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Repetitive Transcranial Magnetic Stimulation-Associated Changes in Neocortical Metabolites in Major Depression: A Systematic Review

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ABSTRACT

Introduction: Repetitive Transcranial magnetic stimulation (rTMS) is an FDA approved treatment for major depressive disorder (MDD). However, neural mechanisms contributing to rTMS effects on depressive symptoms, cognition, and behavior are unclear. Proton magnetic resonance spectroscopy (MRS), a noninvasive neuroimaging technique measuring concentrations of biochemical compounds within the brain *in vivo,* may provide mechanistic insights.

Methods: This systematic review summarized published MRS findings from rTMS treatment trials to address potential neurometabolic mechanisms of its antidepressant action. Using PubMed, Google Scholar, Web of Science, and JSTOR, we identified twelve empirical studies that evaluated changes in MRS metabolites in a within-subjects, pre- vs. post-rTMS treatment design in patients with MDD.

Results: rTMS protocols ranged from four days to eight weeks duration, were applied at high frequency to the left dorsolateral prefrontal cortex (DLPFC) in most studies, and were conducted in patients aged 13-to-70. Most studies utilized MRS point resolved spectroscopy acquisitions at 3 Tesla in the bilateral anterior cingulate cortex and DLPFC. Symptom improvements were correlated with rTMS-related increases in the concentration of glutamatergic compounds (glutamate, Glu, and glutamine, Gln), GABA, and *N*-acetylated compounds (NAA), with some results trend-level.

Conclusions: This is the first in-depth systematic review of metabolic effects of rTMS in individuals with MDD. The extant literature suggests rTMS stimulation does not produce changes in neurometabolites independent of clinical response; increases in frontal lobe glutamatergic compounds, *N*-acetylated compounds and GABA following high frequency left DLPFC rTMS therapy were generally associated with clinical improvement. Glu, Gln, GABA, and NAA may mediate rTMS treatment effects on MDD symptomatology through intracellular mechanisms.

1. Introduction

Major depressive disorder (MDD) is the leading cause of medical disability worldwide, affecting approximately 322 million individuals per year, or four to six percent of the total global population (Murray et al., 2013; Lim et al., 2018; Friedrich, 2017; Bromet et al., 2011). MDD

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is characterized by persistent depressed mood, anhedonia, feelings of worthlessness, indecisiveness, behavioral dysfunction, and suicidal ideation (Otte et al., 2016). These symptoms place a substantial burden on individuals, families, national healthcare systems and the global economy (Wang et al., 2003). Sustained remission of depressive symptoms is currently considered the optimal outcome for clinical management and treatment (Reesal and Lam, 2001). Though gold standard antidepressant pharmacotherapy and psychotherapy are effective and well-established, symptoms persist after treatment in up to half of MDD patients. This form of MDD is referred to as treatment resistant depression (TRD) (Souery et al., 2006; Fava, 2003); for TRD patients, the development of effective, alternative treatments is imperative.

One treatment for MDD which is particularly relevant for TRD is repetitive transcranial magnetic stimulation (rTMS). rTMS is a type of noninvasive brain stimulation delivered to awake patients in ambulatory care settings. During rTMS for MDD, brief, high-intensity magnetic pulses are typically applied to the left dorsolateral prefrontal cortex (DLPFC) via a magnetic coil placed upon the surface of the head (Hallett, 2007). rTMS can be applied at excitatory frequencies ($\geq$ 5 Hz) intended to evoke increased firing of cortical action potentials, or at low frequencies ($\leq$ 1 Hz) which "inhibit" neural activity (Siebner and Rothwell, 2003). The first rTMS device for treating MDD was FDA-cleared in 2008 with a protocol for delivery of 3,000 pulses per session of excitatory rTMS (10 Hz) at 120% resting motor threshold; a series of 20–30 once-daily sessions are given over the course of four to six weeks (McClintock et al., 2018; O'Reardon et al., 2007). As glutamate (Glu) is the brain's principle excitatory neurotransmitter, and γ-aminobutyric acid (GABA) is inhibitory (Godfrey et al., 2018), increases in Glu relative to GABA levels may follow excitatory rTMS, while increases in GABA relative to Glu may follow inhibitory rTMS. Effective rTMS protocols for depression also include low-frequency rTMS applied to the right DLPFC (Berlim et al., 2013), bilateral rTMS (Berlim et al., 2013), and intermittent theta burst stimulation (iTBS), which consists of patterned rTMS and is FDA approved for MDD (Bakker et al., 2015; Huang et al., 2005; Caulfield, 2020). rTMS has demonstrated efficacy in TRD (Gaynes et al., 2014) and has been widely adopted for treatment of MDD in clinical practice (Hutton, 2014). Despite its ubiquity and clinical utility, the biological mechanisms by which rTMS relieves symptoms of MDD and TRD remain unclear. Identification of the neural mechanisms through which rTMS acts to bring clinical benefit in MDD would thus represent a significant advance.

Proton magnetic resonance spectroscopy (MRS), an imaging technique that measures the concentration of specific biochemical compounds in the brain *in vivo*, may inform rTMS mechanisms (Burtscher and Holtås, 2001). Metabolites that can be evaluated using proton MRS include creatine (Cr), choline (Cho), myoinositol (Ins), *N*-acetylaspartate (NAA), γ-aminobutyric acid (GABA), and the glutamatergic compounds (Glx) glutamate (Glu) and glutamine (Gln). Lower levels of Glx, Glu, Gln, GABA, and NAA in the anterior cingulate cortex (ACC) and the prefrontal cortex have been reported in individuals with MDD when compared to healthy controls (Auer et al., 2000; Hasler et al., 2007; Moriguchi et al., 2019; Zhong et al., 2014). Moreover, several studies have reported associations between the extent of metabolite reductions and MDD severity (Auer et al., 2000; Moriguchi et al., 2019; Price et al., 2009; Mirza et al., 2004; Michael et al., 2003a). In a recent *meta*-analysis, reductions in whole brain and ACC GABA were consistently observed in individuals diagnosed with MDD vs. controls. The same *meta*-analysis also observed a trend-level association of low Glx in ACC with MDD diagnosis (Godfrey et al., 2018), but did not replicate whole brain reductions observed in previous *meta*-analyses (Luykx et al., 2012).

MRS studies of various antidepressant treatments have reported changes in metabolite levels. For example, restoration of the metabolites NAA, GABA, Glx, Glu and Gln to levels similar to those of non-depressed individuals have been observed following electroconvulsive therapy (ECT), ketamine, and citalopram (a selective serotonin reuptake inhibitor) (Michael et al., 2003a, b; Bhagwagar et al., 2004; Milak et al., 2020; Lener et al., 2017; Erchinger et al., 2021). Depression improvement has been shown to positively correlate with post-treatment increases in glutamatergic and GABAergic compounds, though not consistently (Michael et al., 2003a, b; Bhagwagar et al., 2004; Milak et al., 2020; Lener et al., 2017; Erchinger et al., 2021; Pfleiderer et al., 2003; Milak et al., 2016; Sanacora et al., 2003). *Meta*-analytic data suggests that at least in the case of GABA, inconsistencies may be state dependent with sub-analyses indicating that GABA reductions were specific to studies examining current, not remitted, depression (Godfrey et al., 2018).

GABA and glutamatergic reductions may underlie alterations in cell morphology and brain connectivity that are characteristic of depression and chronic stress (reviewed in Duman et al., 2019). As the brain's principle inhibitory and excitatory neurotransmitters, the balance GABA and glutamatergic reductions may destabilize brain connectivity. Indeed, recent evidence links normalized connectivity and increased post-infusion GABA and glutamate, to responsiveness to ketamine treatment for MDD (Abdallah et al., 2017). GABA and glutamate changes are associated with multiple neuronal and glial processes implicated in MDD (reviewed in Duman et al., 2019), for example reductions in prefrontal glia and synaptic density in DLPFC are observed postmortem (Rajkowska and Stockmeier, 2013; Sanacora et al., 2008; Kang et al., 2012).

MRS has been used to measure neurometabolic response to rTMS in only a handful of MDD studies conducted over the past 15 years. As a clear evaluation of effective neurometabolic mechanisms will enable clinicians to better understand and optimize rTMS to treat MDD, the field would benefit from a summary of findings to date, in light of observable inconsistencies across the results of individual papers, potential lack of consensus, limitations of the small sample sizes used, and the specialized, technically precise nature of both rTMS and MRS techniques. We thus evaluate and discuss findings to date to further our understanding of mechanisms that may underlie rTMS efficacy in MDD, and to guide future research and treatment efforts. We therefore conducted a systematic review of published MRS studies which used a within-subjects, pre-post rTMS treatment design in patients with a primary diagnosis of MDD. The goal of the review is to summarize (a) baseline metabolic predictors of rTMS treatment outcomes, (b) rTMS-associated effects on brain metabolites irrespective of treatment outcome, i.e., all metabolic changes pre vs. post rTMS, and (c) rTMS-associated changes in brain metabolites which relate to clinical improvement. This review thus summarizes the body of MRS findings associated with rTMS therapy, metabolic mechanisms related to treatment efficacy, and future directions for the field.

2. Methods

2.1. Eligibility Criterion

Eligible studies were peer-reviewed empirical investigations during which MRS imaging was conducted in depressed subjects prior to and following a course of rTMS clinical treatment for MDD. Though status of depression treatment resistance was examined, TRD was not required for inclusion. We excluded: (1) review articles; (2) empirical studies that did not utilize a pre-post rTMS treatment design; and (3) empirical studies that did not evaluate individuals with a diagnosis of MDD. All forms of therapeutic rTMS protocols approved for MDD treatment (i.e., high frequency rTMS, low frequency rTMS, iTBS) were included in this review. Fig. 1 provides the PRISMA chart for study flow and inclusion. Information sources and searches were double verified by two independent researchers to ensure no potentially eligible articles were excluded.

