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Research paper

Effect of repetitive transcranial magnetic stimulation (rTMS) treatment of major depressive disorder (MDD) on cognitive control

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ABSTRACT

Background: Major Depressive Disorder (MDD) is commonly accompanied by cognitive control dysfunction that may persist after remission of clinical symptoms with antidepressant medication treatment. Repetitive Transcranial Magnetic Stimulation (rTMS) is an effective treatment alternative for medication-resistant MDD. In this study, we investigated whether rTMS treatment had a beneficial effect not only on depressive symptoms, but on also cognitive control dysfunction.

Methods: 77 subjects with MDD received a 30-session treatment course of 10 Hz rTMS administered at the left dorsolateral prefrontal cortex (DLPFC). Treatment efficacy was assessed using the Inventory of Depressive Symptomatology Self-Rated (IDS-SR) before and after treatment, with clinical response defined as 50% or greater decrease in the IDS-SR score at treatment 30. Cognitive control function was assessed before and after treatment using the Stroop word-color interference task. We examined changes in Stroop accuracy and reaction time for congruent and incongruent trials, as well as in relation to changes in depressive symptoms.

Results: Performance accuracy improved particularly for the rTMS responders in the incongruent condition, with older subjects benefitting most from the rTMS treatment. Improvement in reaction times was positively associated with clinical improvement, especially in the incongruent condition.

Limitations: We used a single cognitive task in a naturalistic setting without control for individual rTMS treatment parameters or concomitant medication.

Conclusions: Overall, these results indicate that rTMS treatment for MDD has beneficial effects on psychomotor speed and cognitive control. Future studies should extend these findings to larger patient populations and other cognitive domains.

1. Introduction

Major Depressive Disorder (MDD) is a leading cause of disability worldwide, commonly accompanied by cognitive dysfunction that accentuates the functional disability and reduces quality of life (Pehrson et al., 2015; Salagre et al., 2017). Depressed individuals may have global or discrete cognitive deficits, including the domains of attention, memory, psychomotor and information processing speed, as well as executive function (Gualtieri et al., 2006; Baune et al., 2010; Shilyansky et al., 2016). The level of impairment depends on age, depression severity, comorbidities, disease duration, and other factors (Gualtieri et al., 2006; Kertzman et al., 2010; McClintock et al., 2010; Trivedi and Greer, 2014).

Cognitive dysfunction often persists after remission of depressive symptoms with medication treatment (Hammar et al., 2010; Hasselbalch et al., 2011; Pehrson et al., 2015; Solé et al., 2015; Prado et al., 2018). In a large sample of over 1000 patients, no improvement was found in the domains of attention, response inhibition, verbal memory, decision speed and information processing across three different antidepressant drug treatment groups (Shilyansky et al., 2016). Some studies even indicate a detrimental effect of medication on cognition (Sneed et al., 2010; Nagane et al., 2014). Given the association between cognitive impairment and poor daily functioning, there is a great unmet need in finding efficacious treatments for cognitive

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dysfunction in MDD beyond the relief of mood symptoms (Solé et al., 2015; Salagre et al., 2017).

Among the various cognitive domains, executive function (of which a major aspect is cognitive control) is most closely related to treatment outcome, consistent with the depression-executive dysfunction model (McLennan and Mathias, 2010; Etkin et al., 2015). Persistent cognitive control dysfunction can impede recovery from MDD because it limits cognitive flexibility, control of impulsivity, and emotional regulation (Paulus, 2015). A common measure of cognitive control is the Stroop Color-Word Interference Task (Epp et al., 2012). The interference index is an indicator of cognitive control and measures the difference in response latencies between incongruent and congruent stimuli. It has been shown that depressed individuals show difficulties suppressing interference effects which can be related to problems with rumination, worrying, or attentional bias (Paulus, 2015).

