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Review

Stimulating Memory: Reviewing Interventions Using Repetitive Transcranial Magnetic Stimulation to Enhance or Restore Memory Abilities

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Abstract: Human memory systems are imperfect recording devices that are affected by age and disease, but recent findings suggest that the performance of these systems may be modifiable through interventions using non-invasive brain stimulation such as repetitive transcranial magnetic stimulation (rTMS). The translational potential of these rTMS interventions is clear: memory problems are the most common cognitive complaint associated with healthy aging, while pathological conditions such as Alzheimer's disease are often associated with severe deficits in memory. Therapies to improve memory or treat memory loss could enhance independence while reducing costs for public health systems. Despite this promise, several important factors limit the generalizability and translational potential of rTMS interventions for memory. Heterogeneity of protocol design, rTMS parameters, and outcome measures present significant challenges to interpretation and reproducibility. However, recent advances in cognitive neuroscience, including rTMS approaches in addition to a new understanding of functional brain networks and related insights, may offer methodological tools necessary to design new interventional studies with enhanced experimental rigor, improved reproducibility, and greater likelihood of successful translation to clinical settings. In this review, we first discuss the current state of the literature on memory modulation with rTMS, then offer a commentary on developments in cognitive neuroscience that are relevant to rTMS interventions, and finally close by offering several recommendations for the design of future investigations using rTMS to modulate human memory performance.

Keywords: TMS; rTMS; memory; hippocampus; brain networks; non-invasive brain stimulation; mild cognitive impairment; Alzheimer's disease

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1. Introduction

Human memory systems are understood to be imperfect recording devices, and the performance of these systems is negatively impacted by age and disease. Memory loss is the most common cognitive complaint in older adults, while clinically significant memory deficits exaggerate age-related trends and are often attributable to neuropathological disease. The most common form of pathological memory decline is dementia due to Alzheimer's disease (AD) [1]. Unfortunately, current pharmacological interventions for AD-related memory impairment, such as cholinesterase inhibitors, offer limited benefit for memory loss [2,3]; this is also true of other interventions for AD such as lifestyle changes [4–6]. The lack of effective treatments for memory loss, AD-related or not, leaves a significant need unmet: memory loss has negative consequences for independence, autonomy, and identity. Efficacious treatments for memory loss could preserve these faculties [7–9]. Fortunately, recent findings suggest that targeted non-invasive brain stimulation (NBS) may offer meaningful opportunities for treatment [10]. Specifically, transcranial magnetic stimulation (TMS), a form of NBS, has been reported to improve memory in healthy younger adults, healthy older adults, and individuals with AD [11–14]. TMS may therefore

hold promise as a potential symptomatic treatment for memory loss. Still, a review of the current literature reveals substantial variability in methods, outcome measures, and populations. Consistent with the methodological variability, findings from interventions using repetitive TMS (rTMS) to enhance memory have been inconsistent. To address this, our review seeks to summarize the results of recent rTMS studies in patients on the AD continuum, discuss potential sources of heterogeneity, and provide suggestions on how the field could enhance rigor and reproducibility in future work.

2. Review of Prior Work

2.1. Organization of the Review

Investigations testing TMS as a tool for memory enhancement or a treatment for memory loss have varied widely in their approaches. Acknowledging this heterogeneity, we identified two key independent variables that were used to organize our review: first *stimulation site* and then *target population*. As with the independent variables, we noted that outcome measures could similarly be divided into *changes in cognitive abilities (various)* and *changes in brain variables (structure and/or function)*. For a summary of rTMS studies organized and annotated according to these attributes, please refer to Table 1.

Regarding *stimulation sites*, investigators have most often selected rTMS targets within frontal or parietal association areas. Importantly, these regions are located immediately beneath the skull and thus inside the limited range of typical TMS systems (~2–3 cm beneath the scalp). Within the brain's frontal lobe, studies have frequently targeted dorsolateral prefrontal cortex (dlPFC). This popularity of dlPFC as a stimulation target may be attributable to its known contributions to many cognitive processes including working memory [15–18]. dlPFC is, of course, also a common rTMS target for clinical treatment of psychiatric disorders such as major depression [19]. More broadly, dlPFC is generally acknowledged as a brain region that is both feasible and safe for rTMS [20]. A less common alternative for rTMS has been the parietal lobe, and within it, rTMS studies have most frequently targeted posterolateral parietal cortex or angular gyrus (AG) [13,21]. In studies of rTMS and memory, AG has frequently been targeted due to its normative resting-state functional connectivity (RSFC) to hippocampus. Further, AG is thought to be part of a large-scale intrinsic brain network, the default mode network (DMN) which has been implicated in normal memory function [22–26]. Additionally, the DMN is particularly impacted by AD [24,27,28], making modulation of DMN by rTMS of potential interest for individuals with AD. For information on TMS mechanisms, refer to Box 1.

Regarding *target populations*, while many studies of rTMS effects on memory have focused on healthy younger and healthy older individuals, there are an increasing number of studies investigating the potential for rTMS to treat memory loss within clinical populations (e.g., [29–31]). Studies using rTMS have also recruited individuals with clinical conditions that often precede AD, including (amnestic or non-amnestic) mild cognitive impairment (aMCI/MCI) [32–34].

In our review of published work, rTMS interventions for memory most frequently involved *frontal lobe* stimulation targets and *healthy individuals*, so we begin by summarizing findings from those studies.

Table 1. Properties of included studies.

Authors	Target	Intensity	Frequency	Sessions	Session Spacing (Days to Complete)	Cognitive Changes ([+/N/−] for rMTS) [Score Change]	Functional Connectivity Changes ([+/N/-] Area1:Area2)	Target Population	N
Frontal Lobe rTMS									
Cui et al. [35]	(R) dlPFC	90	10	10	CS(WD)	[+]AVLT	[+]PCC:(R)Fusiform Gyrus, [+]PCC:(L)Anterior Cingulate Gyrus	aMCI	25
Schluter et al. [36]	(R) dlPFC	110	10	1	NA	NA	[+]Salience network connectivity	H	15
Bagattini et al. [37]	(L) dlPFC	100	20	20	CS(WD)	[+]Paired-associate learning	NA	AD	50
Bakulin et al. [38]	(L) dlPFC	100	10	1	NA	[+]n-back	NA	HY	12
Beynel et al. [39]	(L) dlPFC	100	5	4	11	[+]Memory Manipulation	NA	H	85
Chung et al. [40]	(L) dlPFC	50	iTBS	1	NA	[N]n-back	[N]EEG	H	16
		75			NA	[+]n-back	[N]EEG		
		100			NA	[N]n-back	[N]EEG		
Davis et al. [41]	(L) dlPFC	120	1	1	NA	[N]Source Memory	[−]Changes in success related activity	HO	15
			5		NA	[N]Source Memory	[+]Changes in success related activity		
Fitzsimmons et al. [42]	(L) dlPFC	110	1	1	NA	[−]Set-shifting	[−]Task-based betweenness centrality of dlPFC	H	16
Li et al. [14]	(L) dlPFC	100	20	30	CS(WD)	[+]MMSE[2.03], [+]ADAS-Cog[−2.89]	[+]Plasticity Response at M1	AD	37
Drumond Marra et al. [34]	(L) dlPFC	110	10	10	CS(WD)	[+]Rivermead Behavioral Memory Test, [−]Logical Memory II, [+]Letter-number sequencing, [−]Trails B	NA	MCI	34

