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Research paper

Association of Major Depressive Disorder with remotely administered measures of cognition and subjective report of cognitive difficulties across the adult age spectrum

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ABSTRACT

Background: Major depressive disorder (MDD) has increasing prevalence with age. Both objective measures of cognitive dysfunction and subjective report of cognitive difficulties related to MDD are often thought to worsen with increasing age. However, few studies have directly evaluated these characteristics across the adult lifespan.
Methods: Participants included 23,594 adults completing objective and subjective measures of cognition on an online research registry. Linear regression including interactions of age group with depression was used to evaluate the association of self-reported MDD with measures of cognition in three age groups: 21–40 years; 41–60 years; 61+ years.
Results: MDD (n = 2127) demonstrated poorer objective cognitive performance and greater subjective ratings of cognitive difficulties across all domains assessed compared to non-depressed individuals (ND; n = 21,467). Significant interactions of age group and MDD status with objective and subjective measures of cognition were observed for both middle age and older adults when compared to young adults but few significant differences between middle-aged and older adults were evident.
Limitations: This study relied on self-report of MDD diagnosis, utilized remotely administered and unsupervised measures of cognition, and the sample was not diverse.
Conclusions: The magnitude of association between MDD and cognitive correlates appears to plateau in middle age. Our results suggest that increased rates of dementia are not due to greater cognitive consequence of MDD in older adults and that age effects, and not greater effects of depression, may lead to increased diagnosis of MDD based on subjective report of cognitive symptoms.

1. Introduction

Major Depressive Disorder (MDD) is a prevalent and disabling psychiatric disorder across the age spectrum with a 7 % to 11 % pooled disease prevalence that increases with age (Luppa et al., 2012; Lim et al., 2018). Specifically, the prevalence of depression has been estimated at 7 % for young adults ages 20 to 39 years, 8 % for middle-aged adults ages 40 to 59 years, and 11 % in older adults ages 60 years and older (Brody, 2018; Steffens et al., 2009). Subjective report of cognitive difficulties are diagnostic criteria of major depression (Association, 2013) and objectively measured cognitive deficits are consistently reported in MDD (Koenig et al., 2014; Goodall et al., 2018; Lee et al., 2012). Further, MDD has been associated with accelerated cognitive decline and up to a four-fold risk of dementia in older adults (Richard et al., 2013).

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However, to date, the degree to which MDD is associated with subjective report of cognitive difficulties and objectively measured cognitive dysfunction across different age groups of adults is understudied. Investigating report of cognitive symptoms associated with MDD across adult age groups will clarify the degree to which subjective report of cognitive difficulties may be a factor associated with higher rates of MDD diagnosis with increasing age. Evaluation of objective measures of cognition across the adult age spectrum is important to clarify the degree to which older adults may have greater cognitive sequelae of MDD that contributes to risk for dementia.

Self-reported perception of cognitive difficulties is a diagnostic criterion for MDD (Association, 2013). Accordingly, it is well documented that cognitive complaints are more prevalent in individuals with MDD compared to non-depressed individuals (ND) (Dhillon et al., 2020; Fischer et al., 2008). Further, subjective cognitive complaints of MDD have been reported widely across the domains of information processing speed, problem solving, attention, concentration, planning, organization, and memory (Fischer et al., 2008; Lawrence et al., 2013; Mohn and Rund, 2016; Morey-Nase et al., 2019; Allott et al., 2020; Bhang et al., 2020; Slavin et al., 2010). However, the degree to which the report of subjective cognitive complaints in MDD individuals differs across the age spectrum has rarely been evaluated. In community-dwelling cohorts, middle-aged adults have been shown to report more subjective cognitive complaints than younger adults, but the frequency of cognitive complaints drops in older adults until the very oldest ages (Begum et al., 2014). Evaluating the severity of subjective cognitive complaints associated with MDD across the adult age spectrum would offer an opportunity to identify the potential for differential rates of cognitive complaints to contribute to greater rates of MDD diagnosis with increased age.

Unlike subjective report of cognitive difficulties, objectively measured cognitive dysfunction is not a diagnostic criterion for MDD but is well documented across several cognitive domains. In younger adults with MDD, objectively measured cognitive dysfunction in domains of memory, attention, executive function, and information processing speed are commonly reported (Hermens et al., 2011; Donix et al., 2019). These cognitive symptoms are also often reported in combined samples of young and middle-aged adults (Hammar et al., 2009; Airaksinen et al., 2004; Porter et al., 2003; Dotson et al., 2020; Liu et al., 2019) as well as in samples of older adults (Thomas et al., 2009; Marazziti et al., 2010). As such, no consistent pattern of age specific deficits associated with MDD has emerged, but meta-analyses do suggest that cognitive dysfunction associated with MDD worsens with age (Lee et al., 2012; Dotson et al., 2020). However, there have been very few studies that have directly evaluated the severity of cognitive dysfunction in middle-aged and older adults with MDD compared to younger adults with MDD and the extant literature is often limited by small sample sizes (Hermens et al., 2011; Donix et al., 2019; Hammar et al., 2009). Therefore, it is not yet clear if cognitive dysfunction associated with MDD worsens with age or if additional factors contributing to age related cognitive decline have influenced the results of these prior studies.

