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Advanced brain age correlates with greater rumination and less mindfulness in schizophrenia

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ABSTRACT

Background: Individual variation in brain aging trajectories is linked with several physical and mental health outcomes. Greater stress levels, worry, and rumination correspond with advanced brain age, while other individual characteristics, like mindfulness, may be protective of brain health. Multiple lines of evidence point to advanced brain aging in schizophrenia (i.e., neural age estimate > chronological age). Whether psychological dimensions such as mindfulness, rumination, and perceived stress contribute to brain aging in schizophrenia is unknown.

Methods: We estimated brain age from high-resolution anatomical scans in 54 healthy controls (HC) and 52 individuals with schizophrenia (SZ) and computed the brain predicted age difference (BrainAGE-diff), i.e., the delta between estimated brain age and chronological age. Emotional well-being summary scores were empirically derived to reflect individual differences in trait mindfulness, rumination, and perceived stress. Core analyses evaluated relationships between BrainAGE-diff and emotional well-being, testing for slopes differences across groups.

Results: HC showed higher emotional well-being (greater mindfulness and less rumination/stress), relative to SZ. We observed a significant group difference in the relationship between BrainAge-diff and emotional well-being, explained by BrainAGE-diff negatively correlating with emotional well-being scores in SZ, and not in HC. That is, SZ with younger appearing brains (predicted age < chronological age) had emotional summary scores that were more like HC, a relationship that endured after accounting for several demographic and clinical variables.

Conclusions: These data reveal clinically relevant aspects of brain age heterogeneity among SZ and point to case-control differences in the relationship between advanced brain aging and emotional well-being.

1. Introduction

Brain aging is not a uniform process. Individual rates of brain aging are influenced by various environmental, genetic, and epigenetic factors (Franke and Gaser, 2019), and advanced brain aging is associated with maladaptive psychological features, like worry and rumination (Karim et al., 2021). Advanced brain aging is well-described in schizophrenia (Shahab et al., 2019; Koutsouleris et al., 2014; Schnack et al., 2016; Hajek et al., 2019; Cropley et al., 2017), including exaggerated widespread gray matter reductions, characteristic of normal aging, (Thambisetty et al., 2010; Driscoll et al., 2009; Pfefferbaum et al., 2013) that are more pronounced in schizophrenia. Further, advanced brain aging in schizophrenia corresponds with poorer functioning and greater clinical severity (Schnack et al., 2016; Kaufmann et al., 2019).

Psychological dimensions related to stress response and vulnerability to negative affect may help to explain the heterogeneity observed in brain aging among individuals with and without psychiatric illness (Schnack et al., 2016; Raz et al., 2010; Lin et al., 2020). This follows, in

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part, from evidence of advanced age-related gray matter degradation in adults (Koutsouleris et al., 2014; Dunlop et al., 2021; Han et al., 2020) and adolescents (Drobinin et al., 2021) with major depressive disorder (MDD). Chronic stress, which engages similar biological systems as depression, is also associated with advanced aging processes (Wolkowitz et al., 2011; Wolkowitz et al., 2010). Conversely, psychological characteristics that lower stress and facilitate well-being may mitigate unfavorable neurobiological trajectories (Schutte et al., 2016). This fits with notions that healthy and resilient aging is supported by greater psychological and emotional well-being (Kim et al., 2021), while greater symptom burden is linked to poorer well-being among individuals with schizophrenia (Strauss et al., 2012; Chan et al., 2018). However, the relationship between well-being and brain aging in schizophrenia has not been characterized. The current study therefore examines this relationship in schizophrenia.

Mindfulness is one characteristic associated with better psychological health and subjective well-being (Keng et al., 2011), greater life satisfaction (Bajaj and Pande, 2016), and reduced stress reactivity (Creswell and Lindsay, 2014). Mindful awareness has been included as a core dimension in conceptual frameworks of well-being (Dahl et al., 2020). Broadly, mindfulness reflects the ability to focus on the present moment, in a non-judgmental or non-reactive manner (Kabat-Zinn, 2003). Mindfulness is believed to help people regulate emotion by allowing them to flexibly attend to their somatic experience, directing attention away from habitual or ruminative cognitive responses that can perpetuate negative affective states (Teper et al., 2013). Brains of long-term meditators, whose practices typically cultivate mindfulness, show less age-related degradation in brain anatomy measures relative to non-meditators (Luders, 2014; Luders et al., 2016); although it is unknown whether these differences reflect meditation-induced changes, pre-existing differences in the brains of long-term meditators, or both (Luders and Kurth, 2019). Individuals with schizophrenia report lower levels of mindfulness compared to unaffected individuals, but those individuals with schizophrenia who reported higher mindfulness also reported more adaptive emotion regulation and lower dysfunctional attitudes (Tabak et al., 2015). Greater mindfulness in individuals with schizophrenia-spectrum disorders positively correlated with physical and psychological health (Bergmann et al., 2021), suggesting that mindfulness may support adaptive functioning and stress reduction in schizophrenia. No studies to date have assessed whether greater mindfulness is associated with more favorable (i.e., slower) brain aging in schizophrenia.