Table 1. *Cont.*

Authors	Target	Intensity	Frequency	Sessions	Session Spacing (Days to Complete)	Cognitive Changes ([+/N/−] for rMTS) [Score Change]	Functional Connectivity Changes ([+/N/-] Area1:Area2)	Target Population	N
Schluter et al. [36]	(L) dlPFC	110	10	1	NA	NA	[−]Salience network connectivity	H	15
W.-C. Wang et al. [43]	(L) dlPFC	120	1	1	NA	[N]Associative memory	[N]Encoding and retrieval similarity	HO	14
			5		NA	[N]Associative memory	[+]Encoding and retrieval similarity		
Wu et al. [44]	(L) dlPFC	70	iTBS	14	CS(D)	[+]Association memory, [+]Recognition, [+]Logical Memory Test, [+]AVLT	[−](L) dlPFC:(R)Precuneus	AD	13
Xue et al. [45]	(L) dlPFC	90	20	1	NA	NA	[+]low-frequency fluctuation in Rostral Anterior Cingulate Cortex, [+]Rostral Anterior Cingulate Cortex:(L)Temporal Cortex	HY	38
Yuan et al. [33]	(L) dlPFC	80	10	20	CS(WD)	[+]MoCA	[+]ALFF for (R)Inferior Frontal Gyrus, (R)Precuneus, (L)AG, (R)Supramarginal gyrus	aMCI	12
Rutherford et al. [11]	(B) dlPFC	100	20	10(+3)	CS(WD)	[+]MoCA, [+]Word/image Association	NA	AD	10
Lynch et al. [46]	(R) Middle Frontal Gyrus	80	cTBS	1	NA	[−]n-back	NA	HY	24
H. Wang et al. [47]	(R) Middle Frontal Gyrus 1	100	10	2	CS(D)	[+]Face/word Pairs	NA	HY	8
	(L) Middle Frontal Gyrus 2				CS(D)	[+]Face/word Pairs	NA		

Table 1. *Cont.*

Authors	Target	Intensity	Frequency	Sessions	Session Spacing (Days to Complete)	Cognitive Changes ([+/N/−] for rMTS) [Score Change]	Functional Connectivity Changes ([+/N/-] Area1:Area2)	Target Population	N
Jung et al. [48]	(L/R) Precentral Gyrus	100	1	1	NA	NA	[−]DMN activity when at rest	H	36
Riedel et al. [49]	(R) Medial Frontopolar cortex	100	1	1	NA	NA	[−](R)Medial Frontopolar cortex:Amygdala	HY	55
			20		NA	NA	[+(]R)Medial Frontopolar cortex:Amygdala		
Parietal Lobe rTMS									
Freedberg et al. [50]	(L) AG	100	20	4	CS(D)	NA	[+](L)AG:(L)Hippocampal Network	HY	6
Hendrikse et al. [51]	(L) AG	100	20	4	CS(D)	[N]Associative Memory	[−]Connectivity within (L)Hippocampal Network,	H	36
Hermiller, et al. [52]	(L) AG	80	cTBS	1	NA	[+]Word Recognition Memory	[+]Hipp:PCC, [+]Hipp:Left medial frontal Gyrus, [+]Hipp:Right Medialfrontal Gyrus	H	24
		80	iTBS		NA	[N]Word Recognition Memory	N		
		100	20		NA	[N]Word Recognition Memory	N		
Hermiller, et al. [53]	(L) AG	100	20	5	CS(D)	[+]Paired-associate learning, [N]Long-term forgetting	NA	HY	16
Kim et al. [54]	(L) AG	100	20	5	CS(D)	[N]Item recognition, [+]Contextual recollection	[+]Posterior-medial network activity	HY	16
Nilakantan et al. [55]	(L) AG	100	20	5	CS(D)	[N]Recollection Success, [+]Recollection Precision	[−]Late-positive evoked potential amplitude, [−]Theta-alpha oscillatory power	HY	12
Nilakantan et al. [13]	(L) AG	100	20	5	CS(D)	[N]Recollection Success, [+]Recollection Precision	[+]Recollection signals throughout the hippocampal-cortical network	HO	15

Table 1. *Cont.*

Authors	Target	Intensity	Frequency	Sessions	Session Spacing (Days to Complete)	Cognitive Changes ([+/N/−] for rMTS) [Score Change]	Functional Connectivity Changes ([+/N/-] Area1:Area2)	Target Population	N
J.X. Wang & Voss [12]	(L) AG	100	20	5	CS(D)	[+]Paired-associate learning	[+]Hipp:Posteior Hipp-cortical network	HY	16 *
Velioglu et al. [56]	(L) AG	100	20	10	14	[+]Wechsler Memory Scale-Visual	[−]Activity in Occipito-fusiform Gyrus, [−]Fusiform Gyrus:Precuneus, [−]Lateral Occipital Cortex:Precuneus, [+]Fusiform Gyrus:Frontal Opercular Cortex, [+]Lateral Occipital Cortex: Frontal Opercular Cortex	AD	11
J.X. Wang et al. [57]	(L) AG	100	20	5	CS(D)	[+]Paired-associate learning	[+]Cortical-hipp network connectivity	HY	16 *
Wynn et al. [58]	(L) AG	90	1	1	NA	[+]Delayed Recall Confidence	NA	H	25
Freedberg et al. [59]	(L) AG	100	20	3	CS(D)	NA	[+]Hipp:Precuneus, [+]Hipp:Fusiform Area, [+]Hipp:Lateral Parietal Area, [+]Hipp:Superior Parietal Area	HY	8
Tambini et al. [60]	(R) AG	80	cTBS	1	NA	[+]Associative memory success and confidence	Response was dependent on AG and Hippocampus connectivity	HY	25
Bonnì et al. [61]	Precuneus	100	cTBS	1	NA	[−]Source Memory Errors	NA	HY	30
Chen et al. [62]	Precuneus	100	10	10	CS(WD)	[+]AVLT	[−](L)Parahippocampal gyrus:Hipp memory network, [−](L)Middle temporal gyrus:Hipp memory Network	SCD	38
Koch et al. [63]	Precuneus	100	20	10	CS(WD)	[+]AVLT Delayed Recall[0.8]	[+]Beta band oscillations	PAD	14
Riberio et al. [64]	Superior Parietal Cortex	80	1	1	NA	[−]Spatial Working Memory	NA	HY	20

