Accelerated aging in the brain, epigenetic aging in blood, and polygenic risk for schizophrenia

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ABSTRACT

Schizophrenia patients show signs of accelerated aging in cognitive and physiological domains. Both schizophrenia and accelerated aging, as measured by MRI brain images and epigenetic clocks, are correlated with increased mortality. However, the association between these aging measures have not yet been studied in schizophrenia patients. In schizophrenia patients and healthy subjects, accelerated aging was assessed in brain tissue using a longitudinal MRI ($N = 715$ scans; mean scan interval 3.4 year) and in blood using two epigenetic age clocks ($N = 172$). Differences ('gaps') between estimated ages and chronological ages were calculated, as well as the acceleration rate of brain aging. The correlations between these aging measures as well as with polygenic risk scores for schizophrenia (PRS; $N = 394$) were investigated.

Brain aging and epigenetic aging were not significantly correlated. Polygenic risk for schizophrenia was significantly correlated with brain age gap, brain age acceleration rate, and negatively correlated with DNAmAge gap, but not with PhenoAge gap. However, after controlling for disease status and multiple comparisons correction, these effects were no longer significant. Our results imply that the (accelerated) aging observed in the brain and blood reflect distinct biological processes. Our findings will require replication in a larger cohort.

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1. Introduction

Schizophrenia is a debilitating psychiatric disorder where the patients' expected lifespan is decreased on average by 15 to 20 years compared to the general population (Laursen et al., 2014; Hjorthøj et al., 2017). This shortened lifespan may be explained in terms of accelerated aging of the body (Kirkpatrick et al., 2008). In two separate studies we have previously reported on accelerated aging of the brain (Schnack et al., 2016) and epigenetic aging in blood (Ori et al., 2021) for schizophrenia patients. However, whether or not these different biomarkers of aging act in concert has not yet been investigated.

Despite progress in our understanding of neuropsychiatric disorders, the etiology of schizophrenia remains largely unknown. There are several indications of aberrant brain development as early as the fetal period (Debnath et al., 2015; Kim et al., 2015; Faa et al., 2016), with progressive changes of the brain even after the onset of psychosis (van Haren et al., 2008; Hulshoff Pol and Kahn, 2008), which is characteristic for a progressive aging disorder (Olabi et al., 2011). Accelerated biological aging occurs when the rate of biological aging is increased as compared to chronological aging, and may in part explain the increase in mortality rate already observed at young adult ages within the patient population (Kirkpatrick et al., 2008; Shivakumar et al., 2014; Nguyen et al., 2018; Laursen et al., 2014). Quantitative assessment of biological aging can be performed using advanced statistical techniques such as machine learning algorithms. These algorithms are trained to discover aging-related patterns in the properties of tissue from a subject or donor (Bzdok, 2017; Cole and Franke, 2017; Jylhävä et al., 2017). Using neuroimaging, the biological age of the brain can be predicted from gray matter distributions (Cole and Franke, 2017; Cole et al., 2017; Valizadeh et al., 2017), white matter properties (Mwangi et al., 2013), or brain-activity related properties (Dosenbach et al., 2010). For patients with schizophrenia, accelerated aging of the brain occurs around the onset of psychosis (Koutsouleris et al., 2014; Schnack et al., 2016; Nenadić et al., 2017; Kaufmann et al., 2019; Jonsson et al., 2019; Kolenic et al., 2018; Chung et al., 2018; Hajek et al., 2019; Shahab et al., 2019) before stabilizing several years after onset (Schnack et al., 2016). Accelerated brain age predicts all-cause mortality (Cole et al., 2018), is highly heritable and has a genetic overlap with common brain disorders, including schizophrenia (Cole et al., 2017; Kaufmann et al., 2019). For biological tissue samples, several molecular and phenotypic biomarkers of aging have been reported from research into

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proteomic, transcriptomics, metabolomics, telomere length, and DNA methylation levels (Jylhävä et al., 2017; Nguyen et al., 2018). The age of a tissue donor can be reliably estimated based on epigenetic methylation of DNA (Horvath et al., 2012; Horvath, 2013; Hannum et al., 2013; Levine et al., 2018). While no significant accelerated epigenetic aging has previously been observed for schizophrenia, neither in post-mortem brain nor blood tissue (Viana et al., 2017; Voisey et al., 2017; McKinney et al., 2017; McKinney et al., 2018), a recent large-scale DNA methylation study now robustly demonstrated that epigenetic age is accelerated in whole blood samples and is strongly correlated with mortality risk (Ori et al., 2021; Higgins-Chen et al., 2020). The study furthermore reports that a subset of cases who carry high polygenic risk for schizophrenia are presented with the fastest age acceleration (Ori et al., 2021). This raises two intriguing questions; (i) do cases who carry high schizophrenia polygenic risk also present with faster brain age acceleration? And (ii) is aging in the brain correlated with epigenetic aging in blood? Previously, no significant correlation between brain aging and epigenetic aging was reported in a population study of typical aging elderly subjects (Cole et al., 2018). However, little is known about the interplay between genetics, epigenetics, and brain morphology with regard to accelerated aging in schizophrenia patients. In particular the association between the aging measures based on the brain and blood of schizophrenia patients has not yet been studied.

