Biological Psychiatry: CNNI

Archival Report

Atypical Brain Aging and Its Association With Working Memory Performance in Major Depressive Disorder

Natalie C.W. Ho, Richard A.I. Bethlehem, Jakob Seidlitz, Nikita Nogovitsyn, Paul Metzak, Pedro L. Ballester, Stefanie Hassel, Susan Rotzinger, Jordan Poppenk, Raymond W. Lam, Valerie H. Taylor, Roumen Milev, Lifespan Brain Chart Consortium, Edward T. Bullmore, Aaron F. Alexander-Bloch, Benicio N. Frey, Kate L. Harkness, Jean Addington, Sidney H. Kennedy, and Katharine Dunlop

ABSTRACT

BACKGROUND: Patients with major depressive disorder (MDD) can present with altered brain structure and deficits in cognitive function similar to those seen in aging. However, the interaction between age-related brain changes and brain development in MDD remains understudied. In a cohort of adolescents and adults with and without MDD, we assessed brain aging differences and associations through a newly developed tool that quantifies normative neurodevelopmental trajectories.

METHODS: A total of 304 participants with MDD and 236 control participants without depression were recruited and scanned from 3 studies under the Canadian Biomarker Integration Network for Depression. Volumetric data were used to generate brain centile scores, which were examined for 1) differences between participants with MDD and control participants; 2) differences between individuals with versus without severe childhood maltreatment; and 3) correlations with depressive symptom severity, neurocognitive assessment domains, and escitalopram treatment response.

RESULTS: Brain centiles were significantly lower in the MDD group than in the control group. Brain centile was also significantly correlated with working memory in the control group but not the MDD group. No significant associations were observed between depression severity or antidepressant treatment response and brain centiles. Likewise, childhood maltreatment history did not significantly affect brain centiles.

CONCLUSIONS: Consistent with previous work on machine learning models that predict brain age, brain centile scores differed in people diagnosed with MDD, and MDD was associated with differential relationships between centile scores and working memory. The results support the notion of atypical development and aging in MDD, with implications for neurocognitive deficits associated with aging-related cognitive function.

https://doi.org/10.1016/j.bpsc.2024.04.008

Aging is associated with gradual physiological changes in the brain and behavior. Age-related cognitive decline occurs in several domains, including memory, attention, and executive function (1,2). For example, a large-scale prospective cohort showed that memory, processing speed, executive function, and global cognition declined with older age (3). In turn, age-related cognitive decline is correlated with global cerebral atrophy, as evidenced by reduced gray matter volume (GMV), cortical thinning, sulcal widening, and ventricular expansion on magnetic resonance imaging (MRI) (4). Using large databases, characterizations of normative brain development and aging have illuminated the healthy aging brain at different ages (5). However, physiological age-related decline in cognition is heterogeneous (6); some individuals decline faster than others of the same age, which may depend on environmental factors, genetics, or both (7).

Major depressive disorder (MDD) may significantly influence age-related decline (8). Individuals diagnosed with MDD exhibit sustained deficits in attention, working memory, and long-term memory, even after remission, and with greater effect in individuals with recurrent MDD (9). Furthermore, patients with MDD present with altered brain structure and function such as that observed in age-related cognitive decline, including gray matter atrophy in regions crucial for memory formation and processing, such as the hippocampus, frontal cortex, putamen, thalamus, and amygdala (10). Unfortunately, relatively few studies have focused on the relationship between aging and psychopathology. A comprehensive understanding of the pathophysiology of MDD is important for developing novel therapeutic strategies and optimizing existing ones. There is a knowledge gap in understanding how depression impacts brain aging and cognitive function.

Brain-based age prediction is one method to understand the interplay between heterogeneous brain- and behavioral-based markers (11). Such approaches typically develop a machine learning model predicting age and trained on normative structural MRI data across the life span. Deviations between the chronological and predicted ages, also called the brain-predicted age difference (brain-PAD), can be applied to find differences between diagnostic groups or associations with behavior. There is considerable variability in the methodological approach (e.g., Gaussian process regression, regularized gradient tree boosting, deep learning), feature extraction (e.g., raw T1-weighted structural image, regional parcellation), and normative sample used for training. However, numerous studies have successfully investigated brain age using this method, including to predict mortality (11), multiple sclerosis progression (12), and dementia risk (13).

Patients with MDD may exhibit accelerated biological indices of aging. For example, patients with MDD have shorter leukocyte telomere lengths than control participants without depression (HCs) (14,15), which may predict poorer response to selective serotonin reuptake inhibitors (16,17). However, brain-PAD–based studies have yielded conflicting findings, with some (18–20) but not all (21) demonstrating higher brain-PAD scores in individuals with MDD than in HCs. Similarly, brain-PAD–based characterizations of aging in MDD conflict with respect to pharmacotherapy response, with one group reporting no correlations between brain-PAD and escitalopram response (22) while another reported an association between accelerated brain aging and poor response to sertraline (23). Furthermore, these studies focused on adult cohorts and not adolescents, which creates limitations for our understanding of risk for psychiatric disorders during critical neurodevelopmental windows.

The development of human brain charts addresses the need for a standardized tool to evaluate individual differences in age-related brain changes across the life span. Like height and weight growth charts, brain charts (5) present normative, nonlinear trajectories of normative aging based on fitting generalized additive models for location, scale, and shape models from a large ($N > 100{,}000$), multisite structural MRI dataset including the UK Biobank, Human Connectome Project, and others. Global brain measures were used in BrainChart, including cortical gray matter, white matter, subcortical gray matter, and ventricular volumes. This approach was empirically optimized, evaluated for confounds such as site, and included consideration of nonlinear age-related changes in volume, examined separately by sex. Centile scores exhibit test-retest reliability in out-of-sample testing and robustness to varying image analysis pipelines. Brain centile scores have potential clinical utility, showing significant differences in individuals with Alzheimer's disease and males with MDD (5). Brain charts could serve as a useful tool to investigate the relationship between aging and brain development. However, it is unknown whether brain centiles scores are related to cognitive factors related to aging, treatment response, or environmental factors that confer risk for MDD (24).

Childhood maltreatment (CM) is one well-documented risk factor for MDD. CM is correlated with earlier depression onset, greater severity, and a higher likelihood of developing treatment-resistant MDD (25,26). Individuals with a history of CM also demonstrate structural changes in brain areas involved in emotional processing and memory, including the hippocampus and dorsomedial prefrontal cortex (27–30). CM interacts with age in predicting the cortical thickness of emotion regulation regions, such as the insular, cingulate, orbitofrontal, dorsolateral, and medial prefrontal cortices (31). Therefore, investigating the effects of CM on brain age may elucidate the mechanism through which it increases MDD risk.

In this study, we aimed to examine the impact of brain aging—measured by brain chart–based centile scores—in MDD using a multisite sample of individuals (ages 12–65 years). We also aimed to investigate the impact of brain aging on age-related cognition, CM, and antidepressant response. We hypothesized that brain centile scores would differ significantly between individuals with MDD and HCs, with greater atypical centile scores being correlated with depression severity. We also expected an association between centile scores and cognitive performance in age-related domains and that this relationship would differ in MDD. Additionally, we predicted that brain centile score would be associated with response to the commonly prescribed first-line antidepressant medication escitalopram. Lastly, we hypothesized that centile scores would differ in individuals with and without a history of CM.

METHODS AND MATERIALS

Recruitment

HCs and participants with depression were recruited for 3 studies associated with the CAN-BIND (Canadian Biomarker Integration Network for Depression) program (32): CAN-BIND-1 (Biomarkers of Antidepressant Response to Medication; NCT01655706), PRO-CAN (Canadian Psychiatric Risk and Outcome Study; NCT02739932), and SARA (Stress and Reward Anhedonia Study; NCT02798094). Details about the aims and design for each study are provided in the Supplement. We were adequately powered to assess differences in treatment response (33) and centile score. Using the results reported by Luo *et al.* (34) at $\alpha = 0.05$ and power = 0.8, we would need 86 participants per group to detect a significant difference.

CAN-BIND-1 aimed to identify biological markers of pharmacotherapy response (33); recruitment occurred at 6 sites across Canada. All participants with MDD (ages 18–60 years) were treated with 8 weeks of flexible-dose open-label escitalopram. HCs had the same age range and language requirements as the participants with MDD but no history of Axis I or II disorders. PRO-CAN sought to identify youths at risk of developing serious mental illnesses (ages 12–25 years); this study recruited individuals with 1) no mental health concerns, 2) an at-risk group with a family history of a serious mental illness, 3) a group with early mood symptoms, or 4) attenuated serious mental illness symptoms (35). For our purposes, we retained HCs and individuals with MDD symptoms who met DSM-IV-TR criteria for a major depressive episode. SARA examined abnormalities in the processing of stressful and rewarding information and their relationship to depression (ages 18–65 years). Participants with MDD and HCs were recruited (36). Eligible participants of all studies provided written informed consent, and all study protocols were

approved by the research ethics board at each participating site.

Clinical Measures

CAN-BIND-1 and SARA measured depression severity using the Montgomery–Åsberg Depression Rating Scale (MADRS) (37), a 10-item clinician-rated questionnaire. For CAN-BIND-1, the MADRS was acquired every 2 weeks throughout treatment. PRO-CAN assessed depression using the Beck Depression Inventory (38), a 21-item self-report questionnaire. Consequently, we used the MADRS and Beck Depression Inventory as the primary measures of depression severity. Values were combined by normalizing scale scores, generating *z* scores.

CM was defined using a continuous measure including emotional, physical, and sexual abuse. For CAN-BIND-1 and SARA, CM history was collected using the Childhood Experience of Care and Abuse (39) scale, which measured emotional and physical abuse on a 4-point scale (little/none, some, moderate, marked) and sexual abuse on a 5-point scale (none, little, some, moderate, marked). PRO-CAN used a trauma documentation form to record trauma or abuse experienced before the age of 18 (35), which included a 5-point impact scale for all measures (none, little, moderate, quite a bit, extreme). For this dataset, we adjusted the 5-point scale to a 4-point scale for emotional and physical abuse to be consistent with CAN-BIND-1 and SARA by combining "none" and "little" selections.

Participants recruited in CAN-BIND-1 were treated with escitalopram. Antidepressant outcomes were quantified as both a percentage change in MADRS scores between baseline and week 8 and a binary outcome of response (≥50% MADRS change) versus nonresponse.

Neurocognitive Measures

CAN-BIND-1 acquired the CNS Vital Signs (RRID: SCR_024475), a tool that assesses 10 neurocognitive domains: cognitive flexibility, executive function, composite memory, processing speed, reasoning, social cognition, sustained attention, visual memory, verbal memory, and working memory. For analysis purposes, we used percentile scores, which standardized an individual's performance relative to an age-matched normative database.

Neuroimaging Acquisition and Preprocessing

The MRI protocols for all CAN-BIND studies have been reported previously (40). To summarize, all 3 studies obtained whole-brain T1-weighted structural scans with a 3-dimensional isotropic resolution of 1 mm. Structural neuroimaging data were acquired using 3T MRI systems, with various scanner models across sites; acquisition parameters are summarized in the Supplement.

