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# Accelerated brain aging in major depressive disorder and antidepressant treatment response: A CAN-BIND report

Pedro L. Ballester [a], Jee Su Suh [a], Nikita Nogovitsyn [b], Stefanie Hassel [d], Stephen C. Strother [e,f,g], Stephen R. Arnott [e], Luciano Minuzzi [b,c], Roberto B. Sassi [b], Raymond W. Lam [h], Roumen Milev [i], Daniel J. Müller [j,k], Valerie H. Taylor [d], Sidney H. Kennedy [f,j,l,m,n], Benicio N. Frey [b,c,*], CAN-BIND Investigator Team

[a] Neuroscience Graduate Program, McMaster University, Hamilton, ON, Canada
[b] Mood Disorders Program, Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada
[d] Department of Psychiatry, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada
[e] Rotman Research Institute, Baycrest, Toronto, ON, Canada
[f] Institute of Medical Science, University of Toronto, Toronto, ON, Canada
[g] Department of Medical Biophysics, University of Toronto, ON, Canada
[c] Women's Health Concerns Clinic, St. Joseph's Healthcare Hamilton, Hamilton, ON, Canada
[h] Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada
[i] Departments of Psychiatry and Psychology, Queen's University, and Providence Care, Kingston, ON, Canada
[j] Department of Psychiatry, University of Toronto, Toronto, ON, Canada
[k] Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada
[l] Centre for Mental Health, University Health Network, Toronto, ON, Canada
[m] Krembil Research Institute, University Health Network, Toronto, ON, Canada
[n] Centre for Depression and Suicide Studies, and Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada

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ABSTRACT

*Objectives:* Previous studies suggest that major depressive disorder (MDD) may be associated with volumetric indications of accelerated brain aging. This study investigated neuroanatomical signs of accelerated aging in MDD and evaluated whether a brain age gap is associated with antidepressant response.
*Methods:* Individuals in a major depressive episode received escitalopram treatment (10–20 mg/d) for 8 weeks. Depression severity was assessed at baseline and at weeks 8 and 16 using the Montgomery-Asberg Depression Rating Scale (MADRS). Response to treatment was characterized by a significant reduction in the MADRS (≥50%). Nonresponders received adjunctive aripiprazole treatment (2–10 mg/d) for a further 8 weeks. The brain-predicted age difference (brain-PAD) at baseline was determined using machine learning methods trained on 3377 healthy individuals from seven publicly available datasets. The model used features from all brain regions extracted from structural magnetic resonance imaging data.
*Results:* Brain-PAD was significantly higher in older MDD participants compared to younger MDD participants [$t(147.35) = -2.35$, $p < 0.03$]. BMI was significantly associated with brain-PAD in the MDD group [$r(155) = 0.19$, $p < 0.03$]. Response to treatment was not significantly associated with brain-PAD.
*Conclusion:* We found an elevated brain age gap in older individuals with MDD. Brain-PAD was not associated with overall treatment response to escitalopram monotherapy or escitalopram plus adjunctive aripiprazole.

## 1. Introduction

Distributed abnormalities in brain structures are common neuroimaging findings in patients with a significant history of major depressive disorder (MDD) (Fu et al., 2020). Illness-associated brain changes can be detected with various neuroimaging measurements. For example, studies by large consortia of neuroimaging data collection for MDD have identified changes in fractional anisotropy, gray matter

* Corresponding author at: 100 West 5th Street, Suite C124, Hamilton, ON L8N 3K7, Canada.
*E-mail address:* freybn@mcmaster.ca (B.N. Frey).

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volume and white matter microstructure (Schmaal et al., 2020). It has been suggested that certain structural characteristics (e.g., reduced hippocampal volume and cortical alterations in frontal, occipital and cingulate regions) have potential as predictive biomarkers in the context of treatment response to antidepressant use and recurrence of MDD (Kang & Cho, 2020). However, due to inconsistent findings, whether structural information can be predictive of treatment response is still unknown. So far, cortical thickness and volumes of certain brain regions have been linked to antidepressant response in some studies (Bartlett et al., 2018; Jung et al., 2014) but not others (Suh et al., 2020).

