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Aging faster: worry and rumination in late life are associated with greater brain age

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ABSTRACT

Older adults with anxiety have lower gray matter brain volume—a component of accelerated aging. We have previously validated a machine learning model to predict brain age, an estimate of an individual's age based on voxel-wise gray matter images. We investigated associations between brain age and anxiety, depression, stress, and emotion regulation. We recruited 78 participants (≥50 years) along a wide range of worry severity. We collected imaging data and computed voxel-wise gray matter images, which were input into an existing machine learning model to estimate brain age. We conducted a multivariable linear regression between brain age and age, sex, race, education, worry, anxiety, depression, rumination, neuroticism, stress, reappraisal, and suppression. We found that greater brain age was significantly associated with greater age, male sex, greater worry, greater rumination, and lower suppression. Male sex, worry, and rumination are associated with accelerated aging in late life and expressive suppression may have a protective effect. These results provide evidence for the transdiagnostic model of negative repetitive thoughts, which are associated with cognitive decline, amyloid, and tau.

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> "Age is an issue of mind over matter. If you don't mind, it doesn't matter."
>
> Mark Twain.

1. Introduction

In the last decade, several studies have reported an independent effect of anxiety on aging. Clinically, anxiety and its disorders have been described as risk factors for multiple age-related medical conditions (Andreescu and Varon, 2015; Lambiase et al., 2014; Tully et al., 2013, 2014). In particular, pathologic worry has been associated with the development of coronary heart disease (Tully et al., 2013), while a higher burden of anxiety symptoms was associated prospectively with increased risk for incident stroke independent of other risk factors (including depression) (Lambiase et al., 2014). In the Nurses' Health Study (Okereke and Grodstein, 2013), a 4-year longitudinal study of community-dwelling older women (N = 16,351), higher midlife anxiety was related to worse later-life overall cognitive function and verbal memory.

Chronic anxiety has been associated with higher beta amyloid burden (Donovan et al., 2018). Moreover, in individuals with similar beta amyloid burden, participants with chronic anxiety had worse longitudinal cognitive decline than those without anxiety (Pietrzak et al., 2014, 2015). In a 2-year observational study, older adults with mildly elevated worry symptoms performed worse on measures of visual learning and memory than older adults with no or minimal worry symptoms (Pietrzak et al., 2012). Multiple animal studies reported impaired neurogenesis in anxiety (Revest et al., 2009), and several human studies described brain structural differences associated with anxiety in midlife (e.g., lower hippocampal volumes and lower gray matter in the amygdala and hippocampus [Ly and Andreescu, 2018]). Our previous reports in a geriatric anxiety sample describe structural gray matter differences such as lower orbital frontal cortex and rostral anterior cingulate cortex volume in late-life generalized anxiety disorder (GAD) compared with non-GAD older controls (Andreescu et al., 2017) and a potential effect of cerebrovascular burden in impairing emotion regulation in late-life GAD (Karim, H. et al., 2016).

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These studies indicate that anxiety and/or worry may contribute to accelerated aging. The putative mechanisms include molecular aging markers (e.g., shortened telomeres [Okereke et al., 2012]) and increased stress response including chronic inflammatory stress, increased hypothalamic-pituitary-adrenocortical activity and excessive autonomic responses (O'Donovan et al., 2010, 2013; Perna et al., 2016). However, research in this area is still in early stages, and the pathways linking anxiety or worry with brain aging remain unclear.

Brain age prediction uses machine learning to estimate an individual's chronological age from neuroimaging data (Cole, 2020; Cole et al., 2015; Cole and Franke, 2017; Ly et al., 2019). Individuals whose brain is estimated to be older than age-matched healthy peers (higher brain age than chronological age) may have experienced a higher cumulative exposure to brain insults or were more impacted by those pathologic insults or alternatively reflect non-neurodegenerative processes. Brain age may indicate a potential discrepancy between biological and chronological age, suggesting that pathologic neuroprogression (combination of neurodegeneration, neurotoxicity, and lowered neuroplasticity) is associated with accelerated aging (Perna et al., 2016). These models have been used recently to demonstrate the association between greater brain age with cognitive impairment, Alzheimer's disease, traumatic brain injury, and mortality (Cole et al., 2015, 2018; Cole and Franke, 2017; Liem et al., 2017; Ly et al., 2019).

We have previously developed a machine learning model for estimating brain age from neuroimaging scans while accounting for amyloid status in a large cohort (n = 757) (Ly et al., 2019). Our brain age prediction model contextualizes whole brain structural information of a test cohort against structural information from a large healthy participant cohort (i.e., without psychiatric disorders, cognitive impairment, or significant brain amyloid) spanning a wide range of ages (20–85 years) to generate a machine learning–based prediction of the test participant's chronological age. In this way, discrepancies between actual chronological age and predicted brain age in test groups may indicate pathologic disruption or acceleration of the aging process. We were able to delineate significant differences in brain age relative to chronological age between cognitively normal individuals with and without significant amyloid beta deposition in the brain (Ly et al., 2019).

