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Heterogeneity of Cognition in Older Adults with Remitted Major Depressive Disorder: A Latent Profile Analysis

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ABSTRACT

Objectives: *To identify data-driven cognitive profiles in older adults with remitted major depressive disorder (rMDD) with or without mild cognitive impairment (MCI) and examine how the profiles differ regarding demographic, clinical, and neuroimaging measures.* ***Design:*** *Secondary cross-sectional analysis using latent profile analysis.* ***Setting:*** *Multisite clinical trial in Toronto, Canada.* ***Participants:*** *One hundred seventy-eight participants who met DSM-5 criteria for rMDD without MCI (rMDD-MCI; n = 60) or with MCI (rMDD + MCI; n = 118).* ***Measurements:*** *Demographic, clinical, neuroimaging measures, and domain scores from a neuropsychological battery assessing verbal memory, visuospatial memory, processing speed, working memory, language, and executive function.* ***Results:*** *We identified three latent profiles: Profile 1 (*poor

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cognition*; n = 75, 42.1%), Profile 2 (*intermediate cognition*; n = 75, 42.1%), and Profile 3 (*normal cognition*; n = 28, 15.7%). Compared to participants with Profile 3, those with Profile 1 or 2 were older, had lower education, experienced a greater burden of medical comorbidities, and were more likely to have MCI. The profiles did not differ on the severity of residual symptoms, age of onset of rMDD, number of depressive episodes, psychotropic medication, cerebrovascular risk, ApoE4 carrier status, or family history of depression, dementia, or Alzheimer's disease. The profiles differed in cortical thickness of 15 regions, with the most prominent effects for left precentral and pars opercularis, and right inferior parietal and supramarginal.* ***Conclusion:*** *Older patients with rMDD can be grouped cross-sectionally based on data-driven cognitive profiles that differ from the absence or presence of a diagnosis of MCI. Future research should determine the differential risk for dementia of these data-driven subgroups.* (Am J Geriatr Psychiatry 2024; 32:867–878)

Highlights

- **What is the primary question addressed by this study?**
  What are the cognitive profiles of older adults with remitted major depressive disorder (rMDD) with or without mild cognitive impairment (MCI)? How do these profiles differ in terms of clinical, demographic, and brain structure features?
- **What is the main finding of this study?**
  Using latent profile analysis, we identified three cognitive profiles, with differences in cognition, physical health, education, and brain structure.
- **What is the meaning of the finding?**
  Older patients with rMDD can be grouped cross-sectionally based on distinct data-driven cognitive profiles that differ from the absence or presence of a diagnosis of MCI.

INTRODUCTION

Current or remitted major depressive disorder (rMDD) in late life is associated with cognitive impairment in executive function, processing speed, attention, episodic memory, visuospatial memory, or language skills.[1] Deficits in executive function and processing speed are most pronounced and frequent.[2,3] Further, about 40% of older patients with MDD concurrently meet diagnostic criteria for mild cognitive impairment (MCI), a known prodrome to dementia, including Vascular dementia and Alzheimer's dementia (AD).[2,4] Cognitive impairment in late-life MDD is linked to poor treatment outcomes; for example, executive dysfunction increases the risk of poor treatment response to antidepressants and is associated with higher recurrence and relapse rates.[5]

Despite the successful treatment of their depression, nearly half of older patients remain cognitively impaired,[6] and a remote major depressive episode (MDE) in remission for many years still increases the risk of developing dementia years later.[7] Surprisingly, a longer interval since an MDD diagnosis has been associated with an increased risk for AD,[7] and recent evidence supports that depression diagnosed in early- or mid-life increases the risk for dementia.[8] While data supports the relevance of rMDD in the risk for AD, few studies have studied rMDD groups with or without MCI. In a recent systematic review of brain-cognition relationships, only two studies focused on those with MDD plus MCI; both of these studies assessed cognition in acutely depressed patients, precluding the determination of whether the acute depression was temporarily affecting cognition or whether the cognitive impairment was more permanent.[9] Therefore, more studies need to focus on rMDD.