Studies of brain age gap estimation (brainAGE) suggest a hypothesis of accelerated brain aging in neuropsychiatric disorders (Dunlop et al., 2021; Han et al., 2020; 2021; Teeuw et al., 2021). The hypothesis posits that a greater gap between chronological age and estimated brain age is associated with unfavorable clinical outcomes in patients with neuropsychiatric illnesses. The brain-predicted age difference (brain-PAD; the difference between chronological age and estimated brain age) has been associated with several clinically meaningful variables, such as mortality risk and fluid intelligence (Cole et al., 2018). Additionally, brain-PAD has been consistently identified in psychotic disorders and neurological diseases (Franke & Gaser, 2012; Gaser et al., 2013; Koutsouleris et al., 2014; Nenadić et al., 2017; Schnack et al., 2016). In this context, brain-PAD has also been associated with clinical scales, such as the positive and negative syndrome scale (PANSS) in schizophrenia (Kay et al., 1987), the mini-mental state examination (MMSE) in mild cognitive impairment and dementia (Folstein et al., 1975), and the expanded disability status scale (EDSS) in multiple sclerosis (Kurtzke, 1983). In all significant associations between brain-PAD and clinical symptoms, a larger brain-PAD was associated with worse clinical outcomes (Kaufmann et al., 2019). There may also be an effect of age on brain-PAD, such that it is more pronounced in older compared to young/mid-life individuals (Christman et al., 2020).

Recently, brainAGE studies have begun to investigate this hypothesis of accelerated brain aging in MDD. The findings so far have been inconclusive, with some studies claiming to have identified signs of accelerated aging in MDD and others indicating the opposite (Besteher et al., 2019; Christman et al., 2020; Kaufmann et al., 2019; Schmaal et al., 2020). A subgroup comparison of medication-free individuals with MDD versus those currently on medications found no differences in brain-PAD (Han et al., 2020) and there is scarce information regarding associations with other clinical characteristics. The disagreements of the field may be attributed to previously identified limitations of imaging research in MDD, such as: (1) the heterogeneity of MDD presentation; (2) variation of clinical characteristics among cohorts; (3) limited sample size; (4) methodological and scanner variability; and/or (5) medication use (type, dosage, duration). Additionally, any time-sensitive relationship between antidepressant use, clinical scales and brain-PAD in MDD has yet to be explored. Finally, epigenetic findings suggest that biological age gaps may be more easily identified in older samples, which also contributes to disagreements in the field (Fries et al., 2020; 2017).

The neuroanatomical markers used for brain age prediction might capture relevant characteristics of an individual's brain health (Cole et al., 2019). A recent study found that brain-PAD in MDD was lower in patients using antidepressants compared with medication-free patients (Han et al., 2021). At a functional level, brain-PAD was associated with impulsivity and disorder severity (Dunlop et al., 2021). All of these findings may be partly explained by an overall worse treatment response throughout the lifespan of the participants, as the lack of neuroprotection from treatment might be one of the factors in accelerated brain aging (Young, 2002). Another study found that older individuals were less likely to respond to escitalopram treatment when they exhibited greater white matter hyperintensities (Gunning-Dixon et al., 2010), which in turn have been associated with advanced brain aging (Habes et al., 2021). However, no previous studies have explicitly tested whether brain age gap itself is a useful biomarker for antidepressant treatment response. Therefore, the current study aims to address two major questions in the literature regarding the brain-PAD and MDD: (1) are there neuroanatomical signs of accelerated brain aging in MDD, and (2) is brain-PAD a useful biomarker of treatment response in MDD? We hypothesized that MDD participants would display larger brain-PAD values than HC. Based on previous research outlined above, in conjunction with the observation of worse clinical outcomes being linked to larger brain-PAD (Kaufmann et al., 2019), we also hypothesized that larger brain-PAD will be associated with worse treatment response.