Most of the studies available regarding the potential effect of late-life anxiety in accelerated aging use heterogenous and often nonspecific measures for anxiety. Anxiety and its disorders encompass multiple clinical constructs such as worry, rumination, and somatization (Zebb and Beck, 1998) and are highly comorbid with both depression and neuroticism (Clark et al., 1994; Hettema et al., 2004, 2006). It is thus more difficult to detangle the specific effect of various phenotypes on accelerated aging (Andreescu et al., 2015a). In addition, the highly heterogenous changes that occur in aging make it difficult to interpret various cross-sectional studies that point toward an association between anxiety and aging.

In the present study, we aimed to test if the different anxiety phenotypes (worry, global anxiety, and rumination) as well as their more frequent comorbidities (depression severity and neuroticism) were associated with brain aging. Given the hypothesis regarding the role of increased stress response, we also included the Perceived Stress Questionnaire (Cohen et al., 1983) in the model. Given our previous reports regarding emotion regulation deficits in late-life anxiety (Andreescu et al., 2015b; Karim et al., 2016a, 2017), we also included in the current model the Emotion Regulation Questionnaire (ERQ), a self-report measure of 2 emotion regulation strategies (cognitive reappraisal and expressive suppression) (Gross and John, 2003).

2. Methods

2.1. Participants and study design

Participants were recruited through the functional neuroanatomy correlates of worry in older adults (FINA) study (R01 MH108509). We recruited participants (n = 78) who were 50 years and older with and without anxiety (generalized anxiety disorder, panic disorder, social phobia, etc.) and/or mood disorders (e.g., major depressive disorder, persistent depressive disorder, or unspecified depressive disorder). Diagnosis was assessed through the structured clinical interview for DSM V (SCID). Our cohort had 23 participants with GAD (29%), 58 with any other anxiety disorder (74%), and 25 with current or lifetime prevalence of major depressive disorder (32%). We also report these and other diagnoses in the results. Inclusion of these variable diagnoses allowed for representation of worry severity along a wide spectrum, such that worry was normally distributed. Participants were excluded if they were diagnosed with autism spectrum disorders, intellectual development disorder, or any form of psychosis or bipolar disorder. Other exclusion criteria were a diagnosis of major neurocognitive disorder (e.g., dementia), a modified mini-mental state examination (3MSE) score <84, a diagnosis of personality disorder, increased suicide risk, use of antidepressants within the last 5 to 14 days, history of drug/alcohol abuse within last 6 months, use of high doses of benzodiazepines (greater than equivalent to 2 mg of lorazepam), uncorrected vision problems that would preclude neuropsychiatric testing, below 6th grade level of reading, clinical diagnosis of cerebrovascular accident, multiple sclerosis, and vasculitis or significant head trauma. Participants with ferromagnetic objects in body, claustrophobia, or too large to fit in an MRI scanner were also excluded.

When appropriate, participants underwent an adequate washout on antidepressants determined by the primary psychiatrist on the study (CA). For fluoxetine, the washout interval was 6 weeks. Participants who were prescribed low-dose psychotropics for pain, sleep disturbances, and/or medical conditions were allowed to continue them in most circumstances. The following common antidepressants were allowed at low doses due to medical reasons: amitriptyline (50 mg/d), doxepin (50 mg/d), trazodone (100 mg/d), and imipramine (50 mg/d). There were 7 participants who had taken psychotropics (although tapered off for the scan) but they did not differ in brain age, although this does not necessarily indicate an association or lack thereof with psychotropics—we do not include psychotropics as a covariate in further analysis. Participants were recruited from the Pittsburgh area via Pitt+Me (website resource from the university), in-person recommendations, flyers, and radio/television advertisements. This study was approved by the University of Pittsburgh Institutional Review Board. All participants gave written informed consent before participating in the study.

2.2. Assessments

Along with demographic information (age, sex, race, and education), we assessed the following: worry (PSWQ, Penn State Worry Questionnaire) (Meyer et al., 1990), overall anxiety (HARS, Hamilton Anxiety Rating Scale) (Hamilton, 1959), depression (MADRS, Montgomery-Asberg Depression Rating Scale) (Montgomery and Asberg, 1979), rumination (Rumination Subscale from RSQ, Response Styles Questionnaire) (Bagby et al., 2004), neuroticism subscale from the 5-Factor Inventory (Costa and McCrae, 1992), perceived stress (PSS, Cohen's Perceived Stress Scale) (Cohen, 1988), and the habitual use of cognitive reappraisal and suppression

subscale (ERQ, Emotion Regulation Questionnaire) (Gross and John, 2003). We also collected data on illness severity (cumulative illness rating scale for geriatrics) (Salvi et al., 2008) and cognitive function (3MSE) (Teng and Chui, 1987).

