ACCELERATED BRAIN AGEING IN MOOD AND PSYCHOTIC DISORDERS

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By Pedro Lemos Ballester, M.Sc.

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AUTHOR: Pedro Lemos Ballester

M.Sc. (Pontifical Catholic University of Rio Grande do Sul).

SUPERVISOR: Dr. Benicio N. Frey M.D., M.Sc., Ph.D.

COMMITTEE: Dr. Luciano Minuzzi, M.D., Ph.D.; Dr. James P. Reilly, Ph.D.

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Abstract

Introduction: Through large neuroimaging consortia, researchers have identified a series of neuroanatomical alterations in mood and psychotics disorders, such as major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SCZ). However, the mechanism behind these alterations is not well understood. One of the existing hypotheses suggests that the observed brain changes are related to a process of accelerated brain ageing. Studies investigating this hypothesis use a measure called the brain age gap (i.e., the difference between machine learning model predictions of brain age and chronological age). Thus far, there is limited understanding on how mood and psychotic disorders affect model predictions, how can predictions be clinically useful, and what is the biological meaning behind the brain age gap. In this thesis, we investigated accelerated brain ageing in mood and psychotic disorders. We sought to estimate the effect of the brain age gap and propose new ways of modeling brain age. We also explored the clinical utility and meaning of the brain age gap.

Results: We confirmed the presence of a brain age gap in MDD, BD, and SCZ through a systematic review and meta-analysis. SCZ presented the highest levels of brain age gap, followed by BD and MDD. We analyzed the clinical utility of brain age for antidepressant treatment response and concluded that the brain age gap is not a predictor of antidepressant treatment response in weeks 8 and 16. We proposed a new method for brain age prediction that is more interpretable than previous approaches while preserving good predictive performance. We have also used model explanation strategies and

identified that the brain age gap is largely associated with total gray matter volume reduction and ventricle enlargement in SCZ.

Conclusion: The results of this thesis suggest that the brain age gap is present across mood and psychotic disorders. The results have also helped to clarify the meaning behind the brain age gap, a largely used but still poorly understood measure in neuroimaging research. So far, there is no indication that the brain age gap can be a useful tool for treatment response prediction in MDD.

Key words: mood disorders, psychotics disorders, machine learning, neuroimaging, accelerated ageing

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Table of Contents

List of Figures

List of Tables

List of Abbreviations

AIBL	Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing
BAG	Brain age gap
BD	Bipolar disorder
BMI	Body mass index
BrainAGE	Brain age gap estimation
brain-PAD	Brain-predicted age difference
CAMH	Centre for Addiction and Mental Health
CAN-BIND	Canadian Biomarker Integration Network in Depression
CNN	Convolutional neural network
COBRE	The Center for Biomedical Research Excellence
COINS	Collaborative Informatics and Neuroimaging Suite Data Exchange tool
CT	Computerized tomography
DLBS	Dallas Lifespan Brain Study
DTI	Diffusion tensor imaging
EDSS	Expanded disability status scale
EEG	Electroencephalogram
FA	Fractional anisotropy
FEP	First-episode psychosis
FES	First-episode schizophrenia-spectrum disorders
fMRI	Functional magnetic resonance imaging
FOV	Field of view
GM	Grey matter
GPR	Gaussian process regression
GSP	Brain Genome Superstruct Project
HC	Healthy comparison
HCP	Human Connectome Project
IQR	Interquartile range
IXI	Information eXtraction from Images
MADRS	Montgomery-Asberg Depression Rating Scale
MAE	Mean absolute error
MCIC	MIND Clinical Imaging Consortium
MDD	Major depressive disorder
ML	Machine learning
MMSE	Mini-mental state examination
MPRAGE	Magnetization prepared rapid gradient echo
MRI	Magnetic resonance imaging

NIH	National Institutes of Health
NKI-Rockland	Nathan Kline Institute Rockland Sample Enhanced
NMI	Neural Maturation Index
OASIS-1	Open Access Series of Imaging Studies-1
PANSS	Positive and negative syndrome scale
PET	Positron emission tomography
RMS	Root mean squared
SALD	Southwest University Adult Lifespan Dataset
SCZ	Schizophrenia
SD	Standard deviation
SHAP	Shapley additive explanations
SSRI	Selective serotonin reuptake inhibitors
TE	Echo time
TI	Inverstion time
TR	Repetition time
UCLA	University of California, Los Angeles Consortium for Phenomics database
WM	White matter

Declaration of Academic Achievement

Chapter 2

P.L. Ballester designed the study, screened papers, conducted the meta-analysis, and interpreted the findings. M.T. Romano screened the papers and interpreted the findings. T.A. Cardoso, S. Hassel, S.C. Strother, S.H. Kennedy, B.N. Frey supervised the work and interpreted the findings. All authors contributed to the writing of the manuscript.

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Chapter 3

P.L. Ballester, L.T. da Silva, M. Marcon, and N.B. Esper designed the study. P.L.B implemented the framework and ran experiments. F. Meneguzzi and A. Buchweitz supervised the implementation and engineering of the work. A.B. and B.N. Frey helped

interpreting the findings and provided neuroimaging-related insights. All authors contributed to writing the manuscript.

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Chapter 4

P.L. Ballester: Conceptualization, Data curation, Formal analysis, Methodology. J.S. Suh: Conceptualization, Formal analysis, Methodology. N. Nogovitsyn: Conceptualization and methodology. S. Hassel: project administration. S.C. Strother: Data curation, funding acquisition, investigation, project administration, resources, supervision. S.R. Arnott: Data curation, resources, visualization. L. Minuzzi: Investigation, resources. R.B. Sassi: Investigation. R.W. Lam: Funding acquisition, investigation, project administration, resources. R. Milev: Funding acquisition, investigation, project administration, resources. D.J. Müller: Funding acquisition, investigation, project administration, resources. V.H. Taylor: Project administration, resources. S.H. Kennedy: Funding acquisition,

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Chapter 5

P. L. Ballester, J.S. Suh, J.P. Reilly, and B.N. Frey designed the study. P.L.B designed the study and ran experiments. J.S.S. designed the study. J.P. Reilly and B.N. Frey supervised the study. All authors contributed to the writing of the manuscript.

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Chapter 1: Introduction

In this thesis, we sought to explore accelerated brain ageing in mood and psychotic disorders, a poorly understood process of brain changes that resembles ageing. We start by providing a summary of some of the theoretical components and technological building blocks that power accelerated brain ageing research. In the subsequent chapters, we demonstrate our contributions to the field. Our original contributions included a systematic review of the brain age gap in mood and psychotic disorders, proposed new methods for the interpretation of brain age models and the brain age gap, and investigation of the clinical utility of the brain age gap for treatment response prediction. Finally, in chapter 6, we discuss and integrate the findings from all chapters and provide critical suggestions to the future of the field. The findings from this thesis shed light on the current state of the field of accelerating brain ageing in mood and psychotic disorders, alongside providing new methods for the investigation of this phenomenon.

1.1 Mood and psychotic disorders

1.1.1 Epidemiology

Mood and psychotic disorders, such as major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SCZ), are severe mental health disorders with high rates of illness burden (Charlson et al., 2018; Frey et al., 2020) and a plethora of biological effects, such as an elevated risk for cardiovascular disease and dementia (Nielsen et al., 2021; Velosa et al., 2020). Each of these disorders have a distinct presentation. MDD is characterized by marked depressive episodes (APA, 2013). During

these episodes, individuals should present depressed mood or a loss of interest. These episodes may be accompanied by disruptions in appetite, sleep, concentration, and other symptoms (APA, 2013). Around 50% of individuals that have a depressive episode will develop a second one, while 80% that have a diagnosis of a second one, will develop a third episode (Burcusa & Iacono, 2007). BD is characterized by two types of episodes, manic or hypomanic and depressive. Manic episodes are characterized by elevated mood and high energy, possibly accompanied by feelings of grandiosity, pressured speech, decrease need for sleep, and impulsive behaviour (APA, 2013). During depressive episodes, individuals will have a similar symptom presentation to the episodes that occur in MDD. SCZ is characterized by psychotic episodes, which may contain hallucinations, delusions, disorganized speech, and cognitive impairment (APA, 2013).

Mood and psychotic disorders are highly prevalent. MDD is estimated to have a lifetime prevalence of 11.2% in Canada (Knoll & MacLennan, 2017). The lifetime prevalence in Canada of BD I and BD II is 0.87% and 0.57% (McDonald et al., 2015). According to the Canadian Chronic Disease Surveillance System, around 1% of the population lives with SCZ (Lix et al., 2018). These disorders have a series of shared risk factors, including childhood trauma, familial risk, and low socioeconomic status (Arango et al., 2021). How these risk factors affect the individual risk for each disorder is still unknown. For instance, a study by Rasic and colleagues (2014) has established that a familial risk for a psychiatric disorder increases the risk of developing any severe mental illness (Rasic et al., 2014).

Psychotropic treatments may vary across disorders, with MDD being predominantly treated with antidepressants (Kennedy et al., 2016), BD being treated with mood stabilizers (Yatham et al., 2013), such as lithium and valproic acid, and SCZ being treated primarily with antipsychotics (Remington et al., 2017). Mood and psychotic disorders may present disruptions in sleep, appetite, functioning, cognition, and increased suicidal thoughts, which tend to be more pronounced during episodes (Dome et al., 2019; Isometsä, 2014; Ventriglio et al., 2016). Therefore, it is of utmost importance to better characterize the biology of these disorders, both in their shared genetic predisposition, but also their differences in symptom profile and treatment response.

A step towards better characterization of mood and psychotic disorders is the investigation of brain scans. Individuals with these disorders present important anatomical and functional differences when compared to healthy comparison (HC) individuals.

1.1.2 Neuroimaging and brain alterations in mood and psychotic disorders

Many studies explore neuroimaging scans in the field of psychiatry. The majority fall under three broad groups: 1) Structural imaging, 2) functional imaging, and 3) diffusion imaging. Structural imaging involves generating snapshots of the brain that are useful for differentiating tissue types. Computerized tomography (CT) and magnetic resonance imaging (MRI) are modalities that can generate static scans that capture tissue integrity. Functional imaging, on the other hand, follows changes in blood flow or metabolic processes. Functional magnetic resonance imaging (fMRI) and positron emission

tomography (PET) are modalities that fall under this category. Parallels between functional neuroimaging and electroencephalogram can be drawn, where the former has a better spatial resolution, and the latter provides a better temporal resolution. Finally, diffusion imaging follows the dispersion direction of molecules in the brain. Diffusion tensor magnetic resonance imaging (DTI) is a popular approach that leverages the fractional anisotropy of water molecules. This modality focuses on the integrity of white matter tracts, allowing us to observe if there are disruptions in the connections between regions. These techniques have been used to investigate neurobiological changes not only in mood and psychotic disorders, but also in Alzheimer's disease, mild cognitive impairment, borderline personality disorder, and many others (Chandra et al., 2019; Goodman et al., 2013).

In the context of mood and psychotic disorders, meta-analyses and large consortia of brain imaging help identify consistencies across studies (Thompson et al., 2020). Total gray matter volume reduction, cortical thinning, ventricle enlargement, white matter hyperintensities, hippocampal volume reduction, and hypothalamus volume reduction, are some of the many differences observed across mood and psychotic disorders. Some of these findings have also been linked to clinical outcomes. For instance, increased positive symptoms in SCZ are linked to cortical thinning in the superior temporal gyrus (Walton et al., 2017), lower hippocampal volume in MDD is associated with recurrence of episodes and early onset of the disorder (Schmaal et al., 2016). Studies have also identified that medication may play a role in the observed brain differences. Lithium use is associated with a larger cortical thickness and a larger volume of subcortical structures (Hibar et al.,

2016; Thompson et al., 2020). On the other hand, antipsychotic use has been associated with cortical thinning (van Erp et al., 2018).

Some of the reported brain changes in mood and psychotic disorders, such as total gray matter volume reduction and ventricle enlargement, are also known to be associated with ageing (Peters, 2006). Are these findings a coincidence or do they represent a process of accelerated ageing in these disorders?

1.1.3 Disorders of accelerated ageing

The similarities between age-related brain changes and the observed in large consortium studies of brain abnormalities in mood and psychotic disorders is extensive (Peters, 2006; Schmaal et al., 2020). Further, clinical studies show patterns of greater cognitive and functioning decline as a function of age (Lewandowski et al., 2014). These studies have led to a series of hypotheses that accelerated ageing partly explains the brain differences in mood and psychotic disorders (Eyler & Jeste, 2018; Kirkpatrick et al., 2008; Teeuw et al., 2021; Verhoeven et al., 2014). Simply put, mood and psychotic disorders would have two components: 1) disorder-specific processes (e.g., metabolic, cardiovascular, and brain changes), and 2) an accelerated ageing process (Schnack et al., 2016). Whether accelerated ageing would be concentrated in the brain or would be a body-wide process remains unclear. For this thesis, we investigate the possibility of accelerated brain ageing.

At this point, the evidence of accelerated brain ageing in severe mental illness is mixed. Epigenetic studies of post-mortem tissue from the cerebellum and hippocampus

have identified accelerated ageing in BD (Fries et al., 2017, 2020), while similar studies with tissue from the superior temporal gyrus and the frontal cortex in SCZ have not (McKinney B.C. et al., 2017; Voisey J. et al., 2017). When looking exclusively into brain ageing measured through MRI data, the findings are also heterogeneous. However, significant differences between brain age and chronological age have been identified in MDD (Christman, Bermudez, Hao, Landman, Albert, et al., 2020), BD (van Gestel H. et al., 2019), and SCZ (Han et al., 2018). To understand more about brain age and accelerated ageing in severe mental illness, one needs to dive deeper into healthy brain ageing and the structural changes that follow it.

1.2 Ageing and the brain

1.2.1 Age-related trajectories of brain volume and brain age

Ageing is a phenomenon that affects the body at the genetic and epigenetic levels. One of the leading theories of ageing suggests that ageing is caused by cumulative genetic and epigenetic damage, leading to cell senescence (Harman, 2001; Sinclair & Oberdoerffer, 2009). Ageing leads to marked alterations all over the body, such as wrinkles in the skin and an increased risk for a wide range of diseases, from diabetes (Ismail et al., 2021) to Parkinson disease (Hou et al., 2019). The brain is not immune to such changes. During early development, the brain goes through rapid changes in volume and thickness (Brown, 2017). Brain maturation is completed at around 25 years of age (Arain et al., 2013). By then, a slow but steady process of gray matter reduction and increased white matter hyperintensities takes place (Peters, 2006). Although individual

differences exist (Brown, 2017), the progressive shrinking of the brain is consistently observed until death.

These trajectories of brain volume and thickness depend on a series of factors, many of which might still be unknown to research. These factors include sex, lifestyle choices (e.g., smoking, alcohol use, and exercise), psychiatric disorders, neurological diseases, and traumatic brain injuries (Ning et al., 2020; Peters, 2006). Given that age-related trajectories are somewhat predictable but contain idiosyncrasies, it is possible to estimate the age of an individual by using statistical and artificial intelligence methods. That is, age can be extracted given radiological scans of the brain. The age estimate derived from brain scans is typically called “brain age”.

1.2.2 Genetic and epigenetic age and its relationship with brain age

The brain, of course, is not the only part of the body that is ageing. Research outside of neuroimaging have also identified measures other than brain age that correlate with chronological age. In genetics, the telomere length (nucleotide chain at the edge of the chromosomes) is inversely correlated with age (i.e., they become shorter as we age). In epigenetics, methylation levels have been correlated with age. A combination of different methylation sites and their levels in a regression is called the epigenetic clock (Horvath, 2013).

Although brain, genetic, and epigenetic age are attempts of capturing biological ageing, recent evidence suggests that these measures do not capture the same processes. The epigenetic clock and telomere length have been shown to correlate with

chronological age and mortality, but the estimation residuals across individuals are not correlated (Marioni et al., 2016). Likewise, individuals with SCZ have uncorrelated values of epigenetic and brain aging (Teeuw et al., 2021). These findings strongly support hypotheses of mosaic ageing, in which senescence is not homogeneous across body structures, but heterogeneous and highly dependent on genetics and environment (Walker & Herndon, 2010).

Although we have differentiated epigenetic age and brain age based on the data (i.e. methylation and MRI data), some studies refer to epigenetic age as brain age when postmortem brain tissue is used for the estimations (Voisey J. et al., 2017). The issue with this overlap in the definition of brain age is that there are not enough studies that compare the behaviour of post-mortem epigenetic brain age with brain age extracted from neuroanatomical scans. It is likely, however, that these processes are not completely aligned, as neuroanatomical scans take several brain areas into consideration simultaneously to estimate brain age, while the epigenetic clock is usually extracted from tissue of a single region. Therefore, when we discuss accelerated brain ageing in this thesis from this point forward, we will be focusing on the neuroanatomical age, as extracted by magnetic resonance imaging data, unless otherwise noted.

1.3 Brain age prediction

1.3.1 Machine learning and deep learning

Machine learning is a field of artificial intelligence concerned with using data to solve problems. From the definition of Dr. Tom M. Mitchell: “The field of machine

learning is concerned with the question of how to construct computer programs that automatically improve with experience.", then expanded by "computer program is said to learn from experience E with respect to some class of tasks T and performance measure P, if its performance at tasks in T, as measured by P, improves with experience E." (Mitchell, 1997). In other words, for a computer program to learn, it needs data (experience), it needs a problem to be solved (task) and it needs a performance measure to evaluate how well it performs in that task. In most cases, the by-product of the learning process is a model that can be used to generate predictions. The learning procedure is commonly referred to as *training* the model.

A series of protocols need to be followed to ensure a sound training procedure. The first concern of these protocols is overfitting. Overfitting is when the model becomes too adjusted to the data used in model training, worsening the performance in other data points. A few approaches exist to circumvent this issue, including a holdout procedure. In holdout, the complete database is separated into two (or more) parts, consisting of training and test sets. The training set is used for generating the model and the test set is used to evaluate the model performance in samples that were not included during training. Model performance is usually assessed in terms of accuracy, sensitivity, specificity, precision, positive predictive value, and negative predictive value.

Deep learning is a subfield of machine learning that focuses on unstructured data (e.g., sound, text, images, and videos). In traditional machine learning, human-designed methods for feature extraction were used in unstructured data, generating a structured (e.g., spreadsheets) dataset that was then used for training. In the case of images, these

methods involved extracting distributions of pixel values, number of edges, and many more (Kumar & Bhatia, 2014). However, some of these extraction methods were limiting, as they removed part of the characteristics that could potentially help predictions. For instance, by extracting pixel value distributions, one completely ignores the spatial representation of the image, which might be of importance for a given task. Additionally, these extraction methods were usually not problem-specific, i.e., they were usually designed for the data type, but not for what problem is being solved. With deep learning, the feature extraction is learned jointly with the prediction model, removing the need for human feature design.

Both traditional machine learning and deep learning methods have been applied in the context of the brain age. These models generally use magnetic resonance imaging (MRI) as their input data modality.

1.3.2 Magnetic resonance imaging processing

MRI is a scanning modality that generates images based on the spin of protons (Berger, 2002). In simple terms, the machine aligns the protons of the target with its magnetic field. Then, this magnetic field is disrupted by a magnetic pulse. The energy released due to spin realignment is measured and used to generate an image. The energy release is dependent on the chemical composition of the tissue, which leads to an image that can be used to distinguish gray matter, white matter, and CSF. Image quality is dependent on the strength of the magnetic field (usually measured in Tesla), the ability of participants to stay still during the exam, and the machine processing speed. For

neuroimaging data, MRI tends to be a better alternative to computerized tomography (CT) as it provides better contrast in soft tissue and does not present any radiation concerns.

After the scan, the image is preprocessed to remove or minimize imaging errors, such as blurs and ghosts. FreeSurfer is a common tool for this process, containing several implemented algorithms that allow for preprocessing of neuroimaging data (Fischl, 2012). Among the tools contained in FreeSurfer, there are registration methods – those that can spatially align several scans or scans to templates –, skull stripping, normalization, and others. Ultimately, after the preprocessing steps, the scans are fed to segmentation methods, also provided by FreeSurfer. Segmentation methods leverage annotations of brain regions, called atlases, to identify brain regions in scans. These methods commonly yield a second image with a category for each voxel (3-dimensional pixel). These voxels are summarized into area, volume, and thickness, and can thus be fed to brain age prediction methods.

1.3.3 Brain age prediction methods

A brain age prediction method is any method that, given a brain scan, estimates the age of an individual. Although there are distinctions across the methods, they have a consistent approach toward training brain age models. First, a large set of brain scans of HC is used for model training. In this case, HC are usually those with no history of neurological diseases, psychiatric disorders, or traumatic brain injury. The assumption behind using just HC for training is that chronological age should match their brain age.

Inclusion and exclusion criteria may vary across studies. Each training instance consists of a pair of a scan and chronological age. This model is then trained to predict the chronological age based on the neuroimaging data. These models are trained to minimize the difference between predicted age and chronological age ($\hat{y} - y$), with some slight variation of the actual error being minimized (e.g., mean squared error, mean absolute error, and others). When training is finished, predictions from this model are frequently referred to as brain age predictions.

These methods also present important differences, impacting how they can be used, interpreted, and their predictive performance (i.e., how accurately they predict brain age). The differences in the methods concentrate on two main components: 1) the machine learning model and 2) the choices of preprocessing. Some of the first methods for brain age prediction used somewhat simple models (such as linear or ridge regression) with input data coming directly from FreeSurfer pipelines (Koutsouleris et al., 2014). These methods tend to be more interpretable, as the influence of each feature can be extracted from their corresponding coefficients. This advantage comes with the downside of the inability of these models to capture higher-order relationships. Newer methods may thus use more complex models, such as gradient boosting (Chen & Guestrin, 2016) and introduce changes to the training protocol by splitting training between males and females due to differences in brain development, for instance (Kaufmann et al., 2019). Some other studies employ convolutional neural networks, a type of deep learning artificial neural network characterized by a series of convolution operations that learn how to extract features from raw data (Bashyam et al., 2020; Jonsson et al., 2019; Peng et al., 2019).

Other studies present completely different approaches to MRI preprocessing, such as structural covariance networks (Kuo et al., 2020). Finally, a few studies use functional MRI and electroencephalogram (EEG) for brain age modelling (Dunlop et al., 2021; Sun et al., 2019). The varying approaches of brain age estimation makes it challenging to interpret what brain age models are capturing. Efforts on improving model interpretability are of utmost importance to help solve this issue.

1.3.4 Model interpretability

A side-effect of modelling complex phenomena is the lack of interpretability of generated models. Anything more complex than a linear regression or a single decision tree poses a challenge for interpretation. In the case of decision trees, although its nodes provide an exact description of the model behaviour, larger trees explode the number of possible paths an instance can take. Beyond decision trees and linear models, more complex models may present thousands, if not millions, of parameters, so extracting interpretations may not only be impractical, but computationally unfeasible. Even approaches that attempt to provide interpretations of these models may fail by leading to imperfect representations (Murdoch et al., 2019).

Naturally, brain age prediction methods present issues with interpretability. So far, studies have shown that feature importance is consistent across different model types and that it corresponds to our knowledge of how ageing in the brain happens (Ball et al., 2021). Deep learning models, on the other hand, are harder to interpret. Model interpretation solutions, such as GradCAM (Selvaraju et al., 2017), have been proposed,

but they are noisy and may not faithfully represent model behaviour. Popescu and colleagues (2021) have proposed the use of voxel-level predictions of brain age to improve interpretability, yielding an individual prediction for each voxel (Popescu et al., 2021). However, this approach currently falls behind other methods of brain age prediction in predictive performance.

As an alternative to interpreting models at the model level, we can extract information on individual predictions. In this case, we are seeking *explanations* of each model predictions, as opposed to a single interpretation of model behaviour. There are a few methods that can be used for this purpose, such as Shapley additive explanations (SHAP) (Lundberg & Lee, 2017) and counterfactual explanations (Wachter et al., 2018). SHAP yields a value for each feature for each participant that represents how features have contributed to individual predictions. SHAP has already been used in the context of brain age, but thus far it has been solely applied to better explain model behaviour for HC, and has not yet been used to investigate clinical conditions in psychiatry (e.g. differences between SCZ and HC in brain age model behaviour) (Ball et al., 2021; Boscolo Galazzo et al., 2022; Lombardi et al., 2021). If used differently, these explanation methods may inform individual brain age predictions, and, consequently, the explain the *brain age gap* differences across groups, the main biomarker extracted from brain age predictions.

1.4 Brain age gap in severe mental illness

1.4.1 The brain age gap

As discussed before, brain age prediction methods are the foundation of accelerated brain ageing research in severe mental illness. However, the most relevant values do not come solely from predicting brain age. Instead, they come from the difference between predicted brain age and chronological age. This difference has been called *brain age gap*, and the procedure for finding it is commonly referred to as *brain age gap estimation* (brainAGE). A positive brain age gap (brain age > chronological age) indicates the resemblance of an older than expected brain, while a negative brain age gap indicates the opposite.

The MDD, BD, and SCZ clinical populations consistently present a higher brain age gap than HC. These levels may be modulated by a series of factors, such as medication use (van Gestel H. et al., 2019), obesity (Kolenic et al., 2018), and mean age of the study sample (Christman, Bermudez, Hao, Landman, Boyd, et al., 2020). Beyond that, Alzheimer's disease and dementia also present a larger brain age gap than HC (Franke & Gaser, 2019). The brain age gap has been associated with a plethora of negative outcomes, such as increased mortality risk and lower fluid intelligence in the general population (Cole et al., 2018), cognitive impairment and disability in MDD (Christman, Bermudez, Hao, Landman, Boyd, et al., 2020), and worse negative symptoms in SCZ (Kaufmann et al., 2019).

Current protocols of brain age prediction involve training models with data from HC of studies in neurology and psychiatry. However, there is evidence to support that some

factors may influence the brain age gap in the HC population, which could impact the assumption that chronological age matches brain age for this group. For instance, long-term meditation practitioners present a negative brain age gap (Luders et al., 2016). Beyond that, factors such as obesity, smoking, and alcohol use, may also play a role in the brain age gap (Ning et al., 2020; Ronan et al., 2016). These findings suggest that the brain age gap is a non-specific biomarker that captures brain health instead of a marker of neuropsychiatric disorders (Cole & Franke, 2017).