In contrast to the health-promoting aspects of mindfulness, rumination and perceived stress are associated with poorer physical and mental health outcomes (Zawadzki, 2015; Watkins and Roberts, 2020; Richardson et al., 2012; Endrighi et al., 2019). Rumination is the tendency to repetitively analyze one's problems, concerns, and/or distress. Perseverative cognitions, including rumination, are a putative pathway through which psychosocial stressors produce chronic activation of several physiological systems (e.g., cardiovascular, immune, hypothalamic pituitary adrenal), resulting in a prolonged stress response that is associated with systemic health problems (Brosschot et al., 2006; Verkuil et al., 2010; Ottaviani et al., 2016). Perceived stress captures the degree to which one regards situations in their life as stressful. Like rumination, perceived stress is associated with negative impacts on physical and affective markers of health, including depression and cardiovascular disorders (Richardson et al., 2012; Rod et al., 2009; Bergdahl and Bergdahl, 2002). A recent study of older adults found that older brain age, based on gray matter measurements, corresponded with greater rumination (Karim et al., 2021). Taken together, individual differences in mindfulness, rumination and perceived stress levels may be relevant to brain health and aging processes.

Rumination can also amplify a negative mood state and exacerbate negative thought processes that increase depressive vulnerability (Nolen-Hoeksema et al., 2008). Roughly one third of individuals with schizophrenia experience depression symptoms (Conley et al., 2007; Siris, 2000). In the context of psychosis, rumination correlates with depressive symptoms, even after accounting for negative and positive symptoms (Thomas et al., 2014). We previously estimated brain age from reward-related neural signals measured during a gambling task using electroencephalography (EEG) (Abram et al., 2020). Similar to results in MDD that used functional and structural MRI-based methods (Dunlop et al., 2021; Han et al., 2021), we found that having a predicted brain age older than one's chronological age corresponded with worse depressive symptoms in schizophrenia. These results raised questions as to whether psychological tendencies that reduce (e.g., mindfulness) or enhance (e.g., rumination, perceived stress) negative affect are associated with brain aging in schizophrenia (Nguyen et al., 2018).

The current study assessed whether individual differences in mindfulness, rumination, and perceived stress correlated with brain aging in schizophrenia. We estimated brain age from high-resolution anatomical brain scans in 52 individuals with schizophrenia (SZ) with 54 healthy controls (HC) using the publicly available estimation tool from the Enhancing NeuroImaging Genetics through meta-analysis (ENIGMA) MDD working group (Han et al., 2020). The same participants completed questionnaires measuring mindfulness, rumination, and perceived stress that were used to derive an emotional well-being summary score. Compared to HC, we expected SZ to report higher rumination and perceived stress, and lower mindfulness, i.e., a pattern characterized by less emotional well-being. We also predicted that greater emotional well-being would correspond with younger brain age, relative to chronological age.

2. Methods

2.1. Participants

Fifty-two SZ (mean age = 34.71, age range = 19.07–64.70, 75% male) and 54 HC (mean age = 33.72, age range = 19.25–64.41 years, 78% male) were recruited from the community, Veterans Affairs San Francisco Healthcare System, and University of California, San Francisco (UCSF) clinics, including the early psychosis-focused UCSF Path Program; 48% of SZ were within 5 years of illness onset (Abram et al., 2020). The HC and SZ groups did not differ in age ($t_{104} = 0.35$, $p = .73$) or sex ($\chi^2 = 0.01$, $p = .91$). The Structured Clinical Interview for DSM-IV (SCID-IV-TR) was used to establish Axis I diagnoses (First et al., 2002). SZ had a diagnosis of schizophrenia ($n = 34$) or schizoaffective disorder ($n = 18$). HC were excluded if they met criteria for a past or current Axis I disorder, or for having a first-degree relative with a schizophrenia-spectrum disorder. SZ and HC were excluded for history of head injury, neurological illness, major medical illness impacting the central nervous system, or a positive toxicology screen for common drugs of abuse (e.g., opiates, cocaine, amphetamines). English fluency was required for study participation. The UCSF Institutional Review Board approved all study procedures. Participants provided written informed consent.

2.2. Psychological questionnaires

Mindfulness was measured using the 39-item Five Facet Mindfulness Questionnaire (FFMQ) (Baer et al., 2006), which captures five components of mindfulness: observing, describing, non-judging, acting with awareness, and non-reactivity. The FFMQ uses a 5-point Likert scale; higher scores on this inventory reflect greater trait mindfulness. The FFMQ has been validated in meditators and non-meditators (Baer et al., 2008) and in those with psychiatric symptomatology (Bohlmeijer et al., 2011). *Rumination* was measured using the 22-item Ruminative Responses Scale (RRS) (Nolen-Hoeksema and Morrow, 1991). RRS uses a 4-point Likert scale; higher scores on this inventory indicate a greater degree of ruminative traits. The RRS is widely used to capture depressive rumination, or the tendency to focus on one's depression symptoms and their potential causes and implications. *Perceived stress* was measured

using the 10-item Perceived Stress Scale (PSS-10) that captures the extent to which a person appraises situations in their life as stressful (Cohen et al., 1998). The PSS uses a 5-point Likert scale; higher scores on this inventory reflect higher levels of perceived stress. The PSS-10 has good internal consistency (Lee, 2012) and correlates with external depression and anxiety measures (Andreou et al., 2011; Roberti et al., 2006). Our analyses used total scores (distributions reported in Table 1).