2.3. MRI Data Acquisition

Magnetic resonance imaging (MRI) scans were obtained at the MR Research Center of the University of Pittsburgh using a 3T Siemens MAGNETOM Prisma scanner and a 32-channel head coil. A sagittal, whole-brain T1-weighted magnetization prepared rapid gradient echo (MPRAGE) was collected with repetition time (TR) = 2400 ms, echo time (TE) = 2.22 ms, flip angle (FA) = 8 deg, field of view (FOV) = 320 × 300 with 208 slices, 0.8 mm^3 isotropic resolution, 0.4 mm slice gap, and GeneRalized Autocalibrating Partial Parallel Acquisition (GRAPPA) with acceleration factor of 2 (total time 6.63 min). We used a suboptimal interslice gap of 0.4 mm as this allowed for higher isotropic resolution. We acknowledge this as a limitation. A sagittal, whole-brain T2-weighted Sampling Perfection with Application optimized Contrasts using different flip angle Evolution (SPACE) was collected with TR = 3200 ms, TE = 563 ms, FA = 120 deg, FOV = 320 × 300 with 208 slices, 0.8 mm^3 isotropic resolution, no slice gap, and GRAPPA with acceleration factor of 2 (total time 5.95 min). An axial, whole-brain T2-weighted fluid-attenuated inversion recovery (FLAIR) was collected with TR = 10,000 ms, TE = 91 ms, FA = 135 deg, inversion time (TI) = 2500 ms, FOV = 320 × 320 with 104 slices, 0.8 mm × 0.8 mm × 1.6 mm resolution, no slice gap, and GRAPPA with acceleration factor of 2 (total time 5.95 min). Participants were in the MR scanner for approximately 45–60 minutes as we also collected functional MRI data as well (not presented).

2.4. Structural processing

Processing was conducted in statistical parametric mapping toolbox (SPM12) (Penny et al., 2011) in MatLab (2018b) (MathWorks, Natick, MA, USA). All interpolation was performed with a 4th degree B-spline and the similarity metric used for coregistration between different image types was normalized mutual information. The T2-SPACE and FLAIR were first independently coregistered to the MPRAGE. All 3 were input into a multispectral segmentation that bias corrects each image and segments them into gray matter, white matter, cerebrospinal fluid, skull, soft tissue, and air (Ashburner and Friston, 2005). Because of the high burden of white matter hyperintensities, we adjusted the number of Gaussians used to identify white matter to 2 to improve identification of gray and white matter (Karim et al., 2016b). This ensures an accurate segmentation of the gray matter. The gray and white matter maps are inputs into a process to generate a study-specific template to estimate gray matter images.

We used Diffeomorphic Anatomical Registration using Exponentiated Lie Algebra (DARTEL) to generate a study-specific template (Ashburner, 2007). DARTEL aligns each participant's gray matter image (along with white matter) to a standard Montreal Neurological Institute (MNI) space template using a combination of linear and nonlinear registrations. Then an average image is generated across all participants—this is the first template. The gray matter images are aligned again and coregistered again. Then another average image is generated. This process is iterated until an increasingly crisp average template is generated, to which the data are iteratively aligned. DARTEL uses an iterative process of averages across participants and iterative coregistration to improve normalization to a standard anatomic space. Once a study-specific template is generated (an iterative average across participants), each image is normalized and then transformed into a gray matter image that preserves the total amount of gray matter by multiplying by the determinant of the Jacobian of the transformations (Ashburner, 2007). All images are normalized to a 1 mm^3 isotropic resolution. The gray matter images were smoothed using a Gaussian kernel of full width at half-maximum of 4 mm. These gray matter images are input into the brain age estimation model.

2.5. Brain age estimation

We have previously validated a brain age estimation algorithm that predicts chronological age with gray matter maps (Ly et al., 2019) using the Pattern Recognition for Neuroimaging Toolbox (Schrouff et al., 2013). Whole brain, voxel-wise gray matter densities were mean-centered and used to calculate a similarity matrix kernel (dot product) (LaConte et al., 2005) that was input into a Gaussian processes regression to predict chronological age. The training set, which includes 757 adult MRIs of individuals without any psychiatric or neurologic disorder as well as Alzheimer's pathology as measured by positron emission tomography, has been previously described (Ly et al., 2019). These data were from the Alzheimer's Disease Neuroimaging Initiative (ADNI), Information eXtraction from Images, and Open Access Series of Imaging Studies (OASIS-3)—which are all publicly available. The cohort (ADNI, Information eXtraction from Images, and OASIS-3) is used as a covariate to account for differences in scanner/site/protocol. The present study's participants were not part of the training set. Using this pretrained model, we can estimate the brain age of each participant in the present study.

While white matter hyperintensities are likely factors that influence brain aging, our brain age model utilizes primarily gray matter and not white matter data. Thus, our brain age marker more accurately could be stated to be a “gray matter” age marker.

2.6. Statistical analysis

We conducted a linear regression analysis in SPSS 26 (IBM, Armonk, NY). We used brain age as the outcome and the following as independent predictors: chronological age, sex, race, education (years), worry (PSWQ), anxiety (HARS), depression severity (MADRS), rumination (RSQ), neuroticism (neuroticism subscale from the 5 Factor Inventory (NEO-FFI)), reappraisal (ERQ, reappraisal subscale), suppression (ERQ, suppression subscale), and stress (PSS). The models conducted all had variance inflation factor below 5, showed normally distributed standardized residuals (based on a histogram and Q-Q plot) and did not violate the assumption of homoscedasticity.