1.4.2 Age-dependency

Due to models being trained to minimize the error of predictions, they tend to have a strong effect of pulling predictions towards the mean age of the dataset. Therefore, brain age prediction models overestimate brain age in individuals with age below the mean and underestimate brain age in those above the mean (Beheshti et al., 2019). Some approaches can be used to mitigate this issue. Beheshti and colleagues (2019) present a straightforward solution to the problem by modelling the relationship between the brain age gap and age for HC with a linear regression. Then, all brain age predictions are adjusted by the slope and intercept of the linear regression model to ensure that the mean brain age gap is consistently close to zero across the lifespan in HC.

Although the brain age gap should have an average of zero across the lifespan in HC, there is a potential effect of age in clinical groups. Christman and colleagues (2020) identified a higher than HC brain age gap in older individuals with MDD, but not younger ones, indicating a role of age in the increase of the brain age gap (Christman, Bermudez,

Hao, Landman, Boyd, et al., 2020). This finding also reinforces the idea of a cumulative effect of accelerated brain ageing in mood and psychotic disorders.

1.5 Main Aims

Due to the limited understanding of the brain age and brain age model behaviour, especially in the context of mood and psychotic disorders, we sought to 1) systematically review and synthesize the findings of the brain age gap in mood and psychotic disorders, 2) propose new methods of brain age prediction that can be more interpretable, 3) explore the associations between brain age and clinical outcomes, and 4) explain the brain age gap in clinical populations.

1.6 Specific Objectives

The specific objectives of this thesis were to:

1) In chapter 2, provide a systematic review and meta-analysis of the brain age gap in mood and psychotic disorders,
2) In chapter 3, create a new method for brain age prediction that alleviates the trade-off between interpretability and predictive performance,
3) In chapter 4, explore the relationship between the brain age gap and antidepressant treatment response in MDD,
4) In chapter 5, explain the brain age gap in SCZ and understand the differences between HC and SCZ in terms of model behaviour.

1.7 Hypotheses

The hypotheses for the first three specific objectives were:

1) All three groups (MDD, BD, and SCZ) will have a larger brain age gap than HC,
2) Brain age prediction can be more interpretable without a substantial decrease in predictive performance,
3) The brain age gap is predictive of treatment response in MDD.

References

1 American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

2 Arain, M., Haque, M., Johal, L., Mathur, P., Nel, W., Rais, A., Sandhu, R., & Sharma, S. (2013). Maturation of the adolescent brain. Neuropsychiatric Disease and Treatment, 9, 449–461. https://doi.org/10.2147/NDT.S39776

3 Arango, C., Dragioti, E., Solmi, M., Cortese, S., Domschke, K., Murray, R. M., Jones, P. B., Uher, R., Carvalho, A. F., Reichenberg, A., Shin, J. I., Andreassen, O. A., Correll, C. U., & Fusar-Poli, P. (2021). Risk and protective factors for mental disorders beyond genetics: an evidence-based atlas. World Psychiatry : Official Journal of the World Psychiatric Association (WPA), 20(3), 417–436. https://doi.org/10.1002/wps.20894

4 Ball, G., Kelly, C. E., Beare, R., & Seal, M. L. (2021). Individual variation underlying brain age estimates in typical development. NeuroImage, 235, 118036. https://doi.org/10.1016/j.neuroimage.2021.118036

5 Bashyam, V. M., Erus, G., Doshi, J., Habes, M., Nasralah, I., Truelove-Hill, M., Srinivasan, D., Mamourian, L., Pomponio, R., Fan, Y., Launer, L. J., Masters, C. L., Maruff, P., Zhuo, C., Völzke, H., Johnson, S. C., Fripp, J., Koutsouleris, N., Satterthwaite, T. D., … Davatzikos, C. (2020). MRI signatures of brain age and disease over the lifespan based on a deep brain network and 14 468 individuals worldwide. Brain, 143(7), 2312–2324.

6 Beheshti, I., Nugent, S., Potvin, O., & Duchesne, S. (2019). Bias-adjustment in neuroimaging-based brain age frameworks: A robust scheme. Neuroimage Clin, 24, 102063.

7 Berger, A. (2002). Magnetic resonance imaging. BMJ (Clinical Research Ed.), 324(7328), 35. https://doi.org/10.1136/bmj.324.7328.35

8 Boscolo Galazzo, I., Cruciani, F., Brusini, L., Salih, A., Radeva, P., Storti, S. F., & Menegaz, G. (2022). Explainable Artificial Intelligence for Magnetic Resonance Imaging Aging Brainprints: Grounds and challenges. IEEE Signal Processing Magazine, 39(2), 99–116. https://doi.org/10.1109/MSP.2021.3126573

9 Brown, T. T. (2017). Individual differences in human brain development. Wiley Interdiscip. Rev. Cogn. Sci., 8(1–2), e1389.

10 Burcusa, S. L., & Iacono, W. G. (2007). Risk for recurrence in depression. Clinical Psychology Review, 27(8), 959–985. https://doi.org/10.1016/j.cpr.2007.02.005

11 Chandra, A., Dervenoulas, G., Politis, M., & Alzheimer's Disease Neuroimaging Initiative. (2019). Magnetic resonance imaging in Alzheimer's disease and mild

cognitive impairment. Journal of Neurology, 266(6), 1293–1302. https://doi.org/10.1007/s00415-018-9016-3

12 Charlson, F. J., Ferrari, A. J., Santomauro, D. F., Diminic, S., Stockings, E., Scott, J. G., McGrath, J. J., & Whiteford, H. A. (2018). Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study 2016. Schizophrenia Bulletin, 44(6), 1195–1203. https://doi.org/10.1093/schbul/sby058

13 Chen, T., & Guestrin, C. (2016). Xgboost: A scalable tree boosting system. Proceedings of the 22nd Acm Sigkdd International Conference on knowledge Discovery and Data Mining, 785–794.

14 Christman, S., Bermudez, C., Hao, L., Landman, B. A., Boyd, B., Albert, K., Woodward, N., Shokouhi, S., Vega, J., Andrews, P., & Taylor, W. D. (2020). Accelerated brain aging predicts impaired cognitive performance and greater disability in geriatric but not midlife adult depression. Transl. Psychiatry, 10(1), 317.

15 Christman, S., Bermudez, C., Hao, L., Landman, B., Albert, K., & Taylor, W. (2020). BRAIN AGE ESTIMATION IN LATE-LIFE DEPRESSION: ASSOCIATION WITH COGNITIVE PERFORMANCE AND DISABILITY. Am. J. Geriatr. Psychiatry, 28(4, Supplement), S88–S89.

16 Cole, J. H., & Franke, K. (2017). Predicting Age Using Neuroimaging: Innovative Brain Ageing Biomarkers. Trends Neurosci., 40(12), 681–690.

17 Cole, J. H., Ritchie, S. J., Bastin, M. E., Valdés Hernández, M. C., Muñoz Maniega, S., Royle, N., Corley, J., Pattie, A., Harris, S. E., Zhang, Q., Wray, N. R., Redmond,

P., Marioni, R. E., Starr, J. M., Cox S R and Wardlaw, J. M., Sharp, D. J., & Deary, I. J. (2018). Brain age predicts mortality. Mol. Psychiatry, 23(5), 1385–1392.

18 Dome, P., Rihmer, Z., & Gonda, X. (2019). Suicide Risk in Bipolar Disorder: A Brief Review. Medicina (Kaunas, Lithuania), 55(8). https://doi.org/10.3390/medicina55080403

19 Dunlop, K., Victoria, L. W., Downar Jonathan and Gunning, F. M., & Liston, C. (2021). Accelerated brain aging predicts impulsivity and symptom severity in depression. Neuropsychopharmacology.

20 Eyler, L. T., & Jeste, D. v. (2018). Aging of the body and the brain in schizophrenia. Schizophr. Res., 196, 1–3.

21 Fischl, B. (2012). FreeSurfer. NeuroImage, 62(2), 774–781. https://doi.org/10.1016/j.neuroimage.2012.01.021

22 Franke, K., & Gaser, C. (2019). Ten Years of BrainAGE as a Neuroimaging Biomarker of Brain Aging: What Insights Have We Gained? Front. Neurol., 10, 789.

23 Frey, B. N., Vigod, S., de Azevedo Cardoso, T., Librenza-Garcia, D., Favotto, L., Perez, R., & Kapczinski, F. (2020). The Early Burden of Disability in Individuals With Mood and Other Common Mental Disorders in Ontario, Canada. JAMA Network Open, 3(10), e2020213. https://doi.org/10.1001/jamanetworkopen.2020.20213

24 Fries, G. R., Bauer, I. E., Scaini, G., Valvassori, S. S., Walss-Bass, C., & Soares Jair C and Quevedo, J. (2020). Accelerated hippocampal biological aging in bipolar disorder. Bipolar Disord., 22(5), 498–507.

25 Fries, G. R., Bauer, I. E., Scaini, G., Wu, M.-J., Kazimi, I. F., Valvassori, S. S., Zunta-Soares, G., Walss-Bass, C., & Soares Jair C and Quevedo, J. (2017). Accelerated epigenetic aging and mitochondrial DNA copy number in bipolar disorder. Transl. Psychiatry, 7(12), 1283.

26 Goodman, M., Mascitelli, K., & Triebwasser, J. (2013). The Neurobiological Basis of Adolescent-onset Borderline Personality Disorder. Journal of the Canadian Academy of Child and Adolescent Psychiatry = Journal de l'Academie Canadienne de Psychiatrie de l'enfant et de l'adolescent, 22(3), 212–219.

27 Han, L. K. M., Aghajani, M., Clark, S. L., Chan, R. F., Hattab, M. W., Shabalin, A. A., Zhao, M., Kumar, G., Xie, L. Y., Jansen, R., Milaneschi, Y., Dean, B., Aberg, K. A., van den Oord, E. J. C. G., & Penninx, B. W. J. H. (2018). Epigenetic Aging in Major Depressive Disorder. Am. J. Psychiatry, 175(8), 774–782.

28 Harman, D. (2001). Aging: overview. Annals of the New York Academy of Sciences, 928, 1–21. https://doi.org/10.1111/j.1749-6632.2001.tb05631.x

29 Hibar, D. P., Westlye, L. T., van Erp, T. G. M., Rasmussen, J., Leonardo, C. D., Faskowitz, J., Haukvik, U. K., Hartberg, C. B., Doan, N. T., Agartz, I., Dale, A. M., Gruber, O., Krämer, B., Trost, S., Liberg, B., Abé, C., Ekman, C. J., Ingvar, M., Landén, M., … Andreassen, O. A. (2016). Subcortical volumetric abnormalities in bipolar disorder. Molecular Psychiatry, 21(12), 1710–1716. https://doi.org/10.1038/mp.2015.227

30 Horvath, S. (2013). DNA methylation age of human tissues and cell types. Genome Biol., 14(10), R115.

31 Hou, Y., Dan, X., Babbar, M., Wei, Y., Hasselbalch, S. G., Croteau, D. L., & Bohr, V. A. (2019). Ageing as a risk factor for neurodegenerative disease. Nature Reviews. Neurology, 15(10), 565–581. https://doi.org/10.1038/s41582-019-0244-7

32 Ismail, L., Materwala, H., & al Kaabi, J. (2021). Association of risk factors with type 2 diabetes: A systematic review. Computational and Structural Biotechnology Journal, 19, 1759–1785. https://doi.org/10.1016/j.csbj.2021.03.003

33 Isometsä, E. (2014). Suicidal behaviour in mood disorders--who, when, and why? Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie, 59(3), 120–130. https://doi.org/10.1177/070674371405900303

34 Jonsson, B. A., Bjornsdottir, G., Thorgeirsson, T. E., Ellingsen, L. M., Walters, G. B., Gudbjartsson, D. F., Stefansson, H., Stefansson, K., & Ulfarsson, M. O. (2019). Brain age prediction using deep learning uncovers associated sequence variants. Nat. Commun., 10(1), 5409.

35 Kaufmann, T., van der Meer, D., Doan Nhat Trung and Schwarz, E., Lund, M. J., Agartz, I., Alnæs, D., Barch, D. M., Baur-Streubel, R., Bertolino, A., Bettella, F., Beyer Mona K and Bøen, E., Borgwardt, S., Brandt Christine L and Buitelaar, J., Celius, E. G., Cervenka Simon and Conzelmann, A., Córdova-Palomera, A., Dale, A. M., de Quervain, D. J. F., di Carlo Pasquale and Djurovic, S., … Westlye, L. T. (2019). Common brain disorders are associated with heritable patterns of apparent aging of the brain. Nat. Neurosci., 22(10), 1617–1623.

36 Kennedy, S. H., Lam, R. W., McIntyre, R. S., Tourjman, S. V., Bhat, V., Blier, P., Hasnain, M., Jollant, F., Levitt, A. J., MacQueen, G. M., McInerney, S. J., McIntosh,

D., Milev, R. v, Müller, D. J., Parikh, S. v, Pearson, N. L., Ravindran, A. v, Uher, R., & CANMAT Depression Work Group. (2016). Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie, 61(9), 540–560. https://doi.org/10.1177/0706743716659417

37 Kirkpatrick, B., Messias, E., Harvey, P. D., Fernandez-Egea, E., & Bowie, C. R. (2008). Is schizophrenia a syndrome of accelerated aging? Schizophr. Bull., 34(6), 1024–1032.

38 Knoll, A. D., & MacLennan, R. N. (2017). Prevalence and correlates of depression in Canada: Findings from the Canadian Community Health Survey. Canadian Psychology/Psychologie Canadienne, 58(2), 116.

39 Kolenic, M., Franke, K., Hlinka, J., Matejka, M., Capkova, J., Pausova, Z., Uher, R., Alda, M., Spaniel, F., & Hajek, T. (2018). Obesity, dyslipidemia and brain age in first-episode psychosis. J. Psychiatr. Res., 99, 151–158.

40 Koutsouleris, N., Davatzikos, C., Borgwardt, S., Gaser, C., Bottlender, R., Frodl, T., Falkai, P., Riecher-Rössler, A., Möller, H.-J., Reiser, M., Pantelis, C., & Meisenzahl, E. (2014). Accelerated brain aging in schizophrenia and beyond: A neuroanatomical marker of psychiatric disorders. Schizophr. Bull., 40(5), 1140–1153.

41 Kumar, G., & Bhatia, P. K. (2014). A Detailed Review of Feature Extraction in Image Processing Systems. 2014 Fourth International Conference on Advanced

Computing & Communication Technologies, 5–12. https://doi.org/10.1109/ACCT.2014.74

42 Kuo, C.-Y., Lee, P.-L., Hung, S.-C., Liu, L.-K., Lee, W.-J., Chung, C.-P., Yang Albert C and Tsai, S.-J., Wang, P.-N., Chen, L.-K., Chou, K.-H., & Lin, C.-P. (2020). Large-Scale Structural Covariance Networks Predict Age in Middle-to-Late Adulthood: A Novel Brain Aging Biomarker. Cereb. Cortex, 30(11), 5844–5862.

43 Lewandowski, K. E., Sperry, S. H., Malloy, M. C., & Forester, B. P. (2014). Age as a predictor of cognitive decline in bipolar disorder. The American Journal of Geriatric Psychiatry : Official Journal of the American Association for Geriatric Psychiatry, 22(12), 1462–1468. https://doi.org/10.1016/j.jagp.2013.10.002

44 Lix, L. M., Ayles, J., Bartholomew, S., Cooke, C. A., Ellison, J., Emond, V., ... & Pelletier, L. (2018). The Canadian chronic disease surveillance system: a model for collaborative surveillance. International Journal of Population Data Science, 3(3).

45 Lombardi, A., Diacono, D., Amoroso, N., Monaco, A., Tavares, J. M. R. S., Bellotti, R., & Tangaro, S. (2021). Explainable Deep Learning for Personalized Age Prediction With Brain Morphology. Frontiers in Neuroscience, 15, 674055. https://doi.org/10.3389/fnins.2021.674055

46 Luders, E., Cherbuin, N., & Gaser, C. (2016). Estimating brain age using high-resolution pattern recognition: Younger brains in long-term meditation practitioners. Neuroimage, 134, 508–513.

47 Lundberg, S. M., & Lee, S.-I. (2017). A Unified Approach to Interpreting Model Predictions. In I. Guyon, U. v Luxburg, S. Bengio, H. Wallach, R. Fergus, S.

Vishwanathan, & R. Garnett (Eds.), Advances in Neural Information Processing Systems 30 (pp. 4765–4774). Curran Associates, Inc.

48 Marioni, R. E., Harris, S. E., Shah, S., McRae, A. F., von Zglinicki, T., Martin-Ruiz Carmen and Wray, N. R., Visscher, P. M., & Deary, I. J. (2016). The epigenetic clock and telomere length are independently associated with chronological age and mortality. Int. J. Epidemiol., 45(2), 424–432.

49 McDonald, K. C., Bulloch, A. G. M., Duffy, A., Bresee, L., Williams, J. V. A., Lavorato, D. H., & Patten, S. B. (2015). Prevalence of bipolar I and II disorder in Canada. The Canadian Journal of Psychiatry, 60(3), 151–156.

50 McKinney B.C., Lin H., Ding Y., & Lewis D.A. (2017). DNA methylation evidence against the accelerated aging hypothesis of schizophrenia. Npj Schizophrenia, 3(1), 13.

51 Mitchell, T. M. (1997). Machine Learning (1st ed.). McGraw-Hill, Inc.

52 Murdoch, W. J., Singh, C., Kumbier, K., Abbasi-Asl, R., & Yu, B. (2019). Definitions, methods, and applications in interpretable machine learning. Proceedings of the National Academy of Sciences, 116(44), 22071–22080. https://doi.org/10.1073/pnas.1900654116

53 Nielsen, R. E., Banner, J., & Jensen, S. E. (2021). Cardiovascular disease in patients with severe mental illness. Nature Reviews. Cardiology, 18(2), 136–145. https://doi.org/10.1038/s41569-020-00463-7

54 Ning, K., Zhao, L., Matloff, W., Sun, F., & Toga, A. W. (2020). Association of relative brain age with tobacco smoking, alcohol consumption, and genetic variants. Sci. Rep., 10(1), 10.

55 Peng, H., Gong, W., Beckmann, C. F., Vedaldi, A., & Smith, S. M. (2019). Accurate brain age prediction with lightweight deep neural networks. In Cold Spring Harbor Laboratory.

56 Peters, R. (2006). Ageing and the brain. Postgrad. Med. J., 82(964), 84–88.

57 Popescu, S. G., Glocker, B., Sharp, D. J., & Cole, J. H. (2021). Local Brain-Age: A U-Net Model. Frontiers in Aging Neuroscience, 13, 761954. https://doi.org/10.3389/fnagi.2021.761954

58 Rasic, D., Hajek, T., Alda, M., & Uher, R. (2014). Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: a meta-analysis of family high-risk studies. Schizophrenia Bulletin, 40(1), 28–38. https://doi.org/10.1093/schbul/sbt114

59 Remington, G., Addington, D., Honer, W., Ismail, Z., Raedler, T., & Teehan, M. (2017). Guidelines for the Pharmacotherapy of Schizophrenia in Adults. Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie, 62(9), 604–616. https://doi.org/10.1177/0706743717720448

60 Ronan, L., Alexander-Bloch, A. F., Wagstyl, K., Farooqi, S., Brayne, C., Tyler, L. K., Cam-CAN, & Fletcher, P. C. (2016). Obesity associated with increased brain age from midlife. Neurobiology of Aging, 47, 63–70. https://doi.org/10.1016/j.neurobiolaging.2016.07.010

61 Schmaal, L., Pozzi, E., C Ho, T., van Velzen, L. S., Veer, I. M., Opel, N., van Someren, E. J. W., Han, L. K. M., Aftanas, L., Aleman, A., Baune, B. T., Berger, K., Blanken, T. F., Capitão, L., Couvy-Duchesne, B., R Cullen, K., Dannlowski, U., Davey, C., Erwin-Grabner, T., … Veltman, D. J. (2020). ENIGMA MDD: seven years of global neuroimaging studies of major depression through worldwide data sharing. Transl. Psychiatry, 10(1), 172.

62 Schmaal, L., Veltman, D. J., van Erp, T. G. M., Sämann, P. G., Frodl, T., Jahanshad, N., Loehrer, E., Tiemeier, H., Hofman, A., Niessen, W. J., Vernooij, M. W., Ikram, M. A., Wittfeld, K., Grabe, H. J., Block, A., Hegenscheid, K., Völzke, H., Hoehn, D., Czisch, M., … Hibar, D. P. (2016). Subcortical brain alterations in major depressive disorder: findings from the ENIGMA Major Depressive Disorder working group. Molecular Psychiatry, 21(6), 806–812. https://doi.org/10.1038/mp.2015.69

63 Schnack, H. G., van Haren, N. E. M., Nieuwenhuis, M., Hulshoff Pol, H. E., Cahn, W., & Kahn, R. S. (2016). Accelerated brain aging in schizophrenia: A longitudinal pattern recognition study. Am. J. Psychiatry, 173(6), 607–616.

64 Selvaraju, R. R., Cogswell, M., Das, A., Vedantam, R., Parikh, D., & Batra, D. (2017). Grad-CAM: Visual Explanations from Deep Networks via Gradient-Based Localization. 2017 IEEE International Conference on Computer Vision (ICCV), 618–626. https://doi.org/10.1109/ICCV.2017.74

65 Sinclair, D. A., & Oberdoerffer, P. (2009). The ageing epigenome: damaged beyond repair? Ageing Research Reviews, 8(3), 189–198. https://doi.org/10.1016/j.arr.2009.04.004

66 Sun, H., Paixao, L., Oliva, J. T., Goparaju, B., Carvalho, D. Z., van Leeuwen, K. G., Akeju, O., Thomas, R. J., Cash, S. S., Bianchi, M. T., & Westover, M. B. (2019). Brain age from the electroencephalogram of sleep. Neurobiology of Aging, 74, 112–120. https://doi.org/10.1016/j.neurobiolaging.2018.10.016

67 Teeuw, J., Ori, A. P. S., Brouwer, R. M., de Zwarte, S. M. C., Schnack, H. G., & Hulshoff Pol Hilleke E and Ophoff, R. A. (2021). Accelerated aging in the brain, epigenetic aging in blood, and polygenic risk for schizophrenia. Schizophr. Res., 231, 189–197.

68 Thompson, P. M., Jahanshad, N., Ching, C. R. K., Salminen, L. E., Thomopoulos, S. I., Bright, J., Baune, B. T., Bertolín, S., Bralten, J., Bruin, W. B., Bülow, R., Chen, J., Chye, Y., Dannlowski, U., de Kovel, C. G. F., Donohoe, G., Eyler, L. T., Faraone, S. v, Favre, P., … ENIGMA Consortium. (2020). ENIGMA and global neuroscience: A decade of large-scale studies of the brain in health and disease across more than 40 countries. Translational Psychiatry, 10(1), 100. https://doi.org/10.1038/s41398-020-0705-1

69 van Erp, T. G. M., Walton, E., Hibar, D. P., Schmaal, L., Jiang, W., Glahn, D. C., Pearlson, G. D., Yao, N., Fukunaga, M., Hashimoto, R., Okada, N., Yamamori, H., Bustillo, J. R., Clark, V. P., Agartz, I., Mueller, B. A., Cahn, W., de Zwarte, S. M. C., Hulshoff Pol, H. E., … Turner, J. A. (2018). Cortical Brain Abnormalities in

4474 Individuals With Schizophrenia and 5098 Control Subjects via the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) Consortium. Biol. Psychiatry, 84(9), 644–654.

70 van Gestel H., Franke K., Petite J., Garnham J., S. C. and, Helmick C., Johnson K., Alda M., U. R. and, & Hajek T. AO - Hajek, T. O. H. O.-0003-0281-8458. (2019). Brain age in bipolar disorders: Effects of lithium treatment. Aust. N. Z. J. Psychiatry, 53(12), 1179–1188.

71 Velosa, J., Delgado, A., Finger, E., Berk, M., Kapczinski, F., & Azevedo Cardoso, T. (2020). Risk of dementia in bipolar disorder and the interplay of lithium: a systematic review and meta-analyses. Acta Psychiatr. Scand., 141(6), 510–521.

72 Ventriglio, A., Gentile, A., Bonfitto, I., Stella, E., Mari, M., Steardo, L., & Bellomo, A. (2016). Suicide in the Early Stage of Schizophrenia. Frontiers in Psychiatry, 7, 116. https://doi.org/10.3389/fpsyt.2016.00116

73 Verhoeven, J. E., Révész, D., Epel, E. S., Lin, J., Wolkowitz, O. M., & Penninx, B. W. J. H. (2014). Major depressive disorder and accelerated cellular aging: results from a large psychiatric cohort study. Mol. Psychiatry, 19(8), 895–901.

74 Voisey J., Lawford B.R., Morris C.P., Wockner L.F., Noble E.P., Young R.M., & Mehta D. AO - Morris, C. P. O. H. O.-0001-8976-619x. (2017). Epigenetic analysis confirms no accelerated brain aging in schizophrenia. Npj Schizophrenia, 3(1), 26.

75 Wachter, S., Mittelstadt, B., & Russell, C. (2018). Counterfactual Explanations without Opening the Black Box: Automated Decisions and the GDPR. Harvard Journal of Law & Technology.

76 Walker, L. C., & Herndon, J. G. (2010). Mosaic aging. Medical Hypotheses, 74(6), 1048–1051. https://doi.org/10.1016/j.mehy.2009.12.031

77 Walton, E., Hibar, D. P., van Erp, T. G. M., Potkin, S. G., Roiz-Santiañez, R., Crespo-Facorro, B., Suarez-Pinilla, P., van Haren, N. E. M., de Zwarte, S. M. C., Kahn, R. S., Cahn, W., Doan, N. T., Jørgensen, K. N., Gurholt, T. P., Agartz, I., Andreassen, O. A., Westlye, L. T., Melle, I., Berg, A. O., … Ehrlich, S. (2017). Positive symptoms associate with cortical thinning in the superior temporal gyrus via the ENIGMA Schizophrenia consortium. Acta Psychiatrica Scandinavica, 135(5), 439–447. https://doi.org/10.1111/acps.12718

78 Yatham, L. N., Kennedy, S. H., Parikh, S. v, Schaffer, A., Beaulieu, S., Alda, M., O'Donovan, C., MacQueen, G., McIntyre, R. S., Sharma, V., & others. (2013). Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disord., 15(1), 1–44.

