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Age-dependent brain morphometry in Major Depressive disorder

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ABSTRACT

Background: Major depressive disorder (MDD) is a complex disorder that affects nearly 264 million people worldwide. Structural brain abnormalities in multiple neuroanatomical networks have been implicated in the etiology of MDD, but the degree to which MDD affects brain structure during early to late adulthood is unclear.
Methods: We examined morphometry of brain regions commonly implicated in MDD, including the amygdala, hippocampus, anterior cingulate gyrus, lateral orbitofrontal gyrus, subgenual cortex, and insular cortex subregions, from early to late adulthood. Harmonized measures for gray matter (GM) volume and cortical thickness of each region were estimated cross-sectionally for 305 healthy controls (CTLs) and 247 individuals with MDD (MDDs), collated from four research cohorts. We modeled the nonlinear associations of age with GM volume and cortical thickness using generalized additive modeling and tested for age-dependent group differences.
Results: Overall, all investigated regions exhibited smaller GM volume and thinner cortical measures with increasing age. Compared to age matched CTLs, MDDs had thicker cortices and greater GM volume from early adulthood until early middle age (average 35 years), but thinner cortices and smaller GM volume during and after middle age in the lateral orbital gyrus and all insular subregions. Deviations of the MDD and CTL models for both GM volume and cortical thickness in these regions started as early as age 18.
Conclusions: The analyses revealed that brain morphometry differences between MDDs and CTLs are dependent on age and brain region. The significant age-by-group interactions in the lateral orbital frontal gyrus and insular subregions make these regions potential targets for future longitudinal studies of MDD.

1. Introduction

Major depressive disorder (MDD) is a debilitating and recurrent disorder that affects approximately 264 million people worldwide (James et al., 2018). While the first onset of MDD commonly occurs during late adolescence and young adulthood (Kessler et al., 2005; Breslau et al., 2017), this recurrent disorder also presents at other life stages, including in middle age and late life (Wisner et al., 2004; Wang et al., 2017; Byers and Yaffe, 2011). Because effective treatment requires knowledge of risk factors and their neurobiological mechanisms, the study of structural brain alterations has been critical in advancing our understanding of the capacity for neuroplasticity in MDD and its implications for treatment (Albert, 2019; Joshi et al., 2016; Korgaonkar et al., 2015). Although the question of whether abnormalities in brain structure contribute to or result from MDD is not resolved (Wei et al., 2020; Geerlings et al., 2013; McKinnon et al., 2009), many studies have reported depression-associated alterations in brain structure, based on commonly used gray matter volume and cortical thickness metrics, in cerebral areas involved in emotion processing including orbitofrontal cortex, cingulate cortex, amygdala, and hippocampus (Palazidou, 2012; Price and Drevets, 2012; for the ENIGMA-Major Depressive Disorder Working Group, Schmaal L, Hibar DP, Sämann PG, Hall GB, Baune BT, et al., 2017; Menon, 2011; Smart et al., 2015; Tekin and Cummings, 2002; Alexander et al., 1986; Videbech, 2004). Recent reports have

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implicated the insular cortex as a neuroanatomical substrate underlying MDD. Additionally, functional connectivity of the insula has been associated with treatment response in MDD in both adolescents and adults (Johnstone et al., 2007; Herwig et al., 2010; Mutschler et al., 2012).

Due to its centrality, the insula is highly interconnected and shares connections with multiple cortical and subcortical regions that can vary by hemisphere and subregion (Ghaziri et al., 2018). It has been consistently shown that individuals with MDD have functional abnormalities (Johnstone et al., 2007; Herwig et al., 2010; Strigo et al., 2008; Giesecke et al., 2005; Bär et al., 2007) and functional reorganization (Mutschler et al., 2012) within the insula. Furthermore, neuroimaging studies illustrate functional subdivisions within the anterior insula, whereby the dorsal anterior portion is more involved in cognitive processing and shows strong functional connections with the dorsal attentional stream, while ventro-medial aspects of the insula relate more to emotional processing and show strong functional connections with the amygdala (Deen et al., 2011; Cauda et al., 2011). In line with functional alterations, effects of MDD on insular gray matter tissue morphometry are reported in age specific cohorts across the lifespan. A number of other cross-sectional studies have reported smaller gray matter volume in the insular cortices of individuals with MDD, cumulatively covering an age range of 18–74 years (Stratmann et al., 2014; Ancelin et al., 2019; Liu et al., 2014). Yet, results differ in associations with the course of disease and treatment response which might be linked to cumulative downstream effects of MDD. For example, one group found in an MDD cohort that the magnitude of disgust recognition correlated with reduced insular gray matter volume (Sprengelmeyer et al., 2011). Several other studies have reported reduced gray matter volume in the anterior insula of MDD adult patients compared to healthy controls (Takahashi et al., 2010; Bora et al., 2013; Peng et al., 2016). Du et al found in a cohort of late-life depression patients, grey matter volume of the right insula was smaller than in healthy controls (Du et al., 2014). Thus, an investigation of MDD effects across a wide age span in a unified analysis as proposed in this study could add to our understanding of how MDD may or may not differentially affect the morphometry of the insula in an age-dependent manner. It should be noted that, although gray matter volume and cortical thickness are considered interchangeable in neuromorphometry studies, studies on cortical thickness alterations in MDD have been largely inconclusive, with mixed reports of greater cortical thinning and thickening in insular cortices in MDD patients (for the ENIGMA-Major Depressive Disorder Working Group et al., 2017; Cafiero et al., 2019).

Although distinct genetic etiologies as well as the distinct growth and pruning patterns (Panizzon et al., 2009; Cafiero et al., 2019; Rakic, 1988) of gray matter volume and cortical thickness could explain these discordant findings, there is a considerable interest in characterizing whether these structural brain findings are age-dependent, as has been observed in other brain regions in the context of MDD. For instance, cohort studies have reported smaller gray matter volume in the orbitofrontal cortex in adult and elderly MDD patients (ages 56–85 years), with limited replication in young adults (specifically at age 24) (Grieve et al., 2013; Lee et al., 2003). Similarly, findings of MDD-associated smaller gray matter volume in the anterior cingulate cortex have been limited to studies of young adult and elderly patients (ages 12–27 and 68–74 years) (Ancelin et al., 2019; Grieve et al., 2013). A recent *meta*-analysis of studies in adolescent (ages $\leq$ 21 years) and adult MDD patients (ages $>$ 21 years) found age-dependent differences between MDDs and healthy controls, such that adult patients had overall thinner cortices in the insula, anterior cingulate cortex, and orbitofrontal cortex (for the ENIGMA-Major Depressive Disorder Working Group, Schmaal L, Hibar DP, Sämann PG, Hall GB, Baune BT, et al., 2017), whereas adolescents did not. Furthermore, despite the large number of studies on hippocampal and amygdala structural abnormalities in MDD across all age groups, findings are inconsistent as well. One cross-sectional study of adult MDD (age 27–76 years) reported smaller bilateral amygdalar gray matter volume while another (ages 18–56 years) reported larger bilateral amygdalar gray matter volume in those with MDD (Kronenberg et al., 2009; van Eijndhoven et al., 2009). Other cross-sectional studies report no differences between MDD and CTL amygdala gray matter volume in adults (age 18–60 years) (e.g., Stratmann et al., 2014). Similarly, findings of the effects of MDD on hippocampal volume vary. Two cross-sectional studies in adolescents and young adults as well as a *meta*-analysis of 351 patients (mean age 46 years) and 279 healthy controls reported smaller bilateral hippocampal volume in MDD (Videbech, 2004; Redlich et al., 2018; Straub et al., 2019), whereas another other cross-sectional study (age 18–65 years) found no differences in hippocampal gray matter volume by group (Vythilingam et al., 2004). Taken together, while previous reports indeed identified MDD-associated alterations in brain morphometry in specific age-groups, corresponding age-related differences in large groups of individuals between early and late adulthood have yet to be determined. Given the recent increase in the number of papers focusing on charting brain changes through imaging over the lifespan (Bethlehem et al., 2021), we believe our investigation is of timely importance.

