMS or tDCS. The identified articles were imported into EndNote X8. In the next step, we removed duplicate articles and screened titles and abstracts of the remaining articles. We included all original work (articles, reviews, case reports and studies) that reported interventions using rTMS or tDCS as treatment in humans with diagnosed catatonia. Articles were excluded if title or abstract did not contain sufficient information to determine that rTMS or tDCS has actually been used as a treatment strategy.

For assessment of eligibility, full texts were read and reviewed by an investigator (MH) with clarification by a senior investigator (AH) as needed. Exclusion criteria at this stage were insufficient patient or treatment data (e.g. stimulation target, intensity and number of sessions). We also searched the reference lists of all eligible publications (e.g.

available non-systematic reviews or systematic reviews covering aspects of our search) to identify other possible articles. Articles included in the final review reported on the successful or unsuccessful use of rTMS or tDCS as treatment possibility for catatonia. Once all eligible studies had been identified, two independent reviewers (MH, EW) extracted relevant data. Each publication was reviewed according to SIGN criteria (grid for grading recommendations). Scores on the Bush-Francis Catatonia Rating Scale (BFRCS) before and after intervention, which were available in eight case reports, i.e. five for rTMS and three for tDCS, were explanatorily compared using a two-sided paired *t*-test (SPSS 25, IBM). If more than one value or a range for BFCRS was reported, we calculated the mean of the available data. One case reported BFCRS scores of "<15" – here, 15 was used for further calculation.

## 3. Results

#### 3.1. rTMS

Fig. 1A displays the PRISMA chart. In the initial search for cataton\* AND rTMS, 71 articles were identified. After the removal of duplicates, 33 articles remained. Of those, 19 were excluded prior to further review due to irrelevance. The remaining 14 articles or abstracts were reviewed in detail. Of those, four were excluded due to insufficient treatment data. After searching the references of the remaining 10 articles, one additional article (Marei and Rashed, 2017) was identified, resulting in a total of 11 articles. Nine of which were case reports (Di Michele and Bolino, 2006; Grisaru et al., 1998; Kate et al., 2011; Marei and Rashed, 2017; Saba et al., 2002; Sharma et al., 2018; Stip et al., 2017; Takamiya et al., 2015; Trojak et al., 2014). We also found two reviews, which addressed our topic of interest (Beach et al., 2017; Stip et al., 2018) as detailed in the introduction. Our search in the trial registries mentioned above revealed two studies, both of which have not yet been completed (Foucher, 2017; Lee, 2012). Preliminary results from one of these two studies (Foucher, 2017) were published as conference abstract prior to end of recruitment (Foucher et al., 2019). Due to the limited information in the abstract (Foucher et al., 2019) and as we had not been able to receive further information to our request for more information, this publication was finally not included. This study used SMA and DLPFC in a randomized crossover design as targets, taking into account novel considerations of the catatonia pathophysiology (see Discussion). Five of the publications reported catatonic symptoms due to schizophrenia, in three subjects mood disorders were diagnosed (bipolar disorder, major depressive disorder) and one case report related to an organic cause (suspected neuroleptic malignant syndrome). Only two patients received ECT prior to the rTMS treatment. The number of rTMS sessions varied between 7 and 108.

For assessment of catatonic symptoms, the BFCRS scores were only reported in five publications. Only one publication reported insufficient improvement of catatonic symptoms.

In the abstract of the prepublication of an ongoing study (Foucher, 2017) the authors report that in two patients rTMS outperformed ECT. Table 1 shows a list of the included case reports, including patient characteristics, technical and treatment details, as well as the underlying psychiatric disorders.