As previously described (5), we preprocessed T1-weighted structural MRI scans using the standard recon-all pipeline in FreeSurfer version 7.1.0 (RRID: SCR_001847). Briefly, the first step of recon-all includes motion correction, nonuniform intensity normalization, projection to the Talairach space, skull stripping, and tissue/subcortical segmentation. Subsequently, the second and third steps serve to smooth, interpolate, and tesselate the data into surface space. We extracted the following tissue volume data for each participant from the aseg.stats file outputted by recon-all: total GMV; total cortical white matter volume; subcortical GMV, which encompassed the thalamus, caudate, putamen, pallidum, hippocampus, amygdala and nucleus accumbens; and ventricular volume (the volume of ventricles and choroid plexus label).

Image quality was considered during acquisition and preprocessing. Participant instructions and support materials were uniform across all sites (40), and acquisition parameters were standardized when possible across all CAN-BIND sites. A participant also traveled to each scanning site to quantify intersite variance. All scans were initially assessed by trained quality control raters, as they were being collected, for motion, field-of-view, or other artifacts. Participants were rescanned if necessary. After preprocessing, we executed quality control and reprocessed for improper segmentations if necessary on 33 randomly selected scans, which represents approximately 5% of samples from different scanners, and scans with a value 2 standard deviations below or above the mean on any output.

Brain Centile Extraction

Participant demographic and clinical data, including age, sex, diagnosis, and MRI measures were compiled. The dataset was uploaded onto BrainChart (http://www.brainchart.io) (5) to obtain individualized centile scores that indicate the presence of any accelerated aging. Each centile score is computed by quantifying the vertical deviation of structural MRI phenotypes to the reference curves, which are stratified by sex. The tool incorporates an out-of-sample estimator of model parameters where maximum likelihood is used to estimate study-specific random effects; this allows the scoring of centiles using the cumulative density function.

Data Analysis

We used R-Studio version 2022.07.0 (RRID: SCR_000432) to examine relationships between variables of interest. To account for scanner differences, we used the harmonization method ComBat on brain centiles and any MRI phenotypes used to generate it (41–43). We used general linear models (GLMs) and the Benjamini-Hochberg method (44) to control for multiple comparisons using the false discovery rate (FDR). By characterizing brain aging with centile scores, the following questions were investigated:

1. Does brain centile score differ in participants diagnosed with depression compared with HCs? We conducted a GLM with diagnosis and ComBat-corrected centile score as the independent and dependent variables, respectively, and age and sex as covariates. Within the MDD group, including both participants with single-episode and those with recurrent MDD, we also used the GLM model to test whether the number of past depressive episodes, current episode duration, age of MDD onset, and depression severity would predict brain centile.
2. Which structural MRI measures drive differences in brain centile score by diagnosis? Analyses were performed separately for males and females; for each GLM model, diagnosis was the predictor variable, ComBat-corrected GMV, white matter volume, subcortical GMV, or

ventricular volume were the outcome variables, and age was a covariate. Results were corrected for multiple comparisons using FDR.

3. Do brain centile scores predict variability in neurocognitive domains associated with aging, and does this relationship differ between people diagnosed with MDD and HCs? In HCs, we first predicted 10 neurocognitive domains separately using ComBat-corrected brain centiles, with both sex and age as covariates. Then, we used brain centiles to predict ranked scores for domains that showed statistically significant results while incorporating several covariates: sex, diagnosis, age, and the interaction between brain centile and diagnosis. FDR multiple comparison correction was performed.
4. Does brain centile score differ in people with versus without a history of CM? Using a GLM, we predicted ComBat-corrected brain centile using overall CM and specific types of maltreatment; we added age, sex, diagnosis, and the interaction between CM and diagnosis as covariates. Multiple comparison correction was done using FDR.
5. Does brain centile score predict antidepressant response to escitalopram? In CAN-BIND-1 participants, a linear mixed-effects model was used to further examine brain centiles with varying individual depression severity over 8 weeks. This model predicting MADRS was generated using the lmerTest package and included time, brain centile score, age, and sex as fixed effects and the intercept as a random effect. We used a time by centile score interaction to determine whether pretreatment centile score was associated with escitalopram-related MADRS response. We also used a logistic GLM model with ComBat-corrected brain centile as the independent variable, antidepressant response as the dependent variable, and included covariates such as age, sex, and baseline depression severity.

RESULTS

Combining the CAN-BIND-1, PRO-CAN, and SARA datasets yielded a large, multisite sample (Table S1) of patients with moderate depression diagnosed with MDD (n = 304) and HCs (n = 236). The MDD group was significantly older than the HC group on average (Table 1). Sex did not differ by diagnostic status (control, single-episode MDD, recurrent MDD) (χ^2 = 2.264, p = .132). Depression severity was normally distributed in both the single-episode and recurrent MDD groups (Figure S1). We included age and sex as covariates in all subsequent models.

Next, we examined whether diagnosis impacted brain aging (Table S2). The overall GLM was significant (R^2 = 0.036, $F_{4,535}$ = 4.968, p < .001), and the MDD group exhibited significantly lower brain centile scores than the HC group (β = −0.055, SE = 0.025, $t_{1,535}$ = −2.194, p = .029, partial f^2 = 0.007). Post hoc analyses stratified by sex indicated that this effect was likely driven by females, although the trend was nonsignificant (Figure 1A, B). We also carried out post hoc analyses to compare brain centiles of HCs with those of participants with single-episode and recurrent MDD (Table S3). Only the recurrent MDD group showed significantly lower brain centiles than HCs (β = −0.058, SE = 0.028, $t_{1,313}$ = −2.094, p = .037, partial f^2 = 0.007) (Figure 1C), indicating that our initial finding was likely driven by brain centile scores in the recurrent MDD group. We further tested whether the cumulative exposure to MDD could influence brain aging (Table S4); past depressive episodes (R^2 = 0.087, $F_{3,176}$ = 5.571, p = .001; β = −0.006, SE = 0.005, $t_{1,176}$ = −1.215, p = .226), current episode duration (R^2 = 0.102, $F_{3,174}$ = 6.601, p < .001; β = 0.001, SE = 0.001, $t_{1,174}$ = 1.535, p = .127), and age of MDD onset (R^2 = 0.077, $F_{3,178}$ = 4.967, p = .002; β = −0.001, SE = 0.002, $t_{1,178}$ = −0.324, p = .746) did not demonstrate a significant relationship with brain centiles. Additionally, while the model was significant (R^2 = 0.030, $F_{3,300}$ = 3.100, p = .027), brain centile scores were not significantly correlated with depression severity in both single-episode and recurrent MDD groups (β = 0.015, SE = 0.017, $t_{1,300}$ = 0.926, p = .355) (Figure 1D; Table S5), as well as only in the recurrent MDD group (β = 0.010, SE = 0.019, $t_{1,219}$ = 0.535, p = .594). In summary, the MDD group had atypical brain centile scores compared with the HC group that were not associated with cumulative MDD exposure and depression severity.

Next, we investigated which global brain measures contributed to altered brain centile scores in MDD (Table S6). We performed these analyses separately because sex differences have been consistently reported in the brain aging literature (45–47), including in global brain measures that drove atypical brain centile scores in neuropsychiatric disorders in our initial report (5). In females (Figure 2A, C, E, G), MDD was significantly associated with a decrease in GMV (β = −13,451.3, SE = 4981.2, $t_{1,341}$ = −2.70, FDR-corrected p [p_{FDR}] = .029, partial f^2 = 0.04) (Figure S2) and white matter volume (β = −13,091.7, SE = 5371.4, $t_{1,341}$ = −2.437, p_{FDR} = .046, partial f^2 = 0.02) but not subcortical GMV (β = −898.75, SE = 521.09, $t_{1,341}$ = −1.725, p_{FDR} = .171) or ventricular volume (β = 472.81, SE = 643.66, $t_{1,341}$ = 0.735, p_{FDR} = .463). No significant differences were observed by diagnosis in males (Figure 2B, D, F, H).

Next, we identified which neurocognitive domains were impacted by brain aging in MDD. To constrain our analysis, we first tested the relationship between brain centiles and cognitive performance in HCs (Table S7). After correcting for multiple comparisons, only working memory was significantly associated with brain centile score (β = 26.343, SE = 7.442, $t_{1,163}$ = 3.540, p_{FDR} = .005, partial f^2 = 0.09) (Figure 3A). Processing speed showed a similar trend; however, this relationship did not survive correction for multiple comparisons (β = 19.109, SE = 7.683, $t_{1,171}$ = 2.487, $p_{uncorrected}$ = .014) (Figure 3B). Based on this, we decided to further analyze these 2 cognitive domains in all participants (Table S8). Because of normality issues impacting GLM assumptions, we rank-transformed our dependent variables. The model for processing speed performance (R^2 = 0.035, $F_{5,379}$ = 2.722, p = .020) revealed a significant main effect of brain centile score (β = 79.116, SE = 29.858, $t_{1,379}$ = 2.650, p = .008, partial f^2 = 0.02), but no significant diagnosis by centile score interaction (β = −49.856, SE = 39.992, $t_{1,379}$ = −1.247, p = .213). Likewise, the GLM predicting working memory performance (R^2 = 0.052, $F_{5,357}$ = 3.939, p = .002) also had a significant main effect for brain centiles (β = 111.383, SE = 28.676, $t_{1,357}$ = 3.884, p < .001, partial f^2 = 0.04). In the latter model, there was a significant 2-way interaction such that there was no significant relationship between working memory and brain centile in

Table 1. Descriptive Statistics for Demographic and Clinical Characteristics

	MDD		Control			
	n	Mean (SD)	*n*	Mean (SD)	Test Statistic[a]	*p*
All Participants						
Age, Years	304	32.806 (12.958)	236	27.987 (11.820)	3.696	2.42×10^{-4}
Sex, Female/Male	202/102	–	142/94	–	2.264	.132
Depression Severity	304	–	–	–	–	–
CAN-BIND-1						
Age, Years	192	34.75 (12.553)	107	32.850 (10.483)	1.726	.086
Sex, Female/Male	125/67	–	69/38	–	0.012	.915
MADRS	192	29.875 (5.619)	–	–	–	–
PRO-CAN						
Age, Years	20	18.15 (2.978)	69	18.826 (3.992)	−0.558	.579
Sex, Female/Male	8/12	–	32/37	–	0.255	.614
BDI	20	27.55 (10.590)	–	–	–	–
SARA						
Age, Years	92	29.554 (12.760)	60	29.85 (14.003)	−0.660	.511
Sex, Female/Male	69/23	–	41/19	–	0.807	.369
MADRS	92	26.859 (7.117)	–	–	–	–

BDI, Beck Depression Inventory; CAN-BIND, Canadian Biomarker Integration Network for Depression; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; PRO-CAN, Canadian Psychiatric Risk and Outcome Study; SARA, Stress and Reward Anhedonia Study.

[a]Analysis used *t* test and χ^2 test.