A total of 69 participants (88.5%) had all data available, however, there were missing values for: 3MSE (4 not collected), HARS (2 lost questionnaires), MADRS (3 not collected, 2 lost questionnaires), RSQ (1 participant error, 1 not collected), NEO-FFI (2 refused, 4 participant error), ERQ (1 refused, 3 participant error), and PSS (1 refused, 3 participant error). We conducted multiple imputations analysis (Newgard and Haukoos, 2007; Schafer, 1999) (5 imputations) in SPSS to impute missing values using the Markov Chain Monte Carlo method (MacKay and Mac Kay, 2003) and fully conditional specification with linear regression, assuming our values were missing at random with an arbitrary missing pattern (Schunk, 2008). We conducted statistical independent *t*-tests or χ^2 tests where appropriate to identify if the 9 participants with missing data differed significantly on demographic and cognitive factors compared with those without missing data. We found that they did not differ on age, sex, race, and 3MSE but did find that education was lower by approximately 1 year in those who were missing data.

Every variable used in the regression as well as the outcome (brain age) were used in the imputation model, as this has been

Table 1
Characteristics of the sample

Variable name	Total sample (n = 78)		Number missing	Imputed mean (pooled)
	Mean	Std.		
Age, y	61.2	8.5	0	N/A
Sex, number female	53 (68%)		0	N/A
Race, W/B/HPI/MR	63 (81%); 13 (17%); 1 (1%); 1 (1%)		0	N/A
Education, years	15.6	2.6	0	N/A
Cumulative illness (CIRSG)	3.0	2.3	1	N/A
Worry (PSWQ)	47.6	14.7	0	N/A
Anxiety (HARS)	8.5	6.9	2	8.5
Depression (MADRS)	8.2	8.1	5	8.6
Rumination (RSQ)	37.7	12.6	2	37.7
Neuroticism (NEO-FFI)	19.5	10.7	6	19.9
Reappraisal (ERQ Subscale)	29.4	7.8	4	29.4
Suppression (ERQ Subscale)	13.8	5.4	4	13.8
Stress (PSS)	15.5	8.6	4	15.6
Overall cognitive (3MSE)	96.7	0.5	4	N/A
Brain age, years	63.6	6.1	0	N/A

Means and standard deviations are reported unless otherwise noted.
Means for both the original data and imputed values (see number of missing data) are reported.
Key: CIRSG, Cumulative Illness Rating Scale for Geriatrics; PSWQ, Penn State Worry Questionnaire; HARS, Hamilton Anxiety Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; RSQ, Response Styles Questionnaire; NEO-FFI, Neuroticism, Extroversion, Openness to Experience-5 Factor Inventory; ERQ, Emotion Regulation Questionnaire; PSS, Cohen's Perceived Stress Scale; 3MSE, modified-mini mental status examination; N/A, not applicable or not imputed; Race: W, white, B, black, HPI, Hawaiian or Pacific Islander, and MR, mixed race.

shown to improve the imputation and is not a "self-fulfilling prophecy," but rather "replays the strength of associations between predictors and outcomes present in the complete cases, to enable valid analyses (Moons et al., 2006)." All variables were constrained to their appropriate values (e.g., HARS ranges from 0 to 56 and thus values may not be imputed outside this range). We report both the imputed pooled results as well as the estimates from the original model with missing data (n = 69). Pooling is computed automatically by SPSS using Rubin's rules (Rubin, 2004).

Each variable was inspected for outliers, and the following variables had some outliers: HARS (n = 1), MADRS (n = 4), RSQ (n = 1), brain age (n = 2), and reappraisal ERQ subscale (n = 1). We conducted the regression with those participants removed (not shown) and found that the estimates did not differ from when they were included in the model.

Factors that are associated with brain age, may also be associated with chronological age and thus may be a confound. To understand whether factors that were significantly related to brain age or chronological age or both, we conducted independent *t*-tests or correlations with chronological age.

2.7. Exploratory analysis

After statistical analysis, we found a significant association between brain age and rumination. The RSQ is increasingly divided into a reflective pondering and ruminative brooding component (Schoofs et al., 2010; Whitmer and Gotlib, 2011), these are largely thought to be adaptive and maladaptive, respectively. We divided the RSQ into those 2 components and then conducted multiple imputations as well as a similar regression analysis, however, replaced RSQ with either reflective pondering (RSQ reflection) or ruminative brooding (RSQ brooding). This helps address whether reflection versus brooding was significantly associated with brain age.

