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Review article

Potential predictors of depressive relapse following repetitive Transcranial Magnetic Stimulation: A systematic review

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ABSTRACT

Background: Repetitive Transcranial Magnetic Stimulation (rTMS) is widely approved treatment for major depressive disorder (MDD). However, around 50% of individuals who recover from depression following rTMS interventions experience a relapse of depressive symptomatology by 12 months. The short-term durability of the rTMS treatment effect has been systematically investigated. However, variables relating to the long-term durability of the antidepressant effect produced by rTMS are less understood. Therefore, the current review systematically assessed the research on variables relating to relapse following rTMS.

Method: This systematic review was performed according to PRISMA guidelines. A comprehensive electronic literature search for terms related to relapse following rTMS treatment for MDD was performed on studies published before the end of October 2018.

Results: A total of 18 studies assessing relapse related variables were identified. While there is some indication that comorbid anxiety, acute response, and residual symptomatology may hold predictive potential for depressive relapse following rTMS treatment, findings were not sufficient to draw reliable conclusions.

Discussion: Identified studies assessed three main categories of variables including demographic information, clinical characteristics and rating scale scores, and rTMS treatment specific factors. Only a small number of studies were available, and considerable inconsistency exists between studies, only limited conclusions were able to be drawn.

Conclusion: More studies assessing a wider range of predictor variables such as cognitive or neuroimaging markers are needed.

1. Introduction

Depression is currently the leading cause of disability worldwide (World Health Organization, 2019). Major depressive disorder (MDD) is characterised by recurrent depressive episodes featuring extreme sadness or melancholy, poor motivation, impaired psychomotor activity, and reductions in appetite, sleep, energy and libido (American Psychiatric Association, 2013). There are three key stages in the treatment for depression: treatment onset, remission and maintenance. While the goal is to eventually cease treatment post maintenance, in many cases, the antidepressant effect does not persist following treatment cessation (Malhi et al., 2015).

It is estimated that around 50% of individuals with a first episode of MDD will go on to experience a second episode (Jelovac et al., 2013; Rush et al., 2006). The risk of further depressive episodes increases with each consecutive episode (Berwian et al., 2017), and individuals that have had three or more previous episodes have a 90% chance of relapse (American Psychiatric Association, 2013). In its long-term clinical course, depression has a substantial disease burden (Malhi et al., 2015). Therefore, the ability to identify individuals at a high risk of relapse is critical, as earlier interventions or provision of more intensive support for these individuals is likely to be helpful for relapse prevention.

Antidepressant pharmacotherapies (ADPs) are the “first line” treatment for MDD (Concerto et al., 2015; Olfson et al., 2006). Traditionally, individuals who do not benefit from multiple trials of ADPs or psychological therapies receive electroconvulsive therapy (ECT) (Malhi et al., 2015). A newer form of treatment now offered in clinical practice is repetitive Transcranial Magnetic Stimulation (rTMS). Several meta-analyses and large scale randomised control studies have demonstrated the effectiveness of rTMS as an MDD treatment

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(Fitzgerald et al., 2006; Berlim et al., 2011; O'Reardon et al., 2007; Schutter, 2009). However, similar to the ADPs, rTMS has its shortcomings specifically relating to its long-term efficacy, beyond the acute treatment phase.

Research assessing individuals after discontinuation of ADPs estimates that around 22% of individuals maintain the antidepressant effect by a 12-month follow-up (Johansson et al., 2015). Meanwhile, meta-analysis by Jelovac et al. (2013) found that 51.1% of individuals relapsed by 12 months following ECT. In a recent meta-analysis Senova et al. (2018) found that 43.6% of individuals who were responders to acute rTMS treatment maintained the antidepressant effect by 12 months. Overall, these studies demonstrate comparable long-term efficacy of ECT and rTMS in MDD treatment, with possibly worse relapse rates following ADPs.