1.1. Current study

Here we investigated the correlation between brain aging, epigenetic aging, and polygenic risk for schizophrenia within a dataset of schizophrenia patients and healthy control subjects. MRI-derived brain ages were estimated from structural MRI scans using a brain age predictor (Schnack et al., 2016), and epigenetic ages were estimated from whole-blood array-based DNA samples profiles for the DNAmAge clock (Horvath et al., 2012) and the PhenoAge clock (Levine et al., 2018). Genotype-based polygenic risk for schizophrenia was estimated using the schizophrenia GWAS summary statistics of the Psychiatric Genome Consortium (Ripke et al., 2014).

2. Materials and methods

2.1. Cohort and sample description

Subjects included in this study were part of two longitudinal schizophrenia cohorts (van Haren et al., 2007; Boos et al., 2012). Brain age in these cohorts has been described before (Schnack et al., 2016), and these cohorts were part of a study on epigenetic aging in schizophrenia (Ori et al., 2021). Here, we included unrelated subjects that had imaging data and either epigenetic or genetic data available (Fig. 1; Table 1), resulting in a dataset of 411 unrelated subjects (193 cases and 218 controls; 36% female) of European descent spanning a wide range of the adult lifespan (mean age = 32.7 years; range = [16.7–67.5] years at baseline). For the majority of subjects (57%) longitudinal imaging data was available (up to five scans), with a mean scanning interval of 3.4 years (range [0.9–7.0] years). All patients met DSM-IV criteria for a nonaffective psychotic disorder (including schizophrenia, schizophreniform disorder or schizoaffective disorder). Most patients were on antipsychotic medication (Schnack et al., 2016). Incidence rate of smoking was significantly higher in patients (~70%) than controls (~25%); $p < 4.56e^{-8}$. Written informed consent was obtained from all subjects, and both studies were approved by the Medical Ethics Committee for Research in Humans (METC) of the University Medical Center Utrecht.

2.2. MRI brain age

Structural magnetic resonance imaging (MRI) scans were acquired on a 1.5 T Philips scanner with a voxel resolution of $1 \times 1 \times 1.2$ mm^3.
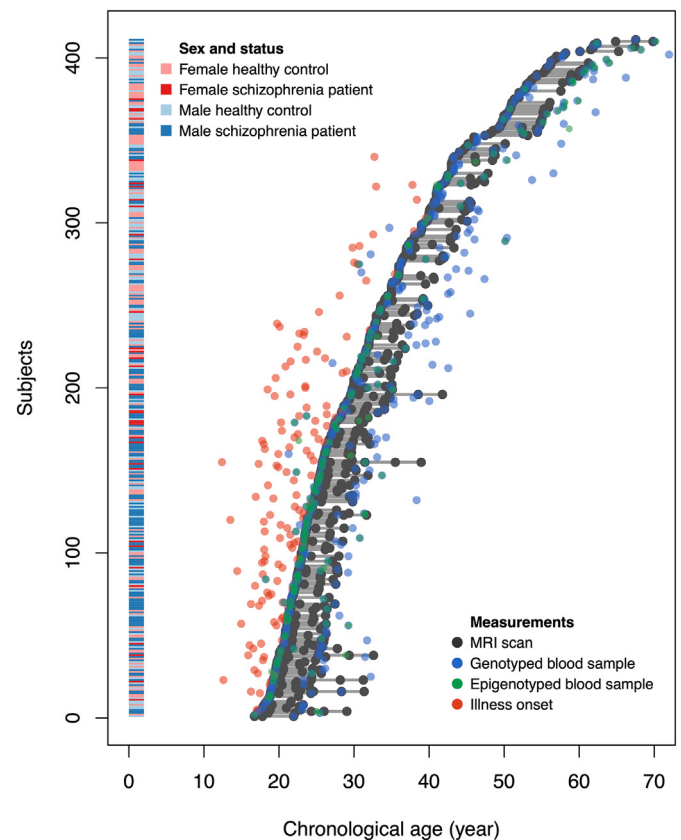

Fig. 1. Overview of all subjects with their age at illness onset (not always available for older schizophrenia patients), and age at MRI scans and blood sample acquisition for DNA and epigenetics.

Images were processed using a validated in-house image-processing pipeline to produce gray matter density maps in standardized space and used to predict individuals' brain age. In brief, the predictor uses a model that predicts chronological age based on the weighted sum of whole brain voxel-wise gray matter densities. The model was trained on a sample of healthy control subjects and applied on schizophrenia patients. See (Schnack et al., 2016) for details.

