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RESEARCH ARTICLE

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Psychostimulant use and clinical outcome of repetitive transcranial magnetic stimulation treatment of major depressive disorder

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Abstract

Background: Repetitive transcranial magnetic stimulation (rTMS) is an effective treatment for major depressive disorder (MDD). Psychostimulant medication use may be associated with improved rTMS outcomes, but a detailed understanding of these relationships is lacking.

Methods: We compared MDD subjects taking psychostimulants ($n = 37$) with those not taking one of these medications ($n = 53$) during a course of 30 rTMS treatments. Changes in the 30-item Inventory of Depressive Symptomatology Self Report (IDS-SR30) subscale scores were examined at treatment 30. We also subdivided subjects into three categories based on drug mechanism and looked at IDS-SR30 total score after treatments 10, 20, and 30.

Results: Subjects taking psychostimulants had a significantly greater overall clinical improvement than those not taking these medications at treatment 30. The psychostimulant group also improved significantly more than the control group in "sleep" and "mood/cognition," but not "anxiety/arousal" IDS-SR30 subscales. No differences were detected among individual drug categories, which may reflect the limited sample size for individual medications. There was a negative dose–response relationship for the lisdexamfetamine/dextroamphetamine group, in which lower doses were associated with better clinical outcome.

Conclusions: Psychostimulant medications may enhance clinical efficacy of rTMS for MDD by preferentially impacting specific symptom domains. For some psychostimulants, these effects may be dose-dependent. Prospective clinical trials are needed to guide psychostimulant augmentation of brain stimulation therapies.

KEYWORDS

brain stimulation, dopamine, major depressive disorder, monoamines, norepinephrine, psychostimulants, repetitive transcranial magnetic stimulation

1 | INTRODUCTION

Major depressive disorder (MDD) is a prevalent, disabling condition associated with significant reductions in quality of life (Hasin et al., 2018; Saarni et al., 2007; Vos et al., 2016). Remission and response rates to first-line treatments are disappointing, indicating a compelling need for novel and effective treatment options (Rush et al., 2006). Repetitive transcranial magnetic stimulation (rTMS) has emerged as one such treatment option. Large, randomized, sham-controlled trials have demonstrated the efficacy and safety of rTMS as monotherapy for depression (George et al., 2010; Levkovitz et al., 2015; O'Reardon et al., 2007). Although rTMS administered to left dorsolateral prefrontal cortex (DLPFC) is an efficacious monotherapy for medication-resistant MDD, in clinical practice, it is usually used in conjunction with psychotropic medications (Carpenter et al., 2012; McClintock et al., 2018).

Large, naturalistic studies support the clinical efficacy and safety of rTMS with concomitant psychotropic medications (Carpenter et al., 2012; Connolly et al., 2012; Dunner et al., 2014). Several studies have investigated effects of rTMS on medication treatment outcomes, but few studies have examined the effects of medications on augmenting clinical rTMS outcomes (Hu et al., 2016; Lefaucheur et al., 2014; Schulze et al., 2017; Wang et al., 2017). rTMS is hypothesized to exert its therapeutic effects through changes in the excitability of neural circuits and long-term synaptic potentiation or depression (LTP or LTD) (Hoogendam et al., 2010; Müller-Dahlhaus & Vlachos, 2013; Wilson et al., 2018). Many drugs that are active in the central nervous system have been demonstrated to enhance, reduce, or even abolish these plasticity mechanisms (Hoogendam et al., 2010; Minzenberg & Leuchter, 2019; Ziemann et al., 2015). It is therefore plausible that such drugs could prime or augment the therapeutic mechanisms engaged by rTMS and a better understanding of such effects could be used to enhance treatment outcomes.