Unsupervised online assessments offer a significant avenue to evaluate the degree to which MDD is associated with both subjective report of cognitive difficulties and objective measures of cognition across the adult age spectrum. Unsupervised remote assessments of subjective report of cognitive difficulties and cognitive dysfunction have been shown to be reliable and valid (Mackin et al., 2018; Nosheny et al., 2018; Ashford et al., 2020a) and can be used to evaluate a large number of participants efficiently. While the use of remote and unsupervised online tests to evaluate cognition specifically in MDD samples has not yet been widely investigated, supervised computerized tests administered in the clinic have shown association of MDD and cognitive dysfunction in the domains of memory, attention, information processing speed, and executive functioning (Hammar et al., 2003; Rock et al., 2014; Weiland-Fiedler et al., 2004; McIntyre et al., 2017; Davis et al., 2017; Chen et al., 2018). Remote and unsupervised assessments of subjective report of cognitive difficulties have similarly been shown to be valid measures (Nosheny et al., 2019; Ashford et al., 2020b) but, to our knowledge, these measures have not been evaluated specifically in MDD individuals.

This study was conducted to evaluate objective cognitive performance and subjective report of cognitive difficulties of younger, middle-aged, and older adults measured with unsupervised and online assessments offered through the Brain Health Registry (BHR; www.brainhealthregistry.org). Based on the current literature, our hypotheses are: 1) Across the combined sample, and in each of our age groups, MDD will be associated with worse performance on objective measures of information processing speed, working memory, attention, and memory compared to ND individuals. 2) The negative association of MDD with objective measures of cognition will be stronger in middle-aged and older adults when compared to younger adults and will be strongest in older adults. 3) MDD participants will report greater subjective report of cognitive difficulties than ND, and 4) The association of subjective report of cognitive difficulties with MDD will be stronger in middle-aged and older adults compared to younger adults and will be strongest in older adults.

2. Methods

2.1. Participants and procedures

The BHR functions within the University of California, San Francisco and is approved by the institutional review board. The BHR was launched in March of 2014 with the goal of establishing a national online research registry and longitudinal observational cohort for all types of research trials using comprehensive assessments of medical, family, and psychiatric history as well as assessments of cognitive functioning. BHR participants are informed that there are no direct benefits to participating in the BHR, the BHR does not provide medical services or medical advice, and that responses to individual questions may not be reviewed. BHR participants receive no compensation for completing study procedures. Currently, >90,000 participants have registered with the BHR. After providing consent, each participant completes a series of questionnaires on the BHR website, including measures of subjective report of cognitive difficulties and objective measures of cognition. All cognitive tests and questionnaires are administered online with no supervision and scores are not reported to participants. Exclusionary criteria for this study included self-reported diagnosis of Alzheimer's disease, Lewy body disease, dementia, Mild Cognitive Impairment, use of cholinesterase inhibitors or NMDA receptor antagonists, multiple sclerosis, frontotemporal dementia, Huntington's disease, amyotrophic lateral sclerosis, current or past autism, current or past schizophrenia, or current psychosis. A total of 23,594 participants met inclusion criteria and were included in our statistical analysis. Not all participants completed all measures.

2.2. Diagnosis of depression

Diagnosis of current major depression was obtained by participant self-report based on the Medical History Questionnaire, in which participants were asked, “Please indicate whether you currently have the following conditions” followed by a list of medical conditions including Major Depression. Participants provided and a “Yes” or “No” response. Participants were classified as MDD if they self-reported a “Yes” response. Those with a “No” response were classified as ND.

2.3. Depression symptom severity

Severity of reported symptoms of depression was measured via the self-administered Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001). The PHQ-9 consists of nine self-reported items based on criteria for MDD, all of which are scored as “0” (not at all) to “3” (nearly every day). Total scores can range from 0 to 27, with greater scores indicating

greater symptom severity.

2.4. Cognition

The Cogstate Brief Battery (CBB) is a computerized cognitive assessment battery that has been validated under supervised administrations in a variety of patient populations (Davis et al., 2017; Maruff et al., 2009; Maruff et al., 2013). All CBB scores used in primary analyses for this study were obtained in the same manner as published methods for supervised administrations. The CBB consists of four cognitive tests:

The Detection Test (DET): The DET is a measure of psychomotor function and information-processing speed that uses a simple reaction time paradigm with playing-card stimuli. The primary outcome variable for this test is reaction time in milliseconds for correct responses normalized using a logarithmic base 10 (Log 10 transformation).