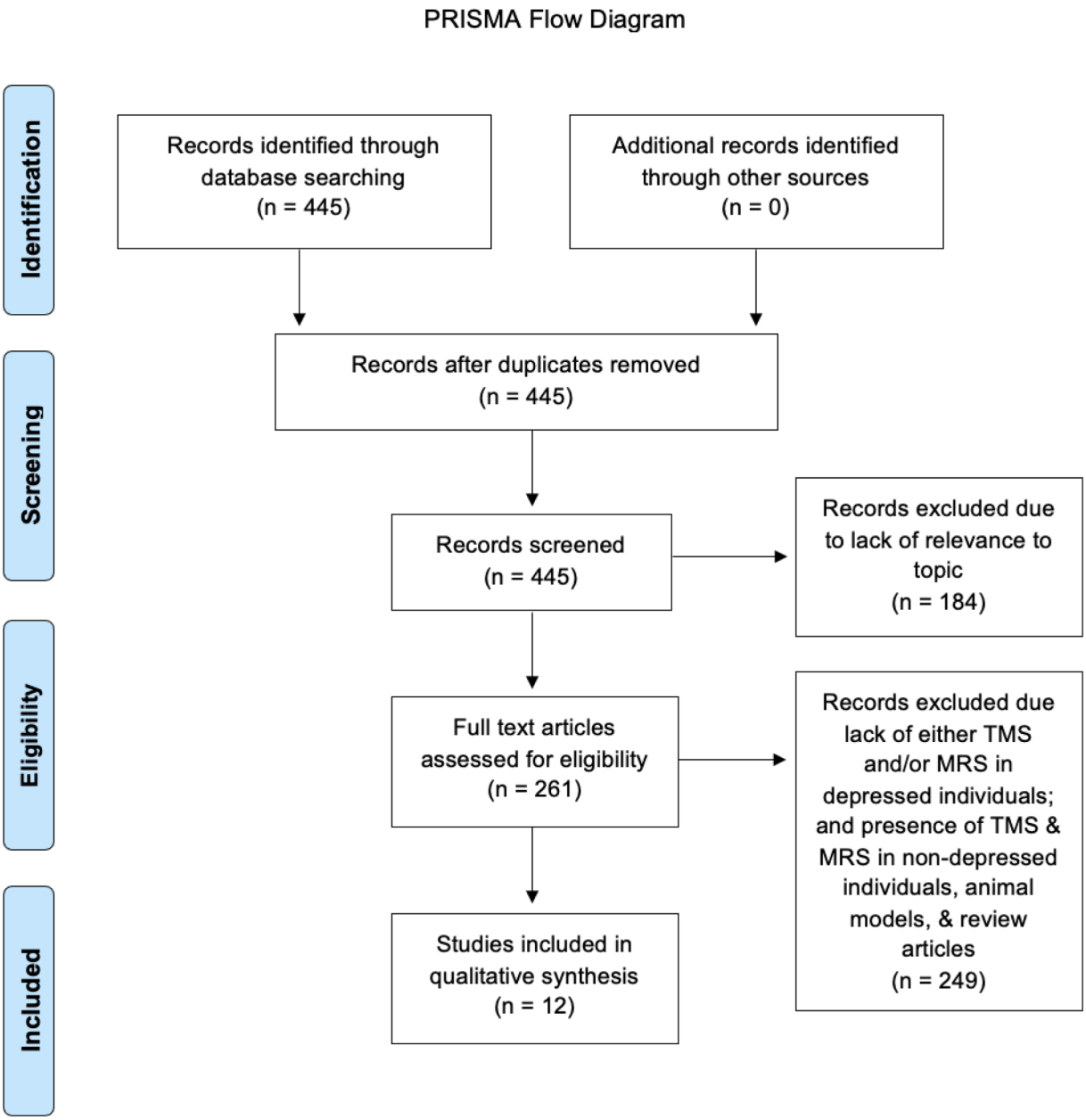

Fig. 1. PRISMA Flowchart of Included Studies.

2.2. Information Sources and Search

Databases of references and abstracts on biomedical topics (i.e., PubMed, Google Scholar, Web of Science, and JSTOR) were systematically searched with the following keyword strings: "TMS AND MRS AND Depression;" "Transcranial Magnetic Stimulation AND Magnetic Resonance Spectroscopy AND Depression;" "Theta Burst AND Magnetic Resonance Spectroscopy AND Depression;" "Transcranial Magnetic Stimulation AND MRS AND Depression;" and "TMS AND Magnetic Resonance Spectroscopy AND Depression." The earliest study identified using this search method was published in 2007 (see PRISMA chart, Fig. 1). Eligible studies were included through January 10th, 2022.

2.3. Data Collection Process

Information pertaining to experimental design, rTMS procedures, MRS methods, and treatment-induced changes in metabolites were extracted and double verified for accuracy (MAG, HEJ, AMF).

2.4. Data Items

The goal of the review was to provide detailed information on the metabolic response to standard-of-care rTMS treatment protocols for MDD, including high frequency 10 Hz rTMS and iTBS. Our overarching objective was to quantify the direction and magnitude of effects of rTMS on metabolites in specific regions of the brain in individuals with MDD. Following (Cuypers and Marsman, 2021), we compiled (1) demographic characteristics, depression diagnoses, medical and neuropsychiatric comorbidities, concurrent medications, MDD severity and treatment resistance, treatment response criteria, and experimental design; (2) rTMS treatment protocol (i.e., rTMS type, target, and basic stimulation parameters such as pulse frequency and number of sessions in the course of therapy, etc.); (3) MRS acquisition parameters (i.e., voxel localization; voxel size; MRS acquisition method; procedures); and three types of MRS findings: (4a) baseline metabolic predictors of rTMS treatment outcomes, (4b) direction and magnitude of changes associated with rTMS effects on brain metabolites, irrespective of treatment outcomes, i.

e., pooled effects of all changes pre vs. post rTMS treatment, and (4c) changes in brain metabolites associated with rTMS treatment outcomes.

2.5. Evaluation of Metabolites.

Metabolites assessed were Glx (Glu + Gln together), Glu, Gln, GABA, NAA, Cho, Ins, and Cr (Blüml et al., 2013). Metabolite levels were quantified relative to both water and other compounds. Historically, Cr has been used as a reference as it has been assumed to be stable in neurological and psychiatric conditions (Li et al., 2003), however, more recently this assumption has been questioned. Cr-referencing does, however, assist to control for various confounds including radio-frequency field inhomogeneities, differences in voxel localization, drifts in instrumental gain, and partial volume cerebrospinal fluid contamination (Li et al., 2002). We discuss all results regardless of referencing and quantification approach (i.e., water- and Cr-referenced metabolites).

3. Results

Twelve studies, comprising a total of $n = 280$ participants with primarily unipolar depression receiving rTMS, met eligibility criteria and were included in the review.

3.1. Experimental Design

3.1.1. Study Design

Studies were small to moderate in size, with samples ranging from 6 to 55 participants, and an overall mean sample size of 23 participants ($SD = 13$) (Table 1). Across studies, 49.6 ± 17.3% (mean ± *SD*) of participants identified as female (range = 11.8%-69.6%). Participants' mean age ranged from 15.5 to 53 years across studies, with an overall mean ± *SD* age of 36.8 ± 11.3. Age composition varied and included studies of adolescents (ages 13–17 (Croarkin et al., 2016)), adolescents to young adults (ages 15–21 (Yang et al., 2014)); and young adults (ages 18–40 (Zheng et al., 2015; Zheng et al., 2010)), with most studies (8/12) focusing on adult patients (ages 20–70 (Baeken et al., 2017; Dubin et al., 2016; Luborzewski et al., 2007; Erbay et al., 2019; Zavorotnyy et al., 2020; Godfrey et al., 2021; Levitt et al., 2019; Bhattacharyya et al., 2021).

3.1.2. Depressive Symptomology and Assessment

With the exception of two studies which included a small number of participants with a primary diagnosis of bipolar II or bipolar I disorder ($n = 3$) (Dubin et al., 2016; Godfrey et al., 2021), participants had a primary diagnosis of current MDD using standard *Diagnostic and Statistical Manual of Mental Disorders* (DSM) DSM-IV, DSM-IV-TR or DSM 5 criteria (American Psychiatric Association, 2013; American Psychiatric Association, 2000). Some level of pharmacoresistance characterized the participants in nine studies; one study did not specify participants' past treatment history or pharmacoresistance (Zavorotnyy et al., 2020), and two did not require treatment resistance (Luborzewski et al., 2007; Erbay et al., 2019). Information on psychiatric comorbidities was available in five studies and included secondary diagnoses of attention deficit hyperactivity disorder, obsessive compulsive disorder, generalized anxiety disorder, social phobia, and post-traumatic stress disorder (Croarkin et al., 2016; Yang et al., 2014; Dubin et al., 2016; Erbay et al., 2019; Godfrey et al., 2021). Use of concurrent medication during rTMS varied across studies. The majority of studies (9/12) allowed continuation of stable doses of antidepressants throughout rTMS/iTBS treatment and MRS scanning (Croarkin et al., 2016; Zheng et al., 2015; Zheng et al., 2010; Dubin et al., 2016; Luborzewski et al., 2007; Zavorotnyy et al., 2020; Godfrey et al., 2021; Levitt et al., 2019; Bhattacharyya et al., 2021), however two studies required participants remain off antidepressant medications (Baeken et al., 2017; Erbay et al., 2019), and one study did not report concurrent medication status (Yang et al., 2014). For all 12 studies, depression symptom severity was assessed using self-report and/or clinician ratings including the Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HAMD), Montgomery-Asberg Depression Rating Scale (MADRS), and the 30-Item Inventory of Depression Symptomatology (IDS-SR30). Seven studies compared metabolite changes across subgroups defined by categorical treatment outcomes, i.e., rTMS responders vs. non-responders (see Table 1 for further details; Dubin et al., 2016; Luborzewski et al., 2007; Levitt et al., 2019; Croarkin et al., 2016; Yang et al., 2014; Zheng et al., 2015; Zheng et al., 2010).

3.2. rTMS Treatment Procedures for MDD

3.2.1. Study Design

rTMS treatment procedures appear in Table 2. Procedures for rTMS treatment and outcome assessment varied, with over half of studies (8/12) using an unblinded, open-label design in which rTMS was administered without a sham (control) condition (Croarkin et al., 2016; Yang et al., 2014; Dubin et al., 2016; Luborzewski et al., 2007; Erbay et al., 2019; Godfrey et al., 2021; Levitt et al., 2019; Bhattacharyya et al., 2021). Three studies used a randomized, controlled design in which participants were assigned to a series of active or sham treatments under double-blind conditions (Zheng et al., 2015; Zheng et al., 2010; Baeken et al., 2017). One study used a within-subjects, crossover design, with participants undergoing both sham and active iTBS treatment conditions in random order (Zavorotnyy et al., 2020). In addition to sham, these four studies included control groups comprised of age- and gender-matched healthy individuals not receiving either stimulation (sample size: *n's* = 15–28; (Zavorotnyy et al., 2020; Zheng et al., 2015; Zheng et al., 2010; Baeken et al., 2017) for comparison of baseline metabolite levels between nondepressed participants and patients with MDD. One study included four healthy controls in order to obtain test–retest reliability of metabolite measurements; these metabolite levels were not compared to baseline metabolite levels in individuals with MDD (Bhattacharyya et al., 2021).