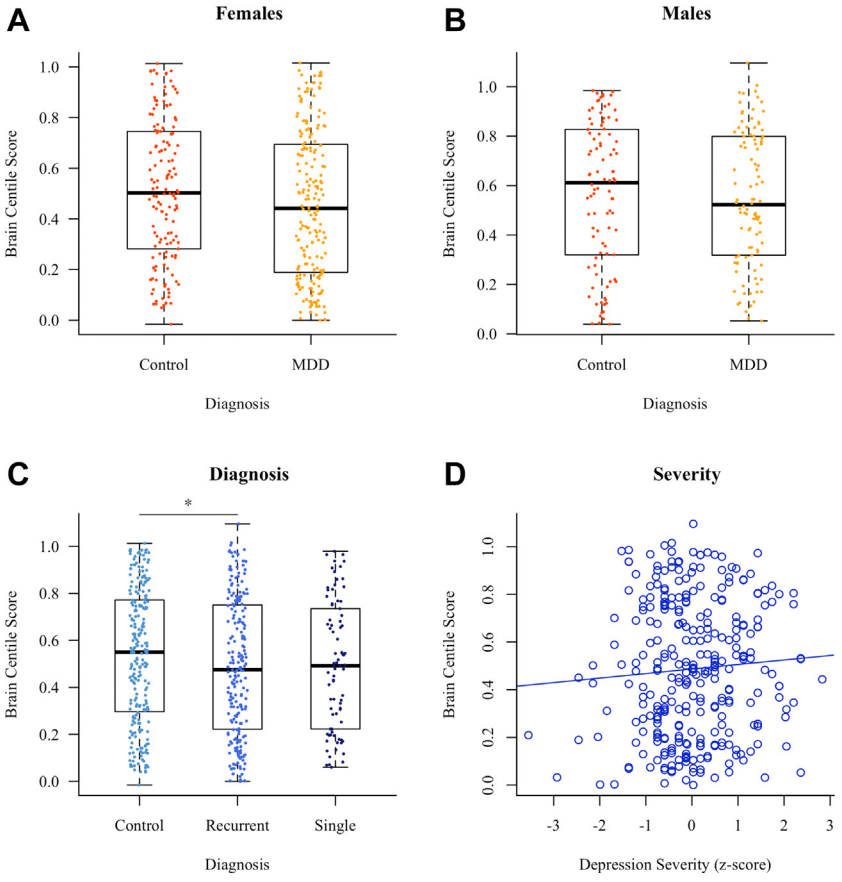

Figure 1. Neither **(A)** female nor **(B)** male participants diagnosed with major depressive disorder (MDD) exhibited significantly different brain centile scores relative to control participants without depression. **(C)** The recurrent MDD group showed significantly lower brain centiles than the control group. **(D)** Depression severity as quantified by the Montgomery–Åsberg Depression Rating Scale or the Beck Depression Inventory showed no significant associations with brain centiles. Brain centile scores were adjusted for sex and age. Error bars represent the 95% CI. $^*p < .05$.

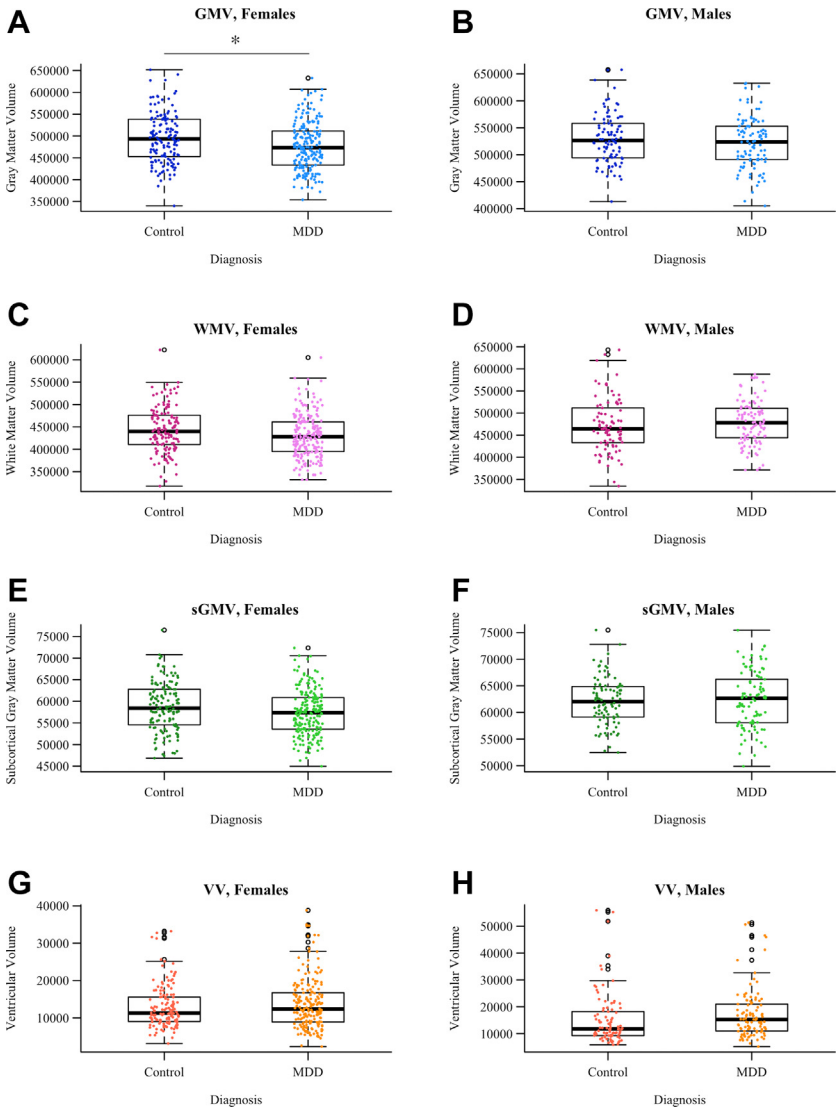

Figure 2. Female participants diagnosed with major depressive disorder (MDD) had significantly lower **(A)** gray matter volume (GMV) and **(C)** white matter volume (WMV) than control participants without depression. This was not seen for **(E)** subcortical GMV (sGMV) or **(G)** ventricular volumes (VVs) or in the **(B, D, F, H)** male cohort. Volumes were adjusted for age. Error bars represent the 95% CI. *$p < .05$.

MDD (β = −82.790, SE = 38.706, $t_{1,357}$ = −2.139, p = .033, partial f^2 = 0.01) (Figure 3C).

Subsequently, we wanted to explore whether the presence of CM explained any variance in brain centile scores for individuals with MDD or HCs (Table S9). We found no statistically significant prediction of brain centile by overall CM (β = 0.009, SE = 0.010, $t_{1,492}$ = 0.855, p_{FDR} = .605) (Figure 4A, B), emotional abuse (β = −0.014, SE = 0.024, $t_{1,493}$ = −0.586, p_{FDR} = .605), physical abuse (β = 0.041, SE = 0.022, $t_{1,493}$ = 1.871, p_{FDR} = .248, $p_{uncorrected}$ = .031), or sexual abuse (β = 0.012, SE = 0.024, $t_{1,492}$ = 0.517, p_{FDR} = .605).

Finally, we assessed whether brain centile scores predicted antidepressant response to 8 weeks of open-label escitalopram (Table S10). While there was a significant effect of time (β = −13.502, SE = 0.574, $t_{4,664}$ = −23.514, $p < .001$), there was no significant main effect of centile score (β = 0.552, SE = 2.033, $t_{1,162}$ = 0.271, p = .786) and no interaction between centile score and time (β = 0.560, SE = 2.101, $t_{1,664}$ = 0.267, p = .790). Antidepressant response measured by MADRS percentage improvement (R^2 = 0.023, $F_{4,162}$ = 0.945, p = .440) did not have a significant main effect (β = 1.338, SE = 9.344, $t_{1,162}$ = 0.143, p = .886) (Figure 4C). A similar trend was observed for response as a dichotomous variable (model R^2 = 0.013, $\chi^2_{4,162}$ = 3.004, p = .557; main effect β = 0.581, SE = 0.591, $t_{1,162}$ = 0.984, p = .325).

DISCUSSION

Brain centile scores provide a quantitative lens to analyze the complex interactions between aging and MDD in the hopes of gaining a deeper understanding of the condition's impact on cognition, treatment response, and the role of risk factors such as CM. Here, we showed that people diagnosed with MDD from adolescence to late adulthood exhibited significantly lower brain centile scores than HCs. However, depression severity was not significantly correlated with centile scores in

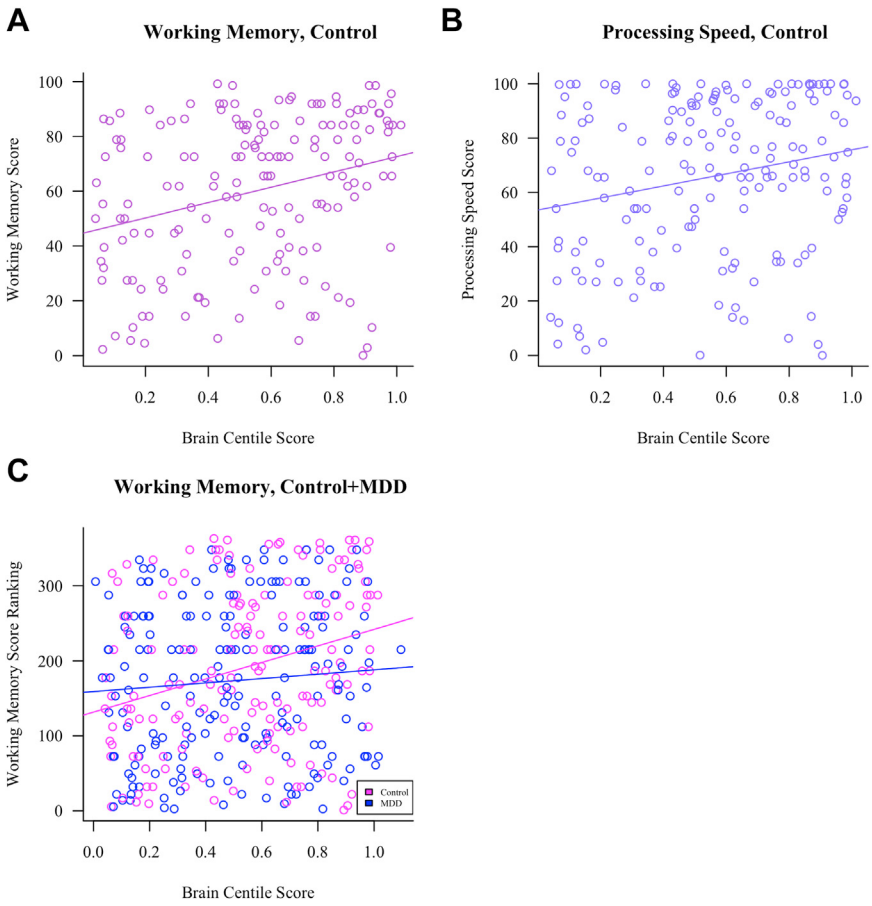

Figure 3. In control participants without depression, **(A)** working memory scores showed significantly positive associations with brain centiles while **(B)** processing speed scores did not. **(C)** In working memory specifically, a significant interaction was seen between brain centiles and diagnosis. Neurocognitive domain scores were adjusted for age and sex. *$p < .05$. MDD, major depressive disorder.

the depressed group. Individuals with recurrent MDD had the largest deviations in brain aging compared with HCs. Deviations in brain centile score were driven by abnormalities in gray matter and white matter volume, which were most prominent for females and not males. Additionally, we found that centile scores were significantly associated with working memory in HCs, and this relationship was not present in participants with MDD. CM and reduction in depression severity after escitalopram treatment were not significantly correlated with brain centile scores. We used aging trajectories from the largest normative dataset to date, and the results offer novel insights into age-dependent deficits in MDD.