## 2. Methods

### 2.1. Participants

Data were collected from participants in the Canadian Biomarker Integration Network in Depression (CAN-BIND) study (Kennedy et al., 2019; Lam et al., 2016). Recruitment was conducted at six academic centers across Canada. The details of recruitment strategy and full spectrum of clinical assessments have been previously published (Lam et al., 2016). Briefly, outpatients meeting DSM-IV-TR criteria for a major depressive episode, aged 18–60 and free of psychotropic medications for at least 5 half-lives were recruited for the treatment group if they scored greater or equal to 24 on the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). The six academic centers and their sample sizes were: Centre for Addiction and Mental Health (CAMH; HC = 7, MDD = 5), McMaster University (HC = 19, MDD = 27), The University of British Columbia (UBC; HC = 12, MDD = 49), Toronto General Hospital and Toronto Western Hospital (HC = 23, MDD = 39) University of Calgary (HC = 35, MDD = 25), and Queen's University (HC = 15, MDD = 15). Major exclusion criteria included another primary diagnosis of a psychiatric disorder, high suicidal risk, substance dependence/abuse in the past 6 months, current psychosis, treatment resistance (failure of 4 pharmacologic interventions) or previous failure to respond to escitalopram or aripiprazole. Age-matched healthy comparison (HC) participants were required to have no history of psychiatric or any unstable medical condition. The full list of inclusion and exclusion criteria can be found elsewhere (Lam et al., 2016). Participants in the treatment group that had complete clinical data up to week 16 and complete imaging data at baseline were included in the analysis. Participants in the HC group that had complete data at baseline (clinical and imaging) were also used for the analysis.

### 2.2. MRI data acquisition

The MRI data acquisition and preprocessing protocols have been previously published (MacQueen et al., 2019). Briefly, 3 T images were obtained using four different scanners at six sites: Discovery MR750 3.0 T (GE Healthcare, Little Chalfont, Buckinghamshire, UK), Signa HDxt 3.0 T (GE Healthcare, Little Chalfont, Buckinghamshire, UK), TrioTim 3.0 T (Siemens Healthcare, Erlangen, Germany), and Intera 3.0 T (Philips Healthcare, Best, Netherlands). Structural T1-weighted images were acquired using a whole-brain turbo gradient echo sequence with the following ranges of parameters: acquisition time = 3:30–9:50 min, repetition time (TR) = 6.4–1760 ms, echo time (TE) = 2.2–3.4 s, flip angle = 8–15 degrees, inversion time (TI) = 450–950 ms, field of view (FOV) = 220–256 mm, acquisition matrix = 256x256 – 512x512, 176–192 contiguous slices at 1 mm thickness with voxel dimensions of 1 mm isotropic. For an initial quality assurance step, raw images were manually checked for artifacts and efforts were made to re-scan participants as necessary, as permitted by study timeline.

### 2.3. Treatment protocol

MDD participants were free of psychotropic medication for at least five half-lives before entering the study. MDD participants were offered

an open-label treatment, escitalopram 10–20 mg, flexible dosage, as a monotherapy for 8 weeks (Lam et al., 2016). Participants who demonstrated a ≥ 50% reduction in their MADRS scores as compared to their baseline measurements were considered responders to first-line antidepressant treatment and continued the same treatment for the second 8-week period of the study. Participants who did not respond to 8-week escitalopram monotherapy were prescribed aripiprazole 2–10 mg as an adjunctive therapy for the 8 additional weeks (Lam et al., 2016). In addition to the continuous variables of MADRS score changes at weeks 8 and 16, a dichotomous classification of treatment response was defined at each timepoint as the change in MADRS score equal or greater than 50% of the baseline value.