Chapter 2: Brain age in mood and psychotic disorders: a systematic review and meta-analysis

Pedro L. Ballester[1]; Maria T. Romano[2]; Taiane de A. Cardoso[3]; Stefanie Hassel[4,5], Stephen C. Strother[6,7], Sidney H. Kennedy[8,9], Benicio N. Frey[3,10]

1. Neuroscience Graduate Program, McMaster University, Hamilton, Ontario, Canada

2. Integrated Science Undergraduate Program, McMaster University, Hamilton, Ontario, Canada

3. Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada

4. Mathison Centre for Mental Health Research and Education, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

5. Department of Psychiatry, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

6. Rotman Research Institute, Baycrest, Toronto, ON, Canada

7. Department of Medical Biophysics, University of Toronto, ON, Canada

8. Centre for Depression and Suicide Studies, and Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada

9. Department of Psychiatry, University of Toronto

10. Mood Disorders Treatment and Research Centre, and Women's Health Concerns Clinic, St. Joseph's Healthcare, Hamilton, Canada

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Abstract

Objective: To evaluate whether accelerated brain aging occurs in individuals with mood or psychotic disorders.

Methods: A systematic review following PRISMA guidelines was conducted. A meta-analysis was then performed to assess neuroimaging-derived brain age gap in three independent groups: (1) schizophrenia and first-episode psychosis, (2) major depressive disorder, and (3) bipolar disorder.

Results: A total of 18 papers were included. The random effects model meta-analysis showed a significantly increased neuroimaging-derived brain age gap relative to age-matched controls for the three major psychiatric disorders, with schizophrenia (3.08; 95%CI [2.32; 3.85]; $p<0.01$) presenting the largest effect, followed by bipolar disorder (1.93; [0.53; 3.34]; $p<0.01$) and major depressive disorder (1.12; [0.41; 1.83]; $p<0.01$). Brain age gap was larger in older compared to younger individuals.

Conclusion: Individuals with mood and psychotic disorders may undergo a process of accelerated brain aging based on patterns captured by neuroimaging data. The brain age gap tends to be more pronounced in older individuals, indicating a possible cumulative biological effect of illness burden.

Keywords: accelerated brain aging; meta-analysis; schizophrenia; bipolar disorder; major depressive disorder.

Summations:

- Signs of neuroimaging-derived brain age gaps are identifiable in schizophrenia, bipolar disorder and major depressive disorder.
- The brain age gap is differentially expressed in each disorder, with schizophrenia presenting the largest gap, followed by bipolar disorder and then major depressive disorder.
- The brain age gap is positively associated with age, contributing to the hypothesis of accelerated brain aging.

Limitations:

- Variable training dataset sizes for each study are not accounted for.
- In some studies the datasets overlap.
- The limitations of each independent study were not considered during the meta-analysis.

2.1 Introduction

Mood and psychotic disorders are mental health conditions associated with high rates of early disability and poor quality of life (1–3). These disorders tend to follow a chronic course with periods of clinical remission alternating with periods of episodic worsening. It has been postulated that repeated illness episodes are associated with brain rewiring, which may eventually diminish responsiveness to treatment (i.e., kindling effect) (4). After years of neuroimaging research suggesting brain changes in individuals with psychiatric disorders (5), recent findings support that brain age estimates in these groups do not match their chronological age due to an illness-related process of accelerated brain aging (6). The difference between predicted brain age and chronological age is called the *brain age gap* or brain-predicted age difference (brain-PAD). Beyond neuropsychiatric disorders, a greater brain-PAD has been associated with other factors, such as increased alcohol and tobacco use (7), lower fluid intelligence, and increased mortality risk (8). Given its complex nature, there are disagreements in the field as to the presence and extent of accelerated brain aging in mood (9,10) and psychotic disorders (11).

A hypothesis of accelerated brain aging is consistent with the current conceptualization of neuroprogression. Neuroprogression is defined by pathological brain rewiring associated with changes in cognition, functioning, inflammation, and neuroanatomy (12,13). Proposed mechanisms to explain accelerated aging in mood (14) and psychotic disorders (15) include telomere length (16), the epigenetic clock (17), and inflammation levels (18). Although there is considerable synergism among these studies examining peripheral markers of aging, brain imaging is ideally suited to investigate

localized and/or circuit-level neurophysiological abnormalities (19,20). Considering neuroimaging-based aging measurements, a recent review acknowledged the important prognostic information contained in brain age estimates (21), while another suggested that brain-PAD will become a valuable aging biomarker (22). However, these reviews have not led to any quantitative conclusions about the current state of the field. The question of whether neuroanatomical accelerated brain aging is present in mood and psychotic disorders and its effect size remain unanswered. In summary, while some studies support the claim of accelerated brain aging in mood and psychotic disorders, others disagree and instead claim accelerated brain aging does not occur in major depressive disorder (MDD) (10), bipolar disorder (BD) (9), or schizophrenia (SCZ) (11).

Given the burgeoning literature investigating accelerated brain aging in mood and psychotic disorders using neuroimaging data, including both functional and structural imaging, a systematic review and aggregation of current findings is needed. Therefore, the aims of this systematic review and meta-analysis are: (1) to examine whether accelerated brain aging occurs in mood and psychotic disorders and, if so, to estimate the extent of the phenomenon for each of these major psychiatric disorders; (2) to discuss the main methodological limitations of the available studies and the future directions in this field. We hypothesized that MDD, BD, and SCZ would all present signs of accelerated brain aging with distinct magnitudes.

2.2 Methods

2.2.1 Search strategy

We followed the PRISMA guidelines for systematic reviews and meta-analyses. The search was conducted on February 1st, 2021 in the databases PsycINFO, Embase, and PubMed without any year or language restrictions. Papers that fit broad criteria including mood or psychotic disorders and the evaluation of brain age were included in the search strategy, which comprised of the following terms: (brain aging OR brain age) AND (mood disorders OR psychotic disorders OR major depressive disorder OR bipolar disorder OR schizophrenia OR psychosis). The actual search included variants of these terms which are included in the supplementary material. This review was registered in PROSPERO under the identification number CRD42020160127.

The search returned a total of 1,084 papers (684 after duplicate removals). We included cross-sectional, longitudinal, and case-control studies, removing systematic reviews, other reviews, case reports, descriptive studies, and meta-analyses. Studies were only included if they had neuroimaging-derived estimates of brain-PAD in SCZ, MDD, or BD compared to healthy controls (HC) with no history of neurological disease or psychiatric disorders. Neuroimaging data included any acquisition protocol and/or modality, such as structural, functional, or diffusion magnetic resonance imaging (MRI). All papers were reviewed for inclusion or exclusion by two independent reviewers (PLB, MTR), and conflicts were resolved by consensus: If consensus could not be achieved, the decision was made by a third reviewer (BNF). Additionally, MTR and PLB searched the

references of all included papers, and through reference check and consensus did not include any additional papers. Figure 1 details the search procedures.

2.2.2 Data extraction

We extracted the following data: aim of the study, study design, participant demographics, sample size, inclusion and exclusion criteria, clinical assessments, main results on brain age, and confounding factors. Data extraction was performed by PLB and MTR. In the case of brain age prediction, most studies followed a standard machine learning protocol, with HC used for model training, validation, and testing and cases used only for testing. Therefore, for the meta-analysis, we extracted the results belonging to the experiments in test datasets (HC and cases) of each study. In studies where no independent HC test set was available and results were reported using a robust validation procedure (e.g. cross-validation), those results were used. Some studies only reported the mean brain-PAD difference between cases and controls or only showed the brain-PAD for the case group and not for the HC group. In these instances, we emailed the corresponding authors to request the information from the HC group. In the case of no-reply or the lack of additional information, the studies were described in the review but could not be included in the meta-analyses. Where studies reported results for multiple brain age prediction models, the one with the lowest error in the HC sample was used.

2.2.3 Statistical analyses

All statistical analyses were conducted using R (version 3.6.3) with the *meta* package (version 4.13-0). Both fixed and random effect models were used to evaluate brain-PAD for each diagnosis independently. The mean and standard deviation of brain-PAD of cases and controls were used. Therefore, the residuals of the prediction models in each original study are compared. Our analyses were executed using the *metacont* function from the *meta* package, with default optional parameters.

2.3 Results

After title and abstract screening (*n = 684*), followed by full-text assessment for eligibility criteria (*n = 53)*, 18 papers remained and were included in the systematic review (Figure 1). Within the included studies, some have analyzed brain-PAD only in SCZ (n=5) (23–27), only in BD (28), and only in MDD (n=4) (10,29–31). Other studies investigated brain-PAD in more than one disorder: SCZ and BD (n=4) (9,32–34), SCZ and MDD (n=3) (35–37), and SCZ, BD, and MDD (6). Details for each study included are listed in Table 1. A more complete version of Table 1 is available in the Supplement (Table S1). The meta-analyses included a total of n=15 studies. Three studies could not be meta-analyzed due to insufficient information (10,34,35). In addition, three studies investigated two independent samples of the same disorder (28,29,32) and, therefore, these studies were included twice in the meta-analyses and forest plots.

Most studies included papers which relied on using traditional machine learning methods for brain age predictions, such as relevance vector machines (38), support vector

machines, or XGBoost (39) for their solutions. Some exceptions involve the use of deep neural networks (36) and more sophisticated techniques to improve training procedures, such as transfer learning (26). Procedures for the estimation of brain age varied considerably, as some studies used parcellations followed by volumetric information extraction (6) while others used structural covariance (37). The common factor in all studies were how group-level brain-PAD was generated: (1) models were trained with HC, (2) trained models were used to estimate brain age at the individual level for both cases and controls, (3) brain age estimates were subtracted by chronological age yielding individualized brain-PADs, (4) brain-PADs were averaged by groups and compared. Of note, some studies have independent test sets for both cases and controls, which, in turn, led to mean brain-PAD values ≠ 0 for healthy controls (33,36). Nonzero brain-PADs for HC may happen when the mean chronological age of the HC training and HC test sets differ.

2.3.1 Systematic review of brain-PAD in psychotic disorders (schizophrenia and first-episode psychosis)

We identified 13 studies that assessed brain-PAD in SCZ or first-episode psychosis (FEP), with a total of n=3,169 cases (6,9,23–27,32–37). Brain-PAD scores were significantly greater in individuals with psychotic disorders in all except two studies (27,32).

The first recorded study to investigate brain-PAD in psychotic disorders included participants with SCZ between the ages of 18 and 65 (35). Koutsouleris et al. (2014) was

the first study to propose the current method of brain age prediction with machine learning for brain-PAD assessments in SCZ (35,40). The main finding of their research, that SCZ presented a brain-PAD, has been replicated extensively. One of these studies had a longitudinal, repeated-measures design, where Schnack et al. (2016) found that acceleration of brain aging was not constant, and that brain-PAD increased soon after the onset of SCZ. After about five years, however, the effects of accelerated brain aging were no longer significant (23); Hence, the brain aging rate was normalized to 1 year/year.

Findings for SCZ have been replicated in increasingly more robust studies. Shahab et al. (2019), collected two independent samples of individuals with SCZ and tested the hypothesis of brain-PAD in both, finding brain-PADs of +7.8 and +6.12 years. The largest study of brain age in SCZ to date also identified similar patterns of brain-PAD (6). In an automated surface-based morphometry study, Kaufmann et al. (2019) trained an XGBoost model using thickness, area, and volume features extracted from MRI data (6). The training set consisted of 35,474 individuals and independent models were trained for each sex. In this analysis, a significant brain-PAD was observed (Cohen's $d = 0.51$). In the same study, using a separate test, brain age prediction models trained using only features from specific regions of the brain showed no increased brain-PAD in cerebellar or subcortical regions, but a large effect in the frontal lobe (Cohen's $d = 0.70$). This might suggest that the neuroanatomical features of brain aging are not homogeneously distributed across the brain, and each region may display an independent aging pattern.

A subset of studies investigated accelerated brain aging after the first psychotic episode. Hajek et al. (2019) measured differences in brain-PAD between first-episode

schizophrenia-spectrum disorders (FES) and HC groups (25). This study recruited n=43 participants with FES and found a statistically significant mean brain-PAD difference of +2.65 years. Another study defined patients with FEP based on factors such as obesity and dyslipidemia, and reported a higher brain-PAD in individuals with FEP compared to controls. In addition, obesity was shown to contribute an additive effect in FEP, such that brain-PAD scores were highest in participants with a combination of FEP and obesity reaching a gap of 3.83 years (24). This finding suggests that obesity is an important factor to include when studying FEP and brain age. Authors also reported no effects of psychotropic medication use or other clinical variables, such as history of hypertension, smoking status, and glucose levels (27).

Another approach used to determine brain age acceleration in a younger sample was the Neural Maturation Index (NMI), which characterizes typical brain maturation patterns and identifies those that deviate from the norm. In this study, an association between SCZ and advanced NMI scores was identified, indicating accelerated neural maturation in SCZ (27). Although used for a different purpose than the straightforward comparison of brain-PAD across groups, the values used by the structural component of NMI are directly comparable to brain age. This study involved participants between the ages of 16 and 22, with a younger mean age and a considerably narrower age range with respect to other studies. Alongside the evidence for FEP, these are consistent findings of accelerated brain aging from very early on in the course of illness.

A set of novel methods for brain age estimation has also been used in the context of SCZ. Chen et al. (2020) showed that models after transfer learning, a machine learning

technique used to leverage models pre-trained in other databases and/or data types, and models trained from scratch for brain age prediction with diffusion MRI led to similar brain-PAD differences between SCZ and HC (26). Structural covariance networks were also used to assess brain-PAD in SCZ, yielding similar results to other approaches (mean brain-PAD difference = 5.52 years) (37). Finally, deep neural networks were also used for brain age prediction, achieving distinct brain-PAD differences between SCZ and HC depending on how well the model was fit to the data (36). Models with a looser fit tended to better discriminate between SCZ and HC, while the best model in terms of mean absolute error (MAE) demonstrated a brain-PAD difference of 3.04.

2.3.2 Meta-analysis of brain-PAD in psychotic disorders (schizophrenia and first-episode psychosis)

The meta-analysis revealed significant brain-PAD differences between individuals with psychotic disorders and HC (Figure 2). The significant findings are demonstrated by both the *fixed effects model* (2.90; 95% CI [2.59; 3.21]; $p<0.01$) and by the *random effects model* (3.08; 95% CI [2.32; 3.85]; $p<0.01$). Another interesting outcome of this meta-analysis is that brain-PAD is also significant in FEP, which suggests that accelerated brain aging may occur early in the course of the illness.

2.3.3 Systematic review of brain-PAD in bipolar disorder

We identified six studies that investigated brain-PAD in BD, including a total of n=938 cases. All studies assessed brain-PAD cross-sectionally at a single time point.

Individually, the results have been contradictory, with two studies reporting non-significant results (9,32), three describing significant differences between groups (6,33,34), and one showing conflicting results based on current medication use (28). Importantly, 49% of the included sample comes from a single large study (6).

Nenadić et al. (2017) analyzed brain-PAD in BD based on previous findings of brain-PAD in SCZ (9,35). Therefore, in an attempt to both replicate previous findings of SCZ and expand them to BD, they predicted brain age for HC, BD, and SCZ, finding no increase of brain-PAD in BD with respect to HC. This small study (n=22 cases), involving euthymic BD participants aged 21 to 58, was likely underpowered. Shahab et al. (2019) conducted a similar experiment including euthymic participants with BD I or II (n=53) (32). Consistent with Nenadić et al. (2017), no differences between BD and HC were identified. Additionally, there were no differences between BD participants with and without psychotic features during an episode and brain-PAD.

Contrasting the negative results observed in smaller studies, a significant association between brain-PAD and BD were found in larger studies. For example, Kaufmann et al. (2019) included several databases, for a total of n=459 participants with BD (6). By comparing cases with an age-matched subset of HC participants, they identified a significant mean difference of brain-PAD of +2.07 years. A study by Van Gestel et al. (2019) divided participants from the BD sample into two groups (n= 84 BD), based on the presence or absence of current lithium treatment. In the group receiving lithium treatment, there were no statistically significant brain-PAD differences compared to HC (mean brain-PAD difference = +0.98). However, statistically significant differences were

evident in the group not receiving lithium treatment (mean brain-PAD difference= +5.11). These findings suggest a possible role of lithium in preventing accelerated brain aging, but given the cross-sectional study design, no definite conclusions can be drawn. Finally, a recent study conducted by Tønnesen et al. (2020) explored the use of white matter extracted by diffusion imaging for brain age prediction (33). By training a model with all available white matter features, a mean brain-PAD difference of 2.75 years was identified. However, the largest group difference in this study was observed when using only fractional anisotropy data, with a mean brain-PAD difference of 3.44 years.

In an attempt to capture different characteristics during brain age prediction, Rokicki et al. (2020) built a machine learning model from white matter variables captured by diffusion MRI (n=135 BD) (34). The results supported previous findings for BD in larger sample sizes, where the BD group showed a larger brain-PAD than HC (+1.6). This model, built with a different modality and thus taking into account a different set of features, reinforces the robustness of previous findings of brain-PAD in BD.

2.3.4 Meta-analysis of brain-PAD in bipolar disorder

Figure 3 summarizes the studies that investigated brain age in BD. Our results suggest that there is a process of accelerated brain aging in BD, as demonstrated by the *fixed effects model* (2.12; 95% CI [1.46; 2.77]; $p<0.01$) and the *random effects model* (1.93; 95% CI [0.53; 3.34]; $p<0.01$).

2.3.5 Systematic review of brain-PAD in major depressive disorder

The evidence for accelerated brain aging in MDD has been somewhat contradictory. From the seven identified studies, three reported increased brain-PAD (29,30,35) and the other four reported non-significant differences (6,31,36,37). Of note, regardless of the significance of findings, all included studies reported a positive brain-PAD difference between MDD and control groups. In total, n=3,565 cases were included across all included studies. However, about 75% of the sample came from a single large study containing n=2,675 cases (30).

Koutsouleris et al. (2014) assessed brain aging in MDD, SCZ, borderline personality disorder, and an additional group with individuals at-risk for psychosis. SCZ (*n = 141*) presented the largest brain-PAD difference, followed by MDD (*n = 104*). The training set consisted of *800* healthy controls, for which their estimated age was calculated using an average of repeated nested cross-validation predictions when the individual was out of the training set. To the best of our knowledge, this was the first accelerated brain aging study conducted in MDD and also the first to find statistically significant brain-PAD differences between HC and MDD. Subsequently, a study with MDD using an MRI trained relevance vector regression model using 743 HC used the model to estimate brain age in the MDD group (n=38) and in an independent control group (n=40). Possibly due to the small sample size, there were no significant differences between groups, but participants in the MDD group presented a mean brain-PAD of +0.41 years (10).

In a subsequent study with a larger sample size, Kaufmann et al (2019), investigated brain-PAD in MDD (n=208), but no significant differences between MDD and HC

groups were identified, although a mean brain-PAD of +0.86 was reported (6). Similarly, Bashyam et al. (2020; n=204) and Christman et al. (2020; n=194) assessed the brain-PAD in MDD, with both reporting non-significant findings in their adult samples (29,36). However, an analysis with a geriatric subset has shown a brain-PAD difference of +4.92 years in an older sample of MDD patients (29). These authors claim that the signs of accelerated brain aging in MDD are more visible later in life, an idea that seems to be supported by their findings. The largest study to date involves the ENIGMA consortium (30) involving n=2,675 cases aged 18-75. A mean brain-PAD difference of +0.88 years between MDD and HC was identified and considered statistically significant. After the adjustment for age, age^2, sex, and scanning site, this difference increased to +1.08 years.

Novel methods for brain age prediction were also proposed in the context of brain age in MDD. Kuo et al. (2020) used structural covariance networks to build a model that takes into account the relationship between brain regions to predict brain age (37). In this new approach, a large brain-PAD difference between MDD and HC was identified (+1.99) although it was not statistically significant, likely due to the small sample size (n=30). Similarly, Dunlop et al. (2021) used a less conventional approach to predict brain age by using resting-state functional MRI data (31). A large brain-PAD standard deviation in the MDD group was reported (12.65) due to the high mean absolute error of their final model. However, Dunlop et al. (2021) still report significant differences between MDD and HC, highlighting the potential of functional imaging as a biomarker for accelerated aging in MDD.

2.3.6 Meta-analysis of brain-PAD in major depressive disorder

Figure 4 summarizes the studies that investigated brain age in MDD. Results from the *fixed effects model* (0.95; [0.55; 1.35]; $p<0.01$) and the *random effects model* (1.12; [0.41; 1.83]; $p<0.01$) suggest that there is a process of accelerated brain aging in MDD. Even though the majority of the studies reported non-significant differences between MDD and HC, they all reported an increased brain-PAD in MDD, with the largest studies to date finding significant differences. It seems that the effect of accelerated brain aging in MDD is less pronounced than it is in psychosis or BD.

2.3.7 Association between age and brain-PAD

Due to the conceptualization that brain-PAD is linked to an accelerated brain aging process, one study analyzed brain-PAD in older participants independently from younger ones (29). In this study, brain-PAD was noticeable in the older, but not in the younger sample. These findings are also consistent with epigenetic studies that showed a larger brain-PAD in older individuals with BD (41). The association of brain-PAD with age is already known to exist, as part of the current standard of procedures for the estimation of brain-PAD is the correction for age. However, the correction mainly targets the effect of prediction bias that comes from age overestimation of participants aged below the training set age mean and underestimation of those above it (42). Therefore, even after correction for age effects due to the prediction biases, a more pronounced effect in older cases should be present. All papers included in the meta-analysis were also included in

this analysis, with the exception of two studies that did not provide the age standard deviation of the case sample (27,36).

Most studies in mood and psychotic disorders have investigated brain-PAD across the lifespan without creating subgroups. With that in mind, we investigated whether brain-PAD was positively correlated with the average age of the case groups across studies. The brain-PAD difference between cases and controls was normally distributed within each diagnostic group, as were the mean ages in the studies. Thus, a Pearson correlation between those two variables was conducted. Positive associations were identified for all groups, with statistical significance observed for SCZ ($r(8)=0.697$ [0.120; 0.922]; $p<0.03$) and MDD ($r(4)=0.815$ [0.009; 0.979]; $p<0.05$), but not BD ($r(4)=0.213$ [-0.723 0.874]; $p=0.684$; Figure 5).

2.4 Discussion

The results from our meta-analyses show that there are signs of accelerated brain aging in mood and psychotic disorders with different magnitudes. For instance, SCZ expresses the highest levels of brain-PAD (3.08 years), followed by BD (1.93 years) and MDD (1.12 years). Our findings also indicate that brain-PAD is more pronounced in older individuals, a tendency observed across all major psychiatric disorders.

Findings from our meta-analysis provide support for the neuroprogression theory. Based on this theory, mood and psychotic disorders have a progressive nature consisting of a series of clinical, functional, and biological changes during the course of illness (13). While the genetic and molecular underpinnings of neuroprogression in major psychiatric

disorders still remain unclear, current research suggests a role of cumulative stress in epigenetic aging (43), which could be one of the underlying factors for the observed neuroanatomical changes that lead to a higher brain-PAD (44). These ideas are also consistent with our findings of a more pronounced brain-PAD in older compared to younger samples. Despite its progressive nature, there is evidence to suggest that signs of brain-PAD may be already present early in the course of illness. For instance, Chung et al. (2018) conducted a longitudinal study on youth at clinical high risk to develop psychosis and found that an increased brain-PAD in those between 12-17 was significantly associated with the onset of psychosis at follow-up (45). Beyond neuroprogression of major psychiatric disorders, other factors may play a role in increasing brain-PAD. It is important to consider that machine learning models take into account neuroanatomical features to make age predictions, and thus are bound to be confounded by lifestyle, comorbidities, treatment history, and genetic predispositions, most of which can be difficult to control for (7). Brain-PAD has been strongly linked to tobacco and alcohol use (7); future research is likely to identify other possible associations such as traumatic events, obesity and comorbid medical conditions. Not only are these relevant factors for any population, but they are particularly important when investigating brain-PAD in populations with neuropsychiatric disorders (46,47). Medication use is also likely a significant factor in brain-PAD. Most available studies, however, do not thoroughly assess the effects of psychotropic medications, which have been shown to have neuroprotective effects (48–50), but see (51).

Other methodologies and approaches have been used to assess accelerated brain aging in mood and psychotic disorders, some of which have similar findings to neuroimaging-derived brain-PAD. Kochunov et al. (2013) used regression models with diagnosis-by-age interaction to assess fractional anisotropy (FA) in individuals with SCZ as a proxy for the detection of age-related decline of white matter (52). They showed a significant age-related trajectory between SCZ and HC groups, which was replicated in a subsequent study (53). Using the same methodology, they found no differences between MDD and HC. Following a similar approach, Sacchet et al. (2017) found a significant group x age interaction in the putamen volume in MDD, which given the context of previous studies, supports the hypothesis of a more localized accelerated brain age in the disorder (54). At the molecular level, the epigenetic clock has also been investigated in the context of accelerated brain aging by extracting DNA methylation data from postmortem brain tissue (11,55,56). Some studies have identified no changes in the epigenetic clock in the superior temporal gyrus (11) and frontal cortex (57) in SCZ. Contradicting these findings, Fries et al. (2020) identified accelerated aging in the hippocampus of BD (58), while Han et al. (2020) also identified accelerated aging in the frontal and cingulate cortex for MDD (56). Findings from the epigenetic clock may be specifically relevant clinically, since a gap in epigenetic age has been linked to increased risk for diseases such as cancer and dementia, and to increased mortality risk (17). Although both epigenetic aging and neuroimaging-derived brain age are considered biological markers of aging, to our knowledge the relationship between these two variables has not been explored. Previous studies have demonstrated that different

biological age estimates, such as telomere length, epigenetic clock, and neuroimaging-derived brain age, may be mismatched in individuals (8,59), thus findings from epigenetic age may not necessarily translate into neuroimaging.

Our study should be interpreted in the light of some limitations. First, there was considerable variability in terms of the training dataset size and methods used for brain age prediction. In order to provide a fair comparison, we only used the size of the test sets in the meta-analysis, but this may not necessarily reflect the total sample that was used to generate a better prediction model. In addition, limited independence of samples, some of which share HC groups (28) or are reported in the same publication, is a limitation (32). On that note, the total overlap between studies is also unclear, as most studies use several distinct datasets to train and test the models. Some studies apply brain-PAD coefficients corrected by age during group comparison and others correct brain age predictions beforehand, this is a particularly important consideration in the age effects section. It is also possible that some studies have underestimated older participants and thus led to a smaller effect of brain-PAD in those individuals. This effect, if corrected, would likely increase the relationship between brain-PAD and age , as older individuals tend to have an underestimated brain age (42). Despite these limitations, this is the first meta-analysis to integrate the findings of neuroimaging-derived brain age in mood and psychotic disorders.

