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Domain-Specific Impairment in Cognitive Control among Remitted Youth with a History of Major Depression

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Abstract

Aim—Impairment in neuropsychological functioning is common in major depressive disorder (MDD), but it is not clear to what degree these deficits are related to risk (e.g., trait), scar, burden, or state effects of MDD. The objective of this study was to use neuropsychological measures, with factor scores in verbal fluency, processing speed, attention, set-shifting, and cognitive control in a unique population of young, remitted, un-medicated, early course individuals with a history of MDD in hopes of identifying putative trait markers of MDD.

Methods—Youth age**d** 18-23 in remission from MDD (rMDD; n = 62) and healthy controls (HC; n = 43) were assessed with neuropsychological tests at two time points. These were from four domains of executive functioning, consistent with previous literature as impaired in MDD; verbal fluency and processing speed, conceptual reasoning and set-shifting, processing speed with interference resolution, and cognitive control.

Results—rMDD youth performed comparably to healthy controls on verbal fluency and processing speed, processing speed with interference resolution, **and conceptual reasoning and set-shifting,** reliably over time. Individuals with rMDD demonstrated relative decrements in cognitive control at Time 1, with greater stability than HC participants.

Conclusion—MDD may be characterized by regulatory difficulties that do not pertain specifically to active mood state or fluctuations in symptoms. Deficient cognitive control may represent a trait vulnerability or early course scar of MDD that may prove a viable target for secondary prevention or early remediation

Introduction

Major depressive disorder (MDD) is a chronic and disabling disorder associated with significant impairment in functioning and high rates of relapse. Cognitive dysfunction is one illness feature particularly important for understanding course and impairment in MDD, as it

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has been linked to increased susceptibility to relapse, poor occupational functioning, and reduced quality of life[1-3]. Active state MDD has been consistently associated with a wide range of cognitive deficits, including attention[4-11], processing speed[9-13], visuospatial abilities[4, 11, 14], memory[4, 8, 9, 15, 16], and executive dysfunction[4, 10, 17-19]. Importantly, performance in several of these neuropsychological domains may be linked to symptom severity[20] and diminished treatment response[18, 21-25]. Despite broad understanding that cognition is reduced during depression, there is still a lack of consensus regarding the specificity of these deficits.

Several other illness features likely contribute to the lack of specificity, or variability in cognitive functioning among depressed individuals[26]; features that many previous MDD studies of cognition in the active state have failed to measure. For instance, in most studies, patient populations are heterogeneous with respect to number or duration of MDD episodes, severity of MDD episodes or current symptoms, age of illness onset, length of illness, current age, treatment and medication status, psychiatric co-morbidity, and even primary diagnosis[27]. Relatively few studies of neuropsychological functioning exist among early course samples of adolescents or young adults[28]. Furthermore, most studies of neuropsychological performance in MDD are small, cross-sectional studies that have compared cognitive abilities in symptomatic patients with those of matched controls[27] offering limited power to consider many of these MDD features outlined above. A recent meta-analysis of 113 studies that revealed significantly impaired performance in MDD across several domains of executive functioning, also examined the role of potential moderating variables such as symptom severity/remission status, age, medication, and psychiatric co-morbidities[29]. Some of these variables were related to the degree of impairment in domains of cognitive functioning (e.g. processing speed, verbal fluency, verbal memory, shifting, inhibition), however the analysis was underpowered to fully dissociate these effects in other domains (e.g. visual working memory, planning, updating).

One strategy to avoid past challenges regarding participant heterogeneity is to study a more homogeneous set of individuals within a more restricted window of MDD characteristics. To optimize understanding of trait features of MDD, it may be advantageous to study those with MDD with few episodes, currently in remission, at a point of both developmental and mood stability. This is a point in the illness when cognitive systems are unlikely to demonstrate changes associated with increasing illness burden or state effects[30]. To understand the methodological advantages of studying cognition in this epoch of MDD, it is helpful to divide illness factors affecting cognition in depression into four broad categories: (1) risk/trait (2) state (3) scar and (4) burden (See Figure 1). Risk/trait effects refer characteristics present prior to illness onset. State effects of MDD include severity of symptoms, duration of current episode, co-morbid psychiatric conditions, and treatment related to the current episode. Scar effects are decrements in abilities and functioning after an episode, inferring a potential failure to achieve complete inter-episode recovery. Burden refers to the repetitive and possibly cumulative effects of illness characteristics over time. This framework suggests that studying cognitive functioning early, in a remitted state, offers a unique window into possible trait vulnerability factors and early neurobiological abnormalities in depression[31].