A recent observational study by our group examined the potential relationship between classes of psychotropic medication and clinical outcome of rTMS treatment of MDD (Hunter et al., 2019). This study found a significant correlation between use of benzodiazepine drugs and lesser improvement with rTMS—a finding supported by other reports (Hunter & Leuchter, 2020; Kaster et al., 2019). In addition, psychostimulant use was associated with significantly greater improvement after 2 and 6 weeks of rTMS treatment (Hunter et al., 2019). Psychostimulants are a class of medications with a broad range of neurochemical effects, most notably enhancement of monoaminergic transmission (e.g., dopamine, norepinephrine, etc.) (Kim et al., 2019). These neurotransmitters are neuromodulators that shape activity in neural circuits, in part, by influencing synaptic plasticity (Meintzschel & Ziemann, 2006; Tegenthoff et al., 2004; Xu & Yao, 2010; Zhou et al., 2013). Thus, psychostimulants may augment rTMS outcomes by acting through dopaminergic and/or noradrenergic signaling pathways to synergistically enhance plasticity (Hunter et al., 2019; Minzenberg & Leuchter, 2019). In this study, we examined psychostimulant data in greater detail by looking at effects on total IDS-SR30 as well as subscales examining separate domains of "mood/cognition," "anxiety/arousal," and "sleep," differences among psychostimulant medication categories, and dose–response relationships.

2 | METHODS

This retrospective study was performed to further explore the association between the use of psychostimulant medications and clinical rTMS outcome (Hunter et al., 2019). All treatment and medication data were collected retrospectively. All subjects provided written informed consent to participate in this UCLA IRB-approved study and were treated in accordance with the 2013 Declaration of Helsinki.

2.1 | Clinical evaluation and medications

Subjects were patients treated in the UCLA TMS Clinical and Research Service between September 2009 and January 2017. Clinical symptoms were assessed using the 30-item Inventory of Depressive Symptomatology Self Report (IDS-SR30) (Rush et al., 1996) at baseline as well as treatments 10, 20, and 30. The sample included 181 subjects treated for nonpsychotic MDD who had baseline medication data available and who received at least 10 rTMS treatment sessions (Figure 1). All medications that were prescribed at the onset of treatment for each subject were obtained from electronic medical records. Subject data were coded for each medication to include the specific drug, prescribed dosage, and medication class (e.g., "psychostimulant") for all 181 subjects. Subjects taking benzodiazepines were excluded ($n = 69$), based on findings from the original study and others which have suggested that this class of medications is associated with a less robust response to rTMS (Hunter & Leuchter, 2020; Hunter et al., 2019; Kaster et al., 2019). Thus, the inclusion of these subjects may have obscured the effect of psychostimulants on treatment outcome. We further excluded five subjects who were taking psychostimulants but for whom there were no data about the specific drug/dose. Finally, we excluded 17 control subjects who were missing at least one IDS score during the treatment course. This left an analyzable subset of patients not taking psychostimulants or benzodiazepines (Category 0: control subjects, $n = 53$); and another subset ($n = 37$) taking known dosages of one or more specific psychostimulant medications. We further divided this subset into three categories, grouping medications that were structurally/mechanistically similar and thus predicted to have similar effects, to increase the statistical power of our analysis. The categories were as follows: Category 1, lisdexamfetamine and dextroamphetamine ("amphetamine," $n = 22$); Category 2, methylphenidate and dexmethylphenidate ("methylphenidate," $n = 9$); and Category 3, modafinil and armodafinil ("modafinil," $n = 7$). One subject was on two psychostimulants and was included in both groups (dextroamphetamine and modafinil). We did not exclude psychostimulant users with missing IDS-SR30 scores due to the low