Future studies should take into account lifestyle factors, medication use, substance use, and body mass index. Larger methodological papers should assess not only the quality of different approaches for brain age prediction, but also their ability to

discriminate cases and controls. In addition, new studies should better investigate age effects in their samples and assess variables that might jointly explain its effects, such as age of onset, episode severity, number of episodes and medication use. Finally, new studies should use more sophisticated model explanations to understand what exactly the brain areas and circuits are that are driving the age gap at an individual level (60,61).

In conclusion, this systematic review and meta-analysis found evidence to support the hypothesis of significant accelerated brain aging in SCZ, MDD, and BD. The fact that brain-PAD differences are more pronounced in older subjects indicates a greater impact associated with cumulative illness burden.

Declarations of interest

P.L.B, M.T.R, T.A.C, S.H., S.C.S, S.H.K., and B.N.F report no conflicts of interest.

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Data availability statement

All data used for this work and the associated code to reproduce the experiments are available at GitHub (https://github.com/Ballester/brain-age-meta-analysis).

References

1. Lim K-L, Jacobs P, Ohinmaa A, Schopflocher D, Dewa CS. A new population-based measure of the economic burden of mental illness in Canada. Chronic Dis Can 2008;28:92–98.

2. McDonald KC, Bulloch AGM, Duffy A et al. Prevalence of bipolar I and II disorder in Canada. The Canadian Journal of Psychiatry 2015;60:151–156.

3. Frey BN, Vigod S, de Azevedo Cardoso T et al. The Early Burden of Disability in Individuals With Mood and Other Common Mental Disorders in Ontario, Canada. JAMA Netw Open 2020;3:e2020213.

4. De Witte P, Pinto E, Ansseau M, Verbanck P. Alcohol and withdrawal: from animal research to clinical issues. Neurosci Biobehav Rev 2003;27:189–197.

5. Schmaal L, Pozzi E, C Ho T et al. ENIGMA MDD: seven years of global neuroimaging studies of major depression through worldwide data sharing. Transl Psychiatry 2020;10:172.

6. Kaufmann T, van der Meer D, Doan NT et al. Common brain disorders are associated with heritable patterns of apparent aging of the brain. Nat Neurosci 2019;22:1617–1623.

7. Ning K, Zhao L, Matloff W, Sun F, Toga AW. Association of relative brain age with tobacco smoking, alcohol consumption, and genetic variants. Sci Rep 2020;10:10.

8. Cole JH, Ritchie SJ, Bastin ME et al. Brain age predicts mortality. Mol Psychiatry 2018;23:1385–1392.

9. Nenadić I, Dietzek M, Langbein K, Sauer H, Gaser C. BrainAGE score indicates accelerated brain aging in schizophrenia, but not bipolar disorder. Psychiatry Research: Neuroimaging 2017;266:86–89.

10. Besteher B, Gaser C, Nenadić I. Machine-learning based brain age estimation in major depression showing no evidence of accelerated aging. Psychiatry Research: Neuroimaging 2019;290:1–4.

11. McKinney B.C., Lin H., Ding Y., Lewis D.A. DNA methylation evidence against the accelerated aging hypothesis of schizophrenia. npj Schizophrenia 2017;3:13.

12. Passos IC, Mwangi B, Vieta E, Berk M, Kapczinski F. Areas of controversy in neuroprogression in bipolar disorder. Acta Psychiatr Scand 2016;134:91–103.

13. Kapczinski F, Berk M, da Silva Magalhães PV. Neuroprogression in Psychiatry. Oxford University Press, 2019https://play.google.com/store/books/details?id=2hqJDwAAQBAJ

14. Fries GR, Zamzow MJ, Andrews T, Pink O, Scaini G, Quevedo J. Accelerated aging in bipolar disorder: A comprehensive review of molecular findings and their clinical implications. Neurosci Biobehav Rev 2020;112:107–116.

15. Eyler LT, Jeste DV. Aging of the body and the brain in schizophrenia. Schizophr Res 2018;196:1–3.

16. Russo P, Prinzi G, Proietti S et al. Shorter telomere length in schizophrenia: Evidence from a real-world population and meta-analysis of most recent literature. Schizophr Res 2018;202:37–45.

17. Fransquet PD, Wrigglesworth J, Woods RL, Ernst ME, Ryan J. The epigenetic clock as a predictor of disease and mortality risk: a systematic review and meta-analysis. Clin Epigenetics 2019;11:62.

18. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol 2018;15:505–522.

19. Drevets WC. Neuroimaging studies of mood disorders. Biol Psychiatry 2000;48:813–829.

20. Keshavan MS, Collin G, Guimond S, Kelly S, Prasad KM, Lizano P. Neuroimaging in Schizophrenia. Neuroimaging Clin N Am 2020;30:73–83.

21. Franke K, Gaser C. Ten Years of BrainAGE as a Neuroimaging Biomarker of Brain Aging: What Insights Have We Gained? Front Neurol 2019;10:789.

22. Cole JH, Marioni RE, Harris SE, Deary IJ. Brain age and other bodily 'ages': implications for neuropsychiatry. Mol Psychiatry 2019;24:266–281.

23. Schnack HG, van Haren NEM, Nieuwenhuis M, Hulshoff Pol HE, Cahn W, Kahn RS. Accelerated brain aging in schizophrenia: A longitudinal pattern recognition study. Am J Psychiatry 2016;173:607–616.

24. Kolenic M, Franke K, Hlinka J et al. Obesity, dyslipidemia and brain age in first-episode psychosis. J Psychiatr Res 2018;99:151–158.

25. Hajek T, Franke K, Kolenic M et al. Brain age in early stages of bipolar disorders or schizophrenia. Schizophr Bull 2019;45:190–198.

26. Chen C-L, Hsu Y-C, Yang L-Y et al. Generalization of diffusion magnetic resonance imaging-based brain age prediction model through transfer learning. Neuroimage 2020;217:116831.

27. Truelove-Hill M., Erus G., Bashyam V. et al. A Multidimensional Neural Maturation Index Reveals Reproducible Developmental Patterns in Children and Adolescents. J Neurosci 2020;40:1265–1275.

28. Van Gestel H., Franke K., Petite J. et al. Brain age in bipolar disorders: Effects of lithium treatment. Aust N Z J Psychiatry 2019;53:1179–1188.

29. Christman S, Bermudez C, Hao L et al. Accelerated brain aging predicts impaired cognitive performance and greater disability in geriatric but not midlife adult depression. Transl Psychiatry 2020;10:317.

30. Han LKM, Dinga R, Hahn T et al. Brain aging in major depressive disorder: results from the ENIGMA major depressive disorder working group. Mol Psychiatry Published Online First: 18 May 2020. doi:10.1038/s41380-020-0754-0

31. Dunlop K, Victoria LW, Downar J, Gunning FM, Liston C. Accelerated brain aging predicts impulsivity and symptom severity in depression. Neuropsychopharmacology Published Online First: 25 January 2021. doi:10.1038/s41386-021-00967-x

32. Shahab S, Mulsant BH, Levesque ML et al. Brain structure, cognition, and brain age in schizophrenia, bipolar disorder, and healthy controls. Neuropsychopharmacology 2019;44:898–906.

33. Tønnesen S, Kaufmann T, de Lange A-MG et al. Brain Age Prediction Reveals Aberrant Brain White Matter in Schizophrenia and Bipolar Disorder: A Multisample Diffusion Tensor Imaging Study. Biol Psychiatry Cogn Neurosci Neuroimaging 2020;5:1095–1103.

34. Rokicki J, Wolfers T, Nordhøy W et al. Multimodal imaging improves brain age prediction and reveals distinct abnormalities in patients with psychiatric and neurological

disorders. Hum Brain Mapp Published Online First: 19 December 2020. doi:10.1002/hbm.25323

35. Koutsouleris N, Davatzikos C, Borgwardt S et al. Accelerated brain aging in schizophrenia and beyond: A neuroanatomical marker of psychiatric disorders. Schizophr Bull 2014;40:1140–1153.

36. Bashyam VM, Erus G, Doshi J et al. MRI signatures of brain age and disease over the lifespan based on a deep brain network and 14 468 individuals worldwide. Brain 2020;143:2312–2324.

37. Kuo C-Y, Lee P-L, Hung S-C et al. Large-Scale Structural Covariance Networks Predict Age in Middle-to-Late Adulthood: A Novel Brain Aging Biomarker. Cereb Cortex 2020;30:5844–5862.

38. Tipping ME. Sparse Bayesian Learning and the Relevance Vector Machine. J Mach Learn Res 2001;1:211–244.

39. Chen T, Guestrin C. Xgboost: A scalable tree boosting system. In: Proceedings of the 22nd acm sigkdd international conference on knowledge discovery and data mining. 2016, 785–794.

40. Kirkpatrick B, Messias E, Harvey PD, Fernandez-Egea E, Bowie CR. Is schizophrenia a syndrome of accelerated aging? Schizophr Bull 2008;34:1024–1032.

41. Fries GR, Bauer IE, Scaini G et al. Accelerated epigenetic aging and mitochondrial DNA copy number in bipolar disorder. Transl Psychiatry 2017;7:1283.

42. Beheshti I, Nugent S, Potvin O, Duchesne S. Bias-adjustment in neuroimaging-based brain age frameworks: A robust scheme. Neuroimage Clin 2019;24:102063.

43. Zannas AS, Arloth J, Carrillo-Roa T et al. Lifetime stress accelerates epigenetic aging in an urban, African American cohort: relevance of glucocorticoid signaling. Genome Biol 2015;16:266.

44. McEwen BS. Brain on stress: how the social environment gets under the skin. Proc Natl Acad Sci U S A 2012;109 Suppl 2:17180–17185.

45. Chung Y, Addington J, Bearden CE et al. Use of Machine Learning to Determine Deviance in Neuroanatomical Maturity Associated With Future Psychosis in Youths at Clinically High Risk. JAMA Psychiatry 2018;75:960.

46. Kessler RC, Nelson CB, McGonagle KA, Edlund MJ, Frank RG, Leaf PJ. The epidemiology of co-occurring addictive and mental disorders: implications for prevention and service utilization. Am J Orthopsychiatry 1996;66:17–31.

47. Regier DA, Farmer ME, Rae DS et al. Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) study. JAMA 1990;264:2511–2518.

48. Fossati P, Radtchenko A, Boyer P. Neuroplasticity: from MRI to depressive symptoms. Eur Neuropsychopharmacol 2004;14 Suppl 5:S503-10.

49. Yucel K, McKinnon MC, Taylor VH et al. Bilateral hippocampal volume increases after long-term lithium treatment in patients with bipolar disorder: a longitudinal MRI study. Psychopharmacology 2007;195:357–367.

50. Velosa J, Delgado A, Finger E, Berk M, Kapczinski F, Azevedo Cardoso T. Risk of dementia in bipolar disorder and the interplay of lithium: a systematic review and meta-analyses. Acta Psychiatr Scand 2020;141:510–521.

51. Voineskos AN, Mulsant BH, Dickie EW et al. Effects of Antipsychotic Medication on Brain Structure in Patients With Major Depressive Disorder and Psychotic Features: Neuroimaging Findings in the Context of a Randomized Placebo-Controlled Clinical Trial. JAMA Psychiatry 2020;77:674–683.

52. Kochunov P, Glahn DC, Rowland LM et al. Testing the Hypothesis of Accelerated Cerebral White Matter Aging in Schizophrenia and Major Depression. Biol Psychiatry 2013;73:482–491.

53. Kochunov P, Ganjgahi H, Winkler A et al. Heterochronicity of white matter development and aging explains regional patient control differences in schizophrenia: Regional Patient Control Differences in Schizophrenia. Hum Brain Mapp 2016;37:4673–4688.

54. Sacchet MD, Camacho MC, Livermore EE, Thomas EAC, Gotlib IH. Accelerated aging of the putamen in patients with major depressive disorder. J Psychiatry Neurosci 2017;42:164–171.

55. Horvath S, Raj K. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. Nat Rev Genet 2018;19:371–384.

56. Han LKM, Aghajani M, Clark SL et al. Epigenetic Aging in Major Depressive Disorder. Am J Psychiatry 2018;175:774–782.

57. Voisey J., Lawford B.R., Morris C.P. et al. Epigenetic analysis confirms no accelerated brain aging in schizophrenia. npj Schizophrenia 2017;3:26.

58. Fries GR, Bauer IE, Scaini G et al. Accelerated hippocampal biological aging in bipolar disorder. Bipolar Disord 2020;22:498–507.

59. Marioni RE, Harris SE, Shah S et al. The epigenetic clock and telomere length are independently associated with chronological age and mortality. Int J Epidemiol 2016;45:424–432.

60. Lundberg SM, Lee S-I. A Unified Approach to Interpreting Model Predictions. In: Guyon I, Luxburg UV, Bengio S, et al., eds. Advances in Neural Information Processing Systems 30. Curran Associates, Inc., 2017, 4765–4774.

61. Schulz M-A, Chapman-Rounds M, Verma M, Bzdok D, Georgatzis K. Inferring disease subtypes from clusters in explanation space. Sci Rep 2020;10:12900.

Figures

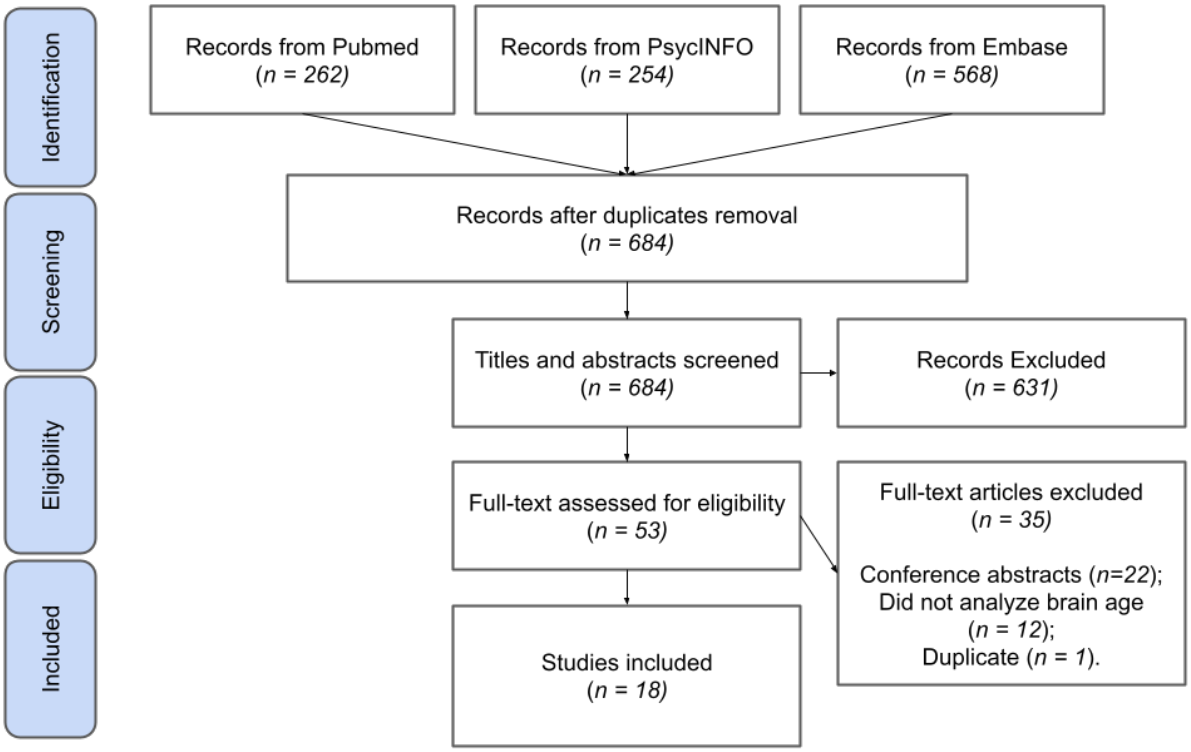

Figure 1. Flow diagram of identification, screening, and eligibility of the systematic review.

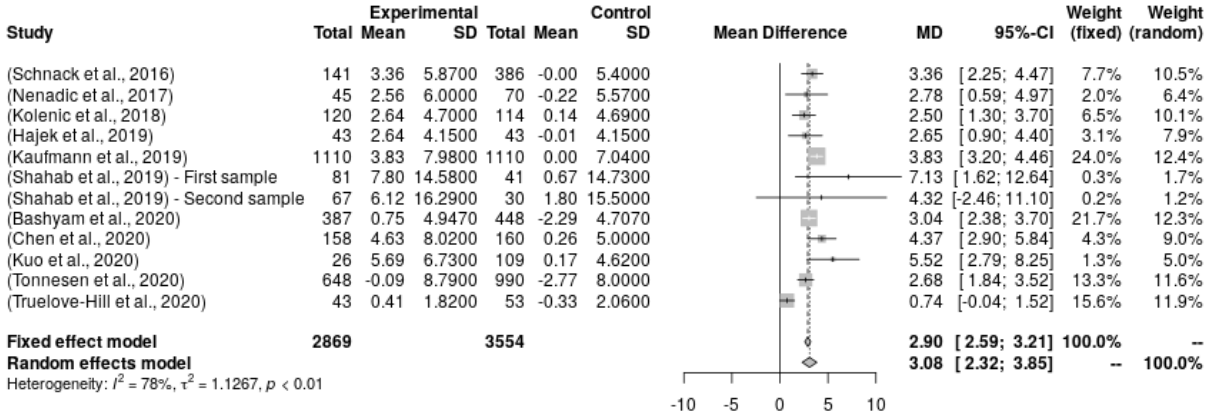

Figure 2. Forest plot for the difference of brain-PAD between psychotic disorders and healthy controls (SD: Standard deviation; MD: Mean difference).

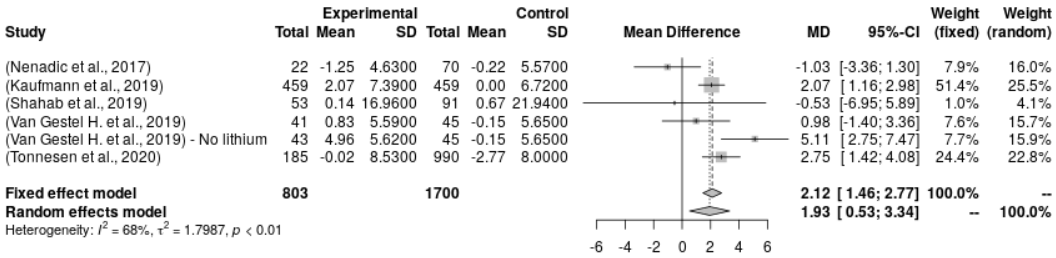

Figure 3. Forest plot for the difference of brain-PAD between bipolar disorder and healthy controls (SD: Standard deviation; MD: Mean difference).

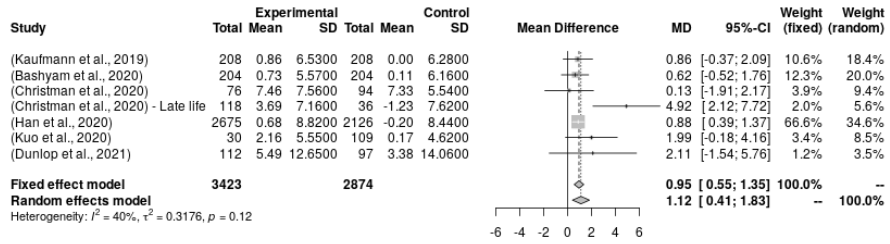

Figure 4. Forest plot for the difference of brain-PAD between major depressive disorder and healthy controls (SD: Standard deviation; MD: Mean difference).

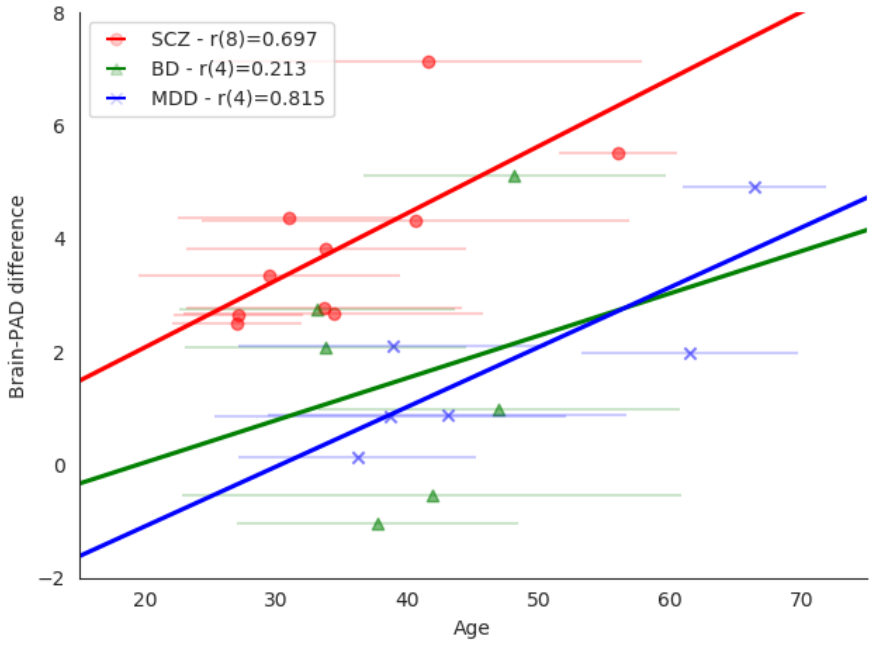

Figure 5. Brain-PAD association with age for SCZ, BD, and MDD. Horizontal error bars represent the standard deviation of age in each study.

Chapter 3: Predicting brain age at slice level: convolutional neural networks and consequences for interpretability

Pedro L. Ballester[1], Laura Tomaz da Silva[2], Matheus Marcon[2,3], Nathalia Bianchini Esper[3,4], Benicio N. Frey[5,6], Augusto Buchweitz[3,5,7], Felipe Meneguzzi[2]

1. Neuroscience Graduate Program, McMaster University, Hamilton, Ontario, Canada

2. School of Technology, Pontifical Catholic University of Rio Grande do Sul (PUCRS), Porto Alegre, Brazil

3. BRAINS - Brain Institute of Rio Grande do Sul, Porto Alegre, Brazil

4. Graduate School of Medicine, School of Medicine, Pontifical Catholic University of Rio Grande do Sul (PUCRS), Porto Alegre, Brazil

5. Mood Disorders Program, Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada

6. Women's Health Concerns Clinic, St. Joseph's Healthcare, Hamilton, ON, Canada

7. Graduate School of Psychology, School of Health and Life Sciences, Pontifical Catholic University of Rio Grande do Sul (PUCRS), Porto Alegre, Brazil

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Abstract

Problem: Chronological aging in later life is associated with brain degeneration processes and increased risk for disease such as stroke and dementia. With a worldwide tendency of aging populations and increased longevity, mental health, and psychiatric research have paid increasing attention to understanding brain-related changes of aging. Recent findings suggest there is a *brain age gap* (a difference between chronological age and brain age predicted by brain imaging indices); the magnitude of the gap may indicate early onset of brain aging processes and disease. Artificial intelligence has allowed for a narrowing of the gap in chronological and predicted brain age. However, the factors that drive model predictions of brain age are still unknown, and there is not much about these factors that can be gleaned from the black-box nature of machine learning models. The goal of the present study was to test a brain age regression approach that is more amenable to interpretation by researchers and clinicians.

Methods: Using convolutional neural networks we trained multiple regressor models to predict brain age based on single slices of magnetic resonance imaging, which included gray matter- or white matter-segmented inputs. We evaluated the trained models in all brain image slices to generate a final prediction of brain age. Unlike whole-brain approaches to classification, the slice-level predictions allows for the identification of which brain slices and associated regions have the largest difference between chronological and neuroimaging-derived brain age. We also evaluated how model predictions were influenced by slice index and plane, participant age and sex, and MRI data collection site.

Results: The results show, first, that the specific slice used for prediction affects prediction error (i.e., difference between chronological age and neuroimaging-derived brain age); second, the MRI site-stratified separation of training and test sets removed site effects and also minimized sex effects; third, the choice of MRI slice plane influences the overall error of the model.

Conclusion: Compared to whole brain-based predictive models of neuroimaging-derived brain age, slice-based approach improves the interpretability and therefore the reliability of the prediction of brain age using MRI data.

Keywords: brain age, deep learning, neuroimaging, convolutional neural networks, model interpretability

3.1 Introduction

Brain age prediction involves estimating chronological age based on information typically gleaned from neuroimaging data. The prediction may be referred to as the biological or neuroanatomical age of the brain. Although brain age can be computed from other approaches, such as the epigenetic clock from brain tissue (1) in this paper we use brain age as a synonym for neuroimaging-derived brain age. The difference between the predicted age and the actual chronological age is called brain age gap, which has been associated with a number of lifestyle factors (2) [e.g., tobacco and alcohol consumption (3), obesity (4), diabetes, schooling, physical activity (5), higher mortality risk (6), lower fluid intelligence, psychiatric disorders (7), and neurological diseases (8)].

Recent advances in machine learning, specifically on deep convolutional neural networks, have gradually improved brain age prediction by lowering prediction error (9). However, brain age prediction methods still receive criticism due to the lack of interpretability (10). The criticism stems from the limited information about what the model uses to predict brain age, and which regions might bias findings. Hidden biases and poor generalization are a recurrent theme in machine learning and deep learning research(11), including its medical imaging applications (12). Thus to fulfill the promise of translational research, AI needs to establish reliable and reproducible prediction methods, and to generate models that are more amenable to clinical interpretation (10). Identification of clinical neural markers and association with clinical and behavioral data may render AI applications more meaningful (10,13,14).

In this article, we report on a model developed for the PAC- 2019 brain age prediction competition. Our goal was to generate competitive predictions using meaningful neuroanatomical information. We developed a deep learning framework whose predictions draw on features from every single slice of brain imaging combined with average or linear regression models. The resulting model associates each slice with an independent age prediction for the same patient, allowing researchers to scrutinize the areas of the brain responsible for the overall brain-age gap. Our hypothesis was that our approach would help understand the behavior of brain age prediction at each part of the brain. We also believe that this method, alongside other approaches that try to move away from single predictions of brain age (15), may help us get a comprehensive picture of the parts and characteristics of the aging brain that inform prediction. Such picture should allow for identification of diverse, slice-level, and eventually voxel-level, neuroanatomical traits of age-related diseases.