Table 1. *Cont.*

Authors	Target	Intensity	Frequency	Sessions	Session Spacing (Days to Complete)	Cognitive Changes ([+/N/−] for rMTS) [Score Change]	Functional Connectivity Changes ([+/N/-] Area1:Area2)	Target Population	N
H. Wang et al. [47]	Superior Parietal Cortex	100	10	2	2	[+]Face/word Pairs	NA	HY	8
Addicott et al. [65]	(R) Postcentral Gyrus	100	10	5	CS(D)	NA	[+](R)Postcentral gyrus:(L)Insula	H	28
Multisite rTMS									
Leocani et al. [66]	(B) Frontal, Parietal, Temporal	120	10	12(+4)	3 sessions a week for 4 weeks	[+]ADAS-Cog[−1.01]	NA	AD	16
Rabey et al. [67]	neuroAD	90–110	10	30(+24)	CS(WD)	[+]ADAS-Cog[3.76]	NA	AD	15
Nguyen et al. [68]	neuroAD	100	10	30	CS(WD)	[+]ADAS-Cog	NA	MCI, AD	10
Sabbagh et al. [69]	neuroAD	110	10	30	CS(WD)	[+]ADAS-Cog([−0.32]	NA	AD	59

Information from included studies including authors, TMS target, stimulation intensity, stimulation frequency, number of rTMS sessions, if cognitive changes were present, if functional connectivity changes were present, the target population, and the number of subjects. Sessions within parentheses indicated maintenance sessions following intervention. Abbreviations: AD, Alzheimer's Disease; ADAS-Cog, The Alzheimer's Disease Assessment Scale-Cognitive Subscale; AG, angular gyrus; aMCI, amnestic mild cognitive impairment; AVLT, Rey Auditory Verbal Learning Test; B, bilateral; CS, rTMS sessions on consecutive days; cTBS, continuous theta-burst stimulation; D, rTMS sessions took place daily; dlPFC, dorsolateral prefrontal cortex; EEG, significant EEG changes present; H, healthy; HO, healthy old; Hip, Hippocampus; HY, healthy young; iTBS, intermittent theta-burst stimulation; L, left; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; N, no change; NA, not applicable; R, right; SCD, subjective cognitive decline; WD, rTMS sessions took place on week days only; *, same set of participants applied; +, change associated with better cognition or positive change in RSFC; −, change associated with poorer cognition or negative change in RSFC.

2.2. rTMS of Frontal Lobe Sites

2.2.1. rTMS of dlPFC: Healthy Young and Healthy Old

Within studies targeting dlPFC in healthy adults, the left hemisphere has been more frequently targeted. rTMS of left dlPFC has produced moderately consistent effects on RSFC but less consistent cognitive outcomes. Regarding cognitive changes associated with left dlPFC rTMS, eight of twelve studies reviewed here reported significant cognitive improvements associated with high-frequency stimulation [14,33,34,37,38,40,41,43–45,70,71]. Further, one study using low-frequency rTMS reported acute cognitive impairment [42].

Heterogeneity in rTMS methods and outcomes can be observed even in the limited domain of rTMS of left dlPFC of healthy adults. In one study, Chung and colleagues applied intermittent theta-burst stimulation (iTBS) rTMS targeting left dlPFC [40]. rTMS at 50%, 75%, and 100% motor threshold (MT) was associated with different results for each intensity. Their study observed a response similar to an inverted U-shaped curve, with no significant results at 50%, cognitive enhancement at 75%, and intermediate enhancement at 100%. In a similar study, Davis and colleagues applied 5 Hz rTMS at 120% MT to left dlPFC but observed no significant change in cognitive ability [41]. Together, these studies suggest that the greater the rTMS stimulation intensity does not directly correspond to greater outcomes, and that there may be ideal intensities for specific frequencies of rTMS.

In these two studies [40,41], rTMS was associated with changes in RSFC or EEG variables. Further, Davis and colleagues observed that RSFC changes were associated with better cognitive performance, including increased representational similarity during encoding and retrieval during a memory task [41,43]. This association is consistent with a mechanistic explanation for cognitive effects of rTMS: rTMS affects the activity or RSFC of brain tissue (for some period of time after stimulation) with consequences for associated cognitive abilities [72].

Intriguingly, prior rTMS studies targeting dlPFC also suggest that brain state during rTMS may influence the brain's response and related cognitive effects. That is, the same rTMS protocol may yield different effects when administered during task performance or at rest. In one study, Bakulin and colleagues applied rTMS to left dlPFC during different phases of a modified Sternberg task and observed differences n-back performance associated with phase of stimulation [38]. Specifically, the authors found that when rTMS was applied in absence of the modified task, 10 Hz rTMS to the left dlPFC was associated with significantly increased scores on the n-back task. Conversely, when rTMS was applied during any phase of the modified task, no significant benefit was observed. Other authors have speculated that rTMS during a task may invert the responses putatively associated with high-frequency and low-frequency rTMS (see Box 1) [61,73,74]. While there is some evidence of efficacy differences between rTMS during task and rest, further study will be required to rigorously evaluate whether effects are truly inverted and if the same inversion is present for other stimulation targets.

Box 1. Parameters for repetitive transcranial magnetic stimulation.

TMS uses a powerful electromagnet to apply a focal, transient pulse to stimulate activity in the neurons of underlying gray matter [20]. When multiple TMS pulses are applied in series or more complex temporal patterns, the procedure is called repetitive transcranial magnetic stimulation (rTMS). Initial research surrounding rTMS has indicated transient effects associated with stimulation. Critically, it has been reported that rTMS can modify the brain's intrinsic functional networks over extended periods [48,59,75].