3. Results

We report the characteristics of the sample in Table 1. Of note, worry is normally distributed around a mean worry severity of 47.6. Demographics match those of the surrounding Pittsburgh area. The mean absolute error between chronological and brain age in our sample was 4.7 with r (76) = 0.75 and $r^2 = 0.56$, which indicates that our model was able to predict chronological age accurately in this sample within the expected tolerance. For characterization, we also report the following diagnoses based on the SCID for DSM V: 23 with GAD (29%), 58 with any other anxiety disorder (74%), 25 with current or lifetime prevalence of major depressive disorder (32%), 10 with either current dysthymic disorder/current or lifetime depressive disorder not otherwise specified/current or lifetime mood disorder due to general medication (13%), 19 with lifetime

Table 2
Regression model explaining variance in brain age

Variable	ß	B (SE)	95% CI	t-statistic, *p*-value
Constant		27.834 (5.76)	(16.295, 39.373)	4.832, $p < 0.001$
Age	**0.81**	**0.567 (0.058)**	**(0.451, 0.684)**	**9.745, $p < 0.001$**
Sex (Male Reference)	**−0.26**	**−3.242 (1.044)**	**(−5.333, −1.151)**	**−3.106, $p < 0.005$**
Race (White Reference)	−0.04	−0.643 (1.323)	(−3.293, 2.007)	−0.486, $p = 0.629$
Education	−0.02	−0.06 (0.198)	(−0.456, 0.336)	−0.304, $p = 0.763$
Worry (PSWQ)	0.17	0.068 (0.053)	(−0.037, 0.174)	1.295, $p = 0.201$
Anxiety (HARS)	−0.10	−0.098 (0.145)	(−0.389, 0.193)	−0.677, $p = 0.501$
Depression (MADRS)	0.09	0.065 (0.109)	(−0.154, 0.284)	0.593, $p = 0.556$
Rumination (RSQ)	**0.29**	**0.143 (0.06)**	**(0.024, 0.263)**	**2.407, $p < 0.05$**
Neuroticism (FFI-N)	−0.15	−0.088 (0.08)	(−0.248, 0.071)	−1.11, $p = 0.272$
Reappraisal (ERQ)	0.00	−0.001 (0.065)	(−0.131, 0.129)	−0.016, $p = 0.987$
Suppression (ERQ)	−0.08	−0.092 (0.092)	(−0.277, 0.093)	−1.001, $p = 0.321$
Stress (PSS)	−0.09	−0.06 (0.085)	(−0.231, 0.111)	−0.707, $p = 0.482$

ß values indicate standardized coefficients while B indicates unstandardized coefficients. We also report 95% confidence intervals and indicate significant associations in bold.

Table 3
Regression model explaining variance in brain age using imputed data

Variable	ß	B (SE)	95% CI	t-statistic, *p*-value
Constant		30.151 (5.606)	(19.163, 41.138)	5.378, $p < 0.001$
Age	**0.742**	**0.534 (0.057)**	**(0.422, 0.646)**	**9.374, $p < 0.001$**
Sex (Male reference)	**−0.322**	**−4.186 (1.037)**	**(−6.218, −2.153)**	**−4.036, $p < 0.001$**
Race (White reference)	0.017	0.264 (1.245)	(−2.176, 2.705)	0.212, $p = 0.832$
Education	−0.047	−0.111 (0.195)	(−0.493, 0.272)	−0.567, $p = 0.571$
Worry (PSWQ)	**0.258**	**0.107 (0.051)**	**(0.008, 0.207)**	**2.107, $p < 0.05$**
Anxiety (HARS)	−0.184	−0.162 (0.14)	(−0.437, 0.113)	−1.158, $p = 0.247$
Depression (MADRS)	0.064	0.046 (0.109)	(−0.168, 0.259)	0.419, $p = 0.675$
Rumination (RSQ)	**0.233**	**0.113 (0.06)**	**(−0.003, 0.23)**	**1.901, $p = 0.057$**
Neuroticism (FFI-N)	−0.107	−0.06 (0.083)	(−0.222, 0.102)	−0.726, $p = 0.468$
Reappraisal (ERQ)	0.077	0.06 (0.062)	(−0.061, 0.181)	0.979, $p = 0.328$
Suppression (ERQ)	**−0.149**	**−0.169 (0.09)**	**(−0.345, 0.007)**	**−1.879, $p = 0.060$**
Stress (PSS)	−0.119	−0.084 (0.086)	(−0.252, 0.085)	−0.97, $p = 0.332$

B indicates unstandardized coefficients. We also report 95% confidence intervals and indicate significant associations in bold.

prevalence of a substance use disorder (24%), and 5 with current/lifetime prevalence of an eating disorder (6%).

We found that brain age was significantly associated with several factors that explained 72% of the variance in brain age [$F(11,57) = 13.3$, $p < 0.001$, $r^2 = 0.72$]. We found the following:

(1) for every year, participant's brain age was greater by 0.57 years (~6.8 months); (2) on average, women's brains were younger by 3.4 years (~41 months) than men's brains; and (3) for every point greater on the RSQ, brain age was greater by 0.14 years (~1.7 months) (see Table 2 and Fig. 1).

After imputing values that were missing for 9 participants (see Table 1), we reconducted our regression and found the following (pooled results, see Table 3): (1) for every year, participant's brain age was greater by approximately 0.53 years (~6.4 months); (2) on average, women's brains were younger by 4.1 years (~49 months) than men's brains; (3) for every point greater on the PSWQ, brain age was greater by 0.11 years (~1.3 months); (4) for every point greater on the RSQ, brain age was greater by 0.11 years (~1.3 months); (5) for every point greater on the ERQ suppression scale, brain age was lower by 0.17 years (~2.0 months).