3.2 Background

The known patterns of brain development associated with aging, such as a decline in gray matter volume (16), are readily identifiable by magnetic resonance imaging (MRI). These images are extensively used for diagnostic and research of disorders associated with brain tissue loss, such as Alzheimer's disease, Parkinsonian dementias, and Fronto-temporal lobe degeneration (17). More recently, machine learning techniques have been used to draw on the rich MR images to predict the brain age of healthy people (18), and the aging processes of neurodegenerative disorders (19). The mismatch in chronological

and brain age has been investigated in schizophrenia (8), bipolar disorder (20), and in association with factors associated with mortality risk, physical and mental fitness, and biological health (6).

Recent advances in deep learning models, specifically Convolutional Neural Networks (CNNs) achieve state-of-the- art performance in computer vision tasks (21), while requiring little to no prior hand-engineering of data. CNN architectures using 3D convolutions have been used to predict brain age with segmented GM and white matter (WM), and raw T1-weighted MRI scans (10,22). The use of 3D convolutions allows the model to take in whole-volume information for convolutional filtering operations, which, given enough data, learn feature detection and extraction. CNN models provide highly accurate predictions for regression and classification tasks on multiple medical imaging datasets (21,23).

CNN models have remarkable predictive power, but the results are typically difficult to interpret. Whereas manual feature selection in classic machine learning simplifies interpretation of the model's results, CNNs require further processing steps to interpret the model's decision processes due to the use of less processed data (24). Examples of interpretation-seeking mechanisms include saliency maps
(Zeiler Matthew D. and Fergus, 2014) and activation mappings (26), which aim to identify the regions in an image that are responsible for assisting model predictions, thus allowing for some visualization of key input features. These maps trace network outputs back to the input image voxels through the computation of their partial derivatives. For example, regression activation mapping applied to age prediction models on newborn

structural MRI generated brain maps of rapid growth during early development (27). Saliency maps have three key limitations. First, they depend on human validation, a time consuming task that also entails the potential for confirmation bias. a Second, these methods can produce results that are independent of model and data, and thus inadequate for model debugging and inspection (28). Finally, additional techniques must be used for combining individual subject saliency maps of into population-level visualizations (29).

3.3 Method

We tested several models and found that the ones with a RESNET18 architecture had a good trade-off between size and prediction error (30). In order to use it in our context with the dimensions of our input, we modified it in three simple ways: (1) the input size had one or two channels, depending on the experiment, (2) the kernel size from the average pool was changed from 7 to 4, (3) the final fully connected layer was changed from 512 to 1,024. The code to build this architecture as well as the steps to reproduce all experiments are available on GitHub (see data availability statement). The input was one brain slice with segmented GM in the first channel and white matter in the second channel. The segmentation was provided by PHOTON-AI[1] and we made no adjustments to it apart from scaling. The output of each model was a brain age estimation for a single segmented slice (GM, WM, or both) from the structural MRI. We illustrate our framework in Figure 1. The framework relies on three different, simultaneously-run models that are combined by three linear regression models and a final average. Each

[1] https://photon-ai.com/

model is trained independently to predict brain age from a single MRI slice and draws on different MRI slice orientation (coronal, sagittal, or axial) as input. Each of these models used the validation set to generate error estimates for each slice and each volume. We then used the error estimates to determine the importance of each slice for the model. All three views were combined to locate specific regions in the brain responsible for a particular classification based on the contribution of each slice for the brain age prediction, which provides an additional source of interpretation. The final age prediction for a single individual was calculated as follows:

$$a_x = M_x\left(s^i\right)\, i \ \in [0, S_x] \quad (1)$$

$$age = \frac{\frac{1}{e_a} * L_a(a_a) + \frac{1}{e_s} * L_s(a_s) + \frac{1}{e_c} * L_c(a_c)}{\frac{1}{e_a} + \frac{1}{e_s} + \frac{1}{e_c}} \qquad (2)$$

where x ∈ a,s,c represents the axial, sagittal, and coronal views, ax is the age vector for each slice for the subject, M_x is one of the CNN models, L_x is the linear regression model, ex is the error of model M_x in the validation set, and S_x is the total number of slices for an orientation x. Our rationale was that each model's contribution was inversely proportional to the error in the validation set with a weighted average. The influence of each slice for the final prediction is weighted by the linear regression model. This slice-level rationale can also be applied to understand the independent contributions of gray and white matter to the brain age estimate. While using gray or white matter alone causes the model to lose predictive power, it improves interpretability by estimating the independent gray and white matter contributions to the age prediction.

All segmented MRI scans for the dataset provided by the competition were shaped (121, 145, 121). To reduce the amount of empty space on the corners of the input, we removed 20% of the image corners, resulting in a (72, 88, 72) image. The input for the model is thus shaped (batch,c, 72, 88) where c = 1 when using either gray or white matter alone or c = 2 when using both types of brain tissue. For the coronal view, we zero-pad the image so that the (72, 72) slice also becomes (72, 88) to keep the consistency across all models. The participants from the PHOTON-AI dataset included healthy individuals from a wide age range, males and females, and from 17 different centers. We included basic demographic information about the sample in Table 1.

We trained the CNN models using an Adam Optimizer set with the learning rate at 6e − 4 and weight decay of 6e − 4. The training also used a sigmoid learning rate rampup for 20 epochs followed by a cosine rampdown until a total of 100 epochs. The batch size was set to 64. We conducted a data augmentation with Elastic Transform (31) with an α range between [28, 30], σ with a range of [3.5, 4.0], and p = 0.3, representing the scaling factors, the Gaussian spatial smoothing of the deformation field, and the probability of the augmentation being applied.; Random Affine transformations with 4.6 degrees, [0.98, 1.02] scale, and translation of 0.03; finally, we used a Random Tensor Channel Shift with the range of [−0.1, 0.1]. Some examples of the augmentation procedure can be seen in Figure 2. All data augmentation procedures were implemented in the medicaltorch framework[2].

[2] https://github.com/perone/medicaltorch

3.4 Results

For the competition, we achieved a mean absolute error of 4.44 years on the test set, with a Spearman correlation of −0.25 between the age estimates and chronological age. The model that won the competition achieved 2.90. Due to time restrictions, we employed axial slice predictions only, combining gray and white matter. In what follows, we present the results for the combined gray and white matter models for each separate orientation, the combined predictions; we also present how predictions improve interpretability and decrease model errors. The results of this article are based on predictions made on the competition's validation set. We did not have access to the test set's ground truth at any point during our experiments, prior to nor after the competition.

Instead of using the validation set to train the linear regression, we applied the regression to the training set, in order to avoid circular analysis. However, we believe this can limit the accuracy that otherwise would be achievable with the linear regression model. We leave the comparison of using the validation dataset and reusing the training set to train the linear regression model for future work with more data available, as we restricted ourselves to use data exclusively from the challenge for this study.

3.4.1 Combined Gray and White Matter

Our approach used slices for both gray and white matter in individual channels. The use of the two tissues simultaneously may have sacrificed obtaining more fine-grained information about brain aging from the each independent tissue, but it was done in favor of feeding additional data to the model. Gray and white matter were concatenated on the

first channel, resulting in an input of (2,72,88). We then trained and evaluated the model, and then assessed the effects of age, sex, and site on its predictions. In the sections, we explain the key findings from our experimental analysis.

3.4.1.1 Models for Different Views of the Brain Have Different Errors

We trained three independent models, taking the input from either axial, coronal, or sagittal views (Note: for the competition, in the interest of time, we used only the axial orientation information). After training, we estimated the error for each slice. The estimate is used to gauge how much each slice contributes to the prediction of brain age.

We identified a pattern, most present in axial and coronal models, but to some extent also visible in the sagittal. With more distal slices, the average prediction error seems to be higher. This could arguably be attributed to several reasons: (1) differences of brain matter across regions of the brain, (2) more age-related changes in some regions than others, and (3) the tendency of noise from the scanner to be concentrated on the extremities of the image (and this tendency is fairly visible in Figure 3).

The three models afforded different final prediction errors (Table 2, which we will further discuss in section 4.1.2. The models also resulted in different estimates for the contribution of slices for predicting brain age. Figure 3 shows the error variation for slices for the axial, coronal and sagittal slice models. We hypothesize that the differences in mean error may stem from: intrinsic and extrinsic factors that contributed to a poorer segmentation (and therefore an input of lesser quality); the randomness of the modeling process; and from sample heterogeneity for each of the regions with respect to age.

3.4.1.2 Final Predictions

Using Equations (1) and (2), we generated the predictions for the final dataset. After pre-training each of three models (one for each view), we evaluated every slice in the dataset and generated a dataset of predictions with a row for each individual and a column for model predictions of every slice. We trained the linear regression for the generated dataset using scikit-learn[3] library.

Table 2 shows the results for the three models. The sagittal slice prediction showed the lowest error, and it outperformed the outputs combined using Equation (2). We argue that this discrepancy in the error is due to the lack of another validation set for proper out-of-sample error estimation. Additionally, the differences present in a model trained with this dataset may not accurately translate to other data sources. To ensure that the sagittal slice prediction is actually superior to the axial and coronal slice predictions, the model needs to be further validated and trained using yet another dataset.

3.4.1.3 Age Effects

Brain age prediction methods usually perform better around the mean chronological age of the dataset. Research shows that models tend to overestimate brain age for participants younger than the mean, and underestimate it for participants older than the mean (32,33).

The behavior of our model's prediction error changed with respect to age, as shown in Figure 4. Not surprisingly, we found the same pattern of over and underestimation of age reported in the literature. One major implication of this type of error is the possibility

[3] https://scikit-learn.org/

of inserting biases when trained models are applied to external test sets that have a different age distribution than the training set. Thus, brain age prediction models should consider or aim for age-matched test sets (if possible), even if the model has been validated in external datasets. That way, if any underestimation or overestimation of age is happening with the target set, it can be identified and properly dealt with before any conclusions are drawn. Other means of mitigating the effect of testing models on datasets with different age ranges has been addressed elsewhere (33,34).

3.4.1.4 Site Effects

The dataset included contributions from 17 different sites. To investigate any biases associated with the different sites, we extracted the age and predicted age for each of our models and each of the 17 sites. We ran a two-tailed dependent t- test to compare age and predicted age among sites and found statistically significant differences for just 6 out of the 17 centers. The data are presented in Table 3 and Figure 5. In four out of the six significantly different centers, all views had significant differences simultaneously, thus suggesting that the models tend to operate in similar manner, and that an actual superiority of the sagittal slice model needs to be further investigated.

3.4.1.5 Sex Effects

Previous papers suggest that sex can play a role in biasing brain age prediction models. For that reason, we assessed how sex influenced our predictions. We executed a two-tailed paired t- test for age and model predictions for both males and females independently and found no significant differences ($p < 0.03$). We ran a two-tailed

unpaired t-test for males and females to see whether predictions or age was significantly different between groups, also with negative findings ($p < 0.03$). Table 4 summarizes our tests. we applied a two-tailed dependent t-test to compare group means, the test showed no significant differences.

3.4.1.6 Voxel-WiseLevel Brain Age Predictions

We investigated whether a voxel-level model could benefit from the three slice predictions. For each axial slice, information was gathered from each intersecting coronal and sagittal slice, and the combined with the axial prediction to generate an average for each voxel. We show an example of its use in Figure 6. We believe there is a multitude of applications and benefits that come with this sort of approach, such as: (1) the exploration of distinct brain aging patterns in different regions of the brain; these patterns do not need to be bounded by anatomically or functionally defined regions, (2) the investigation of region-specific brain aging in neuropsychiatric disorders that present a brain age gap, and (3) the identification of voxel- or region-specific prediction biases (e.g., regions that consistently present higher error). But this approach led to unstable predictions, possibly because the model was not being trained using voxel-level information. There were high frequency changes in predictions for neighboring slices; it is expected that neighboring slices be the opposite. This problem has been documented in deep learning patch-based prediction methods (35). A possible simple but sub-optimal solution is to use gaussian spatial smoothing to remove the high- frequency changes, as we demonstrate in Figure 6. We contend that future approaches may aim to develop means to mitigate the artifacts that come “stitching” slice-level predictions into voxel-level ones. Such a successful approach could improve the current model.

3.4.2 Independent Gray and White Matter

To estimate the contribution of gray and white matter tissue to the prediction, we created another model (for axial slices) to test age predictions using gray matter and white matter separately. Based on the results in Figure 7, the regions that are best predictors of brain age are similar between gray and white matter. The model using solely white matter presented higher errors in most slices. Previous studies have shown that gray matter is a better predictor of brain age than white matter (9).

3.5 Discussion and Conclusion

Identifying the most predictive regions of the brain for brain age models may help interpreting results, but may also introduce model biases that are unrelated to a neurological condition. Our study presents a model that attempted to balance accuracy and interpretability of the results. Our model provides a level of scrutability for the decision-making process, and can thus help researchers and clinicians understand its limitations.

Given the number of perspectives on interpretability for machine learning (36,37), we must clarify exactly what we mean by interpretability. Although the interpretability or explainability are commonly used to refer to strategies that explain model predictions, we use it more broadly to define that the final predicted brain age can be attributed to specific slices or regions of the brain. In case additional explanation is needed for a single slice, the usual strategies, carrying the limitations we discussed in section 2, should be applied.

We believe that for research purposes, knowing the influence of each part of the brain in the final prediction is imperative to guide and interpret findings of research using the brain age gap.

As a whole, neuropsychiatric research on the brain age gap has mostly focused on associating the difference between the chronological and predicted age to clinical populations. Moreover, most of this research was conducted on the assumption that the brain age gap actually encompasses a larger brain-wide phenomenon responsible for accelerated brain aging.

The body of work on the prediction of brain age at specific regions is growing, two contributions of which are of note in comparison to our contribution. First, a preprint paper (37)uses a similar approach to ours, but instead of using slices, they rely on 3d patches that are later combined with averages or linear regression. Second, a recently published approach (38) uses slice-level predictions, but instead of combining it with linear regression, uses a recurrent neural network for the job.

Attention-based, especially Transformers, models, originally purposed for text-based modeling (39), have recently shown to offer substantial improvement on classification accuracy for image-based problems (40). However, at the time we developed our approach, attention models were more popular for text- based than image-based tasks. More importantly, we were not aware of any work with neuroimaging data that had shown substantial improvements using those approaches. Indeed, future work should focus on comparing the explanations we provide in terms of slides to the attention maps generated by attention- based models.

Our experiments corroborate some findings from the field. First, we showed that age effects are significant and should need to be accounted for in predictive models of brain age. Second, our results suggest that proper training and test splits that keep site data proportional may mitigate site effects. Third, gray matter seems to be more predictive of age than white matter. Interestingly, our model had similar performance in both male and female sex, although sex is not explicitly used by the model and no separate models were trained.

Since the competition dataset was preprocessed by segmenting gray and white matter, future work should look at less processed data to try to replicate these results. Differences between the unprocessed and segmented inputs might help us understand the extent that possible segmentation errors may influence the behavior of models of brain age.

3.6 Limitations

The convolutional neural network fails to combine information from different regions of the brain due to its 2D nature. Although aggregated at later stages of our framework, 3D CNNs might be able to capture patterns that our proposed method misses.

We also found that the aggregated information from each slice prediction to form a voxel-level age prediction to be noisy enough to be unusable. Adjacent voxels had usually the same error but occasionally, while changing the slice index, the prediction had a drastic change. This behavior can probably be attributable to several issues, such as lack of regularization for more stable predictions or possible unidentified problems with the segmentation maps.

Data Availability Statement

The code to reproduce our experiments is available at GitHub (https://github.com/lsa-pucrs/pac- 2019). Data was provided by PHOTON-AI (https://www.photon-ai.com/explorer) during the PAC-2019 challenge.

Ethical Statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author Contributions

PB, LT, MM, and NE designed the study. PB implemented the framework and ran experiments. FM and AB supervised the implementation and engineering of the work. AB and BF helped interpreting the findings and provided neuroimaging-related insights. All authors contributed to writing the manuscript.

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References

1. Voisey J., Lawford B.R., Morris C.P., Wockner L.F., Noble E.P., Young R.M., Mehta D. AO - Morris CPOHO-0001-8976-619x. Epigenetic analysis confirms no accelerated brain aging in schizophrenia. npj Schizophrenia (2017) 3:26.

2. Cole JH. Multimodality neuroimaging brain-age in UK biobank: relationship to biomedical, lifestyle, and cognitive factors. Neurobiol Aging (2020) 92:34–42. doi: 10.1016/j.neurobiolaging.2020.03.014

3. Ning K, Zhao L, Matloff W, Sun F, Toga AW. Association of relative brain age with tobacco smoking, alcohol consumption, and genetic variants. Sci Rep (2020) 10:10.

4. Kolenic M, Franke K, Hlinka J, Matejka M, Capkova J, Pausova Z, Uher R, Alda M, Spaniel F, Hajek T. Obesity, dyslipidemia and brain age in first-episode psychosis. J Psychiatr Res (2018) 99:151–158.

5. Steffener J, Habeck C, O'Shea D, Razlighi Q, Bherer L, Stern Y. Differences between chronological and brain age are related to education and self-reported physical activity. Neurobiol Aging (2016) 40:138–144.

6. Cole JH, Ritchie SJ, Bastin ME, Valdés Hernández MC, Muñoz Maniega S, Royle N, Corley J, Pattie A, Harris SE, Zhang Q, et al. Brain age predicts mortality. Mol Psychiatry (2018) 23:1385–1392.

7. Kaufmann T, van der Meer D, Doan Nhat Trung and Schwarz E, Lund MJ, Agartz I, Alnæs D, Barch DM, Baur-Streubel R, Bertolino A, Bettella F, et al. Common brain

disorders are associated with heritable patterns of apparent aging of the brain. Nat Neurosci (2019) 22:1617–1623.

8. Schnack HG, van Haren NEM, Nieuwenhuis M, Hulshoff Pol HE, Cahn W, Kahn RS. Accelerated brain aging in schizophrenia: A longitudinal pattern recognition study. Am J Psychiatry (2016) 173:607–616.

9. Cole JH, Poudel RPK, Tsagkrasoulis D, Caan MWA, Steves C, Spector TD, Montana G. Predicting brain age with deep learning from raw imaging data results in a reliable and heritable biomarker. Neuroimage (2017) 163:115–124.

10. Cole JH, Franke K. Predicting Age Using Neuroimaging: Innovative Brain Ageing Biomarkers. Trends Neurosci (2017) 40:681–690.

11. Geirhos R, Rubisch P, Michaelis C, Bethge M, Wichmann FA, Brendel W. ImageNet-trained CNNs are biased towards texture; increasing shape bias improves accuracy and robustness. 7th International Conference on Learning Representations, ICLR 2019, New Orleans, LA, USA, May 6-9, 2019. OpenReview.net (2019) https://openreview.net/forum?id=Bygh9j09KX

12. Zech JR, Badgeley MA, Liu M, Costa AB, Titano JJ, Oermann EK. Variable generalization performance of a deep learning model to detect pneumonia in chest radiographs: A cross-sectional study. PLoS Med (2018) 15:e1002683. doi: 10.1371/journal.pmed.1002683

13. Just MA, Pan L, Cherkassky VL, McMakin DL, Cha C, Nock MK, Brent D. Machine learning of neural representations of suicide and emotion concepts identifies suicidal youth. Nat Hum Behav (2017) 1:911–919. doi: 10.1038/s41562-017-0234-y

14. Heinsfeld AS, Franco AR, Craddock RC, Buchweitz A, Meneguzzi F. Identification of autism spectrum disorder using deep learning and the ABIDE dataset. Neuroimage Clin (2018) 17:16–23. doi: 10.1016/j.nicl.2017.08.017

15. Popescu SG, Cole JH, Sharp DJ, Glocker B. Deep Learning Methods for Estimating ``Brain Age'' from Structural MRI Scans. (2018)

16. Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage (2001) 14:21–36. doi: 10.1006/nimg.2001.0786

17. Wattjes MP. Structural MRI. Int Psychogeriatr (2011) 23 Suppl 2:S13-24. doi: 10.1017/S1041610211000913

18. Franke K, Ziegler G, Klöppel S, Gaser C, Alzheimer's Disease Neuroimaging Initiative. Estimating the age of healthy subjects from T1-weighted MRI scans using kernel methods: exploring the influence of various parameters. Neuroimage (2010) 50:883–892.

19. Franke K, Gaser C. Longitudinal changes in individual BrainAGE in healthy aging, mild cognitive impairment, and Alzheimer's disease. GeroPsych: The Journal of Gerontopsychology and Geriatric Psychiatry (2012) 25:235.

20. Hajek T, Franke K, Kolenic M, Capkova J, Matejka M, Propper L, Uher R, Stopkova P, Novak T, Paus T, et al. Brain age in early stages of bipolar disorders or schizophrenia. Schizophr Bull (2019) 45:190–198.

21. Krizhevsky A, Sutskever I, Hinton GE. ImageNet Classification with Deep Convolutional Neural Networks. In: Pereira F, Burges CJ, Bottou L, Weinberger KQ, editors. Advances in Neural Information Processing Systems. Curran Associates, Inc. (2012) https://proceedings.neurips.cc/paper/2012/file/c399862d3b9d6b76c8436e924a68c45b-Paper.pdf

22. Jonsson BA, Bjornsdottir G, Thorgeirsson TE, Ellingsen LM, Walters GB, Gudbjartsson DF, Stefansson H, Stefansson K, Ulfarsson MO. Brain age prediction using deep learning uncovers associated sequence variants. Nat Commun (2019) 10:5409.

23. Litjens G, Kooi T, Bejnordi BE, Setio AAA, Ciompi F, Ghafoorian M, van der Laak JAWM, van Ginneken B, Sánchez CI. A survey on deep learning in medical image analysis. Med Image Anal (2017) 42:60–88. doi: 10.1016/j.media.2017.07.005

24. Tomaz Da Silva L, Esper NB, Ruiz DD, Meneguzzi F, Buchweitz A. Visual Explanation for Identification of the Brain Bases for Developmental Dyslexia on fMRI Data. Frontiers in Computational Neuroscience (2021) 15: doi: 10.3389/fncom.2021.594659

25. Zeiler Matthew D. and Fergus R. Visualizing and Understanding Convolutional Networks. In: Fleet David and Pajdla T and SB and TT, editor. Computer Vision – ECCV 2014. Cham: Springer International Publishing (2014). p. 818–833

26. Arslan S, Ktena SI, Glocker B, Rueckert D. “Graph Saliency Maps Through Spectral Convolutional Networks: Application to Sex Classification with Brain Connectivity.,” (2018). p. 3–13 doi: 10.1007/978-3-030-00689-1_1

27. Duffy BA, Liu M, Flynn T, Toga A, Barkovich AJ, Xu D, Kim H. Regression activation mapping on the cortical surface using graph convolutional networks. International Conference on Medical Imaging with Deep Learning – Extended Abstract Track. London, United Kingdom (2019) https://openreview.net/forum?id=rJlhd1S0FE

28. Adebayo J, Gilmer J, Muelly M, Goodfellow I, Hardt M, Kim B. Sanity Checks for Saliency Maps. In: Bengio S, Wallach H, Larochelle H, Grauman K, Cesa-Bianchi N, Garnett R, editors. Advances in Neural Information Processing Systems. Curran Associates, Inc. (2018) https://proceedings.neurips.cc/paper/2018/file/294a8ed24b1ad22ec2e7efea049b8737-Paper.pdf

29. Levakov G, Rosenthal G, Shelef I, Raviv TR, Avidan G. From a deep learning model back to the brain-Identifying regional predictors and their relation to aging. Hum Brain Mapp (2020) 41:3235–3252.