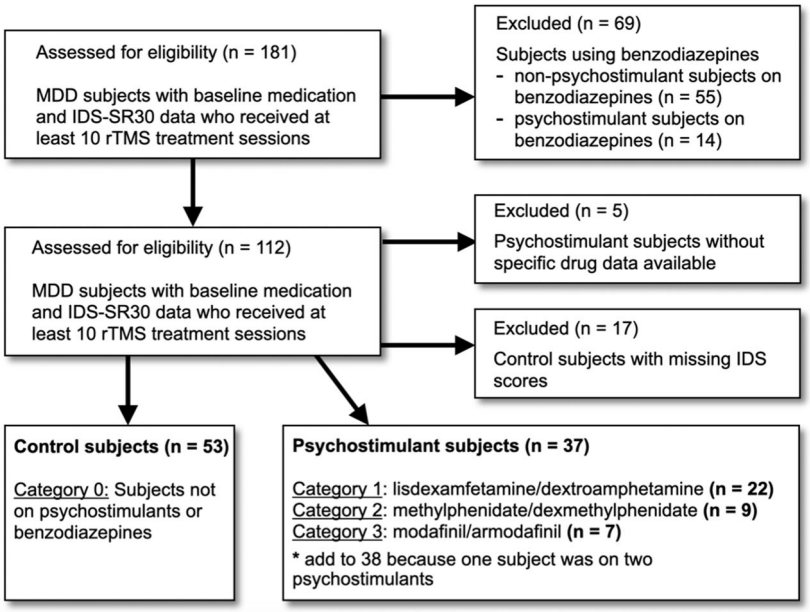

FIGURE 1 Data flow diagram of subject inclusion and sample breakdown

number of subjects. Thus, some comparisons have slightly fewer data points (Category 1, 2 at Tx 30; Category 2, 1 at Tx 20 and 30; Category 3, 1 at Tx 30).

The IDS-SR30 is a multidimensional assessment tool and confirmatory factor analysis based on prior dimensionality reduction appoaches suggests three unidimensional subdomains (Wardenaar et al., 2010). These subscales are nominally classified as, "sleep," "mood/cognition," and "anxiety/arousal." To investigate whether psychostimulant-users had greater improvement than nonusers in these previously validated subdomains, we analyzed data from individual IDS-SR30 response items, grouping these as aggregate scores for each subscale (Wardenaar et al., 2010). Finally, in an exploratory manner, we analyzed IDS-SR30 subdomains for each category of psychostimulant medication in a similar way.

2.2 | rTMS procedures

Subjects were treated using the NeuroStar TMS System (Neuronetics, Inc.) with up to 30 rTMS sessions performed over six weeks as described previously (Dunner et al., 2014; Hunter et al., 2019). Before the first treatment, resting motor threshold (MT) was determined as the minimum intensity (% of max stimulator output), required to elicit a visually detectable hand movement in 50% of single pulse trials targeting primary motor cortex. Treatment began with parameters of 3000 pulses per session at 10 Hz frequency, administered to the left DLPFC with the Beam F3 targeting method (Beam et al., 2009), with a 40-pulse train and intertrain interval of 26 s (total duration 37.5 min). Intensity was titrated up to 120% of the MT as tolerated. After the tenth treatment, adjustments could be made based on changes in symptom severity and physician clinical judgment as described previously (Hunter et al., 2019).

2.3 | Statistical analysis

An initial analysis of variance (ANOVA) was performed to examine overall treatment outcome using IDS-SR30 scores between groups at baseline, treatment 10, 20, and 30, a within-subjects factor "treatment number," and a between-subjects factors of "psychostimulant use (yes/no)": psychostimulant-users ($n = 37$) and nonusers ($n = 53$). A second ANOVA was then performed to examine the effects of specific stimulant medications on outcome using IDS-SR30 scores between groups at baseline, treatment 10, 20, and 30, a within-subjects factor "treatment number," and a between-subjects factor of "psychostimulant category" coded as lisdexamfetamine and dextroamphetamine in Category 1, methylphenidate and dexmethylphenidate in Category 2, and modafinil and armodafinil in Category 3. For four psychostimulant-users that had a missing IDS-SR30 score at treatment 20 or 30, we replaced that value with the median of the other subjects at that treatment number to perform the ANOVA (five total replacements). We did not need to replace missing IDS-SR30 values for nonusers, because of their larger sample and thus, these subjects were already excluded from our analysis. We have also calculated Cohen's *d* effect sizes for the comparison between the pooled psychostimulant-users and nonusers, as well as between each individual psychostimulant category and nonusers. For IDS-SR30 subdomain analysis we used two-tailed *t*-tests to compare baseline score and percent improvement at treatment 30 for each subscale between psychostimulant-users and nonusers.

The correlation analyses were conducted using the Pearson's correlation coefficient to evaluate the association between psychostimulant dose (mg) and change in clinical symptoms after 10 and 30 rTMS treatments. Due to statistical power considerations, the correlations were calculated only for the group of psychostimulant users with $n \geq 10$, which excluded modafinil and methylphenidate groups. For the latter two, we only report effect sizes.