3.2.2. rTMS Protocols, Targets, and Course Features

10 of 12 studies used protocols targeting left DLPFC with high-frequency (≥ 10 Hz) once-daily stimulation sessions (Table 2). One used sequential bilateral or right-sided DLPFC stimulation in addition to left DLPFC stimulation (Levitt et al., 2019), and one used iTBS (Zavorotnyy et al., 2020). Excluding the iTBS protocol, pulse frequency ranged from 10 to 20 Hz (excitatory frequencies) for standard left-sided sessions. The sequential bilateral protocol used by Levitt et al. added 1 Hz stimulation (inhibitory frequency) to the right DLPFC for 19 participants who did not respond to left DLPFC rTMS after the 15th treatment session (Levitt et al., 2019). No other studies used low frequency stimulation. In Levitt et al., one participant was unable to tolerate left DLPFC stimulation, and thus only received rTMS to the right DLPFC (10 Hz); another participant switched from left to right DLPFC rTMS (10 Hz) after their fifth session (Levitt et al., 2019). The iTBS protocol included 50 Hz bursts with a 5 Hz carrier frequency (excitatory frequencies) (Zavorotnyy et al., 2020). A range of 1200 to 4000 pulses was administered per rTMS session. One study used an accelerated schedule which delivered multiple sessions per day (Baeken et al., 2017). The courses of active treatment lasted from 4 days to 8 weeks. 11 of 12 studies aimed to treat at 90%-120% intensity, relative to resting motor threshold (MT), except for one study that delivered intensity as low as 80% MT (Dubin et al., 2016).

3.3. MRS Imaging Protocols

3.3.1. MRS Analysis

All 12 studies evaluated metabolites in one or more brain regions using single voxel MRS data collected pre- and post-rTMS treatment, i.e., at least two serial scans per participant (details in Table 3). Analyses

Table 1
Sample Characteristics and Experimental Design.

Study	Patient Population (*N*)	TRD Definition (where applicable)	Comorbid Psychiatric Diagnoses	Age (*M (SD)*), range (years)	Females *N* (%)	TMS Experimental Design	Treatment Outcome Measures & Definitions	Timing of Post-Treatment MRS Scan	Age/Gender Matched Control Group for Baseline Comparisons? Yes/No (*N*)
Baeken et al. (2017)	Antidepressant-free adults with MDD (18)	Stage III or greater in current MDE; at least 2 failed trials with SSRI and/or SNRI and 1 failed TCA trial	Not described	47.2 (12.5), N/A	12 (66.7%)	Double-blind, sham-controlled, cross-over design	BDI-II; Absolute delta in BDI score	Within a week of final rTMS session (for both sham and active)	Yes (18)
Bhattacharyya et al. (2021)	Adults with MDD on stable doses of antidepressants in combination with neuroleptics ($n = 2$), mood stabilizers ($n = 2$), stimulants ($n = 2$), other augmentation agents ($n = 2$), and low dose anti-anxiety medication ($n = 4$) (12)	Inadequate response to at least one antidepressant despite an adequate dosage for at least 8 weeks	Not described	53 (15), 23–74	8 (66.7%)	Open-label, all active rTMS	HAMD-17 Item; Percent change in HAMD score	After final rTMS session (timing not specified)	Yes (4); data not compared to patient group, used for test–retest reliability of Glx/Cr and GABA/Cr measurements
Croarkin et al. (2016)	Adolescents with MDD on stable dose of antidepressants (10)	At least 1 prior failed trial of antidepressant medication in the current MDE	Comorbid ADHD ($n = 3$)	15.4 (1.2), 13–17	4 (40.0%)	Open-label, all active rTMS	CDRS-R; Responders defined by CGI-I of 1 or 2 and CDRS-R total < 40	After final rTMS session (timing not specified) and at 6-month follow-up	No
Dubin et al. (2016)	Adults with MDD ($n = 21$) or bipolar II DO in a depressive episode ($n = 2$) on stable dose of antidepressants (23)	At least 2 previous antidepressant medication trials for at least 8 weeks during current MDE	Comorbid OCD ($n = 2$), ADHD ($n = 1$), and GAD ($n = 1$)	41.7 (15.9), 23–68	16 (69.6%)	Open-label, all active rTMS	HAMD 24-Item; Response defined by ≥ 50% reduction in HAMD compared to baseline	Mean ± *SD* = 1.0 ± 1.1 days after final rTMS session	No
Erbay et al. (2019)	Antidepressant-free adults with MDD (18)	Sample not specifically characterized by treatment resistance	Comorbid anxiety disorder ($n = 3$)	43.4 (11.1), N/A	10 (55.6%)	Open-label, all active rTMS	HAMD; Did not classify by or define treatment responder	Within 3 days of final rTMS session	No
Godfrey et al. (2021)	Adults with MDD ($n = 26$) or bipolar disorder ($n = 1$) in a depressive episode on stable dose of antidepressants (27)	Insufficient response to at least 2 adequate courses of antidepressant treatments	Comorbid ADHD ($n = 3$), any anxiety disorder ($n = 9$), PTSD ($n = 6$), any comorbidity ($n = 14$)	41.6 (N/A), 19–63	11 (40.7%)	Open-label, all active rTMS	MADRS; Response defined by ≥ 50% reduction in MADRS compared to baseline	After final rTMS session (timing not specified)	No
Levitt et al. (2019)	Adults with MDD on stable dose of antidepressants (26)	At least 2 failed trials of antidepressant medications in current MDE	None	38.4 (13.8), 20–70	14 (53.9%)	Open-label, all active rTMS	IDS-SR30; Responders have ≥ 30% reduction in IDS-SR30 compared to baseline	After final rTMS session (timing not specified)	No
Luborzewski et al. (2007)	Adults with MDD on stable dose of SSRI antidepressants or medication-free (17)	Treatment resistance not defined for entire sample, but 9 of 17 were resistant to at least the current SSRI	Comorbid psychiatric disorders were exclusionary	45 (11), 28–61	2 (11.8%)	Open-label, all active rTMS	HAMD 28-Item, MADRS, & BDI; Responders defined by ≥ 50% in HAMD compared to baseline; % change on each measure	After final rTMS session (timing not specified)	No
Yang et al. (2014)	Teenagers & young adults with MDD; medication status not reported (6)	Failure to respond to an appropriate SSRI trial (at least 8 weeks of a dose) in current MDE	Comorbid GAD ($n = 5$), social phobia ($n = 2$), and ADHD ($n = 1$)	18.7 (2.0), 15–21	4 (66.7%)	Open-label, all active rTMS	HAMD 17-Item, HARS, & BDI; Responders defined by ≥ 50% reduction in HAMD	After final rTMS session (timing not specified)	No

(*continued on next page*)

Table 1 (*continued*)

Study	Patient Population (*N*)	TRD Definition (where applicable)	Comorbid Psychiatric Diagnoses	Age (*M (SD)*), range (years)	Females *N* (%)	TMS Experimental Design	Treatment Outcome Measures & Definitions	Timing of Post-Treatment MRS Scan	Age/Gender Matched Control Group for Baseline Comparisons? Yes/No (*N*)
Zavorotnyy et al. (2020)	Adult inpatients with MDD on stable dose of antidepressants and concurrent CBT (57)	Failure to remit on current regimen of medication and CBT	Not described	43 (12.7), N/A	29 (50.9%)	Single-blind (participants and raters), randomized, sham-controlled	HAMD 21-Item & BDI; % Change on HAMD and BDI; Response defined by 50% decrease on HAMD; Remission defined by HAMD < 7	After final rTMS session (timing not specified)	Yes (15)
Zheng et al. (2010)	Young adults with MDD on stable dose of antidepressants (34)	At least 2 different adequate antidepressant trials (max dose taken > 4 weeks) in current MDE	None allowed	27.2 (5.2), 18–37	12 (35.3%)	Double-blind, randomized, sham-controlled	HAMD 17-item & BDI; Responders defined by 50% reduction on HAMD	Within 24 hours of final rTMS session	Yes (28)
Zheng et al. (2015)	Young adults with MDD on stable dose of antidepressants (32)	At least 2 different adequate antidepressant trials (max dose taken > 4 weeks) in current MDE	None allowed	26.9 (5.4), 18–40	12 (37.5%)	Double-blind, randomized, sham-controlled	HAMD 17-Item & BDI; Responders defined by 50% reduction in HAMD	Within 24 hours of final rTMS session	Yes (28)

Abbreviations: TRD: treatment resistant depression; MDD: major depressive disorder; MDE: major depressive episode; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin norepinephrine reuptake inhibitor; TCA: tricyclic antidepressant; BDI-II: Beck Depression Inventory II; CDRS-R: Children's Depression Rating Scale-Revised; CGI-I: clinical global impressions scale-global improvement; DO: disorder; OCD: obsessive compulsive disorder; ADHD: attention-deficit hyperactivity disorder; GAD: generalized anxiety disorder; PTSD: post traumatic stress disorder; IDS-SR30: 30-item Inventory of Depressive Symptoms; HAMD: Hamilton Depression Rating Scale; MADRS: Montgomery Asberg Depression Rating Scale; BDI: Beck Depression Inventory; HARS: Hamilton Anxiety Rating Scale; CORE: CORE Measurement of Psychomotor Activity; QIDS-A_{17}-SR: Quick Inventory of Depression Symptomatology—Adolescent (17 Item)—Self Report; EMG: electromyography; CBT: cognitive behavioral therapy.

compared post-active rTMS or post-sham treatment data compared with pre-treatment baseline. One study provided a six-month follow-up, informing long-term metabolic response to rTMS treatment in adolescents (Croarkin et al., 2016).

