

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.

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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 Brain-Chart, 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 ($\geq 50\%$ 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 tessellate 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.

- 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.
- 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.
- 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) ($\chi^2 = 2.264, p = .132$). 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 ($\beta = -0.055, SE = 0.025, t_{1,535} = -2.194, p = .029, \text{partial } f^2 = 0.007$). 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 ($\beta = -0.058, SE = 0.028, t_{1,313} = -2.094,$

$p = .037, \text{partial } f^2 = 0.007$) (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 ($R^2 = 0.087, F_{3,176} = 5.571, p = .001; \beta = -0.006, SE = 0.005, t_{1,176} = -1.215, p = .226$), current episode duration ($R^2 = 0.102, F_{3,174} = 6.601, p < .001; \beta = 0.001, SE = 0.001, t_{1,174} = 1.535, p = .127$), and age of MDD onset ($R^2 = 0.077, F_{3,178} = 4.967, p = .002; \beta = -0.001, SE = 0.002, t_{1,178} = -0.324, p = .746$) 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 ($\beta = 0.015, SE = 0.017, t_{1,300} = 0.926, p = .355$) (Figure 1D; Table S5), as well as only in the recurrent MDD group ($\beta = 0.010, SE = 0.019, t_{1,219} = 0.535, p = .594$). 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 ($\beta = -13,451.3, SE = 4981.2, t_{1,341} = -2.70, \text{FDR-corrected } p [p_{\text{FDR}}] = .029, \text{partial } f^2 = 0.04$) (Figure S2) and white matter volume ($\beta = -13,091.7, SE = 5371.4, t_{1,341} = -2.437, p_{\text{FDR}} = .046, \text{partial } f^2 = 0.02$) but not subcortical GMV ($\beta = -898.75, SE = 521.09, t_{1,341} = -1.725, p_{\text{FDR}} = .171$) or ventricular volume ($\beta = 472.81, SE = 643.66, t_{1,341} = 0.735, p_{\text{FDR}} = .463$). 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 ($\beta = 26.343, SE = 7.442, t_{1,163} = 3.540, p_{\text{FDR}} = .005, \text{partial } f^2 = 0.09$) (Figure 3A). Processing speed showed a similar trend; however, this relationship did not survive correction for multiple comparisons ($\beta = 19.109, SE = 7.683, t_{1,171} = 2.487, p_{\text{uncorrected}} = .014$) (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 ($\beta = 79.116, SE = 29.858, t_{1,379} = 2.650, p = .008, \text{partial } f^2 = 0.02$), but no significant diagnosis by centile score interaction ($\beta = -49.856, SE = 39.992, t_{1,379} = -1.247, p = .213$). 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 ($\beta = 111.383, SE = 28.676, t_{1,357} = 3.884, p < .001, \text{partial } f^2 = 0.04$). 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		Test Statistic ^a	p
	n	Mean (SD)	n	Mean (SD)		
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.

^aAnalysis used *t* test and χ^2 test.