While relapse rates are well documented, relapse predictors are less well understood. Currently, there are suggestions that some life events, social stressors, personality traits, longer duration of episodes; greater number of episodes (Martínez-Amorós et al., 2012); comorbidities; and diagnosis other than unipolar MDD (Huuhka et al., 2012) increase the likelihood of depressive relapse following ADPs and ECT. The meta-regression by Senova et al. (2018) examining rTMS treatment durability and relapse associated variables, demonstrated that maintenance treatment resulted in lower relapse rates at 6 and 12 months; while at 3 and 6 months the proportion of females in the studies was an indicator of higher responder rates following rTMS.

However, while Senova et al. (2018) present important information on response, there was little systematic analysis of factors that relate to relapse. Many of the potential predictor variables identified for rTMS have not been systematically assessed, reviewed, or replicated (Wang et al., 2013). Therefore, the current review aims to systematically assess research on factors relating to relapse following rTMS, in order to identify potential predictors of relapse. To the author's knowledge, this is the first review to comprehensively assesse all the relevant components of relapse following rTMS in individuals with MDD.

2. Method

2.1. Protocol and search strategy

This systematic review was performed according to PRISMA Guidelines (Moher et al., 2009). A comprehensive electronic literature search was performed in MEDLINE, EMBASE, PsycINFO, and Web of Science at the end of October 2018. Keywords used for the search are provided in supplementary material Table S1. Titles and abstracts were independently assessed against the inclusion criteria detailed below, following results from the initial search. In the instances that it was unclear if an article met the inclusion criteria, the full-text article was examined. Full-text of articles potentially meeting the inclusion criteria were also examined. Lastly, reference lists of full-text potentially eligible articles were checked for missing studies.

2.2. Selection criteria

Peer-reviewed journal articles published in English from 2000 to October 2018, were initially included. Studies could be either prospective or retrospective, assessing/treating individuals formally diagnosed with MDD (unipolar or bipolar) according to official diagnostic criteria (i.e., DSM-IV), and treated with repetitive and/or deep TMS. Treatment response and remission had to be defined using clinical judgement and/or an objective formal depressive rating scale. Those who were remitters and responders had to be assessed at least two months after the end of rTMS treatment. Lastly, to assess the risk or time to relapse following rTMS, studies assessing variables and their relation to relapse either as a primary or secondary measure were included.

Studies using electroconvulsive therapies, antidepressants, and/or cognitive-behavioural or other psychological therapy treatments only were excluded. Further, case studies or case series where information on less than 4 participants is reported were excluded, due to the lack of reliability/general applicability in their findings. Studies assessing individuals younger than 18 years and reviews or meta-analysis were also excluded. Furthermore, one study was excluded due to a short, one month, follow-up which would not be sufficient time to reliably assess relapse. Additionally, studies with samples of individuals with other primary diagnoses or severe comorbidities including stroke, multiple sclerosis, substance abuse, dementia, schizophrenia, and panic disorder were not eligible. Neither were studies treating postpartum depression. These restrictions were made to ensure that the findings are reflective of the typical treatment population, as standard clinical treatment of MDD with rTMS would exclude these individuals.

3. Results

3.1. Summary of study characteristics

The initial search produced 98 articles after duplicate removal, full-text screening and eligibility was assessed for 25 studies and a final 18 were accepted for inclusion in the review (for a breakdown of selection process see Fig. 1, for detailed breakdown of included and excluded studies, and reasons see supplementary Table S2). The majority of studies included individuals with treatment resistant depression. However, Wang et al. (2017) further included a sub-population of individuals with a first incident of a depressive episode. Dell'Osso et al. (2011) included only bipolar depressive participants, Fitzgerald et al. (2013) and Richieri et al. (2013) included both bipolar and unipolar, and Mogg et al. (2008) included four participants experiencing psychosis in the context of their MDD. A whole sample of medication/ADP free participants was included in Demirtas-Tatlidede et al. (2008), while seven studies included a mix of participants on and off medication (Wang et al., 2017, 2013; Mogg et al., 2008; Cohen et al., 2009; Dunner et al., 2014; Mantovani et al., 2012; Rosenberg et al., 2015). Lastly, most studies were prospective; Cohen et al. (2009) was the only retrospective study, and Philip et al. (2016) was the only randomized-controlled trials (RCTs).