2.3. Neuroimaging acquisition and processing

High-resolution T1-weighted structural brain data were acquired on a 3 T SIEMENS Skyra scanner using a 3D magnetization-prepared rapid gradient-echo (3D-MPRAGE) sequence (repetition time (TR) = 2530 ms, echo time (TE) = 3.55 ms, field-of-view (FOV) = 256 mm, voxel size = 1 × 1 × 1 mm, flip angle = 7°, phase encoding direction = anterior/posterior (AP), readout direction = head/foot (HF), duration = 8:07 min). Structural images were parcellated using FreeSurfer software (version 5.3), which segmented gray matter into cortical areas based on the Desikan-Killiany atlas (Desikan et al., 2006) and subcortical areas based on FreeSurfer's atlas (Fischl et al., 2002), separately for each hemisphere. Each image was manually inspected for errors in FreeSurfer segmentation (i.e., incorrect white matter and gray matter classification). FreeSurfer segmentation errors were subsequently corrected using control points and manual correction of skull stripping prior to being re-run through the FreeSurfer reconstruction pipeline to ensure that white and gray matter boundaries were accurately delineated. Images were also manually checked for large motion artifacts and excluded for excessive motion. Quality assurance was conducted by experienced research assistants who were trained to correct FreeSurfer segmentations on a subset of 10 T1-weighted images from a different study and achieved an average test–retest (ICC) reliability of 0.96. We derived 68 unilateral cortical thickness measurements, 68 unilateral cortical surface area measurements, 14 unilateral subcortical volumes, 2 lateral ventricles volumes, and bilateral intracranial volume; this totaled 77 final metrics when averaged across hemispheres and matched the FreeSurfer features utilized by the ENIGMA estimation tool (which are detailed in the Supplemental Materials of Han et al., 2020).

2.4. Brain age estimation

One well-developed approach for measuring brain age is to build a model that predicts chronological age as a function of brain anatomy in healthy individuals (Cole and Franke, 2017). Here we capitalized on the publicly available estimation tool from the ENIGMA MDD working group (https://www.photon-ai.com/enigma_brainage), which is a multi-site consortium that initially developed and validated this tool (Han et al., 2020). The ENIGMA brain age estimation tool has since been applied to an independent sample of controls and individuals with current MDD and/or anxiety (Han et al., 2021), as well as participants from the ENIGMA post-traumatic stress disorder (PTSD) Consortium (Clausen et al., 2022). Briefly, Han and colleagues estimated healthy aging from FreeSurfer gray matter parcellations (collapsed across hemisphere) in 952 male and 1236 female adult HC (ages 18 – 75) across 19 samples worldwide. Multivariate ridge regression models regressed chronological age onto the 77 structural brain metrics from FreeSurfer, separately for males and females, using 10-fold cross-validation to assess model performance in the training sample. The features in the algorithm were centered and scaled in the cross-validation framework and stored in the model. To validate model performance, Han et al. applied the learned parameters from the trained model to separate holdout samples of 927 male and 1199 female HC. See Supplemental Materials for details on the relative contributions of different features to the final ridge regression model that was implemented in the ENIGMA brain age estimation tool, as well as brain age models built using alternative machine learning algorithms/kernels that performed equivalently to ridge regression.

We entered the same 77 structural brain metrics, for the current sample, into the online ENIGMA-BrainAGE tool, which outputs an estimated brain age for each participant. Male and female participant data, collapsed across group, were entered into the ENIGMA-BrainAGE tool, separately, using the respective male/female learned parameters for prediction. To evaluate the ENIGMA training model performance when applied to our data, we calculated mean absolute error (MAE) between brain age and chronological age (also carried out separately for males and females). We computed our primary dependent variable, the brain predicted age difference (BrainAGE-diff), as the difference between predicted and chronological age (i.e., brain age – chronological age); we note that this metric has also been called brain-predicted age difference or brain-PAD (Han et al., 2020; Cole et al., 2019), brain age gap (Kaufmann et al., 2019), and brain age gap estimates or estimation (abbreviated as BrainAGE) (Hajek et al., 2019; Franke et al., 2014). Positive differences reflect an older appearing brain (predicted age > chronological age) and negative values reflect a younger appearing brain (predicted age < chronological age). These brain predicted age differences putatively reflect brain health at the individual level (Cole and Franke, 2017; Cole et al., 2019).

2.5. Brain age bias adjustment

There is a well-described age-related bias in the literature (Liang et al., 2019; Le et al., 2018; Smith et al., 2019), where brain age is overestimated in younger individuals, underestimated in older individuals, and most accurately estimated for individuals with an age closer to the average age of the training data. Bias-adjustment procedures have been developed to account for this chronological age dependency (de Lange and Cole, 2020). In this study we calculated an offset using the intercept and beta coefficients from regressing BrainAGE-diff onto chronological age (Beheshti et al., 2019), accounting for linear and quadratic relationships between predicted and chronological age (Smith et al., 2019):

$$BrainAGE - diff_i = ß_0 + ß_1 Age_i + ß_2 Age_i^2 + \varepsilon_i$$

for the offset calculation, we used regression parameters estimated from the ENIGMA MDD working group training data (Han et al., 2020):

$$offset_i = ß_0 + ß_1 \times Age_i + ß_2 \times Age_i^2$$

This offset was subtracted from the predicted brain age to produce a bias-adjusted brain age. BrainAGE-diff was recalculated using the bias-adjusted brain age. We adjusted brain age estimates for males and females, separately, using intercepts and coefficients from their respective training models.