The Identification Test (IDN): The IDN is a measure of visual attention and uses a forced choice reaction time paradigm with playing-card stimuli. The primary outcome for this test is reaction time in milliseconds for correct responses normalized using a logarithmic base 10 (Log 10 transformation).

The One Card Learning Test (OCL): The OCL is a measure of visual learning and memory that uses a pattern-separation paradigm with playing-card stimuli. The primary outcome variable is the proportion of correct responses (accuracy) normalized using an arcsine transformation.

The One-Back Test (ONB): The ONB is a measure of working memory and uses a well-validated n-back paradigm with playing-card stimuli. The primary outcome variable for this test is the accuracy of correct response.

2.5. Subjective report of cognitive difficulties

Participant ratings of self-evaluated cognitive difficulties were measured by the Everyday Cognition Scale (ECog) self-report. The ECog is a measure of cognitively relevant everyday abilities comprised of 39 items, covering six cognitively relevant domains: Memory, Language, Visuospatial Abilities, Planning, Organization, and Divided Attention (Farias et al., 2008). For each item, participants compare their current level of everyday functioning with how they functioned 10 years earlier. Participant ratings are made on a four-point scale: 1 = better or no change, 2 = questionable/occasionally worse, 3 = consistently a little worse, or 4 = consistently much worse.

2.6. Statistical analyses

Participant characteristics and measures of objective cognition and subjective report of cognitive difficulties were compared between depression groups (MDD vs. ND). Continuous variables were evaluated using Mann Whitney tests and categorical variables were compared using chi-square tests. We then used linear regression to evaluate the magnitudes of the association of self-reported MDD with measures of objective cognition and subjective report of cognitive difficulties in three age groups: 21–40 years; 41–60 years; 61+ years. We analyzed each cognitive test and subjective report of cognitive difficulties index score separately in regression models that included as predictors the binary depression indicator (self-reported MDD), categorical age group and the interactions of age group with depression. The models also included age as a continuous variable, gender, and education as potential confounders. The analyses focused on the statistical significance of the age group by depression interactions which we tested using Wald chi-square tests with two degrees of freedom and the assessment age group-specific associations of depression with each outcome, which we present as estimated regression coefficients along with associated 95 % confidence intervals (CI). We fit all linear regression models using routines in SAS version 9.4.

3. Results

3.1. Participant characteristics

Descriptive statistics for the cohort with the select outcome and predictor measures are presented in Table 1. Participants with MDD (n = 2127) were more likely to be female (80.2 % vs 72.8 %, $\chi^2 = 54.3$, $p < .001$), had higher depressive symptom severity (PHQ-9), fewer years of education, and were younger compared to ND participants (n = 21,467; all Mann Whitney test p's < .0001). There were no statistically significant differences for minority group participation associated with MDD status (White 86 % vs Other 86.8 %; $\chi^2 = 1.2$, $p = .28$). Across the entire sample, after controlling for age, gender, and education, the MDD and ND groups significantly differed on all measures of objective cognition with the MDD participants demonstrating worse performance across psychomotor function and information-processing speed (Detection Task; $p < .0001$), visual learning and memory (One Card Learning Task, $p < .0001$), visual attention and memory (Identification Task, $p <$

Table 1
Summary of selected outcome and predictor variables comparing Major Depression (MDD) to Non-Depressed (ND) individuals (N = 23,594).

	ND (n = 21,467)		MDD (n = 2127)		p-Value
	Mean ± SD	Range	Mean ± SD	Range	
Demographics					
Age, years	58.7 ± 0.13	15–90	55.2 ± 12.8	18–84	<0.0001
Education, years	16.3 ± 2.35	6–20	15.8 ± 2.41	6–20	<0.0001
Gender, no. female (%)	15,619 (72.8 %)		1705 (80.2 %)		<0.0001
Race, White (%)	18,458 (86.0 %)		1847 (86.8 %)		0.28
PHQ-9	3.8 (4.2)		10.1 (6.34)		<0.0001
Subjective cognitive difficulties					
Executive functioning					
Planning	5.85 ± 1.92	5–20	7.24 ± 3.W5	5–20	<0.0001
Organization	7.69 ± 3.00	6–24	10.4 ± 4.91	6–24	<0.0001
Divided Attention	6.22 ± 2.67	4–16	8.06 ± 3.58	4–16	<0.0001
Visuospatial	8.1 ± 2.32	7–28	9.36 ± 3.85	7–28	<0.0001
Language	13.2 ± 4.86	0–36	16.3 ± 6.71	0–36	<0.0001
Memory	13.8 ± 5.25	8–32	17.3 ± 6.60	8–32	<0.0001
Objective cognitive performance					
One Card Learning Test	0.977 ± 0.135	0.226–1.57	0.956 ± 0.135	0.38–1.32	<0.0001
One-Back Test	2.87 ± 0.0946	2.53–3.43	2.88 ± 0.0966	2.54–3.31	0.0021
Detection Task	2.55 ± 0.0945	2.24–3.37	2.56 ± 0.104	2.33–3.17	<0.0001
Identification Test	2.7 ± 0.0674	2.38–3.31	2.71 ± 0.0772	2.38–3.31	<0.0001