3.2. Potential predictors of relapse following rTMS treatment for MDD

Studies most commonly defined full remission as a score of < 8, categorised as normal/symptoms absent on the Hamilton Depression Rating Scale (HDRS) (Müller et al., 2002), and relapse/recurrence was generally defined as a HDRS score of ≥ 16, spanning from mild to severe depression. Overall, the studies assessed three broad categories of variables that might relate to relapse including demographic information; clinical characteristics and scores; and treatment specific factors. In terms of demographic factors, only one study noted a significant effect of age on long-term durability of treatment response, with older individuals being more likely to relapse (Cohen et al., 2009). No further demographic factors including gender, age, age of onset, marital status, employment status, and family history of depression were linked to relapse (Dell'Osso et al., 2011; Fitzgerald et al., 2013; Richieri et al., 2013; Mogg et al., 2008; Demirtas-Tatlidede et al., 2008; Dunner et al., 2014; Rosenberg et al., 2015; Philip et al., 2016; Donse et al., 2018; Janicak et al., 2010).

In terms of clinical characterises and relapse predictors, the number of past depressive episodes (Dell'Osso et al., 2011), comorbid anxiety (Richieri et al., 2013), and short-term follow-up scores (Mantovani et al., 2012) were found to be related to relapse in at least one study. No other studies noted a significant effect of these variables on relapse rates, and no other clinical characteristics or scores on standardised clinical rating scales were related to the probability of relapse, including current episode duration, depressive type/subtype,

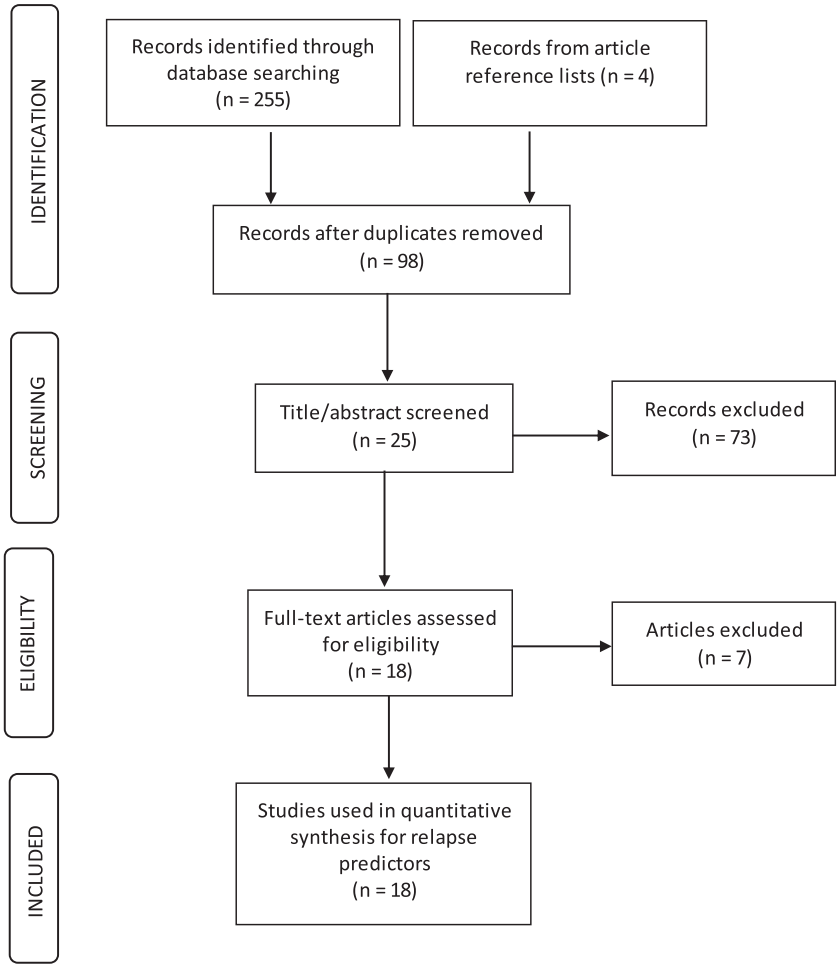

Fig. 1. PRISMA diagram of the study selection process.