There is a large degree of heterogeneity in the cognitive profiles of older patients with MDD or rMDD.[1–3,10–13] This could be attributed to the heterogeneous nature of MDD in terms of depression severity, symptom dimensions, age of onset, medication use, or remission status.[14–17] Other sources of variability could be the various proposed mechanisms underlying cognitive impairment in late-life MDD; these include vascular, peripheral proinflammatory, and AD-related pathology (e.g., β-amyloid) pathways.[18–20]

Identifying group differences between data-driven cognitive subgroups of older patients with rMDD could improve our understanding of the sources of heterogeneity in cognitive performance in this population. Data-driven clustering approaches have been used to disentangle the heterogeneity in MDD.[21] One such approach is Latent Profile Analysis (LPA). LPA is a person-centered data-driven approach used to uncover heterogeneity by generating homogeneous profiles based on a shared set of predictor variables.[22] LPA has gained popularity in studies of MDD, but its use has been limited to generating profiles based on depression symptoms, rather than cognitive scores.[14,23–25] To our knowledge, only one study has used LPA to identify patterns of cognitive performance in MDD in later life.[26] That study had limitations: it used single test scores as predictors (versus composite domain scores), and did not distinguish those with or without MCI.[26] In the current study, we leveraged a well-phenotyped sample of older adults with rMDD and MCI diagnoses to identify data-driven cognitive profiles. We also tested whether the data-driven cognitive groups differ in demographic and clinical variables. Based on the evidence suggesting cortical thinning in the prefrontal, orbitofrontal, anterior/posterior cingulate, and temporal cortices in late-life MDD,[27] we examined whether data-driven groups differed on regional cortical thickness variables. We hypothesized that our model will result in at least two data-driven groups, and that these groups would differ in demographic, cognitive, clinical, and neuroimaging characteristics. Finally, we explored whether the data-driven cognitive profiles align with a diagnosis of MCI or the absence of MCI.

METHODS

We analyzed baseline data from the Prevention of Alzheimer's dementia with Cognitive remediation plus transcranial direct current stimulation in Mild cognitive impairment and Depression (PACt-MD) clinical trial conducted in five academic hospitals in Toronto, Canada (ClinicalTrials.gov: NCT02386670). The methods of PACt-MD have been described previously and are briefly summarized below.[28]

Participants

We included PACt-MD participants with rMDD without MCI (rMDD-MCI; n = 60) or with MCI (rMDD + MCI; n = 118). In PACt-MD, participants were classified as rMDD with normal cognition or rMDD with MCI based on the results of a consensus conference. The eligibility criteria of the rMDD group (with or without MCI) were: 1) age ≥65; 2) a diagnosis of single or recurrent MDD according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) confirmed by the Structured Clinical Interview for the DSM; 3) a score of 10 or lower on the Montgomery–Åsberg Depression Rating Scale (MADRS); 4) ability to read and communicate in English. By design, participants in both groups were remitted from their depression at the time of study recruitment with a duration since their last MDE of at least 2 months; if the most recent MDE occurred more than 5 years ago, it must have received previous treatment for the participant to be eligible. The main exclusion criteria included a DSM-5 diagnosis of Major Neurocognitive Disorder ("dementia") or having received electroconvulsive therapy within 6 months of the assessment. MCI was diagnosed using the DSM-5 criteria for Mild Neurocognitive Disorder.

The PACt-MD study was approved by the Review and Ethics Board of the Centre for Addiction and Mental Health (CAMH), Toronto, Canada. All participants provided written informed consent before any research procedures were conducted.

Participants completed a detailed clinical assessment, a neuropsychological test battery, and were invited to complete a 3T MRI scan.

Cognitive Measures

All participants completed a comprehensive neuropsychological test battery summarized in Table 1. The neuropsychological tests included followed previously published work.[2,29] For each participant and each test, a z-score was calculated using the mean

TABLE 1. Summary of Neuropsychological Test Scores

Cognitive Domain	Neuropsychological Tests
Executive function	Trail-making test (TMT) B/A; clock-drawing test (CDT); Stroop Color and Word Test (SCWT)
Processing speed	Digit symbol subtest from the Wechsler Adult Intelligence Scale (WAIS III) and TMT-A tests
Visuospatial memory	Brief Visuospatial Memory Test−Revised (BMVT-R) total and percent retained
Verbal memory	California Verbal Learning Test II (CVLT-II) total recall, d' hits and false alarms of recognition Yes/No responses, and % retained at long delay trial from trial 5 at immediate recall condition
Working memory	Continuous Performance Test-Identical Pairs version (CPT-IP) 2,3,4 digits − d' and Paced Auditory Serial Addition Task (PASAT) 1.6″ and 2.4″ correct responses.
Language	Boston Naming Test (Split form; total of correct spontaneous responses and correct responses after stimulus cue); Letter Fluency (total F, A, S); Semantic Fluency (number of animals).

and standard deviation from 81 cognitively healthy non-depressed control participants in the PACt-MD trial (Supplementary Figure 2); 71 z-scores were capped ("winsorized") at ± 5 SD. Tests were then sorted into six separate cognitive domains: verbal memory, visuospatial memory, processing speed, working memory, language, and executive function. Domain scores were then calculated by averaging the z-scores of individual test scores within that domain (Table 1). Finally, an overall composite score was created by averaging the z-scores of the six domains.