Analyses were performed using IBM SPSS version 26 or MATLAB. All significant findings are reported at $\alpha = 0.05$. False discovery rate (FDR) correction was applied where appropriate to account for multiple comparisons.

3 | RESULTS

3.1 | Clinical characteristics and outcomes

The analyzable sample of patients taking psychostimulants and not benzodiazepines was $n = 37$ (Figure 1). Fifty-eight percent of the sample was taking lisdexamfetamine/dextroamphetamine (Category 1, $n = 22$), 24% was taking methylphenidate/dexmethylphenidate (Category 2, $n = 9$), and 18% was taking modafinil/armodafinil (Category 3, $n = 7$). Note that one participant was taking two psychostimulants (dextroamphetamine and modafinil) and was thus included in both groups. Table 1 shows comparisons between pooled psychostimulant-users and nonusers for age, gender, and IDS-SR30 at baseline and treatment 30. The absolute magnitude of IDS-SR30 score changes is also included as a supplement (Table S1). There were no age or gender differences between the psychostimulant-users and nonusers. There was also no significant difference in baseline depression severity. Psychostimulant-users had a significantly larger percent decrease in IDS-SR30 than nonusers at treatment 30 ($T = 2.34$, $p = .022$).

There was no significant difference in IDS-SR30 subscale scores at baseline between psychostimulant-users and nonusers (Table 1, Figure 2). However, at treatment 30, the psychostimulant group exhibited significantly greater improvement than the nonuser group in the "sleep" ($T = -2.30$, $p = .024$) and "mood/cognition" ($T = -2.95$, $p = .004$) subscales, but not the "anxiety/arousal" subscale (Table 1, Figure 2). To explore this further, we examined change in subscales by psychostimulant category. For "amphetamine," the largest effect was for "sleep" ($T = -3.06$, $p = .003$), with a strong trend for "mood/cognition" ($T = -2.02$, $p = .052$) (Table S2). Whereas the "methylphenidate" group had no effect for "sleep" ($T = -0.78$, $p = .453$), but a significant effect for "mood/cognition" ($T = -2.88$, $p = .012$) (Table S2). The Modafinil group had no significant subscale specific effects (Table S2).

3.2 | Synergistic effects between psychostimulants and rTMS

Mauchly's test of sphericity indicated that the assumption of sphericity had been violated in both ANOVAs, and therefore, Greenhouse–Geisser corrected numbers are reported below. There was a significant main effect of "treatment number" ($F = 84.40$, $p < .001$), a significant interaction between "treatment number" and "psychostimulant use (yes/no)" ($F = 5.99$, $p = .001$), and a trend for the main effect of "psychostimulant use (yes/no)" ($F = 3.17$, $p = .079$) (Figure 3a). In the second ANOVA, there was a significant main effect of "treatment number" ($F = 47.79$, $p < .001$), but no interaction between "treatment number" and "psychostimulant category" ($F = 1.24$, $p = .301$), and no main effect of "psychostimulant category" ($F = 0.75$, $p = .478$). The results of both ANOVAs are summarized in Table 2. Because no main effect of psychostimulant category was

TABLE 1 Comparisons between pooled psychostimulant-users and nonusers for gender, age, baseline IDS-SR30 overall and subscale scores, and change in scores at treatment 30

	Psychostimulant-users	Nonusers	Test statistic	*p*-value (two-tail)
Gender (male)	51.35%	45.28%	$\chi 2 = 0.32$	.571
Age (SD)	44.73 (15.94)	46.91 (16.75)	$T = -0.62$	.534
Baseline IDS-SR30 (SD)	41.68 (10.44)	41.28 (10.17)	$T = 0.18$	.860
% decrease in IDS-SR30 (SD) at treatment 30	43.68 (26.56)	29.76 (27.30)	$T = 2.34$	.022*
Baseline "sleep" (SD)	4.59 (2.23)	5.26 (2.05)	$T = 1.45$	.152
% decrease "sleep" (SD)	28.78 (34.17)	8.72 (48.54)	$T = -2.30$	.024*
Baseline "mood/cognition" (SD)	20.89 (4.59)	19.96 (4.19)	$T = -0.98$	.330
% decrease "mood/cognition" (SD)	48.92 (29.24)	31.00 (27.05)	$T = -2.95$	.004**
Baseline "anxiety/arousal" (SD)	8.81 (3.60)	8.88 (3.37)	$T = 0.08$	.930
% decrease "anxiety/arousal" (SD)	45.96 (28.25)	39.32 (33.16)	$T = -1.02$	.311

Abbreviations: IDS-SR30, 30-item Inventory of Depressive Symptomatology Self Report; SD, standard deviation.