Consistent with our initial hypothesis, we found a lower brain centile score in individuals with MDD than in HCs, which was associated with lower gray matter and white matter volume in females with MDD than in HCs, possibly indicative of accelerated aging (48–50). These results are consistent with previous research using other prediction models that there is a small but significant change in brain age (brain-PAD) in MDD compared with HCs (18–20,34). In contrast, a previous CAN-BIND report revealed no significant differences in baseline brain-PAD between individuals with MDD and HCs (22). This may be attributed to differences in sample size, normative reference sample, brain-based features, or modeling choices. First, the previous report included only CAN-BIND-1 participants, while this report used data from 2 additional datasets, thereby bolstering our sample size and increasing our age range. Second, the original reference sample was 45,615 individuals ages 3 to 96 years, while BrainChart uses scans from 95,536 individuals from 115 days postconception to up to 100 years old. Third, our previous report used FreeSurfer-generated volume, surface area, and cortical thickness values from the Human Connectome Project atlas. The BrainChart method uses volumetric measures for tissue classes and is not stratified by region (except cortical and subcortical GMV). Lastly, although both brain-PAD and BrainChart attempt to assess individual deviation, they have several methodological differences. Brain-PAD compares an individual's estimated brain age with their chronological age using a machine learning model based on linear gradient tree boosting and tuned using 5-fold cross-validation (51). BrainChart instead uses generalized additive models for location, scale and shape models, which incorporate linear and nonlinear trends in volume related to age. Both procedures generated models stratified by sex.

Depression severity in MDD—and more specifically the recurrent MDD group—was not associated with deviations in brain aging; however, some (20) but not all (19,23) previous studies reported a positive correlation between brain-PAD and depression severity. Future studies should clarify the

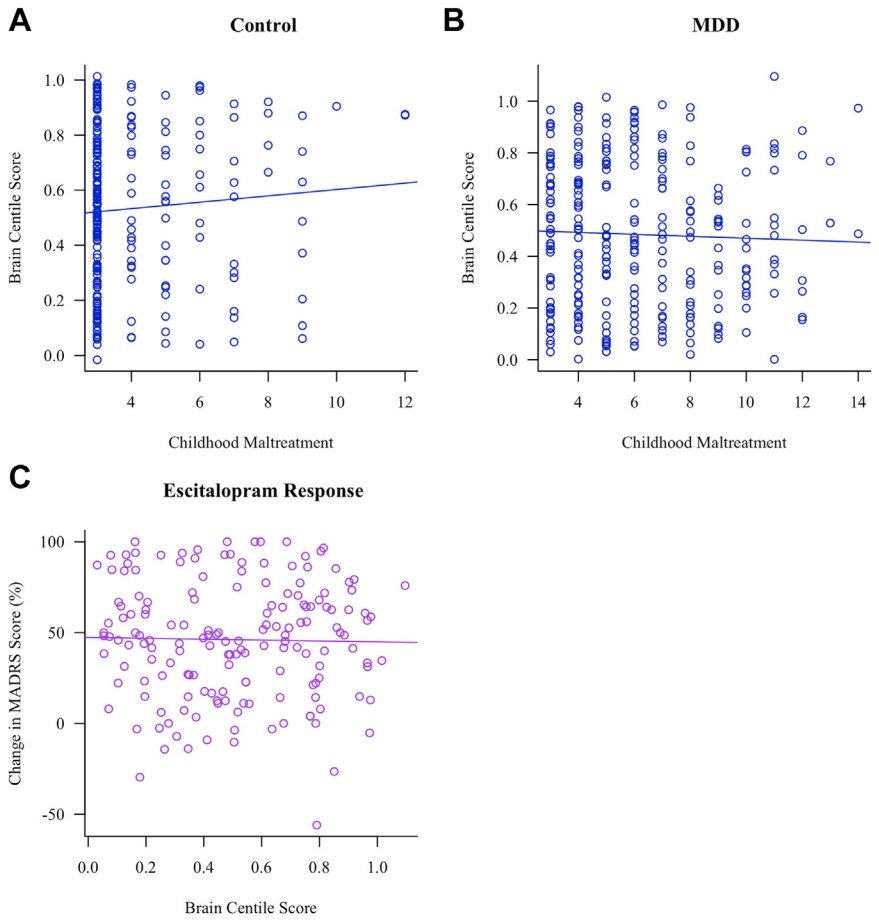

Figure 4. No significant differences were seen between brain centile scores for varying childhood maltreatment scores for both the **(A)** control and **(B)** major depressive disorder (MDD) groups. Brain centiles were adjusted for age, sex, diagnosis, and the interaction between abuse severity and diagnosis. **(C)** Also, no significant correlation was seen between escitalopram response and brain centiles of the MDD group. Percentage changes in Montgomery–Åsberg Depression Rating Scale (MADRS) scores were adjusted for age, sex, and initial depression severity. $^{*}p < .05$.

relationship between brain aging and MDD severity given the notion that MDD is a clinically heterogeneous disorder and not a unitary disease (52–54). Specific symptom profiles may be associated with accelerated brain aging.

We also observed sex differences in the relationship between brain centile score inputs and diagnosis. GMV and WMV were significantly reduced with an MDD diagnosis, but only in females, providing further evidence of sex differences in brain-based markers of MDD (55). These findings are consistent with previous research regarding sex-specific brain structural changes in MDD. In one study, females exhibited GMV reduction, specifically in the left lingual gyrus and dorsal medial prefrontal gyrus (56).

Brain centile score was positively correlated with working memory in HCs; greater neurocognitive performance was associated with a higher brain centile score. This finding follows previous literature generally demonstrating working memory impairment with old age (57–59); however, it is novel in elucidating the relationship between working memory and normative brain aging specifically. In contrast to HCs, there was not a significant relationship between working memory performance and brain centile score in participants with MDD. It appears that an MDD diagnosis may disrupt age-related effects that normally shape the positive relationship seen in the control group. This result is consistent with our expectation that working memory is disrupted in MDD relative to the control group, which has also been well-documented in the literature (60–62). Additional studies are needed to clarify whether an MDD diagnosis influences the protective effect of a high brain centile score.

We did not find a significant correlation between brain aging and CM; this was inconsistent with our hypothesis and results of previous studies. In one study, early CM demonstrated associations with reduced hippocampal GMV (63). Furthermore, a study using the PRO-CAN data demonstrated that volumes of the amygdala nuclei mediated the severity of depression and anxiety symptoms in at-risk individuals (a cohort that was not included in the current analysis) (64). A recent study also showed that sexual abuse during childhood was correlated with a significantly reduced GMV in the right middle occipital gyrus (65). These studies showed reductions in GMV as are commonly seen in normative brain aging. The lack of expected association may be due to differences in measures of CM between the CAN-BIND studies. On the other hand, emotional subtypes of CM have been suggested as stronger predictors of MDD than physical CM (66–68), which was not found in our

analysis. Future studies could also consider other MDD risk factors that are influenced by CM, such as personality traits and coping styles (69,70), or risk factors that commonly co-occur with CM, including early-life socioeconomic status (71,72) and parental separation (73,74).

Similarly, our hypothesis regarding escitalopram response was not supported by the findings, which is consistent with the previous CAN-BIND-1 analysis (22). However, other studies revealed that accelerated brain aging was associated with a change in depression severity as measured by the 17-item Hamilton Depression Rating Scale, specifically a decreased response to 8-week sertraline treatment (23) and an increased response to placebo neuromodulation (20). Therefore, future studies should explore whether brain centiles can predict responses to other antidepressant types of the selective serotonin reuptake inhibitor class or even MDD treatments like transcranial magnetic stimulation. There could also be an exploration into the longitudinal effects of MDD treatment on brain centiles.

We note several limitations of this study. First, our analysis was limited by its cross-sectional nature, which leads to the inability to establish a causal relationship between brain aging and MDD. Prospective data could help to resolve the relationship. For example, one future study could recruit participants who recently experienced a major negative life event like trauma and determine whether brain age at the time of the event or longitudinal changes in brain age increase the risk for posttraumatic symptoms (75). Second, as previously mentioned, the symptoms of MDD are heterogeneous, and many different symptoms can lead to a diagnosis. Some recent studies have used functional MRI to identify MDD subtypes based on connectivity profiles in the brain, which could potentially be integrated into brain centiles (76). Third, BrainChart estimates brain age using global brain measures instead of regions of interest. However, volumetric loss in the dorsolateral prefrontal cortex, insula, and hippocampus have been indicated in recurrent MDD (77,78). Thus, exploring centile scores through structures of specific regions of interest is an area for future exploration. Additionally, although our sample size was smaller than those of other studies like the UK Biobank, our MDD group was robust because it contained individuals with a confirmed—and not just a probable—major depressive episode. Lastly, we have not examined whether brain centiles could reflect longitudinal changes in neurocognitive domain scores with aging or MDD treatment. Longitudinal studies will also help to uncover the directionality of effects, for example whether atypical brain aging is a cause or a consequence of MDD recurrence.

Conclusions

In this article, we attempted to examine the use of brain centiles as a tool to characterize brain aging and its relationship with MDD diagnosis, cognition, CM, and escitalopram response. We provided evidence substantiating the clinical utility of brain centiles as a predictor of MDD diagnosis and possibly long-term working memory performance. Future studies need to address general unresolved issues in the field of brain aging, such as defining causal relationships between brain aging and MDD and incorporating MDD subtypes to consider the heterogeneity of the disorder.

ACKNOWLEDGMENTS AND DISCLOSURES

CAN-BIND is an Integrated Discovery Program carried out in partnership with, and financial support from, the Ontario Brain Institute, an independent non-profit corporation, funded partially by the Ontario government. The opinions, results and conclusions are those of the authors and no endorsement by the Ontario Brain Institute is intended or should be inferred. Additional funding is provided by the Canadian Institutes of Health Research (CIHR), Lundbeck, and Servier. Funding and/or in-kind support is also provided by the investigators' universities and academic institutions.