Neuroimaging Measures

The magnetic resonance imaging (MRI) parameters and measures included in this study have been described in detail elsewhere[30] and in our supplementary material.

Statistical Analysis

Latent profile analysis (LPA)

We performed LPA using the *tidyLPA* package in R (R version 4.2.0).[31] LPA assumes a degree of heterogeneity among the predictor variables within a group of participants; further, it assumes a hidden, or *latent*, structure to the observed distribution of predictor variables. Unlike other clustering techniques, LPA is a model-based approach that identifies the probability of each participant belonging to a profile rather than assigning each participant to a specific cluster.[32] Therefore, it is considered more robust in identifying homogeneous profiles that are distinct from one another.[32]

The six cognitive domain scores were the predictor variables in our model. Before the analysis, we generated a correlation matrix of these predictor variables to test for multicollinearity that could influence our model fit[32]; all our correlation coefficients were less than 0.55. Also, as recommended,[32] we removed four outliers who scored below the 25th percentile or above the 75th percentile by a factor of 1.5*IQR on more than one cognitive domain (CONSORT chart in Supplementary Figure 1). We set the variance in our variables to equal and the covariance to zero. We tested six models (1−6 profiles) and compared them on model statistics, including: 1) fit indices - Akaike Information Criteria (AIC), Bayesian Information Criteria (BIC) and sample-size adjusted BIC (SABIC) (lower value suggests better fit); 2) model testing - bootstrapped likelihood ratio test p-value (BLRT_p) (if significant, indicates that the current number of profiles is a better fit than one fewer profiles); and 3) model characteristics based on the number of generated profiles, profile size, and entropy (suggests better profile separation when its value is closer to 1). We selected the optimal number of profiles based on the listed model fit statistics and on theoretical interpretation of the profiles. After selecting the most optimal model, we saved the posterior membership probabilities for further analysis.

Differences in demographic, clinical, cognitive, and neuroimaging variables

Using the Kruskal-Wallis test for continuous variables, and chi-square test for categorical variables, we compared the data-driven profiles using all available demographic, clinical, and cognitive characteristics. We calculated post-hoc pairwise comparisons between profiles while correcting for multiple comparisons testing using the pairwise Wilcoxon rank sum test (also known as Mann-Whitney U test).

We also compared regional cortical thickness among the three groups using an analysis of

covariance (ANCOVA) while controlling for age, sex, and education. We corrected for multiple comparisons testing using the false discovery rate (FDR) (i.e., using the *p-adjust, method = 'fdr'* function in R). Whenever a significant main effect was present after p-value correction, we ran pairwise comparisons using post-hoc Tukey honest significance test (HSD) on regions with significant differences between profiles to identify profiles that are significantly different from one another.

RESULTS

Participant Characteristics

Of the 206 participants who completed the neuropsychological test battery, 182 (rMDD-MCI: n = 60; rMDD + MCI: n = 122) had a complete set of scores (i.e., no missing values). After removing four statistical outliers, the sample comprised 178 participants (rMDD-MCI: n = 60; rMDD + MCI: n = 118) who remained and were included in the analysis (Supplementary Figure 1). Of the 178 participants included in the analysis, 122 completed a T1-weighted scan, passed quality control, and were included in the analysis of the neuroimaging data.

These 178 participants had a mean (SD) age of 70.9 (5.1) years, were predominantly female (n = 118, 66.3%), and typically had some college education (Table 3). The mean (SD) scores were 28.4 (1.5) for the MMSE, 25.8 (2.7) for the MoCA, and 5.0 (3.1) for the MADRS.

LPA

The model fit statistics from the LPA analysis are summarized in Table 2. Based on the AIC, entropy, and BLRT_p, the four-profile model had the most optimal fit to the data. However, one of the profiles had only seven participants, which is small relative to our total sample size, indicating that this profile was over-extracted due to extreme values of a single predictor variable, resulting in an over-fit.[32] The BLRT_p for the five-profile and six-profile models were not significant and these two models were not considered. Based on the BIC, the principle of parsimony, and the theoretical interpretation of the profiles, we selected the three-profile model as the final model for the remaining analyses.

In the three-profile model, profile 1 had 28 participants (15.7%); profile 2, 75 participants (42.1%); and profile 3, 75 participants (42.1%). The posterior membership probability (i.e., the probability that each participant belongs to their assigned profile) for each participant is presented in Supplementary Table 2.

