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Targeting Cognitive Control Deficits With Neuroplasticity-Based Computerized Cognitive Remediation in Patients With Geriatric Major Depression: A Randomized, Double-Blind, Controlled Trial

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ABSTRACT

Late life major depression (LLD) is often accompanied by cognitive deficits. When patients have specific deficits in cognitive control functions (CCD), they are not only distressing and debilitating, they often predict poor clinical outcomes such as reduced response to SSRI/SNRI antidepressants, increased disability, suicide and all-cause mortality. We recently reported that in an open label trial, our treatment designed to target these specific CCD with neuroplasticity-based computerized cognitive remediation (nCCR) improved depression and CCD in patients who failed to remit with conventional antidepressant treatment. This study tested the hypothesis that in patients with LLD who have failed at least one trial of an SSRI/SNRI antidepressant at an adequate dose for

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Question: Does neuroplasticity-based computerized cognitive remediation (nCCR) targeting cognitive control deficits (CCD) improve clinically relevant CCD and depression more than an active control group?

Findings: In this randomized, controlled, double-blind trial that included 36 late-life depressed, treatment refractory participants, nCCR improved depression, disability and CCD more than the active control.

Meaning: Unlike any treatment currently available, targeting CCD with nCCR in late-life depressed patients (who have failed to achieve remission with antidepressants) improves depression and CCD more than an active control.

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at least 8 weeks, nCCR will improve both depressive symptoms and the CCD associated with poor antidepressant response (i.e. semantic strategy, inhibition of prepotent responses) more than an active control group. Participants were randomized (1:1) to receive either 30 hours/ 4 weeks of neuroplasticity based computerized cognitive remediation (nCCR) designed to target CCD, or the active control condition matched for duration, engagement, reward, computer presentation, and contact with study staff. All participants and raters were blinded. Mixed effects model analysis the time effect (week) ($F(1,71.22)=25.2$, $p<0.0001$) and treatment group X time interaction ($F(1,61.8)=11.37$, $p=.002$) reached significance indicating that the slope of decline in MADRS was steeper in the nCCR-GD group. Further, the nCCR group improved their semantic clustering strategy($t(28)=9.5$; $p=.006$), as well as performance on the Stroop interference condition, and cognitive flexibility (Trails B). Further, results transferred to memory performance, which was not a function trained by nCCR. clinicaltrials.gov. (Am J Geriatr Psychiatry 2020; ■■:■■−■■)

INTRODUCTION

There is currently no efficacious treatment for late-life depression addressing both mood and the cognitive deficits frequently associated with this disorder. Despite modest remission rates, the gold standard treatment for late life depression is SSRI/SNRI antidepressants. For a large portion (roughly 40%)[1] of elderly patients with concomitant cognitive deficits (namely deficits in cognitive control or CCD)[2] the chance of remission is half that of patients without cognitive deficits.[3–5] Even when CCD patients do respond, their cognitive control deficits only show modest improvement, leaving them perpetually at increased risk for poor clinical outcomes.[2,4–10] Psychosocial treatments designed to teach CCD patients to circumvent their deficits that is problem solving therapy (PST) also have limitations including: 1) Modest remission rates; 2) Complicated protocols that require a high skill level, and are difficult for community clinicians to master and maintain[11]; and 3) No direct improvement in CCD.[12] CCD are discrete, measurable behaviors indicative of dysfunction in the cognitive control network; a network preferentially damaged by aging.[13] The specificity, replicability, and clinical significance of these deficits motivated our group to attempt to target and improve CCD, and by inference the functioning of the CCN, with the goal of improved treatment outcomes for a group without options. We chose to focus our efforts on developing an attention demanding cognitive training regimen with dynamic difficulty adjustment designed to layered cognitive control functions with attention demanding, immediately rewarding, individually adaptive exercises delivered via computer.[14] We titled it: neuroplasticity-based computerized cognitive remediation (nCCR) first, to underscore our working model of the intervention which assumes that measurable behavior and/or clinical change would be mediated via neuroplasticity in the targeted neural network; and second, to reflect selected key design parameters we translated from basic animal models on features most likely to induce plasticity within an aging brain.[14–16]