medication use, resistance, previous ECT, baseline scores, end scores, the mean percentage change in depressive scores (Wang et al., 2017; Dell'Osso et al., 2011; Fitzgerald et al., 2013; Mogg et al., 2008; Demirtas-Tatlidede et al., 2008; Cohen et al., 2009; Dunner et al., 2014; Rosenberg et al., 2015; Philip et al., 2016; Donse et al., 2018; Janicak et al., 2010; Jin et al., 2016; Pridmore et al., 2018).

Lastly, three studies noted an effect of maintenance in reducing relapse (Richieri et al., 2013; Haesebaert et al., 2018; Rapinesi et al., 2015), while three studies did not (Philip et al., 2016; Donse et al., 2018; Benadhira et al., 2017). Additionally, only one study noted a significant effect of number of rTMS sessions on the long-term antidepressant durability of rTMS (Cohen et al., 2009). A number of other rTMS treatment specifics were assessed, but none of these were related to later relapse, including the number of re-treatments, rTMS type (i.e., unilateral or bilateral), and rTMS frequency (i.e., high or low) (Fitzgerald et al., 2013; Rosenberg et al., 2015; Philip et al., 2016; Donse et al., 2018; Janicak et al., 2010; Pridmore et al., 2018). The studies and their characteristics are further summarised in Table 1, to visualise the data in checklist format, see supplementary Table S3.

4. Discussion

This systematic review aimed to assess existing research on potential predictors of depressive relapse following rTMS treatment. The studies included in the review examined three main categories of variables including demographic information, clinical characteristics and scores on standardised rating scales, as well as rTMS treatment specifics. None of the studies were truly *predictive* (i.e., no study used measures taken at baseline or treatment end, to make predictions at those time points about later relapse on an individual basis). However, it is possible that the relationships between specific variables and probability of relapse, and measures that differentiated the relapsers from the non-relapsers have the potential to be used as predictors. Despite this, no variables were identified as reliable relapse indicators or predictors. Nevertheless, there are some noteworthy topics for discussion.

First, comorbid anxiety was found to be related to long-term outcome in Richieri et al. (2013), noting that individuals who went on to relapse had significantly higher anxiety symptoms at the end of treatment. Furthermore, while Rosenberg et al. (2015) found a significant difference between relapsing and non-relapsing individuals in terms of anxiety, the relationship was complex, with lower anxiety scores before rTMS but higher anxiety scores after rTMS for relapsers. However, the authors did not assess the relationship of this variable to relapse, but rather compared the difference in anxiety levels between groups (i.e., relapsers versus non-relapsers). Furthermore, Janicak et al. (2010) found no relationship between anxiety scores and relapse.

This notion of higher anxiety and depressive scores as potential relapse predictors might be true for other MDD treatments. The systematic review by Berwian et al. (2017) on relapse following ADPs found two studies that assessed the effects of comorbid anxiety. One study showed a significant effect of anxiety, and the other did not. However, the study that found a significant effect noted an association between residual symptoms of depression, higher anxiety scores and greater likelihood of relapse (Joliat et al., 2004).

The effects of rTMS on anxiety alone or in conjunction with MDD

Table 1
Summary of studies assessing factors relating to MDD relapse/recurrence following rTMS (n = 18).

