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Preliminary evidence concerning the pattern and magnitude of cognitive dysfunction in major depressive disorder using cogstate measures

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Abstract

Background: Cognitive deficits are common in individuals with major depressive disorder (MDD), and are associated with treatment non-responsiveness and poorer functional outcomes. Characterization of the nature and magnitude of deficits in this population has been limited in part by lack of brief, practical, and well-validated assessment measures. The goal of this study was to use a brief, practical, and repeatable computerized cognitive test battery from Cogstate to examine differences in cognitive functioning between individuals with MDD and healthy controls.

Methods: Forty participants (22 healthy controls (HCs), 18 with MDD) completed a battery of six cognitive measures, as well as measures of intellectual functioning (intellect) and depressive symptom severity. A multivariate analysis of covariance (MANCOVA) was conducted to compare cognitive test performance across groups while controlling for intellect.

Results: Individuals with MDD had lower full-scale IQ scores on average, and performed worse on measures of visual attention ($d=1.04$), verbal learning ($d=1.22$) and memory ($d=1.22$), and visuospatial problem solving ($d=0.80$) than HCs after adjustment for differences in intellect. Psychomotor speed, visual memory, and working memory did not differ between groups.

Conclusions: Cogstate measures appear to be sensitive in assessing deficits in attention, verbal learning and memory, and executive function in individuals with MDD. Further research will be useful in establishing the utility of Cogstate measures for standard use in research and clinical practice.

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Contributors

All authors contributed to and have approved the final manuscript. In addition, Margaret Davis: analyzed data and prepared manuscript; Nicole DellaGioia: administered psychological and cognitive assessments, scored data; David Matuskey: aided with selection of tests for the Cogstate battery and subject diagnosis; Brian Harel: aided with selection of tests for Cogstate battery, data analysis; Paul Maruff: provided Cogstate support and background information; Robert Pietrzak: data analysis, study design; Irina Esterlis: study design, subject diagnosis, selection of cognitive tests, data analysis.

Keywords

Major depressive disorder; Cognitive deficits; Cogstate

1. Introduction

Deficits in neurocognitive functioning are a common characteristic of major depressive disorder (MDD), but the pattern and magnitude of these deficits is poorly understood. In two recent reviews, at least 50% of individuals with MDD were found to have significant impairment in at least one domain of executive functioning (EF; e.g. set-shifting, verbal fluency), memory, or attention (Gualtieri and Morgan, 2008); deficits in attention and EF were found to persist even after depressive symptoms remitted (Rock et al., 2013). A growing body of research suggests that these deficits predict impairment in social functioning, as well as reduced work productivity and quality of life (Evans et al., 2014). Further, the presence of cognitive deficits is associated with treatment non-responsiveness in this population (Story et al., 2008). Characterizing and addressing cognitive deficits may thus be important in improving functional outcomes for individuals with MDD.

To date, several factors have limited understanding of the nature and extent of cognitive deficits in MDD. First, in both clinical and research settings, assessment time is limited, making use of many existing assessment batteries impractical, and decreasing the likelihood that cognitive functioning will be assessed. Second, there is no established gold-standard cognitive assessment tool for use in this population, and the use of different tools across studies and settings limits generalizability of results (Ott et al., 2016). Researchers have speculated that both lack of time and consensus on assessment instruments likely contribute to the underestimation of cognitive deficits among individuals with MDD (Bortolato et al., 2014). A brief, well-validated measure of cognitive functioning may thus be useful in improving understanding of cognitive deficits among individuals with MDD.

The purpose of the present study was to characterize the nature and magnitude of cognitive deficits in individuals with MDD using a battery of six Cogstate measures. Cogstate cognitive tests are based on well-validated experimental psychology and cognitive neuroscience paradigms (<http://www.Cogstate.com>). The tasks were shown to demonstrate construct validity (Maruff et al., 2009; Pietrzak et al., 2008), have minimal practice effects as compared to traditional paper and pencil tests, and can be administered within a short time interval (Falleti et al., 2006). To date, however, these tests have been individually evaluated for use in MDD; a single study by Yoshida and colleagues (Yoshida et al., 2012) a Cogstate composite score differentiated MDD participants from controls. Based on prior work (Rock et al., 2013), we hypothesized that individuals with MDD would show moderate-to-large deficits on measures of attention, verbal learning and memory, and executive function.