.0001), and working memory (One-Back Task, $p = .002$). The MDD and ND groups also significantly differed on measures of subjective report of cognitive difficulties in the combined age group sample with MDD participants reporting more cognitive difficulties than the ND group across all domains including executive functioning (planning, organization), divided attention, visuospatial functions, language, and memory (Table 1; all $p < .0001$).

3.2. Interaction of age group and MDD with objective measures of cognition and report of subjective cognitive difficulties

MDD and ND participants did not differ on neuropsychological test performance in any cognitive domain assessed in the younger adult group ($p > .16$ for all). In contrast, both the middle-aged and older adult MDD groups demonstrated poorer performance on all four cognitive tests compared to ND ($p < .0001$ for all). There was a significant overall interaction effect of age and depression group with objective measures of cognition (Wald chi-square tests, $df = 2$, $p < .044$ for all) which is shown as the difference in vertical distance between curves in Fig. 1 for each age group. Relative to the youngest age group, middle-aged and older participants demonstrated significantly greater effects of MDD with poorer performance on measures of objective cognition across all four cognitive outcomes (Table 2). Conversely, the association of MDD with objective measures of cognition did not differ between middle-aged and older adults on any of the four cognitive outcome variables ($p > .05$ for all).

With respect to subjective cognitive difficulties, MDD reported greater cognitive difficulties relative to ND and these differences were observed in each of the three age groups assessed ($p < .0001$ for all). There was a significant overall interaction effect of age and depression group (Wald chi-square tests, $df = 2$) with subjective cognitive complaints of memory ($p = .023$), language ($p = .0018$), visuospatial functioning ($p = .0002$), and organization ($p = .026$). These interactions are shown as the vertical distance between curves in Fig. 2 for each age group. There were not significant interaction effects of age and depression group for planning ($p = .11$) or divided attention difficulties ($p = .29$). Relative to young adults, both middle-aged and older adults showed a significant interaction effect of MDD with greater subjective reports of difficulties with memory, language, and visuospatial functioning (Table 3). Middle-aged adults also showed additional interaction effects of MDD with greater reports of organization and planning difficulties compared to younger adults, whereas the older adults did not (Table 3). When evaluating older adults compared to middle-aged adults, older adults with MDD reported greater visuospatial difficulties than middle-aged adults (+0.263 points, lower CI 0.007; upper CI = 0.519, $p = .044$) and reported fewer organization difficulties (−0.348 points, lower CI = −0.689; upper CI = −0.006, $p = .046$). Older adults and middle-aged adults did not differ in association of MDD with any other type of reported cognitive difficulties.

4. Discussion

In the combined sample our results replicate earlier studies showing an association of MDD with poorer objective cognitive performance and greater subjective ratings of cognitive difficulties across all domains assessed. We also report significant interactions of age group and MDD status with objective measures of cognition for both middle age and older adults when compared to young adults but no significant differences between middle-aged and older adults. Additionally, we show the association of MDD with report of subjective cognitive difficulties was stronger in middle-aged and older adults when compared to younger adults and was quite consistent in older adults compared to middle-aged adults. Each of these findings are discussed below.