Several existing studies have assessed cognitive functioning in the remitted state. A recent review **of adults** concluded that neuropsychological deficiencies persists in remission relative to healthy controls (HCs), particularly in the domains of sustained and selective attention, memory, and executive function[32]. These patients were in remission from depression as defined by cut-off scores on clinician-rated depression scales, however, variability in illness features including subsyndromal symptoms, duration of remission, chronicity, and medication status, made it difficult to estimate the magnitude of cognitive deficits observed during remission. An additional problem with studying risk traits in MDD is that few studies have collected repeated measurements of cognitive functioning; a method that is ideal for evaluating reliability of any impairment. Few longitudinal studies have addressed the stability of neuropsychological deficits over time in active state MDD and longitudinal studies are notably scarce in remitted MDD (for a review see[33]). None of the existing longitudinal studies reviewed were conducted in youth samples (lowest mean age was 41 years[16]) and 14 of these studies were actually in late-life depression, limiting the conclusions that can be drawn about the early stages of illness. Moreover, many are limited by variability in assessment windows that could be overly vulnerable to practice effects, with repeat testing ranging from 1 week[34] to one year later[35-37]. It is also worth noting that only 18 of the 30 studies reviewed included a healthy comparison group[33].

To address these key methodological gaps in the literature, we investigated for trait or scar risk factors in cognitive functions among un-medicated, late-adolescents **in remission from depression** with repeated assessments. Based on previous research[29, 32] we hypothesized that executive functions (processing speed with interference resolution, conceptual reasoning/set-shifting, and cognitive control) would be impaired in the rMDD group relative to HCs, and stable over time. By contrast, we hypothesized that verbal fluency and processing speed would be comparable in the rMDD and HC groups and stable over time. Positive results in this sample would indicate that deficits in executive functions are not exclusively due to state and chronic burden effects.

Method

Participants

Study participants were English-speaking young adults between the ages of 18 - 23 with a history of 1-3 episodes of MDD who are currently in remission (rMDD; n = 62) and similarly aged HCs (n = 43). Participants were recruited from the **community surrounding two study sites;** University of Michigan (n = 40) and the University of Illinois at Chicago (n = 65).

rMDD participants met criteria for the study if they, (a) currently scored seven or below on the Hamilton Depression Rating Scale, 17-item (HAM-D[38]), and (b) reported between one and three prior episodes of MDD. rMDD participants could enroll with current or past co-morbid anxiety disorders, but were excluded if they met criteria for a substance use disorder (last two years) or childhood-onset ADHD. HC participants could not meet current or past criteria for any Axis I or Axis II psychiatric disorder and could not have any first-degree relatives with a history of psychiatric illness. In addition, all enrolled participants were free of any psychiatric medication for 90 days, did not have head injury with loss of conscious

greater than 10 minutes, and did not suffer from any significant birth complications or chronic medical conditions that would affect cognitive functioning.

Procedure

After the initial phone screen, participants completed a diagnostic interview and clinician-rated measures of depression. Previous MDD was established using the Diagnostic Interview for Genetic Studies[39], with single-blind confirmation by phone with a parent/guardian/older sibling using a modified Family Interview for Genetic Studies[39]. Depression was assessed using the HAM-D[38], by a trained interviewer. Anxiety was assessed using the Hamilton Anxiety Rating Scale (HAM-A[40]). Following diagnostic confirmation, participants completed a battery of neuropsychological assessments. This test battery was repeated, spanning 3-15 weeks later. Ninety-one percent of HC participants (n = 39) and 92% of rMDD participants (n = 57) completed the follow-up battery.