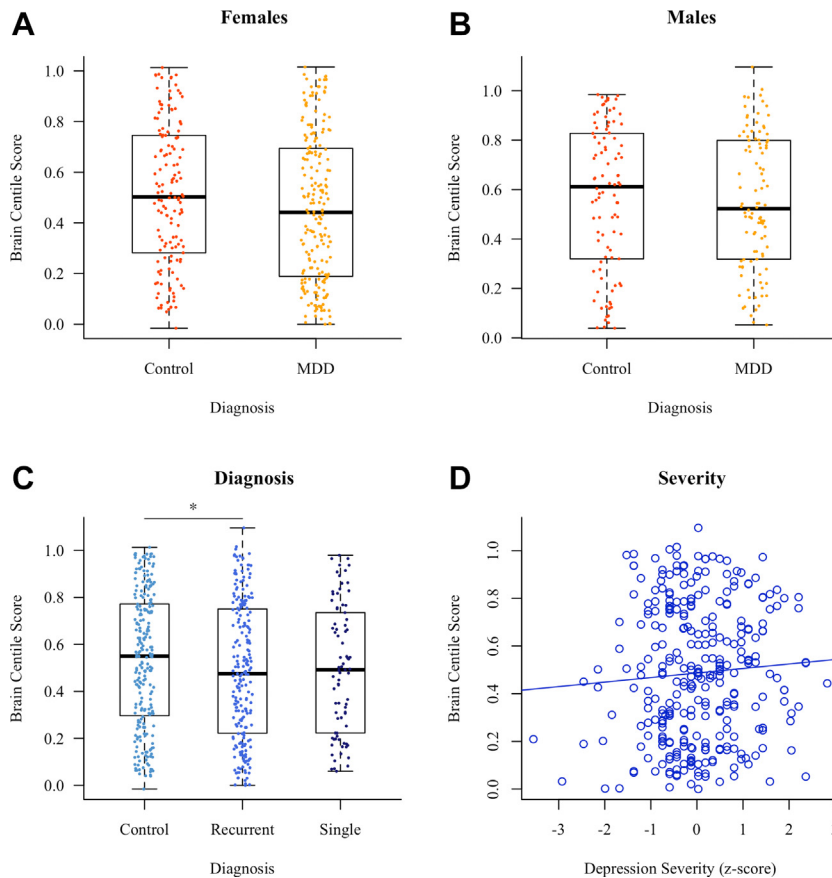


Figure 1. Neither (A) female nor (B) male participants diagnosed with major depressive disorder (MDD) exhibited significantly different brain centile scores relative to control participants without depression. (C) The recurrent MDD group showed significantly lower brain centiles than the control group. (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.

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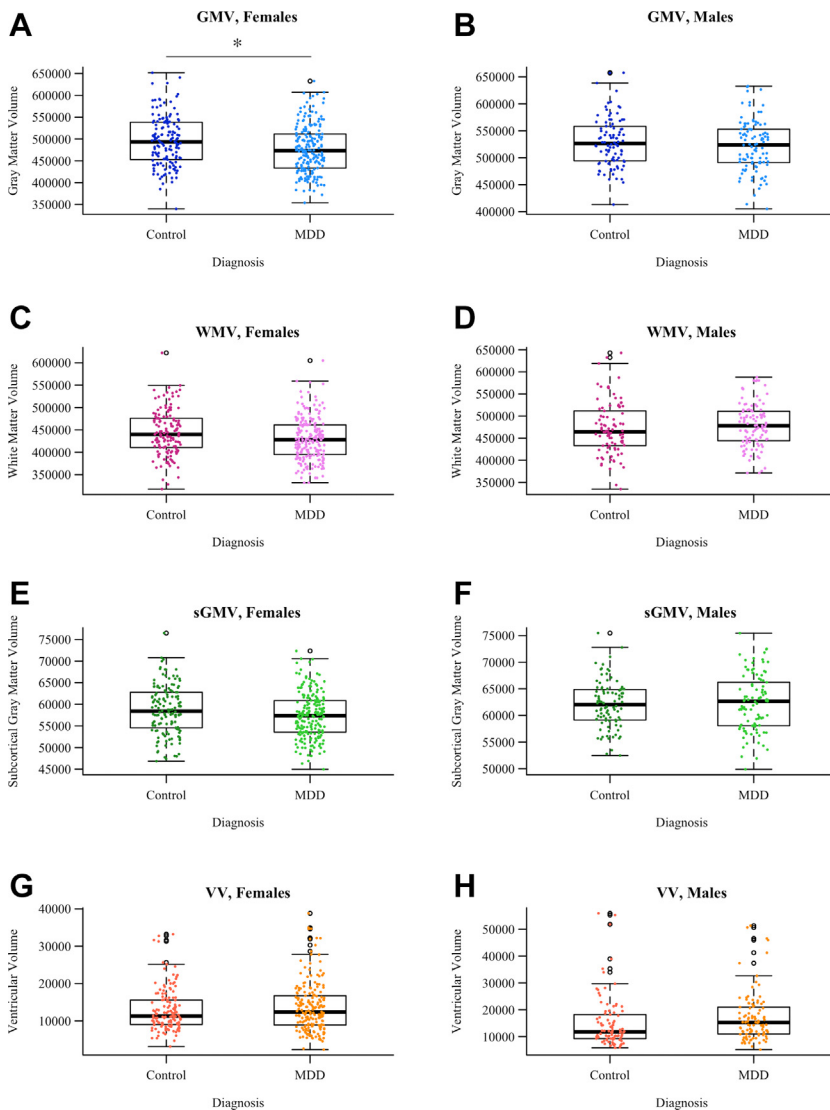