Bias-adjustment effects are illustrated in Fig. S1. Prior to adjustment, we observed an inverse relationship between BrainAGE-diff and

Table 1
Distributions of psychological questionnaires by group.

	HC (n = 54)	SZ (n = 52)	t-stat	[a]d
[b]Five Facet Mindfulness Questionnaire (mean, SD)	139.33 (16.72)	127.30 (17.70)	−3.46***	0.70
[c]Ruminative Responses Scale (mean, SD)	34.69 (10.82)	46.49 (11.80)	5.30***	−1.05
[d]Perceived Stress Scale (mean, SD)	12.04 (5.99)	17.19 (6.59)	4.11***	−0.82

***p <.001.
Abbreviations: *HC* = healthy control participants; *SZ* = individuals with schizophrenia.
[a] Cohen's d effect size based on two-sample t-test.
[b] Three HC with missing data; five SZ with missing data.
[c] Three SZ with missing data.
[d] One HC with missing data; four SZ with missing data.

chronological age across both HC and SZ. After adjustment, we observed the expected attenuation in the BrainAGE-diff and chronological age relationship across all participants. These bias-adjusted BrainAGE-diff estimates were used for analysis.

2.6. Psychological characteristic summary score estimation

To reduce the complexity and account for expected interrelationships among the self-report measures (Table S1), we used a principal components analysis (PCA) to derive a single summary score representing mindfulness, rumination, and perceived stress. We used the `stats` package in R statistical software to perform the PCA on standardized self-report scale totals (Core R Team, 2019), which yielded three components of decreasing eigenvalue. The first principal component (PC1) accounted for 70% of the variance. We extracted component scores from PC1 for subsequent analyses. And though we included all three components in Table S2 for comprehensiveness, we did not further consider components 2 and 3 given their eigenvalues were less than 1 (Fig. S2). PCA scores were derived for participants with complete questionnaire data only, yielding scores for 51 HC and 45 SZ (Table 1 footnote).

2.7. Statistical analysis

Analyses were implemented in R using the `stats` (Core R Team, 2019), `car` (Fox and Weisberg, 2019), `MASS` (Ripley et al., 2021), and `WRS2` (Mair and Wilcox, 2020) packages. Initial analyses used two-sample *t*-tests to assess for group differences in BrainAGE-diff estimates and PCA scores, with follow-up one-sample *t*-tests to determine whether within-group means differed from 0; we also tested for between-group homogeneity of variance for BrainAGE-diff estimates and PCA scores using Levene's test. Our main analysis used robust regression to test the relationship between BrainAGE-diff and PCA scores. We included PCA scores and group (HC, SZ) as main effects, and a PCA score X group interaction term to test for slopes differences across the groups. Following a significant interaction, we calculated within-group BrainAGE-diff and PCA score robust correlations.

Lastly, we asked whether any BrainAGE-diff and PCA score relationships were better explained by other demographic or clinical variables. Specifically, we examined age to further account for systematic relationships between chronological and brain age (Liang et al., 2019), and sex, given evidence for sex differences in brain anatomy (Taki et al., 2011; Sowell et al., 2007) and brain age (Karim et al., 2021). We examined education (in years) and verbal IQ estimate (standard scores from the Wechsler Test of Adult Reading; WTAR) (Wechsler, 2001), which are used to approximate cognitive reserve, as they correlate with brain age and cortical thinning (Steffener et al., 2016; Aycheh et al., 2018). For clinical covariates, we examined illness duration, age at illness onset, chlorpromazine equivalents (CPZeq) (Woods, 2003), diagnosis (i.e., schizophrenia versus schizoaffective disorder), and concomitant anti-depressant usage. We also examined overall functioning (DSM-IV Global Assessment of Functioning Scale; GAF; (American Psychiatric Association, 1994), as well as positive, negative, and general symptoms (Positive and Negative Syndrome Scale; PANSS) (Kay et al., 1987), given prior observations that BrainAGE-diff correlated with functioning and symptom severity (Kaufmann et al., 2019). Distributions of these variables are found in Table 2. We examined relationships between our primary study variables (BrainAGE-diff and PCA score) and covariates using regression for continuous variables and ANOVA for categorical variables. For demographic covariates measured in both HC and SZ, we first tested for between-group slopes differences, followed by common slope tests in the absence of a significant interaction.

Table 2
Distributions of demographic and clinical information.

	HC (n = 54)	SZ (n = 52)	t-stat	[a]d
[b]Education, years (mean, SD)	15.38 (2.02)	14.06 (1.39)	4.04***	0.79
[b]WTAR Premorbid Verbal IQ Estimate (mean, SD)	116.28 (9.32)	111.98 (10.12)	2.25*	0.44
[c]Illness Duration, years (mean, SD)	—	12.25 (14.63)	—	—
[c]Age at Illness Onset, years (mean, SD)	—	20.97 (3.97)	—	—
[d]Chlorpromazine Equivalent (mean, SD)	—	382.66 (329.87)	—	—
Diagnosis (schizophrenia/ schizoaffective)	—	34/18	—	—
Concomitant anti-depressant Usage (yes/no)	—	18/34	—	—
GAF (mean, SD)	—	57.15 (10.05)	—	—
[e]PANSS Positive (mean, SD)	—	16.18 (5.43)	—	—
[f]PANSS Negative (mean, SD)	—	14.98 (4.99)	—	—
PANSS General (mean, SD)	—	31.08 (6.91)	—	—

*p <.05; ***p <.001.
Abbreviations: *GAF* = Global Assessment of Functioning Scale; *HC* = healthy control participants; *PANSS* = Positive and Negative Syndrome Scale; *SZ* = individuals with schizophrenia; *WTAR* = Weschler Test of Adult Reading.
[a] Cohen's *d* effect size based on two-sample *t*-test.
[b] Two SZ with missing data.
[c] Eight SZ with missing data.
[d] Seventeen SZ without CPZeq.
[e] One SZ with missing data.
[f] Two SZ with missing data.