Figure 1A presents the mean cognitive scores for the participants in each of the 3 profiles, showing that the profiles differ in the degree of severity of cognitive impairment for all domains. We labelled each profile based on this attribute: Profile 1 (*poor cognition*) includes participants whose scores were typically between 1.5 and 2 SD below the mean across all domains. Profile 3 (*normal cognition*) includes participants who appeared cognitively intact (i.e., typically at or above the mean) in all domains. Profile 2 (*intermediate cognition*) whose scores were typically between 0.6 and 1 SD below the mean for processing speed and working memory, while maintaining higher verbal and visuospatial memory scores.

Notably, participants' mean scores in the three profiles differed significantly on all six cognitive domains (Supplementary Table 3).

Figure 1B presents the percentages of participants with a consensus diagnosis of rMDD-MCI or rMDD +MCI. Profile 1 (*poor cognition*) comprised 1 (3.6%) participant with a diagnosis of rMDD-MCI and 27 (96.4%) with rMDD+MCI. Profile 2 (*intermediate cognition*) comprised 20 (26.7%) participants with rMDD-MCI and 55 (73.3%) with rMDD+MCI. Profile 3 (*normal cognition*) comprised 39 (52%) participants with rMDD-MCI and 36 with rMDD+MCI (48%) participants.

Differences in Demographic and Clinical Variables

Table 3 presents the clinical and demographic characteristics of the participants in the three data-driven profiles. Participants in Profile 1 (*poor cognition*) or Profile 2 (*intermediate cognition*) were significantly older (Kruskal-Wallis $H(2) = 9.5973$, $p = 0.008$), had lower education ($H(2) = 14.271$, $p = 0.0008$), and experienced a higher burden of physical comorbidities ($H(2) = 11.06$, $p = 0.004$) than those in Profile 3 (*normal cognition*). Participants in Profile 1 also scored significantly lower on the MMSE ($H(2) = 22.562$, $p < 0.001$).

TABLE 2. LPA Model Fit Statistics

Profiles	LogLik	AIC	BIC	SABIC	Entropy	Prob_Min	Prob_Max	BLRT_val	BLRT_p	Profile Size
1	-1516.06	3056.12	3094.30	3056.30	1	1	1	NA	NA	178
2	-1395.84	2829.67	2890.13	2829.96	0.809	0.898	0.969	240.443	0.0099	56/122
3	**-1370.01**	**2792.02**	**2874.75**	**2792.41**	**0.755**	**0.877**	**0.903**	**51.6517**	**0.0099**	**28/75/75**
4	-1353.85	2773.69	2878.69	2774.19	0.822	0.873	0.926	32.3289	0.0099	21/7/78/72
5	-1350.89	2781.78	2909.05	2782.38	0.817	0.601	0.910	5.91456	0.8515	22/6/74/69/7
6	-1342.13	2778.26	2927.81	2778.96	0.761	0.626	0.920	17.5180	0.1386	18/11/24/65/50/10

Notes: Model fit statistics from 6 LPA models (1-6 profiles). LogLik: Log-likelihood of the data based on the model; AIC: Aikake information criteria; BIC: Bayesian information criteria; SABIC: sample size-adjusted Bayesian information criteria; prob_min: minimum of the diagonal of the average latent profile probabilities for most likely class membership by assigned profile; prob_max: maximum of the diagonal of the average latent profile probabilities for most likely class membership by assigned profile; BLRT_val: bootstrapped likelihood test; BLRT_p: p-value for the bootstrapped likelihood ratio test.

Participants in the three profiles differed on their MoCA scores ($H(2)= 52.508$, $p < 0.001$), with Profile 1 scoring the lowest and those in Profile 3 the highest.

Participants across the three profiles did not differ on the MADRS, age of onset of first MDE, number of MDEs, psychotropic medication status, Framingham risk score, Apolipoprotein E4 (ApoE4) allele carrier status, or family history of depression, dementia, or Alzheimer's disease (Table 3).

FIGURE 1. Profile plot of mean cognitive scores and distribution of clinical diagnoses for the three data-driven profiles. [A] represents a profile plot of mean cognitive scores belonging to each data-driven profile. Error bars represent standard error of the mean. [B] represents the percentage breakdown of each data-driven profile by diagnosis (i.e., rMDD or rMDD+MCI).