Here, our primary interest was on the age-dependent effects of MDD on brain morphometry, and how this may differ in the subregions of the insula – i.e., dorsal anterior insula, ventral anterior insula, and posterior insula – compared to other brain regions invariably, regardless of age, implicated in MDD including the amygdala, hippocampus, anterior cingulate cortex together with subgenual cortex, and lateral orbitofrontal cortex. Cerebral morphometry measures of gray matter tissue volume and cortical thickness for each region of interest were estimated from the structural T1-weighted (T1w) magnetic resonance (MR) images of 247 patients with current MDD who were unmedicated at the time of imaging (MDDs) and 305 healthy control participants (CTLs) with ages between 18 and 85 years. In the absence of a single data set that spans the target age range, we pooled images from four different research cohorts using a statistical imaging data harmonization approach that eliminates imaging site effects. We used generalized additive models to characterize morphometry measures as a function of age to investigate age-dependent group differences in gray matter volume and cortical thickness measures across most of the adult lifespan.

2. Materials and methods

2.1. Study design

This collaborative cross-sectional investigation was designed to assess the age-dependent effect of MDD on brain morphometry across an age range of 18 to 85 years by leveraging four research cohorts of MDDs and demographically matched CTLs, recruited at two academic research centers. The T1w MR scans from these two sites were aggregated through a statistical harmonization approach. Each study was approved by the Internal Review Board (IRB) at the primary institute and all research was conducted following data sharing regulations of each institute and IRB regulations at UCSF. Each study protocol also addressed human subjects research ethics in accordance with the Declaration of Helsinki.

2.2. Participants

The University of California, San Diego (UCSD) contributed data from two separate research cohorts with overlapping ages, acquired between 2006 and 2018. The first cohort (UCSD local) consisted of 47 MDDs and 54 CTLs, with age ranges of 18–49 and 18–38 years respectively, from an observational study on neural substrates of pain modulation in subjects with current MDD [MH080003 and MH077205 (Strigo et al., 2008; Strigo et al., 2013). The second cohort (UCSD multi-site) consisted of 63 MDDs and 46 CTLs, with age ranges of 18–54 and 30–63 years, respectively, from longitudinal studies examining the impact of a psychosocial intervention [R61MH113769, UL1TR001442

(Taylor et al., 2020a; Taylor et al., 2017; Taylor et al., 2020b)].

The University of California, San Francisco (UCSF) contributed data from three separate studies with overlapping ages, conducted between 2008 and 2018. The first cohort (UCSF 3T) consisted of 86 MDDs and 152 CTLs, with age ranges of 65–85 and 56–85 years, respectively, from a longitudinal neuroimaging study assessing psychotherapy treatment response for late life major depressive disorder [R01MH101472, (Bickford et al., 2018; Bickford et al., 2020). The second cohort (UCSF 4T) came from two observational studies, one that focused on cognitive and neuroimaging predictors of disability in late life depression [K08MH081065, (Mackin et al., 2013) and another that focused on hippocampal volume differences in patients with depression [R01MH083784, (Lindqvist et al., 2014). The entire UCSF 4T cohort consisted of 56 MDDs and 67 CTLs, with age ranges of 25–84 and 25–85 years, respectively.

Detailed information on inclusion/exclusion criteria for each study can be found in the Supplemental Material. Only baseline neuroimaging data were assessed in this study and at the time of the baseline scan all MDD patients were required to be unmedicated, although information regarding prior medication history was not available. Participants from each study with one time point MRI scan data acquired at unmedicated state were included in this collaborative study design based on the availability of demographic data (age and sex) and availability of clinical diagnosis of CTL or MDD. No other additional exclusion criteria were imposed when merging the data from the four study cohorts.

2.3. MRI data acquisition

Subjects in UCSD local cohort were imaged on a 3 T GE MR750 scanner at the UCSD Center for Functional MRI (http://fmri.ucsf.edu/). MRIs for the UCSD multi-site cohort were obtained from the INTRuST imaging data repository. MRI scans were acquired on three scanner models across six facilities using imaging protocols calibrated and standardized for 3 T Phillips Achieva, 3 T GE MR750, and 3 T Siemens TimTrio scanners. There were no statistically significant differences in the distribution of groups by scanner ($\chi^2 = 7.38, p > 0.1$) (Bomyea et al., 2020).

The MDDs in UCSF 3 T cohort were imaged on a Siemens 3 T Skyra scanner using a standardized Alzheimer's Disease Neuroimaging Initiative-2 (ADNI-2) imaging protocol. The CTL cases for UCSF 3 T cohort were taken from the ADNI-2 data set, which pools data across multiple sites. Although scanners may be different at each site, the ADNI protocol ensures that the acquisition parameters are tailored to each site to produce the same image quality across the population (Wyman et al., 2013). The UCSF 4 T cohort was imaged on a 4 T Siemens Bruker scanner.

Image acquisition parameters for all cohorts are provided in Table 1.

2.4. Raw MRI data quality assurance

Each T1w MR image was inspected visually for outstanding artifacts and the overall quality of the acquisition.

2.5. MR image processing

A fully automated processing pipeline, Advanced Normalization Tools (ANTs) cortical thickness pipeline, was applied to each T1w scan. Pre-processing involved correction of magnetic field intensity inhomogeneity (e.g., N4 bias correction) (Tustison et al., 2010), extraction of brain tissues, Atropos n-tissue segmentation (Avants et al., 2011), and registration-based cortical thickness estimation (Das et al., 2009). The T1w MRI volume of each subject was spatially normalized to a widely used T1w MRI template in stereotaxic space, the Montreal Neurological Institute/International Consortium for Brain Mapping (MNI-152), where insular subfields (dorsal anterior insula, ventral anterior insula, and posterior insula – Fig. 1a) and cortical and subcortical regions of interest including anterior cingulate cortex, amygdala, hippocampus, subgenual frontal cortex, and lateral orbitofrontal cortex were defined as illustrated in Fig. 1b.

Spatial normalization and ROI segmentation results for each scan were inspected visually for accuracy. Morphometric measures including total gray matter volume in mm^3 and average cortical thickness in mm were estimated using ANTs built-in functions for each ROI. The relative ICV-to-template size was determined by calculating the determinant of the affine registration matrix from the ANTs registration. The relative intracranial volume (ICV) value was then multiplied by the ICV of the MNI-152 template to calculate a total ICV value per subject.

2.6. Harmonization of neuroimaging measures

To remove confounding site, scanner, protocol effects while retaining the biological information, morphometric measures in this multicenter study was first harmonized. Various neuroimaging data harmonization techniques have been proposed in the literature, including statistical approaches (Fortin et al., 2017; Fortin et al., 2016; Pomponio et al., 2020) and dictionary- and deep-learning approaches (St-Jean et al., 2020; Dewey et al., 2019). We harmonized individual ROI gray matter volume and cortical thickness measures using a model that builds upon a statistical harmonization technique, ComBat, which was originally developed as a batch adjustment method for genomics data (Johnson et al., 2007). ComBat is well suited for retrospective studies without requiring matching subjects between sites or supplemental data acquisitions and has been proven effective and robust in neuroimaging data harmonization in small sample sizes (<10) using empirical Bayesian framework (Johnson et al., 2007). Furthermore, it has shown success in harmonizing neuroimaging metrics across different field strengths (Pomponio et al., 2020), making ComBat data harmonization widely adapted among the neuroimaging communities in recent years (Fortin et al., 2017; Fortin et al., 2018; Yu et al., 2018).