The imputed models explained 68%–72% (range) of the variance in brain age across imputations (variance is not a pooled metric). We showed associations between these factors in Fig. 1 using nonimputed data.

We found that men and women did not differ by chronological age [$t(76) = 0.9$, $p = 0.346$]. We found that greater chronological age was correlated with lower rumination [RSQ, $r(75) = -0.37$, $p < 0.005$] but not with worry [PSWQ, $r(77) = -0.21$, $p = 0.069$] or suppression [ERQ suppression, $r(76) = -0.05$, $p = 0.685$]. Pooled results did not differ.

3.1. Exploratory results

When replacing RSQ with RSQ reflection, we found no significant association between RSQ reflection and brain age in the imputed [$t = 0.9$, $p = 0.360$, B (SE) = 0.173 (0.189), ß = 0.025, CI = (−0.199, 0.546)] or original data [$t = 1.2$, $p = 0.238$, B (SE) = 0.232 (0.194), ß = 0.113, CI = (−0.158, 0.621)]. When replacing RSQ with RSQ brooding, we found a significant association between RSQ brooding and brain age in the imputed [$t = 2.2$, $p < 0.05$, B (SE) = 0.514 (0.233), ß = 0.228, CI = (0.057, 0.972)] and original data [$t = 2.6$, $p < 0.05$, B (SE) = 0.605 (0.235), ß = 0.303, CI = (0.135, 1.075)].

4. Discussion

Our results indicate that worry and rumination in late life are associated with an accelerated brain aging process. Surprisingly, there was no effect of perceived stress and the propensity to use suppression seems to have had a protective effect on brain aging in this sample. Brain age in men was greater than brain age in women.

Worry and rumination share common phenomenological features such as difficult to control and repetitive negative thinking. However, worry and rumination have been typically described as 2 distinct processes, with worry being usually associated with prospective negative thinking and generalized anxiety disorder and rumination with retrospective negative thinking and depression (Nolen-Hoeksema, 2000). Classically, rumination is triggered by sad mood and maintains depressive symptoms by promoting negative cognitive biases (Just and Alloy, 1997). Similarly, classic worry theoretical models such as Borkovec's cognitive avoidance model posit that worry serves as a cognitive avoidance strategy that inhibits the emotional processing of highly anxiogenic material (Borkovec, 1994). However, newer theories propose a transdiagnostic approach that 1) includes both worry and rumination under the umbrella of repetitive negative thoughts (RNT) and 2) describe the detrimental effect of RNT throughout multiple categorical diagnoses including major depression, GAD, social phobia, bipolar disorder, obsessive compulsive disorder, eating disorders, and post-traumatic stress disorder (Aldao et al., 2010; Ehring, 2008). Several authors have proposed RNT as the core of anxiety-depression comorbidity (Gustavson et al., 2018; McEvoy et al., 2013), while others emphasized the association of RNT with worse psychological, physical, and cognitive health in older adults (Segerstrom et al., 2010).

Recently, RNTs have been “imported” into the aging and dementia field. As such, in 2015, Marchant and Howard advanced a model of Cognitive Debt that would involve certain symptoms/disorders actively depleting cognitive reserve and increase vulnerability to Alzheimer's disease (AD) (Marchant and Howard, 2015). Thus, there is building evidence that depression, anxiety, sleep disorders, neuroticism, and post-traumatic stress disorder increase the risk for AD, and the authors suggest that RNT is the shared process which may drive the acquisition of Cognitive Debt through diverting cognitive and emotional resources to distressing thought processes (Marchant and Howard, 2015). The neurobiological signature of Cognitive Debt and AD might rely on the relationship between hippocampus, prefrontal cortex, and amygdala with the hypothalamic-pituitary-adrenocortical stress response (Marchant and Howard, 2015). More recently, RNT was cross-sectionally associated with cognitive decline, beta-amyloid deposits, and entorhinal tau (Marchant et al., 2020).

Our results, that single out both worry and rumination as predictors of accelerated aging, would fit well into the overall model of RNT as contributing to increased Cognitive Debt. These results also emphasize the need for preventative interventions targeting RNT in older adults (e.g., mindful meditation, cognitive behavioral therapy,