*p-values are statistically significant.

**$p < 0.01$.

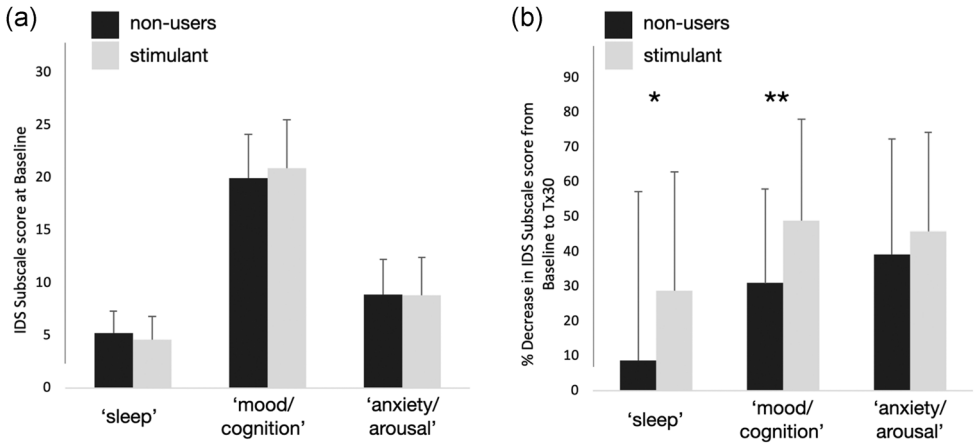

FIGURE 2 Depressive symptoms by subscale for nonuser and combined psychostimulant-user groups, (a) baseline IDS-SR30 subscale scores, and (b) percent decrease in 30-item Inventory of Depressive Symptomatology Self Report (IDS-SR30) subscale scores from baseline to treatment 30. Statistics represent mean mean ± SD, $^{*}p < .05$, $^{**}p < .01$

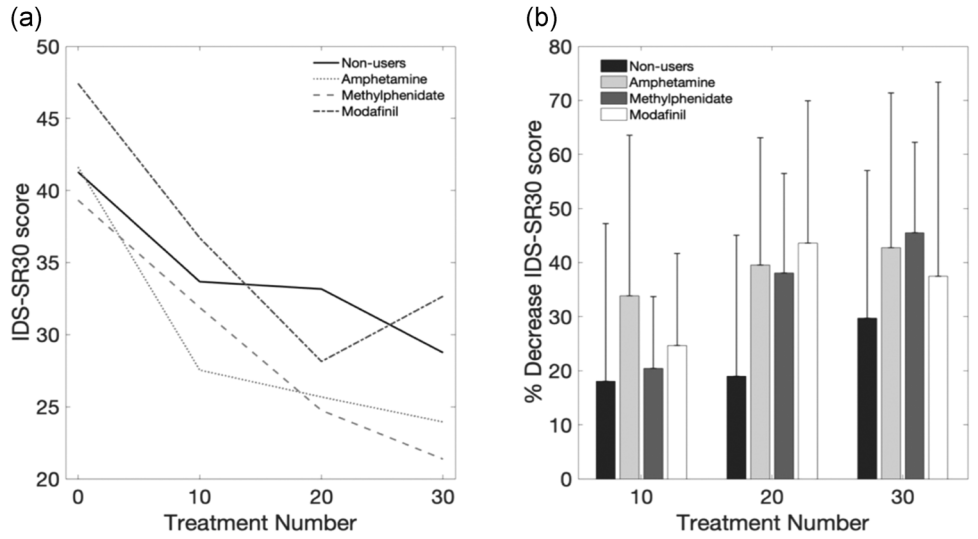

FIGURE 3 For nonusers and the three categories of psychostimulant-users, (a) change in mean 30-item Inventory of Depressive Symptomatology Self Report (IDS-SR30) at baseline, treatment 10, 20, and 30 and (b) percent decrease in IDS-SR30 (and standard deviation) from baseline to treatment 10, baseline to treatment 20, and baseline to treatment 30