Repetitive transcranial magnetic stimulation (rTMS) to the left dorsolateral prefrontal cortex (DLPFC) has been shown to be a safe and efficacious alternative for treatment resistant depression (George et al., 2010; Carpenter et al., 2012). There is preliminary evidence showing that rTMS could also improve cognitive function in MDD including verbal memory (Kuroda et al., 2006; Fitzgerald et al., 2009; Wajdik et al., 2014), attention (Höppner et al., 2003; O'Connor et al., 2005; Naim-Feil et al., 2016), and executive function (Moser et al., 2002); cf. (Salagre et al., 2017). While the exact clinical mechanism of action (MOA) of rTMS is incompletely understood, it has been shown that rTMS can affect functional neural networks involving the stimulation site (Fox et al., 2012; To et al., 2018). Because the stimulation site at DLPFC is part of the central executive network (CEN) (Liston et al., 2014), we hypothesized that rTMS treatment might specifically improve cognitive control as measured by the Stroop task. We investigated the effect of 30-session course of 10 Hz rTMS treatment administered to the DLPFC on cognitive control performance, and specifically hypothesized that effective rTMS treatment of MDD would result in improved cognitive control and decreased Stroop interference effect.

2. Methods

2.1. Subjects

Subjects were 77 clinically-stable outpatients with a primary diagnosis of MDD (Mini International Diagnostic Interview, MINI; (Sheehan et al., 1998) referred for treatment in the TMS Clinical and Research Service at UCLA. The research protocol was approved by the UCLA IRB and all subjects provided informed consent prior to research procedures. Subjects presented with at least moderately severe depressive symptoms based upon a 17-item Hamilton Depression Rating Scale Score (Ham-D_{17}, Hedlund and Vieweg, 1979) $\geq$ 17 and had failed to enter remission after at least 3 adequate antidepressant trials. Subjects were allowed to continue receiving psychotropic medication concurrent with rTMS and underwent standard safety screening and medical clearance before receiving rTMS treatment. All were fluent English speakers and had normal or corrected-to-normal vision.

2.2. Study design

Depressive symptoms were assessed at baseline and weekly during the course of treatment with the 30-item Inventory of Depressive Symptomatology Self Report version (IDS-SR, Trivedi et al., 2004). The Stroop task was administered at the pre-treatment baseline and after treatment 30. on a Dell Inspiron 14″, model 5458 laptop with an attached button box with red, green, and blue buttons for patient response (USB Buttons, https://www.usbbuttons.com/) and using a custom Matlab script similar to the procedures described previously (Minzenberg et al., 2014). Specifically, on each trial, visual color-word stimuli were presented in the center of the visual field for 1 s (as the response window), followed by a fixation crosshair for an average of 1.5 s (randomized equally between 1, 1.5 and 2 s) before the next color-word trial was presented. Colors and words consisted of red, green, and blue, each equally distributed over the total trials and balanced for congruence and incongruence, and presented in a fully-randomized order. Fifty percent of all trials were congruent color-word stimuli (color and word matched), and the remainder incongruent (color and word not matched). Subjects were instructed to press one of the three color-coded buttons corresponding to the color observed of the color-word as fast as they could without mistakes. Prior to each session, subjects completed a 10 trial un-timed practice block to reduce learning confounders on response speed. Each subject completed 5 blocks with a total of 120 trials.

2.3. rTMS procedures

All TMS treatments were performed with either the Magstim Rapid 2 stimulator using a 70 mm coil (Magstim, Whitland, South Wales, UK) or the Neuronetics' Neurostar treatment system (Neuronetics, Malvern, PA, USA). Motor threshold (MT) determination was performed prior to the first treatment, with MT defined as the minimum stimulus intensity necessary to elicit an overt motor response in the right abductor pollicis brevis (APB) or first dorsal interosseus (FDI) muscles for $\geq$ 50% of applied stimuli. Following MT determination, treatments were performed with patients seated in a semi-reclined position using standard safety procedures and ear protection. All patients underwent treatment initially with 10 Hz stimulation to left DLPFC (defined using the Beam F3 method, (Beam et al., 2009). Clinicians adjusted stimulation intensity, coil angle, and number of pulses administered as needed to manage patient comfort, and% MT was increased as tolerated towards a maximum of 120% MT to maximize therapeutic benefit. Patients unable to tolerate 10 Hz stimulation by the fifth treatment session due to anxiety, agitation, or pain, or who had worsening depressive symptoms underwent sequential bilateral treatment (10 Hz at left DLPFC followed by 1 Hz stimulation to right DLPFC, $n = 34$). One-way analysis of variance (ANOVA) did not show any differences between treatment groups in changes in performance accuracy or reaction time. All groups were thus pooled for all further analyses.