3. Results

3.1. Brain age prediction performance

MAE for HC was 5.61 ± 6.84 years for males and 4.91 ± 6.24 years for females, while MAE for SZ was 7.74 ± 9.69 years for males and 8.77 ± 9.93 years for females. Fig. 1A shows the correlations between brain age and chronological age for both groups, collapsed across sex (HC: $r_{52} = 0.90$, $p < .001$, $R^2 = 0.80$; SZ: $r_{50} = 0.74$, $p < .001$, $R^2 = 0.55$).

3.2. Between-group comparison of BrainAGE-diff

HC and SZ did not differ in average BrainAGE-diff ($t_{104} = 0.36$, $p = .72$; Fig. 1B), although the groups differed in variance ($F_{1,104} = 6.54$, $p = .01$), reflecting more BrainAGE-diff variability in SZ. Within-group *t*-tests indicated that average BrainAGE-diff did not differ from 0 for either group (both $p > .10$).

3.3. Between-group comparison of emotional well-being scores

SZ reported higher rumination and perceived stress, and lower mindfulness, relative to HC (all $p < .001$; Fig. S3; Table 1). PC1 had positive loadings on mindfulness and negative loadings on rumination and perceived stress (Fig. 2A; Table S2); we conceptualized PC1 scores as *emotional well-being summary scores*. We observed a significant between-group difference in these summary scores ($t_{94} = -4.99$, $p < .001$, Cohen's $d = 1.02$; Fig. 2B). Follow-up one-tailed *t*-tests revealed more positive emotional well-being summary scores among HC (mean = 0.62 ± 1.29, $t_{50} = 3.45$, $p = .001$), versus more negative summary scores among SZ (mean = −0.71 ± 1.31, $t_{44} = -3.61$, $p < .001$). That is, HC generally reported higher emotional well-being, as defined by greater mindfulness and less rumination and perceived stress, whereas SZ showed the opposite pattern. There was no evidence for unequal variances in summary scores ($F_{1,94} = 0.22$, $p = .64$).

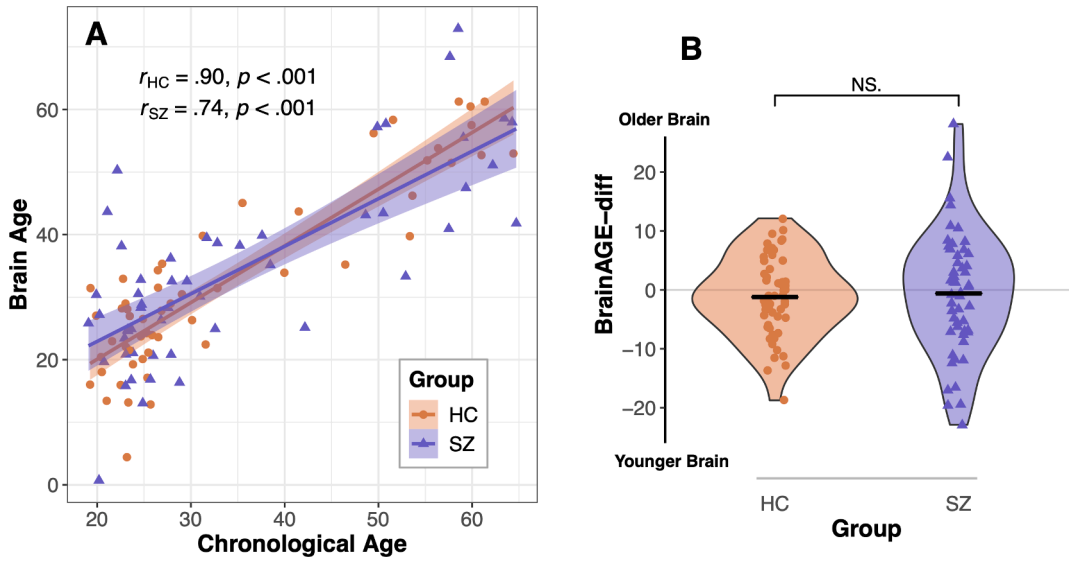

Fig. 1. Estimation of brain age and BrainAGE-diff. A) Brain age positively correlated with chronological ages in HC and SZ. Shaded bands represent 95 % confidence intervals. B) BrainAGE-diff (i.e., predicted age minus chronological age) did not differ between groups. Horizontal black lines represent group means. Abbreviations: *BrainAGE-diff* = brain predicted age difference; *HC* = healthy control participants; *SZ* = individuals with schizophrenia.