A specialized form of rTMS also exists called theta-burst stimulation (TBS), which applies pulses in frequencies putatively mirroring neural oscillatory patterns associated with cognition [76,77]. While frequency usually sets one rTMS study apart from another, the response to theta-burst rTMS (50 Hz) varies by the rest period between stimulation Although in theta-burst rTMS, periods of stimulation, also called trains, are often repeated at a 5 Hz frequency [78], the train is further split into two different paradigms. The first frequently uses a single 40-s train and is called continuous theta-burst stimulation (cTBS), and displays similar properties to low-frequency stimulation. Otherwise, the train can be fragmented into 20 smaller segments of 2 s of stimulation repeated at 10-s intervals called iTBS, which exhibits outcomes similar to high-frequency rTMS. Application of TBS rTMS in different patterns can produce divergent effects on brain activity, cognition, and behavior [20]. iTBS tends to promote brain activity, while cTBS has been putatively associated with increased long-term depression of synaptic transmission [79–81].

The different intensities at which rTMS is administered can also alter rTMS outcomes. Stimulation intensity is often individualized by first gauging an individual's *motor threshold*. This involves measuring the elecotromyographic (EMG) response to single-pulse TMS of primary motor cortex in a distal muscle either at rest (resting motor threshold, RMT) or in flexion (active motor threshold, AMT) [20]. The TMS pulse causes the target corticospinal tract to fire and trigger an overt response in the target muscle. After the cortical area associated with the predetermined muscle of interest, frequently the abductor pollicis brevis of the right hand, is located, an adaptive staircase procedure is used determine the individual's RMT/AMT. This procedure is a guided titration of TMS intensities near the strength that caused the initial EMG response. For RMT, the target intensity is the minimum stimulation strength required to generate a 50 μV or greater peak-to-peak intensity in five of ten stimulations as measured by EMG. The active motor threshold is similar but employs a higher threshold, 200 μV. This higher threshold is required to determine the measured response is due to stimulation and not flexion-related noise in the EMG. Following the motor thresholding procedure, the intensity of the rTMS protocol can then be individualized so that, for example, all participants receive rTMS at 110% of their unique RMT.

2.3. rTMS of dlPFC: MCI and AD

Although AD and MCI (especially aMCI) are often associated with clinical memory deficits, rTMS studies in these populations have frequently assessed general cognitive outcomes rather than memory-specific outcomes. Still, studies of rTMS in individuals with MCI and AD have yielded some consistent results. Much of this consistency may be derived from greater homogeneity of rTMS parameters selected for studies of these populations than in studies of healthy individuals.

For example, in our survey of this literature, primarily high-frequency rTMS was used. In several studies that applied high-frequency rTMS to left dlPFC, stimulation was associated with improved scores on one or more common cognitive assessments, including the MoCA, MMSE, and/or ADAS-Cog [14,33,35,44]. In a smaller number of studies, significant improvements were also reported on domain-specific assessments of memory cognitive abilities such as associative memory and relational memory [37,44,74,82]. Other cognitive domains including attention and language have also been observed to significantly improve. Notably, significant improvements in cognitive measures were often associated with ten or more rTMS sessions. Specifically, improvements in AVLT, paired associate learning, MMSE, ADAS-cog, Rivermead Behavioral Memory Test, letter-number sequencing, association memory, recognition, logical memory, MoCA, and word/image association were observed following ten or more sessions of rTMS for cognitively impaired individuals [11,14,33–35,37,44]. Although a wide variety of cognitive abilities have been observed to improve following ten or more sessions of high frequency rTMS, no studies were found in cognitively impaired individuals applying fewer sessions of rTMS.

In another study, Rutherford and colleagues recruited patients with AD (N = 10) and applied 20 Hz rTMS at 100% RMT to bilateral dlPFC (serially, one hemisphere at a time) across 13 sessions [11]. Of special note, longitudinal follow-up with participants also revealed they had significantly attenuated rates of decline compared to participants randomly assigned to a control condition. Replication of this promising finding would be an important step toward generalization to clinical treatment.

Finally, it has also been reported that low-frequency rTMS of right dlPFC was associated with cognitive improvement [32,83–85]. This finding is fascinating in the context of both healthy and pathological aging, as there is some evidence that right dlPFC exhibits hyperactivity associated with diminished cognitive performance [86,87].

2.4. rTMS of Other Frontal Lobe Areas

While the dlPFC is the most common target for rTMS in the frontal lobe, several other sites in frontal regions have also been targeted. Among these sites are precentral gyrus, middle frontal gyrus, and medial frontopolar cortex. Jung and colleagues have explored the effects of 1 Hz (low-frequency) rTMS to left and right precentral gyrus, two additional non-association areas [48]. Within their study, precentral gyrus was stimulated either under rest or active conditions. They observed decreased connectivity between the DMN and the right motor network, the insular network, and the visual network attributable to rTMS. Additionally, rTMS during task engagement resulted in decreased connectivity between the DMN and the dorsal attention network and increased connectivity between the DMN and the frontoparietal network.

Regarding right medial frontopolar cortex as a target, one study investigated the effects of single-session 20 Hz or 1 Hz rTMS [49]. In this instance, the authors reported RSFC changes associated with improved cognition for the 20 Hz stimulation group and changes associated with poorer cognition following 1 Hz rTMS in the low-frequency stimulation group.

rTMS of middle frontal gyrus (MFG) has also been explored by Wang and colleagues [47]. Whole-brain RSFC with bilateral hippocampus was measured and used to localize potential rTMS targets in MFG which showed strong positive RSFC with hippocampus. This analysis identified two MFG stimulation targets, one each in the left and right hemispheres. While improvements in hippocampal-dependent relational memory were found following stimulation of the right hemisphere target, no such changes were present following rTMS to the left site. Different effects of rTMS applied to left and right MFG could be attributable to laterality, but replication would be an important step to aid the interpretation of these findings.

Interestingly, the second study of rTMS applied to MFG also used RSFC to determine an rTMS target, albeit using a different method. Lynch and colleagues applied a connectome-based approach to identify independent targets for each subject within right MFG based on within-network RSFC [46]. The authors applied a single session of cTBS rTMS to right MFG, and they observed reduced working memory performance associated with stimulation.

2.5. rTMS of Parietal Lobe Sites

2.5.1. rTMS of AG: Healthy Young and Healthy Old

Outside of the frontal lobe, much of the association cortex that is accessible to typical TMS approaches lies in lateral portions of the parietal lobe. In the context of memory-related rTMS studies, locations in the inferior parietal lobule have been targeted most frequently. This is likely due to associations with memory task performance based on neuropsychological and neuroimaging studies [88–91]. In particular, left AG has been a popular choice for rTMS-based modulation of memory function.

rTMS of AG has proved fruitful for memory researchers, illustrated most clearly by the work of Voss and colleagues [12,21,53,60]. Angular gyrus is a cortical area within the effective range of rTMS that exhibits strong RSFC with hippocampus. By targeting a DMN

component functionally connected to hippocampus, many researchers have applied rTMS to improve hippocampal-dependent memory function. In particular, Voss and colleagues have frequently demonstrated success using a paradigm involving 20 Hz rTMS to left AG at 100% RMT [12,13,51–54,57,59]. The only significant source of heterogeneity within the application of this paradigm was the number of rTMS sessions applied.