Article	Intervention after rTMS	Follow-up	n start follow-up	n end follow-up	Variables assessed	Findings
Benadhira et al. (2017)	M + NM	6 months	M = 10 NM = 7	M = 6 NM = 5	Maintenance rTMS	No significant effects
Cohen et al. (2009)	ADP	6 months	22	–	Gender, age, refractoriness, BL score, tricyclics, previous ECT, n of rTMS sessions	In a final model, ↑age and ↓rTMS sessions = shorter remission time
Dell'Osso et al. (2011)	ADP	12 months	6	4	Age, age at onset, marital status, employment status, diagnostic subtype, duration of illness, n of failed ADPs in current episode, and family history of mental disorders	No significant findings *Note.* Some NS indication that individuals with greater acute response more likely to maintain benefit later on
Demirtas-Tatlidede et al. (2008)	Nil + Returning	4 years	14	7	Gender, age, mean percentage change on HDRS, number of rTMS treatment courses	No significant findings
Donse et al. (2018)	M + NM	6 months	M = 39 NM = 73	–	Age of onset, BL scores, acute rTMS response, rTMS type	No significant findings *Note.* Some NS indication that greater changes from BL to session 10 are predictive of response and remission
Dunner et al. (2014)	ADP + Returning	12 months	120	75	Gender, age, BL score, medication n + type, acute rTMS response	No significant findings *Note.* Some NS indication ↑acute response = longer effects, non-relapsing responders had ↓ residual symptoms at follow-up entry (sig. different between relapsers vs non-relapsers)
Fitzgerald et al. (2013)	Returning + M	Up to 12 months	35	–	Gender, age, depression type, BL score, medication type, acute rTMS response, rTMS type	No significant findings *Note.* NS trend for more bipolar vs unipolar depressed participants relapsing
Haesebaert et al. (2018)	M + NM/ADP + ADP	12 months	M = 16 NM/ADP = 12 CEP = 17	M = 2 NM/ADP = 1 CEP = 1	Maintenance rTMS vs. maintenance ADP vs. maintenance rTMS + ADP	ADP and combined ADP + rTMS maintenance equally effective at producing preventing relapse
Janicak et al. (2010)	Returning	6 months	99	89	Gender, age, employment, current episode duration, depression duration, comorbidities, course of illness, resistance status, presence of atypical depression, BL score, acute rTMS response, n of rTMS sessions, rTMS intensity, BL motor threshold	No significant findings *Note.* Some NS indication, ↑robust acute response = longer effects/ less likely to require retreatment
Jin et al. (2016)	ADP	Up to 16 months	300	–	rTMS versus ECT treatment and different classifications of recurrent MDD	Long-term RFS estimates same in both treatment groups, classifications of recurrent MDD did not influence RFS estimates
Mantovani et al. (2012)	ADP	3 months	–	–	Medication, acute rTMS response	↑HDRS scores at 1 mo in relapsers vs. non-relapsers*Note.* N of failed medications related NS to 12-week outcome, ↑failure = ↓HDRS scores
Mogg et al. (2008)	ADP	4 months	–	–	Age, psychosis, medication type	No significant findings
Philip et al. (2016)	M + NM	12 months	M = 23 NM = 26	M = 9 NM = 9	Gender, age, BL score, end score, ADP resistance, M rTMS	No significant findings
Pridmore et al. (2018)	M only	10 months	39	20	N of re-treatment, n of weeks between retreatment, BL and end rTMS scores	No significant findings
Rapinesi et al. (2015)	M + NM	12 months	M = 12 NM = 12	–	Maintenance rTMS	At 6 months, NM had a sig. increase in depressive symptoms that further increased at 12 months
Richieri et al. (2013)	M + NM	5 months	–	–	Gender, age, depression duration, depression type, comorbidities, end score, acute rTMS response, rTMS frequency, M rTMS	Relapsers had significantly ↑anxiety, ↑depression, and ↓ remission vs non-relapsers at the end of rTMS treatment. Sig. less relapse in M vs. NM group.
Rosenberg et al. (2015)	ADP	Up to 27 months	17	6	Age, age of onset, current episode duration, medication, n of episodes, comorbidities, BL score, end score, n of rTMS sessions, rTMS intensity	↓HARS before rTMS but ↑HARS after rTMS in relapsers vs non-relapsers
Wang et al. (2017)	M + M+ADP	12 months	M = 91 M+ADP = 82	M = 69 M+ADP = 69	n of episodes, BL score, medication use, rTMS M vs. rTMS M+ADP	Significant association between n of relapsed participants and n of episodes, ↓relapse in participants treated with rTMS (vs ADP) for 1st episode depression