## 3.2. tDCS

Fig. 1B displays the PRISMA chart. In the initial search for cataton\* AND tDCS, 34 articles were identified. After the removal of duplicates, 13 articles remained. Of those, seven were excluded prior to further review due to irrelevance. The remaining six articles or abstracts were reviewed in detail. Of those, two were excluded due to insufficient treatment data leaving four case reports (Baldinger-Melich et al., 2016; Chen et al., 2018; Costanzo et al., 2015; Shiozawa et al., 2013). Our search for registered clinical studies in the mentioned trial registries yielded no

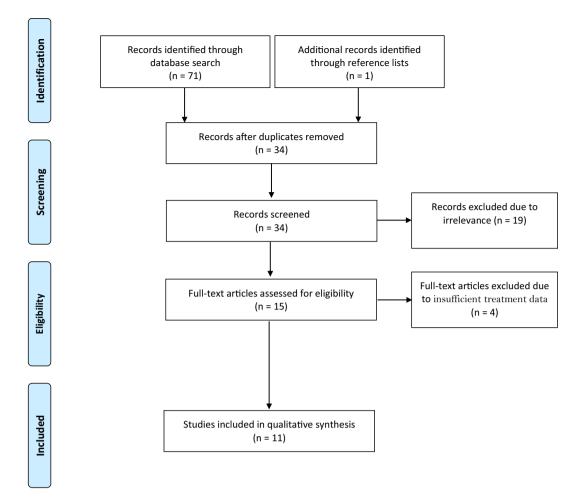


Fig. 1A. PRISMA flow diagram rTMS.

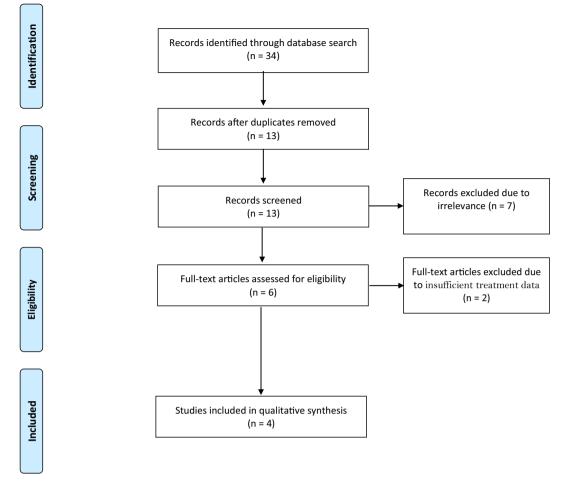
results. Table 2 shows a list of all details regarding the identified tDCS reports. Three of the publications reported catatonic symptoms related to schizophrenia, one to autism spectrum disorder. In three case reports, the patients were female. Two patients received ECT prior to the tDCS treatment. The number of tDCS sessions varied between 10 and 28. In three cases, the DLPFC was targeted and the fourth case report did not mention the stimulation target (but refers to Shiozawa et al. (2013))

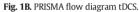
where the left DLPFC was stimulated). Three publications reported the BFCRS scores. Two publications reported rapid and long-term improvement of the catatonic symptoms, only one case report showed shortterm effects without operationalising these outcomes. One publication reported insufficient improvement of the catatonic symptoms (see Table 2 for all details). We could not find any clinical trials on this topic enlisted in the mentioned study registries.

#### Table 1

Characteristics of rTMS case reports: BRFCS, Bush-Francis Catatonia Rating Scale; DLPFC, dorsolateral prefrontal cortex; OFC, orbito-frontal cortex L, left; R, right; MT, motor threshold; p/s, pulses per session; F, female; M, male.