2.3. Blood-based epigenetic aging markers

DNA methylation data was obtained from whole-blood DNA samples using the Illumina Infinium Human Methylation Beadchip technology according to manufacturer's guidelines. A total of 172 samples were assayed with either the 27 K ($n = 108$ samples) or 450 K ($N = 64$ samples) platform, which interrogate 27,578 and 485,512 CpG sites across the genome, respectively. These data are a subset of previously published DNAm cohorts (Gene Expression Omnibus (GEO) ID: GSE41037 and GSE41169) for which brain age estimates from MRI scans were available. Blood-based DNAm age was estimated using two different clocks: DNAmAge (Horvath, 2013) and PhenoAge (Levine et al., 2018). These two epigenetic clocks were designed for use with both the 27 K and 450 K platform allowing us to maximize our sample size. See Supplementary Methods for details.

2.4. Polygenic risk for schizophrenia

Whole-blood DNA samples were processed on Illumina's HumanOmniExpressExome-8 v1.2 and Illumina's 550 K platform. After quality control (see Supplementary Methods for details), SNPs were imputed on the Michigan server (Das et al., 2016) using the HRC r1.1 2016 reference panel with European samples after phasing with

Table 1
Demographics table for individuals with data from the three modalities.

Measure	Population	Subjects with MRI brain age[a]	Subjects with epigenetic ages	Subjects with polygenic risk scores
Subjects	Total	411 [715]	172	394
(count)	Controls	218 [345]	63	212
	Patients	193 [370]	109	182
Age at baseline[b] (mean ± SD) (year)	Total	32.72 ± 11.41	32.31 ± 13.01	35.46 ± 12.47
	Controls	34.92 ± 12.10	32.62 ± 15.17	37.55 ± 13.17
	Patients	30.24 ± 10.05	32.13 ± 11.65	33.02 ± 11.16
Sex[c] (female:male)	Total	149:262	57:115	142:252
	Controls	115:103	37:26	110:102
	Patients	34:159	20:89	32:150
Smoking[d] (yes:no)	Total	108:107	75:62	99:99
	Controls	19:64	13:40	18:59
	Patients	89:43	62:22	81:40

Abbreviations (in alphabetical order): MRI = magnetic resonance imaging; SD = standard deviation from the mean.

[a] Longitudinal imaging data is available for 57% of the subjects. Total number of scans between brackets.

[b] Controls were on average slightly older than patients for MRI brain age and polygenic risk scores ($p < 2.51e^{-4}$), but not for epigenetic ages ($p = 0.825$).

[c] Proportion of males in the patients group is significantly greater than in the controls group ($p < 1.50e^{-7}$).

[d] Smoking has a significantly higher incidence rate in the patient population than the control population ($p < 4.56e^{-8}$).

Eagle v2.3. Polygenic risk for schizophrenia was calculated from the SNP data using the schizophrenia GWAS summary statistics of the Psychiatric Genome Consortium excluding Dutch subjects (Ripke et al., 2014). Polygenic scores were calculated using PLINK's score function at ten GWAS p-value thresholds of significance of the correlation: $p < 5e10^{-8}, 10^{-6}, 10^{-4}, 10^{-3}, 0.01, 0.05, 0.10, 0.20, 0.5$, and 1.0.

Polygenic risk scores were then harmonized to reduce the variation due to acquisition on different platforms through principal component analysis on the full sample. The first principal component contained the majority of the differential disease risk. This component was standardized and used for subsequent analyses, as previously described (Bergen et al., 2019). See Supplementary Methods for details.

2.5. Data preparation

We used a linear mixed-effects regression models to correct the MRI brain age and epigenetic age estimates for regression towards the mean (Le et al., 2018) and differences in acquisition platform within the non-psychiatric controls (**Supplementary Table S1**; **Supplementary Fig. S1**). Age gaps were defined as the difference between the corrected age estimates and the chronological age, and brain age acceleration as the annual rate of change in corrected brain age estimates between consecutive scans. The effects of sex were removed from all age measures by linear regression regardless of statistical significance and prior to further statistical analyses (**Supplementary Table S2**; **Supplementary Fig. S2**).

2.6. Statistical analysis

First, linear mixed-effects regression models were applied with each of the corrected aging measures as the dependent variable and diagnosis status as fixed effect independent variable to test for differences between the healthy control and schizophrenia patient groups. The models included random intercepts to account for the repeated measures of the longitudinal MRI scans. In a post-hoc analysis, tobacco smoking behavior was added as covariate to test for the effect of smoking on accelerated aging.

Secondly, the correlations between brain aging (age gap and age acceleration), epigenetic aging (DNAmAge gap and PhenoAge gap), and polygenic risk for schizophrenia (PRS SCZ) were determined using Spearman's correlation for all ten pairwise combinations. Since the MRI scans and the blood samples may have been acquired at different visitations, partial correlations were computed between brain age and epigenetic age measures while accounting for the difference in age of the participant at which the samples were acquired. No interval correction was applied for correlations involving the polygenic risk for schizophrenia. To assess whether potential correlations were driven by mean differences between patients and controls for both traits, we repeated these analyses while correcting for disease status.