TABLE 2 Results of the two repeated measures ANOVAs with a within-subjects factor of treatment number and a between-subjects factor of (1) psychostimulant use (yes/no) and (2) psychostimulant category

		SS	df	MS	*F*	*p*-value (two-tail)
ANOVA 1	Treatment number	11385.32	2.44	4672.82	84.40	<.001*
	Psychostimulant-users versus nonusers	1543.42	1.00	1543.42	3.17	.079
	Interaction	807.88	2.44	331.57	5.99	.001*
ANOVA 2	Treatment number	5728.32	2.10	2731.52	47.79	<.001*
	Category 1 versus Category 2 versus Category 3	916.46	2.00	458.23	0.75	.478
	Interaction	297.52	4.19	70.94	1.24	.301

*p-values are statistically significant.

Abbreviations: ANOVA, analysis of variance; df, degrees of freedom; *F*, *F* ratio; MS, mean squares; SS, sum-of-squares.

observed, we did not perform post hoc tests between the psychostimulant categories (Figure 3b).

The effect size was $d = 0.32$ for differences at treatment 10 between pooled psychostimulant-users and nonusers; and $d = 0.46$, $d = 0.14$, $d = -0.23$ for Category 1, 2, and 3 versus nonusers, respectively. The effect size for differences at treatment 30 for pooled psychostimulant-users and nonusers was $d = 0.35$; and $d = 0.35$, $d = 0.58$, and $d = -0.27$ for Category 1, 2, and 3 versus nonusers, respectively.

3.3 | Dose–response relationship

The correlation between the amphetamine dose and treatment response reached significance (uncorrected) and remained at trend level after FDR correction with $r = -0.44$ and $p = .038$ (uncorrected)/$p = .069$ (corrected) at treatment 10 and $r = -0.41$ and $p = .069$ (uncorrected)/$p = .069$ (corrected) at treatment 30 (Figure 4). Effect sizes were $d = 1.08$ and $d = 1.37$ for treatment 10 and 30, respectively. Notably, the association was negative indicating that smaller doses (<20 mg) of lisdexamfetamine/dextroamphetamine may be beneficial to boost rTMS treatment response. Given the small sample size for the modafinil and methylphenidate groups, we did not compute the correlation coefficient for these groups. Their effect sizes were 0.82 and 0.70 at treatment 10; and 0.84 and 1.86 at treatment 30 for modafinil and methylphenidate groups, respectively.

4 | DISCUSSION

This report confirms earlier findings that patients taking psychostimulants had significantly greater improvement than nonusers from rTMS treatment for depression and suggests that this greater overall improvement may be driven by particular symptom domains. Our report also suggests that there were no differences attributable to specific psychostimulant drug category, although limited sample sizes may have prevented detection of such differences. The effect sizes for individual psychostimulant drugs vary between small to moderate ($d = 0.2–0.5$). We did detect a novel finding of a dose–response relationship, with smaller doses of lisdexamfetamine/dextroamphetamine associated with better rTMS treatment outcome.

These data are consistent with the findings from Hunter et al. and suggest that psychostimulant medication provided before and during rTMS treatment might effectively prime neural circuits for an enhanced therapeutic response. Intriguingly, we found that the psychostimulant group had significantly greater improvement than the control group in IDS-SR30 "sleep" and "mood/cognition" subscales, but not in the "anxiety/arousal" subscale. An analysis of subscales for each medication class may suggest additional specificity, with the "amphetamine" group improving more in "sleep," and "methylphenidate" improving more in "mood/cognition" subscales. The subscales examined were identified using dimensionality reduction and validated with confirmatory factor analysis (Wardenaar et al., 2010). Thus, these results may indicate specificity in the neural mechanisms impacted by the interaction between specific psychostimulants and rTMS. However, caution is warranted in interpreting these data given the relatively small sample sizes involved.