Neuropsychological Test Battery

Neuropsychological tests focused heavily upon areas known to be impaired in active state MDD, including memory, processing speed, attention, and executive functioning. Specific tasks included the Stroop Color and Word Test[41], the Controlled Oral Word Association Test[42], Digit Symbol from the Wechsler Adult Intelligence Scale-IV[43], the Trail Making Test–Parts A and B[44], and the Parametric Go/No-Go Task[45-47]. The Parametric Go/No-Go Task is a measure of cognitive control. It has demonstrated reliability and validity in previous studies [11, 46]. The task consists of three conditions or levels that ascend in difficulty. For all three levels, a series of sequential letters are presented rapidly on a computer screen, and participant responses were recorded on a designated computer keyboard key. In the first level of the task, the “Go” condition, participants respond to three target letters every time they are presented. In levels 2 and 3, “Go/No-Go” conditions, the participant is expected to keep track of the last target to which they had responded and inhibit responding to that target until they had seen and responded to either 1 or 2 alternate targets (non-repeating rule), respectively.

Data Analytic Approach

All analyses were conducted in SPSS with an alpha threshold of .05. Primary analyses sought to assess differences between rMDD and HC participants on neuropsycholgical domains. Next, we used factor analysis to obtain more reliable estimates of underlying cognitive constructs, minimizing measurement error and consistent with prior convention[11, 48, 49]. Standard data reduction techniques (confirmatory principal axis factor analysis with oblique rotation) were used to reduce the tests using conceptually and theoretically categorized variables, consistent with our prior studies[50, 51]. Any scores with negative scale properties were inverted; as a result, lower factor scores reflect poorer performance.

Mixed-effects regression models[52] (MRMs) were conducted to examine changes in neuropsychology functions over time, group differences between rMDD and HC participants in performance and, group × time interactions in performance. MRMs are well suited for repeated measures: they are robust to the data dependency that occurs with repeated

assessments of individuals over time. MRMs are efficient in handling missing data by using all available data for a given participant to estimate group trends at each time point. Models for each neuropsychological domain as a dependent variable, included both fixed (time, diagnosis [coded HC =0, rMDD = 1]) and random (patient) effects. Chronbach's alpha and intraclass correlation coefficients were computed to evaluate the stability of performance over time.

Results

Sample Composition

Participants were an average age of 21.14 (SD 1.70), 65% female (n = 68), with approximately 14.63 years of education (SD = 1.50). Additional descriptive statistics for demographic and clinical characteristics of the sample are presented in Table 1. rMDD and HC groups were of similar age, IQ, years of education, sex distribution, racial distribution, and time between neuropsychological assessments. Participants from UIC and UM were of comparable age, race, sex, and education. Participants recruited from UM had higher IQ (UM: $M = 111.21$, $SD = 8.96$; UIC: $M = 103.66$, $SD = 8.96$), $p < .001$) and lower levels of anxiety (UM: $M = 1.31$, $SD = 2.01$; UIC: $M = 2.63$, $SD = 3.40$), $t(50) = -2.10$, $p = .036$.

Though in the remitted state, rMDD participants had higher depression and anxiety rating scores than HCs. All rMDD participants scored seven or below on these measures (range = 0 - 7); the average score for both ratings in the rMDD group was substantially lower than this cutoff. rMDD participants were medication free for a minimum of 6 months, 70% were medication naïve. rMDD participants were on average of 2.68 (SD = 2.94) years since the end of the last episode. Modal number of previous depressive episodes was 1 and 90% were never hospitalized. Average age of onset was 16.53 (SD = 3.38).

Factor Scores

The resulting factor scores included verbal fluency and processing speed, conceptual reasoning and set-shifting, processing speed with interference resolution, and cognitive control. Factor loadings are reported in Table 2.