### 2.4. Brain age estimation

A brain age package available for R (brainageR; v2.1) was used for the prediction of brain age for every individual with available neuroimaging data at baseline. The complete steps to reproduce the brain-PAD values using the brainageR package are available at GitHub[1]. In summary, the package is based on previously published approaches and uses SPM12 for segmentation and spatial normalization (Cole et al., 2018). Images are segmented into grey matter, white matter, and cerebrospinal fluid compartments, which then undergo normalisation to MNI space using DARTEL. The normalized images were handled in R using the RNifti package. Principal component analysis (PCA) is used to retain 80% of the variance for dimensionality reduction and overfit prevention. After PCA transformation, a gaussian process regression (GPR) model from the kernlab package generates the brain age value (Karatzoglou et al., 2004). The GPR model was trained using 3377 healthy comparison participants from several neuroimaging databases in an attempt to build a model that is invariant to scanner effects and perform well across a wide range of ages [mean age = 40.6 (21.4) years, range 18–92 years]. The databases included in the brainageR model were the following: Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL), Dallas Lifespan Brain Study (DLBS), Brain Genome Superstruct Project (GSP), Information eXtraction from Images (IXI), Nathan Kline Institute Rockland Sample Enhanced (NKI-Rockland), Open Access Series of Imaging Studies-1 (OASIS-1), and Southwest University Adult Lifespan Dataset (SALD) (Ellis et al., 2009; Holmes et al., 2015; Marcus et al., 2007; Nooner et al., 2012; Wei et al., 2018). More detailed information on brainageR and its training sets is available in the supplement material. The brain-PAD is thus the individual difference between the predicted value generated by the pre-trained GPR model and the chronological age of the participant. The model was not trained with any of the scans from the CAN-BIND database to prevent biased results. All analyses used brain-PAD generated with CAN-BIND baseline images, since changes in brain age during the 16-week period were likely to be minimal. Table 1 displays the results for the GPR brain age prediction model in mean absolute error (MAE; the mean absolute difference between predicted and expected values) for the CAN-BIND sample.

### 2.5. Statistical analysis

Statistical analyses were performed in R (3.6.3). Outlier predictions of brain age (based on the brain-PAD) were removed following the interquartile range (IQR) criterion, otherwise known as Tukey's boxplot method (Shevlyakov et al., 2013). Individuals with a brain age gap smaller than $Q1 - 1.5*IQR$ or larger than $Q3 + 1.5*IQR$ were removed from analyses, where Q1 and Q3 are the values for the first and third quartiles, respectively.

Group differences of brain-PAD between the MDD and HC groups were assessed with Welch's two sample *t*-test to avoid formal testing of equal variance for every comparison. For individual items of the MADRS, absolute instead of relative change of each item at weeks 8 and 16 were used due to zeros at baseline. The statistical significance of associations between absolute change of individual items of the MADRS score and brain-PAD were assessed using Pearson correlations and Bonferroni-corrected for multiple comparisons. For MADRS items that were identified to have significant associations with brain-PAD, an additional multiple regression analysis was conducted to include covariate terms: age, sex, site, BMI, treatment arm (escitalopram or escitalopram + aripiprazole), and baseline values of the item. All correlations are reported, but findings from the multiple regression analyses should be regarded as most reliable due to the correction for important covariates.

**Table 1**
Model parameters for the prediction of brain-PAD within the MDD and HC groups, with and without age-correction. Note that the corrected versions are likely artificially inflated due to CAN-BIND examples being used for correction. For comparison purposes, the original model presented a test set performance (based on a random subset of the data) of r = 0.973, mean absolute error = 3.933 years, R^2 = 0.946.

| Metric | Correction for age | HC (N = 111) | MDD (N = 160) |
|---|---|---|---|
| Mean Absolute Error | Uncorrected | 5.82 | 5.35 |
| | Corrected | 5.58 | 5.29 |
| r | Uncorrected | 0.78 | 0.86 |
| | Corrected | 0.85 | 0.90 |
| $R^2$ | Uncorrected | 0.60 | 0.73 |
| | Corrected | 0.72 | 0.82 |

It should be noted that, in general, brain age prediction models suffer from an age bias. Specifically, brain age prediction models often overestimate the brain age of individuals who are younger than the mean age of the training set and underestimate brain age for those who are older. Ideally, brain-PADs should be close to 0 throughout the lifespan in HC to be an adequate point of comparison for assessing accelerated aging in clinical populations. A bias-adjustment procedure is required to mitigate this issue by removing the age-dependency of brain-PADs in HC (Beheshti et al., 2019). We generated brain-PAD values for our HC sample which were used to fit a regression model with age as the independent variable and brain-PAD as the dependent variable; the age coefficient and intercept were then used to correct brain age predictions and mitigate age-related prediction bias. The age-corrected brain age ($age_{cb}$) for a participant is given by $age_b - (\beta^* age_c + Intercept)$ , where $age_b$ is the uncorrected predicted brain age and $age_c$ is the chronological age. The corrected brain-PAD is subsequently given by $age_{cb} - age_c$. These age-corrected brain-PAD values were used in all subsequent analyses.