The ComBat method is formulated to remove unwanted sources of variability, specifically site/scanner differences, while preserving variations due to other biologically-relevant covariates in the data, as described in detail elsewhere (Fortin et al., 2017). The ComBat harmonization approach posits a unique linear model of measurement scale differences at each morphometric measure, making the assumption that scanners and imaging protocols (referred to as cohort differences hereon) have both an additive and multiplicative effect on the data. In this study, a unified model was used to estimate the mean (additive effect)

Table 1
MRI acquisition parameters.

Cohort		TR (ms)	TE (ms)	TI (ms)	Flig Angle	Slices	FOV (cm)	Matrix (mm)	Resolution (mm3)	Acquisition type
UCSD local 3 T	GE	8	3	450	12	Sag, 172	25	256 × 256	1 × 0.97 × 0.97	FSGR
UCSD multi-site 3 T	GE	9.16	3.71		10	Sag, 176	25.6	256 × 256	1 × 1 × 1	FSGR
	Philips	7.64	3.56		7					3D Turbo Field Echo
	Siemens	2350	3.32		7					MPRAGE
UCSF 3 T	Siemens	2300	2.98	900	9	Sag, 176	25.6	256 × 256	1 × 1.2 × 1.2	MPRAGE
UCSF 4 T	Siemens	2300	3	900	7	Sag, 157	25.6	256 × 256	1 × 1 × 1	MPRAGE

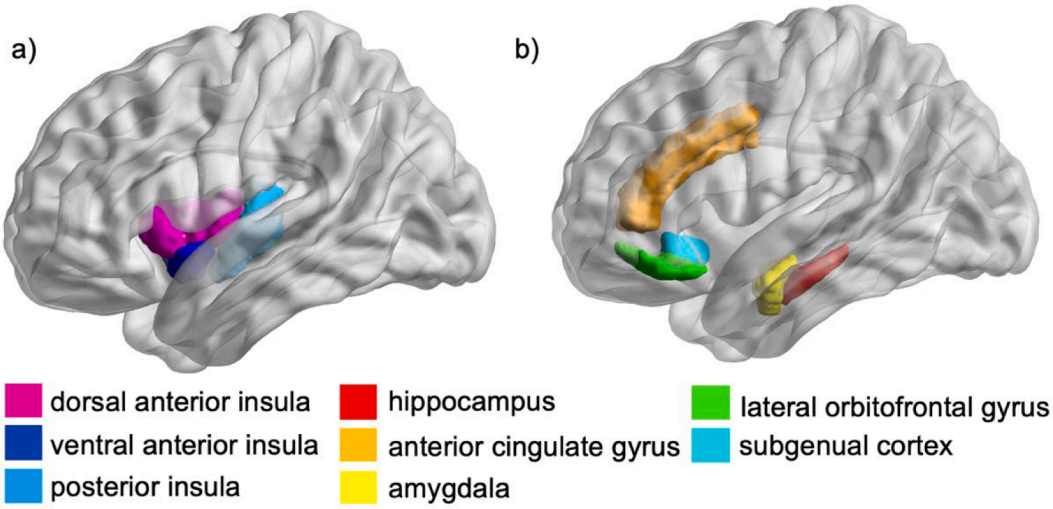

Fig. 1. Regions of interest a) Subregions of the insular cortex that are grouped into the following subdivisions: dorsal anterior insula, ventral anterior insula and posterior insula. b) Brain regions implicated in MDD, including amygdala hippocampus, anterior cingulate gyrus, lateral orbitofrontal gyrus, and subgenual cortex.

and variance (multiplicative effect) of cohort differences in morphometric measurements together with variations due to biologically-relevant covariates in the data. The additive and multiplicative effects due to cohort differences were then removed from the morphometric measures while preserving variations in the data due to biologically-relevant covariates. In this study, biologically-relevant covariates were *a priori* selected as age and sex for both morphometric measures of interest, with ICV as an additional covariate only for gray matter volume. While sex and ICV were considered linear factors inducing biological variances, effect of age as a biological covariate was modeled as a non-linear factor using the recently proposed extension of ComBat with generalized additive models (i.e., ComBat-GAM) (Fortin et al., 2016). This was done to accommodate the fact that regional brain volume and age have an established nonlinear and non-parametric relationship (Ziegler et al., 2012) that cannot be accurately captured by a linear or parametric non-linear model (Fjell et al., 2010). GAM is an additive modeling technique where the impact of the variables is captured through smooth functions which can be nonlinear depending on the underlying patterns in the data (Hastie and Tibshirani, 1986). When the model contains nonlinear effects, i.e., effect of age on morphometric measures, GAM provides a regularized and interpretable solution. Flexible fitting against data also allows GAM to capture common nonlinear patterns that a classic linear model would miss.

The additive and multiplicative correction factors to harmonize the morphometric data across cohorts were estimated using the data from CTL participants only, and then applied to the MDD participant data according to the corresponding cohort information. All ComBat-GAM harmonization was run in R v. 3.6.1 (R Core Team, 2017).

2.7. Statistical analysis

Chi-squared analyses and independent samples *t*-tests were conducted to assess differences in demographic characteristics between CTLs and MDDs.

To characterize the nonlinear associations between age and brain morphometry measures, we used a GAM with a logit link function. As mentioned above, regional brain tissue volume and age have an established nonlinear and non-parametric relationship that cannot be accurately captured by a linear or parametric non-linear model (Ziegler et al., 2012; Fjell et al., 2010). The flexibility of GAMs allows the shape of this trajectory to be non-parametric, as it is estimated from the data and not determined a priori (Hastie and Tibshirani, 1986). Specifically, in addition to a parametric linear term of age, the model also included a nonparametric cubic spline term for age (Hastie, 1996).

The deviance between the models with and without the spline term was compared using a χ^2 test; a significant test indicates that the spline term improves the model fit, thus supporting a nonlinear relationship of age with the dependent variable. For each ROI separately, we examined the generalized smooth association of age with each morphometry metric covarying for the fixed effects of diagnostic group (CTL, MDD), sex, and ICV (for volumes only). We modeled the interaction term of age and group; significant interaction effects indicated a group difference over time. Significance was determined by adjusting the *p*-value for the number of brain morphometry measures in total (two: gray matter volume and cortical thickness). We further probed all significant interaction effects to determine the ages that showed significant group differences. Specifically, we used the model to estimate gray matter volume and cortical thickness values for both groups across the full age range and then compared them using independent *t*-tests with a sliding window approach. The windows spanned 5 years (e.g., 18–22) sliding by 2 years to characterize with finer granularity the ages at which morphometry differed between groups.

All statistical analyses were conducted using statistical software in R (R Core Team, 2017). The *mgcv* packages were used to apply the GAM function (Wood, 2011).

3. Results

3.1. Cohort characteristics

Out of 252 MDD and 319 CTL cases, 5 MDD and 4 CTL images from the UCSD local cohort, 1 MDD and 1 CTL image from the UCSD multi-site cohort, and 8 CTL images and 1 MDD image from the UCSF 3 T cohort were removed due to imaging artifacts (e.g., aliasing) and/or overall poor quality. Following an outlier detection criterion of 3 absolute z-scores from the mean of the distribution from all participants of the respective group, 17 CTL and 15 MDD were excluded from the gray matter volume analysis and 14 CTL and 12 MDD were excluded from the cortical thickness analysis. The final study cohort including cases from both the gray matter volume and cortical thickness analysis consisted of 245 MDDs and 306 CTLs.