2. Methods

2.1. Participants

This study was approved by the Yale University Institutional Review Board, and written informed consent was obtained from all participants prior to data collection. Participants from both groups were recruited from the community using advertisements (newspaper, bus, online) seeking individuals suffering from depression as well as healthy individuals to participate in a study. Participants were 1. individuals who met DSM-IV-TR (Association and Association, 1994) diagnostic criteria for MDD (N =18) based on the Standardized Clinical Interview for DSM-IV (First, 2005), were currently in a major depressive episode, had at least one prior major depressive episode, had no other psychiatric conditions (with the exception of anxiety disorders), and free of psychotropic medications for at least 2 months. 2. healthy controls (HCs) who did not meet criteria for MDD or any other Axis I psychiatric condition in their lifetime based on the SCID. Five MDD participants met criteria for one or more anxiety disorder on the SCID (i.e. PTSD, OCD, or panic disorder). A majority of participants across groups had some college education (M years of education =15.47 (HC), 14.88 (MDD)). Across groups participants were predominantly Caucasian (72.22% (MDD), 54.54% (HC)).

2.2. Assessments

A brief (20–30 min) battery of 6 computerized Cogstate measures designed to assess key domains of cognition of interest, was administered to all participants. The battery consisted of six tests: Detection (DET) test measuring psychomotor speed; Identification (IDN) test measuring psychomotor speed, alertness, and visual attention; One Card Learning (OCL) test measuring visual memory; One Back (ONB) test measuring working memory; Groton Maze Learning (GML) test measuring visuospatial problem solving – a measure of executive functioning; and the International Shopping List (ISL)/ International Shopping List-delayed recall (ISL-DR) tests measuring verbal learning and memory. All tests were administered in a fixed sequence presented to each subject on a laptop computer in a quiet room to minimize distraction. Scoring for each test was automated. Detailed information of each measure is available both on the Cogstate website (<https://Cogstate.com/computerized-tests>) and in several recent publications (Maruff et al., 2009; Shiroma et al., 2014).

The Wechsler Test of Adult Reading (Wechsler, 2001) was administered to assess intellectual functioning (intellect). Participants in the MDD group also completed two brief measures to assess depressive symptom severity: Beck Depression Inventory, 2nd edition (Beck et al., 1996) and the Montgomery-Asberg Depression Rating Scale (Montgomery and Asberg, 1979).

2.3. Data analysis

Data analyses proceeded in two steps. First, independent samples t-tests and chi-square tests were conducted to compare HC and MDD groups with respect to age, sex, handedness, and intellect (WTAR scores). Second, two multivariate analyses of covariance (MANCOVA) were conducted, the first to compare cognitive test performance in HC and MDD groups, and the second to compare response time (RT) variability in IND and DET subtests. The

second analysis was conducted in recognition of findings implicating RT variability as a marker of potential cognitive dysfunction in some groups (Burton et al., 2006). Group (HC vs. MDD) was entered as a fixed factor, WTAR standardized scores as a covariate in both cases. Cognitive test scores and RT variability scores for IND and DET were entered as dependent variables in the first and second MANCOVA respectively. Cohen's d was computed to estimate effect sizes of group differences. A conventional significance level of 0.05 was applied to identify group differences in cognitive test scores.

3. Results

3.1. Sample characteristics

Table 1 shows demographic and clinical characteristics of the sample. The MDD and HC groups did not differ significantly with respect to age, sex, years of education, or handedness. Mean depressive symptom ratings in the MDD group were indicative of moderate to severe depression (MADRS $M=29.5 \pm 4.7$; BDI-I $M=29.6 \pm 8.7$). There was a significant difference in intellect between groups ($t=2.14$, $p=0.041$, $d=0.75$), with the MDD group having lower scores than the HC group.

3.2. Cognitive functioning

Table 1 shows results of 2 MANCOVAs adjusted for intellect. The first revealed a significant omnibus main effect of MDD diagnosis on cognitive performance ($F=4.82$, $p=0.002$). Compared to the HC group, the MDD group performed significantly worse on IDN and measures of verbal learning and memory, and visuospatial problem-solving (all p 's 0.024). There were no significant differences in performance on measures of psychomotor speed, visual memory, and working memory (all p 's 0.18). As shown in Fig. 1, effect sizes for group differences were large for IDN ($d=1.04$), verbal learning ($d=1.22$) and memory ($d=1.22$), and visuospatial problem-solving ($d=0.80$); small-to-moderate for psychomotor speed ($d=0.46$) and working memory ($d=0.46$), and small for visual memory ($d=0.22$). The second showed no significant main effect of MDD diagnosis on RT variability ($F=1.83$, $p=0.103$). Of note, additional MANCOVAs were completed with years of education entered as a covariate in place of intellect and yielded comparable results in both cases except that observed group differences in IDN were no longer significant ($p=0.08$).