Our hypothesis that self-reported major depression would be

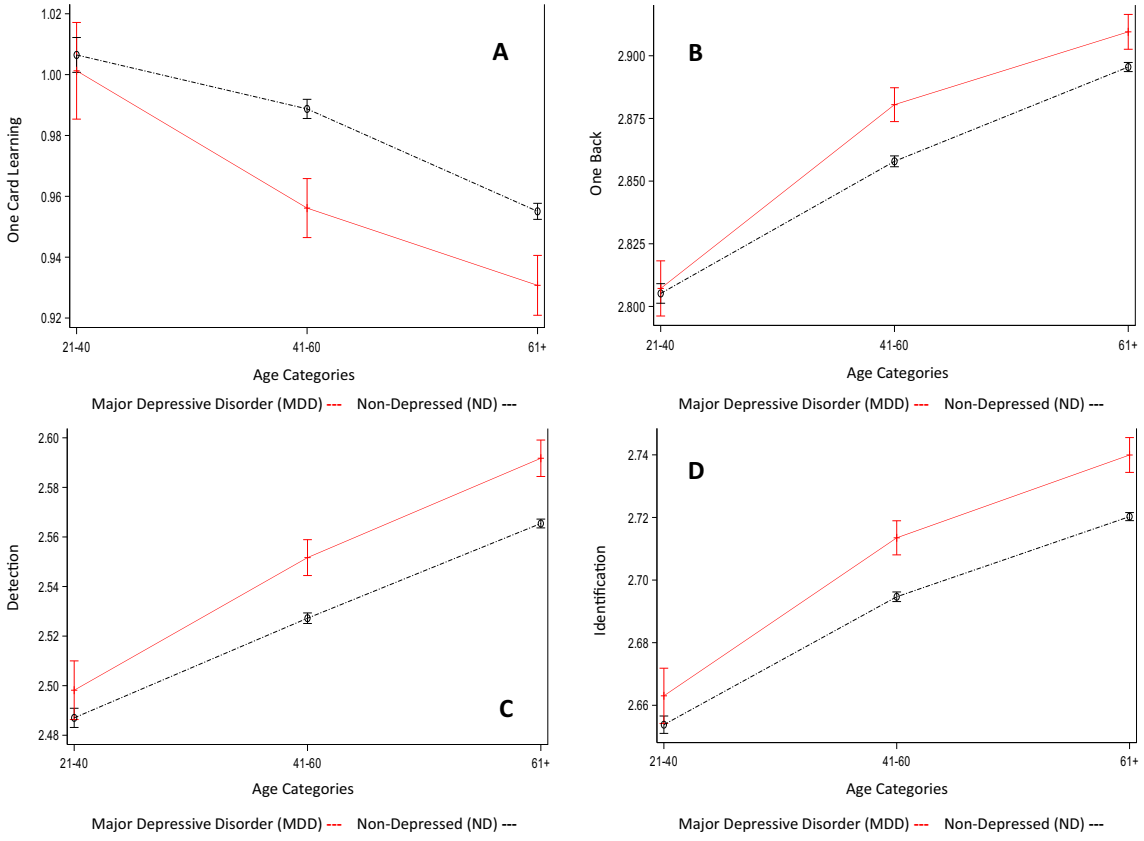

Fig. 1. Plots of the least squares mean of the CBB cognitive tests vs age in MDD participants. Panel A: One Card Learning Task, panel B: One Back Task, panel C: Detection Task, panel D: Identification Task.

Table 2
Estimated differences in depression effects of middle age (age 41–60) and older adults (age 61+) relative to young adults (age 21–40) for objective measures of cognition.

Cognitive test	41–60				61+			
	Estimated difference	Lower CI	Upper CI	*p*	Estimated difference	Lower CI	Upper CI	*p*
OCL	−0.028	−0.046	−0.009	0.0034	−0.019	−0.038	−0.000	0.045
ONB	0.022	0.035	0.009	0.0007	0.013	0.000	0.026	0.047
DET	0.015	0.002	0.027	0.023	0.017	0.004	0.030	0.010
IDN	0.011	0.001	0.020	0.023	0.011	0.002	0.021	0.017