Demographic and clinical characteristics of the volunteers at each site are summarized in Table 2. The age overlaps across the four research cohorts are shown in Fig. S1a. While the sampling densities by age were slightly different between MDDs and CTLs, the full age range covered by both groups was the same. There were no differences in the distribution

Table 2
Characteristics of 4 research cohorts from two academic research centers. For the category of age, the average age is presented with the standard deviation in parentheses and the interval in brackets. For the category of sex, the percentage of females is reported.

	UCSD local	UCSD multi-site	UCSF 3 T	UCSF 4 T
Controls				
N	50	45	144	67
Age (years)	25.5 ± 5.31	44.0 ± 9.88	70.5 ± 5.03	58.1 ± 17.2
Sex (% female)	42.0	46.7	68.8	52.2
Medication history	No psychotropic meds in last 30 days	No more than one psychotropic med in last 90 days	No psychotropic medications (time not specified)	No psychotropic medications (time not specified)
PHQ-9[1]	–	1.27 ± 2.24	–	–
CDI[2]	–	–	–	–
BDI-II[3]	1.52 ± 2.86	–	–	–
GDS[4]	–	–	0.90 ± 1.00	1.5 ± 1.42* (41.8% of sample)
MDD				
N	42	62	85	56
Age (years)	25.8 ± 6.57	28.0 ± 9.48	71.0 ± 4.98	60.5 ± 18.3
Sex (% female)	57.1	61.3	62.4	63.6
Age of Onset	19.8 ± 6.7** (90% of sample)	N/A	N/A	N/A
Medication History	No psychotropic medication (time not specified)	No concurrent psychotropic medication (history not mentioned)	No psychotropic medications (time not specified)	No psychotropic medications (time not specified)
PHQ-9	–	14.93 ± 4.65	–	–
BDI-II	26.8 ± 8.10	–	–	–
HAMD-24[5]	–	–	25.5 ± 4.56	23.9 ± 4.99* (71.4% of sample)

*Missing GDS scores from 39 control participants and HAMD-24 scores from 16 MDD participants in the UCSF 4 T cohort.
**Missing age of onset data from 5 MDD participants in the UCSD local cohort.
[1] Patient health questionnaire-9.
[2] Children's depression inventory.
[3] Beck depression inventory-II.
[4] Geriatric depression scale.
[5] Hamilton rating scale for depression-24.

of sex across MDDs and CTLs of the entire cohort ($\chi^2 = 0.87$, $p = 0.35$). MDDs had moderate to severe symptoms in all age groups, based on PHQ-9 between 15 and 19 (Kroenke et al., 2001), and BDI-II scores between 20 and 28 (Smarr and Keefer, 2011) in the young adult and middle age groups, and HAMD-24 between 19 and 38 (Sharp, 2015) in the elderly group.

3.2. Harmonization of structural measures among cohorts

Volume and cortical thickness measures for a sample region (left dorsal anterior insula) are shown in Fig. 2 as a function of age before and after removal of cohort effects using the ComBat-GAM harmonization process. Visualizations of pre- and post-harmonization morphometry measures from all other ROIs are provided in the Supplementary Material (Figs. S3-S6). For each cohort, the distribution of additive and multiplicative correction factors for the gray matter volume and cortical thickness measures across all ROIs are shown in Fig. S7.

3.3. Models of Age-dependent regional morphometry in CTL and MDD

Estimated GAM models of all regions for CTL and MDD between the ages of 18–85 years are shown in Figs. 3 and 4 for gray matter volume and cortical thickness, respectively. The detailed model parameters for both metrics in all regions are provided in Tables S2 and S3.

3.4. Interaction between age and diagnosis

Gray Matter Tissue Volume: We observed significant interaction effects between age and diagnosis for bilateral dorsal anterior insula (left: $F = 9.62$; $df = 2.23$; $p < 0.001$, right: $F = 6.46$; $df = 1.96$; $p < 0.001$), posterior insula (left: $F = 0.36$; $df = 0.89$; $p = 0.04$, right: $F = 0.55$; $df = 1.00$; $p = 0.02$), lateral orbitofrontal gyrus (left: $F = 1.00$; $df = 1.23$; $p = 0.001$, right: $F = 4.20$; $df = 1.77$; $p < 0.001$), and the right ventral anterior insula ($F = 0.71$; $df = 2.40$; $p = 0.03$, see Table S2), suggesting that the age-volume model of individuals with MDD between the ages 18–85 is significantly different than the age-volume model observed for healthy CTL over the same age range.

Specifically, bilateral dorsal anterior insula and lateral orbital frontal gyrus, as well as the right posterior insula exhibited significantly greater gray matter volume in MDD participants than controls starting as early as age 18 (average: 19.6 years; Fig. 5a; Table S4). Starting around later middle-age (average: 59 years), MDD individuals had smaller gray matter volume in all insular subregions (except for the left dorsal anterior insula) and orbitofrontal cortex compared to CTL (Fig. 5b; Table S4). Bilaterally in the hippocampus, MDD had consistently smaller gray matter volume than CTL across the full age range. Interestingly, the gray matter volume of MDD participants was consistently larger in the right amygdala and consistently smaller in the left amygdala compared to CTL across the full age span of 18–85 years.

Cortical Thickness: Bilaterally the anterior cingulate cortex (left: $F = 0.40$; $df = 0.91$; $p = 0.03$, right: $F = 0.22$; $df = 0.96$; $p = 0.003$), posterior insula (left: $F = 0.62$, $df = 1.02$, $p = 0.001$, right: $F = 1.61$; $df = 1.38$; $p = 0.001$), left dorsal anterior insula ($F = 1.1$, $df = 1.38$, $p = 0.001$), left subgenual cortex ($F = 0.56$; $df = 1.05$; $p = 0.02$), right ventral anterior insula ($F = 1.19$; $df = 2.10$; $p = 0.002$), and right orbitofrontal cortex ($F = 3.20$; $df = 1.91$; $p < 0.001$) exhibited a significant age-by-diagnosis interaction (Table S3). Additionally, all these regions exhibited significant cortical thickness differences between the groups, many as early as age 18 (average: 18.75 years), with thicker cortices in MDD than CTL (Fig. 5c; Table S5). Starting again at around late middle-age years (average: 64.7 years), MDD individuals had cortical thinning in the left dorsal anterior insula, right ventral anterior insula, right posterior, right anterior cingulate, right lateral orbitofrontal gyrus, and left subgenual cortex, compared to CTL (Fig. 5d; Table S4).

3.5. Main effect of group

MDD participants had smaller gray matter volume than CTL in bilateral ventral anterior insular (left: ß=-27.7; $p = 0.03$, right: ß=-40.3; $p = 0.003$), bilateral hippocampal (left: ß=-41.1; $p = 0.0004$, right: ß=-37.4; $p = 0.004$), left posterior insular (ß=-55.3; $p = 0.03$), and left amygdala (ß=-106; $p < 0.001$), but larger right amygdalar volume (ß=60.3, $p < 0.001$; Table S2) than CTL. MDD participants had significantly thinner cortex than CTL in the right ventral insula (ß=-0.12; $p = 0.017$; Table S3).