2.4. Data analysis

We first computed the percentage accuracy and reaction times for congruent and incongruent conditions. Six patients whose overall performance accuracy was below 50% were excluded from further analysis because it was uncertain whether they correctly understood the Stroop task or were able to maintain adequate vigilance in order to perform. This resulted in a final sample size of $n = 71$. Stroop task reaction times prior to treatment were compared to age matched group norms (40 years old ± 5) (Uttl and Graf, 1997) corresponding to median patient age of 40 years using a T-test. Effects of rTMS treatment on the Stroop performance were assessed with a linear mixed effect model conducted separately for accuracy and reaction time data. To evaluate rTMS treatment specific effects on Stroop performance, we created a dummy variable representing response (a decrease in IDS-SR score $\geq$ 50%, $n = 23$) vs. non-response (a decrease in IDS-SR score $<$ 50%, $n = 48$) to treatment.

The linear mixed effects models included the following terms: intercept, time (pre vs post rTMS), condition (congruent vs. incongruent), clinical outcome (responders vs. non-responders), depression severity prior to treatment (covariate 1), age (covariate 2), as well as the interaction terms time*clinical outcome (testing rTMS specific improvement), time*clinical outcome*condition (testing rTMS specific change in interference effect) and time*clinical outcome*condition*age (testing the interaction of age and rTMS on cognitive control). Linear mixed model analyses were conducted using SPSS v26. Post-hoc tests of main effects of age and depression severity were performed using a

Table 1
Demographics, clinical scores, and medication data. Results show pre vs. post rTMS changes in IDS-SR scores, the corresponding test statistics, as well as the proportions of patients taking five different classes of medication.

	Responders (n = 23)	Non-responders (n = 48)	Test statistic	p-value
Gender (% male)	34.8%	41.7%	Chi^2 = −0.3	n.s.
Age	43.4 (± 16.7)	42.6 (± 14.5)	T-test = −0.2	n.s.
IDS-SR Pre	37.8 (± 10.9)	44.8 (± 10.4)	T-test = −2.6	< 0.05
IDS-SR Post	12.9 (± 6.8)	36.2 (± 11.6)	T-test = −8.9	< 0.001
Antidepressants	60.9%	60.4%	Chi^2 = −0.001	n.s.
Anxiolytics/Sedative hypnotics	26.1%	29.2%	Chi^2 = −0.076	n.s.
Antipsychotics	13%	25%	Chi^2 = −1.826	n.s.
Stimulants	26.1%	23%	Chi^2 = −0.082	n.s.
Anticonvulsant/Mood stabilizers	26.1%	35.4%	Chi^2 = −0.702	n.s.

median-split comparison of the groups (cutoffs: age median = 40 years; depression severity median (IDS-SR = 40). To evaluate the relationship between the change in Stroop performance and clinical improvement, we also calculated the correlation coefficient between percent change in IDS-SR score and accuracy and reaction time, separately for congruent and incongruent conditions.

3. Results

Sample characteristics, rTMS treatment outcomes, and concomitant medication data are presented in Table 1. There were no significant differences in demographic data or medication status between responders and non-responders. Surprisingly, Stroop reaction times were better than the age norm reported by (Uttl and Graf, 1997) (p < 0.000). There was a significant decrease in IDS-SR following treatment, confirming that rTMS reduced depressive symptomatology (T-test, p = 7.858e-9, Fig. 1 and Table 1).