3.3.2. MRS Acquisition Parameters

MRS parameters are in Table 3. All 12 studies acquired data from voxels placed in one to three discrete cortical areas per scan; one study imaged three separate areas (Baeken et al., 2017), five studies examined voxels in two areas (Croarkin et al., 2016; Zheng et al., 2015; Zheng et al., 2010; Luborzewski et al., 2007; Godfrey et al., 2021), and six acquired data from a single voxel (Yang et al., 2014; Dubin et al., 2016; Erbay et al., 2019; Zavorotnyy et al., 2020; Levitt et al., 2019; Bhattacharyya et al., 2021). Most studies ($n = 8$) included a voxel placed over the left DLPFC with dimensions ranging from 1.5 × 1.5 × 1.5 cm to 2.5 × 3.5 × 3.0 cm (Croarkin et al., 2016; Yang et al., 2014; Baeken et al., 2017; Luborzewski et al., 2007; Erbay et al., 2019; Godfrey et al., 2021; Levitt et al., 2019; Bhattacharyya et al., 2021). Other areas investigated were the right DLPFC ($n = 1$; (Baeken et al., 2017), the right anterior cingulate cortex (ACC; $n = 2$; (Zheng et al., 2015; Baeken et al., 2017)), the left ACC ($n = 1$; (Zheng et al., 2015)), the bilateral ACC placed over the midline ($n = 3$; (Croarkin et al., 2016; Luborzewski et al., 2007; Zavorotnyy et al., 2020)), the bilateral medial prefrontal cortex placed over the midline and incorporating the rostral ACC ($n = 1$; (Dubin et al., 2016)), the left prefrontal cortex (PFC; $n = 1$; (Zheng et al., 2010)), and the right PFC ($n = 1$; (Zheng et al., 2010)). One study investigated right-sided primary motor cortex (M1) as a control region for the left DLPFC (Godfrey et al., 2021). All studies obtained MRS data via point resolved spectroscopy (PRESS), with four using variations of PRESS including Meshcher-Garwood PRESS (MEGA-PRESS; (Dubin et al., 2016; Godfrey et al., 2021; Levitt et al., 2019; Bhattacharyya et al., 2021) to measure GABA and one using 2-dimensional J-resolved averaged PRESS (Croarkin et al., 2016) specifically to measure Glu. Full MRS acquisition details including repetition time (TR) and echo time (TE) are in Table 3.

3.4. rTMS treatment effects and brain metabolites

Findings are summarized regarding baseline predictors of rTMS treatment outcomes; overall effect of rTMS on metabolites irrespective of rTMS responder status, i.e., overall effects of changes pre vs. post rTMS procedures, pooled across treatment responders and non-responders; and metabolic changes associated with symptom improvement following rTMS, i.e., effects in treatment responders (details in Table 4). Findings are considered significant at an alpha of 0.05, with select results presented at $p > .05$ to reduce Type II error, which has significant adverse impact on scientific progress (see Amrhein et al., 2019 for discussion).

3.4.1. Glutamatergic Compounds (Glx)

Seven studies evaluated rTMS effects on Glx using water-referenced (Godfrey et al., 2021; Levitt et al., 2019; Zheng et al., 2015; Zheng et al., 2010; Baeken et al., 2017; Dubin et al., 2016) and Cr-referenced methods (Zheng et al., 2015; Zheng et al., 2010; Bhattacharyya et al., 2021). Baseline Predictors. In Godfrey et al., baseline concentrations of Glx in the M1 (control) region positively predicted percent change in MADRS scores following rTMS ($r = 0.53$, $p = .01$, $n = 23$), where lower levels of Glx were associated with greater antidepressant response (Godfrey et al., 2021). In comparison, Baeken et al. demonstrated a pattern of greater baseline Glx in the left DLPFC predicting degree of improvement in BDI scores following rTMS ($\tau = -0.34$, $p = .06$, $n = 16$)

Table 2
rTMS Treatment Protocol Features and Course Characteristics.

Study	Treatment Target	Treatment Intensity relative to Resting Motor Threshold (MT)	Frequency	Number of Sessions/Course Duration	Number of rTMS Pulses per Session
Baeken et al. (2017)	Left DLPFC	110%	20 Hz	20 sessions over 4 days (5 sessions per day); counterbalanced with 20 sham sessions at same schedule	1560
Bhattacharyya et al. (2021)	Left DLPFC	120%	10 Hz	30 sessions over 6 weeks	3000
Croarkin et al. (2016)	Left DLPFC	120%	10 Hz	30 sessions over 6–8 weeks	3000
Dubin et al. (2016)	Left DLPFC	80%-120%	10 Hz	25 sessions over 5 weeks	3000
Erbay et al. (2019)	Left DLPFC	not reported	10 Hz	20 sessions over 2 weeks	3000
Godfrey et al. (2021)	Left DLPFC	120%	10 Hz	20 sessions over 4 weeks	4000
Levitt et al. (2019)	Left DLPFC, right DLPFC, or sequential bilateral (left followed by right DLPFC)	100%-120%	10 Hz (left), 10 Hz (right), 1 Hz (sequential bilateral protocol)	30 sessions over 6 weeks	3000 (adjustments allowed; not reported for total on each side)
Luborzewski et al. (2007)	Left DLPFC	100%	20 Hz	10 sessions over 2 weeks	2000
Yang et al. (2014)	Left DLPFC	120%	10 Hz	15 sessions over 3 weeks	3000
Zavorotnyy et al. (2020)*	Left DLPFC	90%	50 Hz triplets at 5 Hz	20 sessions over 4 weeks	1200
Zheng et al. (2010)	Left DLPFC	110%	15 Hz	20 sessions over 4 weeks	3000
Zheng et al. (2015)	Left DLPFC	110%	15 Hz	20 sessions over 4 weeks	3000

*Intermittent theta burst (iTBS) stimulation protocol used.
Abbreviations: DLPFC: dorsolateral prefrontal cortex; ACC: anterior cingulate cortex; MPFC: medial prefrontal cortex; iTBS: intermittent theta burst stimulation; PFC: prefrontal cortex.

Table 3
MRS parameters.

Study	Voxel Location & Size	MRS Acquisition Type	Magnet Strength (Tesla)	Metabolites Analyzed	MRS Acquisition Details
Baeken et al. (2017)	Left DLPFC (15 × 15 × 15 mm); Right DLPFC (15 × 15 × 15 mm); Right ACC (30 × 30 × 15 mm)	PRESS	3 T	GABA, Glx, tNAA/tCr	TR = 2000 ms, TE = 40 ms, 128 averages
Bhattacharyya et al. (2021)	Left DLPFC (2 × 2 × 2 cm)	MEGA-PRESS	3 T	GABA/tCr, Glx/tCr	TR = 2700 ms, TE = 68 ms, 128 averages per session
Croarkin et al. (2016)	Bilateral (over midline) ACC (2 × 2 × 2 cm); Left DLPFC (2 × 2 × 2cm)	PRESS (Glu and Gln); 2-dimensional J-resolved averaged PRESS (2DJ; for Glu)	3 T	Glu (PRESS, 2DJ), Gln (PRESS), Gln/Glu (PRESS, 2DJ)	PRESS: TR = 2000 ms, TE = 80 ms, 8 excitations, 128 averages; 2DJ PRESS: TR = 2000 ms, TE = 35–195 ms in 16 steps, 8 averages at each step
Dubin et al. (2016)	Bilateral (over midline) MPFC that includes a rostral component of the ACC (2.5 × 2.5 × 3.0 cm)	MEGA-PRESS (J-edited)	3 T	GABA, Glx	TR = 1500 ms, TE = 68 ms, 256 interleaved averages (512 total)
Erbay et al. (2019)	Left DLPFC (15 × 20 × 15 mm)	PRESS	3 T	NAA/Cr, Cho/Cr, Ins/Cr, Glu/Cr, Lac/Cr, GSH/Cr, Gln/Cr	TR = 2000 ms, TE = 30 ms
Godfrey et al. (2021)	Left DLPFC (25 × 35 × 30 mm); Right M1 (25 × 35 × 30 mm)	MEGA-PRESS	3 T	GABA, Glx	TR = 2000 ms, TE = 68 ms, 96 interleaved excitations (192 total)
Levitt et al. (2019)	Left DLPFC (30 × 20 × 10 mm), with adjustments in size to maximize grey matter content	MEGA-PRESS	3 T	GABA, Glx	TR = 2000 ms, TE = 68 ms, 192 excitations
Luborzewski et al. (2007)	Left DLPFC (2 × 2 × 2cm); Bilateral (over midline) ACC (2.5 × 4 × 2 cm)	PRESS	3 T	tCho, tCr, NAA, Glu	TR = 3000 ms, TE = 80 ms, 128 averages (ACC) & 256 averages (DLPFC)
Yang et al. (2014)	Left DLPFC (4.5 cm^3)	PRESS	3 T	Glu	TR = 2000 ms, TE = 30 ms, 128 averages
Zavorotnyy et al. (2020)	Bilateral (over midline) ACC (20 × 20 × 20 mm)	PRESS	3 T	NAA, Cho, Cho/NAA, NAA/Cr, Cho/Cr	TR = 1390 ms, TE = 135 ms, used CHESS pulses for water suppression
Zheng et al. (2010)	Left PFC (1 × 1 × 1.5 cm); Right PFC (1 × 1 × 1.5 cm)	PRESS	3 T	NAA, Ins, Cho, Cr, Glx, Ins/Cr, Cho/Cr, NAA/Cr, Glx/Cr	TR = 1700 ms, TE = 30 ms, acquisition repeated 3 times
Zheng et al. (2015)	Right ACC (1 × 1 × 1.5 cm); Left ACC (1 × 1 × 1.5 cm)	PRESS	3 T	NAA, Ins, Cho, Cr, Glx, Ins/Cr, Cho/Cr, NAA/Cr, Glx/Cr	TR = 1700 ms, TE = 30 ms, acquisition repeated 3 times

Abbreviations: DLPFC: dorsolateral prefrontal cortex; ACC: anterior cingulate cortex; MPFC: medial prefrontal cortex; CHESS: chemical shift selective saturation; PFC: prefrontal cortex; GSH: glutathione; PRESS: point resolved spectroscopy; MEGA-PRESS: Meshcher-Garwood point resolved spectroscopy; TR: repetition time; TE: echo time; M1: primary motor cortex; T: Tesla.

Table 4
Summary of rTMS-Related Changes in MRS Compounds.