We also found evidence of a potential dose–response relationship for the effects of psychostimulants on improvement in depression. For lisdexamfetamine/dextroamphetamine users, low dosage regimens seemed to result in the largest improvement. This did not appear to reflect differences in baseline symptom severity among subjects. These findings suggest a pharmacological augmentation strategy in

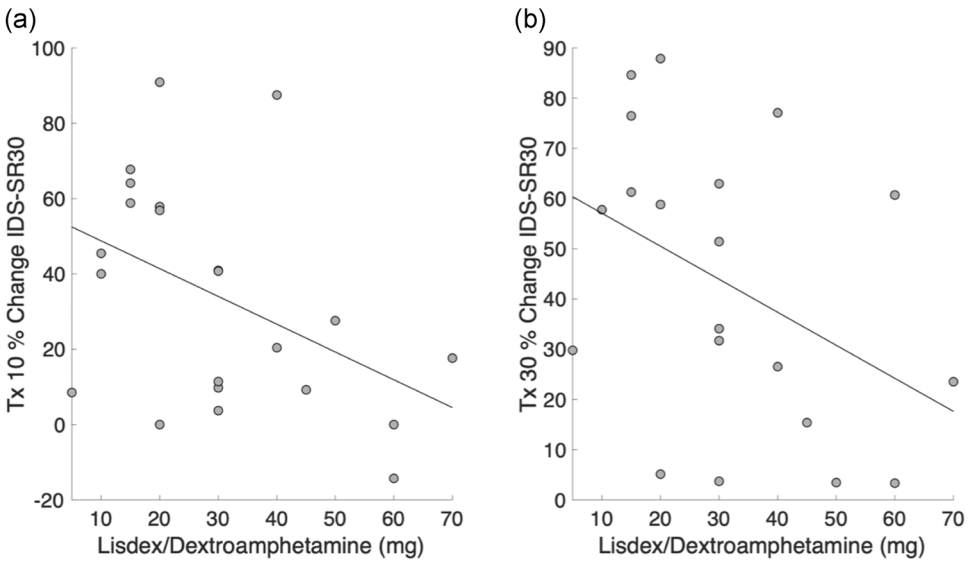

FIGURE 4 For Category 1 psychostimulants, relationships between dosage and percent decrease in 30-item Inventory of Depressive Symptomatology Self Report (IDS-SR30) from (a) baseline to treatment 10 ($r = -0.44$, p uncorrected = 0.038*/p corrected = 0.069) and (b) baseline to treatment 30 ($r = -0.41$ and p uncorrected = 0.069/p corrected = 0.069)

which low-dose lisdexamfetamine/dextroamphetamine might be used to enhance response to rTMS treatment for depression.

There are several potential mechanisms that could explain a therapeutic synergy between psychostimulant drugs and rTMS. These medications can elicit psychomotor activation, trigger reinforcement learning, and modulate cognitive function by directly driving increased levels of monoamine neurotransmitters, particularly dopamine (DA) and norepinephrine (NE) (Arnsten & Dudley, 2005; Berridge & Stalnaker, 2002; Spencer et al., 2015). Notably, TMS stimulation of the DLPFC also reliably enhances monoamine neurotransmission in multiple brain regions implicated in depression (Cho & Strafella, 2009; Pogarell et al., 2006, 2007; Strafella et al., 2001; Zangen & Hyodo, 2002). Monoamine neuromodulators elicit state-dependent effects on activity in neural circuits and are especially important for prefrontal cortex, which is the primary target of rTMS for depression (Goto et al., 2010; Xing et al., 2016). From a mechanistic perspective, psychostimulant drugs do not tend to affect cortical excitability as measured by MT, but have profound effects on measures of TMS-induced plasticity in motor systems (Gilbert et al., 2006; Meintzschel & Ziemann, 2006; Minzenberg & Leuchter, 2019; Tegenthoff et al., 2004; Ziemann et al., 1997). A range of other pharmacologic investigations has also demonstrated the direct involvement of DA and NE systems in the plasticity-inducing effects of TMS (Korchounov & Ziemann, 2011; Lim et al., 2010; Monte-Silva et al., 2011; Nitsche et al., 2012). Thus, our results extend this study by further implicating these systems as critical for the clinical effectiveness of rTMS for depression.