4. Discussion

We observed significant deficits in performance on IDN, verbal learning and memory, and visuospatial problem-solving tasks in the MDD group. These results are largely consistent with prior findings using more resource-intensive neuropsychological test batteries. Consistent with previous research (Sackeim et al., 1992), the MDD group had significantly lower estimated full-scale IQ scores than the HC group. As hypothesized, even when intellect was controlled for, the MDD group had large magnitude deficits in visual attention, verbal learning and memory, and visuospatial problem solving (executive functioning) performance relative to the HC group. Effect sizes for the differences between groups were large for all three domains, suggesting clinically meaningful differences between the MDD and HC groups. Importantly, observed effect sizes for these constructs were comparable in

magnitude to mean effect sizes observed using different assessment measures in two recent meta-analyses (Rock et al., 2013; Snyder, 2013). No differences were observed on psychomotor speed (based on the DET task), visual memory, working memory, or RT variability. Finally, when years of education was controlled for in place of intellect, differences in IDN across groups were no longer observed, suggesting that the relationship between years of education and the IDN task (a measure of psychomotor speed, alertness, and visual attention may warrant additional exploration. These findings provide preliminary support for the validity of these Cogstate measures in assessing specific forms of cognitive dysfunction in this population.

Of note, our hypotheses were formulated based on the preponderance Of evidence in the literature concerning performance on various cognitive domains among individuals with MDD. However, findings concerning the relationship between MDD and cognitive deficits in the domains where no statistically significant differences were observed (e.g. psychomotor speed) have been mixed (Snyder, 2013). A meta-analysis by Rock and colleagues (Rock et al., 2013) focusing on one extensive computerized cognitive assessment battery (CANTAB) found moderate deficits in all domains examined. However, studies utilizing different assessment measures have reported discrepant results. For example, Porter and colleagues (Porter et al., 2003) did not find evidence of impairment in psychomotor speed in a group of unmedicated patients with MDD using a paper and pencil digit symbol substitution task. Notably in the present study while no differences were found on the DET psychomotor speed task, robust differences were observed in IDN, a choice reaction time task reflecting psychomotor speed in addition to alertness and visual attention. As these discrepant findings suggest, a number of variables, including the nature of the test administered and mode of presentation (computerized. vs. paper and pencil) must be considered as potentially accounting for observed discrepancies in study results (Bortolato et al., 2014). Factors including administration error and patient fatigue during completion of extended and complex paper and pencil batteries can potentially skew results toward apparent deficit. Computerized measures are automated, ensuring standard administration, reducing participant burden, and facilitating creation of multiple test forms to avoid practice effects standard paper and pencil measures might be affected by. Thus, comparison of results across different measures administered via different modalities, though theoretically designed to assess the same cognitive domain, is difficult. Additional studies that employ large-scale validation and adoption of a single, brief test battery validated for use in assessing cognitive impairment in MDD specifically are needed to help increase understanding of cognitive deficits associated with MDD.

4.1. Limitations

A few limitations should be considered when interpreting results of this study. As noted, the study sample was relatively small. Power analyses suggested that the sample size was sufficient to detect moderate to large effect sizes, but not small effect sizes (0.25). Further, the sample consisted of predominantly college-educated, Caucasian individuals who self-selected to participate in a research study from a select geographic region (the northeastern United States). As such, generalizability of these results to a larger, more diverse sample may be limited. Additionally, individuals in both the MDD and HC groups who met criteria