Neuropsychological Functioning

Statistical parameters for each model reported below are presented in Table 3. rMDD participants demonstrated domain-specific decrement in cognitive control relative to HCs at Time 1. At time 2, performance of HC's declined (low stability in this sample), such that the between group performance difference in cognitive control (stable performance) no longer remained significant. rMDD and HC participants demonstrated comparable performance on verbal fluency and processing speed, processing speed with interference resolution, and conceptual reasoning and set-shifting. Performance on these domains was stable over time in both groups.

Reliability

Table 4 reports the internal consistency values for neuropsychological performance across domains among all participants and according to diagnosis. Alpha and intra-class correlation

coefficients were generally in the acceptable to excellent range. Overall internal consistency was excellent for verbal fluency and processing speed (α = .92), good for processing speed with interference resolution (α = .80), acceptable for conceptual reasoning and set-shifting (α = .63) and cognitive control (α = .67).

Notably, internal consistency in the rMDD group was higher than HC's across all domains. In particular, the rMDD deficit in cognitive control was more reliable over time (α = .74) than cognitive control among HC's (α = .58), which was poor.

Clinical Correlates of Cognitive Control

Illness characteristics of rMDD, such as residual symptoms or scar effects from prior episodes may contribute to the observed relative deficit in cognitive control in rMDD at Time 1. Therefore, we evaluated the association between the cognitive control domain and clinical attributes specific to MDD among the rMDD group. Residual depressive symptoms (HAM-D; $r = -.04$, $p = .773$.), residual anxiety symptoms (HAM-A; $r = -.08$, $p = .574$.), number of prior depressive episodes ($r = -.06$, $p = .862$), age at onset ($r = .07$, $p = .666$), number of hospitalizations ($r = -.02$, $p = .905$), longest episode duration ($r = .08$, $p = .631$), years since last episode ($r = .20$, $p = .219$), and being medication naïve ($r = .11$, $p = .521$) were unrelated to the rMDD deficit in cognitive control.

Discussion

In the current study, deficits in inhibitory regulatory processes persisted during remission from depressive episodes in rMDD. rMDD participants demonstrated poorer cognitive control relative to HCs. This is the first study to show that these cognitive control markers were reliable and stable over time in rMDD, and unrelated to residual depressive symptoms or chronicity of illness. That cognitive control was unrelated to sub-threshold symptoms or illness burden rules out the possibility that active illness is the sole *cause* of poor inhibition regulation. If deficits in inhibition were associated with symptom severity, prior illness characteristics, or vulnerable to state fluctuations in depression, then interference in cognitive performance could be interpreted as temporal repercussions or concomitants of depressive symptoms, and would be minimally informative about underlying mechanisms or vulnerabilities. In contrast, deficits in cognitive control were present independent of current severity in rMDD, suggesting a more robust signature, or intermediate phenotype, of MDD exists. This intermediate phenotype is similar to that observed in bipolar disorder (impairment in executive functioning, attention, memory, fine motor function[53]), though the intermediate phenotype of rMDD constitutes a more specific domain of executive functioning.

rMDD participants demonstrated more stable performance in cognitive control relative to HC's, **of a small to medium effect size.** Although HC's converged with rMDD on cognitive control performance at Time 2, declining performance among HC's over time is common with repeat performance of neuropsychological tests and likely representative of distraction and suspect effort rather than true abnormalities in cognitive performance[54, 55]. The HC group may also be more prone to boredom in a study with no direct or long term benefits and only being compensated for their time. In contrast, the higher reliability scores of this

relative deficit in rMDD suggest the possibility it is a more stable and robust measure of a potential trait illness characteristic. It is unclear whether the effect observed at Time 1 translates to observable clinical impairment in the real world, highlighting that neuropsychological screenings provide can provide valuable, and potentially otherwise undetectable information about illness characteristics that may constitute vulnerabilities. This distinction could be clarified in future studies by incorporating **neuropsychological assessments in a** longitudinal high-risk design to evaluate whether the same differences are present before the first onset of MDD, and whether the differences are related to the clinical outcomes in the long-term.