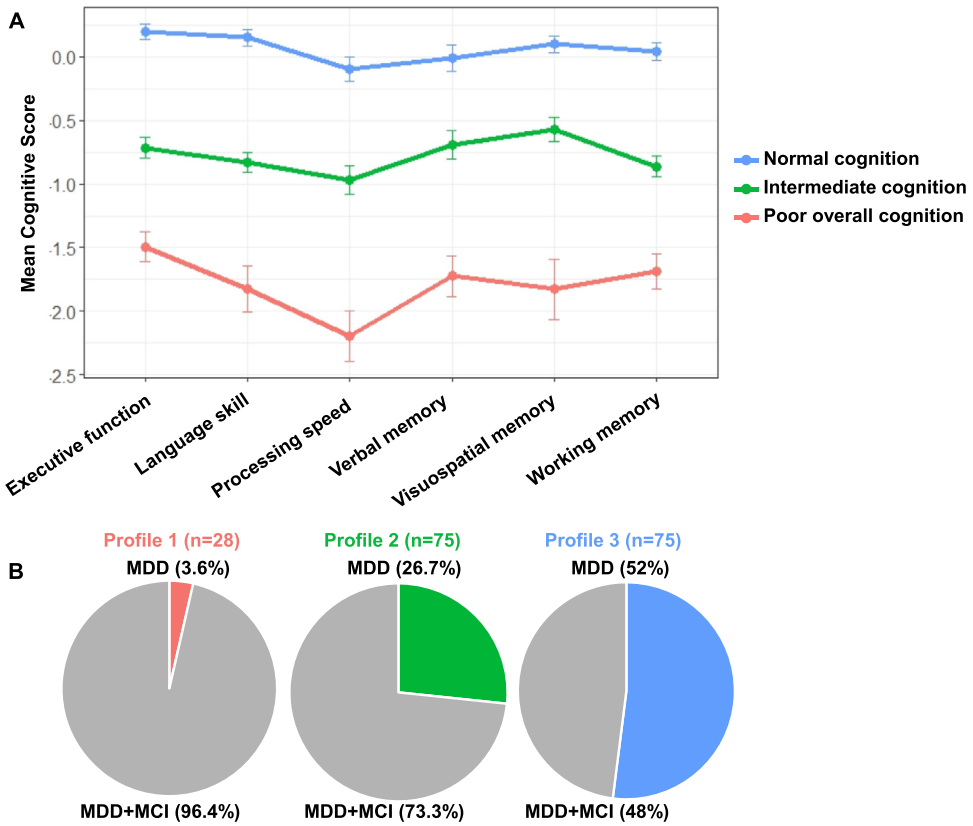


TABLE 3. Demographic and Clinical Characteristics of the Three Data-Driven Profiles

	Profile 1[g] (n = 28)	Profile 2[h] (n = 75)	Profile 3[i] (n = 75)	Statistics, p-Value	Post-Hoc Results
Age (years)	72.7 ± 5.8	71.8 ± 5.5	69.4 ± 3.8	H(2) = 9.5973, p = 0.008	1,2>3
Self-reported female at birth n (%)	20 (71.4)	45 (60)	53 (70.7)	X2 (2) = 2.3017, p = 0.32	-
Education level[a]	5.1 ± 1.6	5.7 ± 1.3	6.2 ± 0.8	H(2) = 14.271, p = 0.0008	1,2<3
MMSE score[b]	27.2 ± 1.6	28.4 ± 1.5	28.9 ± 1.2	H(2) = 22.562, p <0.001	1<2,3
MoCA score	23.0 ± 2.4	25.4 ± 2.3	27.3 ± 2.0	H(2) = 52.508, p <0.001	1<2<3
MADRS	5.4 ± 2.9	4.6 ± 3.0	5.1 ± 3.3	H(2) = 1.6727, p = 0.43	-
CIRS-G (total score)[c]	6.3 ± 3.7	5.4 ± 3.2	4.1 ± 2.9	H(2) = 11.06, p = 0.004	1,2>3
Age at onset of most recent MDE (years)[d]	42.0 ± 17.7	40.8 ± 20.1	37.2 ± 16.0	H(2) = 1.6416, p = 0.44	-
Number of MDE[e] **(n − 1/2/3/4/5)**	7/8/5/1/5	16/16/15/6/18	15/10/19/10/21	p = 0.59	
Family history of depression n (%)	14 (50.0)	34 (45.3)	37 (49.3)	X2 (2) = 0.30774, p = 0.86	-
Family history of dementia n (%)	12 (42.9)	27 (36.0)	41 (54.7)	X^2 (2) = 5.3391, p = 0.07	-
Family history of Alzheimer's disease n (%)	8 (28.6)	12 (16.0)	17 (22.7)	X^2 (2) = 2.2352, p = 0.33	-
ApoE4 status n (%) (carrier)[a]	7 (30.4)	26 (37.1)	18 (28.1)	X^2 (2) = 1.2913, p = 0.52	
Taking psychotropic medication (yes/no)	21 (75.0)	51 (68.0)	54 (72.0)	X^2(2) = 0.5754, p = 0.75	-
Framingham risk score[f] **(%)**	16.8 ± 8.5	19.6 ± 8.5	15.8 ± 9.3	H(2) = 5.3487, p = 0.07	-