NIMH priorities include developing interventions informed by cognitive and affective neuroscience (strategy 3.1) that can be disseminated to the community (strategy 3.3). Our nCCR meets both criteria in that it assumes that CCD play an important role in treatment response, and thus, improving the CCD (and by inference the underlying cognitive control network) it may be possible to influence treatment response. Our nonrandomized preliminary pilot study suggested that in these patients, nCCR reduced depression, with a response rate 81% of and a remission rate of 72% after 4 weeks of treatment.[17] Unlike both SSRI antidepressant treatments, and psychosocial treatments designed for CCD patients, nCCR improved both targeted (semantic strategy; inhibition of prepotent responses) and nontargeted cognitive control functions (Trails B) (so-called near transfer phenomenon). Further, patients with pronounced cognitive control deficits had the most robust

response to nCCR suggesting a "match" between patients and treatment intended to target their disease phenotype.[18]

Encouraged by our results we completed a pilot randomized controlled, double-blind trial of nCCR against an active control condition matched for duration, engagement, reward, computer presentation, and contact with study staff. The latter condition was designed to be educational, rewarding and generally stimulating, but was not designed to target CCD functions. This study tested the hypothesis that in patients who have failed at least one trial of an antidepressant at an adequate dose for at least 8 weeks, nCCR will improve both depressive symptoms and the cognitive control functions that have been associated with poor antidepressant treatment response (i.e., semantic strategy) more than an active control group. We based these hypotheses on the assumption that resistance to antidepressants is contributed by abnormal CCN function clinically expressed as cognitive control dysfunction, as well as mounting evidence suggesting that positive plasticity in aging prefrontal cortical areas can be harnessed with specific parameters designed for cognitive enhancement.[19,20]

METHODS

Participants

Participants were older adults (60−89) with major depression (by SCID-R/DSM-IV), who failed to achieve remission (Montgomery-Asberg Depression Rating Scale, MADRS >15) after treatment with therapeutic dosages of an SSRI or SNRI antidepressant for at least 8 weeks. In addition, we asked that they and/or their physicians had no plan to change medication or dosages for the duration of the study (4 weeks) unless required by significant worsening of clinical symptoms.

The Weill Cornell Medical College Institutional Review Board approved all procedures. After a complete description of the study to subjects, written informed consent was obtained.

Thirty six of 42 patients who met criteria and were approached signed the informed consent and entered the study (mean age = 73.5 years; SD = 7.8). Participants were randomized (1:1) to receive either nCCR or the active control condition. All participants were blinded to their treatment assignment. The sample was 63.6% female, 36.4% male. Of the 36 patients, 30 completed the 4-week trial. Three patients were removed by the investigators due to exclusionary psychiatric diagnoses, two patients were removed due to diagnosis of exclusionary medical conditions during the trial; one patient dropped at week 2 due to an inability to maintain the required frequency of clinic visits. All participants were questioned weekly about any changes to their medications; all maintained the same medication and dosage throughout the treatment period. Participants underwent a neuropsychological battery at baseline, and after 4 weeks of treatment.

All participants met DSM-IV-TR criteria and Research Diagnostic Criteria for unipolar major depression and had a MADRS score greater than 15. Exclusion criteria were 1) major depression with psychotic features (according to DSM-IV-TR); 2) history of other psychiatric disorders (except personality disorders) before the onset of depression; 3) severe medical illness (i.e., metastatic cancer, brain tumors, unstable cardiac, hepatic, or renal disease, myocardial infarction, or stroke) within the 3 months preceding the study; 4) neurological disorders (i.e., dementia or delirium according to DSM-IV criteria, history of head trauma, Parkinson's disease, and multiple sclerosis); 5) conditions often associated with depression (i.e., endocrinopathies other than diabetes, lymphoma, and pancreatic cancer); 6) drugs causing depression (i.e., steroids, α-methyl-dopa, clonidine, reserpine, tamoxifen, and cimetidine); and 7) Mini-Mental State Examination[21] score less than 25 or Mattis dementia rating scale scores below 130; 8) Amnestic or Multiple-Domain MCI; 9) Current psychotherapy; and 10) Inability to speak English (nCCR games are in English only); corrected visual acuity <20/70 or color blindness. These criteria resulted in a group of elderly patients with nonpsychotic unipolar major depression without a diagnosable dementing disorder.