The bulk of the 20 Hz rTMS studies from Voss and colleagues targeting left AG applied five rTMS sessions [12,13,53–55,57]. Perhaps unsurprisingly, rTMS studies applying five rTMS sessions with other similar parameters have frequently observed similar outcomes. These studies reported improvement in both measures of memory and RSFC. More specifically, RSFC changes associated with improved cognition are observed in the DMN. These changes primarily consist of strengthened RSFC between left AG and left hippocampus. In addition to these primary findings, it has also been reported that rTMS promotes hippocampal RSFC with DMN components beyond AG [12]. Consistent with a mechanistic explanation for rTMS effects on memory, these changes in RSFC were also accompanied by significant cognitive changes [12,13,53–55,57]. The aforementioned improvements in relational memory performance following rTMS were significantly greater compared to participants in the placebo-sham conditions. Further cementing AG as a viable rTMS target, similar increases in cognitive performance and changes in RSFC have also been observed under several rTMS protocols [54,92,93].

Dosage, operationalized as number of stimulation sessions, may be a key factor in determining the efficacy of AG rTMS as a memory-enhancing therapy. Several studies have varied rTMS dosing to investigate this relationship. In one study, Freedberg and colleagues observed that both three or four sessions of rTMS to left AG resulted in similar RSFC changes as when five stimulation sessions were applied, but did not assess changes in memory [59]. Surprisingly, Hendrikse and colleagues reported finding no significant cognitive benefit following four rTMS sessions [51]. To explore this potential minimum threshold, a dose-finding study was carried out by Freedberg and colleagues and discovered that a minimum of 5 rTMS sessions was required for significant change in RSFC reliably [50]. While these studies indicate that a minimum number of rTMS sessions may be necessary to obtain reliable effects, Hermiller and colleagues also reported a single session of cTBS rTMS was adequate to induce comparable changes in RSFC to the aforementioned studies [52]. While the 20 Hz rTMS studies report some consensus around a handful of sessions being required to generate reliable RSFC changes, the presence of this final cTBS study reportedly requiring only a single session suggests no universal number of ideal sessions may exist. Instead, the possibility exists that different stimulation frequencies or different sets of stimulation parameters may possess a unique number of minimum rTMS sessions for significant changes to be observed. Future research exploring this possibility is warranted.

Right AG has also been targeted with rTMS. In a single study, Tambini and colleagues applied cTBS rTMS to right AG [60]. Following this, significant cognitive improvement was present coupled with related RSFC changes. Unfortunately, this was the only identified study targeting right AG, and additional research into right AG rTMS in healthy individuals is warranted.

2.5.2. rTMS of AG: MCI and AD

Although results from healthy young and old adults demonstrate the potential for rTMS to improve memory abilities, similar findings have not been reported yet for AD and (a)MCI. Although new clinical trials are proceeding at the time of this writing [94], only one recent study was identified applying rTMS to AG in individuals with mild to severe AD [56]. Velioglu and colleagues administered ten sessions of 20 Hz rTMS at 100% MT to left angular gyrus [56]. Visual recognition memory performance and the clock drawing test improved after stimulation, but there were no other cognitive benefits reported. Notably, the cognitive improvements were associated with changes in RSFC and, somewhat surprisingly, significant changes in other blood-derived, neurally-relevent biomarkers. Following

rTMS, individuals were reported to have elevated blood brain derived neurotrophic factor measures and lower oxidative status measures. While intriguing, caution is warranted when interpreting these findings because biomarker measures derived from peripheral blood and CSF do not always exhibit strong correlation [95].

2.5.3. rTMS of Other Parietal Lobe Sites

Several parietal regions beyond AG have been targeted with rTMS. The next most common stimulation site was precuneus with three of the nineteen studies targeting this location [61–63]. As precuneus lies at the core of the default mode network [96], several studies have identified significant cognitive or brain changes following rTMS targeting precuneus.

One such study by Chen and colleagues applied ten sessions of 10 Hz rTMS to precuneus in individuals with subjective cognitive decline [62]. Following stimulation, these researchers observed significantly improved episodic memory and RSFC between precuneus and posterior hippocampus. Improvement in these domains is reminiscent of AG stimulation, mainly due to the notable hippocampal RSFC changes. A similar outcome was also reported by Koch and colleagues [63]. Here again, ten sessions were administered but with 20 Hz stimulation. Following stimulation, the authors noted significant improvement in episodic memory coupled with changes in RSFC and EEG profiles. These results contrast with those found for the rTMS study targeting AG in memory-impaired individuals, but not for the studies in unimpaired individuals. Several studies also targeted precuneus with low-frequency or cTBS rTMS and found transient impairments in memory or metacognition [61,97–99].

Two studies reported applying rTMS to superior parietal regions, and both reported cognitive changes in healthy young adults. Both studies here again report consistent outcomes to those expected with high-frequency and low-frequency rTMS stimulation. Specifically, Wang and colleagues observed significant improvement in recalling face/word pairs following two sessions of 10 Hz rTMS of the area of superior parietal cortex exhibiting the strongest RSFC with hippocampus [47]. Alternatively, Ribeiro and colleagues observed acute cognitive impairment following one session of 1 Hz of rTMS to superior parietal cortex [64]. Postcentral gyrus has also been targeted due to its functional connections with the insula, despite it not being association cortex [65]. Following five sessions of 10 Hz rTMS, Addicott and colleagues reported increased RSFC between the target and left insula. The directionality of these findings is consistent with the putative associations between high- and low-frequency stimulation and cognitive enhancement/impairment, although the efficacy of one or two stimulation sessions may be surprising.

3. Multitarget Stimulation

While rTMS studies have most frequently targeted a single cortical region, some investigators have also tested the effect of multitarget rTMS. As the name suggests, multitarget rTMS involves targeting multiple, distal brain regions for stimulation within the same paradigm either serially or, less often, simultaneously. The potential benefits of multitarget stimulation include modulation of brain activity in locations in one or more functional brain networks, and this approach could provide additive or interactive cognitive enhancement [100].