Note. – = relevant information could not be obtained, n = number of, M = maintenance, NM = no maintenance, ADP = antidepressants pharmacotherapies, PT = psychotherapy, mo = month, n = number of participants, HDRS = Hamilton Depression Rating Scale, BL score = baseline score on standardised depression rating scale, end score = score on standardised depression rating scales at the end of treatment phase, RSF = relapse-free survival, ECT = electroconvulsive therapy, NS = not significant.

are not conclusive but show promise for treating symptoms of anxiety (Berlim et al., 2011; Greenberg et al., 1998; Kedzior et al., 2015; Pallanti and Bernardi, 2009). In the present review, studies including participants with higher anxiety scores on standardises measures also demonstrated that these participants had higher depressive scores. Therefore, it could be that individuals with higher depressive and anxiety scores after treatment are partially resistant to the effects of rTMS altogether, and as such, did not achieve full remission on either depression or anxiety. This is supported by Richieri et al. (2013) who not only reported higher anxiety but significantly higher depressive scores at the end of treatment as indicative of future relapse.

The effects of higher depressive scores (or lower acute response) at the end of treatment on the probability of relapse have been assessed in several studies (Dell'Osso et al., 2011; Fitzgerald et al., 2013; Richieri et al., 2013; Dunner et al., 2014; Mantovani et al., 2012; Rosenberg et al., 2015; Philip et al., 2016; Donse et al., 2018; Janicak et al., 2010; Pridmore et al., 2018). While only one study found a significant effect (Richieri et al., 2013), several others noted a non-significant but observable relationship between lower relapse rates and greater acute response to rTMS (Dell'Osso et al., 2011; Fitzgerald et al., 2013; Dunner et al., 2014; Donse et al., 2018; Janicak et al., 2010). That is, individuals with lower depression scores (i.e., less residual symptomatology following rTMS) were less likely to relapse. Furthermore, Mantovani et al. (2012) noted depression scores at one month were significantly higher in those who went on to relapse 3 months after treatment. Further support for the relationship between poor initial response and increased probability of relapse is provided in the meta-analysis by Senova et al. (2018), who found a near significant trend for worse response rates at 3 and 6 months in individuals with lower response to initial rTMS.

Residual symptomatology and its relation to relapse is similar for other MDD treatments. For example, Berwian et al. (2017) noted a trend between higher depression rating scores at discontinuation of ADP treatment and relapse but were unable to draw clear conclusions. There are several reasons that might explain why this trend is observed but not found to be significant across the literature. Most importantly, many of the studies did not disclose the ways in which residual symptoms were assessed and how many residual symptoms were being reported. Results from the STAR*D study – the largest and longest study conducted on a population of individuals with depression being treated with ADPs (Nierenberg et al., 2010) – found that the probability of relapse was associated with a greater number of residual symptom domains on the Quick Inventory for Depressive Symptomatology (QIDS-SR) (Nierenberg et al., 2010). Therefore, the effects of residual symptomatology on relapse might vary based on both magnitude and number. For this to be better understood, research papers will need to start clearly defining how they assessed residual symptomatology, and the magnitude and number of symptoms reported.

Furthermore, maintenance rTMS was found to be an important factor relating to lower relapse rates in half of the studies (Richieri et al., 2013; Haesebaert et al., 2018; Rapinesi et al., 2015), while the other half found no effect (Philip et al., 2016; Donse et al., 2018; Benadhira et al., 2017). Furthermore, some studies that utilised maintenance either did not assess its effect on long-term outcomes, or more often did not include a comparison group. However, maintenance treatment has been found to link to lower relapse rates at specific follow-up time points in studies that looked specifically at assessing the durability of the rTMS response (Senova et al., 2018). The results of the current review are inconclusive and should be taken with caution as very few studies assessed the relationship between relapse and maintenance rTMS. Furthermore, it should be noted that maintenance protocols vary considerably across the included studies, and there is no conclusive research or evidence that maintenance TMS is effective, or if used which protocol should be implemented.