For most subjects, more than one MRI scan was available. In the correlation analyses, the brain age gap from the last MRI scan and the longitudinal brain age acceleration of the first two MRI scans were used. This choice was made based on previous results that show brain age acceleration for schizophrenia patients is maximal around the time of onset (i.e. typically around the acquisition date of the earliest MRI scan) and that its cumulative effect results in a maximal brain age gap for schizophrenia patients 5 years later before stabilizing (Schnack et al., 2016).

A Bonferroni correction was used to account for multiple testing. The corrected significance threshold was set at $p = 0.05/5 = 0.01$ for group differences and $p = 0.05/10 = 0.005$ for the tests of pairwise correlations.

3. Results

Linear mixed-effects models with random intercepts revealed statistically significant effects of disease status for the MRI-derived brain age gap, longitudinal brain age acceleration, PhenoAge gap, and polygenic risk scores for schizophrenia indicating accelerated age or increased risk for schizophrenia patients, but not for DNAmAge gap (Table 2;

Table 2
Group-differences between schizophrenia patients and non-patient controls in brain aging, epigenetic aging, and polygenic risk scores for schizophrenia.

Measure	Healthy controls (Mean ± SD)	SCZ patients (Mean ± SD)	Effect of disease status (years)	Post-hoc effect of smoking (years)
MRI brain age gap (years)	−0.06 ± 6.23	+3.98 ± 7.24	**+4.03 ($p = 2.69e^{-9}$)***	+0.20 ($p = 0.847$)
MRI brain age acceleration (years/year)	1.01 ± 1.38	2.01 ± 2.26	**+1.00 ($p = 7.58e^{-5}$)***	+0.02 ($p = 0.948$)
DNAmAge gap (years)	+0.00 ± 3.56	−0.52 ± 5.69	−0.52 ($p = 0.510$)	+0.91 ($p = 0.307$)
PhenoAge gap (years)	+0.00 ± 6.95	+2.27 ± 6.74	**+2.27 ($p = 3.54e^{-2}$)**	+0.37 ($p = 0.791$)
Polygenic risk for schizophrenia (Z-score)	+0.00 ± 1.00	+0.83 ± 0.96	**+0.83 ($p = 6.18e^{-16}$)***	−0.00 ($p = 0.972$)

Nominal p-values are reported with a significance threshold of $p = 0.05$ in **boldface**. Differences that survive Bonferroni correction for multiple testing are marked with *. Abbreviations (in alphabetical order): SCZ = schizophrenia; SD = standard deviation from the mean.
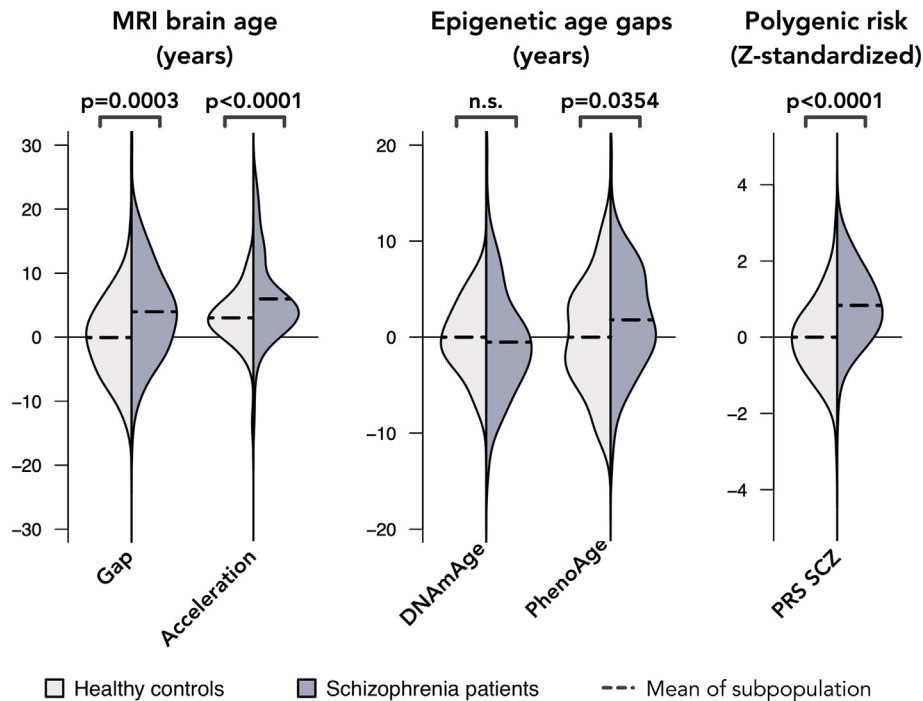
Fig. 2. Status effect on the means for MRI-derived brain age gap and acceleration, epigenetic age gaps (DNAmAge and PhenoAge), and polygenic risk for schizophrenia (PRS SCZ). Violin plots show an approximation of the distribution of scores within a subpopulation where density is smoothed by a Gaussian kernel and max height scaled to unit value. Abbreviations (in alphabetical order): PRS = polygenic risk score; SCZ = schizophrenia.