Study	Pooled Findings	rTMS Treatment Responder Findings	rTMS Treatment Non-Responder Findings
Baeken et al. (2017)	1. No significant post-treatment changes in GABA, Glx, or the tNAA/tCr ratio in any region (left DLPFC, right DLPFC, rostral ACC) 2. Left DLPFC changes in GABA were significantly negatively correlated with changes in depression scores post-rTMS 3. Nonsignificant trend for higher baseline Glx in the left DLPFC to predict better treatment outcomes	N/A	N/A
Bhattacharyya et al. (2021)	1. No significant post-treatment changes in Glx/tCr or GABA/tCr 2. Significant inverse correlation between post-treatment HAMD score and pretreatment levels of left DLPFC Glx/tCr 3. Significant inverse correlation between change in HAMD score post-treatment and pre-treatment left DLPFC Glx/tCr 4. Significant correlation observed between change in HAMD score post-treatment and change in left DLPFC Glx/tCr 5. No significant correlations observed between HAMD scores and GABA/tCr	N/A	N/A
Croarkin et al. (2016)	1. Gln/Glu ratio significantly increased in the ACC from baseline to six months post–treatment 2. Gln/Glu ratio in the left DLPFC showed trend-level increase from baseline to six months 3. Post-treatment increases in left DLPFC and ACC Gln/Glu ratios correlated with depression symptom improvement over 6 months following rTMS	1. No significant differences between responders vs non-responders in metabolite change over time	2. No significant differences between responders vs non-responders in metabolite change over time
Dubin et al. (2016)	1. GABA in the MPFC significantly increased post treatment (mean change = 13.8%) 2. No significant effects of treatment on the Glx in the MPFC 3. Percent change in MPFC GABA was not significantly associated with responder status	1. GABA in the MPFC significantly increased after rTMS (mean change = 17.4%)	1. Nonsignificant trend toward increased GABA in the MPFC after rTMS (mean change = 11.9%)
Erbay et al. (2019)	1. NAA/Cr, GSH/Cr, and Gln/Cr ratios in the left DLPFC significantly increased post-treatment 2. Post-treatment increases of NAA/Cr, GSH/Cr, and Gln/Cr ratios in the left DLPFC were not significantly correlated with changes in depression severity	N/A	N/A
Godfrey et al. (2021)	1. No significant change in GABA in the left DLPFC or right M1 between baseline and post-treatment 2. Glx significantly increased post-treatment in both the left DLPFC and right M1 3. No significant correlations were found between changes in metabolite levels in either voxel and changes in MADRS scores 4. Presence of psychiatric comorbidities was a predictor of post-treatment changes in Glx in the left DLPFC 5. Significant positive correlation between baseline right M1 Glx levels and change in MADRS score	N/A	N/A
Levitt et al. (2019)	1. GABA levels in the left DLPFC significantly increased post-treatment (mean change = 10%) 2. Change in GABA was not significantly correlated with change in depression score (IDS-SR30)	1. GABA levels significantly increased in treatment responders (mean change = 23.6%)	1. GABA levels did not significantly increase in treatment non-responders (mean change = 4.1%)
Luborzewski et al. (2007)	1. No significant changes identified in post-rTMS treatment metabolites (Glu, tCr, NAA, tCho) in the ACC 2. No significant changes in tCr and NAA concentrations were observed in the DLPFC post rTMS. 3. Increases in DLPFC Glu after rTMS were significantly correlated with % improvement in symptoms measured by the HAMD, MADRS, and the BDI	1. Treatment responders had significantly lower baseline levels of Glu and tCho in the left DLPFC in comparison to non-responders 2. tCho in the DLPFC significantly increased post-treatment in responders	1. DLPFC Glu levels significantly decreased in non-responders after rTMS
Yang et al. (2014)	N/A	1. Treatment responders showed an increase in Glu in the left DLPFC post-treatment (mean = 11%)	1. Treatment non-responders had elevated Glu levels at baseline, which decreased after rTMS (mean = -10%)
Zavorotnyy et al. (2020)	1. In the ACC, changes in absolute NAA and Cho were not related to outcome, but symptom improvement was significantly associated with decrease in Cho/NAA ratio across both active and sham groups; change in NAA mediated that relationship. 2. Significant NAA increase was associated with symptom improvement following active iTBS but not sham	N/A	N/A
Zheng et al. (2010)	1. There was a significant correlation between change of Ins levels in the left PFC and reduction in HAMD scores	1. Responders showed a trend towards an elevation of Cho/Cr ratios in the left PFC after treatment	1. Non-responders presented no significant metabolite changes
Zheng et al. (2015)	1. Performance improvement on executive function task post-(active) rTMS correlated with % change NAA in the ACC across the sample	1. Responders showed significant increase of NAA post-rTMS	1. In non-responders, NAA decreased, though non-significantly

Abbreviations: BDI-II: Beck Depression Inventory II; CDRS-R: Children's Depression Rating Scale-Revised; IDS-SR30: 30-item Inventory of Depressive Symptoms; HAMD: Hamilton Depression Rating Scale; MADRS: Montgomery Asberg Depression Rating Scale; BDI: Beck Depression Inventory; CORE: CORE Measurement of Psychomotor Activity; QIDS-A_{17}-SR: Quick Inventory of Depression Symptomatology-Adolescent (17 Item)-Self Report; M1: primary motor cortex; GSH: glutathione.

(Baeken et al., 2017). Bhattacharyya et al. identified a similar pattern, where higher pre-treatment left DLPFC Glx/tCr predicted lower post-treatment HAMD scores ($p < .0005$, $n = 7$) and greater change in HAMD scores following rTMS ($p = .001$, $n = 7$) (Bhattacharyya et al., 2021). The other four studies did not evaluate Glx as a baseline predictor of rTMS outcomes (Zheng et al., 2015; Zheng et al., 2010; Dubin et al., 2016; Levitt et al., 2019). Overall Effects. Godfrey et al. demonstrated a significant post-rTMS increase in Glx in the left DLPFC and right M1 in a pooled sample ($F(1,21) = 4.48$, $p = 0.046$) which was unconnected to clinical outcome (Godfrey et al., 2021). Additionally, three studies did not find any significant differences in Glx post-rTMS at the group level (Baeken et al., 2017; Dubin et al., 2016; Bhattacharyya et al., 2021), and three studies did not examine such relationship (Zheng et al., 2015; Zheng et al., 2010; Levitt et al., 2019). Symptom Improvement. rTMS effects on Glx or Glx/Cr in voxels in the left ACC, right ACC, left PFC, right PFC, or bilateral MPFC did not differ as a function of clinical response to rTMS in three studies (Zheng et al., 2015; Zheng et al., 2010; Dubin et al., 2016); four studies did not analyze this relationship by responder status (Baeken et al., 2017; Godfrey et al., 2021; Levitt et al., 2019; Bhattacharyya et al., 2021). However, Bhattacharyya et al. found a significant positive correlation between change in left DLPFC Glx/tCr and change in HAMD score ($n = 6$, $p = .02$) (Bhattacharyya et al., 2021). Interpretation. These data indicate baseline Glx may predict rTMS treatment outcomes, though the directionality of results was inconsistent between studies; currently, there is mixed evidence for significant rTMS-associated changes on Glx at the group level and their relationship with symptom improvement.

3.4.2. Glutamate (Glu)

Four studies evaluated rTMS effects on Glu, a component of Glx, using water-, Gln-, and Cr-referenced approaches (Glu, Glu/Gln, Glu/Cr, (Croarkin et al., 2016; Yang et al., 2014; Luborzewski et al., 2007; Erbay et al., 2019). Baseline Predictors. One study showed treatment responders had significantly lower baseline level of Glu compared to non-responders ($p = .035$, $n = 17$) (Luborzewski et al., 2007); another study had similar findings in the left DLPFC, though significance was not calculated (Yang et al., 2014). The two other studies did not evaluate Glu as a baseline predictor of rTMS outcomes (Croarkin et al., 2016; Erbay et al., 2019). Overall Effects. Water-referenced Glu rose with stimulation intensity in one pooled sample ($r = 0.47$, $p = .064$, $n = 15$) (Luborzewski et al., 2007), and rTMS effects were not identified for Gln- or Cr-referenced Glu in two other pooled samples, despite rTMS-related symptom improvement (Croarkin et al., 2016; Erbay et al., 2019). One study did not calculate changes in Glu post-rTMS by pooled sample (Yang et al., 2014). Symptom Improvement. rTMS-associated increases in Glu in the left DLPFC significantly correlated with symptom improvement on the HAMD ($r = -0.89$, $p < .001$), MADRS ($r = -0.80$, $p < .001$), and BDI ($r = -0.64$, $p = .008$) in Luborzewski et al. (Luborzewski et al., 2007). rTMS was associated with increased Glu in the left DLPFC of treatment responders ($M = +1.19$ mmol/l (Luborzewski et al., 2007); $M = +10.37$ mmol/kg ((Yang et al., 2014); significance not calculated) in two pilot samples ($n = 6$ (Luborzewski et al., 2007); $n = 3$ (Yang et al., 2014)). In non-responders, rTMS was associated with decreases in Glu in the left DLPFC ($M = -1.16$ mmol/l, $p = .007$, $n = 11$ (Luborzewski et al., 2007)); significance not calculated) in one study (Yang et al., 2014). Two studies did not analyze the relationship between changes in Glu and depression scores (Croarkin et al., 2016; Erbay et al., 2019). Interpretation. These data indicate baseline Glu predicts rTMS treatment outcomes in studies that analyzed this relationship; rTMS-associated increases in Glu characterizes treatment responders and is associated with symptom improvement; according to one study, rTMS-associated reduction in Glu characterizes non-responders.

3.4.3. Glutamine (Gln)

Two studies evaluated specific rTMS effects on Gln, the other subcomponent of Glx, using water-, Cr-, and Glu-referenced methods (Gln, Gln/Cr, Gln/Glu (Croarkin et al., 2016; Erbay et al., 2019)). Baseline Predictors. Gln at baseline was not evaluated as a predictor of rTMS outcomes (Croarkin et al., 2016; Erbay et al., 2019). Overall Effects. Croarkin et al. found rTMS in teens was associated with increased Gln/Glu in the bilateral ACC immediately after treatment, with continued increases observed at six months post treatment ($F(2,10) = 5.32$, $p = .02$) (Croarkin et al., 2016). Furthermore, Gln/Glu effects from baseline to post-treatment (hedges' $g = 1.064$), post-treatment to six-month follow-up (hedges' $g = 1.242$), and baseline to six-month follow-up (hedges' $g = 1.474$) were large in size (Croarkin et al., 2016). In adults, Erbay et al. found an increase in Gln/Cr in the left DLPFC following rTMS ($p = .008$, $n = 18$) (Erbay et al., 2019). Symptom Improvement. rTMS effects on mean change in Gln/Glu (above) increased as depression severity decreased, as measured by the CDRS-R in teen patients ($p = .003$) in Croarkin et al. (Croarkin et al., 2016). Increases in Gln/Cr in the left DLPFC were unrelated to HAMD improvement in Erbay et al. (Erbay et al., 2019). Interpretation. These data indicate a dearth of information on predictive features of baseline Gln; rTMS is associated with increases in various referenced forms of Gln, though there is conflicting evidence on if this increase is related to symptom improvement.