RAIB, JS, ETB, and AFA-B are directors of and hold equity in Centile Bioscience. ETB serves on the scientific advisory board of Sosei Heptares and as a consultant for GlaxoSmithKline, Boehringer Ingelheim, SR One and Monument Therapeutics. AFA-B receives consulting income from Octave Bioscience. SR holds a patent "Teneurin C-Terminal Associated Peptides (TCAP) and methods and uses thereof." RWL has received honoraria for ad hoc speaking or advising/consulting, or received research funds, from Allergan, Asia-Pacific Economic Cooperation, BC Leading Edge Foundation, CIHR, Canadian Network for Mood and Anxiety Treatments, Healthy Minds Canada, Janssen, Lundbeck, Lundbeck Institute, Michael Smith Foundation for Health Research, MITACS, Myriad Neuroscience, Ontario Brain Institute, Otsuka, Pfizer, Unity Health, Vancouver Coastal Health Research Institute, and Vancouver General Hospital-University of British Columbia Hospital Foundation. RM reports grants from CIHR, Janssen, and Lundbeck during the conduct of the study. Outside of the submitted work, RM reports personal fees from Allergan, Janssen, Kye Pharmaceuticals, Lundbeck, and Otsuka; grants and personal fees from Pfizer; personal fees from Sunovion; and grants from Lallemand, Nubiyota, and Ontario Mental Health Foundation. JA receives research support from the National Institute of Mental Health. SHK reports grants from Lundbeck, Bristol-Myers Squibb, Pfizer, Servier, and CIHR during the conduct of the study. SHK also reports grants from Abbott, personal fees from Alkermes, grants from Allergan, grants and personal fees from Janssen, grants and personal fees from Lundbeck, personal fees from Lundbeck Institute, grants and personal fees from Otsuka, personal fees from Pfizer, and personal fees from Servier. KD holds an Academic Scholars Award from the Department of Psychiatry, University of Toronto. She is listed as an inventor for Cornell University patent applications on neuroimaging biomarkers for depression that are pending or in preparation. Lifespan Consortium disclosures: SA was supported by the Rosetrees Trust (A2665). EA and the Province of Ontario Neurodevelopmental Disorders Network (POND) study data collection are funded by the Ontario Brain Institute. KA is an employee of Neumora Therapeutics. DEA was supported by Medical Research Council (MRC) Programme (Grant No. MC-A0606-5PQ41). MA is supported by National Institutes of Health (NIH) (Grant No. 1R01MH112904-01). GB was supported by an National Health and Medical Research Council (NHMRC) Investigator Grant (#1194497) and the Royal Children's Hospital Foundation. RB was supported by a Royal Children's Hospital Foundation Grant. VB and cVEDA are jointly funded by the Indian Council for Medical Research (Grant No. ICMR/MRC/3/M/2015-NCD-I) and the Newton Grant from the MRC (Grant No. MR/N000390/1), United Kingdom. JB and the Genetics of Brain Structure and Function project was funded by the NIH (Grant Nos. MH078143, MH083824, and MH078111). JPB and TEBC data collection was funded by Theirworld. JBB was supported by Brain Canada (Grant No. 243030), the Fonds de recherche du Québec Healthy Brains Healthy Liles Fonds de recherche du Québec/Canada-Cuba–China Axis (246117), the Canada First Research Excellence Fund/Healthy Brains Healthy Liles BigBrain Analytics and Learning Laboratory, and Helmholtz (Grant No. 252428). VDC was supported by National Science Foundation (Grant No. 2112455) and NIH (Grant No. R01MH123610). MMC is supported by Fonds Recherche. GC and the Imagerie Multimdale de la maladie d'Alzheimer a un stade Precoce (IMAP) study were funded by Programme Hospitalier de Recherche Clinique (Grant Nos. PHRCN 2011-A01493-38 and PHRCN 2012 12-006-0347) and Agence Nationale de la Recherche (LONGVIE 2007). GC's research including the IMAP study was also funded by Institut National de la Santé et de la Recherche Médicale, Fondation Plan Alzheimer (Alzheimer Plan 2008–2012); Région Basse-Normandie; Association France Alzheimer et maladies

apparentées, Fondation Vaincre Alzheimer. YSC and the Growing Up in Singapore Towards healthy Outcomes (GUSTO) study is supported by the Singapore National Research Foundation under its Translational and Clinical Research Flagship Programme and administered by the Singapore Ministry of Health's National Medical Research Council (NMRC), Singapore (Grant Nos. NMRC/TCR/004-NUS/2008; NMRC/TCR/012-NUHS/2014). Additional funding is provided by the Singapore Institute for Clinical Sciences, Agency for Science Technology and Research (A*STAR), Singapore. EC is supported by grants: NIMH (Grant Nos. P50-MH081755, R01-MH036840, R01-MH110558, U01-MH108898), NIDCD (Grant No. R01-DC016385). NC is supported by the Agencia Nacional de Investigación y Desarrollo Chile through grants FONDECYT regulator 1200601, ANILLO PIA ACT192064. RJD is supported by the Max Planck Society. The Drakenstein Child Health Study is funded by the Bill & Melinda Gates Foundation (OPP 1017641; authors KAD, HJZ, and DJS). KAD and aspects of the research are additionally supported by the National Research Foundation, an Academy of Medical Sciences Newton Advanced Fellowship (NAF002/1001) funded by the UK Government's Newton Fund, by National Institute on Alcohol Abuse and Alcoholism (Grant No. R21AA023887), by the Collaborative Initiative on Fetal Alcohol Spectrum Disorders developmental grant (Grant No. U24 AA014811), and by the United States Brain and Behaviour Foundation Independent Investigator grant (Grant No. 24467). KD is supported by a Canadian Institutes for Health Research Banting Postdoctoral Fellowship. The Developing Human Connectome Project (ADE) was supported by the European Research Council under the European Union Seventh Framework Programme (Grant No. FP/2007-2013)/European Research Council (Grant Agreement No. 319456). The Baby Connectome Project (BCP) was supported by NIH (Grant Nos. U01MH110274 and R01MH104324) (JTE). PCF is supported by the Wellcome Trust (Reference No. Reference No. 206368/Z/17/Z) and by the Bernard Wolfe health Neuroscience Fund. PF is supported by MRC (reference MR/V049941/1) and National Institute for Health Research (NIHR) (reference NIHR131339). CEF is supported by NIH (Grant Nos. R01s AG050595, AG022381, AG037985, and P01 AG055367). The content is the sole responsibility of the authors and does not necessarily represent official views of the National Institute on Aging (NIA), NIH, or Department of Veterans Affairs. The United States Department of Veterans Affairs, Department of Defense; National Personnel Records Center, National Archives and Records Administration; National Opinion Research Center; National Research Council, National Academy of Sciences; and the Institute for Survey Research, Temple University provided invaluable assistance in the creation of the Vietnam Era Twin Registry. The Cooperative Studies Program of the US Department of Veterans Affairs provided financial support for development and maintenance of the Vietnam Era Twin Registry. We would also like to acknowledge the continued cooperation and participation of the members of the Vietnam Era Twin Registry and their families. AG is supported by NIH (Grant Nos. R01 EB018988, R01 NS106030, and R01 EB031849). The Genetics of Brain Structure and Function project (DCG) was funded by the NIH (Grant Nos. MH078143, MH083824, and MH078111). Contributed data (TH) were collected with support from P01AG036694 and R01AG053509. TH is supported by NIH (Grant Nos. R01AG053509 and P30AG066514). RNH is supported by MRC Programme (Grant No. SUAG/046 G101400). OH has acquired research support (for the institution) from ADx, AVID Radiopharmaceuticals, Biogen, Eli Lilly, Eisai, Fujirebio, GE Healthcare, Pfizer, and Roche. In the past 2 years, he has received consultancy/speaker fees from AC Immune, Amylyx, Alzpath, BioArctic, Biogen, Cerveau, Fujirebio, Genentech, Novartis, Roche, and Siemens. JH received funding from NIH (Grant No. R01HD074051). HH is funded by NIH (Grant Nos. R01MH092535, R01EB031285, and R01MH125333). DTJ received funding from NIH (Grant No. U01 AG06786). PBJ has consulted for MSD, and was funded by the Wellcome Trust (Grant No. 095844/Z/11/Z) and NIHR (Grant No. RP-PG-0616-20003). FinnBrain was funded by Jane and Aatos Erkko Foundation, Signe and Ane Gyllenberg Foundation (HK). LK was funded by the NARSAD Young Investigator Award from the Brain & Behavior Research Foundation (Grant No. #1956) and the Academy of Finland Profi 5 (#325292). EAK is funded by the Masonic Foundation of Ontario, the National Institute of Mental Health, and the Ontario Brain Institute. SK was financed by grants from the Swedish state under the agreement between the Swedish government and the county councils, the ALF-agreement (Grant Nos. ALFGBG-965923, ALFGBG-81392, ALFGBG-771071), the Alzheimerfonden (Grant Nos. AF-842471, AF-737641, AF-939825), and the Swedish Research Council (2019-02075). SK has served at scientific advisory boards and/or as consultant for Geras Solutions and Biogen. The KNE96 study (KK) was supported by a grant of the Korean Health Technology R&D Project, Ministry for Health, Welfare, and Family Affairs, Republic of Korea (Grant No. I09C1379 [A092077]). The Biomarkers of Depression (BIODEP) study (MGK) was sponsored by the Cambridgeshire and Peterborough NHS Foundation Trust and the University of Cambridge and funded by a strategic award from the Wellcome Trust (Grant No. 104025) in partnership with Janssen, GlaxoSmithKline, Lundbeck and Pfizer. WSK was supported by the NIA (Grant Nos. R01s AG050595, AG022381, AG037985, and P01 AG055367). The POND study (JL) was supported by the Ontario Brain Institute (Grant No. IDS-I 1-02). This organization did not play a role in the design of the study, the collection, analysis and interpretation of the data, and in writing the manuscript. JL was supported by the China Postdoctoral Science Foundation (Grant No. BX2021057). WL was supported by the National Natural Science Foundation of China (Grant No. 61871077). CO was supported by the NIH National Heart, Lung, and Blood Institute (Grant No. K23HL141602) (CMO) and the Mend A Heart Foundation. Dr Palaniyappan reports personal fees from Janssen Canada for participating in an Advisory Board (2019) and Continuous Professional Development events (2017–2020), Otsuka Canada for Continuous Professional Development events (2017–2020), SPMM Course Limited, UK for preparing educational materials for psychiatrists and trainees (2010 onwards), Canadian Psychiatric Association for Continuous Professional Development events (2018–2019); book royalties from Oxford University Press (2009 onwards); institution-paid investigator-initiated educational grants with no personal remunerations from Janssen Canada, Sunovion and Otsuka Canada (2016–2019); travel support to attend a study investigator's meeting organized by Boehringer Ingelheim (2017); travel support from Magstim Limited (UK) to speak at an academic meeting (2014); none of these activities are related to submitted work. Data for this study (Dr. Palaniyappan) was funded by CIHR Foundation (Grant No. 375104/2017); Schulich School of Medicine Clinical Investigator Fellowship; Bucke Family Fund; Grad student salary support by Natural Sciences and Engineering Research Council of Canada Discovery Grant (No. RGPIN2016-05055); Canada Graduate Scholarship. Data acquisition was supported by the Canada First Excellence Research Fund to BrainSCAN, Western University (Imaging Core); Compute Canada Resources were used in the storage of imaging data. Dr. Palaniyappan acknowledges salary support from the Tanna Schulich Chair of Neuroscience and Mental Health. Data acquisition supported by Drs. Khan and Gati, and the research staff at the Centre of Functional and Metabolic Mapping, Robarts Imaging and the clinical staff at the Prevention and Early Intervention Program for Psychoses Clinic, London, Ontario, Canada. This study was conducted according to the approval by the Research Ethics Board of the University of Western Ontario (Project #108268; Oct 19, 2020). Brazilian High-Risk Study for Mental Conditions (PMP) was supported with grants from the National Institute of Development Psychiatric for Children and Adolescent (INPD). Grant: Fapesp 2014/50917-0—CNPq 465550/2014-2. CP was supported by a NHMRC Senior Principal Research Fellowship (Grant No. 1105825), an NHMRC L3 Investigator Grant (Grant No. 1196508) and NHMRC Program Grant (ID: 1150083). KP is supported by NIMH (Grant Nos. R01-MH080134 and R01-MH104446). This research/project (AQ) is supported by the National Science Foundation (Grant No. NSF:2010778) and National Research Foundation, Singapore under its AI Singapore Programme (AISG Award No: AISG-GC-2019-002). Additional funding is provided by the Singapore Ministry of Education (Academic research fund Tier 1; NUHSRO/2017/052/T1-SRP-Partnership/01), NUS Institute of Data Science. TR has received honoraria from Oxford Biomedica. Alzheimer's Disease Neuroimaging Initiative (ADNI): NIH funding (TR). Data used in preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf. NACC: The NACC database is funded by NIA/NIH (Grant U01 AG016976). NACC data are contributed by the NIA-funded ADCs (Grant Nos. P30 AG019610 [principal investigator (PI) Eric Reiman, M.D.], P30 AG013846 [PI Neil Kowall,