rMDD participants did not differ from HCs in processing speed with interference resolution, verbal fluency and processing speed, **or** conceptual reasoning and set-shifting. Even within the umbrella of executive functions, relatively lower order cognitive processes, such as sustained or divided attention, may remain intact in the early course of MDD, and that challenges in these areas is an artifact of either active symptoms or chronic illness burden. In contrast, the higher order process of responding flexibly to new information or inhibiting pre-potent impulses in response to changing goals may uniquely represent either an early course scar or risk factor for MDD. In this sense, the failure of the higher order ability to manage and direct lower order cognitive processes or impulses, may constitute a vulnerability in the cognitive system that precedes impairment in more basic processes with prolonged persistence of depression. This possibility is consistent with a prior comprehensive review of cognition among young adults with internalizing disorders that suggests executive dysfunction is present in early course MDD, but that other domains of cognition are not consistently impaired[56].

A key strength of this study is that detection of cognitive deficits was optimized by restricting the sample to individuals early in their illness course whose performance is not affected by a chronic illness burden. However, results of this study cannot fully dissociate whether observed differences constitute trait risk for the illness, or potential early scar effects on brain structure and function deriving from a less than full recovery from the index episode. An additional limitation of the study is that although no participants were informed of the specific hypotheses of the study, rMDD participants were aware that they were recruited based on a past history of depression, which could have operated as a demand characteristic or stereotype threat leading them to perform more poorly in cognitive control. It would be more likely, though, to have broader based cognitive difficulties if stereotype threat were at play in this sample. Further, while it is generally considered that executive functioning development asymptotes between 14-15 and peaks around age 18[57], brain regions that support executive functions continue to consolidate and myelinate/prune through the early-to-mid twenties[58-60]. Thus, it is a critical future endeavor to follow rMDD individuals in longitudinal, developmental designs to dissociate points of impairment and whether this impairment in cognitive control persists or resolves. Last, despite the need for studies of cognition in depression that are not confounded by repeated episodes or complex treatment histories, it deserves emphasizing that these findings cannot, at this point, be generalized beyond a relatively high-functioning group of young individuals early in their illness course. Individuals outside this window may demonstrate more severe impairments

across more domains of cognition. In addition, those who were unable to reach remission by our strict criteria may have been more likely to exhibit cognitive difficulties.

Nonetheless, our findings have important implications for the pathoetiology of MDD. Active state MDD is characterized by altered inhibition-related activity most prominently in the rostral anterior cingulate cortex (ACC) and the dorsal lateral prefrontal cortex (dlPFC)[61]. The ACC is thought to play an essential role in shifting flexibly between cognitive tasks and response sets, whereas the lateral structures of the dlPFC are recruited when competing responses need to be inhibited[62, 63]. These regions operate within a cognitive control network that maintains goals by flexibly adjusting attention and working memory to changing environments and demands[64]. Indeed, increased activity in these areas has been linked with successful inhibition trials on a Go/No-go task[18], suggesting potential compensatory mechanisms, and with impairment on interference resolution tasks such as the Stroop or continuous performance tasks[65, 66]. Thus, the direction of inhibition related activity may differ depending on the particular nature of the task, or potentially clinical confounds such as depressive severity and chronicity[67]. Evaluating the circuitry involved in regulatory deficits among early course, remitted individuals may help to clarify the nature of these abnormalities by reducing confounds of active illness, complex treatment histories, or neural scarring resulting from decades of illness.

These findings have important clinical implications. Patterns of inflexible, maladaptive, and ruminative thinking styles common in depression may be related, in part, to decreased attentional resources and cognitive control[68]. Advances in neurobehavioral training strategies, such as computer-based cognitive control exercises, to recruit the networks and resources necessary for executive control via repeated behavioral exercises, suggest that it is possible to strengthen cognitive and emotional functions. Actively depressed participants who have received cognitive control training exhibited reduced negative affect and rumination, and improved concentration[69]. Given that cognitive control deficits persist in remission of MDD, the application of cognitive control training during the euthymic phase may prove useful in reducing vulnerability to MDD relapse and warrant future study.