3.4.4. γ-Aminobutyric Acid (GABA)

Five studies evaluated rTMS-associated effects on water-referenced GABA (Baeken et al., 2017; Dubin et al., 2016; Godfrey et al., 2021; Levitt et al., 2019) and tCr-referenced GABA (Bhattacharyya et al., 2021). Baseline Predictors. Baeken et. al., Godfrey et. al., and Bhattacharyya et al. found that baseline GABA and GABA/tCr concentrations did not significantly predict clinical outcomes (Baeken et al., 2017; Godfrey et al., 2021; Bhattacharyya et al., 2021); the other two studies did not investigate GABA as a baseline predictor of depression improvement (Dubin et al., 2016; Levitt et al., 2019). Overall Effects. Levitt et al. found GABA increased post-rTMS in the left DLPFC ($M = 10\%$, $F(1,20) = 6.8$, $p = .017$) in the pooled sample (Levitt et al., 2019). Dubin et. al. (2016) also found increased MPFC GABA following rTMS in a pooled sample ($M = 13.8\%$, $t(22) = 2.69$, $p = .013$ (Dubin et al., 2016). Godfrey et. al. (2021) did not observe significant post-treatment changes in GABA in the left DLPFC or right M1 (Godfrey et al., 2021), nor did Baeken et. al. in the left DLPFC or bilateral ACC (Baeken et al., 2017). Bhattacharyya et al. also did not observe any significant post-treatment changes in left DLPFC GABA/tCr (Bhattacharyya et al., 2021). Symptom Improvement. Levitt et. al. found larger rTMS-associated increases in GABA in responders ($M = 23.6\%$, $p = .015$, $n = 12$) than non-responders ($M = 4.1\%$, $n = 14$, not significant) (Levitt et al., 2019). Dubin et al. found post-rTMS increase in MPFC GABA was significantly greater ($M = 17.4\%$) in responders than non-responders ($M = 11.9\%$) (Dubin et al., 2016). Baeken et al. found rTMS-associated changes in GABA related to clinical outcome, with greater degree of clinical improvement (BDI-II) associated with greater increase in left DLPFC GABA ($\tau = -0.44$, $p = 0.04$) (Baeken et al., 2017). Godfrey et al. and Bhattacharyya et al. did not find any significant correlations between changes in metabolite levels and antidepressant response (Godfrey et al., 2021; Bhattacharyya et al., 2021). Interpretation. These data indicate baseline GABA may not predict rTMS-associated clinical improvement; rTMS is associated with mixed effects (i.e., increase or no change in GABA) in pooled samples of responders and non-responders; and rTMS-associated increases in GABA relate to symptom improvement in treatment responders.

3.4.5. N-Acetylaspartate (NAA)

Six studies evaluated rTMS/iTBS effects on NAA using water- and Cr-referenced methods (NAA, NAA/Cr, tNAA/tCR; (Zheng et al., 2015; Zheng et al., 2010; Baeken et al., 2017; Luborzewski et al., 2007; Erbay et al., 2019; Zavorotnyy et al., 2020). Baseline Predictors. Luborzewski et. al. did not detect a significant relationship between baseline NAA and treatment outcome (Luborzewski et al., 2007). The other five studies did not investigate NAA as a baseline predictor of post-rTMS/iTBS depression improvement (Erbay et al., 2019; Zavorotnyy et al., 2020; Zheng

et al., 2015; Zheng et al., 2010; Baeken et al., 2017). Overall Effects. Erbay et. al. demonstrated rTMS-associated increases of NAA/Cr in the left DLPFC in a pooled sample ($p = .016$, $n = 18$) (Erbay et al., 2019). In comparison to participants receiving sham, participants receiving iTBS had an increase in NAA post-treatment in Zavorotnyy et al. (Zavorotnyy et al., 2020). Three studies did not identify overall rTMS-associated treatment effects on frontal NAA, tNAA/tCr, or NAA in pooled samples (Zheng et al., 2010; Baeken et al., 2017; Luborzewski et al., 2007); one study did not calculate changes in NAA post-rTMS by pooled sample (Zheng et al., 2015). Symptom Improvement. Two studies showed differential NAA changes as a function of clinical outcomes (Zheng et al., 2015; Zavorotnyy et al., 2020). Zheng et. al. (2015) demonstrated significant increases in left ACC NAA only in rTMS responders ($p = .004$, $n = 11$) and not in non-responders ($n = 7$) (Zheng et al., 2015). In this study, increases in NAA significantly correlated with percent improvement in perseverative errors on the Wisconsin Card Sorting Task ($r = 0.835$, $p < .001$, $n = 18$) a behavioral measure of inhibitory control. Zavorotnyy et al. observed a significant interaction revealing increases in NAA were associated with clinical improvement for the active iTBS group, but not the sham iTBS group (Zavorotnyy et al., 2020): a 10% increase in anterior cingulate NAA predicted BDI score improvement of 73.9 ± 1.77% ($R^2 = 0.221$, $n = 57$); in contrast NAA did not predict outcomes on the HAMD scale (Zavorotnyy et al., 2020). Erbay et al. did not observe a significant relationship between increases in NAA/Cr and changes in HAMD scores (Erbay et al., 2019). Zheng et al. (2010) and Luborzewski et al. did not observe a change in NAA in active responders (Zheng et al., 2010; Luborzewski et al., 2007) and Baeken et al. did not find a significant correlation between changes in tNAA/tCr and depressive symptoms (Baeken et al., 2017). Interpretation. These data indicate limited information on predictive features of baseline NAA, and that NAA might not predict rTMS outcomes; rTMS was associated with mixed effects on NAA (i.e., increase or no change in NAA) at the group level; and rTMS-associated increases in NAA related to symptom improvement in treatment responders for a handful of studies.

3.4.6. Choline (Cho)

Five studies evaluated rTMS/iTBS effects on Cho using Cr and NAA-referencing (Cho/Cr, Cho/NAA) and water-referencing (Cho, total choline (tCho)) (Zheng et al., 2015; Zheng et al., 2010; Luborzewski et al., 2007; Erbay et al., 2019; Zavorotnyy et al., 2020). Baseline Predictors. At baseline, tCho was significantly decreased in the left DLPFC of rTMS responders in comparison to non-responders in one study ($p = .044$, $n = 17$) (Luborzewski et al., 2007). The relationship of baseline Cho and treatment outcomes was not analyzed in the four other studies (Zheng et al., 2015; Zheng et al., 2010; Erbay et al., 2019; Zavorotnyy et al., 2020). Overall Effects. In two studies, no overall rTMS treatment effects were identified for Cho or Cho/Cr in the left DLPFC ($n = 18$ (Erbay et al., 2019)) or bilateral ACC ($n = 18$ (Zheng et al., 2015)) in pooled samples. Three studies did not analyze post-rTMS changes in Cho, Cho/Cr, or Cho/NAA in pooled samples (Zheng et al., 2010; Luborzewski et al., 2007; Zavorotnyy et al., 2020). Symptom Improvement. Three studies reported changes in Cho associated with symptom improvement. Zavorotnyy et. al. (2020) found that iTBS-associated increases in Cho/NAA in the bilateral ACC are a significant predictor of improvement on the BDI ($F(1,38) = 5.190$, $p < .028$, $R^2 = 0.12$) (Zavorotnyy et al., 2020). Though groups were relatively small in other studies, treatment responders showed significant rTMS-associated increases in left DLPFC tCho post treatment in one study ($p = .028$, $n = 6$) (Luborzewski et al., 2007) and a marginally significant increase of Cho/Cr in the left PFC in another study ($p = .056$, $n = 12$ (Zheng et al., 2010). Zheng et al. (2015) did not find a significant change in Cho in rTMS treatment responders or non-responders (Zheng et al., 2015). One study did not analyze the relationship between changes in Cho/Cr and depression symptoms (Erbay et al., 2019). Interpretation. These data indicate a relative dearth of information on the predictive features of baseline Cho, though one study identified predictive features of low baseline Cho; rTMS-associated null effects on Cho and Cho/Cr at the group level; and rTMS-associated increases in Cho related to symptom improvement in treatment responders for the majority of studies that analyzed such relationship (3/4).

3.4.7. Myoinositol (Ins)

Three studies evaluated rTMS effects on water- and Cr- referenced Ins (Zheng et al., 2015; Zheng et al., 2010; Erbay et al., 2019). Baseline Predictors. Ins at baseline was not investigated as a predictor of rTMS outcomes in all three studies (Zheng et al., 2015; Zheng et al., 2010; Erbay et al., 2019). Overall Effects. All three studies did not report any significant changes in Ins at the group-level post-rTMS (Zheng et al., 2015; Zheng et al., 2010; Erbay et al., 2019). Symptom Improvement. Zheng et. al. (2010) identified a significant increase in Ins in the left PFC ($p < .001$, $n = 12$) and a marginally significant increase in the right PFC ($p = .062$, $n = 12$) in treatment responders; no significant differences in Ins were found in non-responders following rTMS (Zheng et al., 2010). Zheng et. al. (2010) also found a significant positive relationship of post-treatment change in Ins and change in HAMD scores ($r = 0.86$, $p < .0001$, $n = 19$) (Zheng et al., 2010), consistent with increased Ins in patients with symptom reduction. The other two studies did not identify any significant relationships between changes in Ins and depression symptoms (Zheng et al., 2015; Erbay et al., 2019). Interpretation. These data indicate a dearth of information on predictive features of baseline Ins; rTMS-associated increases in Ins in treatment responders; and rTMS-associated increases in Ins which correlate with MDD symptom improvement in one of three studies.

3.4.8. Creatine (Cr)

Four studies evaluated rTMS effects on Cr using water-referenced measures (Cr, total creatine (tCr); (Zheng et al., 2015; Zheng et al., 2010; Luborzewski et al., 2007; Erbay et al., 2019)). Baseline Predictors. Cr at baseline was not investigated as a predictor of rTMS outcomes (Zheng et al., 2015; Zheng et al., 2010; Luborzewski et al., 2007; Erbay et al., 2019). Overall Effects. Cr and tCr were not significantly altered by rTMS at the group level in any of the four studies (Zheng et al., 2015; Zheng et al., 2010; Luborzewski et al., 2007; Erbay et al., 2019). Symptom Improvement. Additionally, Cr and tCr did not relate to rTMS-associated depression improvement in these studies (Zheng et al., 2015; Zheng et al., 2010; Luborzewski et al., 2007; Erbay et al., 2019). Interpretation. These data indicate a dearth of information on predictive features of baseline Cr; and rTMS is not associated with change in Cr, irrespective of symptom improvement or treatment outcome.