Figure 2. Female participants diagnosed with major depressive disorder (MDD) had significantly lower (A) gray matter volume (GMV) and (C) white matter volume (WMV) than control participants without depression. This was not seen for (E) subcortical GMV (sGMV) or (G) ventricular volumes (VVs) or in the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

MDD ($\beta = -82.790$, $SE = 38.706$, $t_{1,357} = -2.139$, $p = .033$, partial $r^2 = 0.01$) (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 ($\beta = 0.009$, $SE = 0.010$, $t_{1,492} = 0.855$, $p_{FDR} = .605$) (Figure 4A, B), emotional abuse ($\beta = -0.014$, $SE = 0.024$, $t_{1,493} = -0.586$, $p_{FDR} = .605$), physical abuse ($\beta = 0.041$, $SE = 0.022$, $t_{1,493} = 1.871$, $p_{FDR} = .248$, $p_{Uncorrected} = .031$), or sexual abuse ($\beta = 0.012$, $SE = 0.024$, $t_{1,492} = 0.517$, $p_{FDR} = .605$).

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 ($\beta = -13.502$, $SE = 0.574$, $t_{4,664} = -23.514$, $p < .001$), there was no significant main effect of centile score ($\beta = 0.552$, $SE = 2.033$, $t_{1,162} = 0.271$, $p = .786$) and no interaction between centile score and time ($\beta = 0.560$, $SE = 2.101$, $t_{1,664} = 0.267$,

$p = .790$). 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 ($\beta = 1.338$, $SE = 9.344$, $t_{1,162} = 0.143$, $p = .886$) (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 $\beta = 0.581$, $SE = 0.591$, $t_{1,162} = 0.984$, $p = .325$).