M.D.], P50 AG008702 [PI Scott Small, M.D.], P50 AG025688 [PI Allan Levey, M.D., Ph.D.], P50 AG047266 [PI Todd Golde, M.D., Ph.D.], P30 AG010133 [PI Andrew Saykin, Psy.D.], P50 AG005146 [PI Marilyn Albert, Ph.D.], P50 AG005134 [PI Bradley Hyman, M.D., Ph.D.], P50 AG016574 [PI Ronald Petersen, M.D., Ph.D.], P50 AG005138 [PI Mary Sano, Ph.D.], P30 AG008051 [PI Thomas Wisniewski, M.D.], P30 AG013854 [PI Robert Vassar, Ph.D.], P30 AG008017 [PI Jeffrey Kaye, M.D.], P30 AG010161 [PI David Bennett, M.D.], P50 AG047366 [PI Victor Henderson, M.D., M.S.], P30 AG010129 [PI Charles DeCarli, M.D.], P50 AG016573 [PI Frank LaFerla, Ph.D.], P50 AG005131 [PI James Brewer, M.D., Ph.D.], P50 AG023501 [PI Bruce Miller, M.D.], P30 AG035982 [PI Russell Swerdlow, M.D.], P30 AG028383 [PI Linda Van Eldik, Ph.D.], P30 AG053760 [PI Henry Paulson, M.D., Ph.D.], P30 AG010124 [PI John Trojanowski, M.D., Ph.D.], P50 AG005133 [PI Oscar Lopez, M.D.], P50 AG005142 [PI Helena Chui, M.D.], P30 AG012300 [PI Roger Rosenberg, M.D.], P30 AG049638 [PI Suzanne Craft, Ph.D.], P50 AG005136 [PI Thomas Grabowski, M.D.], P50 AG033514 [PI Sanjay Asthana, M.D., F.R.C.P.], P50 AG005681 [PI John Morris, M.D.], P50 AG047270 [PI Stephen Strittmatter, M.D., Ph.D.]). CKR was supported the NIH including the NINDS K23NS101120 (CKR), the National Heart, Lung, and Blood Institute K23HL141602 (CMO), NIBIB R01EB013248 (SKW), R01EB018988 and R01NS106030 (AG), and a National Heart, Lung, and Blood Institute Pediatric Heart Network Scholar Award (CKR); the American Academy of Neurology Clinical Research Training Fellowship (CKR); the Brain and Behavior Research Foundation NARSAD Young Investigator (CKR) and Distinguished Investigator (SKW) Awards; the McKnight Foundation Technological Innovations in Neuroscience Award (AG); Office of Faculty Development at Boston Children's Hospital Career Development Awards (AG, CKR); and the Mend A Heart Foundation (CMO). RRG was supported by the Guarantors of Brain, Cancer Research UK Cambridge Centre and the EMERGIA Junta de Andalucía program. LR was supported by the Bernard Wolfe Health Neuroscience Fellowship. MDR is supported by Bill & Melinda Gates Foundation INV-015711. DHR was supported by the NIHR Cambridge BRC. TDS is supported by NIH (Grant Nos. R01MH112847, R01MH120482, and R01MH113550). MS is supported by the Knut and Alice Wallenberg Foundation (Wallenber Centre for Molecular and Translational Medicine), the Swedish Research Council, the Swedish Alzheimer Association, the Swedish Brain Foundation and the Swedish State under the ALF-agreement. APS had consulted for Janssen, Biogen, Qynapse, and NervGen. RTS has received consulting income from Octave Bioscience and compensation to scientific review duties from the American Medical Association, the US Department of Defense, the Emerson Collective, and the NIH (Grant No. R01MH112847). IS is supported by the Swedish Research Council (Grant No. 2019-01096), Swedish state under the ALF-Agreement, Swedish Brain Foundation, Swedish Alzheimer Foundation. CDS effort on this project is supported by Bill & Melinda Gates Foundation INV-015711 and NIH (Grant No. P50 HD103525). RAS has consulted for Janssen, AC Immune, NervGen, Genentech, and is supported by NIH (Grant No. P01 AG036694 and R01 AG03689). DJS has received research grants and/or consultancy honoraria from Discovery Vitality, Johnson & Johnson, Lundbeck, Sanofi, Servier, Takeda and Vistagen. STRADL study (AS) was supported and funded by the Wellcome Trust Strategic Award "Stratifying Resilience and Depression Longitudinally" (ref. 104036/Z/14/Z). Data processing used the resources provided by the Edinburgh Compute and Data Facility (http://www.ecdf.ed.ac.uk/). AS was funded as part of the STRADL study and indirectly through the Lister Institute of Preventive Medicine award ref. 173096. J.SS. has consulted for GW Pharmaceuticals, Claritas HealthTech, Fundacion La Caixa, Fondazione Cariplo. KAT was funded by the Guarantors of Brain (Grant No. G101149). JJT was supported by the Finnish Medical Foundation, Sigrid Juselius Foundation and Emil Aaltonen Foundation. The preparation and initiation of the i-Share project was funded by the program Invest for future (reference ANR-10-COHO-05). The i-Share Project (CT) is currently supported by an unrestricted grant of the Nouvelle-Aquitaine Regional Council (Conseil Régional Nouvelle-Aquitaine) (Grant No. 4370420) and by the Bordeaux Initiatives d'excellence program of the University of Bordeaux (Grant No. ANR-10-IDEX-03-02). It has also received grants from the Nouvelle-Aquitaine Regional Health Agency (Agence Régionale de Santé Nouvelle-Aquitaine, Grant No. 6066R-8), Public Health France (Santé Publique France, Grant No. 19DPPP023-0), and the National Institute against cancer (Grant No. INCa_11502). SNV was supported by NIH (Grant No. R01MH123563). PEV is a fellow of MQ:Transforming Mental Health (MQF_17_24). JWV was supported by NIH (Grant No. T32MH019112). KSW was supported by the Wellcome Trust (Grant No. 215901/Z/19/Z). SKW was supported in part by NIH (Grant No. R01 EB013248 and R01 EB019483). SRW was funded by UK Research and Innovation MRC (Grant No. MC_UU_00002/2) and was supported by the NIHR Cambridge Biomedical Research Centre (Grant No. BRC-1215-20014). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. LIFE (AVW) is funded by means of the European Union, by the European Regional Development Fund and by funds of the Free State of Saxony within the framework of the excellence initiative. AVW was supported by grants from the German Research Foundation (Grant No. WI 3342/3-1; 209933838-02). BTTY is supported by the Singapore National Research Foundation Fellowship (Class of 2017), the NUS Yong Loo Lin School of Medicine (Grant No. NUHSRO/2020/124/TMR/LOA), the NMRC LCG (Grant No. OFLCG19May-0035), NMRC STaR (STaR20nov-0003), Singapore Ministry of Health Centre Grant (Grant No. CG21APR1009) and the United States National Institutes of Health (Grant No. R01MH120080). A Zalesky was supported by an NHMRC Senior Research Fellowship (ID: 1,136,649). HJZ is funded by the SA-MRC. A Zetterrgren was supported by the Swedish Alzheimer Foundation (Grant Nos. AF-968431, AF-939988, AF-930582, AF-646061, AF-741361). JHZ is funded by National Medical Research Council, Singapore and the National University of Singapore Yong Loo Lin School of Medicine (Grant No. NUHSRO/2020/124/TMR/LOA). XNZ has received funding support from the Child Brain-Mind Development Cohort Study in China Brain Initiative (Grant No. SQ2021AAA010024), the National Natural Science Foundation of China (81,220,108,014), the National Basic Research (973) Program (Grant No. 2015CB351702), the National Basic Science Data Center 'Chinese Data-sharing Warehouse for In-vivo Imaging Brain' Program (Grant No. NBSDC-DB-15), the Major Project of National Social Science Foundation of China (Grant No. 20&ZD296), the Beijing Municipal Science and Technology Commission (Grant Nos. Z161100002616023 and Z181100001518003), the China–Netherlands CAS-NWO Programme (Grant No. 153111KYSB20160020), the Startup Funds for Leading Talents at Beijing Normal University, Guangxi BaGui Scholarship (201,621), and the Key Realm R&D Program of Guangdong Province (Grant No. 2019B030335001).

All other authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Keenan Research Centre for Biomedical Research, Unity Health Toronto, Toronto, Ontario, Canada (NCWH, SR, SHK, KD); Centre for Depression & Suicide Studies, Unity Health Toronto, Toronto, Ontario, Canada (NCWH, NN, SR, SHK, KD); Faculty of Arts and Sciences, University of Toronto, Toronto, Ontario, Canada (NCWH); Department of Psychology, University of Cambridge, Cambridge, United Kingdom (RAIB); Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania (JS, AFA-B); Department of Child and Adolescent Psychiatry and Behavioral Science, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (JS, AFA-B); Lifespan Brain Institute, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (JS, AFA-B); Institute of Translational Medicine & Therapeutics, University of Pennsylvania, Philadelphia, Pennsylvania (JS, AFA-B); Department of Psychiatry, University of Calgary, Calgary, Alberta, Canada (PM, SH, VHT, JA); Genetics and Genome Biology, The Hospital for Sick Children, Toronto, Ontario, Canada (PLB); Hotchkiss Brain Institute and Mathison Centre for Mental Health Research and Education, University of Calgary, Calgary, Alberta, Canada (SH, VHT, JA); Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada (SR, SHK, KD); Mood Disorders Treatment and Research Centre, St Joseph's Healthcare, Hamilton, Ontario, Canada (SR, BNF); Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada (SR, BNF); Centre for Neuroscience Studies, Queen's University, Kingston, Ontario, Canada (JP); Department of Psychology, Queen's University, Kingston, Ontario, Canada (JP, RM, KLH); School of Computing, Queen's University, Kingston, Ontario, Canada (JP); Department of Psychiatry, University of British Columbia, Vancouver, British Columbia, Canada (RWL); Department of Psychiatry, Queen's University, Kingston, Ontario, Canada (RM, KLH);

Providence Care Hospital, Kingston, Ontario, Canada (RM); and Department of Psychiatry, University of Cambridge, Cambridge, United Kingdom (ETB).