for significant medical, neurological or other psychiatric illnesses were excluded from participation. Given that MDD has a high rate of comorbidity with other mental disorders (Kessler et al., 2003), generalizability to the broader MDD population may be limited. Replication is warranted to confirm these findings in a wider population, as well as to evaluate cognitive profiles of specific subpopulations of individuals with MDD (e.g., chronic vs. first episode). Similarly, additional research would be required to establish the sensitivity of Cogstate measures for cognitive impairment in remitted MDD. The nature of this study (e.g. the fact that a standard battery of neuropsychological assessments was not co-administered for concurrent validity) does not allow for full psychometric validation of Cogstate measures. In light of this major limitation, the present findings should be considered preliminary in nature. Completion of a large-scale study designed explicitly to evaluate the reliability and validity of these measures in MDD individuals is a crucial next step, and in light of the present findings and those of Yoshida and colleagues (Yoshida et al., 2012), should be prioritized. Finally, comparison data on the BDI-II and MADRS was not collected for control individuals after it was established that they did not meet diagnostic criteria for MDD on the SCID, which prevented group comparisons using these measures. Without covarying for current mood symptoms (MADRS scores), it is not possible to definitively establish whether observed group differences represent trait differences associated with MDD.

5. Conclusions

Despite recognition of the fact that cognitive deficits in individuals with MDD are associated with poorer treatment responsiveness and worse functional outcomes, understanding of the pattern and persistence of these deficits remains limited in clinical settings. As noted, lack of a well-validated, practical (e.g. easy to use, low time-cost), and widely accepted assessment measure for cognitive deficits in this population has limited more widespread evaluation of such deficits. The Cogstate measures used in this study are brief, easy to administer (automated and computerized), and well-validated tests of constructs demonstrated to be relevant to MDD in previous research (Rock et al., 2013). The results of this study provide promising preliminary evidence for the utility of this battery as a standard tool to use in assessing cognitive performance of individuals with MDD. The battery of Cogstate measures used in this study (simplicity, brevity, automated scoring) renders it an excellent fit for busy clinical and research settings where time is often limited and in which excessively complex and more resource-intensive neuropsychological assessments are unlikely to be used regularly. Future research should focus on replication and extension of these findings toward validation of the Cogstate measures used in this study, and other brief computerized test batteries in individuals with MDD. Characterization and monitoring of cognitive deficits in individuals with MDD is essential to developing more targeted treatment strategies for these deficits and ultimately improving functional outcomes in this population.

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Fig. 1.

Effect sizes of cognitive deficits in individuals with MDD compared to healthy control.

Notes. Cognitive performance of healthy controls is represented by the “0” line; effect sizes are adjusted for IQ score.

Table 1

Demographic and clinical characteristics of the sample.

N	HC Mean 22 (SD) or n (%)	MDD 18 Mean 18 (SD) or n (%)	Test of difference	p
Age	33.5 (11.8)	35.5 (13.3)	0.52	0.61
Sex (1)	10 (45.5%)	10 (55.6%)	0.40	0.52
Right-handed (1)	15 (68.2%)	15 (83.3%)	2.29	0.32
Years of Education	15.47 (2.15)	14.58 (2.88)	1.64	0.056
Standardized IQ score	112.2 (13.2)	101.5 (15.4)	2.14	0.041
MADRS total score	–	29.5 (4.7)	–	–
BDI-II total score	–	29.6 (8.7)	–	–
MANCOVA (Cognitive test scores)				
	Mean (SE)	Mean (SE)	F	p
Psychomotor speed	2.50 (0.03)	2.56 (0.03)	1.88	0.18
Identification	2.66 (0.02)	2.74 (0.03)	5.66	0.024
Visual memory	0.97 (0.02)	0.95 (0.02)	0.42	0.52
Verbal learning	27.4 (2.3)	14.7 (2.5)	13.28	0.001
Verbal memory	9.7 (0.8)	5.0 (0.9)	13.01	0.001
Working memory	1.35 (0.05)	1.24 (0.06)	1.89	0.18
Visuospatial problem solving	47.79 (3.37)	63.78 (3.71)	9.51	0.004
MANCOVA (Variability)				
	Mean (SE)	Mean (SE)	F	p
Variability on DET	0.097 (0.007)	0.094 (0.007)	0.085	0.773
Variability on IND	0.098 (0.007)	0.080 (0.006)	3.61	0.061
				Cohen d
				1.04
				0.102

Notes. Cognitive test scores are adjusted for WTAR standardized IQ scores. MADRS=Montgomery-Asberg Depression Rating Scale; BDI-II=Beck Depression Inventory-II; Identification = IDN task assessing psychomotor speed, alertness, and visual attention; DET = Detection task. Bold signifies p 0.05.