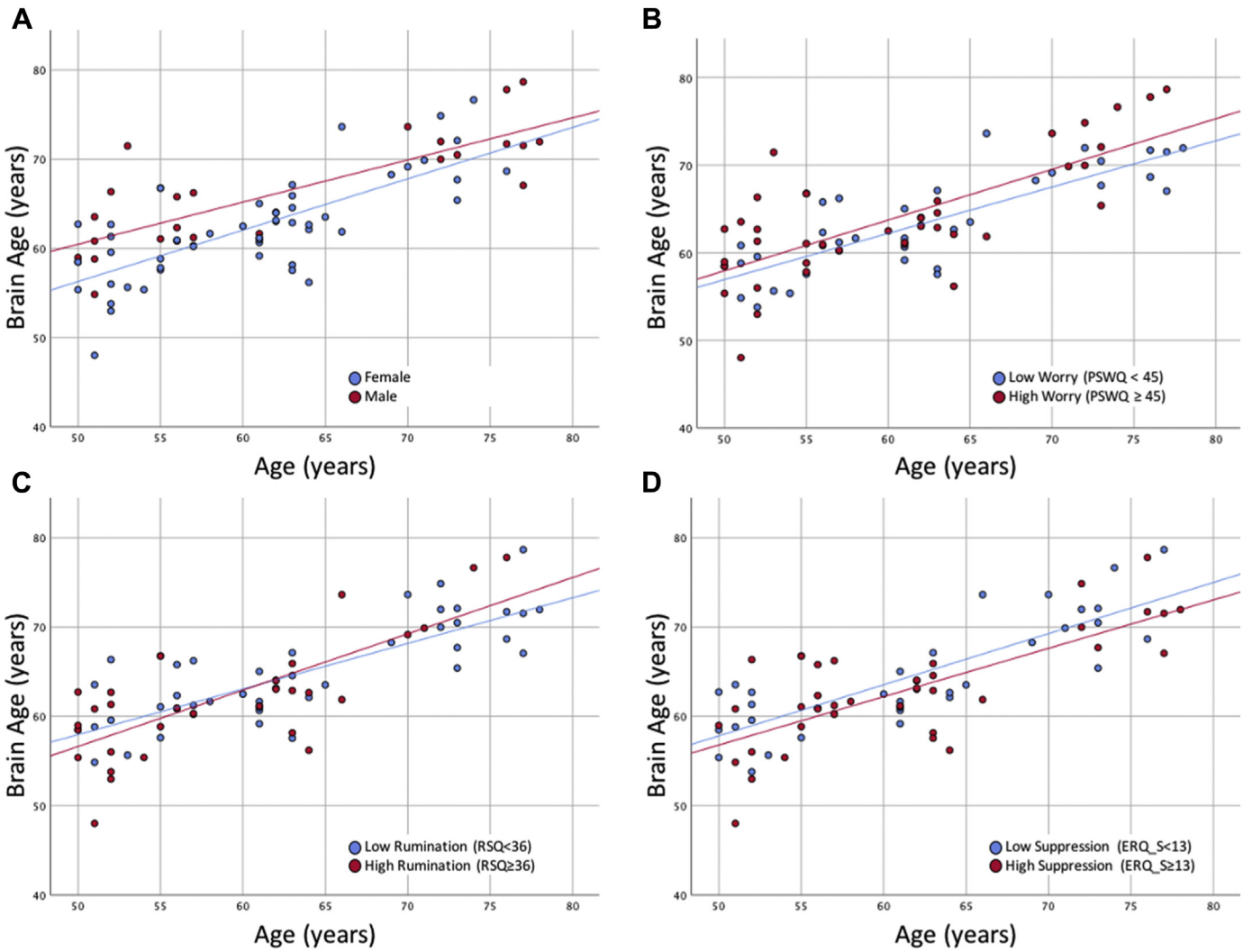

Fig. 1. Significant associations between brain age and sex (A), worry (B), rumination (C), and suppression (D) adjusting for chronological age. Cutoffs for PSWQ, RSQ, and ERQ suppression were based off of the medians of the sample as these are meant to illustrate associations that used continuous measures. Greater brain age is associated with greater age, being men (than women), greater worry, greater rumination, and lower suppression.

or positive reappraisal therapy—a newer attempt to incorporate mindful meditation into cognitive therapy [Hanley and Garland, 2014]).

The exploratory analysis regarding subtypes of rumination also rendered relevant results. Treynor, Gonzales, and Nolen-Hoeksema (Treynor et al., 2003) differentiated between "reflective pondering" and "brooding" factors of rumination, and subsequent research confirmed that the brooding subtype of rumination encompasses the more maladaptive aspects of rumination and it is more often associated with mood/anxiety pathology in midlife (Treynor et al., 2003) and late-life (Sutterlin et al., 2012) while reflective pondering may be conducive to problem-solving strategies (Sutterlin et al., 2012). Our preliminary results pointing toward the brooding subtype as predictive of brain aging suggest that further refinement of RNT phenomenology may be required for both future interventions and mechanistic studies analyzing the biological underpinning of RNT.

Our brain age model was fit from data on participants who were without significant beta-amyloid in the brain, which made our brain age measure more sensitive to amyloid (i.e., individuals with significant amyloid had greater brain age) (Ly et al., 2019). Given the link between RNT and dementia as well as beta-amyloid, there is some reason to suspect a possible link in our study as well. Future studies should investigate whether and how RNT impacts brain aging with measures of beta amyloid to understand its role in impacting brain aging.

Regarding the protective role of expressive suppression, a response-focused form of emotion regulation that seeks to prevent the outward expression of an already-generated emotion (Gross, 1998), several studies have indicated a positive association between expressive suppression and volumes of the anterior insula, dorsomedial prefrontal cortex, and dorsal anterior cingulate (Cutuli, 2014; Giuliani et al., 2011a,b; Hermann et al., 2014). Although there are data linking expressive suppression to anxious and depressive symptoms (Gross and John, 2003) as well as memory impairment (Hayes et al., 2010), we may cautiously interpret these results through the use-dependent brain plasticity theory (Classen et al., 1998; Giuliani et al., 2011a) that posits a “use it or lose it” approach. Thus, chronic preferential use of expressive suppression may maintain a higher volume in prefrontal brain regions counterbalancing the thinning effect of aging. An additional explanation involves the age group used in the present study—emotion regulation strategies effective in younger adults may become less effective with age (Urry, 2010), and although older adults report

using cognitive reappraisal more than younger adults, it is possible that older adults may rely less on a resource-demanding strategy such as reappraisal and use simpler techniques such as distraction or suppression (Livingstone and Isaacowitz, 2018).