For example, one study employing multitarget stimulation targeted several temporal and parietal stimulation locations serially [101]. Here, the researchers used 20 Hz stimulation over frontal and parietal targets every workday for six weeks. Following stimulation, adults with AD exhibited a significant increase in ADAS-cog performance, and there was evidence that this effect endured for up to 12 weeks. The reported durability of this improvement is unusual in the literature and could reflect persistent modulation of underlying functional brain networks.

The "neuroAD protocol" is another line of research using a multitarget rTMS approach [67,68,102,103]. The protocol involves stimulation of six distinct targets regions:

left and right dlPFC, left and right somatosensory association cortex, Broca's area, and Wernicke's area. Targeting these areas, the authors seek to improve multiple behaviorally relevant functional networks impacted in AD [69]. During each stimulation session, three of the six targets were stimulated in series. Three different brain regions were selected for stimulation every session, with each site being stimulated in 15 sessions [102]. Studies stimulating at 100–110% RMT reported significant improvement in ADAS-Cog performance following rTMS [69]. Meanwhile, stimulation at 90% RMT reported observed increases in MMSE scores [104]. Unique among rTMS therapies for memory, the neuroAD protocol was recently submitted to the FDA for consideration as an intervention for patients with MCI or AD. At the time of writing, the FDA determined that the cognitive benefits were not substantial enough to warrant approval due to their modest efficacy (less than 3 point improvement on ADAS-Cog) [105]. Setting aside the matter of what constitutes significant efficacy, it is possible that the magnitude of cognitive benefit associated with the neuroAD protocol could be due to the inclusion of individuals with substantial cognitive impairment. For individuals with more mild impairment, evidence of greater cognitive improvement was present, with nearly a third of individuals improving by four or more points on the ADAS-Cog [69]. If upheld, this funding would suggest that the neuroAD intervention is more effective in earlier disease stages, such as MCI rather than AD.

Where the neuroAD protocol targeted several locations serially during a session, the development of new TMS coils has also allowed stimulation of multiple cortical areas simultaneously. The ability to broadly stimulate bilateral frontal, temporal, and parietal areas has been explored with "H"-style TMS coils. Specifically, 10 Hz rTMS has been applied using an H coil for twelve consecutive sessions in individuals with AD [66]. Improvements were noted in ADAS-Cog scores but not in several other measures (MMSE, depression, or caregiver ratings of subjective improvement).

4. Developments Relevant to Treating Memory Loss with rTMS

Approaches using rTMS to treat memory loss have evolved substantially over the last two decades, as have insights from neuroscience regarding functional brain organization, neurodegenerative diseases, and brain mechanisms supporting memory processes. These developments are important considerations for investigators designing new rTMS interventions for memory loss. Furthermore, the integration of key concepts into new paradigms could improve the efficacy and reproducibility of future rTMS research. Here, we review some key developments including acknowledgment of the brain's large-scale functional networks, computational modeling of rTMS stimulation fields, and frequency-specific effects of rTMS.

4.1. Functional Brain Networks

The last decade has seen a tremendous expansion of the field's understanding of the brain's intrinsic functional organization. Readily identifiable, large-scale functional brain networks have been reliably observed both in group studies and at the level of individual participants. This development may offer benefits for rTMS approaches similar to those provided by stereotactic alignment of structural MRI data with the physical brain: improved rigor and reproducibility through precision alignment to previously identified stimulation targets. Here, a key concept is the identification of stimulation targets using individualized maps of functional networks overlaid onto the physical brain. Similar targeting has already been applied with success in rTMS studies seeking to treat depression [106,107]. If implemented, this approach could supplement and refine earlier approaches that identify targets based on physical distance, gross neuroanatomical landmarks, or coordinate-based targets derived from brain atlases.

Acknowledging functional network architecture in the design of rTMS interventions will help to ensure that the same functional network is being stimulated across different participants. For example, while dorsolateral prefrontal cortex (dlPFC) has shown promise as an rTMS target for treating memory loss [34,40,74], dlPFC is a large region of association

cortex which includes several distinct functional networks [108,109]. Furthermore, the territory of these networks varies between individuals [110,111]. Stimulation of the same dlPFC location based on neuroanatomy or template-derived coordinates could therefore affect a different selection of functional networks between subjects unless targets are selected for each participant according to their brain's unique functional organization.

A related consideration is that stimulation of different functional networks would be expected to affect different cognitive processes. A strong implication of rTMS not guided by functional network consideration is that cognitive benefits of rTMS interventions could vary between individuals as a function of the stimulated networks rather than stimulation efficacy per se. Alternatively, otherwise similar cognitive benefits might be attributable to changes in different cognitive processes between individuals. Taking memory performance as an example, deficits in executive functions [112,113] or depressed mood [114] have been associated with memory impairments, so by inference, rTMS-associated improvements in executive functions or mood might be expected to enhance apparent memory performance, but without affecting underlying memory processes. While positive outcomes for patients are always welcome, interpretation of this type of finding could be confounded if superficially similar outcomes are attributable to different mechanisms. Integration of functional neuroimaging data into new TMS protocols to support network-specific targeting could help to avoid key confounds.

While integration of functional neuroimaging data in rTMS intervention design is expected to enhance rigor, approaches to processing neuroimaging data can vary greatly and affect interpretation. Specifically, it has been well documented that even when using the same dataset, different groups can generate significantly different findings [115]. This is not surprising because the number of possible analysis paths available to investigators is enormous; one recent report estimated that a typical fMRI dataset might afford nearly 7,000 unique analysis pipelines [116]. Thorough documentation of all steps of functional neuroimaging analysis is therefore essential, and widely-used workflows for analysis might be considered. For example, the Human Connectome Project [117] provides a standardized "minimal preprocessing pipeline" for structural and functional MRI data that appears to deliver reliable results [118]. This and similar pipelines can provide investigators with a predetermined workflow for MRI data processing, ensuring that all groups perform the same steps in the same order. Adoption of a common approach to analyzing neuroimaging data could reduce a significant source of heterogeneity for rTMS interventions that include neuroimaging outcomes.

4.2. Modeling of TMS Field Locale/Stimulation Strength

Selection of TMS stimulation sites can be refined by anatomical and functional considerations as described above, and recent advances in computational modeling of electrical fields induced by non-invasive brain stimulation techniques (including TMS but also transcranial electrical stimulation) may support still further enhancement. Tools such as the SimNIBS toolkit [119] allow researchers to model the induced magnetic and electrical fields for an individual brain based on structural imaging data. The models then estimate the spatial extent of brain tissue affected by each TMS pulse [119]. These estimates are important when considering the anatomical focality of the stimulation produced by a set of TMS parameters.