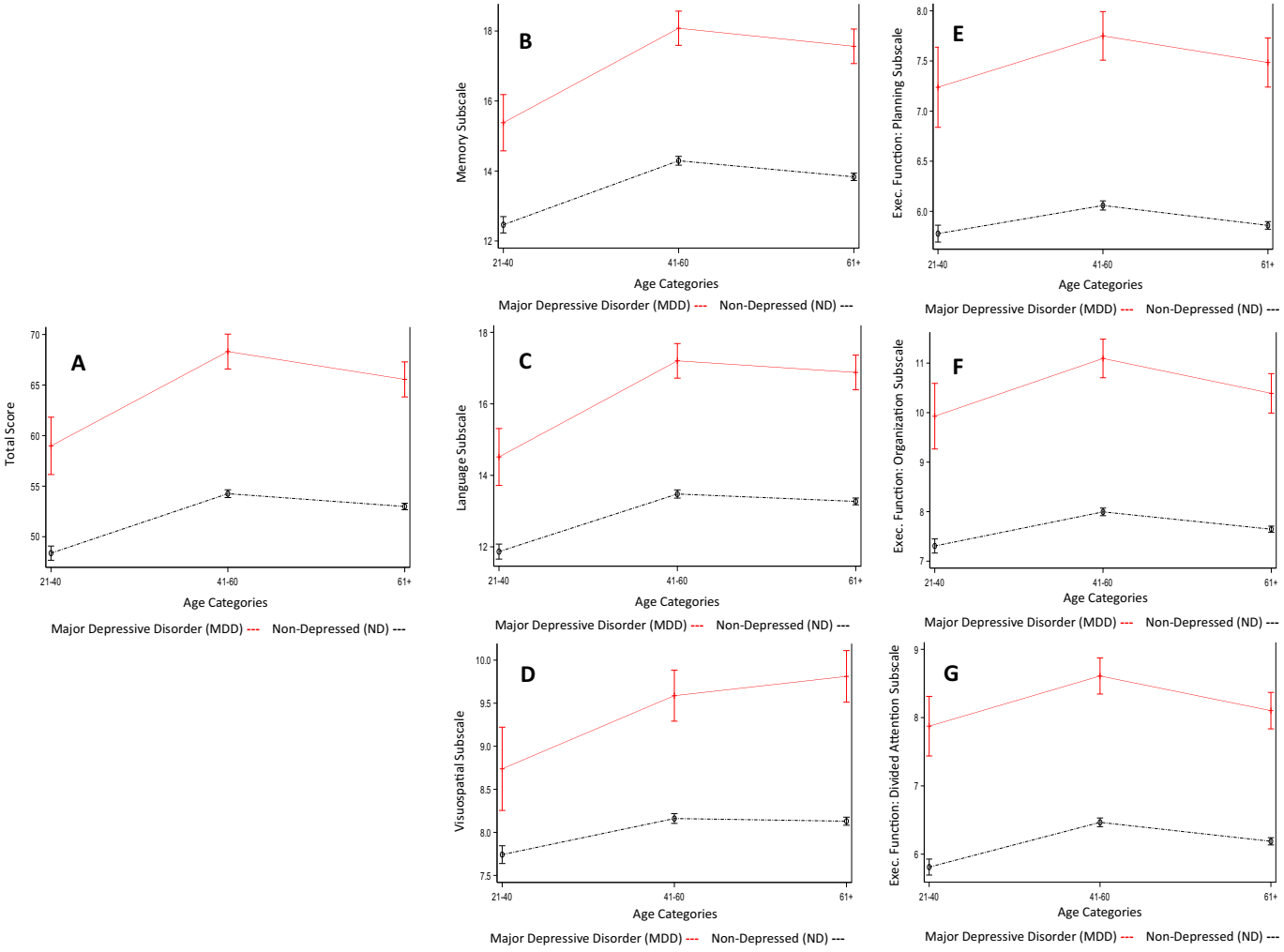

Fig. 2. Plots of the least squares mean of the Everyday Cognition Scale (ECog) vs age in MDD participants.
Panel A: ECog Total, panel B: ECog Memory Subscale, panel C: ECog Language Subscale, panel D: ECog Visuospatial Subscale, panel E: ECog Executive Function Planning Subscale, panel F: ECog Executive Function Organization Subscale, panel G: ECog Executive Function Divided Attention Subscale.

Table 3
Estimated differences in depression effects of middle age (age 41–60) and older adults (age 61+) relative to young adults (age 21–40) for reports of subjective cognitive difficulties.

	41–60				61+			
ECog subscales	Estimated difference	Lower CI	Upper CI	*p*	Estimated difference	Lower CI	Upper CI	*p*
Memory	1.055	0.288	1.82	0.007	0.948	0.173	1.72	0.017
Language	1.244	0.542	1.95	<0.0001	1.131	0.422	1.84	0.002
Visuospatial	0.508	0.146	0.869	0.006	0.771	0.404	1.14	<0.0001
Planning	0.312	0.018	0.806	0.038	0.254	−0.043	0.552	0.094
Organization	0.600	0.103	1.10	0.018	0.252	−0.251	0.755	0.330
Divided attention	0.159	−0.232	0.550	0.420	−0.057	−0.452	0.338	0.780

associated with poorer performance on objective tests of cognitive functioning in each of the four cognitive domains assessed was supported when evaluated in the combined sample of participants of all ages. These results are consistent with previous studies that have used supervised computer administered cognitive tests to demonstrate depression associated cognitive dysfunction (Hammar et al., 2003; Rock et al., 2014; Weiland-Fiedler et al., 2004; McIntyre et al., 2017; Davis et al., 2017; Chen et al., 2018). These results are important as we utilized unsupervised, remotely administered tests of cognition and these findings provide evidence of the validity of these measures for evaluating cognitive dysfunction remotely for individuals with MDD. However, these results were not observed in all age groups; in the youngest age group there were no significant effects of depression on objective cognition which is inconsistent with other studies that have reported cognitive dysfunction in young adults with MDD using clinically administered measures (Hammar et al., 2009; Airaksinen et al., 2004; Porter et al., 2003; Dotson et al., 2020; Liu et al., 2019). Therefore, our findings suggest that cognitive dysfunction is more strongly associated with MDD in middle-aged and older adults than young adults even after controlling for diminished cognitive reserve and/or increased risk for neurodegenerative processes starting in middle age (Ferreira et al., 2017). However, we cannot rule out the possibility that the unsupervised cognitive measures that we utilized for this study may have decreased validity for detecting cognitive dysfunction in young adults with MDD.