3.6. Main effect of age

All regions examined in this study exhibited reductions in gray matter volume and cortical thickness with age by up to 30% over the age span investigated (Tables S2 and S3; Figs. 3 and 4).

4. Discussion

In this study, we have mapped significant age-dependent group differences in brain morphometry operationalized as gray matter volume and cortical thickness in a large sample of individuals with MDD and

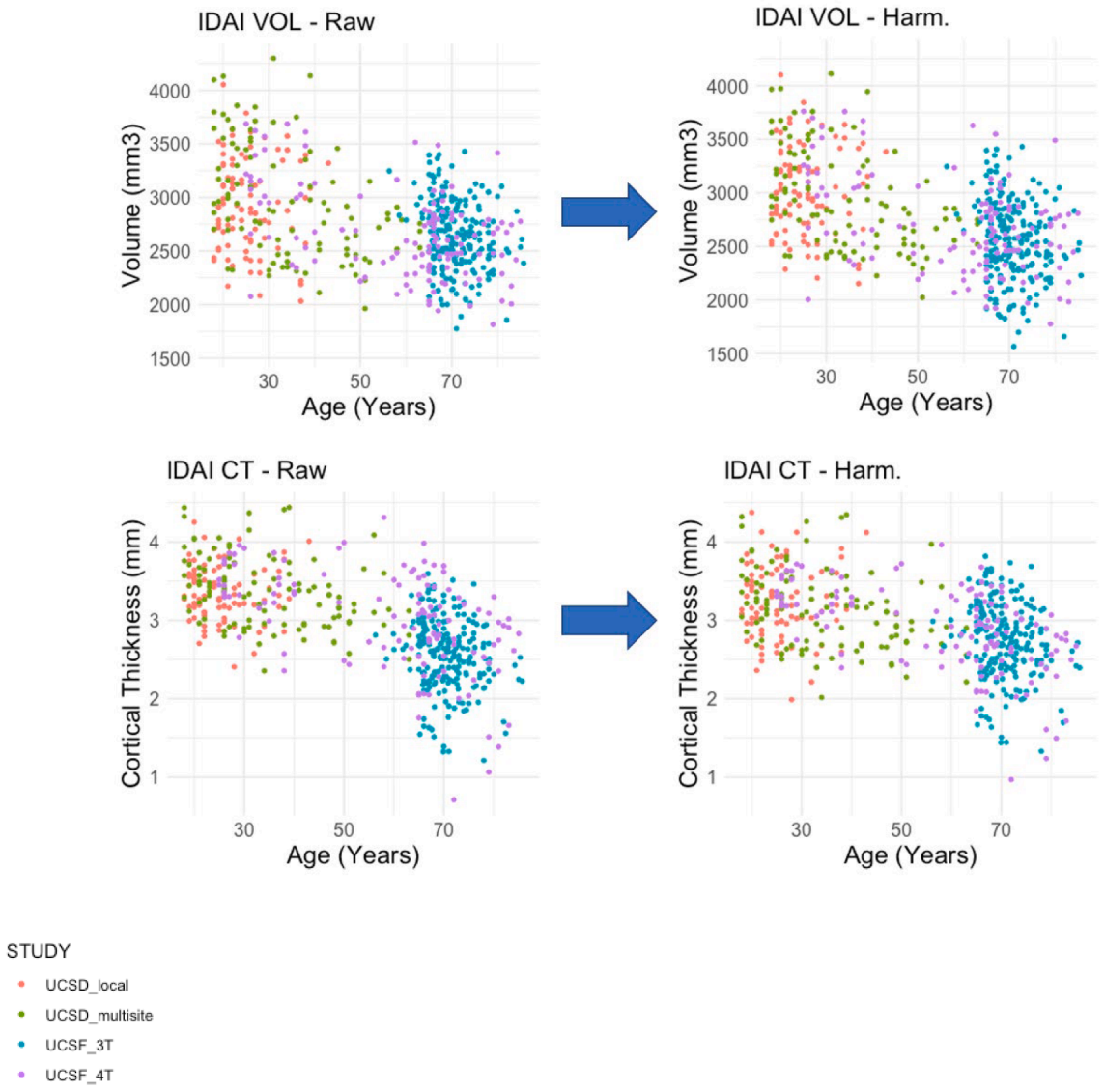

Fig. 2. Harmonization of gray matter volume and cortical thickness measures across four research cohorts. Distribution of the original versus ComBat-GAM harmonized volume and cortical thickness measures as a function of age for a sample ROI, the left dorsal anterior insula (DAI).

healthy CTLs, spanning a wide age range of 18 to 85 years, assembled by harmonizing T1w MR imaging data from four independent research cohorts. Our results showed significant *age-dependent* group differences, such that individuals with MDD generally presented with greater gray matter volume and cortical thickness during young adult and early middle-age years (on average around the age of 19 years for gray matter volume and the age of 18.6 years for cortical thickness), but often smaller gray matter volume and cortical thickness than CTL predominantly starting at later middle-age years (on average around the age of 58.5 years for gray matter volume and the age of 63.8 years for cortical thickness).

When comparing groups in an age-dependent way, MDDs compared to CTLs exhibited greater gray matter volume in the bilateral dorsal anterior insula and bilateral lateral orbitofrontal cortex only up to 45 years of age, while cortical thickness follows a similar pattern only in the left dorsal anterior insula and right orbitofrontal cortex. Studies that examined cognitive aspects of emotional processing (e.g., appraisal) reported the strongest association with cortical morphometry in more dorsal aspects of the anterior insula (Mutschler et al., 2012; Kurth et al., 2010), while studies that examined a more visceral response associated with emotional experience (e.g., heart rate, galvanic skin response) found the strongest association in more ventral aspects of insula (Mutschler et al., 2009). The dorsal insula has been shown to be predominantly involved in cognitive processing (Mutschler et al., 2012; Kurth et al., 2010; Craig (Bud), n.d.; Kurth et al., 2010; Nelson et al., 2010; Chang et al., 2013; Touroutoglou et al., 2012). As such, it would be interesting to see in a future analysis if certain cognitive measures correlate with the age-dependent morphometric differences we observed between MDDs and CTLs. Additionally, it is interesting to note that the other subregions of the insula (posterior insula and ventral anterior insula) did not exhibit such drastic age-dependent differences. Indeed, MDD gray matter volume was observed to be only ever higher than CTL gray matter volume briefly in early adulthood in the right posterior insula. These results echo those reported by Tang et al in an investigation of insular morphometry in patients with bipolar depression (Tang et al., 2014), where left dorsal anterior insular gray matter volume was increased and right posterior insular and left ventral anterior insular gray matter volume was decreased in patients relative to healthy controls. Considering connections between the ventral anterior insula and limbic areas and its role in affective processing, decreased gray matter volume in the ventral anterior insula could be related to limbic overactivity (Uddin et al., 2017; Sliz and Hayley, 2012).