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

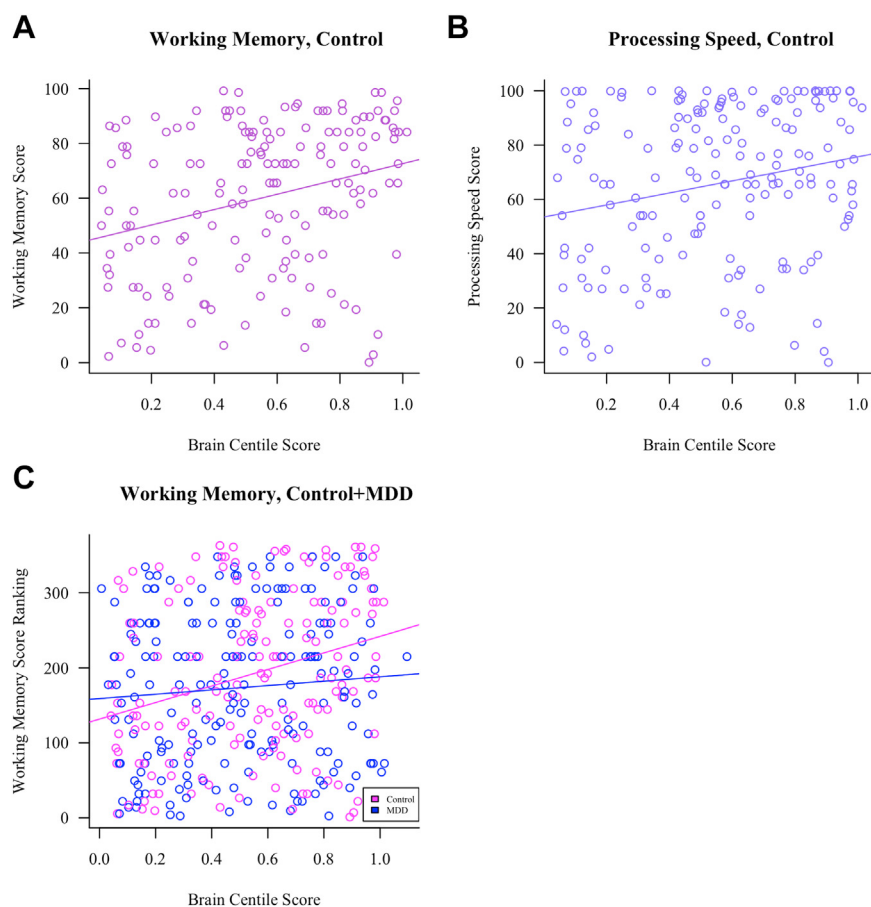


Figure 3. In control participants without depression, **(A)** working memory scores showed significantly positive associations with brain centiles while **(B)** processing speed scores did not. **(C)** In working memory specifically, a significant interaction was seen between brain centiles and diagnosis. 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

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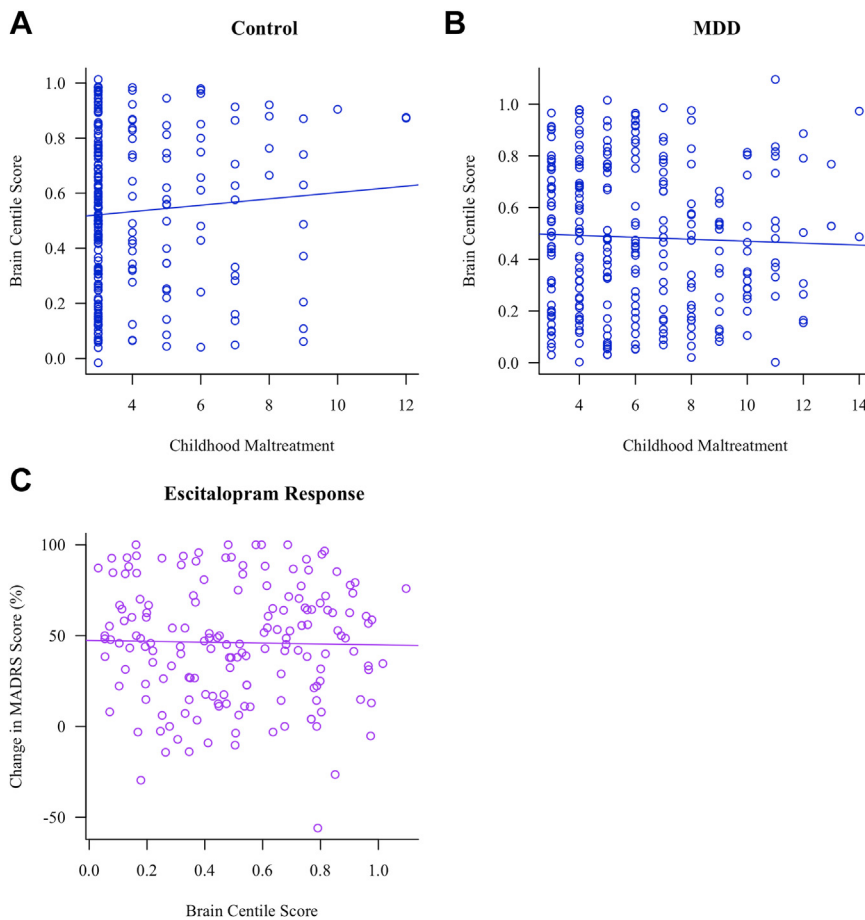


Figure 4. No significant differences were seen between brain centile scores for varying childhood maltreatment scores for both the **(A)** control and **(B)** major depressive disorder (MDD) groups. Brain centiles were adjusted for age, sex, diagnosis, and the interaction between abuse severity and diagnosis. **(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, Brain-Chart estimates brain age using global brain measures instead of regions of interest. However, volumetric loss in the dorso-lateral 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.

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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 (RALB); 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 Cábés, 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. Croyley, 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 Mistic, Sarah E. Morgan, David Mothersill, Cynthia Ortinau, Rik Ossenkopppe, 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 Stolycyn, John Suckling, Gemma Sullivan, Benjamin Thyreau, Roberto Toro, Nicolas Traut, Kamen A. Tsvetanov, Nicholas B. Turk-Browne, Jetro J. Tuulari, Christophe Tzourio, Étienne Vachon-Preseu, 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 Warrior, 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.

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