Our results did not show greater effect of MDD status on measures of objective cognition in older adults when compared to middle-aged adults. These results were both unexpected and inconsistent with previous studies suggesting that cognitive dysfunction associated with MDD progressively worsens with increasing age through older adulthood (Lee et al., 2012; Dotson et al., 2020). Of note, our methodology differed from these previous studies in that we specifically evaluated MDD and age interactions across three predetermined age groups. Our findings thus raise the potential that previous results implicating progressive worsening of cognition with MDD were influenced by confounding non-depression factors, most notably age effects. This interpretation is supported by our data showing age effects in our sample were progressive through older adulthood, i.e., continued decline was evident with increasing age across all three age groups. We believe we are among the first to employ this methodological approach in a large sample of MDD adults to show the association of MDD with cognition is similar in middle-aged and older adults. Further, these results would suggest that increased risk for dementia associated with MDD (Richard et al., 2013) could, in part, reflect an additive effect of MDD with neurodegenerative changes that begin in midlife (Ferreira et al., 2017) more so than greater cognitive consequences MDD in older adults.

Across the entire sample, and within each age group, MDD was associated with greater subjective report of cognitive difficulties when compared to ND. As report of subjective cognitive difficulties are a diagnostic criterion for MDD these findings were expected and are consistent with the extant literature (Fischer et al., 2008; Lawrence et al., 2013; Mohn and Rund, 2016; Morey-Nase et al., 2019; Allott et al., 2020; Bhang et al., 2020; Slavin et al., 2010). However, we believe this is the first study to show these relationships of MDD with remotely administered measures of subjective report of cognitive difficulties. In conjunction with lack of objective cognitive dysfunction in younger adults, these results suggest that perception of cognitive difficulties may be a more sensitive marker of MDD than actual cognitive dysfunction in younger adults. Alternatively, report of cognitive symptoms may simply lead to greater rates of MDD diagnosis in the absence of objective cognitive dysfunction in this age group. We are not aware of previous studies evaluating concordance of objective cognitive performance assessed remotely with reports of subjective cognitive difficulties specifically among young adults with MDD, but further investigation of these relationships is warranted to clarify these relationships.

Our hypothesis that MDD would show interaction effects across age groups on measures of subjective cognitive complaints was only partially supported. We report that MDD was associated with report of greater subjective cognitive difficulties for memory, language, and visuospatial functioning in middle-aged and older adults when compared to younger adults. Of note, greater reports of cognitive difficulties in these domains generally corresponds with evidence of greater objective dysfunction for these age groups for the tests we administered but we did not specifically assess cognitive measures of language and visuospatial abilities. Thus, these findings support subjective cognitive complaints as a general marker of underlying cognitive dysfunction. Furthermore, middle-aged adults showed an interactive effect of MDD with planning and organization difficulties as compared to young adults, whereas the older adults did not. These results suggest that older adults may be less impacted in these cognitive domains or have less insight into cognitive dysfunction in these domains, than middle-aged adults. Unfortunately, we do not have objective cognitive tests for these executive domains and further study is necessary to evaluate this interpretation. Nonetheless, our results do not show any increased report of subjective cognitive difficulties in planning or organization that are associated with depression in older adults relative to young adults.

Our finding that the association of MDD and subjective cognitive complaints did not differ for older adults compared to middle-aged adults for the majority of cognitive complaint types we assessed again suggests that cognitive dysfunction associated with MDD does not have a differential effect on older adults. More specifically, while depression was consistently associated with greater report of cognitive difficulties, this association was not stronger in older adults except for difficulties related to visuospatial functioning. As visuospatial deficits are not commonly associated with MDD this was an unexpected finding but not likely to influence diagnosis of MDD. In contrast, older adults with MDD had a weaker association with organization difficulties compared to middle-aged adults and did not differ on any of the remaining cognitive complaints. Additionally, the association of age with reported cognitive difficulties in our sample of MDD and ND plateaued in middle age and diminished somewhat in older adults similar to a previous study in ND (Begum et al., 2014). Collectively these results would suggest that increased rates of MDD in older adults compared to middle-aged adults may be in part due to greater report of cognitive complaints but the origin of this increased rate of complaints is due to age effects and does not reflect an increased sensitivity to MDD.

Our study had many strengths. First, our sample consisted of a much larger number of individuals with self-reported MDD across the entire adult age spectrum than has previously been employed to evaluate objective measures of cognition and report of subjective cognitive difficulties. Additionally, by evaluating the interaction of MDD with our three age groups, we were able to evaluate the degree to which depression was associated with both objective and subjective cognitive measures independent of age effects which, to our knowledge, has not been previously evaluated. Lastly, because our study was conducted remotely, participants were not required to visit the clinic for evaluation, which allowed for the inclusion of participants that may otherwise have barriers to participating in onsite clinical studies.