The linear mixed model assessing the effect of rTMS on Stroop performance accuracy revealed a significant main effect of age (p < 0.000) and depression severity (p = 0.044), indicating that less depressed and younger subjects performed overall better than more depressed and older subjects (Fig. 1A and C). However, the overall rTMS-induced change in performance did not differ between these groups (Fig. 1B and D, both T-tests not significant). We also observed a

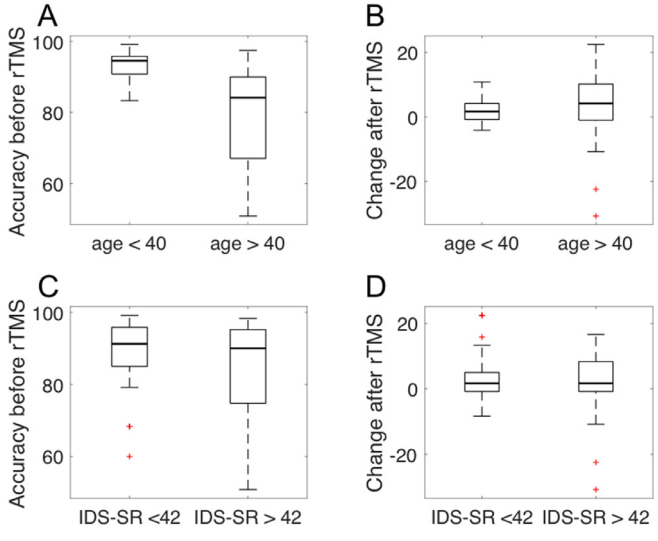

Fig. 1. Effect of age and depression severity on pre- and post-treatment Stroop accuracy scores. A) Younger subjects performed better than older subjects (cutoff at median of 40 years). B) The pre-post rTMS change in Stroop accuracy did not differ between the two age groups (T-test n.s.). C) Less severely depressed patients performed better than more severely depressed individuals (cutoff at median of IDS-SR = 42). D) The pre-post rTMS change in Stroop accuracy did not differ between these two clinical groups (T-test n.s.).

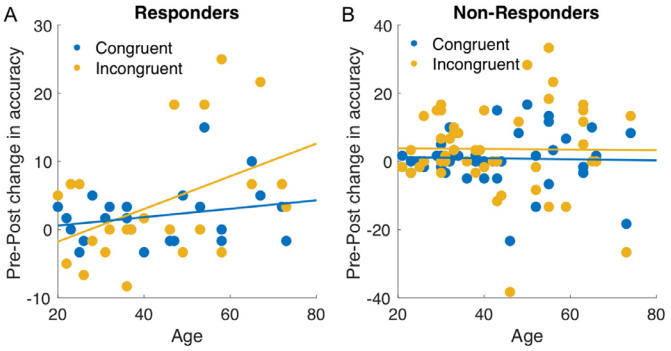

Fig. 2. Change in Stroop accuracy for rTMS responders (A) and non-responders (B). Accuracy improvement occurred selectively in the incongruent condition for the responder group, with strongest benefit in older subjects, as indicated by the significant four-way interaction between time (pre vs. post), condition (congruent vs. incongruent), clinical outcome (responders vs. non-responders) and age (p < 0.001).

significant four-way interaction among clinical outcome, condition, time and age (p < 0.000), suggesting a specific effect of rTMS in the incongruent condition for the rTMS responders, with older subjects benefitting most (Fig. 2). The linear mixed model evaluating changes in reaction times has also shown a significant main effect of age (p < 0.000), in addition to a significant three-way interaction among time, clinical outcome and condition (p = 0.007). The positive association between clinical and reaction time improvement suggests a selective effect of rTMS on the incongruent condition for clinical responders (Fig. 3). The correlation between improvement in Stroop and clinical symptoms has reached trend level only for incongruent reaction time change and percent change in IDS-SR score (r = 0.22, p = 0.07).

4. Discussion

rTMS treatment significantly reduced depressive symptoms in the overall sample of subjects. In addition, clinically successful treatment selectively improved both accuracy and reaction times on the Stroop test in a condition-specific manner, suggesting a decreased interference effect. Notably, improvement in accuracy was strongest for older subjects in the incongruent condition, indicating that older patients may benefit most from rTMS treatment to enhance cognitive control. The effects of rTMS Stroop interference effect in those who responded to rTMS treatment of MDD may indicate decreased psychomotor slowing commonly observed in MDD (Kertzman et al., 2010).

Overall, these findings suggest that rTMS treatment for MDD has a beneficial effect on cognitive inhibition and flexibility (reflected by the decreased interference effect), which is associated with the ability to suppress negative, intrusive thoughts (Ottowitz et al., 2002; Hammar et al., 2010; Paulus, 2015). These results are consistent with previous work successfully using 25 Hz rTMS stimulation for treatment of MDD and the amelioration of cognitive function (Şalçini et al., 2018).