4. Discussion

We conducted an in-depth systematic review of metabolic effects of rTMS in individuals with clinical depression. Open-label designs and small samples were common, as is typical in an emerging field. In consequence, variability between studies was considerable. Differences in the types of stimulation used, MRS imaging and analysis methods, sample sizes, clinical demographics, depression severity, and inclusion or exclusion criteria related to treatment resistance, concurrent psychotropic medication use, and psychiatric comorbidities likely contribute to relative variation in results. These caveats aside, collectively, the findings generally indicate there are no rTMS-associated metabolite changes independent of clinical response, with antidepressant response to rTMS associated with relative increases in mean levels of metabolites (Glu in 2 of 4 studies; Gln in 1 of 2 studies; GABA in 3 of 5 studies; NAA in 2 of 6 studies; Cho in 3 of 5 studies) though findings were trend-level in some instances. Evidence suggesting a role of increased Ins (1 of 3 studies) and Glx (1 of 7 studies) in treatment response was less consistent. The present studies do not suggest a role of Cr in treatment response (0 of 4 studies). Most findings arise from imaging voxels in bilateral DLPFC and ACC, with results from a single study showing significant increase of GABA in MPFC. Interestingly, baseline

Glx levels predicted rTMS treatment outcomes, but the directionality of Glx levels was inconsistent across studies (i.e., one study showed lower levels leading to better outcomes (Godfrey et al., 2021), while two studies showed higher levels leading to depression symptom reduction (Baeken et al., 2017; Bhattacharyya et al., 2021). Despite variability, neurometabolic changes observed with rTMS are generally consistent with the neurometabolic responses reported for these same frontal brain regions following other successful treatments for depression such as ECT and antidepressant medications. Of note, while *increases* in frontal metabolite concentrations were found to be associated with clinical improvement in these 12 rTMS studies, none of the rTMS MRS studies we reviewed imaged the occipital regions, where *decreased* GABA has been shown to be a marker of antidepressant effects following psychotherapy and pharmacotherapy (Sanacora et al., 2002). All but two of the 12 studies we reviewed included patients who were receiving psychotropic medications in addition to rTMS therapy, inherently complicating findings. This said, stability of ongoing psychotropic medication agents and doses prior to and during rTMS therapy in the study participants lends confidence to the conclusions drawn by the individual studies evaluated in this review.

4.1. rTMS mechanisms via the glutamate/GABA-glutamine pathway

MRS is limited to detecting signals at mM concentrations. Thus it is primarily sensitive to intracellular signals (Blüml et al., 2013; White et al., 2018; Savtchenko and Rusakov, 2007), and cannot detect metabolic changes that occur on a nm scale, such as exocytosis, transport, and reuptake (Burtscher and Holtås, 2001). Changes in the latter, extracellular processes thus cannot explain the present findings, which occur at a mM scale. Potential intracellular mechanisms involved in these rTMS-related increases in Glu, Gln and GABA may include increases in rate of synthesis and/or reduction in catabolism within the examined voxels. Changes in these processes in the Glu/GABA-Gln pathway affect the rate of Glu-Gln cycling in excitatory neurons, GABA-Gln cycling in inhibitory neurons, and Glu/GABA-Gln cycling in glia (Bak et al., 2006).

4.1.1. rTMS Effects on Glu and Gln. Changes in Glu and Gln volume observed following successful treatment suggest increased glucose utilization and upregulation of the tricarboxylic acid (TCA, or "Krebs") cycle are key components of depression reduction (Fig. 2A; see (Bak et al., 2006; Flanagan et al., 2018) for details). Regional cerebral glucose metabolism (rCMRglu) and cerebral blood flow (rCBF) in the frontal cortex are altered in depression, indicating dysregulation in frontal utilization of glucose, a precursor for Glu and Gln (Baxter et al., 1989; Kimbrell et al., 2002; Bench et al., 1995; Hyder et al., 2006; Kimbrell et al., 1999; Conca et al., 2002; Li et al., 2010). Chronic unpredictable stress, which is associated with depression (Katz, 1982), decreases TCA cycle activity, thereby also reducing Glu and Gln synthesis (Kim et al., 2014; Rae, 2014). Recent *meta*-analyses link unmedicated depression with low Glx in the mPFC (Moriguchi et al., 2019). Successful treatment with antidepressants (Chen et al., 2014) and ECT (Njau et al., 2017) has been associated with increased Glx in medial PFC (inclusive of rostral ACC). Augmenting glucose utilization and/or upregulation of phosphate-activated glutaminase (PAG) and glutamine synthetase (GS; green arrows, Fig. 2A) may accelerate Glu and Gln synthesis. Together these data suggest rTMS may achieve its therapeutic effects via an increase in glucose utilization and generation of new Glu and Gln in frontal region voxels through an upregulation of the glycolytic pathway and TCA cycle (Blüml et al., 2002; Van Den Berg et al., 1969; Hertz and Chen, 2018; Gibbs, 2015; Jueptner and Weiller, 1995; Yelamanchi et al., 2016). Notably, in two studies reviewed here, decreases in Glu and Gln were linked to treatment non-response (Yang et al., 2014; Luborzewski et al., 2007), lending ancillary support to this hypothesis.

4.1.2. rTMS Effects on GABA. GABA is the major inhibitory neurotransmitter in the human brain and plays an important role in depression (Petroff, 2002; Kalueff and Nutt, 2007). GABA is powered by glucose in the TCA cycle, is synthesized by glutamate decarboxylase (GAD), and is stored intracellularly (Bak et al., 2006; Flanagan et al., 2018; Waller and Sampson, 2018; Jin et al., 2004) (Fig. 2B). In rats, rTMS-administered theta burst stimulation upregulates GAD65, an isoform of GAD (green arrows, Fig. 2B), preceding increases in intracellular GABA production (Peng et al., 2018; Mix et al., 2010; Trippe et al., 2009). The findings summarized in this review are consistent with upregulation of GS and PAG and increased glucose utilization in neurons and glia when there is clinical response to rTMS (green arrows, Fig. 2B). Another possibility is that this occurs in the context of decreases in catabolic compounds, such as succinate (Suc), which could contribute to net increases in GABA. However, because this proposed mechanism would selectively decrease astrocytic Glu (Savtchenko and Rusakov, 2007), a pattern discordant with the coupled nature of Glu and GABA fluctuations, PAG or GS upregulation is the more likely mechanistic pathway. While promising, it bears reminding that sample size limitations may be especially germane to interpretation of GABA findings; results from an evaluation of power in MRS studies suggest that with a MEGA-PRESS acquisition, $>$ 20 subjects are needed to detect a 20% within-subjects change in GABA concentrations (Sanaei Nezhad et al., 2020). Indeed, issues of power and effect size may help to explain heterogeneity between an initial study ($n = 10$) reporting increased GABA post-ECT (Knudsen et al., 2019) and several failed replications (Yue et al., 2009).

4.1.3. Downstream effects. rTMS treatment-related increases in Glu, Gln and GABA likely influence downstream cellular signaling. In rats, rTMS-induced membrane depolarizations modulate synaptic transmission via ionotropic receptors, facilitating an increase in Glu (Gallo and Ghiani, 2000). Glutamate is removed from synapses by glia, affecting function in astrocytes (Volz et al., 2013). Theta burst stimulation also increases vesicular glutamate transporter 1 (VGLUT1) expression (Rajkowska, 2000), which is consistent with overall upregulation of Glu. Depressed patients show decreased glia in the PFC (Kempermann et al., 2018), suggesting Glu-mediated rTMS changes in glial activity contribute to clinical improvement (Croarkin et al., 2016; Zheng et al., 2010).

4.2. rTMS mechanisms via NAA-related adult neurogenesis

Several lines of evidence potentially suggest that rTMS-related increases in NAA may reflect changes in the rate or efficacy of adult neurogenesis, with downstream effects on functional activity, monoaminergic processes, cerebral glucose utilization and neurometabolism. In humans, adult neurogenesis occurs in the hippocampus and the striatum, regions involved in the etiology and treatment of MDD (Ernst and Frisen, 2015; Spalding et al., 2005; Ernst et al., 2014; White and Gonsalves, 2021; White et al., 2021). In healthy volunteers, the level of NAA in the dACC relates to an aspect of emotional functioning termed neuroaffective reserves, which encompasses capacities for emotional fluidity, positive agency, and resilience (Ueyama et al., 2011). Increased NAA observed following successful rTMS treatment of MDD is thus possibly consistent with treatment-related increases in the rate and/or uptake of adult neurogenesis in treatment-responders. In animal models, high-frequency rTMS increases hippocampal neurogenesis (Piatti et al., 2011). Adult neurogenesis takes approximately 3–6 weeks for new neurons to generate, mature and integrate into existing circuitry (Inta et al., 2013). This timeframe is similar to the time course of clinical rTMS therapy, which when effective, requires daily treatments for 2–6 weeks to produce remission (McClintock et al., 2018). In animal models, the rate and efficacy of adult neurogenesis is modulated by neural activity and physical activity (Inta et al., 2013); in humans with depression, stimulation alters local neural activity and regional cerebral blood flow in those responsive to clinical rTMS treatment (McClintock et al., 2018;