Reference	Grisaru et al., 1998	Saba et al., 2002	Di Michele and Bolino, 2006	Kate et al., 2011	Trojak et al., 2014	Takamiya et al., 2015	Stip et al., 2017	Marei and Rashed, 2017	Sharma et al., 2018
Subtype	Schizophrenia	Schizophrenia	Bipolar disorder	Organic	Schizophrenia	Bipolar disorder	Schizophrenia	Depression	Schizophrenia
Initial BFCRS	N/A	19	N/A	32	23	N/A	31-46	N/A	10
Final BFCRS	N/A	3	N/A	9	20	N/A	<15	N/A	2
Target	DLPFC R	DLPFC L	DLPFC L	DLPFC bilateral	DLPFC L and R and OFC (sequential)	DLPFC L	DLPFC bilateral	DLPFC L	DLPFC L
Frequency	20 Hz	10 Hz	20 Hz	10-20 Hz	10 Hz	10 Hz	20 Hz	N/A	10 Hz
Intensity	65-100% MT	80% MT	80% MT	80% MT	110% MT	120% MT	110% MT	45% MT	100% MT
Pulses/session	800 p/s	1600 p/s	400 p/s	1480 p/s	2000 p/s	3000 p/s	3000 p/s	2000 p/s	1200 p/s
Number of sessions	10	10	7	10	80	20	108	10	19
Total pulses	8000	16,000	2800	14,800	160,000	60,000	32,400	20,000	22,800
Sex	F	F	F	F	M	М	М	Μ	F
Age	24	18	75	22	45	63	N/A	17	16
Previous ECT	Considered	no	N/A	Refused	1 session	yes	556 sessions	No	No
Improvement	Rapid	Rapid	Rapid and long-term	Rapid and long-term	Insufficient	Rapid	Sufficient, but variable	Rapid	Rapid and long-term





## 3.3. Changes of BFRCS pre and post stimulation

Exploratory two-sided paired-sample *t*-tests showed an significant improvement following rTMS/tDCS (mean BFCRS values before intervention:  $25.38 \pm 12.76$ ; after intervention:  $11.69 \pm 12.10$ ,  $t_{(7)} = 3.670$ , p = 0.008). For rTMS this significant effect could be confirmed (before intervention:  $24.50 \pm 11.12$ ; after intervention:  $9.80 \pm 7.73$ ,  $t_{(4)} = 3.620$ , p = 0.022), but not for tDCS, where due to the limited sample size only a numeric improvement in BFRCS values was detected (before intervention:  $26.83 \pm 17.82$ ; after intervention  $14.83 \pm 19.21$ ,  $t_{(2)} = 1.409$ , p = 0.294).

## 4. Discussion

Despite NTBS are discussed as a treatment alternative to ECT in catatonia (Sienaert et al., 2014; Stip et al., 2018), we could only identify single case reports using rTMS (nine reports) or tDCS (four reports), but no open or controlled clinical trials. Not only the sparse number of publications but also the fact, that catatonia covers a very heterogeneous group of symptoms, caused by various medical disorders, limit the possibility to define evidence-based treatment recommendations. However, most reports showed a beneficial effect of the intervention, but it must be critically noted that BFCRS scores were not reported in all publications

#### Table 2

Author	Shiozawa et al., 2013	Costanzo et al., 2015	Baldinger-Melich et al., 2016	Chen et al., 2018
Subtype	Schizophrenia	Autism spectrum disorder	Schizophrenia	Schizophrenia
Initial BFCRS	32	N/A	40-43	7
Final BFCRS	3	N/A	37	3 (6 after one month)
Target	Anodal over L DLPFC	Anodal over L DLPFC	N/A	Anodal over L DLPFC
Current intensity	2 mA	1 mA	2 mA	2 mA
Stimulation duration	20 min	20 min	20 min	20 min
Number of sessions	10	28	10	10
Sex	F	F	M	F
Age	65	14	42	40
Previous ECT	20 sessions	Considered, but not undertaken due to safety concerns	15 sessions	No
Improvement	Rapid and long-term	Rapid and long-term	Insufficient	Rapid, but not long ter

and that improvements were mostly rated very vaguely as "rapid", "insufficient" or "long-term".