Members of the Lifespan Brain Chart Consortium are Chris Adamson, Sophie Adler, Aaron F. Alexander-Bloch, Evdokia Anagnostou, Kevin M. Anderson, Ariosky Areces-Gonzalez, Duncan E. Astle, Bonnie Auyeung, Muhammad Ayub, Jong Bin Bae, Gareth Ball, Simon Baron-Cohen, Richard Beare, Saashi A. Bedford, Vivek Benegal, Richard A.I. Bethlehem, Frauke Beyer, John Blangero, Manuel Blesa Cábez, James P. Boardman, Matthew Borzage, Jorge F. Bosch-Bayard, Niall Bourke, Edward T. Bullmore, Vince D Calhoun, Mallar M. Chakravarty, Christina Chen, Casey Chertavian, Gaël Chetelat, Yap S. Chong, Aiden Corvin, Manuela Costantino, Eric Courchesne, Fabrice Crivello, Vanessa L. Cropley, Jennifer Crosbie, Nicolas Crossley, Marion Delarue, Richard Delorme, Sylvane Desrivieres, Gabriel Devenyi, Maria A. Di Biase, Ray Dolan, Kirsten A. Donald, Gary Donohoe, Lena Dorfschmidt, Katharine Dunlop, Anthony D Edwards, Jed T. Elison, Cameron T. Ellis, Jeremy A. Elman, Lisa Eyler, Damien A. Fair, Paul C. Fletcher, Peter Fonagy, Carol E. Franz, Lidice Galan-Garcia, Ali Gholipour, Jay Giedd, John H. Gilmore, David C. Glahn, Ian M Goodyer, P. E. Grant, Nynke A. Groenewold, Shreya Gudapati, Faith M. Gunning, Raquel E. Gur, Ruben C. Gur, Christopher F. Hammill, Oskar Hansson, Trey Hedden, Andreas Heinz, Richard N. Henson, Katja Heuer, Jacqueline Hoare, Bharath Holla, Avram J. Holmes, Hao Huang, Jonathan Ipser, Clifford R. Jack Jr, Andrea P. Jackowski, Tianye Jia, David T. Jones, Peter B. Jones, Rene S. Kahn, Hasse Karlsson, Linnea Karlsson, Ryuta Kawashima, Elizabeth A. Kelley, Silke Kern, Ki-Woong Kim, Manfred G. Kitzbichler, William S. Kremen, François Lalonde, Brigitte Landeau, Jason Lerch, John D. Lewis, Jiao Li, Wei Liao, Conor Liston, Michael V Lombardo, Jinglei Lv, Travis T Mallard, Machteld Marcelis, Samuel R. Mathias, Bernard Mazoyer, Philip McGuire, Michael J. Meaney, Andrea Mechelli, Bratislav Misic, Sarah E. Morgan, David Mothersill, Cynthia Ortinau, Rik Ossenkoppele, Minhui Ouyang, Lena Palaniyappan, Leo Paly, Pedro M Pan, Christos Pantelis, Min Tae M. Park, Tomas Paus, Zdenka Pausova, Deirel Paz-Linares, Alexa Pichet Binette, Karen Pierce, Xing Qian, Anqi Qiu, Armin Raznahan, Timothy Rittman, Amanda Rodrigue, Caitlin K. Rollins, Rafael Romero-Garcia, Lisa Ronan, Monica D. Rosenberg, David H. Rowitch, Giovanni A. Salum, Theodore D. Satterthwaite, H. Lina Schaare, Jenna Schabdach, Russell J. Schachar, Michael Schöll, Aaron P. Schultz, Jakob Seidlitz, David Sharp, Russell T. Shinohara, Ingmar Skoog, Christopher D. Smyser, Reisa A. Sperling, Dan J. Stein, Aleks Stolicyn, John Suckling, Gemma Sullivan, Benjamin Thyreau, Roberto Toro, Nicolas Traut, Kamen A. Tsvetanov, Nicholas B. Turk-Browne, Jetro J. Tuulari, Christophe Tzourio, Étienne Vachon-Presseau, Mitchell J. Valdes-Sosa, Pedro A. Valdes-Sosa, Sofie L. Valk, Therese van Amelsvoort, Simon N. Vandekar, Lana Vasung, Petra E. Vértes, Lindsay W. Victoria, Sylvia Villeneuve, Arno Villringer, Jacob W. Vogel, Konrad Wagstyl, Yin-Shan S. Wang, Simon K. Warfield, Varun Warrier, Eric Westman, Margaret L. Westwater, Heather C. Whalley, Simon R. White, A. Veronica Witte, Ning Yang, B.T. Thomas Yeo, Hyuk Jin Yun, Andrew Zalesky, Heather J. Zar, Anna Zettergren, Juan H. Zhou, Hisham Ziauddeen, Dabriel Zimmerman, Andre Zugman, and Xi-Nian N. Zuo.

Address correspondence to Katharine Dunlop, Ph.D., at katharine.dunlop@unityhealth.to.

Received Jan 10, 2024; revised Apr 4, 2024; accepted Apr 11, 2024.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsc.2024.04.008.

REFERENCES

1. Grady C (2012): The cognitive neuroscience of ageing. Nat Rev Neurosci 13:491–505.
2. Murman DL (2015): The impact of age on cognition. Semin Hear 36:111–121.
3. Zaninotto P, Batty GD, Allerhand M, Deary IJ (2018): Cognitive function trajectories and their determinants in older people: 8 years of follow-up in the English Longitudinal Study of Ageing. J Epidemiol Community Health 72:685–694.
4. Blinkouskaya Y, Caçoilo A, Gollamudi T, Jalalian S, Weickenmeier J (2021): Brain aging mechanisms with mechanical manifestations. Mech Ageing Dev 200:111575.
5. Bethlehem RAI, Seidlitz J, White SR, Vogel JW, Anderson KM, Adamson C, *et al.* (2022): Brain charts for the human lifespan. Nature 604:525–533.
6. Lorenzon G, Poulakis K, Mohanty R, Kivipelto M, Eriksdotter M, Ferreira D, Westman E (2022): Heterogeneity in normal aging: Longitudinal trajectories of grey matter. Alzheimers Dement 18:e063162.
7. Nyberg L, Lövdén M, Riklund K, Lindenberger U, Bäckman L (2012): Memory aging and brain maintenance. Trends Cogn Sci 16:292–305.
8. American Psychiatric Association (2013): Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC: American Psychiatric Association.
9. Semkovska M, Quinlivan L, O'Grady T, Johnson R, Collins A, O'Connor J, *et al.* (2019): Cognitive function following a major depressive episode: A systematic review and meta-analysis. Lancet Psychiatry 6:851–861.
10. Dai L, Zhou H, Xu X, Zuo Z (2019): Brain structural and functional changes in patients with major depressive disorder: A literature review. PeerJ 7:e8170.
11. Cole JH, Ritchie SJ, Bastin ME, Valdés Hernández MC, Muñoz Maniega S, Royle N, *et al.* (2018): Brain age predicts mortality. Mol Psychiatry 23:1385–1392.
12. Cole JH, Raffel J, Friede T, Eshaghi A, Brownlee WJ, Chard D, *et al.* (2020): Longitudinal assessment of multiple sclerosis with the brain-age paradigm. Ann Neurol 88:93–105.
13. Biondo F, Jewell A, Pritchard M, Aarsland D, Steves CJ, Mueller C, Cole JH (2022): Brain-age is associated with progression to dementia in memory clinic patients. Neuroimage Clin 36:103175.
14. Vance MC, Bui E, Hoeppner SS, Kovachy B, Prescott J, Mischoulon D, *et al.* (2018): Prospective association between major depressive disorder and leukocyte telomere length over two years. Psychoneuroendocrinology 90:157–164.
15. Pisanu C, Tsermpini EE, Skokou M, Kordou Z, Gourzis P, Assimakopoulos K, *et al.* (2020): Leukocyte telomere length is reduced in patients with major depressive disorder. Drug Dev Res 81:268–273.
16. Hough CM, Bersani FS, Mellon SH, Epel ES, Reus VI, Lindqvist D, *et al.* (2016): Leukocyte telomere length predicts SSRI response in major depressive disorder: A preliminary report. Mol Neuropsychiatry 2:88–96.
17. Rampersaud R, Wu GWY, Reus VI, Lin J, Blackburn EH, Epel ES, *et al.* (2023): Shorter telomere length predicts poor antidepressant response and poorer cardiometabolic indices in major depression. Sci Rep 13:10238.
18. Han LKM, Dinga R, Leenings R, Hahn T, Cole JH, Aftanas LI, *et al.* (2022): A large-scale ENIGMA multisite replication study of brain age in depression. Neuroimage: Reports 2:100149.
19. Han LKM, Dinga R, Hahn T, Ching CRK, Eyler LT, Aftanas L, *et al.* (2021): Brain aging in major depressive disorder: Results from the ENIGMA major depressive disorder working group. Mol Psychiatry 26:5124–5139.
20. Dunlop K, Victoria LW, Downar J, Gunning FM, Liston C (2021): Accelerated brain aging predicts impulsivity and symptom severity in depression. Neuropsychopharmacology 46:911–919.
21. Besteher B, Gaser C, Nenadić I (2019): Machine-learning based brain age estimation in major depression showing no evidence of accelerated aging. Psychiatry Res Neuroimaging 290:1–4.
22. Ballester PL, Suh JS, Nogovitsyn N, Hassel S, Strother SC, Arnott SR, *et al.* (2021): Accelerated brain aging in major depressive disorder and antidepressant treatment response: A CAN-BIND report. Neuroimage Clin 32:102864.
23. Jha MK, Chin Fatt C, Minhajuddin A, Mayes TL, Trivedi MH (2023): Accelerated brain aging in adults with major depressive disorder predicts poorer outcome with sertraline: Findings from the EMBARC study. Biol Psychiatry Cogn Neurosci Neuroimaging 8:462–470.
24. Llorente JM, Oliván-Blázquez B, Zuñiga-Antón M, Masluk B, Andrés E, García-Campayo J, Magallón-Botaya R (2018): Variability of the prevalence of depression in function of sociodemographic and environmental factors: Ecological model. Front Psychol 9:2182.