Despite these strengths, our study is not without limitations. First, our categorization of depression was based on self-report of a single question. We acknowledge that not all participants may be familiar with the term major depression, that some participants may not have endorsed this item despite having a diagnosis, and that we did not have clinical confirmation of MDD diagnosis. Our results that the MDD group reported significantly greater depressive symptom severity than ND participants offers support for the validity of this approach, however future work should attempt to replicate these findings with clinically confirmed diagnoses of participants. Given this, despite our results showing MDD was associated with significantly greater depressive symptom severity, we interpret our results with caution. Our evaluation of cognitive functioning and subjective report of cognitive difficulties also utilized online measures without analogous clinically administered

measures which would offer further opportunity to evaluate our hypotheses. Further, we recognize that individuals who are experiencing cognitive difficulties may be less likely to participate in this study due to study demands of being able to use a computer. Additionally, our measure of cognitive difficulties utilized a reference point of cognitive functioning ten years prior and, as such, may be less sensitive for our youngest age group. Similarly, we did not evaluate the relationship of observed cognitive dysfunction with reports of subjective cognitive difficulties as this was beyond the scope of our stated aims. As previous studies have reported a relatively low degree of association between actual and perceived cognitive dysfunction in MDD (Allott et al., 2020; Serra-Blasco et al., 2019; Brown et al., 2020), further investigation of these relationships using unsupervised measures will be important. Our remote evaluation of participants also required English language proficiency, access to the internet and a computer, and a majority of the sample was White, and is therefore not generalizable to all adults with depression. Lastly, we investigated three specific age groups for this study and recognize that evaluating more age groups could influence our results.

Overall, our study provides evidence that unsupervised and remotely administered measures of cognition and subjective cognitive complaints are sensitive to dysfunction in MDD participants. These depression characteristics are important for studies of MDD across the lifespan and also cognitive decline in aging and neurodegenerative disease and remote assessments offer an important potential tool for this work. Our results also suggest objective and subjective cognitive correlates of MDD are not progressive throughout the entirety of the adult age spectrum and instead appear to plateau in middle age. In contrast, age effects on objective measures of cognition were seen to be progressive through older adulthood and subjective report of cognitive difficulties again plateaued in middle age. Collectively, our results suggest that age effects, and not greater effects of depression, may lead to increased rate of diagnosis of MDD based on cognitive symptomatology in older adults and that MDD associated increased risk for dementia is likely due to the additive effects of age and MDD on cognition, and not a greater cognitive consequence of MDD in older adults.

Credit authorship contribution statement

R. Scott Mackin: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Chengshi Jin:** Formal analysis, Writing – original draft, Writing – review & editing. **Emily Burns:** Writing – original draft, Writing – review & editing. **Michelle Kassel:** Writing – original draft, Writing – review & editing. **Emma Rhodes:** Writing – original draft, Writing – review & editing. **Rachel Nosheny:** Writing – original draft, Writing – review & editing. **Miriam Ashford:** Writing – original draft, Writing – review & editing. **Tim Banh:** Writing – original draft, Writing – review & editing. **Joseph Eichenbaum:** Writing – original draft, Writing – review & editing. **Kristen Knight:** Writing – original draft, Writing – review & editing. **Rachana Tank:** Writing – original draft, Writing – review & editing. **Monica R. Camacho:** Writing – original draft, Writing – review & editing. **Juliet Fockler:** Writing – original draft, Writing – review & editing. **Diana Truran:** Writing – original draft, Writing – review & editing. **John Neuhaus:** Formal analysis, Writing – original draft, Writing – review & editing. **Michael Weiner:** Funding acquisition, Writing – original draft, Writing – review & editing, Project administration.

Conflict of interest

During the past three years, Dr. Mackin has received research support from The National Institute of Mental Health and Janssen Research and Development, LLC. Dr. Weiner has served on the Scientific Advisory Boards for Pfizer, BOLT International, Neurotrope Bioscience, Alzheon, Inc., Alzheimer's Therapeutic Research Institute (ATRI), Eli Lilly, U. of Penn's Neuroscience of Behavior Initiative, National Brain Research Centre (NBRC), India, Dolby Family Ventures, LP, and ADNI. Dr. Neuhaus has received research support from The National Institute on Aging. Dr. Nosheny has received research support from The National Institute on Aging; the California Department of Public Health; Genentech, Inc.; and the Alzheimer's Association. Dr. Ashford has received research support from the National Institute of Aging. Drs. Rhodes, Kassel, Knight, Banh, Ashford, and Tank, and Emily Burns, Monica R. Camacho, Diana Truran, Chengshi Jin, and Joseph Eichenbaum reported no biomedical financial interests or potential conflicts of interest.

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