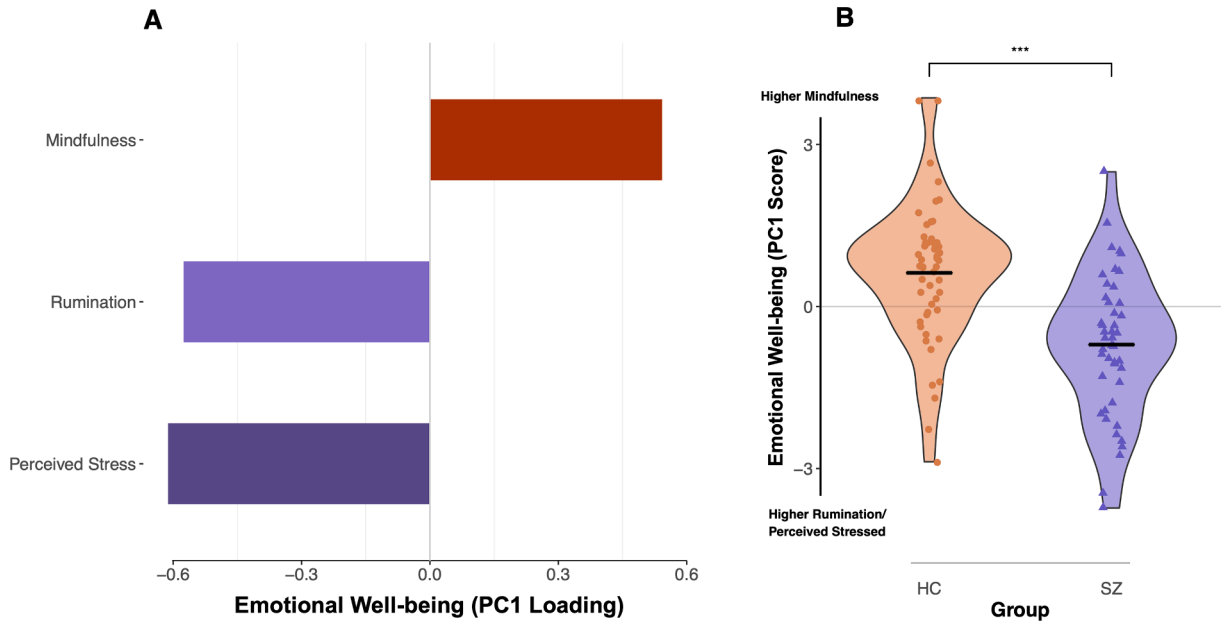

Fig. 2. Results of PCA on psychological questionnaires. A) The first principal component (PC1) reflected positive loadings on mindfulness and negative loadings on rumination and perceived stress; conceptualized as *emotional well-being summary scores*. B) Significant between-group differences in emotional well-being summary scores (standardized PC1 scores); characterized by a large effect size (Cohen's d = 1.02). Abbreviations: *HC* = healthy control participants; *SZ* = individuals with schizophrenia.

3.4. Emotional well-being predicts brain predicted age difference in the schizophrenia group

Fig. 3 shows the significant interaction between emotional well-being summary scores and group ($F_{1,92}$ = 7.04, p = .01); i.e., BrainAGE-diff was negatively correlated with summary scores in SZ (r_{43} = −0.47, p = .001), and unrelated in HC (r_{49} = −0.07, p = .61). More specifically, SZ with greater (i.e., "older") BrainAGE-diff, for which predicted age > chronological age, had more negative well-being summary scores indicating higher rumination/perceived stress, and lower mindfulness. Conversely, SZ with lower (i.e., "younger") BrainAGE-diff, for which predicted age < chronological age, had summary scores more similar to HC indicating more mindfulness, and less rumination/perceived stress. BrainAGE-diff significantly correlated with all three psychological questionnaires among SZ (Table S3). Results are comparable when using raw (not bias-adjusted) BrainAGE-diff scores (between-group interaction p = .01; within-group HC p = .29; within-group SZ p < .001). See Supplemental Materials for the within-group, pairwise correlations between BrainAGE-diff and the individual mindfulness, rumination, and perceived stress questionnaires.

3.5. Controlling for demographic and clinical covariates

There were no significant between-group slopes differences for age, sex, education, premorbid verbal IQ estimates with BrainAGE-diff or PCA scores (all p > .10). Across both groups, BrainAGE-diff estimates

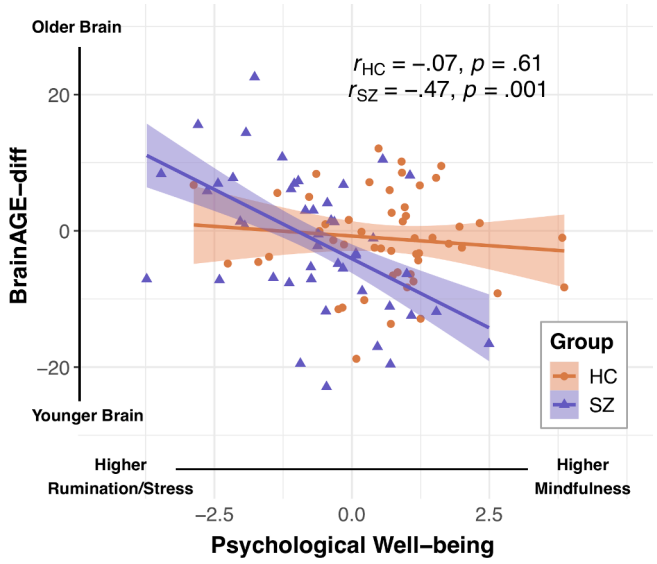

Fig. 3. PCA-derived emotional well-being predicts BrainAGE-diff in SZ. Significant interaction between emotional well-being summary scores and group ($F_{1,92} = 7.04$, $p = .01$); specifically, more negative summary scores (i.e., higher rumination and stress, lower mindfulness) were associated with more positive BrainAGE-diff (i.e., relatively older brains) in SZ. Conversely, SZ with more positive summary scores, had more negative BrainAGE-diff (i.e., relatively younger brains). Emotional well-being summary scores were unrelated to BrainAGE-diff in HC. Abbreviations: *HC* = healthy control participants; *SZ* = individuals with schizophrenia.