Fig. 2). A post-hoc analysis revealed no significant effect of smoking behavior on any of the aging measures, and did not affect the significance of the disease status effects except for the PhenoAge gap where the disease status effect was no longer significant ($+1.77$ years; $p = 0.120$).

The correlations between aging measures from the three modalities revealed statistically significant positive correlations between polygenic risk for schizophrenia and MRI-derived brain age gap and brain age acceleration, and a negative correlation between polygenic risk for schizophrenia and DNAmAge gap (Table 3A; Fig. 3). Within the modalities, there were significant positive correlations between the MRI-derived brain age gap and brain age acceleration, and between the DNAmAge and PhenoAge gaps (Table 3A; Fig. 3).

After including disease status as a covariate in the partial correlation, the correlation between the MRI-derived brain age gap and acceleration with polygenic risk for schizophrenia were no longer significant (Table 3B).

4. Discussion

We investigated the correlations between different biological aging markers and with polygenic risk for schizophrenia. We found suggestive evidence of correlations between polygenic risk for schizophrenia with MRI-derived brain aging and with DNAmAge, but not between polygenic risk for schizophrenia and PhenoAge or between brain aging and the epigenetic aging clocks.

4.1. Brain aging in schizophrenia and its correlation with polygenic risk for schizophrenia

Disease status (schizophrenia vs. healthy) had a highly significant effect on brain aging. The age gap, i.e. the difference between estimated age and chronological age, was $+4$ years in patients, and the brain age acceleration rate was double the rate of healthy controls, consistent with the previously reported results for the broader sample (Schnack et al., 2016) and with other studies reporting accelerated aging of the brain in schizophrenia patients (Koutsouleris et al., 2014; Nenadić et al., 2017; Kaufmann et al., 2019; Jonsson et al., 2019) and in subjects at clinically high-risk for psychosis and first-episode patients (Kolenic et al., 2018; Chung et al., 2018; Hajek et al., 2019; Shahab et al., 2019).

Polygenic risk for schizophrenia (PRS), as expected, was significantly higher in the patients as compared to the control subjects. We found nominal significant correlations between polygenic risk for schizophrenia and MRI-derived brain age gap ($rho = +0.10$) and longitudinal acceleration ($rho = +0.15$). These correlations were largely moderated by disease status, indicating that cases who carry higher polygenic risk for schizophrenia display faster brain age acceleration. Our results are in line with recent work that observed an overlap between common genetic variants associated with brain aging and common variants associated with schizophrenia in the population (Kaufmann et al., 2019). Here, we observe a direct correlation between brain aging and schizophrenia polygenic risk within individuals. While these findings provide evidence for a shared mechanism between genetic risk of schizophrenia and aging in the brain, replication and further work in a larger sample should be a first priority for future work. This study nevertheless reports the first efforts and value of such analyses. Structural brain aging could thus be used as an intermediate phenotype for psychosis (Palaniyappan et al., 2017; Dukart et al., 2017) and may show promise in predicting transition to psychosis in at-risk populations (Koutsouleris et al., 2014).

4.2. Epigenetic aging in schizophrenia and its correlations with polygenic risk for schizophrenia

We found that epigenetic age was significantly accelerated by $+2.3$ year in schizophrenia patients as compared to healthy controls for the PhenoAge clock, but not for the DNAmAge clock. Previous reports suggested no accelerated epigenetic aging or association with premature mortality for schizophrenia in blood or post-mortem brain samples (McKinney et al., 2017; Voisey et al., 2017; McKinney et al., 2018; Kowalec et al., 2019), with some exceptions (Okazaki et al., 2019; Ori et al., 2021; Higgins-Chen et al., 2020). Methodological differences,

Table 3

Bivariate analysis between MRI-derived brain age gap, brain age acceleration, epigenetic ages, and polygenic risk scores for schizophrenia.