The dose-dependence observed in patients taking lisdexamfetamine/dextroamphetamine is consistent with prior results on the neurobiological effects of psychostimulants, which exhibit strikingly nonlinear dose–response relationships known as an "inverted-U" (Spencer et al., 2015). As DA and NE concentrations increase, distinct receptor subtypes, often with opposing functions are engaged (Xing et al., 2016). For example, in the prefrontal cortex, low levels of dopamine may promote LTD, moderate levels LTP, and higher levels may have no effect on plasticity at all (Goto et al., 2010). Moreover, several lines of evidence suggest deficits in dopamine and other monoamines might underlie symptom domains central to depression (anhedonia, motivation, concentration, etc.) (Belujon & Grace, 2017; Dunlop & Nemeroff, 2007; Hamon & Blier, 2013). Thus, by normalizing DA and/or NE levels in key brain regions, psychostimulants might enable plasticity in mood or cognition-related circuits that are therapeutically modulated by rTMS. Alternatively, if the therapeutic effects of rTMS result directly from their effect on DA and/or NE, then by enhancing release psychostimulants may directly potentiate those effects. While it is unclear whether the observed effect is related to DA, NE, or both, compelling hypotheses can be generated for each.

These findings suggest a novel pharmacologic augmentation strategy for patients undergoing rTMS treatment of depression. Because many patients have a limited response to rTMS treatment (Berlim et al., 2014), an augmentation approach to maximize treatment benefit by harnessing psychopharmacology would be a significant advance. Our study suggests that low-dose lisdexamfetamine or dextroamphetamine may enhance outcome. One safety consideration with this approach is that psychostimulants are associated with an increased risk of seizure generally. Current safety guidelines do not rule out use of rTMS in patients taking psychostimulants and direct effects on cortical excitability have generally not been seen (McClintock et al., 2018; Minzenberg & Leuchter, 2019), and none of the subjects in this study suffered a seizure. However, detailed studies have not been done and thus caution is warranted when combining psychostimulants with rTMS. Moreover, it is important to consider other risks such as potential for abuse and side effects and/or other adverse events. Importantly, if it is possible to augment using low-dose psychostimulants, this might significantly mitigate concerns about potential adverse consequences. Moreover, it may be possible to use low-dose psychostimulants as part of a time-limited strategy only during the actual rTMS course, which would also limit such concerns.

Our study has several important limitations which should be considered. First, the sample sizes for some medication classes are small and limit interpretation of those results. Second, because it is unclear how long patients had been taking these medications, we cannot draw conclusions about how the duration of psychostimulant treatment might impact the observed effects. Moreover, although psychostimulants were generally being prescribed off-label to augment treatment of depression, we cannot rule out that they were sometimes prescribed to treat other concomitant conditions. Finally, although the findings are suggestive, they are correlative and cannot address causal relationships. Thus, the clinical implications of combining psychostimulants and rTMS are unclear and caution is warranted until prospective trials can establish the safety and efficacy of such interventions.

5 | CONCLUSION

The findings of this study suggest that psychostimulant medications, possibly via their effect on neuroplasticity, may enhance clinical efficacy of rTMS treatment for depression. We propose that these findings should motivate randomized, placebo-controlled trials using low-dose psychostimulants to prime and therefore enhance rTMS treatment response. If successful, such studies would support a new time-limited treatment paradigm that combines psychopharmacology and brain stimulation for better outcomes in treatment-resistant depression and potentially other indications.

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CONFLICTS OF INTEREST

Dr. Wilke, Crystal Johnson, Dr. Corlier, Dr. Marder, and Christopher Pleman have no disclosures to report. Andrew Wilson has served as a consultant to HeartCloud, Inc. within the past 36 months. Dr. Leuchter discloses that within the past 36 months he has received research support from the National Institutes of Health, Neuronetics, Department of Defense, CHDI Foundation, and NeuroSigma, Inc. He has served as a consultant to NeoSync, Inc., Ionis Pharmaceuticals, Inc., and ElMindA. He is Chief Scientific Officer of Brain Biomarker Analytics LLC (BBA). Dr. Leuchter owns equity interest in BBA.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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