Lastly, age and the number of rTMS sessions were found to be significantly related to relapse in at least one study (Cohen et al., 2009). However, the effects of these variables were not replicated in several other studies. The meta-analysis by Kedzior et al. (2015) noted a significant effect of age on relapse. However, the meta-analysis by Senova et al. (2018) did not produce the same finding. Given that Kedzior et al. (2015) examined the effects of age on studies assessing the effects of rTMS at the end of treatment and at short follow-up period whereas, Senova et al. (2018) assessed to 3 and 6 months, it could be that age is important only for initial rTMS response for a brief period following the end of treatment. Alternatively, it might not be a reliable predictive variable, of the 3 studies identified in Berwian et al. (2017) no one reported significant effects of age on relapse following ADPs. However, studies assessing relapse following ECT note contradictory findings with some indication that less relapse occurs in older age (Prudic et al., 2013), and others finding no differences (Itagaki et al., 2017; Verwijk et al., 2015).

Additionally, fewer treatment sessions have been associated with a higher risk for relapse, possibly because less of an antidepressant effect is produced. In Cohen et al. (2009), there was great variability in how many treatment sessions participants received likewise, the studies reviewed in Kedzior et al. (2015) used 10–15 acute treatment sessions. Current rTMS treatment guidelines state that five consecutive days of treatment for 4–6 weeks, is effective in producing a meaningful response (Perera et al., 2016). Therefore, it could be that the fewer number of rTMS treatment sessions in earlier studies influenced relapse rates. With current treatment guidelines of 15+ sessions, the number of sessions might not be a confounding factor, as studies incorporating 15+ treatment sessions found no relationship between relapse and number of treatment sessions (Janicak et al., 2010; Berlim et al., 2014).

When interpreting the results of this systematic review, certain limitations should be remembered. First, many of the studies assessed factors relating to relapse as secondary or post hoc measures. Furthermore, some studies assessed only one factor or variable. Second, many of the assessed studies are small, underpowered, and predominantly observational. Very few RCTs with long-term follow-up periods of 6 months and beyond, exist. Third, there is substantial variability amongst the included studies relating to the design, methodology, quality, statistical reporting, and patient selection criteria. These are all variables that significantly influence outcomes, and could be an explanation for why some studies have found significant relapse-factor relationships while other studies have not.

On the other hand, it could be the factors assessed thus far are not suitable for the purpose of assessing long-term durability and relapse following rTMS, and a new approach might be needed. No rTMS treatment studies of relapse rates have used or assessed neuroimaging markers or other concurrent factors (i.e., interpersonal difficulties and social support). Neuroimaging factors are worth exploring given that the continued presence of depressive symptomatology is reflected by abnormal functioning of different brain regions (Brakowski et al., 2017). For example, amygdala function, insula and hippocampal structure, and resting state functional connectivity between the amygdala, DLFPC, and ventromedial PFC, have been independently associated with long-term prognosis in follow-up studies of antidepressant and psychological therapies (Canli et al., 2005; Dichter et al., 2015; Frodl et al., 2004; Fu et al., 2013; Soriano-Mas et al., 2011). Additionally, social support, interpersonal difficulties, and coping strategies have been found to produce the best fitting model for depressive relapse at a one year follow-up period following ADPs (Martínez-Amorós et al., 2012).

5. Conclusion

The risks and predictors of relapse following rTMS treatment for depression have been assessed to limited capacity. While there is some indication that variables including comorbid anxiety, acute response, and residual symptomatology may have the potential for prediction, the data relevant to this question remains limited. This is due to few

studies, great inconsistencies, and the near absence of RCTs in this area. Furthermore, since only half of the studies examining the effect of rTMS maintenance treatment on relapse prevention have shown positive effects, the recommendation of maintenance rTMS is not supported by the current literature.

Considering the high relapse rate of MDD, understanding the risk or predictive factors of relapse will help shape future research and assist in MDD treatment management. Specifically, the ability to predict individual relapse could aid in the development of treatment and maintenance strategies that will benefit MDD management and improve long-term outcomes within the clinic, across the illness course, and throughout the individuals' life. Therefore, until large scale RCTs can be conducted, a call for research focusing on brain-based biomarkers is warranted.

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Supplementary materials

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