A

Correlations	MRI brain age gap	MRI brain age acceleration	DNAmAge gap	PhenoAge gap	SCZ PRS
MRI brain age gap	–	$+0.36$ $(p = 1.68e^{-8})$*	-0.08^{a} $(p = 0.319)$	$+0.02^{a}$ $(p = 0.839)$	$+0.10$ $(p = 0.048)$
MRI brain age acceleration	HC: 109 SCZ: 126	–	$+0.02^{a}$ $(p = 0.874)$	$+0.03^{a}$ $(p = 0.747)$	$+0.15$ $(p = 2.58e^{-2})$
DNAmAge gap	HC: 63 SCZ: 109	HC: 39 SCZ: 68	–	$+0.42$ $(p = 1.01e^{-8})$*	-0.20 $(p = 1.29e^{-2})$
PhenoAge gap	HC: 63 SCZ: 109	HC: 39 SCZ: 68	HC: 63 SCZ: 109	–	$+0.08$ $(p = 0.326)$
SCZ polygenic risk scores	HC: 212 SCZ: 182	HC: 105 SCZ: 121	HC: 57 SCZ: 98	HC: 57 SCZ: 98	–

B

Partial correlations accounting for disease status	MRI brain age gap	MRI brain age acceleration	DNAmAge gap	PhenoAge gap	SCZ PRS
MRI brain age gap	–	$+0.31$ $(p = 1.29e^{-6})$*	-0.05^{a} $(p = 0.533)$	-0.04^{a} $(p = 0.574)$	-0.01 $(p = 0.778)$
MRI brain age acceleration	HC: 109 SCZ: 126	–	$+0.04^{a}$ $(p = 0.700)$	$+0.03^{a}$ $(p = 0.846)$	$+0.06$ $(p = 0.347)$
DNAmAge gap	HC: 63 SCZ: 109	HC: 39 SCZ: 68	–	$+0.45$ $(p = 1.07e^{-9})$*	-0.17 $(p = 3.13e^{-2})$
PhenoAge gap	HC: 63 SCZ: 109	HC: 39 SCZ: 68	HC: 63 SCZ: 109	–	$+0.03$ $(p = 0.755)$
SCZ polygenic risk scores	HC: 212 SCZ: 182	HC: 105 SCZ: 121	HC: 57 SCZ: 98	HC: 57 SCZ: 98	–

Spearman's correlation coefficients and their significant values are reported in the upper right triangle. Samples sizes are reported in the lower left triangle. Statistically significant correlations (nominal $p < 0.05$) are printed in **boldface**. Correlations that survive Bonferroni correction are marked with *.

[a] Correlations between MRI brain age gap or age acceleration and epigenetic age gaps were corrected for interval between acquisition of MRI scan and blood sample using partial correlations. Abbreviations (in alphabetical order): HC = healthy controls; PRS = polygenic risk score; SCZ = schizophrenia (patients); SD = standard deviation from the mean.

such as which epigenetic clock was used to measure accelerated aging (Belsky et al., 2018), but also tissue source and sample size (Jaffe and Kleinman, 2016), may explain inconsistencies in the results of these studies. Several epigenetic clocks have been constructed that each measure overlapping and distinct aspects of aging (Horvath and Raj, 2018). A distinction can be made between predictors of chronological or biological age (Bell et al., 2019; Horvath and Raj, 2018). Where chronological age (e.g. pan-tissue DNAmAge; Horvath, 2013) can benefit forensic sciences, it may not accurately reflect biological aging (e.g. PhenoAge or GrimAge; Levine et al., 2018; Lu et al., 2019). This distinction is present in a comprehensive comparison of biomarkers for measuring accelerated aging in schizophrenia, where biomarkers that measure biological aging are accelerated in schizophrenia but measures of chronological age are not (Higgins-Chen et al., 2020). However, there is no gold standard to measure biological age (Bell et al., 2019), and several factors can influence the apparent biological age, including lifestyle factors such as smoking (Gao et al., 2016; Ryan et al., 2019). In this study, accelerated PhenoAge in schizophrenia patients can be partially explained by tobacco smoking, as has previously been reported for biological aging (Levine et al., 2018; Higgins-Chen et al., 2020; Lu et al., 2019). However, the increased incidence of smoking in schizophrenia makes it difficult to disentangle the effect of disease status from smoking status. In addition, the use of antipsychotic medication may have a protective effect against accelerated aging (Schnack et al., 2016; Higgins-Chen et al., 2020; Janssens et al., 2019). Most patients in this study were on antipsychotic medication, which may explain the absence of accelerated epigenetic aging in schizophrenia reported here.

In addition, we found a significant negative correlation ($rho = -0.20$) between polygenic risk for schizophrenia and DNAmAge gap regardless of diagnosis status, but not for PhenoAge gap ($rho = +0.08$; [n.s.]). However, the negative correlation for DNAmAge gap did not survive correction for multiple testing and the correlation was not significant in our previous analysis in a much larger sample from multiple cohorts (Ori et al., 2021). Moreover, the previous analysis in the broader sample did find a significant correlation between polygenic

risk for schizophrenia and PhenoAge gap that was age- and sex-specific, with female patients above age 36 showing an increase in PhenoAge gap of $+3$ years (Ori et al., 2021). However, the current sample is a relatively younger population (mean age = 32 years) compared to the multicohort sample in our previous study (mean age = 40), and too small to stratify by age group or sex. Findings from our previous study should take precedence over what we report here; the previous results were consistent with another study with a large sample size that reported an association between polygenic risk for schizophrenia and mortality predictions based on the PhenoAge clock and suicidal behavior (Laursen et al., 2017). The inconsistent results in the current study emphasizes the need for large samples in studies investigating epigenetic aging. Although epigenetic aging is a compound score based on multiple indicators, its margin of error is large compared to the effect sizes typically reported, leading to potential false positive reports due to sampling bias in smaller samples. In addition, epigenetic aging may be more dynamic across the lifespan, as we have previously shown the existence of age- and sex-specific effect (Ori et al., 2021), that requires not only large sample sizes, but also calls for longitudinal studies.