In Table 1, we present the performance metrics of the brain age model with and without correction in our dataset. Importantly, although age-corrected values are more reliable for comparisons between clinical groups and the investigation of clinical outcomes, performance metrics of age predictions are artificially inflated by the age-correction procedure (Butler et al., 2020). Thus, uncorrected brain-PAD values provide a better indication of age prediction errors than the age-corrected ones. To test the dependence of age on brain-PAD, we separated all participants from the MDD group into two cohorts, those who were below or above the median age of the MDD group (33 years). This resulted in two subgroups: the younger group, below 33 years of age (mean age = 25.57 (4.72)) and the group older than the median age (mean age = 46.99 (7.98)). A similar procedure was performed for the HC group (mean ages 26.06 (3.87) and 44.98 (7.92) for the younger and older group, respectively), using the median of the MDD group. The median age was chosen due to previous work that identified signs of accelerated aging in older, but not younger participants with MDD (Christman et al., 2020). In addition, splitting the groups by the median age also aligns our study with a previously published methodology studying hippocampal

[1] https://github.com/james-cole/brainageR

epigenetic aging (Fries et al., 2020). Pearson correlations of age and brain age (both uncorrected and age-corrected) were calculated for each of the four groups. As uncorrected brain age predictions suffer from age-bias, we expected to find significant differences of brain-PAD in both analyses for the MDD group, but only in the uncorrected analysis for the HC group.

## 3. Results

### 3.1. Demographics and clinical characteristics

A total of 160 participants in the MDD group completed the 16-week follow-up and had neuroimaging data collected at baseline. For the HC group, 111 participants completed baseline clinical and neuroimaging data. Table 2 describes the characteristics of the study sample. There were no significant differences in demographic variables. Only a single participant was removed during the outlier removal procedure (brain-PAD = 22.88 belonging to the MDD group).

### 3.2. Brain-PAD group differences

There were no differences in brain-PAD between HC and MDD groups at baseline ($t(225.51) = -0.86$, $p = 0.39$). The findings remained non-significant with and without outlier removal and before and after correction for age-related prediction bias.

### 3.3. Age-dependent brain-PAD differences

As expected for uncorrected values (Beheshti et al., 2019), the HC group exhibited overestimation of brain age in younger participants (+1.63 (SD = 6.85)) and underestimation in older participants (-2.72 (SD = 6.90)). The difference in brain-PAD between older versus younger controls was significant ($t(83.394) = 3.22$, $p < 0.01$). The same pattern was identified in the MDD group: overestimation in the younger group (+1.40 (SD = 6.25)) and underestimation in the older group (-1.28 (SD = 6.95)). This difference was also statistically significant ($t(148.18) = 2.54$, $p < 0.03$). Importantly, when testing group differences, corrected brain-PAD values are more reliable because they remove the age-dependency of uncorrected values (Beheshti et al., 2019). When using age-corrected brain-PAD, the difference between older and younger HC is no longer significant [$t(85.88) = -0.12$, $p = 0.91$], which indicates that the age-correction method properly removed the age-dependency. The difference between older and younger MDD participants is significant after age-correction [$t(147.35) = -2.35$, $p < 0.03$]. The younger MDD subjects exhibited mean brain-PADs close to 0 (-0.40 (6.07)), while the older MDD subjects exhibited a brain-PAD of + 2.02 (6.83). The association between brain-PAD and age was significant in the full MDD group [$r(157) = 0.17$, $p = 0.017$]. Similarly, the association between brain-PAD and age$^2$ was also significant in the MDD group [$r(157) = 0.18$, $p = 0.011$] (Fig. 1).