Notes: Demographic and clinical characteristics of participants in the three data-driven profiles. All results are reported as mean ± SD unless otherwise indicated. Abbreviations: Apolipoprotein E (ApoE); CIRS-G: Cumulative Illness Rating Scale-Geriatric; MADRS: Montgomery−Åsberg Depression Rating Scale; MDE: major depressive episode; MMSE: The Mini Mental State Examination; MoCA: Montreal Cognitive Assessment. a21 values missing (i.e., n=157).

[a] Education level: 1 − Less than 7th grade; 2 − Junior high (9th grade); 3 − Partial high school (10th or 11th); 4 − High school graduate; 5 − Partial college (at least one year); 6 − College education; 7 − Graduate degree.

[b] 1 value missing;

[c] 7 value missing.;

[d] 2 values missing;

[e] 6 values missing;

[f] 58 values missing.

[g] Profile 1: poor cognition.

[h] Profile 2: intermediate cognition.

[i] Profile 3: normal cognition.

Differences in Neuroimaging Variables: Cortical Thickness

Figure 2 and Supplementary Table 4 present the comparison of the cortical thickness of participants in the three profiles. The model identified significant differences in 15 of 32 regions of interest (Supplementary Table 4). The largest effect size was for frontal and parietal regions including the left precentral ($F_{(2,116)}$ = 11.2, p <0.001, $\eta 2$ = 0.10), right inferior parietal ($F_{(2,116)}$ = 11.1, p = <0.001, $\eta 2$ = 0.12), left pars opercularis ($F_{(2,116)}$ = 8.6, p = 0.004, $\eta 2$ = 0.08), and right supramarginal ($F_{(2,116)}$ = 7.8, p = 0.004, $\eta 2$ = 0.09) (Figure 2).

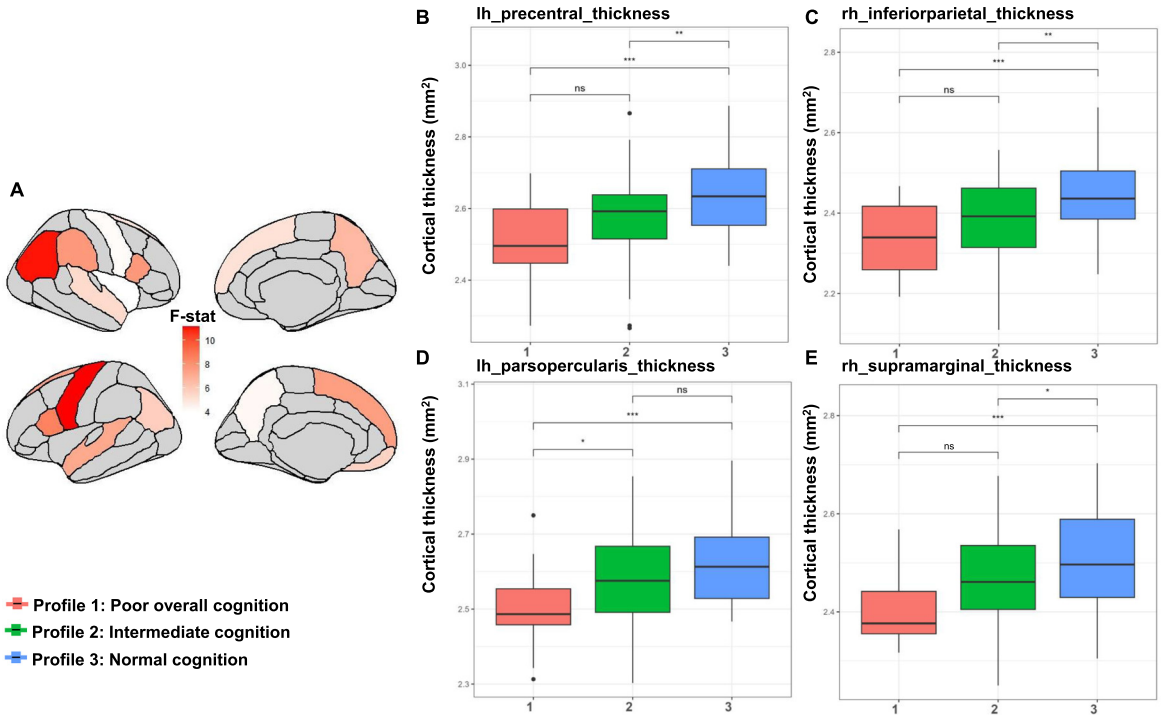
In the post-hoc Tukey HSD tests, participants in Profile 1 (*poor cognition*) had lower cortical thickness than those in Profile 3 (*normal cognition*) for 14/15 regions. Participants in Profile 2 (*intermediate cognition*) had lower thickness than those in Profile 3 on 9/15 regions, all of them being frontal, temporal, and. Participants in Profile 1 had lower thickness than those in Profile 2 in 3/15 regions - the right and left pars opercularis and the left medial orbitofrontal cortex (Supplementary Table 5).