Our results confirm the multiple previous reports indicating that sex differences influence brain morphology and atrophy rates. Past studies have shown greater volume loss in the gray matter in men than women (Armstrong et al., 2019). Throughout adulthood, research indicates that the female brain is more youthful than the male brain, with studies in women showing less loss of cerebral blood flow after puberty, more brain glycolysis during young adulthood, and less loss of protein synthesis–related gene expression during aging (Goyal et al., 2019). These young/middle age adult characteristics might provide some degree of resilience to aging-related changes and would apply to observations in large epidemiological studies of aging that associated male sex with worse memory and lower hippocampal volume among cognitively normal individuals (Jack et al., 2015).

We found that there were no differences in chronological age between men and women in our study, and chronological age was not correlated with worry or expressive suppression. This further helps show that brain age is an independent correlate of sex, worry, and expressive suppression. We did find that rumination was negatively correlated with chronological age, but positively correlated with brain age. This may explain the crossing between lines for low/high rumination. Future studies should test whether age has a moderating role on the association between rumination and brain age.

Our study has several limitations: we do not have longitudinal data to follow-up on the effect of the predictive factors described previously; we also do not have any other biological markers of aging to corroborate the current results (e.g., inflammatory cytokines, cortisol levels, and cerebral beta-amyloid burden). Most participants had mild if any depressive symptoms; thus, we cannot make inferences about the added effect of clinical depression on accelerated aging. Given the cross-sectional nature of our study, it is unclear whether brain aging is a result of atrophy or damage or differences in non-neurodegenerative processes (e.g., may be due to differences in other interindividual differences). The use of full-width at half-maximum (FWHM) of 4 mm is based on previous brain age models which have used 4 mm (Cole et al., 2015, 2018; Ly et al., 2019; Smith et al., 2019), this likely can bias the results and is ultimately somewhat arbitrary. In the past, smoothing has been used to boost statistical power (i.e., greater smoothing reduces complexity of multiple comparisons problem), however, in brain aging models is largely meant to deal with greater structural variability due to aging. We used an MPRAGE with a slice gap of 0.4 mm^3 due to the high resolution of the sequence (0.8 mm^3), and this may affect segmentation as other images were acquired at 1 mm^3 isotropic resolution. All images are resolved to a 1 mm^3 isotropic resolution with an FWHM of 4 mm, which help account for small differences. There are differences in the sites, scanners, and sequences for each site including this one which may inadvertently affect the results or conclusions of the present study. Typically, structural MRI scans are adequately harmonized for scanning parameters, however, our approach used a post hoc correction. Past studies have shown that this generates reliable brain age estimates (Cole et al., 2017), but this may nonetheless affect the current results. Our sample is relatively well-educated (average 15 years), and because education has been shown to be associated with markers of reserve, this may mean that these results may not generalize well to the general population. Future studies should recruit samples with a broader education range and should also measure markers such as intelligence quotient as this may impact reserve as well. Another limitation is that the participants who were missing some data differed on education by approximately 1 year, which may influence these results, however, they did not differ on cognitive function (3MSE). Future studies should investigate these associations in larger samples using approaches that utilize regularization and cross-validation as it is possible that a more parsimonious model (e.g., fewer predictors with maximized variance explained) may be a better fit. The brain age marker used in this analysis utilizes only gray matter maps and reflects a “gray matter” age rather than brain age in general so should be interpreted as such. Our analysis regarding brooding versus reflection was exploratory and should be interpreted with caution, but future studies should investigate the divergent mechanisms of these 2 constructs and their effect on brain age.

In conclusion, we present novel data suggesting a deleterious effect on aging of both worry and rumination in older adults as well as a potential protective effect of using expressive suppression. These results also emphasize the role of preventative interventions in reducing accelerated aging by targeting modifiable factors such as worry and rumination in late life.

CRediT authorship contribution statement

Helmet T. Karim: Conceptualization, Methodology, Data curation, Formal analysis, Funding acquisition, Writing - original draft, Writing - review & editing. **Maria Ly:** Data curation, Writing - review & editing. **Gary Yu:** Data curation, Writing - review & editing. **Robert Krafty:** Conceptualization, Data curation, Formal analysis, Writing - review & editing. **Dana L. Tudorascu:** Conceptualization, Methodology, Data curation, Formal analysis, Funding acquisition, Writing - review & editing. **Howard J. Aizenstein:** Conceptualization, Methodology, Funding acquisition, Writing - review & editing. **Carmen Andreescu:** Conceptualization, Methodology, Data curation, Formal analysis, Funding acquisition, Writing - original draft, Writing - review & editing.

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