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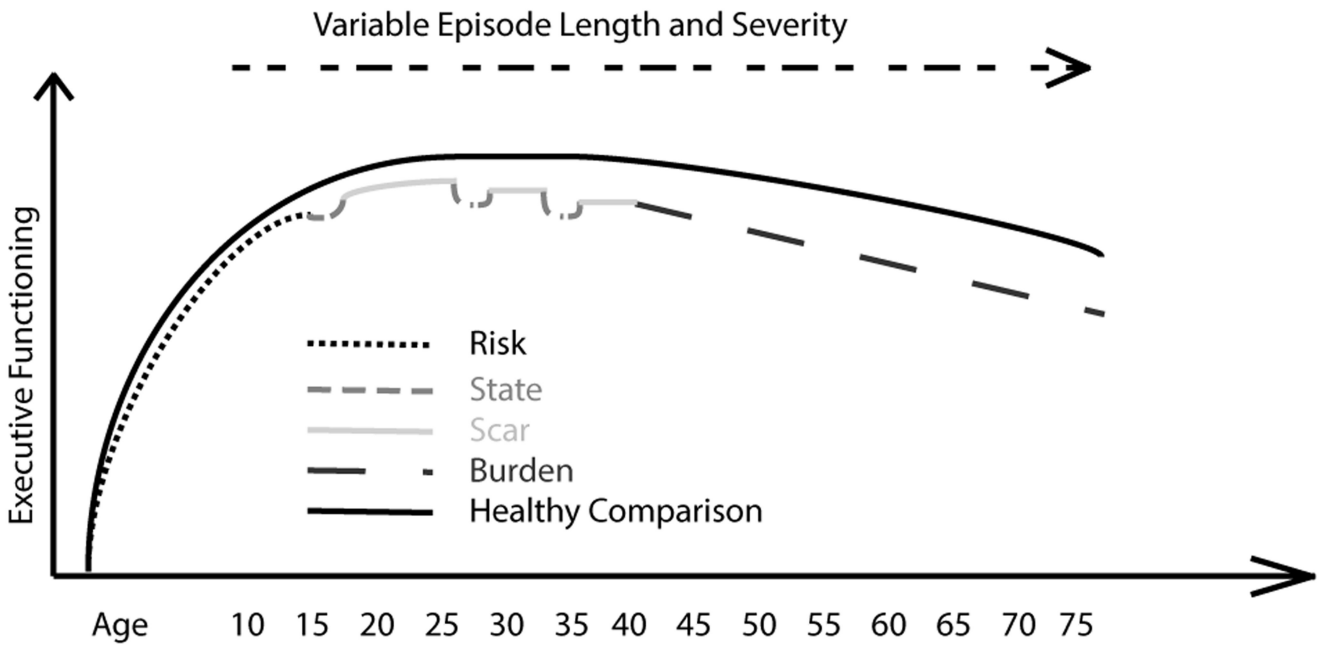

Figure 1.

Table 1

Clinical and Demographic Characteristics of rMDD and HC participants

Variable	rMDD (n = 62)	HC (n = 43)
Age	20.92 (1.61)	20.73 (1.66)
Shipley Verbal IQ	106.25 (9.65)	106.73 (9.30)
Years of education	14.31 (1.38)	14.53 (1.41)
Depressive severity (HAM-D) **	2.71 (3.43)	.42 (1.03)
Anxiety severity (HAM-A) **	3.20 (3.35)	.65 (1.56)
Female (%)	47 (72.3)	23 (57.5)
Caucasian (%)	34 (53.1)	28 (70.0)
Days between neuropsychological assessments	50.79 (25.97)	55.88 (36.56)
Age of onset	16.53 (3.38)	
Years since most recent MDD episode	2.68 (2.94)	
Medication naïve (%)	28 (70.0)	
Never hospitalized (%)	46 (90)	
Longest MDD duration (weeks)	32.23 (36.71)	

() denotes SD unless otherwise noted, percentages are calculated based on percent of available cases