25. Nelson J, Klumparendt A, Doebler P, Ehring T (2017): Childhood maltreatment and characteristics of adult depression: Meta-analysis. Br J Psychiatry 210:96–104.
26. Medeiros GC, Prueitt WL, Minhajuddin A, Patel SS, Czysz AH, Furman JL, *et al.* (2020): Childhood maltreatment and impact on clinical features of major depression in adults. Psychiatry Res 293:113412.
27. Frodl T, Reinhold E, Koutsouleris N, Donohoe G, Bondy B, Reiser M, *et al.* (2010): Childhood stress, serotonin transporter gene and brain structures in major depression. Neuropsychopharmacology 35:1383–1390.
28. Teicher MH, Samson JA, Anderson CM, Ohashi K (2016): The effects of childhood maltreatment on brain structure, function and connectivity. Nat Rev Neurosci 17:652–666.
29. Tozzi L, Carballedo A, Wetterling F, McCarthy H, O'Keane V, Gill M, *et al.* (2016): Single-nucleotide polymorphism of the FKBP5 gene and childhood maltreatment as predictors of structural changes in brain areas involved in emotional processing in depression. Neuropsychopharmacology 41:487–497.
30. Rowe J, Poppenk J, Squires S, Mazurka R, Nogovitsyn N, Hassel S, *et al.* (2023): Anxious arousal predicts within-person changes in hippocampal volume in adults with a history of childhood maltreatment: A CAN-BIND4 report. J Psychopathol Clin Sci 132:797–807.
31. Tozzi L, Garczarek L, Janowitz D, Stein DJ, Wittfeld K, Dobrowolny H, *et al.* (2020): Interactive impact of childhood maltreatment, depression, and age on cortical brain structure: Mega-analytic findings from a large multi-site cohort. Psychol Med 50:1020–1031.
32. Kennedy SH, Downar J, Evans KR, Feilotter H, Lam RW, MacQueen GM, *et al.* (2012): The Canadian Biomarker Integration Network in Depression (CAN-BIND): Advances in response prediction. Curr Pharm Des 18:5976–5989.
33. Lam RW, Milev R, Rotzinger S, Andreazza AC, Blier P, Brenner C, *et al.* (2016): Discovering biomarkers for antidepressant response: Protocol from the Canadian biomarker integration network in depression (CAN-BIND) and clinical characteristics of the first patient cohort. BMC Psychiatry 16:105.
34. Luo Y, Chen W, Qiu J, Jia T (2022): Accelerated functional brain aging in major depressive disorder: Evidence from a large scale fMRI analysis of Chinese participants. Transl Psychiatry 12:397.
35. Addington J, Goldstein BI, Wang JL, Kennedy SH, Bray S, Lebel C, *et al.* (2018): Youth at-risk for serious mental illness: Methods of the PROCAN study. BMC Psychiatry 18:219.
36. Cunningham S, Mazurka R, Wynne-Edwards KE, Milev RV, Pizzagalli DA, Kennedy S, Harkness KL (2021): Cortisol reactivity to stress predicts behavioral responsivity to reward moderation by sex, depression, and anhedonia. J Affect Disord 293:1–8.
37. Montgomery SA, Åsberg M (1979): A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382–389.
38. Beck AT, Epstein N, Brown G, Steer RA (1988): An inventory for measuring clinical anxiety: Psychometric properties. J Consult Clin Psychol 56:893–897.
39. Bifulco A, Bernazzani O, Moran PM, Jacobs C (2005): The childhood experience of care and abuse questionnaire (CECA.Q): Validation in a community series. Br J Clin Psychol 44:563–581.
40. MacQueen GM, Hassel S, Arnott SR, Jean A, Bowie CR, Bray SL, *et al.* (2019): The Canadian Biomarker Integration Network in Depression (CAN-BIND): Magnetic resonance imaging protocols. J Psychiatry Neurosci 44:223–236.
41. Johnson WE, Li C, Rabinovic A (2007): Adjusting batch effects in microarray expression data using empirical Bayes methods. Biostatistics 8:118–127.
42. Fortin J-P, Parker D, Tunç B, Watanabe T, Elliott MA, Ruparel K, *et al.* (2017): Harmonization of multi-site diffusion tensor imaging data. Neuroimage 161:149–170.
43. Fortin J-P, Cullen N, Sheline YI, Taylor WD, Aselcioglu I, Cook PA, *et al.* (2018): Harmonization of cortical thickness measurements across scanners and sites. Neuroimage 167:104–120.
44. Benjamini Y, Hochberg Y (1995): Controlling the false discovery rate: A practical and powerful approach to multiple testing. J R Stat Soc B 57:289–300.
45. Forde NJ, Jeyachandra J, Joseph M, Jacobs GR, Dickie E, Satterthwaite TD, *et al.* (2020): Sex differences in variability of brain structure across the lifespan. Cereb Cortex 30:5420–5430.
46. Sang F, Chen Y, Chen K, Dang M, Gao S, Zhang Z (2021): Sex differences in cortical morphometry and white matter microstructure during brain aging and their relationships to cognition. Cereb Cortex 31:5253–5262.
47. Armstrong NM, An Y, Beason-Held L, Doshi J, Erus G, Ferrucci L, *et al.* (2019): Sex differences in brain aging and predictors of neurodegeneration in cognitively healthy older adults. Neurobiol Aging 81:146–156.
48. Hafkemeijer A, Altmann-Schneider I, De Craen AJM, Slagboom PE, Van Der Grond J, Rombouts SARB (2014): Associations between age and gray matter volume in anatomical brain networks in middle-aged to older adults. Aging Cell 13:1068–1074.
49. Farokhian F, Yang C, Beheshti I, Matsuda H, Wu S (2017): Age-related gray and white matter changes in normal adult brains. Aging Dis 8:899–909.
50. Liu H, Wang L, Geng Z, Zhu Q, Song Z, Chang R, Lv H (2016): A voxel-based morphometric study of age- and sex-related changes in white matter volume in the normal aging brain. Neuropsychiatr Dis Treat 12:453–465.
51. Kaufmann T, van der Meer D, Doan NT, Schwarz E, Lund MJ, Agartz I, *et al.* (2019): Common brain disorders are associated with heritable patterns of apparent aging of the brain. Nat Neurosci 22:1617–1623.
52. Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, *et al.* (2017): Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nat Med 23:28–38.
53. Sun X, Sun J, Lu X, Dong Q, Zhang L, Wang W, *et al.* (2023): Mapping neurophysiological subtypes of major depressive disorder using normative models of the functional connectome. Biol Psychiatry 94:936–947.
54. Musil R, Seemüller F, Meyer S, Spellmann I, Adli M, Bauer M, *et al.* (2018): Subtypes of depression and their overlap in a naturalistic inpatient sample of major depressive disorder. Int J Methods Psychiatr Res 27:e1569.
55. Talishinsky A, Downar J, Vértes PE, Seidlitz J, Dunlop K, Lynch CJ, *et al.* (2022): Regional gene expression signatures are associated with sex-specific functional connectivity changes in depression. Nat Commun 13:5692.
56. Yang X, Peng Z, Ma X, Meng Y, Li M, Zhang J, *et al.* (2017): Sex differences in the clinical characteristics and brain gray matter volume alterations in unmedicated patients with major depressive disorder. Sci Rep 7:2515.
57. Klencklen G, Banta Lavenex P, Brandner C, Lavenex P (2017): Working memory decline in normal aging: Is it really worse in space than in color? Learn Motiv 57:48–60.
58. Pliatsikas C, Veríssimo J, Babcock L, Pullman MY, Glei DA, Weinstein M, *et al.* (2019): Working memory in older adults declines with age, but is modulated by sex and education. Q J Exp Psychol (Hove) 72:1308–1327.
59. Gazzaley A, Cooney JW, Rissman J, D'Esposito M (2005): Top-down suppression deficit underlies working memory impairment in normal aging. Nat Neurosci 8:1298–1300.
60. Rose EJ, Ebmeier KP (2006): Pattern of impaired working memory during major depression. J Affect Disord 90:149–161.
61. Yang J, Ouyang X, Tao H, Pu W, Fan Z, Zeng C, *et al.* (2020): Connectomic signatures of working memory deficits in depression, mania, and euthymic states of bipolar disorder. J Affect Disord 274:190–198.
62. Nikolin S, Tan YY, Schwaab A, Moffa A, Loo CK, Martin D (2021): An investigation of working memory deficits in depression using the n-back task: A systematic review and meta-analysis. J Affect Disord 284:1–8.
63. Chaney A, Carballedo A, Amico F, Fagan A, Skokauskas N, Meaney J, Frodl T (2014): Effect of childhood maltreatment on brain structure in adult patients with major depressive disorder and healthy participants. J Psychiatry Neurosci 39:50–59.
64. Nogovitsyn N, Addington J, Souza R, Placsko TJ, Stowkowy J, Wang J, *et al.* (2022): Childhood trauma and amygdala nuclei volumes in youth at risk for mental illness. Psychol Med 52:1192–1199.

65. Kim SY, An SJ, Han JH, Kang Y, Bae EB, Tae W-S, *et al.* (2023): Childhood abuse and cortical gray matter volume in patients with major depressive disorder. Psychiatry Res 319:114990.
66. Norman RE, Byambaa M, De R, Butchart A, Scott J, Vos T (2012): The long-term health consequences of child physical abuse, emotional abuse, and neglect: A systematic review and meta-analysis. PLoS Med 9:e1001349.
67. Khan A, McCormack HC, Bolger EA, McGreenery CE, Vitaliano G, Polcari A, Teicher MH (2015): Childhood maltreatment, depression, and suicidal ideation: Critical importance of parental and peer emotional abuse during developmental sensitive periods in males and females. Front Psychiatry 6:42.
68. Gerke J, Koenig AM, Conrad D, Doyen-Waldecker C, Pauly M, Gündel H, *et al.* (2018): Childhood maltreatment as risk factor for lifetime depression: The role of different types of experiences and sensitive periods. Ment Health Prev 10:56–65.
69. Dagnino P, Ugarte MJ, Morales F, González S, Saralegui D, Ehrenthal JC (2020): Risk factors for adult depression: Adverse childhood experiences and personality functioning. Front Psychol 11:594698.
70. Ho CSH, Chua J, Tay GWN (2022): The diagnostic and predictive potential of personality traits and coping styles in major depressive disorder. BMC Psychiatry 22:301.
71. Weeks M, Cairney J, Wild TC, Ploubidis GB, Naicker K, Colman I (2014): Early-life predictors of internalizing symptom trajectories in Canadian children. Depress Anxiety 31:608–616.
72. Yang C, Chen P, Xie J, He Y, Wang Y, Yang X (2021): Childhood socioeconomic status and depressive symptoms of Young adults: Mediating role of childhood trauma. Front Psychiatry 12:706559.
73. Bohman H, Låftman SB, Päären A, Jonsson U (2017): Parental separation in childhood as a risk factor for depression in adulthood: A community-based study of adolescents screened for depression and followed up after 15 years. BMC Psychiatry 17:117.
74. Tyrka AR, Wier L, Price LH, Ross NS, Carpenter LL (2008): Childhood parental loss and adult psychopathology: Effects of loss characteristics and contextual factors. Int J Psychiatry Med 38:329–344.
75. Stevens JS, Harnett NG, Lebois LAM, Van Rooij SJH, Ely TD, Roeckner A, *et al.* (2021): Brain-based biotypes of psychiatric vulnerability in the acute aftermath of trauma. Am J Psychiatry 178:1037–1049.
76. Goldstein-Piekarski AN, Ball TM, Samara Z, Staveland BR, Keller AS, Fleming SL, *et al.* (2022): Mapping neural circuit biotypes to symptoms and behavioral dimensions of depression and anxiety. Biol Psychiatry 91:561–571.
77. Lemke H, Klute H, Skupski J, Thiel K, Waltemate L, Winter A, *et al.* (2022): Brain structural correlates of recurrence following the first episode in patients with major depressive disorder. Transl Psychiatry 12:349.
78. Schmaal L, Veltman DJ, Van Erp TGM, Sämann PG, Frodl T, Jahanshad N, *et al.* (2016): Subcortical brain alterations in major depressive disorder: Findings from the ENIGMA Major Depressive Disorder working group. Mol Psychiatry 21:806–812.