Participants in both conditions completed 30 hours of cognitive remediation over 4 weeks on computer stations in private treatment rooms at the Institute of Geriatric Psychiatry. The brief 4-week time period was chosen to mitigate several factors: The selected participants were treatment resistant and quite symptomatic; nCCR's efficacy has yet to be determined, and participants were continuing to take a dose of medication that was ineffective.

Participants had access to the supervising psychologist (blinded) and research assistants for questions at any time, but after the initial program set up, participants worked on their own without intervention. Participants were allowed up to one additional week (>5 weeks) to reach the 30-hour dose, and accommodate schedule changes due to: Inclimate weather, fatigue, illness or other conflicts. All participants remained under the care of their treating/prescribing psychiatrist. In all cases, psychiatrists were informed of the added intervention and encouraged to coordinate treatment planning with Institute faculty.

nCCR

Three "Bottom Up" training exercises were used: one low level auditory tone sweep, one phonemic discrimination task, and one low level visual discrimination training exercise from "Brain HQ."[19,22] These programs were designed for older adults to enhance basic processing of sensory stimuli with the goal to improve fidelity of initial auditory and visual encoding.[19,22,23] Our goal was to improve speed of initial auditory and visual processing to facilitate cognitive control training.

"Top Down" training exercises were newly developed by our group and incorporated into two user interfaces. The first is "Catch the Ball": (Individually titrated training in visual attention, inhibition of prepotent responses, working memory, cognitive flexibility and dual task performance.): Participants view moving balls on a blue screen and are instructed to press the button when the ball turns to a target color. Balls change from yellow to the target or foil color (blue, red, green) at random intervals (1.5−3.5 seconds). Initial difficulty levels focus on sustained attention, balls simply turn to the target color of red, with the duration of the target color progressively decreased to increase difficulty. Next levels introduce blue foils to require discriminatory attention and response inhibition. Next, response inhibition demands are increased and cognitive flexibility introduced by having the target switch back and forth between red and blue at random intervals. All variations are then repeated first with two balls on the screen and then with three to increase overall demand, and add divided attention demands. Speed at which the balls move is adaptively tracked. Subjects are moved from one difficulty level to the next when they demonstrate sustained accuracy at the fastest ball speed or when they fail to show continued performance at a slower speed. The second program is "Semantic Strategy": This interface was designed based on our previous work suggesting that semantic strategy is associated with treatment remission with SSRI.[4,5] Participants are asked to rearrange multiple, increasingly complex word lists into categories with individually titrated decreases in allotted processing time. Task demands increase further by including components of "cognitive control"; using previous sort stimuli as proactive interference. Both speed and accuracy are adaptively tracked.

Training task parameters were set to keep performance between 75% and 85% correct; a balance between challenge and reward that in animal studies seems optimal for producing neuroplastic change.[14,24] As this was the first trial (to our knowledge) of this kind, there were no guiding treatment schedules or dosages suggested by the literature. Based on our initial open label trial, our recommended schedule to participants was every other day for 2−3 hours each session, however, participants were encouraged to select the duration of sessions and a weekly schedule most desirable to them.[25] nCCR programs give immediate, multisensory rewards for correct responses,[26] and employ dynamic difficulty adjustment in order to minimize frustration from incorrect responses[19] as well as keep performance levels in the desired range.