Accelerated epigenetic aging is heritable (Marioni et al., 2015; Li et al., 2015), with an important role for the TERT locus related to telomerase and aging, and nine other loci related to metabolism and immune system pathways (Lu et al., 2018; Gibson et al., 2019). No overlap between genetic variants identified for schizophrenia and epigenetic aging is reported in a relatively small sample (Lu et al., 2018). There is an indication for colocalization of genetic and epigenetic loci implicated in schizophrenia (Hannon et al., 2016), however, epigenetic loci used to predict epigenetic age do not overlap with known epigenetic loci implicated in schizophrenia (Mill et al., 2008; Hannon et al., 2016). Instead, it is possible that the correlation between epigenetic age and polygenic risk for schizophrenia is mediated by other factors, e.g. a shared pathway that increases risk of early mortality (Marioni et al., 2015; Levine et al., 2018; Laursen et al., 2014) such a genetic predisposition to smoking (Boardman et al., 2010) or stressful life events (Wolf et al., 2018).
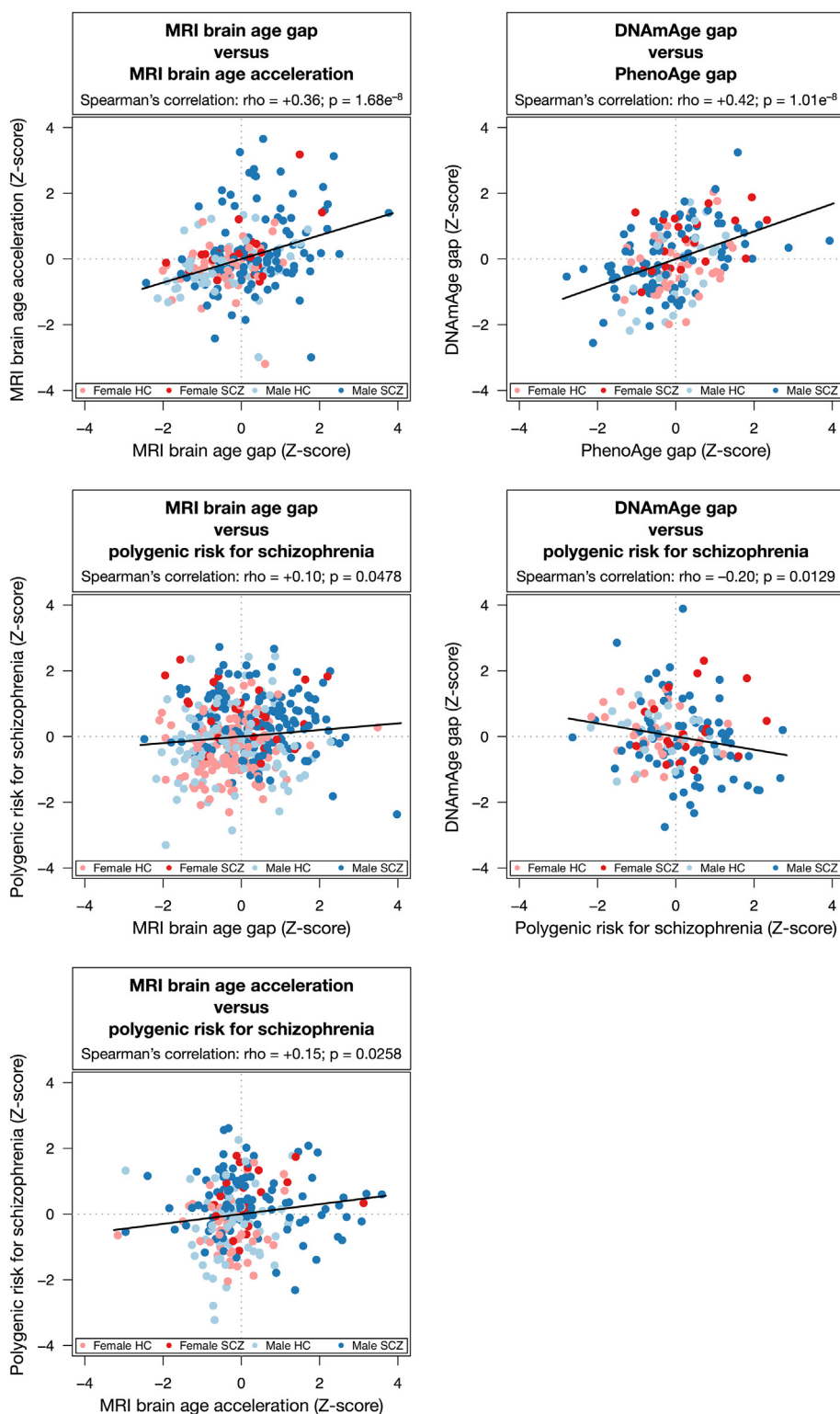
Fig. 3. Statistically significant correlations between MRI brain aging, epigenetic aging, and polygenic risk for schizophrenia. Abbreviations (in alphabetical order): HC = healthy controls; SCZ = schizophrenia.