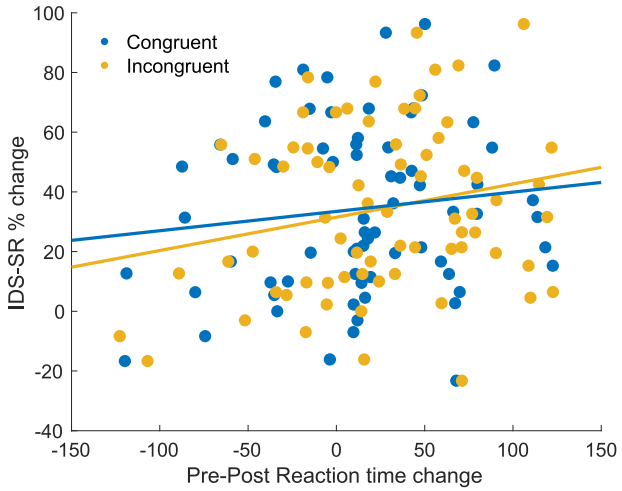

Fig. 3. Change in Stroop reaction times pre and post rTMS. Reaction times improved differentially for responders vs. non-responders, with largest improvement observed in the incongruent condition for subjects with most clinical benefit (three-way interaction between time, clinical outcome and condition $p = 0.01$).

These results also suggest that rTMS may have differential effects on accuracy and reaction times. While the four-way interaction among time, clinical outcome, condition and age was significant for Stroop performance accuracy, reaction times showed a three-way interaction with no effect of age. It is not clear how to interpret this difference. It could indicate that there is a relatively greater age-dependent impairment in accuracy that is ameliorated by rTMS treatment. Conversely, it could indicate that rTMS is less efficacious at ameliorating deficits in reaction time with increasing age. Future studies should further examine the variability of rTMS effects on cognitive function across the lifespan.

It is important to note that the positive effects of rTMS on cognitive control in this sample are moderate compared to the beneficial effects on mood. The association between mood improvement and Stroop performance measures reached only a trend level, suggesting that the effect on cognitive control may be at least in part independent of the effect on mood. The sample size of 77 subjects is relatively large in comparison to other studies, and may explain the previously reported limited benefits of treatment on Stroop performance (Kim et al., 2012; Li et al., 2017; Martin et al., 2017). However, an alternative explanation is that task performance accuracy was within normal limits prior to treatment (Van der Elst et al., 2006) and there may therefore have been a ceiling effect that limited the benefits of treatment on cognitive control.

Previous studies have found that medication treatment for MDD often does not ameliorate cognitive dysfunction even after remission of mood symptoms (Hasselbalch et al., 2011; Shilyansky et al., 2016; Salagre et al., 2017). Certain medications such as citalopram may exacerbate cognitive symptoms (Sneed et al., 2010). rTMS therefore may represent a more promising treatment strategy for those patients suffering from concomitant cognitive dysfunction in MDD. Our finding of modest improvement in cognitive control tasks is consistent with previous studies that found improvement of executive function following rTMS treatment (Moser et al., 2002; Noda et al., 2017, 2017), along with improvement in other domains including verbal memory (Kuroda et al., 2006; Fitzgerald et al., 2009; Wajdik et al., 2014) and attention (Höppner et al., 2003; O'Connor et al., 2005; Naim-Feil et al., 2016).