Active Control Condition

The active control condition was designed to match nCCR in audio-visual presentation, length, contact with study staff, and to engage participants' attention, and learning, but not to target cognitive control functions specifically. We designed a learning-based approach utilizing hour-long documentary series on arts, culture, nature, philosophy, physics, history, geology, sociology, anthropology and architecture. Participants chose their courses of study with random intervals of increasingly difficult questions to track attention and engagement, maintaining their performance to 75%−80% correct. Correct responses were rewarded with immediate, multisensory feedback matching nCCR.

Outcome Measures

Institute of Geriatric Psychiatry research assistants blinded to treatment condition, and unaware of the study's hypotheses collected clinical ratings, neuropsychological tests and self-report measures under the supervision of a neuropsychologist (SSM). A second research assistant was available to assist with troubleshooting, and participant questions during treatment sessions.

Depressive symptoms were assessed using the 10-item MADRS. Disability was measured with the World Health Organization Disability Assessment Schedule-II (WHODAS-II).[27] Neuropsychological measures: Baseline gross cognitive status was rated with the Mini-Mental State Examination.[21] Overall cognitive dysfunction was assessed with the Mattis dementia rating scale. Executive functioning was assessed with measures: *Inhibiting prepotent responses* with the Stroop Color-Word Test,[28] and *cognitive flexibility* with Trail Making Test B;[29] nonverbal cognitive flexibility with design fluency switching from the Delis Kaplan Executive Functioning System (D-KEFS); *working memory* was assessed with digit span backwards from the WAIS IV;[30] *semantic clustering* index of the CVLT-ii,[31] *verbal memory* with the CVLT-ii long delay recall; verbal fluency was assessed with the Controlled Oral Word Association Test (COWAT).[32] Alternate forms, where available, were used during the follow-up administrations.

Statistical Analysis

Baseline demographic and clinical characteristics of the two treatment groups were compared using independent sample *t* tests (Tables 1 and 2). Efficacy (MADRS score over time) of treatment groups was compared with longitudinal mixed models analysis with a random intercept and time (weeks from baseline), treatment group, and a time by treatment group interaction as fixed effects. As nCCR was designed to improve cognitive control functions, we compared the change in test scores reflecting cognitive control (Trails B, Stroop CW) over time (baseline, end of study) between the two treatment groups using change scores with paired t tests.

We also compared change in self-report measures of functional disability (WHODAS) over time by group using paired t tests.

RESULTS

The average reduction in MADRS scores over 4 weeks in participants randomized to receive nCCR was 12.1 points (SD = 7.7), the average reduction in participants randomized to receive the control condition was 6.6 (SD = 8.0). Of the 18 participants receiving nCCR, 58% reached remission (defined as MADRS <10); and 58% responded (>50% reduction in MADRS). In the control condition 8% reached remission, and 16% responded. Mixed effects model analysis showed no significant group main effect ($F(1,.278) = 0.019$, $p = 0.60$). However, the time effect (week) ($F(1,71.22) = 25.2$, $p < 0.0001$) and treatment group X time interaction ($F(1,61.8) = 11.37$, $p = 0.002$) reached significance indicating that the slope of MADRS decline was steeper in the nCCR-GD group (Fig. 1).

A paired t test comparing change in semantic clustering standard scores over time (4 weeks) by group (nCCR vs. control) reached statistical significance suggesting that the nCCR group improved their semantic clustering strategy to a greater extent than the control group over the 4-week trial ($t(26) = 3.12$; $p = 0.006$)

Five more paired t tests were completed to compare change in other related, but not specifically targeted cognitive control functions. Results indicated that there was a statistically significant difference, with greater effects in the nCCR group than in the control group on measures of: Inhibiting prepotent responses (Stroop Color Word $t(26)$ −2.97; $p = 0.007$); Cognitive flexibility (Trails B: $t(28)$ 2.2; $p = 0.04$), verbal fluency (FAS: $t(28)$ 2.27; $p = 0.03$); and working memory (Digits backward from the WAIS-IV: t (24) 2.59; $p = 0.03$). There was no difference pre- post-treatment between groups on nonverbal fluency including cognitive flexibility and inhibition (design fluency switching $t(28)$ 1.16; $p = 0.26$). Taken together, these findings indicate that participants in nCCR improved on tests of related, but not directly targeted cognitive control functions more than the active control group.