were higher in younger individuals ($t_{103} = -2.91$, $p = .004$) and females ($F_{1,103} = 8.17$, $p = .01$), and emotional well-being scores were positively correlated with age ($t_{93} = 2.28$, $p = .03$) and unrelated to sex ($p > .25$). Education and verbal IQ estimates were unrelated to BrainAGE-diff and emotional well-being scores (all $p > .40$). When accounting for age and sex, the significant PCA score X group interaction remained significant ($F_{1,90} = 4.14$, $p = .04$).

For clinical covariates specific to SZ, emotional well-being, but not BrainAGE-diff, corresponded with lower general symptom severity ($r_{43} = -0.48$, $p < .001$), a schizophrenia versus schizoaffective diagnosis ($F_{1,43} = 4.50$, $p = .04$), and concomitant anti-depressant usage ($F_{1,43} = 4.54$, $p = .04$), with lower emotional well-being for those with a schizoaffective diagnosis and those taking anti-depressant medication. Neither BrainAGE-diff nor emotional well-being significantly correlated with illness duration, age at illness onset, CPZeq, GAF functioning, positive, or negative symptoms (all $p > .05$). Hierarchical regression was used to test if the relationship between emotional well-being and BrainAGE-diff remained significant in SZ when accounting for significant demographic (i.e., age, sex) and clinical (i.e., diagnosis, concomitant anti-depressant usage, general symptom severity) covariates. The BrainAGE-diff and emotional well-being summary score relationship remained significant ($\beta = -0.44$, $t_{38} = -2.67$, $p = .01$; Model 2, Table S4), after first entering these covariates (Model 1, Table S4). Moreover, a change in F-test revealed a significant increase in variance explained when adding summary scores to the model ($F_{38,39} = 8.93$, $p = .005$).

4. Discussion

Our study finds that greater emotional well-being covaried with younger appearing brains among individuals with schizophrenia. We estimated brain age from high-resolution anatomical brain scans, and computed BrainAGE-diff as the delta between predicted and chronological age. HC and SZ did not differ in average BrainAGE-diff. We empirically reduced self-reported tendencies towards mindfulness, rumination, and perceived stress into a primary dimension that indicated higher levels of mindfulness along with lower levels of rumination and perceived stress (which we termed, "emotional well-being"). The groups differed in overall emotional well-being, with HC reporting greater mindfulness and less rumination and perceived stress, whereas SZ showed the opposite pattern. Our primary analysis correlated BrainAGE-diff with emotional well-being. SZ who reported greater rumination and perceived stress, and less mindfulness, had older appearing brains (predicted age > chronological age), whereas SZ reporting greater mindfulness, and lower rumination and stress (i.e., more like HC), had younger appearing brains (predicted age < chronological age). Emotional well-being and BrainAGE-diff remained correlated in SZ after accounting for several significant demographic and clinical covariates (age, sex, schizophrenia versus schizoaffective diagnosis, concomitant anti-depressant usage, general symptom severity). This study highlights psychological and emotional factors associated with brain preservation in schizophrenia.

One explanation for our finding associating emotional well-being with more resilient brain aging in schizophrenia is that mindfulness protects the brain against psychological and physiological stress (Epel et al., 2009; Conklin et al., 2019). Mindfulness may dampen stress-inducing cognitions and/or associated negative arousal states (e.g., higher cortisol, chronic inflammation, oxidative stress) that can lead to advanced aging. Consistent with this hypothesis, recent studies found that older brain age correlated with higher levels of rumination and worry in adults over 50 years old (Karim et al., 2021), and with higher levels of anxiety and somatic depressive symptoms among individuals with MDD (Han et al., 2021); though additional research is needed to determine the causal direction of these observations. Prolonged physiological stress via rumination may have detrimental effects on brain health (perhaps through a mechanism similar to the global brain volume reductions that are consistently reported in individuals with PTSD (Bromis et al., 2018). Conversely, long-term meditation practitioners exhibit larger brain volume and thickness (Luders and Kurth, 2019), and decelerated brain aging (Luders et al., 2016). And though it remains unknown whether these anatomical differences result from ongoing meditation practice or pre-date the onset of meditative practices (Luders and Kurth, 2019), our findings are consistent with prior literature in suggesting that psychological dimensions of mindfulness vs stress/rumination may be associated with opposing impacts on brain health.

Similar to our report of EEG-derived brain age in this sample (Abram et al., 2020), HC and SZ did not differ in average BrainAGE-diff when measured from anatomical brain scans. This null finding deviates from earlier reports indicating older brain age in SZ based on structural neuroimaging methods (Shahab et al., 2019; Schnack et al., 2016; Nenadić et al., 2017; Teeuw et al., 2021). BrainAGE-diff was also not related to emotional well-being in HC. One possible explanation is that the HC lacked variance in their emotional well-being summary scores (only 14 HC had scores less than 0 compared to 32 SZ).