* p<.05,

** p<.01

Table 2

Confirmatory Factor Analysis of Neuropsychological Test Scores in rMDD and HC

		Time 1			Time 2		
Factor	**Test**	**rMDD Raw Score**	**HC Raw Score**	**Factor Loading**	**rMDD Raw Score**	**HC Raw Score**	**Factor Loading**
Verbal Fluency and Processing Speed	Phonemic and Category Fluency Stroop Color Word Test	45.56 (11.92)	46.81 (9.87)	.67	50.81 (12.65)	48.42 (10.29)	.56
	Stroop Word Condition	105.33 (22.65)	110.54 (17.26)	.88	109.67 (15.79)	110.75 (20.75)	.90
	Stroop Color Condition	78.45 (14.84)	76.78 (25.08)	.84	83.77 (10.96)	83.58 (12.15)	.89
Conceptual Reasoning and Set-Shifting	Parametric Go/No-go *						
	Level 2 Accuracy Target Trials	95.98%	97.17%	.79	96.66%	98.09%	.88
	Level 3 Accuracy Target Trials	88.37%	90.58%	.85	91.09%	91.91%	.80
Processing Speed with Interference Resolution	Trail Making Test B Stroop Color Word Test	53.35 (17.92)	51.51 (16.78)	.43	51.92 (19.44)	50.88 (12.92)	.51
	Interference Condition	57.20 (7.02)	56.33 (7.18)	.29	59.13 (7.58)	57.67 (8.84)	.62
	Parametric Go/No-go *						
	Level 2 Target Response Time^	−422.99 (46.79)	−415.32 (41.59)	.90	−429.91 (49.30)	−414.47 (42.41)	.70
	Level 3 Target Response Time^	−495.44 (51.37)	−489.10 (48.35)	.88	−490.30 (57.11)	−499.97 (92.24)	.70
Cognitive Control	Parametric Go/No-go						
	Level 2 Inhibitory Accuracy	74.68%	78.26%	.85	72.44%	74.95%	.81
	Level 3 Inhibitory Accuracy	59.87%	66.19%	.84	64.77%	61.48%	.80

() denotes mean(SD) unless otherwise noted

* Time permitting, participants received a practice administration of the PGNG. rMDD and HC groups did not differ in proportion of participants completing practice at Time 1 (79% vs. 70%, x^2 = .98; p =. 322) or at Time 2 (84% vs. 78%, x^2 = .47; p =.492)

Table 3

Effects of Time and Diagnosis on Neuropsychological Factor Scores in rMDD and HC

Mixed Effects Regression Models					Effect Sizes (*d*)	
	Variable	***b***	**SE**	***p***	**Time 1**	**Time 2**
Verbal Fluency and Processing Speed	Diagnosis	−.07	.24	.755	**.18**	**.03**
	Time	−.09	.20	.653		
	Time × Diagnosis	−.02	.12	.847		
Conceptual Reasoning and Set-Shifting	Diagnosis	−.43	.23	.063	**.38**	**.28**
	Time	−.17	.22	.434		
	Time × Diagnosis	.13	.13	.301		
Processing Speed with Interference Resolution	Diagnosis	−.23	.31	.462	**.16**	**.11**
	Time	−.03	.33	.928		
	Time × Diagnosis	−.08	.19	.676		
Cognitive Control	Diagnosis	−.66	.32	**.042**	**.38**	**.01**
	Time	−.47	.31	.134		
	Time × Diagnosis	.31	.19	.095		

Table 4

Internal Consistency and Test-Retest Reliability of Neuropsychological Domains in HC and rMDD Participants

	All Participants		Healthy Controls		rMDD	
	Alpha	**ICC**	**Alpha**	**ICC**	**Alpha**	**ICC**
Verbal Fluency and Processing Speed	.92	.91	.90	.90	.93	.92
Conceptual Reasoning and Set-Shifting	.63	.64	.60	.60	.82	.81
Processing Speed with Interference Resolution	.80	.80	.66	.66	.86	.86
Cognitive Control	.67	.66	.58	.59	.74	.74