The effects must be also explored with regard to a possible publication bias. As negative case reports are very unlikely to be published (Albrecht et al., 2005), the findings presented here (including the preliminary and exploratory statistical analysis of changes in BFCRS scores) can be seen as a first indication of a therapeutic potential for NTBS in catatonia, however, randomized controlled trials are needed to support a wider clinical application. Using the SIGN methodology, case reports represent a level of evidence of three, allowing open recommendations with a D as a grade of recommendation (SIGN, 2013). Such recommendations could e.g. be defined as: 'rTMS or tDCS may be offered as treatment option for catatonia in cases where benzodiazepines and ECT were not effective or are not possible'.

In detail, eight out of nine rTMS reports showed beneficial effects on catatonic symptoms. However, it must be taken into account that the underlying causes differ between the publications (one organic, eight psychiatric disorders). Only one (Trojak et al., 2014) publication reported insufficient effects. This case differs from the others to the effect that bilateral as well as prefrontal and orbito-frontal cortices were stimulated.

Reviewing the four tDCS reports, only one was negative. This publication reported a male schizophrenia patient, while the remaining three positive reports included female patients (two schizophrenia, one autism spectrum disorder). Gender-specific effects of tDCS were discussed in prior physiological reports (Kuo et al., 2006), but the here presented data is too sparse to relate a lacking effect of tDCS in catatonia to such effects. In all detected publications, patients suffered from the "stuporous subtype" of catatonia with predominant hypoactivity. Regarding the underlying pathophysiology and the clinical presentation, one could speculate that patients suffering from a stuporous subtype of catatonia may benefit from excitability enhancing rTMS and tDCS applied to the DLPFC. In this context, some authors discuss that the response to rTMS defines the evidence for an involvement of the DLPFC in the pathophysiology of catatonia (Ellul and Choucha, 2015). Moreover, a decreased activity of the DLPFC and other regions has been linked to catatonia in studies where motor tasks were used supporting these lines of argumentation (Northoff et al., 2000). However, as recently reviewed, hypokinetic catatonia seems to be associated with increased neural activity in premotor areas as a consequence of structural and functional impairments within the motor-system (e.g. cortico-cortical inhibition; excess activity of inhibitory cortico-basal ganglia loops) (Walther and Mittal, 2017; Walther et al., 2019). In this regard, ongoing rTMS randomized-controlled trials using inhibitory rTMS applied to the SMA to reduce the increased neural activity (for review see: (Walther et al., 2019); see also: ClinicalTrials.gov Identifier: NCT03275766). These new developments highlight the need to define the optimal stimulation target and stimulation procedure (inhibitory or facilitatory) when using NTBS for the treatment of catatonia beyond the here reported DLPFC as primary target.

Due to the limited available data, our work has several limitations. The major limitation being that all of the articles included in the review were case reports with lower levels of evidence compared to controlled trials. Case reports alone are not suitable to draw general conclusions about the efficacy of NTBS in the treatment of catatonic symptoms. The found case reports also represent a heterogeneous group of patients with different aetiologies and severity of catatonic symptoms. This severely limits the comparability of the reported results. In addition, information regarding co-medication was often insufficient. Nevertheless, the strength of our review is the first systematic approach with search in several databases and the comprehensive between-report comparisons.

# 5. Conclusion

Despite the availability of a magnitude of literature on the subject of catatonia and its treatment, we offer the first systematic review focusing

on alternative treatment strategies using NTBS. In summary, rTMS and tDCS might be promising alternative treatment strategies for patients who do not respond to benzodiazepines or if ECT is not available or contraindicated. From the identified reports, there is some weak evidence that rTMS or tDCS might be an option in patients who responded to ECT but need long-term treatment to control catatonic symptoms. In these cases, rTMS and tDCS may be offered as post-ECT maintenance treatment. However, in order to be able to provide evidence-based statements and clinically meaningful recommendations, randomizedcontrolled clinical trials with sufficient statistical power are needed to evaluate the impact of rTMS and tDCS on the waxing and waning course of catatonia. Finally, as different psychiatric disorders are associated with impairments in different neuronal networks, different stimulation targets and protocols are needed. Such comparative studies are needed to understand the efficacy and the modes of actions of NTBS in catatonia across various conditions.

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