We completed a paired t test to compare change in long-term memory between the nCCR and control groups over time. Our hypothesis was that improvement in cognitive control functions would transfer to improved memory scores, though the data from our

TABLE 1. Baseline Participant Characteristics

	nCCR	Control	*t* (28)	Significance
Baseline MADRS	25.7 (8.8)	25.3 (8.2)	0.032	0.975
MMSE	28.8 (.9)	28.8 (1.4)	0.238	0.424
Age	74.7 (7.6)	72.2 (9.9)	0.760	0.454
Education	15.8 (3.1)	17.0 (1.8)	−1.096	0.283
Mattis dementia rating	139.2 (5.1)	138.0(4.8)	0.619	0.542
Disability	23.9 (9.5)	27.0 (9.0)	−0.834	0.413

Note: Baseline characteristics for 30 treatment-resistant depressed older adults randomized to receive nCCR or an expectancy matched control.

TABLE 2. Baseline and After 4 Weeks of Treatment in Treatment Resistant Depressed Participants Randomized to Receive 4 Weeks of nCCR Versus Comparison Control

	Baseline	Week 4	Statistic	p Value	D
MADRS			$F(1,61.8) = 11.37$	0.002*	−0.64
nCCR	25.7 (8.9)	13.2 (5.9)			
Control	25.6 (8.2)	18.9(8.0)			
WHODAS			$t(28)2.98$	0.006*	−1.17
nCCR	23.87 (9.4)	18.8 (5.4)			
Control	25.9 (9.0)	27.3(8.1)			
Stroop CW			$t(26)$ −2.97	0.007*	−1.21
nCCR	34.4 (9.3)	36.4 (8.7)			
Control	33.4 (9.4)	34.0 (9.5)			
Trails B			$t(28)$ 2.2	0.04*	−0.86
nCCR	157.6 (101.2)	140.9 (102.4)			
Control	150.6 (96.2)	158.0 (80.2)			
Digit span			$t(26)$ 2.56	0.02*	−1.08
nCCR	6.1 (2.2)	7.0 (2.4)			
Control	6.9 (2.2)	6.9 (1.7)			
Semantic Clus. (StandardScore)	**SS**	**SS**	$t(26) = -3.12$	0.006*	1.39
nCCR	0.56 (1.7)	0.96(1.5)			
Control	0.2(0.9)	−1.0 (.85)			
Verbal memory			$t(24) = 2.84$	0.03*	−0.97
nCCR	8.1 (3.8)	9.6 (4.9)			
Control	7.8 (4.5)	6.6 (3.8)			
Design fluency switch			$t(28) = 1.16$	0.26	**
nCCR	8.1 (3.8)	9.6 (4.9)			
Control	7.8 (4.5)	6.6 (3.8)			
FAS			$t(28) = 2.27$	0.03*	−0.99
nCCR	8.1 (3.8)	9.6 (4.9)			
Control	7.8 (4.5)	6.6 (3.8)			

*$p < .05$.