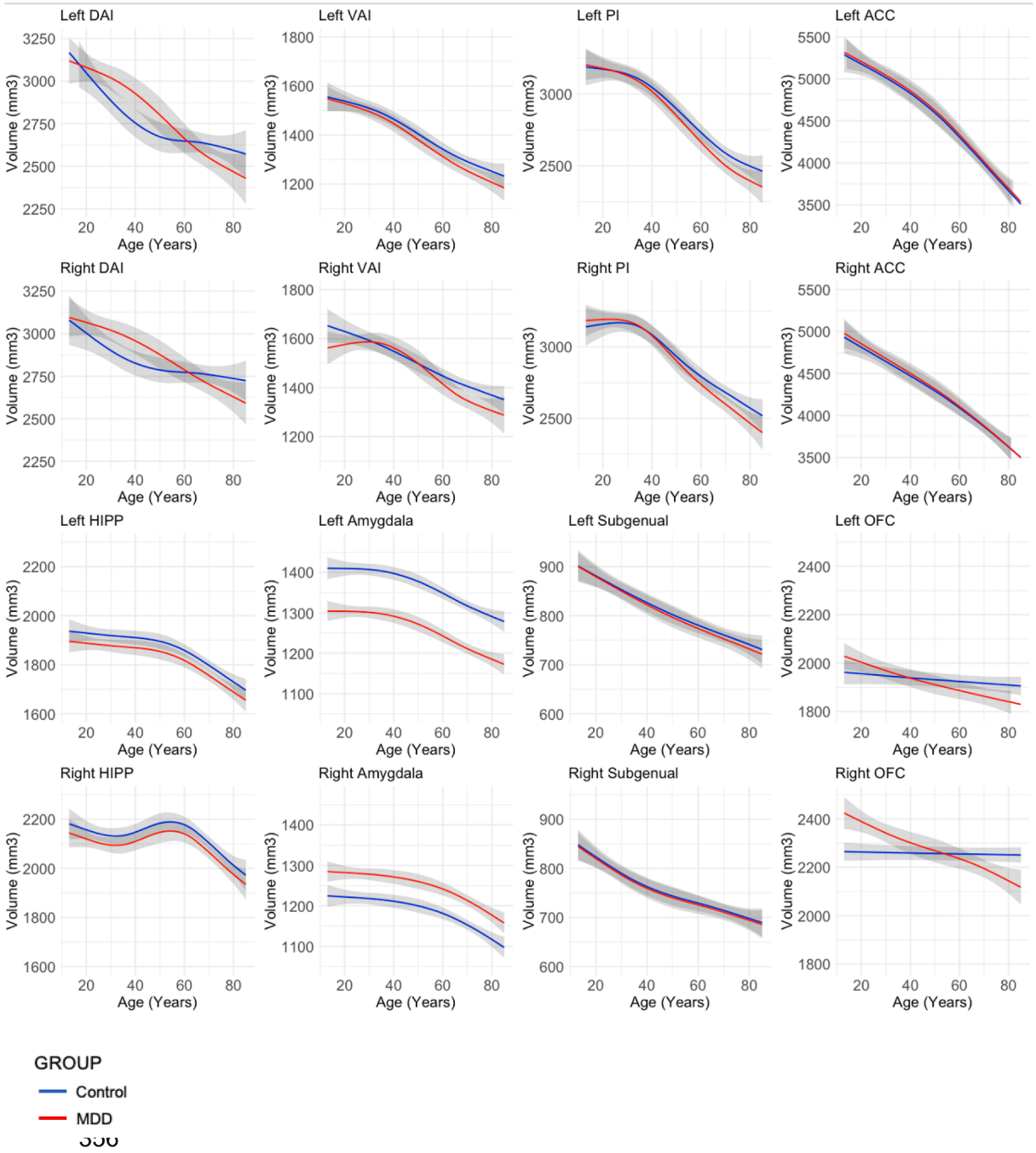

Fig. 3. Age-Gray Matter Volume Models of all regions. GAM predicted gray matter volumes against age after accounting for ICV and sex differences for the left and right sides of each region (DAI = dorsal anterior insula, VAI = ventral anterior insula, PI = posterior insula, ACC = anterior cingulate cortex, SUB = subgenual cortex, OFC = orbital frontal cortex).

Regarding differences in cortical thickness, our findings suggest that this measure differs between MDDs and CTLs in a largely age-dependent way. Half of the regions included in this analysis exhibited age-dependent trajectories of cortical thickness such that MDDs exhibit thicker cortices than CTLs from early to middle-age years. In the remaining regions, MDD cortices are thicker than CTL cortices starting as early as 18 years of age, and in some cases (e.g., left orbitofrontal cortex) this trend extends to 85 years.

Our findings in this study are mostly consistent with the current literature, with a few regional exceptions. For instance, the difference between our insula findings compared to other results may be due to differences in chosen analytical approaches (e.g., overall average group effect as opposed to an age-dependent effect) or differences in cohort composition (Stratmann et al., 2014) (Liu et al., 2014). Similarly, Ancelin et al (Ancelin et al., 2019) and Grieve et al (Grieve et al., 2013) reported smaller gray matter volume in the anterior cingulate cortex of MDD patients compared to controls, which is different from the findings reported in this study. From a cohort perspective, Ancelin et al focused only on a group of elderly individuals with a diagnosis of lifetime MDD, while our cohort spanned 18–85 years with varying degrees of MDD duration. Additionally in both studies results were reported as an overall average group effect as opposed to an age-dependent effect. Furthermore, investigations focusing on cortical thickness in MDD in regions like the insula, anterior cingulate cortex, and orbitofrontal cortex have