BMI was significantly associated with age-corrected brain-PAD in MDD [$r(155) = 0.19$, $p < 0.03$]. This replicates a previous finding that BMI is associated with larger brain-PAD in some psychiatric disorders (Kolenic et al., 2018). Illness duration was not associated with age-corrected brain-PAD in MDD.

### 3.4. Association of brain-PAD with treatment response

There was no difference in brain-PAD between responders and nonresponders at either week 8 or week 16, before or after correction for age bias. A secondary analysis was conducted using individual items of the MADRS at week 16. Only *reported sadness* showed an association with brain-PAD after outlier removal [$r(157) = 0.22$, $p < 0.01$, uncorrected]. However, after controlling for baseline values of reported sadness, site, age, sex, BMI, and treatment arm in a multiple linear regression model with a Bonferroni correction considering all MADRS items, this association was no longer significant ($p_{adj} = 0.052$).

**Table 2**
Demographic characteristics of the study sample.

| | Control (N = 111) | Treatment (N = 160) | Total (N = 271) | p-value |
|---|---|---|---|---|
| **Age** | | | | 0.074 |
| Mean (SD) | 33.05 (10.78) | 35.68 (12.60) | 34.60 (11.94) | |
| Range | 18.00–60.00 | 18.00–61.00 | 18.00–61.00 | |
| **Sex** | | | | 0.806 |
| Female | 71 (64.0%) | 100 (62.5%) | 171 (63.1%) | |
| Male | 40 (36.0%) | 60 (37.5%) | 100 (36.9%) | |
| **Predicted brain age** | | | | 0.052 |
| Mean (SD) | 33.07 (10.59) | 35.94 (12.78) | 34.76 (11.99) | |
| Range | 14.54–59.77 | 12.94–75.72 | 12.94–75.72 | |
| **Brain-PAD** | | | | 0.783 |
| Mean (SD) | 0.02 (7.16) | 0.26 (6.81) | 0.16 (6.94) | |
| Range | −15.49–18.80 | −13.39–17.07 | −15.49–18.80 | |
| **Predicted brain age (c)[1]** | | | | 0.050 |
| Mean (SD) | 33.05 (12.69) | 36.55 (15.43) | 35.11 (14.45) | |
| Range | 11.41–65.45 | 10.53–81.88 | 10.53–81.88 | |
| **Brain-PAD (c)** | | | | 0.298 |
| Mean (SD) | 0.00 (6.68) | 0.86 (6.74) | 0.51 (6.72) | |
| Range | −13.91–18.29 | −13.45–22.88 | −13.91–22.88 | |
| **MADRS[2] score** | | | | <0.001 |
| Mean (SD) | 0.84 (1.69) | 29.89 (5.48) | 17.99 (14.96) | |
| Range | 0.00–10.00 | 21.00–47.00 | 0.00–47.00 | |
| **MADRS change at week 16** | | | | |
| Mean (SD) | NA | −19.46 (8.89) | −19.46 (8.89) | |
| Range | NA | −47.00 – 10.00 | −47.00–10.00 | |

1. (c) stands for age-corrected values.
2. MADRS: Montgomery-Åsberg Depression Rating Scale.

## 4. Discussion

The present study examined brain-PAD in medication-free individuals with MDD and its association with subsequent antidepressant treatment response. We found that age-corrected brain-PAD was significantly larger than controls in older but not in younger individuals with MDD. These findings are consistent with previous neuroimaging studies (Christman et al., 2020; Han et al., 2020; Koutsouleris et al., 2014), as well as epigenetic studies showing larger epigenetic age gaps in older individuals with neuropsychiatric disorders (Fries et al., 2020; 2017). This finding contrasts with studies in individuals diagnosed with schizophrenia, where the highest rates of accelerated aging were observed in the first few years after disease onset (Schnack et al., 2016).