30. He K, Zhang X, Ren S, Sun J. Deep Residual Learning for Image Recognition. 2016 IEEE Conference on Computer Vision and Pattern Recognition (CVPR). IEEE (2016). p. 770–778 doi: 10.1109/CVPR.2016.90

31. Simard PY, Steinkraus D, Platt JC. Best practices for convolutional neural networks applied to visual document analysis. Seventh International Conference on Document

Analysis and Recognition, 2003. Proceedings. (2003). p. 958–963 doi: 10.1109/ICDAR.2003.1227801

32. Aycheh HM, Seong J-K, Shin J-H, Na DL, Kang B, Seo SW, Sohn K-A. Biological Brain Age Prediction Using Cortical Thickness Data: A Large Scale Cohort Study. Front Aging Neurosci (2018) 10:252. doi: 10.3389/fnagi.2018.00252

33. Liang H, Zhang F, Niu X. Investigating systematic bias in brain age estimation with application to post-traumatic stress disorders. Hum Brain Mapp (2019) 40:3143–3152. doi: 10.1002/hbm.24588

34. Le TT, Kuplicki RT, McKinney BA, Yeh H-W, Thompson WK, Paulus MP, Tulsa 1000 Investigators. A Nonlinear Simulation Framework Supports Adjusting for Age When Analyzing BrainAGE. Front Aging Neurosci (2018) 10:317. doi: 10.3389/fnagi.2018.00317

35. Pielawski N, Wählby C. Introducing Hann windows for reducing edge-effects in patch-based image segmentation. PLoS One (2020) 15:e0229839. doi: 10.1371/journal.pone.0229839

36. Lundberg SM, Lee S-I. “A Unified Approach to Interpreting Model Predictions.,” In: Guyon I, Luxburg U v, Bengio S, Wallach H, Fergus R, Vishwanathan S, Garnett R, editors. Advances in Neural Information Processing Systems 30. Curran Associates, Inc. (2017). p. 4765–4774

37. Bintsi K-M, Baltatzis V, Kolbeinsson A, Hammers A, Rueckert D. Patch-based Brain Age Estimation from MR Images. (2020)

38. Lam PK, Santhalingam V, Suresh P, Baboota R, Zhu AH, Thomopoulos SI, Jahanshad N, Thompson PM. Accurate brain age prediction using recurrent slice-based networks. In: Brieva J, Lepore N, Romero Castro E, Linguraru MG, editors. 16th International Symposium on Medical Information Processing and Analysis. SPIE (2020). p. 32 doi: 10.1117/12.2579630

39. Vaswani A, Shazeer N, Parmar N, Uszkoreit J, Jones L, Gomez AN, Kaiser Ł ukasz, Polosukhin I. Attention is All you Need. In: Guyon I, Luxburg U von, Bengio S, Wallach H, Fergus R, Vishwanathan S, Garnett R, editors. Advances in Neural Information Processing Systems. Curran Associates, Inc. (2017) https://proceedings.neurips.cc/paper/2017/file/3f5ee243547dee91fbd053c1c4a845aa-Paper.pdf

40. Parmar N, Vaswani A, Uszkoreit J, Kaiser L, Shazeer N, Ku A, Tran D. Image Transformer. In: Dy J, Krause A, editors. Proceedings of the 35th International Conference on Machine Learning. Proceedings of Machine Learning Research. PMLR (2018). p. 4055–4064 https://proceedings.mlr.press/v80/parmar18a.html

Figures

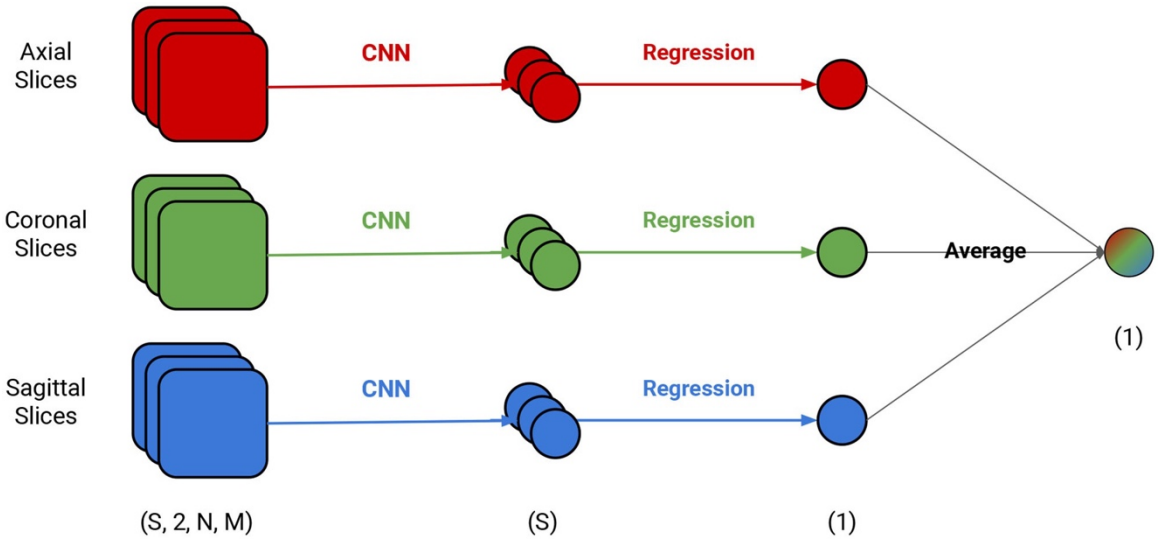

Figure 1. Depiction of the brain age prediction framework. Each view has an independent CNN model and an independently-trained linear regression model. S is the number of slices and N and M are the dimensions of the slice (e.g., if evaluating the axial slice, the N and M are the dimensions for the sagittal and coronal views).

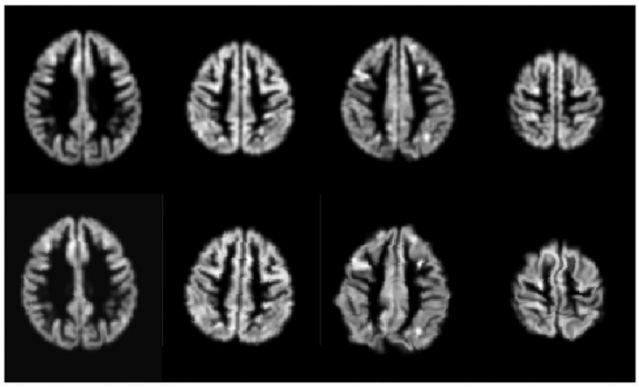

Figure 2. Examples of the augmentation procedure. First row are gray matter segmented images before augmentation; the second row are their augmented counterparts.

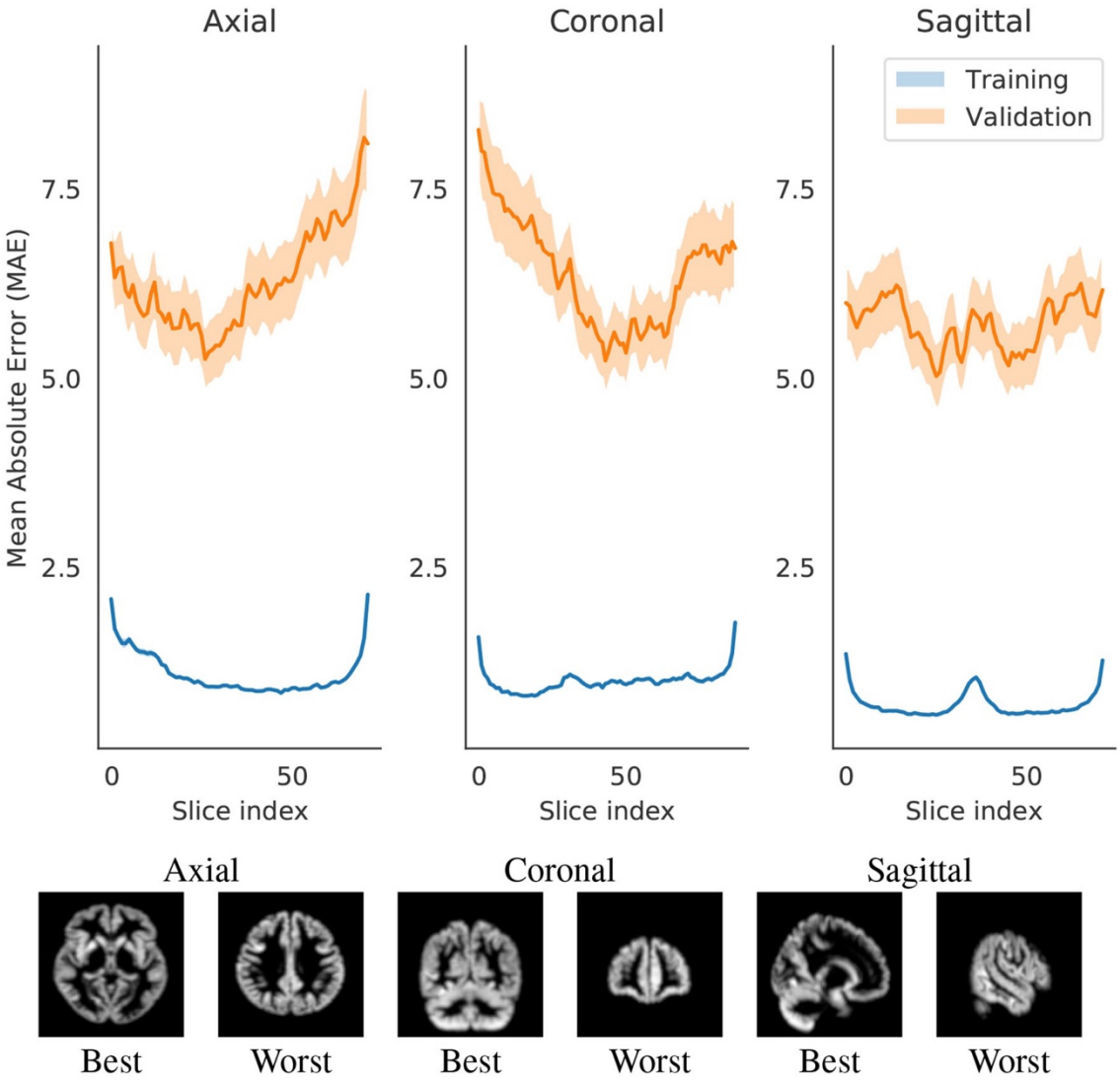

Figure 3. Change in Mean Absolute Error (MAE) with respect to changing the slice that is evaluated by the network. Each slice index value are an average of either all training set or all validation set. The shade represents the 0.95 confidence interval for those points. The slices in the image are examples of the index that best or worst predicts brain age.

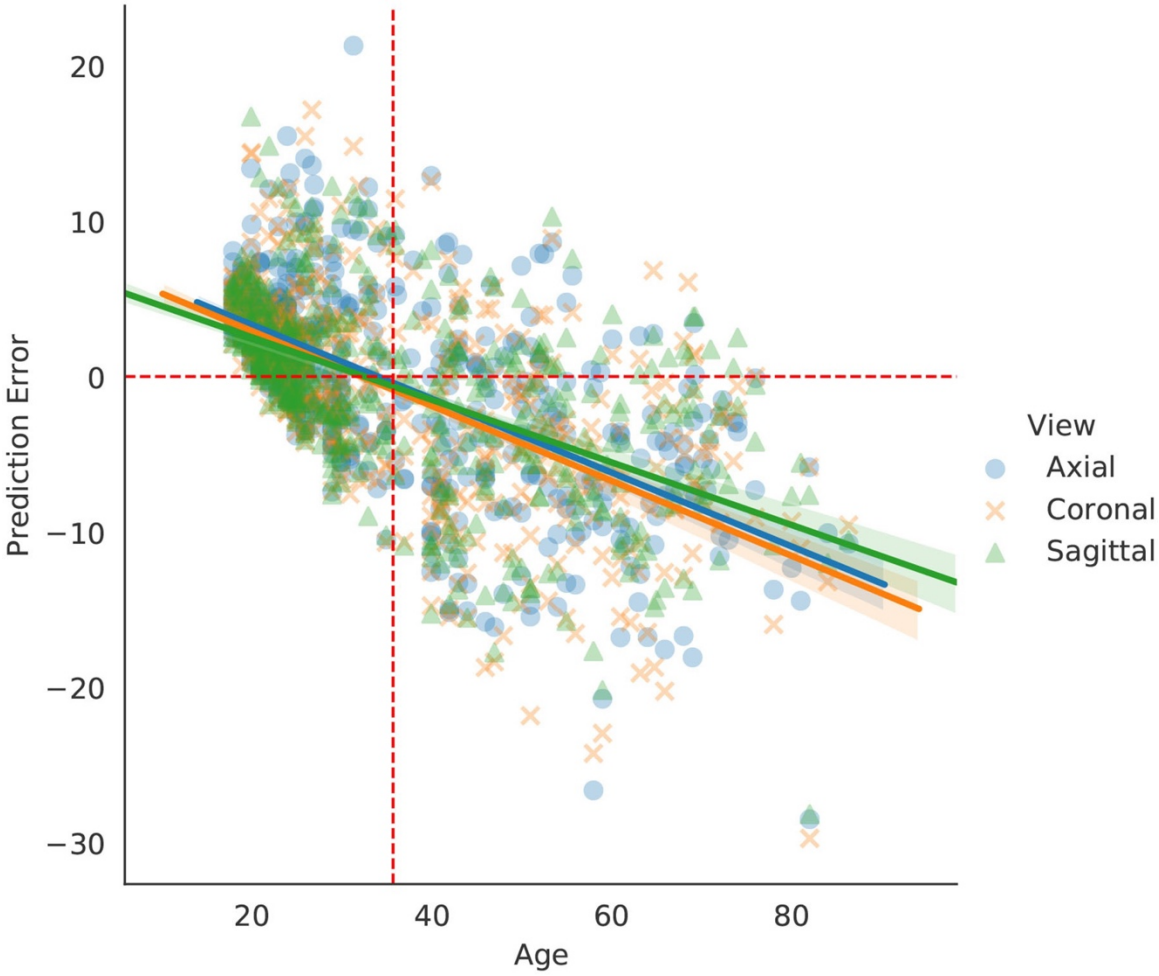

Figure 4. Regression curves for the validation set. Every point represents a person (each person is presented three times, one for each view). Dashed red orthogonal to the x-axis is the age average of the dataset, while the horizontal dashed line is aligned to 0 error as a reference.

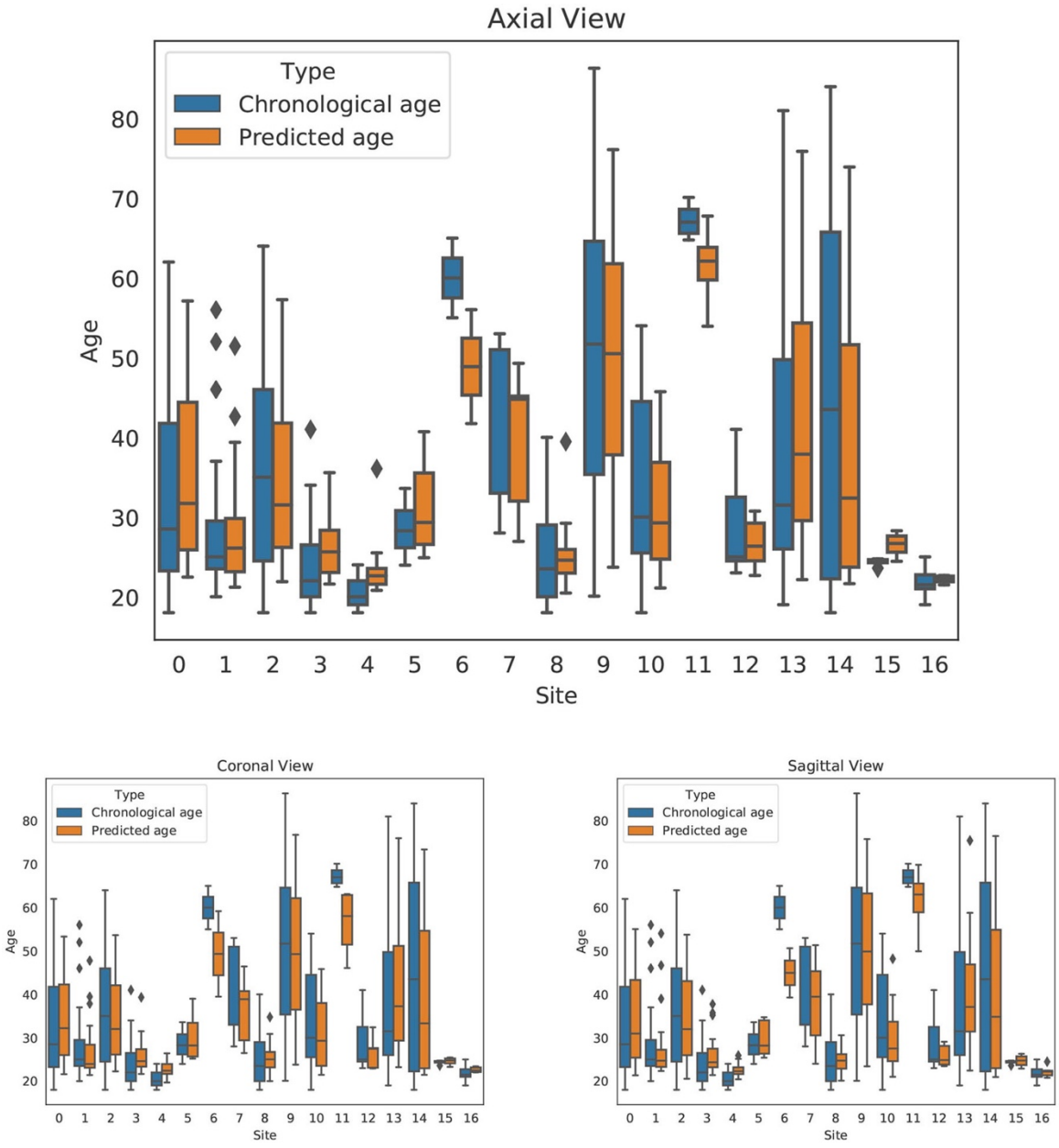

Figure 5. Site effects for axial, coronal, and sagittal views. For each orientation, the chronological age and predicted age are shown side-by-side by site.

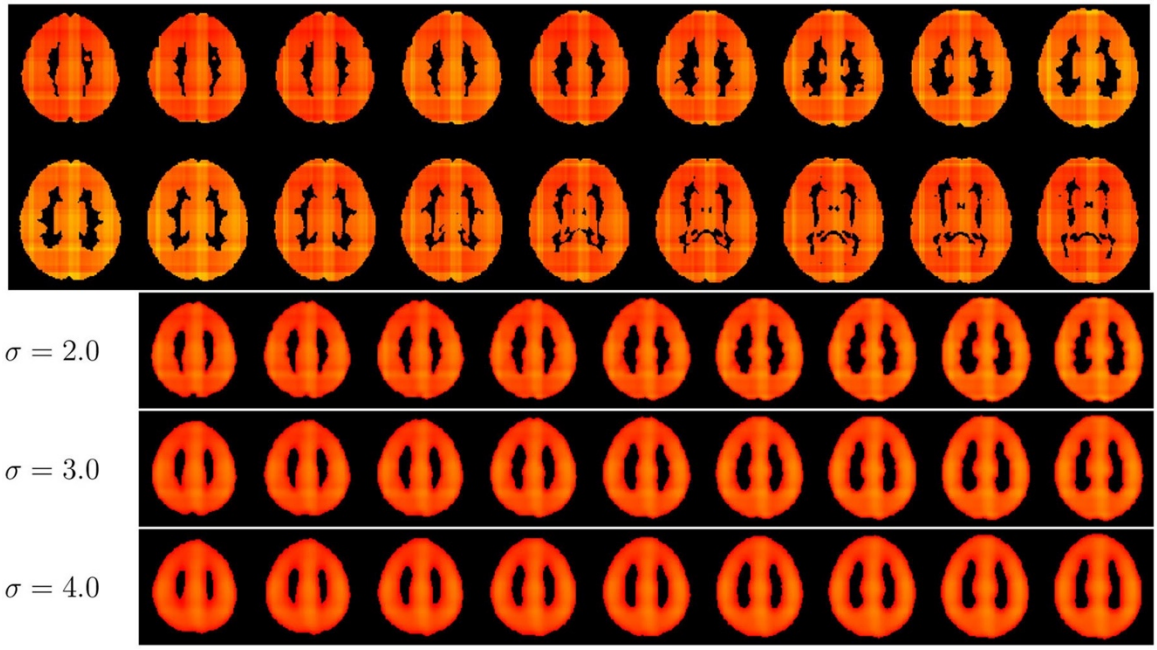

Figure 6. Lightbox view of axial slices age predictions following the voxel-level approach. The value for σ indicates the amount of gaussian spatial smoothing applied to the predictions. Images on a range from 20 (red) to 60 (yellow).

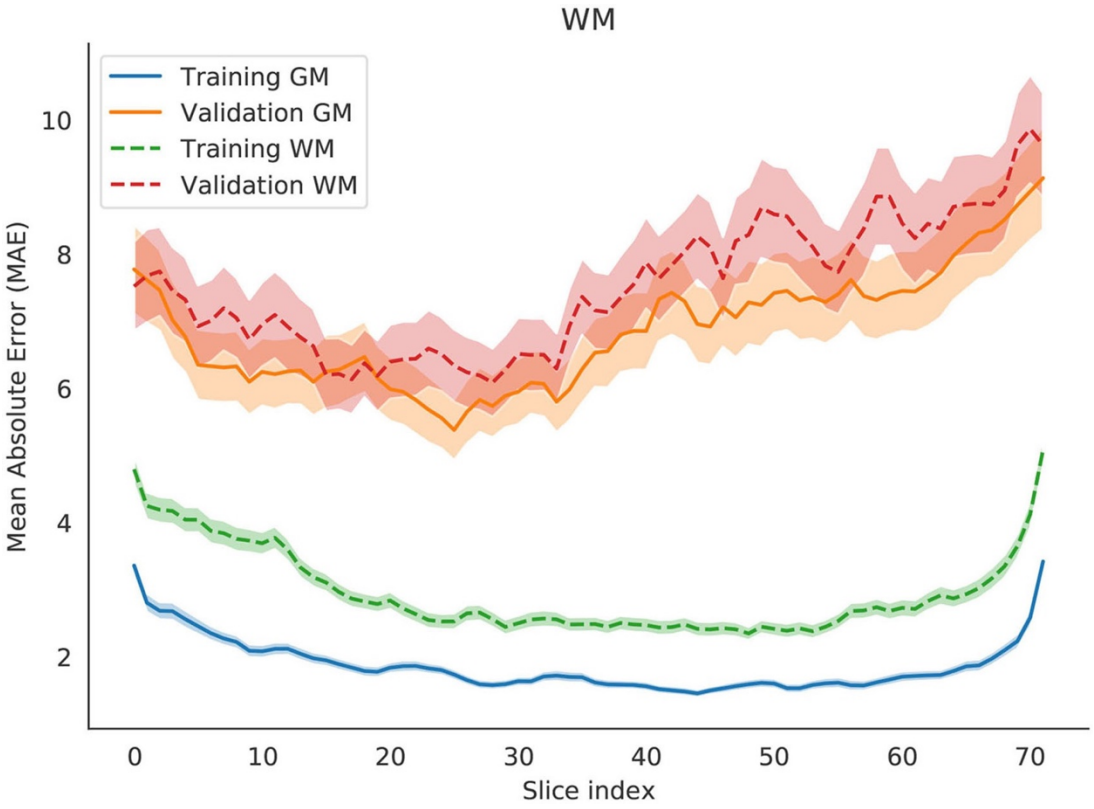

Figure 7. Change in Mean Absolute Error (MAE) with respect to changing the slice that is evaluated by the network. Two independent models are evaluated, one for gray matter (solid lines) and another one for white matter (dashed lines). Each slice index value is an average of the entire training set or the entire validation set. The shade represents the 0.95 confidence interval for those points.

Tables

Table 1. Participants information.

Center	Age mean (std)	Sex (F-M)
0	34.24 (12.67)	197 – 133
1	26.76 (9.23)	79 – 55
2	25.51 (12.18)	331 – 244
3	25.76 (6.62)	18 – 129
4	21.24 (2.01)	85 – 58
5	31.25 (7.46)	21 – 18
6	62.70 (6.75)	3 – 7
7	43.44 (11.27)	15 – 10
8	24.82 (5.16)	121 – 137
9	49.13 (16.62)	255 – 194
10	33.19 (11.34)	23 – 51
11	69.92 (7.97)	9 – 9
12	28.77 (7.77)	16 – 15
13	41.00 (17.80)	52 – 76
14	44.41 (22.81)	142 – 88
15	23.27 (1.27)	16 – 3
16	22.76 (2.80)	20 – 9
Total	35.88 (16.21)	1,403 – 1,236

Table 2. Final validation results for all views.

View	**Average slice error**	**Average error**	**Regression error**	$\boldsymbol{R^2}$
Axial	6.28	4.88	5.09	0.82
Coronal	6.38	4.91	5.04	0.83
Sagittal	**5.71**	**4.45**	**4.52**	**0.86**
Combined			4.62	0.86

The Average Slice Error column evaluates the final error of our model by doing a simple average across all slices of the volume. The Average Error column uses the same information for the slice column, but instead of calculating the average error for each slice, calculates the mean prediction of all slices, and compare with the actual age. The Regression Error column is the error of using linear regression instead of an average to classify the whole volume. All values are mean absolute errors.

Table 3. Site effects for each orientation and each site. $p < 0.03$ in bold.

Site	View	t-Statistic	p-value
0	Axial	-2.825	**0.006**
	Coronal	-1.581	0.119
	Sagittal	-1.985	0.051
1	Axial	0.829	0.415
	Coronal	1.904	0.068
	Sagittal	1.788	0.085
2	Axial	3.248	**0.002**
	Coronal	3.248	**0.002**
	Sagittal	3.097	**0.002**
3	Axial	-3.006	**0.005**
	Coronal	-2.335	**0.027**
	Sagittal	-2.845	**0.008**
4	Axial	-5.293	**0.000**
	Coronal	-6.040	**0.000**
	Sagittal	-5.188	**0.000**
5	Axial	-1.945	0.093
	Coronal	-1.111	0.303
	Sagittal	-1.323	0.227
6	Axial	5.178	0.121
	Coronal	2.203	0.271

	Sagittal	22.157	**0.029**
7	Axial	-0.010	0.092
	Coronal	1.080	0.341
	Sagittal	0.529	0.625
8	Axial	-1.436	0.157
	Coronal	-1.921	0.060
	Sagittal	-0.957	0.343
9	Axial	0.698	0.487
	Coronal	1.845	0.068
	Sagittal	0.914	0.363
10	Axial	0.801	0.437
	Coronal	0.961	0.353
	Sagittal	1.675	0.116
11	Axial	3.146	0.051
	Coronal	3.574	0.037
	Sagittal	1.575	0.213
12	Axial	0.873	0.416
	Coronal	1.203	0.274
	Sagittal	1.387	0.215
13	Axial	-1.973	0.060
	Coronal	-1.293	0.208
	Sagittal	-1.296	0.207

14	Axial	4.478	**0.000**
	Coronal	3.960	**0.000**
	Sagittal	4.114	**0.000**
15	Axial	-2.058	0.132
	Coronal	-0.393	0.721
	Sagittal	-0.336	0.759
16	Axial	-0.527	0.621
	Coronal	-0.858	0.430
	Sagittal	-0.418	0.693

Table 4. Sex effects for each combination of age and prediction and males and females.

Group 1	**Group 2**	**Variable 1**	**Variable 2**	**Test type**	***t***	***p*-value**
Sex M	Sex F	Age	Age	I	$t(531) = -1.957$	0.051
Sex M	Sex F	Pred	Pred	I	$t(531) = -2.088$	0.037
Sex M	Sex M	Age	Pred	D	$t(237) = 0.558$	0.578
Sex F	Sex F	Age	Pred	D	$t(293) = 1.423$	0.156

All tests are two-tailed. Results presented here are for the axial orientation model in the validation set. Values in parentheses are the degrees of freedom for each test. I, independent (or unpaired); D, dependent (or paired); Pred, Prediction.

Chapter 4: Accelerated brain aging in major depressive disorder and antidepressant treatment response: A CAN-BIND report

Pedro L. Ballester[1], Jee Su Suh[1], Nikita Nogovitsyn[2], Stefanie Hassel[4], Stephen C. Strother[5,6,7], Stephen R. Arnott[5], Luciano Minuzzi[2,3], Roberto B. Sassi[2], Raymond W. Lam8, Roumen Milev[9], Daniel J. Müller[10,11], Valerie H. Taylor[4], Sidney H. Kennedy[6,10,12,13,14], Benicio N. Frey[2,3], CAN-BIND Investigator Team

1. Neuroscience Graduate Program, McMaster University, Hamilton, ON, Canada.

2. Mood Disorders Program, Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada.

3. Women's Health Concerns Clinic, St. Joseph's Healthcare Hamilton, Hamilton, Ontario, Canada.

4. Department of Psychiatry, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada.

5. Rotman Research Institute, Baycrest, Toronto, ON, Canada.

6. Institute of Medical Science, University of Toronto, Toronto, ON, Canada.

7. Department of Medical Biophysics, University of Toronto, ON, Canada.

8. Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada.