The beneficial effects of rTMS treatment of cognitive control may be mediated by treatment effects on neural circuits involving the left DLPFC-cingulate cortex, which has been shown to mediate Stroop task performance in healthy subjects and patient populations (MacDonald et al., 2000; Harrison et al., 2005). Other regions commonly involved also include multiple prefrontal and cingulate cortical areas, middle and inferior frontal gyri, parietal cortex, the striatum as well as connectivity among these areas (Bush et al., 1998; Peterson et al., 1999; Leung et al., 2000; Mead et al., 2002; Chen et al., 2011; Pompei et al., 2011, 2013; Ovaysikia et al., 2011; Kikuchi et al., 2012; Coderre and van Heuven, 2013; Wolf et al., 2014; Jahanshahi et al., 2015; Kaiser et al., 2015). Most of these regions are components of the frontoparietal control network (FCN, also referred to as cognitive control or central executive network, or CEN) (Liston et al., 2014). This network has been implicated in executive control and attention, and both activity and the connectivity within this network have been shown to be diminished in patients with MDD relative to healthy controls (Pompei et al., 2011; Liston et al., 2014; Kaiser et al., 2015). While the exact MOA of rTMS treatment for MDD are not yet fully understood, there is accumulating evidence that the stimulation has network-wide effects beyond the stimulation target (Fox et al., 2012; To et al., 2018) which may lead to "resetting" network function (Leuchter et al., 2015). It is possible that improvement in executive function is driven by the change in FCN function directly, or the interaction of this network with others (such as the default mode network) via the DLPFC. The use of a combined TMS-EEG approach in future studies will help exploring the mechanisms through which differential changes in reaction time between congruent and incongruent conditions are induced, and how this reduction differs between treatment responders and non-responders.

The results of this study should be interpreted in the context of a number of limitations. First, because the subjects were patients treated in a clinical context, treatment parameters were not randomly assigned. Although we did not detect differences in treatment laterality in the different outcome groups, it is possible that some other uncontrolled parameter may have contributed to the results reported here. Second, depressive symptoms were assessed with a self-administered questionnaire rather than an observer rating scale, which may influence these findings. The IDS-SR is a well-validated and established scale which was used as the primary outcome measure in the STAR*D trial, one of the largest clinical trials conducted on depression including over 4000 patients (Trivedi et al., 2006). Third, we did not examine the effects of stimulation intensity, which has been shown to affect rTMS effects on Stroop performance (Levkovitz et al., 2009), or whether fewer than 30 sessions of rTMS might have beneficial effects on cognitive control processes. Previous work suggests that even a single rTMS session may alter Stroop performance (Vanderhasselt et al., 2009). Future studies should examine which of these factors or several other rTMS treatment strategies (i.e., 10 Hz left, sequential bilateral, intermittent theta burst stimulation, 25 Hz) might be most beneficial for ameliorating cognitive control deficits (Brunoni et al., 2016; Mutz et al., 2019). Fourth, we did not examine other cognitive domains in these subjects and it is possible that they had other deficits that could have affected these results. Future studies should assess a complete battery of cognitive tests in a single patient sample pre- and post-rTMS treatment, similar to previous studies of medication treatment effects on cognition (Shilyansky et al., 2016). Lastly, the great majority of subjects received concomitant pharmacological treatment. Because certain drugs can have positive or negative effects on cognitive control and/or psychomotor function (Culang et al., 2009; Mendhe et al., 2017) and interact with rTMS (Breden Crouse, 2014; Hunter et al., 2019), medication effects may have contributed to some of the findings presented here.

In conclusion, we have shown that 10 Hz rTMS treatment for MDD has beneficial effects on cognitive control functions as indicated by reduced Stroop interference effects. These findings suggest that rTMS may be more beneficial than medication treatment to target both clinical *and* cognitive symptoms of MDD. Future studies should more systematically study the effect of rTMS on other cognitive domains, and elucidate the neurophysiological MOA of rTMS on cognitive function using combined rTMS and neuroimaging approaches (Wagner et al.,

2006; Li et al., 2017).

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CRediT authorship contribution statement

Juliana Corlier: Formal analysis, Writing - original draft. **Elizabeth Burnette:** Formal analysis, Writing - original draft. **Andrew C. Wilson:** Formal analysis, Data curation. **Jerry J. Lou:** Conceptualization, Data curation. **Adrian Landeros:** Writing - original draft. **Michael J. Minzenberg:** Conceptualization, Data curation. **Andrew F. Leuchter:** Conceptualization, Writing - original draft.

Declaration of Competing Interest

Dr. Corlier, Dr. Minzenberg, Ms Burnette, Mr. Lou and Mr. Landeros have no disclosures.

Mr. 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 stock options in NeoSync, Inc. and has equity interest in BBA.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.01.068.

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