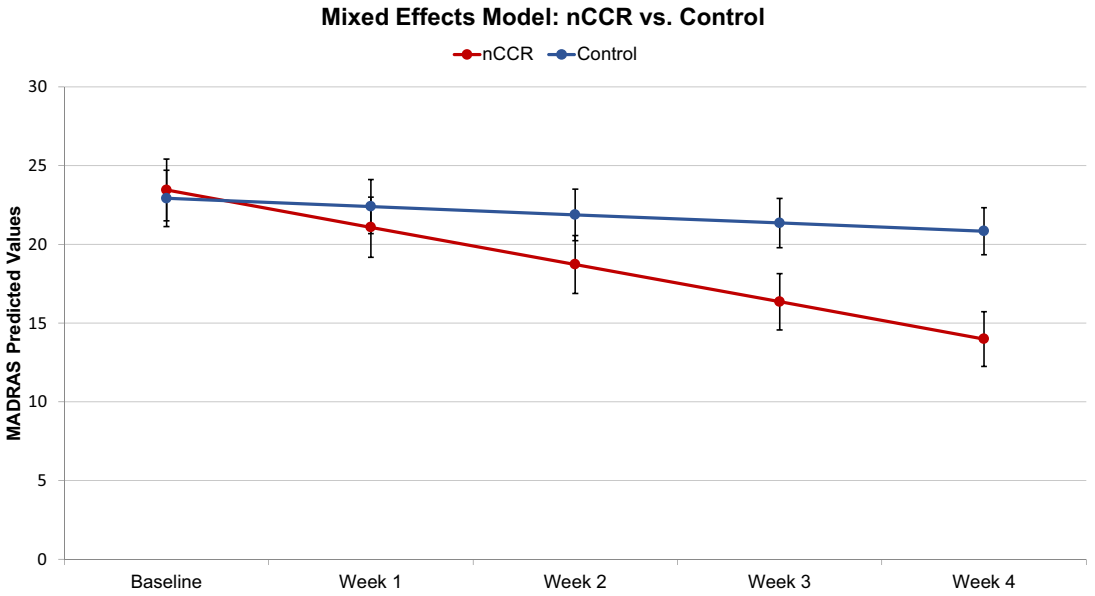
previous preliminary trial did not show transfer to memory improvement. There was a statistically significant difference between the two groups over 4 weeks of treatment ($t(28) = 2.84$; $p = 0.03$) on the Long Delay portion of the CVLT ii, which suggests that improvements transferred to a more distal function that relies on in-tact cognitive control circuitry; e.g., Memory.

Last, we examined change in functional disability between the nCCR and control groups over time using the WHODAS-II. Our hypothesis was that given the relationship of CCD and persistent disability, improving cognitive control may improve functional capacity reflected in a self-report measure. There was a statistically significant difference in the change in WHODAS: $t(28)2.98$;$p = 0.006$ over 4 weeks favoring the nCCR group. Further, nCCR reduced disability 4.7 points, which is equivalent to the reduction in WHODAS induced after 12 weeks of PST in elderly depressed patients with CCD.[33]

DISCUSSION

The principal finding of this study is that in late-life depressed patients who had failed to remit after

FIGURE 1. Mixed models predicted values. Efficacy (MADRS score over time) of treatment groups was compared with longitudinal mixed models analysis with a random intercept and time (weeks from baseline), treatment group, and a time by treatment group interaction as fixed effects.



adequate treatment with an antidepressant, nCCR improved both depressive symptoms and cognitive control deficits more than an active control condition. Targeting CCD with nCCR, induced remission in an additional 58% of participants, versus 8% in the control condition. Further, nCCR not only appeared to induce improvements in targeted cognitive control functions, but effects transferred to both nontarget cognitive control functions that rely on the CCN (near transfer), and to memory (far transfer). In addition, in this group we saw an advantage of nCCR treatment versus the control in the reduction of reported disability over the 4-week treatment trial similar to those seen in patients treated with 12-weeks of PST.

This study replicates and extends the findings of our preliminary, open-label pilot trial of nCCR which was the first study, to our knowledge, to document that nCCR targeting cognitive control and related network functions can improve both mood and cognitive control functions in treatment-resistant, late-life depression.[34] In addition to the reduction in depression scores, the nCCR participants' scores improved on measures of cognitive flexibility (Trails B), inhibiting prepotent responses (Stroop Color-Word); verbal fluency (COWAT); and working memory (CVLT-Long delay recall) over the treatment trial more than the control group. These functions are purported to be subserved by cognitive control network (e.g., medial prefrontal and dorsolateral prefrontal cortex). This finding, if replicated, is of particular clinical significance as late-life depression with CCD is less likely to respond to conventional SSRI/SNRI antidepressant treatment. In addition, even if the depressive syndrome subsides, antidepressants are unlikely to improve CCD leaving patients perpetually vulnerable to disability and relapse.[8,9,35] These findings suggest that improved CCD, through nCCR, may increase both the number of late-life depressed patients who are able to reach remission, as well as the number who are able to sustain prolonged remission.