9. Departments of Psychiatry and Psychology, Queen's University, and Providence care, Kingston, On, Canada

10. Department of Psychiatry, University of Toronto, Toronto, ON, Canada.

11. Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada.
12. Centre for Mental Health, University Health Network, Toronto, ON, Canada.
13. Krembil Research Institute, University Health Network, Toronto, ON, Canada.
14. Centre for Depression and Suicide Studies, and Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada.

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Abstract

Objectives: Previous studies suggest that major depressive disorder (MDD) may be associated with volumetric indications of accelerated brain aging. This study investigated neuroanatomical signs of accelerated aging in MDD and evaluated whether brain age gap is associated with antidepressant response.

Methods: Individuals in a major depressive episode received escitalopram treatment (10-20mg/d) for 8 weeks. Depression severity was assessed at baseline and at weeks 8 and 16 using the Montgomery-Asberg Depression Rating Scale (MADRS). Response to treatment was characterized by a significant reduction in the MADRS (≥ 50%). Nonresponders received adjunctive aripiprazole treatment (2-10mg/d) for a further 8 weeks. The brain-predicted age difference (brain-PAD) at baseline was determined using machine learning methods trained on 3377 healthy individuals from seven publicly available datasets. The model used features from all brain regions extracted from structural magnetic resonance imaging data.

Results: Brain-PAD was significantly higher in older MDD participants compared to younger MDD participants [$t(147.35)= -2.35$, $p<0.03$]. BMI was significantly associated with brain-PAD in the MDD group [$r(155) = 0.19$, $p<0.03$]. Response to treatment was not significantly associated with brain-PAD.

Conclusion: We found an elevated brain age gap in older individuals with MDD. Brain-PAD was not associated with overall treatment response to escitalopram monotherapy or escitalopram plus adjunctive aripiprazole.

Keywords: treatment response; major depressive disorder; brain age; machine learning.

4.1 Introduction

Distributed abnormalities in brain structures are common neuroimaging findings in patients with a significant history of major depressive disorder (MDD) (Fu, Fan, & Davatzikos, 2020). Illness-associated brain changes can be detected with various neuroimaging measurements. For example, studies by large consortia of neuroimaging data collection for MDD have identified changes in fractional anisotropy, gray matter volume and white matter microstructure (Schmaal et al., 2020). It has been suggested that certain structural characteristics (e.g., reduced hippocampal volume and cortical alterations in frontal, occipital and cingulate regions) have potential as predictive biomarkers in the context of treatment response to antidepressant use and recurrence of MDD (Kang & Cho, 2020). However, due to inconsistent findings, whether structural information can be predictive of treatment response is still unknown. So far, cortical thickness and volumes of certain brain regions have been linked to antidepressant response in some studies (Bartlett et al., 2018; Jung et al., 2014) but not others (Suh et al., 2020).

Studies of brain age gap estimation (brainAGE) suggest a hypothesis of accelerated brain aging in neuropsychiatric disorders (Dunlop, Victoria, Downar, Gunning, & Liston, 2021; Han et al., 2020, 2021; Teeuw et al., 2021). The hypothesis posits that a greater gap between the chronological age and estimated brain age is associated with unfavorable clinical outcomes in patients with neuropsychiatric illnesses. The brain-predicted age difference (brain-PAD; the difference between chronological age and estimated brain age) has been associated with several clinically meaningful variables, such as mortality risk

and fluid intelligence (J. H. Cole et al., 2018). Additionally, brain-PAD has been consistently identified in psychotic disorders and neurological diseases (Franke & Gaser, 2012; Gaser et al., 2013; Koutsouleris et al., 2014; Nenadić, Dietzek, Langbein, Sauer, & Gaser, 2017; Schnack et al., 2016). In this context, brain-PAD has also been associated with clinical scales, such as the positive and negative syndrome scale (PANSS) in schizophrenia (Kay, Fiszbein, & Opler, 1987), the mini-mental state examination (MMSE) in mild cognitive impairment and dementia (Folstein, Folstein, & McHugh, 1975), and the expanded disability status scale (EDSS) in multiple sclerosis (Kurtzke, 1983). In all significant associations between brain-PAD and clinical symptoms, a larger brain-PAD was associated with worse clinical outcomes (Kaufmann et al., 2019). There may also be an effect of age on brain-PAD, such that it is more pronounced in older compared to young/mid-life individuals (Christman et al., 2020).

Recently, brainAGE studies have begun to investigate this hypothesis of accelerated brain aging in MDD. The findings so far have been inconclusive, with some studies claiming to have identified signs of accelerated aging in MDD and others indicating the opposite (Besteher, Gaser, & Nenadić, 2019; Christman et al., 2020; Kaufmann et al., 2019; Schmaal et al., 2020). A subgroup comparison of medication-free individuals with MDD versus those currently on medications found no differences in brain-PAD (Han et al., 2020) and there is scarce information regarding associations with other clinical characteristics. The disagreements of the field may be attributed to previously identified limitations of imaging research in MDD, such as: (1) the heterogeneity of MDD presentation; (2) variation of clinical characteristics among cohorts; (3) limited sample

size; (4) methodological and scanner variability; and/or (5) medication use (type, dosage, duration). Additionally, any time-sensitive relationship between antidepressant use, clinical scales and brain-PAD in MDD has yet to be explored. Finally, epigenetic findings suggest that biological age gaps may be more easily identified in older samples, which also contributes to disagreements in the field (Fries et al., 2020, 2017).

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

outlined above, in conjunction with the observation of worse clinical outcomes being linked to larger brain-PAD (Kaufmann et al., 2019), we also hypothesized that larger brain-PAD will be associated with worse treatment response.

4.2 Methods

4.2.1 Participants

Data were collected from participants in the Canadian Biomarker Integration Network in Depression (CAN-BIND) study (Kennedy et al., 2019; Lam et al., 2016). Recruitment was conducted at six academic centers across Canada. The details of recruitment strategy and full spectrum of clinical assessments have been previously published (Lam et al., 2016). Briefly, outpatients meeting DSM-IV-TR criteria for a major depressive episode, aged 18-60 and free of psychotropic medications for at least 5 half-lives were recruited for the treatment group if they scored greater or equal to 24 on the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979). The six academic centers and their sample sizes were: Centre for Addiction and Mental Health (CAMH; HC=7, MDD=5), McMaster University (HC=19, MDD=27), The University of British Columbia (UBC; HC=12, MDD=49), Toronto General Hospital and Toronto Western Hospital (HC=23, MDD=39) University of Calgary (HC=35, MDD=25), and Queen's University (HC=15, MDD=15). Major exclusion criteria included another primary diagnosis of a psychiatric disorder, high suicidal risk, substance dependence/abuse in the past 6 months, current psychosis, treatment resistance (failure of 4 pharmacologic interventions) or previous failure to respond to escitalopram or

aripiprazole. Age-matched healthy comparison (HC) participants were required to have no history of psychiatric or any unstable medical condition. The full list of inclusion and exclusion criteria can be found elsewhere (Lam et al., 2016). Participants in the treatment group that had complete clinical data up to week 16 and complete imaging data at baseline were included in the analysis. Participants in the HC group that had complete data at baseline (clinical and imaging) were also used for the analysis.

4.2.2 MRI data acquisition

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

4.2.3 Treatment protocol

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

4.2.4 Brain age estimation

A brain age package available for R (brainageR; v2.1) was used for the prediction of brain age for every individual with available neuroimaging data at baseline. The complete steps to reproduce the brain-PAD values using the brainageR package are available at GitHub[4]. In summary, the package is based on previously published approaches and uses SPM12 for segmentation and spatial normalization (J. H. Cole et al., 2018). Images are segmented into grey matter, white matter, and cerebrospinal fluid compartments, which then undergo normalisation to MNI space using DARTEL. The normalized images were

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

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

4.2.5 Statistical analysis

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

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

It should be noted that, in general, brain age prediction models suffer from an age bias. Specifically, brain age prediction models often overestimate the brain age of

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

In Table 1, we present the performance metrics of the brain age model with and without correction in our dataset. Importantly, although age-corrected values are more reliable for comparisons between clinical groups and the investigation of clinical outcomes, performance metrics of age predictions are artificially inflated by the age-correction procedure (Butler et al., 2020). Thus, uncorrected brain-PAD values provide a better indication of age prediction errors than the age-corrected ones. To test the dependence of age on brain-PAD, we separated all participants from the MDD group into two cohorts, those who were below or above the median age of the MDD group (33 years). This resulted in two subgroups: the younger group, below 33 years of age (mean

age = 25.57 (4.72)) and the group older than the median age (mean age = 46.99 (7.98)). A similar procedure was performed for the HC group (mean ages 26.06 (3.87) and 44.98 (7.92) for the younger and older group, respectively), using the median of the MDD group. The median age was chosen due to previous work that have identified signs of accelerated aging in older, but not younger participants with MDD (Christman et al., 2020). In addition, splitting the groups by the median age also aligns our study with a previously published methodology studying hippocampal epigenetic aging (Fries et al., 2020). Pearson correlations of age and brain age (both uncorrected and age-corrected) were calculated for each of the four groups. As uncorrected brain age predictions suffer from age-bias, we expected to find significant differences of brain-PAD in both analyses for the MDD group, but only in the uncorrected analysis for the HC group.

4.3 Results

4.3.1 Demographics and clinical characteristics

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

4.3.2 Brain-PAD group differences

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

4.3.3 Age-dependent brain-PAD differences

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

association between brain-PAD and age^2 was also significant in the full MDD group [r(157)=0.18, p=0.011] group (Figure 1).

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

4.3.4 Association of brain-PAD with treatment response

There was no difference in brain-PAD between responders and nonresponders at either week 8 or week 16, before or after correction for age bias. A secondary analysis was conducted using individual items of the MADRS at week 16. Only *reported sadness* showed an association with brain-PAD after outlier removal [r(157)= 0.22, p< 0.01]. After controlling for baseline values of reported sadness, site, age, sex, BMI, and treatment arm in a multiple linear regression model and a Bonferroni correction considering all MADRS items, this association was no longer significant (p_{adj}= 0.052). Additionally, an interaction between changes in *reported sadness* and response status (responder or nonresponder) including all covariates was conducted. The interaction term of that analysis was not significant.

4.4 Discussion

The present study examined brain-PAD in medication-free individuals with MDD and its association with subsequent antidepressant treatment response. We found that age-

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

We found no association between brain-PAD and overall treatment response, as defined as a decrease in MADRS total scores. Interestingly, brain-PAD was highly correlated with changes in *reported sadness*, a single item of the MADRS. *Reported sadness* explained 60% of the variance of total MADRS scores ($R^2 = 0.61$) and represents a core symptom of depression. Ultimately, the link between brain-PAD and changes in *reported sadness* may suggest that brain-PAD reflects only certain dimensions of depression and treatment response to antidepressants. Other variables that were explored as covariates, including sex, site, and BMI, did not affect the significance of the findings. However, BMI was independently associated with brain-PAD in both the full MDD group and the older subgroup, but more strongly with the older subgroup. This supports the hypothesis of an additive effect of BMI and psychiatric disorders in brain-PAD (Kolenic et al., 2018).

Brain-PAD has been previously associated with clinically meaningful variables, such as increased mortality risk (J. H. Cole et al., 2018) and cognitive decline (Elliott et al., 2019), possibly mediated by lifestyle choices, such as meditation (Luders, Cherbuin, &

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

Our study has some limitations. First, the mean absolute error of the brain age predictions is larger than what was reported in the original test set for the software package, possibly due to scanner variability in this sample. A possible step for improving the prediction error would be to run separate models for males and females (Ritchie et al., 2018), which would require a larger sample size. Beyond improving predictions, our findings may also have been different with other proportions of males and females.

Evidence suggests that male brains appear to be metabolically older than female brains and that the male brain age is more dependent on individual health (Franke, Ristow, Gaser, & Alzheimer's Disease Neuroimaging Initiative, 2014; Goyal et al., 2019). We may also have encountered type II error, given correction for the large number of comparisons. Important mediator links that have not been investigated in this study may influence findings, such as: lifestyle factors, including exercise (Steffener et al., 2016) and meditation (Luders et al., 2016), tobacco smoking, and alcohol consumption (Ning, Zhao, Matloff, Sun, & Toga, 2020). Overall, the CAN-BIND study had a relatively young sample of participants with MDD, which may lead to findings that are not generalizable across the lifespan and are more relevant for earlier in the course of illness.

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

samples and longer follow-up could test this hypothesis in MDD, as the effect may be more difficult to detect due to clinical heterogeneity, as well as the more subtle brain changes that are typically observed in MDD in comparison with what is seen in psychosis.

4.5 Conclusion

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

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References

1. Bartlett, E. A., DeLorenzo, C., Sharma, P., Yang, J., Zhang, M., Petkova, E., … Parsey, R. V. (2018). Pretreatment and early-treatment cortical thickness is associated with SSRI treatment response in major depressive disorder. Neuropsychopharmacology: Official

Publication of the American College of Neuropsychopharmacology, 43(11), 2221–2230. doi:10.1038/s41386-018-0122-9

2. Beheshti, I., Nugent, S., Potvin, O., & Duchesne, S. (2019). Bias-adjustment in neuroimaging-based brain age frameworks: A robust scheme. NeuroImage. Clinical, 24, 102063. doi:10.1016/j.nicl.2019.102063
3. Besteher, B., Gaser, C., & Nenadić, I. (2019). Machine-learning based brain age estimation in major depression showing no evidence of accelerated aging. Psychiatry Research: Neuroimaging, 290, 1–4. Retrieved from http://libaccess.mcmaster.ca/login?url=https://search.proquest.com/docview/2269453918?accountid=12347
4. Butler, E. R., Chen, A., Ramadan, R., Ruparel, K., Moore, T. M., Zhang, F., … Shinohara, R. T. (2020). Statistical Pitfalls in Brain Age Analyses (p. 2020.06.21.163741). doi:10.1101/2020.06.21.163741
5. Christman, S., Bermudez, C., Hao, L., Landman, B. A., Boyd, B., Albert, K., … Taylor, W. D. (2020). Accelerated brain aging predicts impaired cognitive performance and greater disability in geriatric but not midlife adult depression. Translational Psychiatry, 10(1), 317. doi:10.1038/s41398-020-01004-z
6. Cole, J. H., Ritchie, S. J., Bastin, M. E., Valdés Hernández, M. C., Muñoz Maniega, S., Royle, N., … Deary, I. J. (2018). Brain age predicts mortality. Molecular Psychiatry, 23(5), 1385–1392. doi:10.1038/mp.2017.62

7. Cole, James H., Marioni, R. E., Harris, S. E., & Deary, I. J. (2019). Brain age and other bodily 'ages': implications for neuropsychiatry. Molecular Psychiatry, 24(2), 266–281. doi:10.1038/s41380-018-0098-1

8. Dunlop, K., Victoria, L. W., Downar, J., Gunning, F. M., & Liston, C. (2021). Accelerated brain aging predicts impulsivity and symptom severity in depression. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology. doi:10.1038/s41386-021-00967-x

9. Elliott, M. L., Belsky, D. W., Knodt, A. R., Ireland, D., Melzer, T. R., Poulton, R., … Hariri, A. R. (2019). Brain-age in midlife is associated with accelerated biological aging and cognitive decline in a longitudinal birth cohort. Molecular Psychiatry. doi:10.1038/s41380-019-0626-7

10. Ellis, K. A., Bush, A. I., Darby, D., De Fazio, D., Foster, J., Hudson, P., … AIBL Research Group. (2009). The Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging: methodology and baseline characteristics of 1112 individuals recruited for a longitudinal study of Alzheimer's disease. International Psychogeriatrics / IPA, 21(4), 672–687. doi:10.1017/S1041610209009405

11. Fjell, A. M., Westlye, L. T., Grydeland, H., Amlien, I., Espeseth, T., Reinvang, I., … Alzheimer Disease Neuroimaging Initiative. (2013). Critical ages in the life course of the adult brain: nonlinear subcortical aging. Neurobiology of Aging, 34(10), 2239–2247. doi:10.1016/j.neurobiolaging.2013.04.006

12. Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research, 12(3), 189–198. doi:10.1016/0022-3956(75)90026-6

13. Franke, K., & Gaser, C. (2012). Longitudinal changes in individual BrainAGE in healthy aging, mild cognitive impairment, and Alzheimer’s disease. GeroPsych: The Journal of Gerontopsychology and Geriatric Psychiatry, 25(4), 235. Retrieved from https://psycnet.apa.org/record/2012-32697-006

14. Franke, K., Ristow, M., Gaser, C., & Alzheimer’s Disease Neuroimaging Initiative. (2014). Gender-specific impact of personal health parameters on individual brain aging in cognitively unimpaired elderly subjects. Frontiers in Aging Neuroscience, 6, 94. doi:10.3389/fnagi.2014.00094

15. Fries, G. R., Bauer, I. E., Scaini, G., Valvassori, S. S., Walss-Bass, C., Soares, J. C., & Quevedo, J. (2020). Accelerated hippocampal biological aging in bipolar disorder. Bipolar Disorders, 22(5), 498–507. doi:10.1111/bdi.12876

16. Fries, G. R., Bauer, I. E., Scaini, G., Wu, M.-J., Kazimi, I. F., Valvassori, S. S., … Quevedo, J. (2017). Accelerated epigenetic aging and mitochondrial DNA copy number in bipolar disorder. Translational Psychiatry, 7(12), 1283. doi:10.1038/s41398-017-0048-8

17. Fu, C. H. Y., Fan, Y., & Davatzikos, C. (2020). Widespread Morphometric Abnormalities in Major Depression: Neuroplasticity and Potential for Biomarker Development. Neuroimaging Clinics of North America, 30(1), 85–95. doi:10.1016/j.nic.2019.09.008

18. Gaser, C., Franke, K., Klöppel, S., Koutsouleris, N., Sauer, H., & Alzheimer's Disease Neuroimaging Initiative. (2013). BrainAGE in Mild Cognitive Impaired Patients: Predicting the Conversion to Alzheimer's Disease. PloS One, 8(6), e67346. doi:10.1371/journal.pone.0067346

19. Goyal, M. S., Blazey, T. M., Su, Y., Couture, L. E., Durbin, T. J., Bateman, R. J., … Vlassenko, A. G. (2019). Persistent metabolic youth in the aging female brain. Proceedings of the National Academy of Sciences of the United States of America, 116(8), 3251–3255. doi:10.1073/pnas.1815917116

20. Gunning-Dixon, F. M., Walton, M., Cheng, J., Acuna, J., Klimstra, S., Zimmerman, M. E., … Alexopoulos, G. S. (2010). MRI signal hyperintensities and treatment remission of geriatric depression. Journal of Affective Disorders, 126(3), 395–401. doi:10.1016/j.jad.2010.04.004

21. Habes, M., Pomponio, R., Shou, H., Doshi, J., Mamourian, E., Erus, G., … iSTAGING consortium, the Preclinical AD consortium, the ADNI, and the CARDIA studies. (2021). The Brain Chart of Aging: Machine-learning analytics reveals links between brain aging, white matter disease, amyloid burden, and cognition in the iSTAGING consortium of 10,216 harmonized MR scans. Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 17(1), 89–102. doi:10.1002/alz.12178

22. Han, L. K. M., Dinga, R., Hahn, T., Ching, C. R. K., Eyler, L. T., Aftanas, L., … Schmaal, L. (2020). Brain aging in major depressive disorder: results from the ENIGMA major depressive disorder working group. Molecular Psychiatry. doi:10.1038/s41380-020-0754-0

23. Han, L. K. M., Schnack, H. G., Brouwer, R. M., Veltman, D. J., van der Wee, N. J. A., van Tol, M.-J., … Penninx, B. W. J. H. (2021). Contributing factors to advanced brain aging in depression and anxiety disorders. Translational Psychiatry, 11(1), 402. doi:10.1038/s41398-021-01524-2

24. Holmes, A. J., Hollinshead, M. O., O'Keefe, T. M., Petrov, V. I., Fariello, G. R., Wald, L. L., … Buckner, R. L. (2015). Brain Genomics Superstruct Project initial data release with structural, functional, and behavioral measures. Scientific Data, 2(1), 1–16. doi:10.1038/sdata.2015.31

25. Jung, J., Kang, J., Won, E., Nam, K., Lee, M.-S., Tae, W. S., & Ham, B.-J. (2014). Impact of lingual gyrus volume on antidepressant response and neurocognitive functions in Major Depressive Disorder: a voxel-based morphometry study. Journal of Affective Disorders, 169, 179–187. doi:10.1016/j.jad.2014.08.018

26. Kang, S.-G., & Cho, S.-E. (2020). Neuroimaging Biomarkers for Predicting Treatment Response and Recurrence of Major Depressive Disorder. International Journal of Molecular Sciences, 21(6). doi:10.3390/ijms21062148

27. Karatzoglou, A., Smola, A., Hornik, K., & Zeileis, A. (2004). kernlab -- An S4 Package for Kernel Methods in R. Journal of Statistical Software, Vol. 11, pp. 1–20. Retrieved from http://www.jstatsoft.org/v11/i09/

28. Kaufmann, T., van der Meer, D., Doan, N. T., Schwarz, E., Lund, M. J., Agartz, I., … Westlye, L. T. (2019). Common brain disorders are associated with heritable patterns of apparent aging of the brain. Nature Neuroscience, 22(10), 1617–1623. Retrieved from

http://libaccess.mcmaster.ca/login?url=https://search.proquest.com/docview/2369526729?accountid=12347

29. Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia Bulletin, 13(2), 261–276. doi:10.1093/schbul/13.2.261

30. Kennedy, S. H., Lam, R. W., Rotzinger, S., Milev, R. V., Blier, P., Downar, J., … CAN-BIND Investigator Team. (2019). Symptomatic and Functional Outcomes and Early Prediction of Response to Escitalopram Monotherapy and Sequential Adjunctive Aripiprazole Therapy in Patients With Major Depressive Disorder: A CAN-BIND-1 Report. The Journal of Clinical Psychiatry, 80(2). doi:10.4088/JCP.18m12202

31. Kolenic, M., Franke, K., Hlinka, J., Matejka, M., Capkova, J., Pausova, Z., … Hajek, T. (2018). Obesity, dyslipidemia and brain age in first-episode psychosis. Journal of Psychiatric Research, 99, 151–158. Retrieved from http://libaccess.mcmaster.ca/login?url=https://search.proquest.com/docview/2024146447?accountid=12347

32. Koutsouleris, N., Davatzikos, C., Borgwardt, S., Gaser, C., Bottlender, R., Frodl, T., … Meisenzahl, E. (2014). Accelerated brain aging in schizophrenia and beyond: A neuroanatomical marker of psychiatric disorders. Schizophrenia Bulletin, 40(5), 1140–1153. Retrieved from http://libaccess.mcmaster.ca/login?url=https://search.proquest.com/docview/1604738796?accountid=12347

33. Kurtzke, J. F. (1983). Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology, 33(11), 1444–1452. doi:10.1212/wnl.33.11.1444

34. Lam, R. W., Milev, R., Rotzinger, S., Andreazza, A. C., Blier, P., Brenner, C., … CAN-BIND Investigator Team. (2016). Discovering biomarkers for antidepressant response: protocol from the Canadian biomarker integration network in depression (CAN-BIND) and clinical characteristics of the first patient cohort. BMC Psychiatry, 16, 105. doi:10.1186/s12888-016-0785-x

35. Luders, E., Cherbuin, N., & Gaser, C. (2016). Estimating brain age using high-resolution pattern recognition: Younger brains in long-term meditation practitioners. NeuroImage, 134, 508–513. doi:10.1016/j.neuroimage.2016.04.007

36. MacQueen, G. M., Hassel, S., Arnott, S. R., Jean, A., Bowie, C. R., Bray, S. L., … CAN-BIND Investigator Team. (2019). The Canadian Biomarker Integration Network in Depression (CAN-BIND): magnetic resonance imaging protocols. Journal of Psychiatry & Neuroscience: JPN, 44(4), 223–236. doi:10.1503/jpn.180036

37. Marcus, D. S., Wang, T. H., Parker, J., Csernansky, J. G., Morris, J. C., & Buckner, R. L. (2007). Open Access Series of Imaging Studies (OASIS): cross-sectional MRI data in young, middle aged, nondemented, and demented older adults. Journal of Cognitive Neuroscience, 19(9), 1498–1507. doi:10.1162/jocn.2007.19.9.1498

38. Montgomery, S. A., & Asberg, M. (1979). A new depression scale designed to be sensitive to change. The British Journal of Psychiatry: The Journal of Mental Science, 134, 382–389. doi:10.1192/bjp.134.4.382

39. Nenadić, I., Dietzek, M., Langbein, K., Sauer, H., & Gaser, C. (2017). BrainAGE score indicates accelerated brain aging in schizophrenia, but not bipolar disorder. Psychiatry Research: Neuroimaging, 266, 86–89. Retrieved from http://libaccess.mcmaster.ca/login?url=https://search.proquest.com/docview/1938690105?accountid=12347

40. Ning, K., Zhao, L., Matloff, W., Sun, F., & Toga, A. W. (2020). Association of relative brain age with tobacco smoking, alcohol consumption, and genetic variants. Scientific Reports, 10(1), 10. doi:10.1038/s41598-019-56089-4

41. Nooner, K. B., Colcombe, S. J., Tobe, R. H., Mennes, M., Benedict, M. M., Moreno, A. L., … Milham, M. P. (2012). The NKI-Rockland Sample: A Model for Accelerating the Pace of Discovery Science in Psychiatry. Frontiers in Neuroscience, 6, 152. doi:10.3389/fnins.2012.00152

42. Ritchie, S. J., Cox, S. R., Shen, X., Lombardo, M. V., Reus, L. M., Alloza, C., … Deary, I. J. (2018). Sex Differences in the Adult Human Brain: Evidence from 5216 UK Biobank Participants. Cerebral Cortex , 28(8), 2959–2975. doi:10.1093/cercor/bhy109