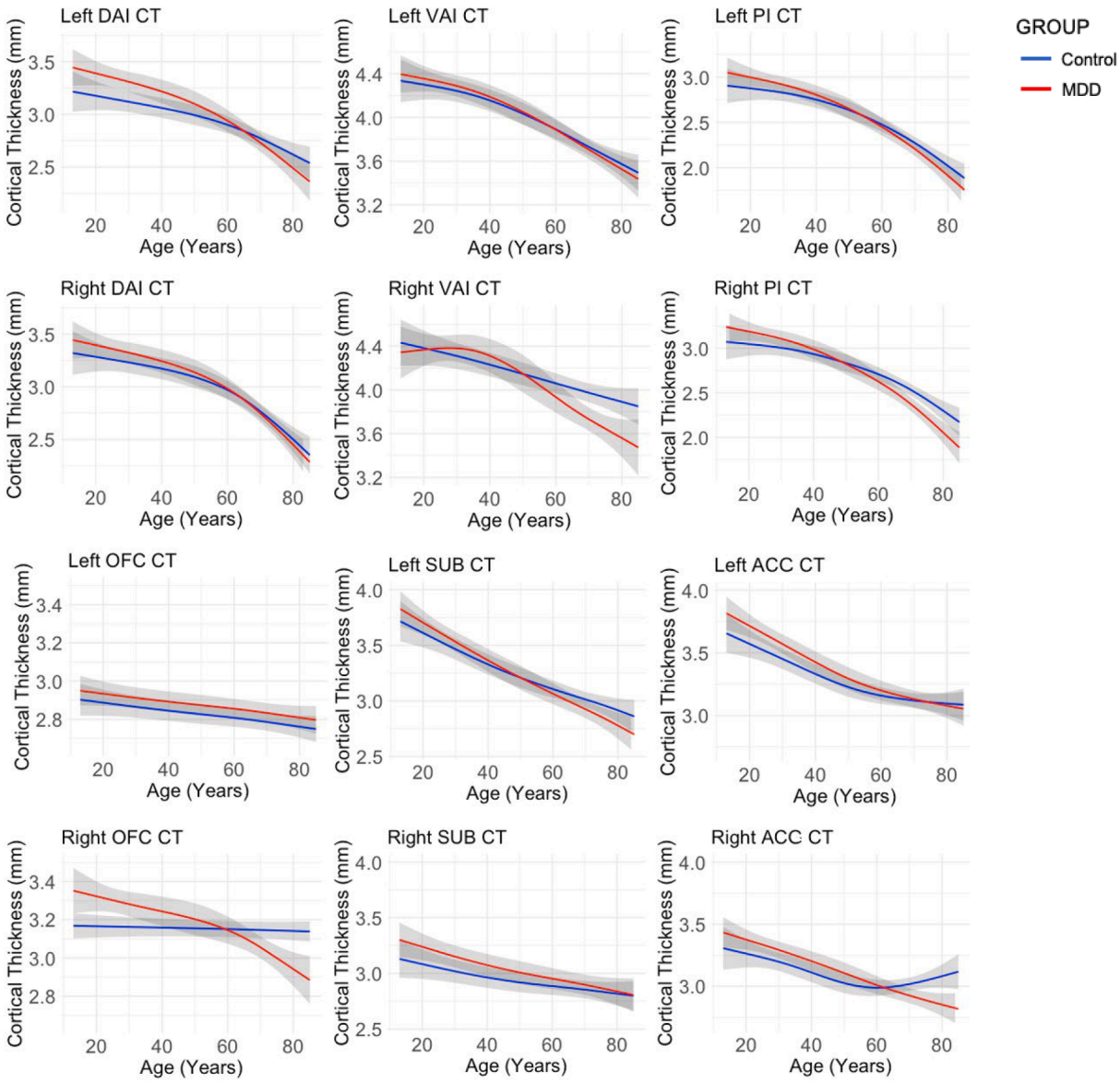

Fig. 4. Age-Cortical Thickness Models for all regions. GAM predicted cortical thickness against age after adjusting for sex differences for the left and right sides of each region. MDD trajectories are red and CTL trajectories are blue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

reported conflicting findings. One *meta*-analysis (Schmaal et al., 2017) reported thinner cortices in adult MDD patients (ages > 21 years) in these regions and no differences in adolescents. Our results do not align with these findings, given that cortices of MDD patients are found to be thicker than CTLs in most regions included in this analysis, often in the young adult to middle-age years. These seemingly contradictory results may again be due to the methodological differences between studies and highlights the importance of focusing on an age-dependent angle.

While others have established the impact of MDD on brain structure on targeted age groups, e.g., middle age (Chaney et al., 2014; Huang et al., 2013) or late life (Sexton et al., 2013; Andreescu et al., 2008; Disabato and Sheline, 2012) separately, two unique aspects of our study compared to previous reports need to be highlighted. First, by combining data from several independent but clinically well-characterized cohorts, we observed patterns in the morphometry of healthy controls and patients with MDD over a wide span of 18 to 85 years. Second, by employing generalized additive regression in our analyses we created non-linear models of the structural brain and age associations in MDDs and CTLs. Our analyses suggested that both the direction and magnitude of MDD vs CTL brain morphometry differences varied across the lifespan in an age-dependent fashion. While the main effect of MDD on brain structure in our lifespan cohort was consistent with previous more age-specific studies, our age-dependent findings suggested that using traditional categorization by age, such as young adults (ages 18–35 years), middle-aged adults (ages 36–55 years), or older adults (aged older than 55 years), for relative comparison to normal aging may result in artificially diluted effect estimates, particularly during the early to late middle age window. Furthermore, the etiology of the MDD vs CTL brain morphometry differences might vary with age. As previously noted in the literature, findings depicting thicker cortex in teens with MDD we observed here could be attributed to irregular or delayed pruning during neurodevelopment (Reynolds et al., 2014; Jernigan and Tallal, 2010). Conversely, as one of the early brain regions to form during gestation, greater insular volume in teens with MDDs compared to CTL teens might be a result of an inherent neurodevelopmental difference in cortical folding patterns (Straub et al., 2019; Rana et al., 2019; Sarrazin et al., 2018; Chechik et al., 1999; Courchesne et al., 2001). Furthermore, our finding of smaller gray

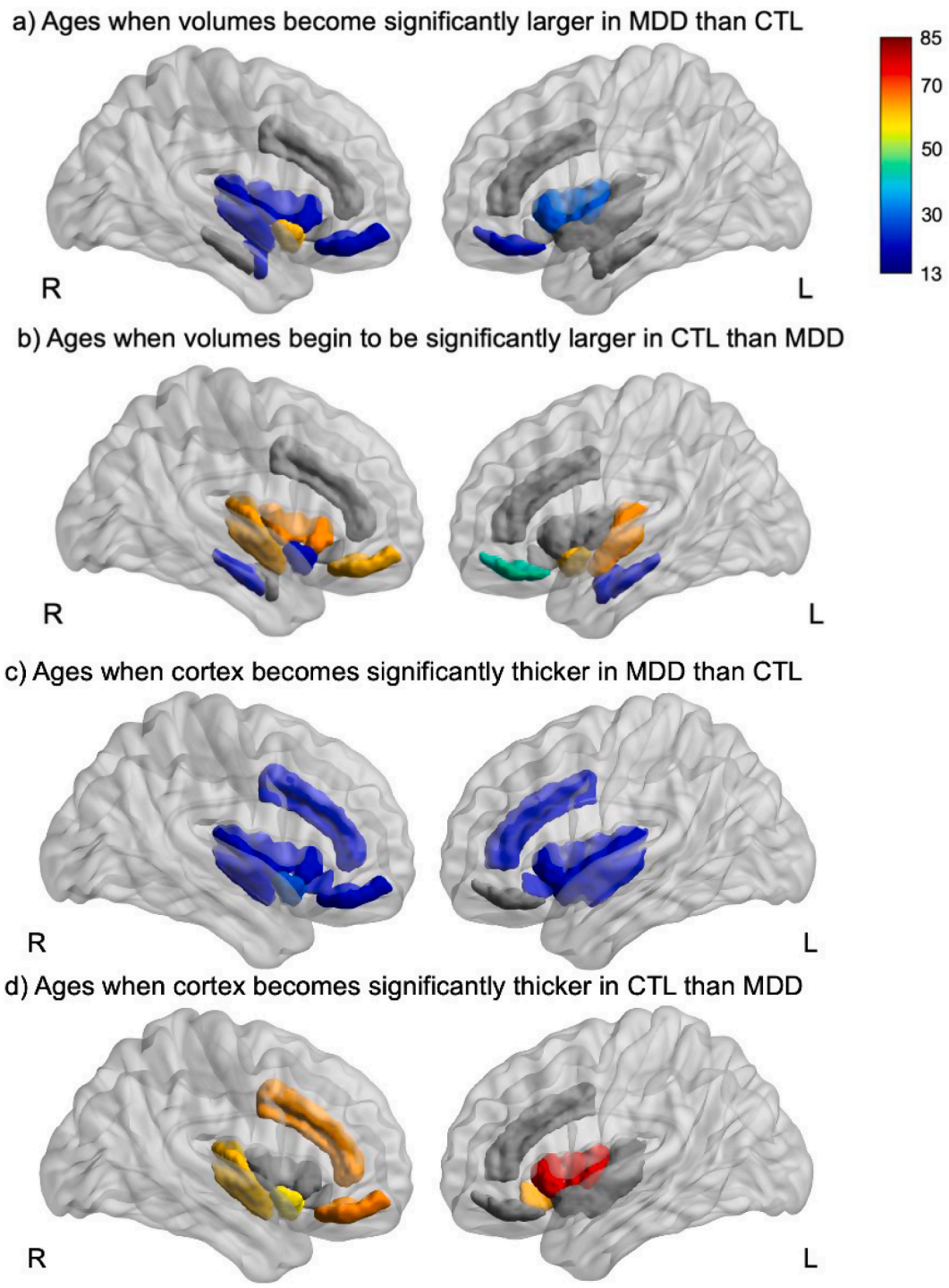

Fig. 5. Gray matter volume and cortical thickness comparisons by region. In cortical regions such as the bilateral dorsal anterior insula and bilateral orbitofrontal cortex (cold colors), MDDs exhibited larger gray matter volume and thicker cortices starting in early adulthood and lasting until middle age. In other regions like the bilateral hippocampus (hot colors), CTL gray matter volume was consistently higher than MDD gray matter volume across the observed age span. Gray shading indicates regions that did not meet the conditions outlined in each subfigure.