4.3. Brain aging and its correlation with epigenetic aging

We did not find any significant correlation between the MRI-derived brain age gap or age acceleration with the DNAmAge or PhenoAge gap (range of *rho* = [−0.08; +0.03]; nominal *p* > 0.319 [n.s.]). An absence of a correlation between the MRI-derived brain age gap and DNAmAge

gap in blood samples has previously been reported in elderly subjects (Cole et al., 2018). Here we complement the previous finding by not only replicating the null result for the DNAmAge clock (that is a reliable predictor of chronological age regardless of tissue type or disease), but also investigating the correlation between MRI brain aging and the PhenoAge clock in blood – which might be more sensitive to aberrant

biological aging due to the inclusion of extrinsic factors more representative of apparent phenotypic aging (Levine et al., 2018). However, the correlations remained absent despite the effects of disease status and the correlations with polygenic risk for schizophrenia in the individual aging measures. As previously reported in broader samples, epigenetic aging in schizophrenia shows an age- and sex-specific effect in a larger study that included this cohort (Ori et al., 2021), and accelerated aging of the brain is already present in the first years following the onset of psychosis before it stabilizes several years afterward (Schnack et al., 2016). The absence of a correlation between these two aging measures might be due to distinct aging processes. Epigenetic aging, in particular the DNAmAge clock, is a measure of cellular aging rather than cellular senescence (Lowe et al., 2016; Kabacik et al., 2018). In contrast, the aging of the brain, in our study reflecting decreases in gray matter tissue, is likely due to cell senescence rather than cellular aging (Fernandez-Egea and Kirkpatrick, 2017), and it reflects changes in the morphology of the cells or composition of the neuropil. This argument is used to explain the absence of accelerated epigenetic aging in post-mortem samples of the brains of schizophrenia patients (McKinney et al., 2017; Voisey et al., 2017; McKinney et al., 2018). The possibility of two independent aging processes was previously suggested given the lack of correlation between the MRI-derived and epigenetic age gaps and the fact that combining information from the two clocks improved mortality predictions (Cole et al., 2018). The absence of a correlation with PhenoAge gap, one that takes into account extrinsic factors of typical aging, from our results affirms the conclusion that aging of the brain and epigenetic aging in blood might be two distinct processes in the etiology of schizophrenia, despite their commonality in predicting mortality (Cole et al., 2018; Marioni et al., 2015; Chen et al., 2016). A similar conclusion on the dissociation between brain aging and epigenetic aging can be concluded for related psychiatric disorders based on the reports from several independent studies. For bipolar disorder, accelerated epigenetic aging (Nenadić et al., 2017) but not aging of the brain (Fries et al., 2017; Shahab et al., 2019; Nenadić et al., 2017) has been reported, although lithium use may have confounded these results, since patients who were not treated with lithium have been found to show increased brain age (Van Gestel et al., 2019). For major depressive disorder, a large ($N = 1689$) international multicenter study (Han et al., 2020) has found accelerated aging of the brain, but results are inconclusive within smaller samples (Koutsouleris et al., 2014; Besteher et al., 2019; Kaufmann et al., 2019). Epigenetic aging in blood (Han et al., 2018) but not epigenetic aging in post-mortem brain samples (Li et al., 2018) has been reported. These studies suggest the possibility for distinct aging processing for brain tissue and blood across psychiatric disorders.

4.4. Limitations and future directions

There are a few limitations to this study that should be taken into account. First, the sample size of this study, while large for a longitudinal neuroimaging study, is very modest for a genetic or epigenetic study. Secondly, due to limited availability of information on antipsychotic drug usage, we could not disentangle medication effects on the aging measures. Finally, the cross-sectional design for epigenetics limits our ability to detect a possible age acceleration rate in the blood and its correlation to accelerating brain age (Nelson et al., 2019; Marioni et al., 2019). Depending on the time lag between illness onset and accelerated epigenetic aging, and because of the fact that most of the blood sample were acquired at baseline, the effects of the disease on DNA methylation may have yet to occur, especially in the younger adolescent population when onset of psychosis typically occurs (Paus et al., 2008). Future studies, measuring both brain aging and epigenetic aging in large longitudinal studies should further elucidate the possible (dynamic) relationships between these different measures of biological aging.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2021.04.005.

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