Model estimates of stimulation extent may also help investigators to understand which functional brain networks are most likely to be affected by TMS at a specific location. In combination with processed functional neuroimaging data, stimulation models can highlight functional networks that are most likely to be affected by TMS at a specific location. New studies could clearly benefit from this approach, and previous studies might benefit retroactively if the necessary data (structural MRI, resting-state fMRI, stimulation coordinates, and stimulation intensity) were collected.

4.3. Stimulation Frequency and Patterning

Historically, rTMS frequencies have sometimes been dichotomized into either "excitatory" or "inhibitory" stimulation [20] as a function of stimulation frequency (>1 Hz vs. <1 Hz, respectively). Classification as excitatory or inhibitory has been driven by changes observed in the motor evoked potential following rTMS to the primary motor cortex. Unfortunately, this simple scheme for classification may be overly reductionist, not addressing potentially important complexities while limiting exploration of new rTMS protocols.

We respectfully suggest that the current "excitatory vs. inhibitory" dichotomy might benefit from a different characterization: high-frequency vs. low-frequency stimulation. Our suggestion for revised terminology arises from the neurophysiology of TMS. Crucially, it is not the case that "excitatory" stimulation causes an overt response at the rTMS target while "inhibitory" stimulation suppresses this response. Rather, irrespective of stimulation frequency, some neurons at the target location depolarize, making "inhibitory" a mischaracterization of the stimulatory effect from the standpoint of a cellular response. Findings from active rTMS, or rTMS performed during task performance, also weigh against the historical labeling of rTMS protocols. Active rTMS has been documented to invert the expected rTMS response [20,39,120,121]. During active rTMS, typical "inhibitory" rTMS protocols have been associated with improvements in cognitive performance in some cases, whereas the same protocol at rest would be associated with reduced performance. "Excitatory" protocols similarly have been reported to swap responses in active conditions further supporting that such classification may be improper. Finally, evidence from studies applying physiological considerations in rTMS protocol determination also suggests that these classifications may be unfitting. One example of the importance of physiological considerations is "inhibitory" rTMS to the right dlPFC. In this instance, it has been observed that following rTMS, episodic memory performance is reported to significantly increase despite the "inhibitory" classification of stimulation [32,85]. It is important to note that right dlPFC does exhibit increased connectivity associated with reduced cognition [86,87]. In this way, although the "inhibitory" protocol improved cognition, it may have also acted to reduce the associated increase in connectivity. From a RSFC standpoint, "inhibitory" rTMS may be properly named in this instance, but the opposing cognitive outcomes add unnecessary confusion to the rTMS field. In this way, the classification of rTMS frequencies into "excitatory" or "inhibitory" only speaks to manipulation of variables in a few specific instances and may inaccurately map onto neurophysiological (or other) outcomes.

As recent studies have enriched our understanding of how brain tissues and brain networks respond to rTMS frequencies and patterns, investigators now have a larger menu of frequencies from which to choose along with a better understanding of likely effects on underlying brain activity. For example, high-frequency rTMS protocols have been associated with increased within-network connectivity of a targeted functional network [41,49]. This may be an important consideration for efficacy because in other work, stronger within-network connectivity has been associated with better cognitive outcomes in neurological disease such as stroke [122]. Meanwhile, low-frequency rTMS has sometimes been associated with decreases in within-network connectivity accompanied by increases in between-network connectivity [41,85]. While this association may not be as robust as the association of high-frequency rTMS with stronger within-network connectivity, the potential for frequency-dependent effects on connectomic measures presents exciting possibilities for basic and clinical research.

Regarding the effects of different frequencies within the "high" or "low" categories, little is known. Very few published studies have measured whether different rTMS frequencies with the same expected activation valence (e.g., high-frequency, 10 Hz vs 20 Hz) produce different effects. Instead, published work has more often contrasted high and low frequencies or the same stimulation frequency at one stimulation location versus another [41,43,49]. This gap in the literature may be important because the few publications on the topic suggest that varying stimulation frequency can affect cognitive outcomes.

In one important demonstration, rTMS at 20 Hz and iTBS were associated with different cognitive outcomes following one session of rTMS targeting left AG [52]. Future research on rTMS methods may help to titrate stimulation frequencies and patterns that combine continued safety with greater efficacy. For the immediate future, new rTMS interventions may benefit by simply acknowledging the expected strengthening of within-network connectivity associated with typical high-frequency rTMS.

5. Suggestions for Studies Using rTMS to Treat Memory Loss

While rTMS shows promise as a potential intervention to enhance declarative/relational memory abilities or to treat memory loss (age-related or pathological), substantial between-study heterogeneity in design has made direct comparisons difficult. Here, we will close our review by discussing study design features and rTMS parameters that we expect will enhance the rigor, reproducibility, and efficacy of new investigations. These include, but are not limited to, selecting a functional network to target, finding suitable stimulation locations within that network, thoughts on TMS coil placement, selection of rTMS frequency to utilize, numbers of rTMS sessions, and the importance of longitudinal follow-ups.

5.1. Stimulation Site Selection

Any rTMS study must select one or more stimulation sites. Predictably, stimulation at different sites has been associated with different cognitive and behavioral outcomes. Acknowledging this, studies focused on memory enhancement or treatment of memory loss should select one (or more than one) site previously associated with memory abilities. Based on prior work and insights from the normative functional organization of the brain, we offer two broad insights and several more specific recommendations.

Perhaps our strongest recommendation is that investigators should consider selecting targets based on functional network locations in addition to structural features or coordinates. The parallel, interdigitated nature of the brain's functional networks makes reliably targeting a specific network through structural features impractical [123]. Conversely, functional targeting is a relatively simple enhancement that can be readily implemented [106,107]. Regarding which networks to target, two may be especially important for normal memory function [23,124]: the default mode network, which is often described as including the medial temporal lobes and hippocampus, structures essential for normal memory; and the frontoparietal network [91], which has been frequently implicated in fMRI studies observing "subsequent memory effects" (increases in activation related to remembered versus forgotten items). Importantly, functionally determined rTMS targets could potentially be derived from resting-state or task-based neuroimaging data (or both); each offers advantages. Resting-state fMRI is relatively easy to collect from most populations and affords the opportunity to readily identify intrinsic networks [125–127]. Alternatively, task-based fMRI, perhaps collected during memory task performance, might offer even more refined targets because of the direct association with memory performance [128]. In either case, individualized stimulation targets derived from analysis of functional neuroimaging data are strongly predicted to provide more consistent results than other approaches.