We found no association between brain-PAD and overall treatment response, as defined as a decrease in MADRS total scores. Interestingly, brain-PAD was highly correlated with changes in *reported sadness*, a single item of the MADRS. *Reported sadness* explained 61% of the variance of total MADRS scores ($R^2 = 0.61$) and represents a core symptom of depression. Ultimately, the link between brain-PAD and changes in *reported sadness* may suggest that brain-PAD reflects only certain dimensions of depression and treatment response to antidepressants. Other variables that were explored as covariates, including sex, site, and BMI, did not affect the significance of the findings. However, BMI was independently associated with brain-PAD in both the full MDD group and the older subgroup, but more strongly with the latter. This supports the hypothesis of an additive effect of BMI and psychiatric disorders in brain-PAD (Kolenic et al., 2018).

Brain-PAD has been previously associated with clinically meaningful variables, such as increased mortality risk (J. H. Cole et al., 2018) and

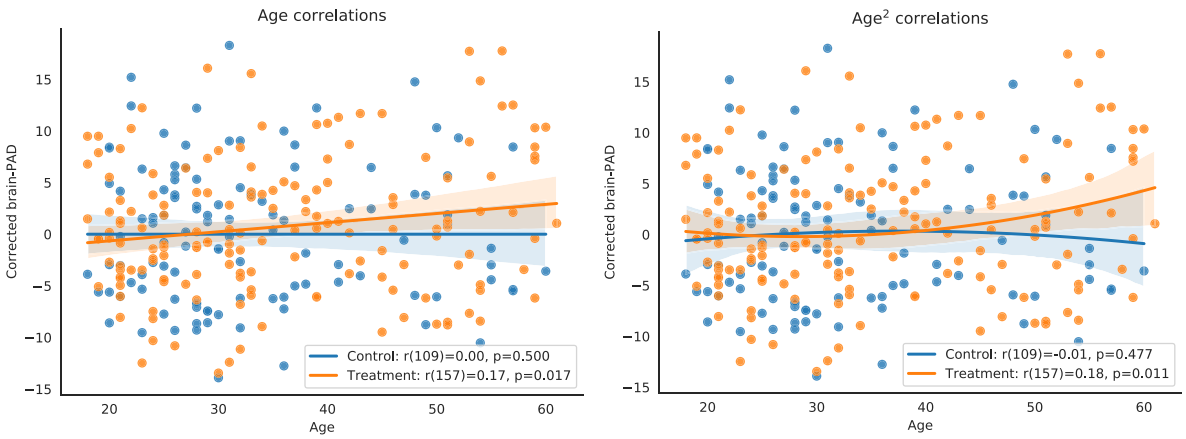


**Fig. 1.** Associations between age-corrected brain-PAD and chronological age for healthy control and treatment groups. On the left, chronological age is significantly associated with brain-PAD in the treatment group. Similarly, on the right, chronological age$^2$ was significantly associated with brain-PAD in the treatment group. Outliers have been removed from this analysis.

cognitive decline (Elliott et al., 2019), possibly mediated by lifestyle choices, such as meditation (Luders et al., 2016). Brain-PAD has also been shown to be associated with dementia risk and the conversion from mild cognitive impairment to Alzheimer's disease, suggesting its applicability in the screening for dementia (Gaser et al., 2013; Wang et al., 2019). In depression, brain-PAD was associated with the severity of depressive symptoms and impulsivity (Dunlop et al., 2021). Similar findings for illness severity were observed in schizophrenia as measured by the PANSS (Kaufmann et al., 2019). Some of the associations observed in schizophrenia are only present when brain age is predicted using specific brain regions, an approach affording greater statistical power. Longitudinal assessments in schizophrenia also point to an increased rate of brain aging right after illness onset that decreases over time, still resulting in higher brain age later in life due to cumulative effects (Schnack et al., 2016). Taken together, these studies not only demonstrate the similarities in brain-PAD findings across disorders, but also highlight potential applications of brain-PAD in investigating etiology, treatment and diagnosis of MDD. In MDD, some remaining gaps include determining conversion of MDD to other psychiatric disorders, prediction of treatment response with region-specific brain-PAD and longitudinal changes in brain-PAD.