We also examined differences in regional cortical thickness between the two diagnostic groups (i.e., rMDD-MCI versus rMDD+MCI); there were no significant differences in any of the 32 regions (Supplementary Table 6).

DISCUSSION

We used LPA to examine the heterogeneity in cognitive function in older adults with rMDD (with or without MCI). We report the following main findings: a three-profile model best fits our data, and these three profiles overlap only partially with the two traditional diagnostic groups of rMDD or rMDD+MCI. The profiles differed in severity of cognitive impairment, some demographic and clinical characteristics, and in cortical thickness of regions implicated in cognition of late-life MDD. Of the three

FIGURE 2. Cortical thickness in regions of interest for the three data-driven groups. [A] represents a brain map of the group differences in regional cortical thickness according to the Desikan-Kiliany atlas. The f-statistics of the 15 significant regions of interest are represented in scaled color. Significant regions are summarized in Table S3. [B–E] represent post-hoc Tukey HSD comparisons between profiles of selected regions with the largest effect sizes. Abbreviations: rh, right hemisphere; lh, left hemisphere; ns, not significant (i.e., p >0.05). *=p <0.50; **=p <0.01; ***=p <0.001.



profiles, we found one cognitively 'preserved' group, a cognitively 'impaired group,' and an intermediate group. These findings suggest that among older adults with rMDD, a data-driven method can distinguish at least three subgroups of patients who are expected to have different risks for developing dementia.

The three data-driven profiles (Fig. 1) primarily differed in their mean cognitive scores, with Profile 1 performing the worst, Profile 3 performing the best, and Profile 2 with an intermediate performance. The profiles were not specific to cognitive domains, likely due to relatively high correlations among these domains. Our findings are consistent with previous findings from a hierarchical agglomerative clustering study showing three cognitive profiles on a severity continuum.[33] In our sample, varying levels of cognitive performance were not related to the severity of residual depressive symptoms or age of onset of depression; this is not unexpected given the remitted status of our participants and the majority having early-onset depression. However, similar findings have been reported in participants with current depression.[26,33] Profiles 1 and 2 had a lower level of education than Profile 3, consistent with prior evidence that a lower education level is a risk factor for worse cognition in late life and dementia, including AD.[34] Our findings confirm that among older adults with rMDD (with or without MCI), higher education is a protective factor against lower cognition. Our finding that the three data-driven profiles did not differ in vascular risk is congruent with some[26] but not all[33,35] previous studies. While vascular risk may not always be associated with varying cognitive impairment in late-life rMDD, future studies should assess more extensive measures of vascular risk and associated imaging biomarkers (e.g., white matter hyperintensities).

Our data-driven profiles may be capturing variation in cognitive performance that is not fully captured by diagnostic labels.[36] Our model's cognitively normal and intermediate profiles included a substantial number of participants with an MCI diagnosis. For instance, the cognitively normal Profile 3 was equally divided between those with and without MCI. This is likely due to the diagnostic criteria for MCI, which are based on current cognitive function relative to estimated premorbid cognitive function. Our sample is highly educated and thus many participants in Profile 3 likely had very high premorbid function with current average function. As a result, they warrant a diagnosis of MCI (because they have presumably declined) but are currently functioning in the overall average range. While we did not detect differences in cortical thickness when comparing rMDD and rMDD+MCI diagnostic groups potentially due to overlapping neural mechanisms,[37] Profiles 1 and 2 showed reduced cortical thickness compared to Profile 3. The heterogeneity in diagnostic labels likely reflects a continuum in clinical presentation and the overlap between diagnoses in terms of underlying neurobiological mechanisms.[36] Data-driven approaches such as LPA can address this issue by identifying homogenous subgroups of patients and characterizing shared traits and neurobiological profiles that are not typically captured by diagnostic labels.