Turning to specific cortical locations, one possibility is the left posterior lateral parietal lobule, or more specifically, left angular gyrus (AG). Left AG is a region of association cortex that has well-characterized structural connections with the medial temporal lobe and RSFC with the hippocampus [21]. This connectivity and the necessity of hippocampus for normal memory functions [25,129] make left AG an appealing target. Indeed, significant prior work has demonstrated that rTMS of left AG can improve declarative/relational memory in healthy young and healthy older participants [12,13,50,57]. Additionally, stimulation of left AG does not have any known association with relief from depressive symptoms or executive functions, potential confounds related to stimulating other sites (e.g., dlPFC).

rTMS of left dlPFC has also been previously associated with improved memory performance. However, the above concerns regarding potential confounds related to mood and executive functions may apply to stimulation of this region. Irrespective of which location is selected, we strongly recommend individual targeting of a specific functional network rather than a location guided by simple distance, neuroanatomical features, or transformed atlas coordinates.

5.2. Stimulation Site Targeting

Less complex but no less important than selection of a stimulation site is targeting of the stimulation site during an rTMS session. Earlier methods using EEG or scalp landmarks [36,64,101] can be substantially improved upon by TMS instruments that support real-time stereotactic alignment of structural MRI data and the participant's physical brain [52,55,57,130]. Extending the same stereotactic coordinates to the TMS coil allows accurate, reproducible targeting of a specific brain region during one or more TMS sessions. Recently, stereotactic localization of a target brain region has been further enhanced by robotic systems that can maintain precise head-coil positioning to account for head motion during rTMS sessions [130]. Whether automated or manual, stereotactic alignment systems substantially enhance experimental rigor.

5.3. Frequency Selection

rTMS frequencies and protocols are dichotomized into "excitatory" (high-frequency and iTBS) or "inhibitory" (low-frequency and cTBS) frequencies [20]. While this dichotomy may reflect certain trends, factors beyond rTMS frequency also contribute the excitatory or inhibitory influence of rTMS. One such factor is the underlying physiology of the rTMS target and the functional network to which it belongs. rTMS of right dlPFC is a prime example of the role target physiology can play. Multiple reports suggest that 1 Hz rTMS of right dlPFC caused significant improvement in cognitive abilities [32,83–85]. That might be consistent with an "excitatory" influence of an "inhibitory" frequency. Whatever the underlying mechanism, this outcome exemplifies the complex relationship between rTMS parameters and cognitive outcomes. Neurophysiological considerations may also provide insight into what rTMS frequencies may generate potent responses. For example, Chung and colleagues investigated whether iTBS at a frequency matched to an individual's brain activity would outperform the "excitatory" 50 Hz iTBS rTMS [131]. While both the individual and 50 Hz iTBS were reported to significantly improve cognition, individualized iTBS was also associated with significant changes in EEG measures. These reports illustrate the potential impact of neurophysiological considerations on rTMS outcomes. Stimulation frequency is an rTMS parameter that could benefit from more study, including refinement of methods for determining individualized stimulation frequencies based on observed neurodynamics of a given brain.

5.4. Number of Sessions

Perhaps the greatest degree of consensus in the rTMS literature lies in the number of rTMS sessions necessary for reliable memory enhancement. Specifically, multiple consecutive days of rTMS appear to be necessary to reliably observe improvements in memory performance that endure for one or more days after stimulation. Regarding the absolute number of sessions required, some research has been conducted with the explicit goal of dose estimation. Following up on prior work that tested the effects of rTMS applied to left AG, one studied estimated that a minimum of five sessions was required for benefits to memory performance [50], while a similar study by the same group estimated that as few as three simulation sessions was adequate to observe significant changes in RSFC between the stimulation site in left AG and the hippocampus [59]. To the best of our knowledge, these two studies are the only published works examining the effects of different numbers of rTMS sessions for left AG rTMS. More research on dosing of rTMS to treat memory impairment would be helpful. However, based on these dose-finding studies and other

studies reporting significant changes after left AG stimulation, a minimum of five stimulation sessions appears to be a reasonable criterion [50,59]. Notably, ongoing clinical trials in patients with MCI or AD may incorporate even more sessions, such as the "20 weekday sessions during a period of 2 to 4 weeks" in a trial by Taylor and colleagues [94].

5.5. Longitudinal Follow-Up

rTMS therapies for memory would be most beneficial if the effects endured for some prolonged period after stimulation. Unfortunately, many rTMS publications do not report longitudinal measures. Without longitudinal follow-up, the durability and dose-response curves of rTMS therapies are impossible to determine, and this creates challenges for future efforts to translate rTMS research to clinical applications. Collection of longitudinal follow-up measures, perhaps one, three, and six months after completion of an rTMS protocol, would be a welcome addition to the design of future studies.

5.6. Notes on Methodological Heterogeneity versus Discovery Science

We have noted the heterogeneous methodologies of rTMS interventions for memory, and we have suggested that this creates challenges for interpretation and generalization. In that context, the suggestions we offer in this section of our review are intended to highlight opportunities for investigators to enhance their study designs based on recent advances and best practices. However, we do not wish to promote a rigidly proscriptive methodological homogeneity; the field of rTMS for memory (or other cognitive) enhancement is much too young to suggest that any single approach is optimal. Discovery science and exploratory research remain essential to progress in rTMS interventions for memory. So, while departures from typical rTMS protocols should be well-justified, as long as they are conducted with great scientific rigor, such efforts may well prove effective, informative, or both. Standard approaches for rTMS will only be enhanced by novel efforts, and we fully expect that a review of best practices written a decade from now would differ significantly from our current work due to new basic science findings.

6. Conclusions

The brain systems that support declarative/relational memory are imperfect recorders that are negatively impacted by age and disease. Potential treatments for memory loss (or interventions to enhance memory performance) would be beneficial, and rTMS interventions offer preliminary evidence that non-invasive brain stimulation may offer symptom-modifying therapies. Our review of the current literature highlights many published examples of rTMS interventions that successfully modulated memory, often through multi-day high-frequency stimulation of regions in frontal or parietal association cortex. Unfortunately, the current rTMS literature suffers from significant heterogeneity which creates challenges for interpretation and comparison. To address this, we have offered suggestions for the design of future rTMS investigations with the goal of enhancing rigor and reproducibility. Our intent is not proscriptive; rather, we hope to encourage best practices that will speed the transition of rTMS-based memory modulation from laboratories to memory clinics where new therapies are sorely needed. By reducing methodological heterogeneity, introducing neuroimaging measures, and incorporating longitudinal follow-up, forthcoming memory-related rTMS studies have the opportunity to prove the method's validity, generalizability, and translational potential to treat clinical memory loss.

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