Several demographic and clinical variables correlated with BrainAGE-diff and emotional well-being. General symptom severity correlated with lower emotional well-being in SZ; this is unsurprising given that the general symptom scale encompasses symptoms of anxiety, guilt, and depression. Critically, the relationship between BrainAGE-diff and emotional well-being remained after accounting for shared variance between emotional well-being and general symptom severity. Age positively correlated with emotional well-being, indicating that older individuals were more mindful and less ruminative/stressed. This finding is consistent with evidence of greater mindfulness in older relative to younger adults, which may contribute to greater well-being among older adults (Shook et al., 2017). It also highlights conceptual distinctions between chronological and brain age: while older chronological age equated to greater well-being across all participants, a younger brain age correlated with greater well-being in SZ; it is possible these variables separably tap factors such as wisdom/maturity versus brain health. Females ($n = 25$), collapsed across group, had higher

BrainAGE-diff than males. SZ with a schizoaffective diagnosis ($n = 18$) or those taking anti-depressant medication ($n = 18$) had lower emotional well-being; that is, depression-related clinical features were associated with more ruminative and stress tendencies, which are elevated in depression (Watkins, 2008). The proportion of these subgroups in our sample were small, emphasizing the need for independent samples to replicate these effects. Importantly, none of these covariates explained our primary finding that BrainAGE-diff and emotional well-being were related in SZ. This set of findings underscores the unique contributions of emotional well-being to brain health in schizophrenia.

In this study we assessed how a person's tendency toward mindfulness, rumination, and perceived stress correlated with their estimated brain age; a logical next question for future research is whether promoting mindfulness and decreasing rumination and stress via targeted interventions could have therapeutic effects on individual markers of brain health, and perhaps slow the advanced aging process that is well-described in schizophrenia (Shahab et al., 2019; Koutsouleris et al., 2014; Schnack et al., 2016). This follows, in part, from a growing evidence base indicating that mindfulness-based interventions increase mindfulness and reduce depression in individuals with psychosis (for meta-analysis, see Jansen et al., 2020; Louise et al., 2018). Negative tendencies like rumination and perceived stress are pervasive in other psychological disorders, like MDD and PTSD (Elwood et al., 2009; Nolen-Hoeksema, 1991; Lee et al., 2014; Hu et al., 2014); it is thus possible that the correlation between these psychological dimensions and brain age is not specific to schizophrenia. Future research warrants transdiagnostic assessment of these relationships. Similarly, understanding how psychological dimensions relate to brain health may have implications for populations with relatively preserved brain function and neuroanatomy, such as "superagers" (Sun et al., 2016). Finally, our findings may inform research concerning other biological age markers in schizophrenia (Nguyen et al., 2018), particularly those impacted by stress.

This study is not without limitations. Foremost, given the limitations inherent to our cross-sectional design, we cannot address whether lower emotional well-being in schizophrenia leads to advanced brain aging, if premature aging represents a vulnerability to poor emotional well-being, or whether these psychological and emotional characteristics and brain aging share a common etiology leading them to be correlated without a causal link (Han et al., 2019). Further, not all psychological dimensions relevant to brain age metrics were assessed; for example, other perseverative cognitions (like worry) may also impact stress and biological health (Brosschot et al., 2006). Likewise, other positive psychological dimensions, like optimism, may effect biological markers of aging (Schutte et al., 2016). Lifestyle factors, such as smoking and alcohol use, also have demonstrated relationships with advanced biological aging (Ning et al., 2020; Ryan et al., 2020); although disentangling these factors from their higher incidence rates in schizophrenia is a challenge (Teeuw et al., 2021). Nicotine and alcohol use were too low in this SZ sample to permit analysis of these factors. Our study solely used gray matter anatomy to compute brain age, allowing us to harness an algorithm derived from a well-powered training set; however, we acknowledge the enhanced prediction accuracy of brain age models that include multiple neuroimaging modalities (Cole, 2020; Niu et al., 2020). Finally, recent brain age analyses highlight the value of measuring the marginal contributions of individual features to model performance using approaches like Shapley Additive Explanations (SHAP), which estimates model-agnostic feature importance (Ball et al., 2021). While not implemented for the current study, such approaches can relate brain aging with specific, regional feature contributions (Ran et al., 2022).

In summary, we observed a novel relationship between measures of emotional well-being and brain aging among SZ. Our findings highlight a relationship between clinically relevant emotional characteristics and brain health, encouraging future mechanistic clinical intervention studies seeking to understand what factors contribute to emotional well-being and brain health as a complement to the more well-studied deficits associated with poor outcomes in this population.

CRediT authorship contribution statement

Samantha V. Abram: Methodology, Formal analysis, Visualization, Writing – original draft. **Brian J. Roach:** Methodology, Software, Formal analysis, Data curation, Writing – review & editing. **Jessica P.Y. Hua:** Methodology, Software, Writing – review & editing. **Laura K.M. Han:** Methodology, Software, Writing – review & editing. **Daniel H. Mathalon:** Conceptualization, Methodology, Writing – review & editing. **Judith M. Ford:** Conceptualization, Methodology, Writing – review & editing. **Susanna L. Fryer:** Funding acquisition, Conceptualization, Methodology, Investigation, Supervision, Project administration, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

De-identified data available from the corresponding author upon reasonable request.

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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.2022.103301.

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