We identified a small group of patients (Profile 1) with rMDD+MCI with the most severe cognitive impairment associated with cortical thinning across frontal and temporal regions of the brain. These participants did not have dementia, but they have the lowest overall cognitive function and the thinnest cortical thickness. Also, most of them have a clinical diagnosis of MCI. Thus, we expect that they would be the group at the highest risk to develop dementia among our participants with rMDD who are all at risk for developing dementia.[8] Our finding that Profile 3 had the highest level of education and higher cortical thickness than Profiles 1 and 2 across frontal and temporal regions is consistent with previous findings suggesting that the superior frontal gyri and precuneus are two regions implicated in higher brain reserve among healthy and mildly impaired older adults.[38] While we found that Profile 1 was characterized by low processing speed, another group using LPA identified another vulnerable subgroup of older adults labelled "*amnestic depression*" that was characterized by poor verbal memory.[39] However, no study has examined the longitudinal risk of such data-driven groups for dementia. A direct examination of the predictive power of data-driven subgroups is critical to determine their clinical utility for adopting a personalized clinical care approach.[40] If validated longitudinally, our results and others could: 1) inform the design of cognitive decline prevention studies by prioritizing those who are at an increased risk; and 2) encourage clinicians to routinely assess the cognitive function of older patients with depression for early detection of cognitive impairment and early preventive intervention for dementia. Moreover, our results support a move away from case-control approaches to a dimensional view to avoid the assumption of homogeneity of this disorder.

Strengths of our study include using a comprehensive neuropsychological battery,[28] and composite cognitive domain scores (versus test scores) to assess cognition. We included a well-characterized sample of participants, with older patients with rMDD and varying levels of cognition. Our participants were also diagnosed based on operationalized diagnostic criteria at a consensus conference. We used LPA instead of other traditional clustering approaches (e.g., k-means clustering), which is model-based, allows for model fit evaluation, and is a more robust approach for clustering.[32] Our study also has limitations. Our participants' MDD was remitted, and over 80% had early-onset MDD; our results may not be generalizable to those with current, late-onset, or treatment-resistant MDD. Our participants have a relatively high level of education, with most participants having some college education; our results may not be generalizable to those with lower education. To create composite domain scores, we assigned each neuropsychological test to a specific cognitive domain based on the dominant cognitive skill required for its performance. Nevertheless, nearly all neuropsychological tests tap multiple domains. Our and other studies[39] group verbal learning and delayed recall scores in the "verbal memory" domain. However, certain aspects of executive function (e.g., attention, organization) impact rote verbal learning.[41] Therefore, part of a low verbal memory domain score could be due to executive dysfunction. Moreover, analyzable neuroimaging data were available in only two-thirds of our participants. Lastly, our cross-sectional

design does not allow us to assess longitudinal risk for developing dementia.

In conclusion, we identified three distinct data-driven cognitive profiles in older adults with rMDD. While these profiles showed differences in brain structure, these differences were not detected when directly comparing diagnostic groups. This suggests that our data-driven profiles may be more likely to uncover the heterogeneity in underlying neurobiological pathways contributing to the variability in cognitive presentation. Future longitudinal studies should assess the ability of these data-driven cognitive subgroups versus traditional diagnostic subgroups to predict the progression to dementia. These studies should also examine additional predictors of heterogeneity including multimodal measures of brain structure and other biomarkers (e.g., inflammation, immune function) to identify patients most vulnerable to dementia.

AUTHOR CONTRIBUTIONS

TM: substantially contributed to the conception or design of the work, analysis, and interpretation of the data, drafting the manuscript, and revising it, and agreeing to be accountable for all aspects of the work. PZ: substantially contributed to the analysis and interpretation of the data, drafting the manuscript, revising it, and approving the final version for publication. HB: substantially contributed to the analysis and interpretation of the data, revising the manuscript, and approving the final version for publication. CRB, MAB, CEF, AJF, NH, KL, LM, BGP, TKR, ANV: substantially contributed to the interpretation of the data, revising the manuscript, and approving the final version for publication. BHM: substantially contributed to the conception or design of the work and interpretation of the data, drafting the manuscript, and revising it, providing formal supervision for all aspects of the work, and agreeing to be accountable for all aspects of the work.

DATA STATEMENT

These data have been presented as a poster at the Canadian Conference on Dementia in November 2023 (Toronto, Canada), and accepted for a poster presentation at the American Association for Geriatric Psychiatry Annual Meeting to be presented in March 2024 (Atlanta, Georgia).

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SUPPLEMENTARY MATERIALS

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