matter volume and thinner cortex in MDDs compared to CTL in adult to late life years is consistent with the previously cited literature (Jones et al., 2019; Stratmann et al., 2014; Ancelin et al., 2019; Liu et al., 2014; Grieve et al., 2013; Lee et al., 2003; Kronenberg et al., 2009) and might be a reflection of age effects modulated by MDD through other neurodegenerative mechanisms, including but not limited to neuroinflammation, proteinopathies, and synaptic dysfunction (Maes et al., 2011; Furtado and Katzman, 2015; Brites and Fernandes, 2015; Gatchel et al., 2017; Rial et al., 2016; Duman and Aghajanian, 2012). Additionally, geriatric depression is often comorbid with chronic illness (e.g. insulin resistance/diabetes, heart disease, COPD) that may be linked to neurodegeneration in multiple brain regions (Alexopoulos et al., 2002; Rasgon et al., 2011; Alosco and Hayes, 2015). Volume and CT measures may be differentially sensitive to these different neural processes, even across different age spans, making these structural measures complementary for the understanding of neural changes in MDD over the lifespan. Age also seems to modulate other clinical and cognitive measures in a similar but separate MDD cohort between the

ages of 19 and 65 years. Only the individuals with MDD below 37 years of age had lower peripheral cortisol levels than age-matched healthy controls, which was associated with better anti-depressant treatment outcome and better memory performance (Jain et al., 2019).

We chose to include two subcortical regions (the amygdala and hippocampus) in this analysis given their frequent investigation in MDD studies. The amygdala is highly implicated in depression yet reports of amygdalar gray matter volume differences between MDD and CTL are inconsistent. Some publications provide evidence for gray matter volume reductions in MDDs, others report no change, whereas none reported any significant differences by hemisphere (Stratmann et al., 2014; Ancelin et al., 2019; Kronenberg et al., 2009; Redlich et al., 2018). In this investigation, we found a unique lateralization within amygdalar volume such that amygdala gray matter volume was consistently higher in the right hemisphere across the lifespan compared to CTL, but consistently lower in the left hemisphere. It is important to note that if the analyses in this paper had not been conducted by hemisphere and the gray matter volume from the left and right amygdala for MDDs had been averaged, this would have erased the unique lateralization and group difference. Alternatively, these results may also reflect the challenges of accurately segmenting the amygdala with an automated method. Additionally, some studies point to lateralization of specific functions and processes in the amygdala. For example, Markowitsch found that in healthy individuals, the right amygdala may play a role in gross analysis of affect-related information more so than the left (Markowitsch, 1999). The finding in this study of significantly higher right amygdala gray matter volume in MDD vs CTL could indicate increased processing of emotional information that may contribute to certain symptoms of depression (e.g., rumination). Our hippocampal findings of group volume differences confirm previous reports (Vythilingam et al., 2004; Elbejjani et al., 2015). It is important to note the complexity of this region and its role in cognitive functions, especially memory function, that are central to many neurodegenerative diseases such as Alzheimer's disease and dementia (McEwen and Sapolsky, 1995; Ginsberg et al., 2010), but which are also impaired in individuals with MDD (Videbech, 2004; Vythilingam et al., 2004; Sampath et al., 2017).

Though these results are significant, and the directions and magnitudes of differences fit a biologically coherent pattern, there are a few limitations that must be considered when interpreting our findings. The cross-sectional nature of the data limits any inferences about longitudinal change or future ageing-associated atrophy in either group. That is, it is possible that the age-dependent trajectories of gray matter volume and cortical thickness measures in MDD that deviate from those in CTL in this study sample might increase over time as a result of chronic effects of MDD that accumulated over the years from past and current episodes. Thus, it will be important to determine whether the group differences in the models we identified here are replicated in a longitudinal investigation that includes chronicity of depression. In addition, as medication history was not collected in all MDD cohorts, differential medication usage over time or differences in prescribed medications to specific age groups could have potentially influenced these models. Further, due to disparate clinical measures administered to each cohort, we were not able to link our findings to specific symptoms of MDD, associated functional disability (Jaeger et al., 2006; Spijker et al., 2004) or cognitive impairment (Bora et al., 2013; Pan et al., 2019). Additionally, history of MDD was not necessarily an exclusion criterium for all control groups of this analysis; therefore, we cannot eliminate the possibility that potential history of depression in controls may have affected these models. We also acknowledge that sex differences have been reported both in normal neurodevelopment and MDD (Bao and Swaab, 2011; Yang et al., 2017; Hanamsagar and Bilbo, 2016), and that future studies are warranted to assess such age-dependent MDD effects on sex-stratified cohorts with larger sample sizes.

With regards to our applied technical methods, the use of a standardized image processing framework followed by statistical harmonization to minimize measurement variations due to study-specific acquisition differences is considered a strength of this lifespan analysis study. However, segmentation of certain subregions of the insula tends toward volumetric overestimation with older age, which is related to contrast changes resulting from white matter demyelination that can lead to boundary ambiguity (Wardlaw et al., 2015). To avoid this oversegmentation, scans of participants older than 85 years were not included in this analysis. We should also note the uneven distribution of the number of MDDs and CTLs participants across different age groups as a computational limitation. Additionally, while we understand the importance of investigating age-dependent effects of MDD on subdivisions of regions like the amygdala, accurate segmentation of such regions requires finer image resolution than the data included in this study. Furthermore, while we were able to include the subgenual region of the anterior cingulate cortex, as well as the caudal, dorsal, and rostral anterior cingulate cortex (referred to simply as the anterior cingulate cortex in this paper), we were limited by the exclusion of other anterior cingulate cortex subregions (i.e., perigenual cortex) from the atlas used in this analysis. Therefore, we defer to future studies with the capability to leverage datasets with better image resolution and atlases with finer subdivisions. Another limitation to this study is the lack of motion correction performed on the structural MR images. We were limited by the fact that our data came from an archival data set in which prospective motion correction was not available. We acknowledge that motion is a limitation in the quantification of certain imaging measures (Godenschweger et al., 2016) and an extensive raw image quality control to rule out any motion artifacts was performed.

Overall, we believe this MR study has made a substantial contribution to MDD research from both a technical and clinical perspective. It exemplifies utilization of ComBat-GAM to harmonize imaging data from multiple sites, which here enabled the analysis of MDD across different phases of adulthood and subsequently identified unique age- and brain region-dependent differences between MDD and CTL groups. Given the specific age-related findings in MDD of the extant research literature as well as our new findings of significant interactions of age and diagnosis, we believe these brain regions warrant further examination of MR-derived characteristics in relation to MDD clinical and cognitive characteristics.

Author contributions

RSM, CTT, SM, DM, IS and DT were all integral in the acquisition of data, provided input for the analysis and interpretation of the data, and gave final approval of the version to be published. AM, AL, IS, and DT provided substantial contributions to the design of the work, and/or analysis and interpretation of the data. AM, IS, and DT were mainly responsible for drafting the work and revising it critically for important intellectual content and are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: CTT declares that in the past 3 years he has been a paid consultant for Homewood Health and receives payments for editorial work for UpToDate. AM, AL, DM, RSM, IS, SM, and DT have nothing to disclose.

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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.2021.102924.

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