Our study has some limitations. First, the mean absolute error of the brain age predictions is larger than what was reported in the original test set for the software package, possibly due to scanner variability in this sample. A possible step for improving the prediction error would be to run separate models for males and females (Ritchie et al., 2018), which would require a larger sample size. Beyond improving predictions, our findings may also have been different with other proportions of males and females. Evidence suggests that male brains appear to be metabolically older than female brains and that male brain age is more dependent on individual health (Franke et al., 2014; Goyal et al., 2019). We may also have encountered type II error, given correction for the large number of comparisons. Important mediator links that have not been investigated in this study may influence findings, such as: lifestyle factors, including exercise (Steffener et al., 2016) and meditation (Luders et al., 2016), tobacco smoking, and alcohol consumption (Ning et al., 2020). Overall, the CAN-BIND study had a relatively young sample of participants with MDD, which may lead to findings that are not generalizable across the lifespan and are more relevant for earlier in the course of illness.

Future studies should conduct further age-dependent brain-PAD analyses in MDD to characterize the relationship between age and brain-PAD more precisely. This can include additional analyses for nonlinear associations between brain-PAD and age, which can subsequently be compared between cases and controls. As suggested by findings in Fig. 1, higher-order associations between brain-PAD and age are promising and may exhibit better fit, as brain structure is known to display nonlinear developmental trajectories (Fjell et al., 2013). Additionally, future studies should analyze dimensions of clinical scales of MDD with brain-PAD using region-based predictions, particularly those that measure affective symptoms. Further, although we did not observe a significant relationship between brain-PAD and illness duration, the question of whether accelerated aging is related to age of onset is still a promising avenue of research as demonstrated by previous findings in schizophrenia (Schnack et al., 2016). Future studies with larger samples and longer follow-up could test this hypothesis in MDD, as the effect may be more difficult to detect due to clinical heterogeneity, as well as the more subtle brain changes that are typically observed in MDD in comparison with what is seen in psychosis.

## 5. Conclusion

This study found a greater brain-PAD for older individuals compared to the younger in the MDD group. No significant associations between brain-PAD and antidepressant treatment response were found. Future work should probe further associations of brain-PAD with other clinical features of depression and investigate age-dependent rates of accelerated aging longitudinally.

### *CRediT authorship contribution statement*

**Pedro L. Ballester:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Jee Su Suh:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Nikita Nogovitsyn:** Conceptualization, Methodology, Writing – review & editing. **Stefanie Hassel:** Data curation, Investigation, Project administration, Resources, Writing – review & editing. **Stephen C. Strother:** Data curation, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – review & editing. **Stephen R. Arnott:** Data curation, Resources, Visualization, Writing – review & editing. **Luciano Minuzzi:** Investigation, Resources, Writing – review & editing. **Roberto B. Sassi:** Investigation, Writing – review & editing. **Raymond W. Lam:** Funding acquisition, Investigation, Project administration, Resources, Writing – review & editing. **Roumen Milev:** Funding acquisition, Investigation, Project administration, Resources, Writing – review & editing. **Daniel J. Müller:** Funding acquisition, Investigation, Project administration, Resources, Writing – review & editing. **Valerie H. Taylor:** Project administration, Resources, Writing – review & editing. **Sidney H. Kennedy:** Funding acquisition, Investigation, Project administration,

Resources, Writing – review & editing. **Benicio N. Frey:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

## Declaration of Competing Interest

RM has received consulting and speaking honoraria from AbbVie, Allergan, Eisai, Janssen, KYE, Lallemand, Lundbeck, Otsuka, and Sunovion, and research grants from CAN-BIND, CIHR, Janssen, Lallemand, Lundbeck, Nubiyota, OBI and OMHF.

RWL has received honoraria or research funds from Allergan, Asia-Pacific Economic Cooperation, BC Leading Edge Foundation, Canadian Institutes of Health Research, 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, and VGH-UBCH Foundation.

VHT has received honoraria from Novonordisk.

PLB, JS, SH, NN, and BNF, SS, SA, LM, RS, DJM, SHK have no conflicts of interest to report.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2021.102864.

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