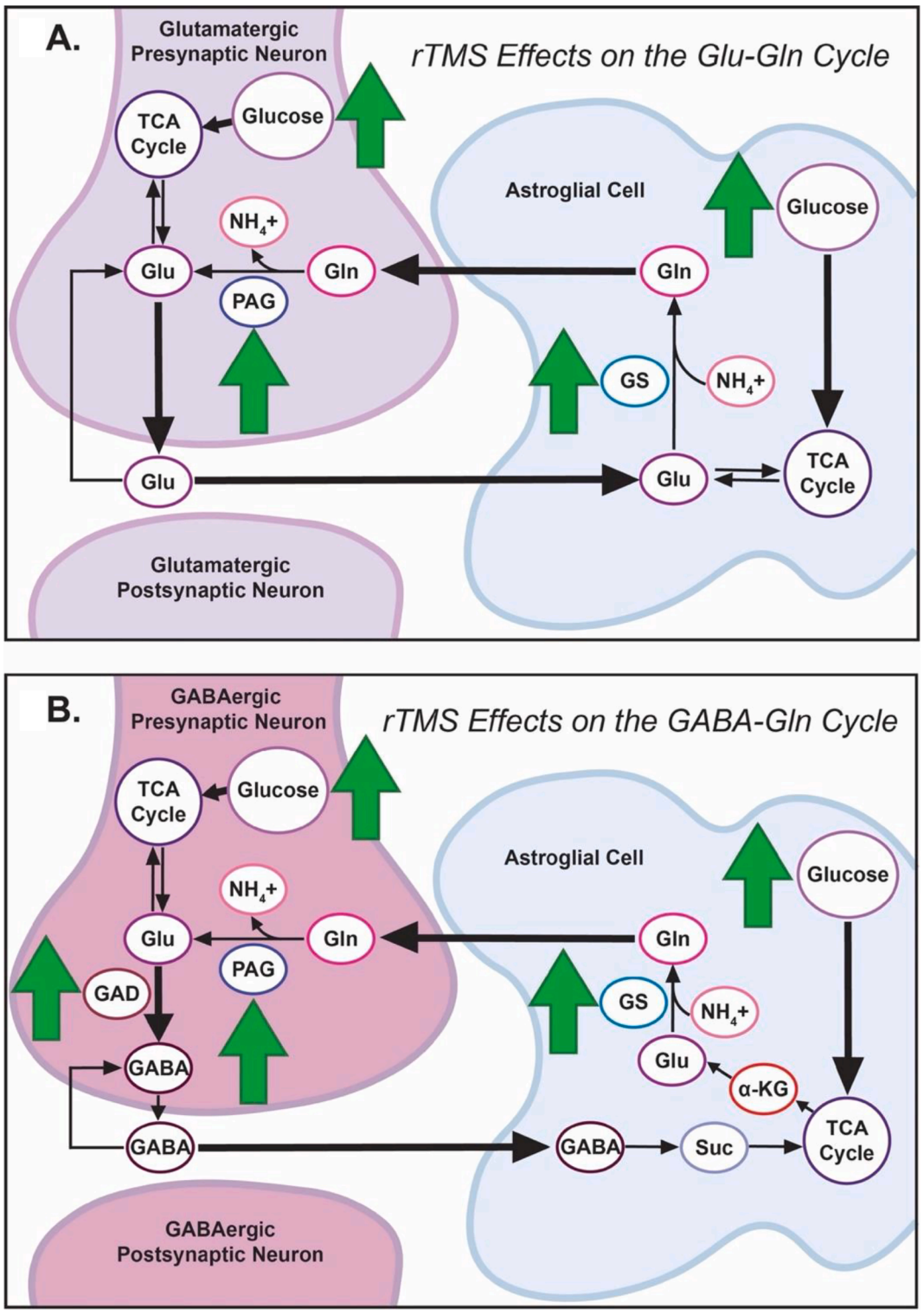

Fig. 2. Hypothesized rTMS Intracellular Effects on the Glu/GABA-Gln Pathway. A schematic representation of hypothesized rTMS intracellular effects on the Glu/GABA-Gln cycle, overlaid on neural-astrocyte Glu/GABA-Gln pathway of Bak et al. (2006). Fig. 2A: In the Glu-Gln pathway, green arrows represent rTMS-induced increases in glucose, phosphate-activated glutaminase (PAG), and glutamine synthetase (GS), leading to tricarboxylic acid (TCA) cycle upregulation and increased intracellular glutamate (Glu) and glutamine (Gln) production. Fig. 2B: In the GABA-Gln pathway, green arrows represent rTMS-induced increases in glucose, phosphate-activated glutaminase (PAG), glutamine synthetase (GS), and glutamate decarboxylase (GAD) leading to tricarboxylic acid (TCA) cycle upregulation and increased intracellular GABA and glutamine (Gln) production. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

O'Reardon et al., 2007). Neurogenic effects are also thought to play a role in the clinical improvement to other treatment modalities, including ECT (Madsen et al., 2000; Ohira et al., 2013) and SSRIs (Samuels and Hen, 2011) (see (Zhang et al., 2017) for a review). Direct evidence of a neurogenesis-NAA relationship is found in animals, where successful neural stem cell implants produce an increase in NAA in hippocampus (Baslow, 2010). Neurons display a > 200-fold intracellular/extracellular NAA gradient, allowing NAA to provide a marker for neurons, neuronal health and neuronal integrity in regions assessed by MRS (Chang et al., 2009; Dager et al., 2008). Moreover, as the MRS peak for tNAA typically contains two metabolites, NAA and *N*-acetylaspartyl-glutamate (NAAG), increases in tNAA following successful rTMS therapy suggest several downstream effects. These effects are not mutually exclusive and include (1) NAA-related contributions to functional activity, facilitating patients' capacity to respond to low-intensity positive stimuli, (2) NAAG-related modulation of monoamines, ACh and GABA, lowering neural thresholds for perception, experience and action, and (3) NAAG-related potentiation of local glucose utilization in neurons, which improves continuity and depth of recurrent processing (Ueyama et al., 2011). These sequelae are discussed in detail in White et al. (2021) and Ueyama et al. (2011) and are potentially relevant to proximal mechanisms of clinical improvement in MDD after rTMS treatment. To validate such hypotheses, future research measuring NAA levels in the hippocampus and/or striatum prior to and following rTMS treatment is required. This has not yet been collected, as existing rTMS studies have restricted MRS data collection to voxels in the frontal lobe. Potential rTMS-related effects on neurogenesis in these two areas, indexed by NAA, is thus worthy of evaluation in future work.

4.3. Strengths and limitations

This review has several limitations. First, only a small number of studies ($N = 12$) have been conducted, and most ($n = 8$) evaluated effects in samples of < 30 participants. Power estimates vary by metabolite and voxel location, but detection of change may require at least 50 subjects (Sanaei Nezhad et al., 2020), perhaps more in older adult samples (Fitzgerald, 2021). The included studies are thus underpowered to detect small and medium effect sizes of successful rTMS on MRS metabolites. Second, the included studies focused upon metabolic effects predominantly in the frontal lobe (i.e., MPFC, PFC, ACC, M1, and DLPFC), excluding other regions implicated in depression, including temporal, parietal, and occipital structures. Addressing this gap in our knowledge will be important for understanding the full impact of rTMS, as metabolic alterations have been observed throughout the brain in MDD (Near et al., 2021). Third, all reviewed studies applied rTMS to the left DLPFC, with one study also using sequential bilateral protocol and right DLPFC rTMS (Levitt et al., 2019). A left sided coil placement is common in clinical practice and effectively reduces depression symptoms (Mullins et al., 2014). As such, the present conclusions are mainly restricted to rTMS applied to the left DLPFC. Additional studies evaluating sequential bilateral protocol and right DLPFC on metabolites are warranted. Finally, we note that limitations inherent to MRS may contribute to the lack of cohesion across studies. Few studies report findings for both GABA and Glu, making it difficult to examine each metabolite's differential contributions to clinical recovery. Different pulse sequences and acquisition parameters (i.e., TR, TE, number of averages, editing pulses, quantification of compounds independently or derived from co-edited signals) are optimal for the quantification of GABA versus Glu. Moreover, quantifying metabolic peaks from GABA is more difficult due to the degree of spectral overlap (Sanaei Nezhad et al., 2020). Post-acquisition techniques and workflows vary considerably between the reviewed studies and may have contributed to differences in results and interpretation. Expert consensus and emerging standards regarding preprocessing, quantification, and analysis (Near et al., 2021) will be helpful for the MRS field going forward. Techniques that improve signal-to-noise ratio, such as PRESS or MEGA-PRESS acquisitions at a higher field strength (i.e., 7 Tesla) may improve quantification of GABA and other compounds (Mullins et al., 2019) in future work.

Strengths of the review include the consistency of the directionality of rTMS effects on metabolites, and the timeliness of examining understudied molecular mechanisms of rTMS, a relatively new depression treatment. While the reviewed studies are small and underpowered, the alignment of metabolite effects of therapeutic rTMS with metabolic responses observed following other effective MDD treatments (i.e., ECT and antidepressants (Michael et al., 2003a, b; Bhagwagar et al., 2004; Milak et al., 2016)), makes it unlikely that the changes described following rTMS are specific to this treatment modality. Rather, the findings provide convergent support for the observed neurometabolic effects associated with recovery from depression across multiple treatment types. Furthermore, the effects summarized in this review were generally consistent across age groups, indicating a common pathway through which rTMS and other clinical treatments achieve efficacy against MDD.

4.4. Future directions

Future work should recruit larger sample sizes, evaluate metabolites in regions beyond the frontal lobe and in the context of depressive relapse following a treatment-induced remission. Future studies should also identify relationships between metabolites and symptom response within dimensions of depression (e.g., mood, appetite, lethargy, anhedonia, and psychomotor agitation). To date, existing studies typically evaluate only the change in overall depression scores. Particularly in the setting of rTMS treatment for depression where patients are seen daily and frequently assessed with standardized measures, there is substantial opportunity to explore the specific ways in which metabolic changes relate to improvement in cognitive, affective, and behavioral outcomes in MDD. rTMS is a large commitment in terms of patients' time (4–6 weeks) and financial cost ($6,000-$12,000) (McClintock et al., 2018). Identification of metabolites that serve as readouts of clinical progress could be used to optimize treatment course length for individual patients. Though more research on right DLPFC applications is needed, hemispheric differences in metabolite concentrations may be useful for matching coil applications to specific patients. The potential utility of neuroimaging predictors of rTMS response has been demonstrated using imaging modalities (Corlier et al., 2019, Drysdale et al., 2017), Based on the reviewed evidence, MRS shows promise as a potential source of novel predictors of rTMS treatment efficacy for depression. Future work using machine learning tools and baseline metabolite levels may assist in a personalized medicine approach of determining which patients will most benefit from rTMS treatment for MDD.

4.5. Conclusions and implications

This systematic review identifies rTMS treatment-related effects on MRS compounds in individuals with depression. Several metabolites present preliminary reasonable evidence for a specific metabolic change in response to left DLPFC rTMS (i.e., Glu, Gln, GABA, and NAA), and not all demonstrate a correlation with symptom severity, either before or after treatment (i.e., Cr). Several of these relationships are similar to findings with other depression treatments, such as ECT and citalopram, which indicate treatment effects on Glu, Gln, GABA, and NAA that relates to improvement in depression symptoms. These findings are generally consistent with those of rTMS and suggest common metabolic mechanisms by which patients' depression resolves. The body of MRS data we review here extends and informs our understanding of the mechanisms of improvement in individuals with severe depression and has potential utility as a future clinical tool for guiding clinical care.

Author contributions

This review was conceptualized, initiated, and designed by MAG,

TLW, and LLC. MAG wrote the first draft of the manuscript, MAG and TLW edited and revised the initial draft, MAG, TLW, and JB edited and revised the final draft. MAG and AMF tailored the scope of the literature search. MAG completed the literature search, determined which articles were eligible, and compiled the included articles. MAG, HJ, AMF extracted and verified the relevant data from the articles. MAG performed the data analyses. MAG created the tables and figures. MAG and TLW created the model. MAG, TLW, HEJ, AMF, ADH, JB, and LLC provided input on data analysis and results and revised the manuscript. All authors read and approved the final manuscript.

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6. Disclosures

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