A potential interpretation of our findings is that nCCR reduces depression by remediating deficits in cognitive control functioning. A behavioral interpretation of these data may be that nCCR-driven cognitive control benefits may promote selection of effortful actions over habitual ones for the sake of more optimal long-term outcomes (e.g., enhanced cognitive control may promote the conscious reframing of unrealistic negative thoughts, despite

the automaticity of these thoughts). A potential neurobiological interpretation of these data is that increased activation, and plastic changes, induced by nCCR, may modify CCN function, and thus improve a network abnormality contributing to poor response to antidepressants. These hypotheses open up avenues for future research, including mediation analyses and neuroimaging studies to determine the specific brain regions implicated in these findings, and provide direct impetus to develop and test combination therapies for this vulnerable population.

There are several important limitations that have variable impacts on generalizability of our results. We, therefore, encourage an appropriately tempered interpretation of these findings. The first, and perhaps most important is the study's small sample size. Given the small number of participants in this trial, we can only speculate as to how this intervention would generalize to a larger sample of treatment resistant patients. It should be noted, in addition, that all patients remained on a stable dose of antidepressant medication, and thus it remains unknown whether patients who are not currently taking antidepressants would experience similar benefits. Second, assessing neuropsychological performance before and after treatment required that some measures be repeated, and it is possible that the difference in scores may be partially explained by a practice effect. However, it is unlikely that there would be a larger effect in one randomized group versus the other. Last, there has been discussion in the literature about the best intervention control for nCCR. It has been argued that an active control group must be expectancy-matched and/or differ on one or very few parameters or elements; that is, the "active" ingredients. Though this is a logical argument, we specifically chose NOT to include an intervention that only differed in one key area. We made this decision based on two main objectives: First, challenging participants to solve problems requires engagement of cognitive control functions. It would be nearly impossible to remove all set shifting, strategy generation, etc. We argue that testing this type of game as a control for nCCR is analogous to testing for a threshold, or optimal dose of cognitive control training to induce desired change. That is, if an intervention with less, but not NO cognitive control functional training does not improve targeted functions, it informs us of the AMOUNT of training needed to change the functioning of a target circuit. Second, we attempted to establish the efficacy of a new treatment with this pilot randomized trial. Given that the expected enrollment would be small, we strategically chose a more disparate analog to maximize the chances we would find a difference between groups, without sacrificing scientific merit.

Future Directions: This is a preliminary study conducted to test the feasibility and preliminary efficacy of a nCCR in an elderly treatment resistant depressed population. Future iterations of this investigation must include larger samples. A larger sample will allow for further investigation of the targeted neural circuits in the pathogenesis of geriatric depression as well as their relationship to treatment response by answering (for example): If changes in executive function induced by nCCR are related to changes in depressive symptoms?; If executive dysfunction at baseline is a moderator of treatment response?; If targeting other circuitry achieves similar results or if this result is only achieved with specificity in target selection? nCCR was designed to be mutable as well as to give incremental feedback to investigators about whether programs are performing as designed. This design allows for a data intensive analysis of which parameters are necessary, and sufficient to induce desired change. Further, as cognitive and affective neuroscience progresses, nCCR designs can progress in parallel, with new discoveries serving as targets for newly developed nCCR protocols using similar design parameters.

It will also be important to determine whether nCCR can be a stand-alone intervention for late-life depression, or if it is best suited as an augmentation strategy to existing treatments (such as we report in this study) with ongoing pharmacotherapy. The possibility exists that nCCR could also catalyze treatment with a behavioral treatment for cognitive control dysfunction such as PST by enhancing cognitive control functions whereby facilitating learning within therapy sessions, and accelerating adaptation of skill to the patient's environment.

Though both mood and cognitive findings from the preliminary pilot were replicated, participants randomized to nCCR in this trial did not achieve the same level of mood improvement. Though both studies are underpowered to detect meaningful differences in effect size, this difference could be attributable

to several factors. First, there is evidence that open trials have a greater effect on depressive symptoms than RCTs. Second, it has been well documented in other populations (such as schizophrenia), that nCCR improvement is directly related to motivation and engagement in treatment.[36,37] These populations, similarly to geriatric depressed patients, suffer from anhedonia and apathy. In the initial unblinded study, the P.I. answered participant questions, explained the neurobiological theory to the patients, and worked briefly with participants who were frustrated or amotivated, which may have enhanced their expectations and their engagement in the treatment thus improving depression scores through nonspecific mechanisms. We intend to operationalize, and investigate motivational enhancements in the administration of nCCR in future iterations of this intervention.

Pre-nCCR neuroimaging studies can help us to identify circuitry predictors of response to nCCR that can be used for the following purposes: 1) To help us to optimize the design of future nCCR iterations; 2) To inform the design of a battery of performance-based measures that can use used in clinical settings to select optimal candidates for nCCR. Further, pre-post neuroimaging studies may facilitate more direct testing of the engagement of cognitive control circuitry in response to nCCR and will allow us to explore the influence that nCCR may have on other networks (e.g., default mode network) disrupted among individuals with geriatric depression[38] and can be modulated indirectly by improving functioning of the cognitive control network.[39]

In conclusion, though the data remain preliminary, nCCR-GD appears to improve affective symptoms more than an active control condition (presented in the same modality) in patients who have previously failed to respond to pharmacotherapy. In addition, nCCR-GD may improve both targeted and nontargeted CCD while pharmacotherapy does not.

AUTHOR CONTRIBUTIONS

SSM: I am conceived of and designed the intervention. I was the PI of the trial and clinically responsible for all participants. I ran the analyses and interpreted the findings. I wrote the majority of the manuscript.

RAA: Chief Engineer of nCCR, led program-generated data analysis, data driven upgrades to programs, technical solutions offered to the clinical team in real time. Led design of user interface, and reward deployment. Designed and built back end HIPAA compliant data transfer and storage. Drafted portions of the manuscript.

FMG: A consultant on the original design of the clinical trial, specifically consulted on measures, and evaluation of preliminary efficacy, provided scientific guidance throughout the trial, as well as analysis of results. Consultant on K23 for Dr. Morimoto (KMH095830). Drafted portions of and reviewed manuscript.

JCL: Built the original "catch the ball" game, worked with the first author in initial alpha testing of the game with elderly depressed participants, as well as redesign of parameters where necessary. Aided in design of back-end data capture for analysis.

WH: Under the instruction of the first author, engineered "word game," worked on alpha and beta testing with the game, and administered the intervention to participants, as well as tests and measures used in analysis.

SEC: Administered the intervention to participants, performed evaluations of potential participants, provided trouble shooting support while participants engaged with the intervention, aided in the design of behavioral portions of the intervention, drafted the manual, edited this paper.

JN: Administered the intervention to participants, as well as neuropsychological tests and mood measures. Drafted the manual with the SEC and the first author.

GSA: Primary mentor to Dr. Morimoto on K MH095830, provided scientific guidance in the design of the intervention, the clinical trial, the interpretation of results, and the writing of the manuscript.

DISCLOSURE

Conflicts of Interest: SSM: Received grants from NIMH; RAA: Received grants from NIH; FMG: Received grants from NIMH; JCL, WH, SEC, JN: Declare that they have no conflict of interest; GSA: Served on Advisory Board of Eisai and of Janssen Pharmaceuticals. He also served on the Speakers Bureaus of Allergan, Otsuka, and Takeda-Lundbeck. Received grants from NIMH.

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