43. Schmaal, L., Pozzi, E., C Ho, T., van Velzen, L. S., Veer, I. M., Opel, N., … Veltman, D. J. (2020). ENIGMA MDD: seven years of global neuroimaging studies of major depression through worldwide data sharing. Translational Psychiatry, 10(1), 172. doi:10.1038/s41398-020-0842-6

44. Schnack, H. G., van Haren, N. E. M., Nieuwenhuis, M., Hulshoff Pol, H. E., Cahn, W., & Kahn, R. S. (2016). Accelerated brain aging in schizophrenia: A longitudinal pattern recognition study. The American Journal of Psychiatry, 173(6), 607–616. Retrieved from

http://libaccess.mcmaster.ca/login?url=https://search.proquest.com/docview/1821806624?accountid=12347

45. Shevlyakov, G., Andrea, K., Choudur, L., Smirnov, P., Ulanov, A., & Vassilieva, N. (2013, May). Robust versions of the Tukey boxplot with their application to detection of outliers. 2013 IEEE International Conference on Acoustics, Speech and Signal Processing, 6506–6510. doi:10.1109/ICASSP.2013.6638919

46. Steffener, J., Habeck, C., O'Shea, D., Razlighi, Q., Bherer, L., & Stern, Y. (2016). Differences between chronological and brain age are related to education and self-reported physical activity. Neurobiology of Aging, 40, 138–144. doi:10.1016/j.neurobiolaging.2016.01.014

47. Suh, J. S., Minuzzi, L., Raamana, P. R., Davis, A., Hall, G. B., Harris, J., … Frey, B. N. (2020). An investigation of cortical thickness and antidepressant response in major depressive disorder: A CAN-BIND study report. NeuroImage. Clinical, 25, 102178. doi:10.1016/j.nicl.2020.102178

48. Teeuw, J., Ori, A. P. S., Brouwer, R. M., de Zwarte, S. M. C., Schnack, H. G., Hulshoff Pol, H. E., & Ophoff, R. A. (2021). Accelerated aging in the brain, epigenetic aging in blood, and polygenic risk for schizophrenia. Schizophrenia Research, 231, 189–197. doi:10.1016/j.schres.2021.04.005

49. Wang, J., Knol, M. J., Tiulpin, A., Dubost, F., de Bruijne, M., Vernooij, M. W., … Roshchupkin, G. V. (2019). Gray Matter Age Prediction as a Biomarker for Risk of Dementia. Proceedings of the National Academy of Sciences of the United States of America, 116(42), 21213–21218. doi:10.1073/pnas.1902376116

50. Wei, D., Zhuang, K., Ai, L., Chen, Q., Yang, W., Liu, W., … Qiu, J. (2018). Structural and functional brain scans from the cross-sectional Southwest University adult lifespan dataset. Scientific Data, 5(1), 1–10. doi:10.1038/sdata.2018.134

51. Young, L. T. (2002). Neuroprotective effects of antidepressant and mood stabilizing drugs. Journal of Psychiatry & Neuroscience: JPN, 27(1), 8–9. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11836978

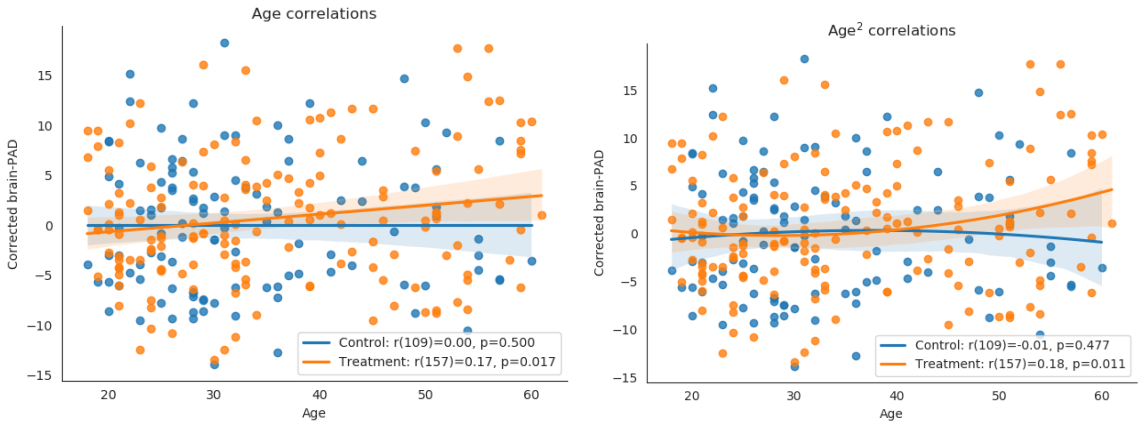

Figure 1. Associations between age-corrected brain-PAD and chronological age for healthy control and treatment groups. On the left, chronological age is significantly associated with brain-PAD in the treatment group. Similarly, on the right, chronological age^2 was significantly associated with brain-PAD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

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

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

Table 2. Demographic characteristics of the study sample

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

1. (c) stands for age-corrected values

2. MADRS: Montgomery-Asberg Depression Rating Scale

Chapter 5: Gray matter volume and ventricle size drive the brain age gap in schizophrenia: A SHAP study

Pedro L. Ballester[1]; Jee Su Suh[1], James P. Reilly[2], Benicio N. Frey[3,4]

1. Neuroscience Graduate Program, McMaster University, Hamilton, Ontario, Canada

2. Department of Electrical and Computer Engineering, McMaster University, Hamilton, Ontario, Canada

3. Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada

4. Mood Disorders Treatment and Research Centre, and Women's Health Concerns Clinic, St. Joseph's Healthcare, Hamilton, Canada

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Abstract

Brain age is a neuroimaging biomarker that is generated by machine learning predictions. The brain age gap (BAG) is typically defined as the difference between the brain age prediction and chronological age. Studies have consistently reported a positive BAG in individuals with schizophrenia (SCZ). However, there is little understanding of which specific factors drive the machine learning-based brain age predictions, leading to limited biological interpretations of the BAG. We gathered data from three publicly available databases - COBRE, MCIC, and UCLA - and calculated brain age with pre-trained gradient-boosted trees. Then, we applied SHapley Additive Explanations (SHAP) to identify which brain features influence brain age predictions. We investigated the interaction between the SHAP score for each feature and group as a function of the BAG. These identified *total gray matter volume* (group x SHAP interaction term β=2.36 [1.16; 3.56]; $p_{corr} < 0.01$) and *right lateral ventricle volume* (β=1.02 [0.30, 1.74]; $p_{corr} < 0.05$) as the two features that most influence the BAG observed in SCZ. Other brain features also presented differences in SHAP values between SCZ and HC, but they were not significantly associated with the BAG. This study has important implications in the understanding of brain age prediction models and the BAG in SCZ and, potentially, in other psychiatric disorders.

Keywords: brain age; brain age gap; machine learning; model explanation; schizophrenia.

5.1 Introduction

Schizophrenia (SCZ) is a major psychiatric disorder characterized by psychotic episodes, marked alterations in cognition and impaired functioning with high rates of disability[1]. Brain imaging studies have shown that schizophrenia presents a chronic course accompanied by progressive brain alterations, such as gray and white matter volume loss and ventricle enlargement[2–4]. Some of these alterations have been postulated to be associated with a process named "accelerated aging"[5,6]. This hypothesis has led to a growing number of studies evaluating brain patterns suggestive of accelerated aging in psychotic and other major mental disorders[6–9]. These analyses involve the training of machine learning (ML) regression models to generate brain age predictions. The ML models are trained with structural neuroimaging data from healthy individuals paired with their chronological age. The underlying assumption is that the brain age of healthy individuals should match their chronological age. It was then demonstrated that these models overestimate brain age in individuals with SCZ (i.e., their brain age, based on ML model predictions, is higher than their chronological age)[8,10–12]. This difference between predicted brain age and chronological age is called the *brain age gap* (BAG). Meta-analyses of BAG in SCZ found that it was associated with chronological age[13], and longitudinal findings have demonstrated that the BAG increases in the first few years after illness onset[6].

At first glance, these findings support the hypothesis of the neurobiological theory of accelerated aging in schizophrenia[14]. However, the reasons behind these increased prediction values have yet to be explored. Thus far, studies have solely investigated

model-level explanations by extracting feature importance metrics from ML models, summarizing the contribution of all training data[15,16]. These findings have identified the thickness of cortical areas, the size of the ventricles, and the volume of subcortical regions such as the thalamus and the putamen as the most relevant features for brain age prediction. The feature relevance analyses published thus far carry two limitations: 1) model-level feature importance precludes any investigation of whether or how certain features differentially contribute to individual model predictions; and 2) the most relevant features for the prediction of brain age in healthy subjects or in individuals with SCZ may not be the same features that are associated with the BAG in SCZ. *Participant-level* explanations may help circumvent both limitations. SHapley Additive exPlanations[18] (SHAP) is a participant-level explanation method that measures the marginal contribution of each feature to a given prediction generated by a tree-based nonlinear model. In other words, SHAP values are obtained for all features for each individual participant, resulting in a data matrix of the same dimensions as the original dataset of imaging features. Therefore, SHAP values can: 1) enable the comparison of the mean and standard deviation of SHAP values of brain features between groups; and 2) enable a more granular characterization of the relationships between BAG and the influence of individual features on each participant's brain age prediction.

Given the consistent findings of larger BAG in SCZ but with little understanding of the behavior of the brain age prediction models, we used 3 publicly available datasets (COBRE, MCIC, UCLA) with individuals with SCZ and healthy comparison participants (HC) to understand what drives the BAG in SCZ using SHAP values. Our primary

objective was to identify which features from the brain age model more strongly drive the higher BAG in SCZ. Our secondary objectives were: 1) to replicate previous findings on the positive BAG observed in SCZ and 2) to estimate the group differences in feature contributions (SHAP values) to the brain age prediction.

5.2 Results

5.2.1 Group differences in brain age gap (BAG)

The mean absolute errors (MAE) of the brain age prediction model for HC in the COBRE, MCIC, and UCLA datasets were 7.21, 5.61, and 8.02 years, respectively. Their respective mean absolute percentage errors were 21.87%, 16.84%, and 28.16%, with Pearson correlations of $r=0.71$ ($p<0.01$); $r=0.80$ ($p<0.01$); and $r=0.73$ ($p<0.01$) between predicted brain age and chronological age. The group difference in BAG was significant in two of the three datasets, after adjusting for chronological age and sex. For COBRE, the group term was significantly associated with BAG ($\beta= 4.80$ [2.40; 7.20]; $p < 0.01$), with SCZ presenting a higher BAG than HC; chronological age was also significantly associated with BAG ($\beta=-0.27$ [-0.36; -0.17]; $p < 0.01$). The results were similar for the MCIC dataset: the SCZ group exhibited a larger BAG compared to HC ($\beta=6.87$ [4.67; 9.04]; $p < 0.01$) and age was also significantly associated with the BAG ($\beta=-0.11$ [-0.21; -0.02], $p < 0.03$). However, in the UCLA dataset, the BAG was not associated with group ($\beta=2.10$ [-0.40; 4.54]; $p=0.10$), but it was significantly associated with both age ($\beta=-0.15$ [-0.27; -0.03]; $p < 0.03$) and sex ($\beta=-3.67$ [-5.87; -1.46]; $p < 0.01$).

5.3 Group differences in SHAP values for brain age prediction

Following the generation of brain age predictions, we calculated the SHAP value for each feature, i.e., the absolute value of its contribution to the brain age prediction, for each participant. These absolute values were then averaged over all participants, regardless of group, in each dataset. The top ten most relevant features based on mean absolute contribution to the prediction were extracted from all three databases. The union of the top 10 most relevant features of each database led to a total of 11 features. Mean SHAP values for these 11 features were compared between SCZ and HC (Figure 1). We adjusted for multiple comparisons with the false discovery rate method. The SHAP for total gray matter volume was the only variable that was consistently different between groups across the three datasets ($p_{corr} < 0.05$). For the COBRE dataset, the group difference in SHAP values was additionally significant for volume of the right putamen. For the MCIC dataset, the following features exhibited SHAP values that were also significantly different between groups: volumes of the brain stem and right thalamus, and thickness of both the right superior temporal sulcus (ventral anterior and dorsal posterior parts) and the left superior temporal sulcus (ventral posterior part). In the UCLA dataset, no mean SHAP value other than that of total gray matter volume was significantly different between groups.

5.4 BAG as a function of group and SHAP

All three databases were combined to test the interaction between the mean SHAP values of each feature and group with respect to the BAG. This analysis identified brain

features whose contributions to brain age prediction were more strongly associated with the BAG in one group more than in the other. For each of the 11 top brain features identified in the previous section, we tested a model of the relationship between BAG and the group x SHAP interaction, with group, SHAP, age, sex, and database as independent variables. In this analysis, only two group x SHAP interactions were significant: total gray matter volume (β=2.36 [1.16; 3.56]; $p_{corr} < 0.01$) and right lateral ventricle (β=1.02 [0.30, 1.74]; $p_{corr} < 0.05$). The univariate relationships between 1) BAG and SHAP values of total gray matter volume and 2) BAG and SHAP values of right lateral ventricle volume are displayed in Figure 2.

5.5 Discussion

The findings from this study shed light on the brain features underlying the consistent, yet mechanistically poorly understood, finding of a positive BAG in SCZ. Using SHAP analyses, we found that total gray matter volume and right lateral ventricle volume were the strongest features influencing the BAG in SCZ. The thickness of the bilateral superior temporal sulcus and the volumes of certain subcortical structures - brain stem, putamen, and thalamus - also differed in SHAP values between SCZ and HC, but these respective interactions did not seem to be associated with the BAG. These findings have important implications in the way we interpret the BAG in SCZ and, possibly, other psychiatric disorders.

The strongest interaction signal in the BAG analysis came from the SHAP for total gray matter volume. The second strongest signal from the interaction analysis was the

SHAP for the right ventricle volume. These results are aligned with a large body of research describing both gray matter reduction and ventricle enlargement in SCZ[20–23]. Total gray matter volume reduction has been widely reproduced in SCZ research[2] as well as being associated with the natural process of aging[24]. Ventricle enlargement is also a product of gray matter volume loss, as CSF fills the space vacated by impacted areas[25,26]. These two related features represent large portions of the brain, which may partly explain their contribution to the BAG in SCZ. Likewise, other interactions with features representing smaller portions of the brain might exist that were not significant in our analysis due to the limitations imposed by the resolution of the MRI data and/or a stringent correction for multiple comparisons. Based on current pipelines of brain age prediction in SCZ, the BAG is mostly a reflection of the alterations observed in these two brain features. Moreover, our analysis revealed at least two other characteristics of the relationship between the BAG and brain age predictions. First, the feature importance order for brain age prediction (ranks from Figure 1) does not determine the most relevant features for BAG group differences. For instance, the top 3 variables for brain age prediction (third ventricle volume, right hemisphere dorsal posterior superior temporal sulcus, and left hemisphere ventral posterior superior temporal sulcus) had no significant interaction with group when regressed on the BAG, meaning they did not influence the BAG in SCZ more than in HC. Secondly, group differences in SHAP values of certain features (p-values from Figure 1) do not reflect the influence of those features on the BAG observed in SCZ. For instance, the right lateral ventricle volume was one of the two significant variables driving the BAG in SCZ as per the interaction analysis, but there

were no statistically significant differences in SHAP values of this variable between SCZ and HC in any dataset.

Beyond providing an explanation for the BAG in SCZ, our analyses have also contributed to the understanding of the behavior of brain age prediction models in SCZ. Our first analysis replicated previous findings of BAG in SCZ. Most previous studies, with a few exceptions in epigenetic analyses[27,28], have consistently demonstrated patterns suggesting "accelerated aging" in SCZ[6–8,10,11]. Although the UCLA dataset did not present a significant group difference in BAG, it also has the smallest sample size and an age-matching issue. Our secondary analysis presents a novel finding that the SHAP values of certain brain features differ significantly between HC and SCZ, which indicates that the ML model behaves differently between the groups. Overall, these results suggest that specific structural brain characteristics of individuals with SCZ affect the behavior of the model when predicting brain age in those individuals. Total gray matter volume was the only feature whose SHAP values were consistently different between groups across all databases, while the thickness of the superior temporal sulcus and subcortical structures presented differences in contribution in one out of three datasets. These results can likely be attributed to the heterogeneity within and between cohorts and differences in MRI acquisition across datasets. This analysis on its own, however, does not indicate that the brain features identified are implicated in the observed difference of the BAG in SCZ. For that, testing the interaction between SHAP values and group as a function of the BAG was necessary, as discussed above.

Our study should be interpreted in the light of some limitations. First, algorithms other than XGBoost might exhibit different behavior than what was uncovered in this study, although recent studies have demonstrated that different model types lead to similar results in brain age and feature importance[30]. Specific characteristics of the training sets used in different studies may lead to different outcomes. Also, the training dataset from Kaufmann et al.[12] may have included some of the samples from the COBRE and MCIC datasets. We analyzed the potential for overfitting and only a small subset of participants had a prediction error of less than one year. This indicates that our findings are unlikely to be affected by this issue. Potential MRI scanner/site effects were not investigated, although database was included as a factor in the interaction analyses using the combined sample to account for at least part of this effect. Finally, this study was based on structural brain features, which may not capture the association of brain age/BAG with functional brain features as assessed with functional MRI or electroencephalography. This study also presents several strengths. The use of public datasets and publicly available models allows this study to be fully reproducible and its findings may be independently verified. Additionally, to the best of our knowledge, the use of SHAP for comparing groups is a relatively novel approach in brain age research. Irrespective of the technical specifics of how the BAG is defined and how the model behaves, BAG has been shown to be an important imaging marker for the disorder[29,31]. From predicting mortality risk[32] to predicting risk of dementia[33], there are many potential applications of the BAG in health-related research.

Future studies should consider exploring a wider set of machine learning models and their different behaviors in predicting brain age. Feature importance methods other than SHAP may also be useful to further investigate model behavior, such as LIME[34] and counterfactual generation[35]. Other datasets and analyses in SCZ with more in-depth clinical characterization may also help to identify the effects of medication use, lifestyle, quality of life, BMI, smoking status, and other measures that may impact findings. A natural next step is to investigate model behaviour in other neurological diseases and psychiatric disorders, such as bipolar disorder and Alzheimer's disease, both of which have been reported to exhibit a BAG[36,37].

In conclusion, this study has demonstrated the potential of feature explanation methods to better explain brain age prediction models and the BAG. In this case, the BAG in SCZ was found to be driven mainly by two brain imaging features, *total gray matter volume* and *right lateral ventricle volume*. These findings may open new venues to improve the interpretation of BAG findings in SCZ and other psychiatric disorders.

5.6 Methods

5.6.1 Databases

Three databases were included in this study: a study from The Center for Biomedical Research Excellence (COBRE)[38,39], the MCIC database[40], and the UCLA Consortium for Phenomics database[41,42] (UCLA). The demographic characteristics of the participants from each independent database that were included in this study is presented in Table 1.

The COBRE dataset includes HC participants (N=93) and participants diagnosed with SCZ (N=90). A multi-echo MPRAGE sequence was used to collect neuroimaging data from all participants alongside basic sociodemographic and clinical information. The database also includes functional neuroimaging data that was not used in this study.

The MCIC is a database of participants in the early course of their illnesses and includes HC participants (N=109) and participants diagnosed with SCZ/schizoaffective disorder (N=94) The MCIC database also includes functional and diffusion-weighted imaging data that were not used in this study. Data used in the preparation of this work were obtained from the Mind Clinical Imaging Consortium database through the Mind Research Network (www.mrn.org). The MCIC project was supported by the Department of Energy under Award Number DE-FG02-08ER64581. MCIC is the result of efforts of co-investigators from University of Iowa, University of Minnesota, University of New Mexico, Massachusetts General Hospital, where participants were recruited.

The UCLA database includes HC participants (N=125) and participants diagnosed with SCZ (N=50). The database includes extensive neuropsychiatric and cognitive assessments alongside anatomical and functional neuroimaging data. Participants were recruited through the community and local clinics. A 3T Siemens Trio scanner was used to collect the data. Functional and diffusion-weighted imaging data are also available and were not used in this study. This data was obtained from the OpenfMRI database (https://openfmri.org/dataset/ds000030/). Its accession number is ds000030.

5.6.2 Brain age prediction and age correction

The brain age prediction models (one for males and one for females) were pretrained in a large database in another study[12]. The authors of this study made their models available online[5]. The code was executed in R (version 3.6.3). In line with the original study, we used separate models for males and females. The models are gradient boosted trees generated by the XGBoost[43] method. The models rely on 1084 features from the Human Connectome Project (HCP) atlas[44]. There are 360 features for volume, 360 for surface area, and 360 for cortical thickness (180 from each hemisphere), alongside 30 subcortical volumes and 8 summary variables. The average chronological ages from the pretrained models were 48.01 for males and 46.63 for females.

Brain age predictions suffer from an age-dependency[45], for which an age-correction procedure was conducted[45]. This procedure fits a linear model between predicted age and age of HC participants. Then, an age-corrected predicted age is derived for both HC and SCZ based on the slope, intercept, and predicted age extracted from the HC group. The rationale for this method is to ensure that the model has a consistent error across the lifespan for HC participants. This procedure was done independently for each database. All further analyses, except for group comparisons of the BAG to avoid circular analysis, used the age-corrected BAG.

[5] https://github.com/tobias-kaufmann/brainage

5.6.3 Image preprocessing

All three databases underwent the same pipeline of feature extraction with slight adjustments in their processing steps. Images that were available in DICOM format were converted into NIFTI format using the *dcm2niix* tool. For the COBRE dataset, which had multi-echo scans, the root mean squared (RMS) equivalent volume was used. Then, the *recon-all* command from FreeSurfer (version 6.0.0) was run for each scan. We used the multimodal HCP[44] atlas to extract the features that are expected by the brain age prediction model, spanning volume, area, and thickness measures. The segmentations were checked for major registration and out-of-the-brain segmentation errors using the platform VisualQC[6] (0.5.2).

5.6.4 Deriving participant-level explanations using SHAP

Unlike linear regression models, where each feature is associated with a coefficient that may be interpreted as its average contribution across samples, nonlinear models are not as simple. In the case of nonlinear tree-based models, each feature may have a different contribution depending on the path an individual prediction took in the tree. Therefore, model-level interpretations based on average feature contribution do not fully explain each prediction. To circumvent this issue, model explanations need to be derived at a participant level, detailing how each independent prediction was derived. SHAP is a method based on game theory that extracts marginal contributions of features from predictions[46]. The SHAP value for a specific feature for an individual prediction may be

[6] https://github.com/raamana/visualqc

understood as the difference in the prediction when that feature is left out of the decision tree (marginal contribution). To illustrate, in a database with N participants and M features, SHAP generates a table of N x M explanations, where each value $V^{(i,j)}$ represents the contribution of feature *j* to the model prediction of participant *i*. SHAP values were extracted using the SHAPforxgboost package in R[7]. In the case of XGBoost, SHAP values represent the contribution of each feature to the deviation of the prediction from the mean age of the database (the starting point of the XGBoost model).

5.6.5 Statistical analyses

All statistical analyses were performed in Python (version 3.7.4) with Scipy (version 1.3.1) and Statsmodels (version 0.10.1). The statistical analyses are separated in three parts: 1) replication of previous findings of BAG differences between SCZ and HC, 2) group comparison of SHAP values for each of the 11 most important features, and 3) BAG as a function of the interaction between group and SHAP and other covariates.

First, we analyzed whether there were significant differences in the BAG between HC and SCZ participants separately for each database. This difference was assessed using a general linear model, with BAG as the dependent variable and group as the independent variable, with age and sex included as covariates. To avoid circular analysis, this part was done with the BAG prior to age-correction. Subsequent analyses were conducted with the age-corrected values.

[7] https://cran.r-project.org/web/packages/SHAPforxgboost/index.html

Second, we investigated whether the SHAP values were different between groups separately for each database. We limited the comparisons to the union of the 10 most relevant features based on their mean absolute contribution across groups from the three databases. We employed a Mann-Whitney U-test due to the non-normal distribution of SHAP values.

Finally, we combined datasets to assess whether there was a differential effect of feature contribution to the BAG between groups using an interaction term. This modeling was done using robust regression to avoid the shortcomings of linear models[47]. The age-corrected BAG was the dependent variable, while age, sex, group, SHAP, and group x SHAP were the independent variables. The group x SHAP term was of interest, as it represents the difference between groups in how SHAP values relate to the BAG.

Competing Interests

P.L.B, J.S, J.P.R, and B.N.F report no conflicts of interest.

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Data availability statement

All data used for this work and the associated code to reproduce the experiments are available at GitHub (https://github.com/Ballester/brain-age-shap).

References

1. Charlson, F. J. *et al.* Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study 2016. *Schizophrenia bulletin* **44**, 1195–1203 (2018).

2. Cropley, V. L. *et al.* Accelerated Gray and White Matter Deterioration With Age in Schizophrenia. *Am. J. Psychiatry* **174**, 286–295 (2017).

3. Olabi, B. *et al.* Are there progressive brain changes in schizophrenia? A meta-analysis of structural magnetic resonance imaging studies. *Biological psychiatry* **70**, 88–96 (2011).

4. Keshavan, M. S. *et al.* Neuroimaging in Schizophrenia. *Neuroimaging Clin. N. Am.* **30**, 73–83 (2020).

5. Kirkpatrick, B., Messias, E., Harvey, P. D., Fernandez-Egea, E. & Bowie, C. R. Is Schizophrenia a Syndrome of Accelerated Aging? *Schizophr. Bull.* **34**, 1024–1032 (2008).

6. Schnack, H. G. *et al.* Accelerated brain aging in schizophrenia: A longitudinal pattern recognition study. *Am. J. Psychiatry* **173**, 607–616 (2016).

7. Hajek, T. *et al.* Brain age in early stages of bipolar disorders or schizophrenia. *Schizophr. Bull.* **45**, 190–198 (2019).

8. Nenadić, I., Dietzek, M., Langbein, K., Sauer, H. & Gaser, C. BrainAGE score indicates accelerated brain aging in schizophrenia, but not bipolar disorder. *Psychiatry Research: Neuroimaging* **266**, 86–89 (2017).

9. Koutsouleris, N. *et al.* Accelerated brain aging in schizophrenia and beyond: A neuroanatomical marker of psychiatric disorders. *Schizophr. Bull.* **40**, 1140–1153 (2014).

10. Shahab, S. *et al.* Brain structure, cognition, and brain age in schizophrenia, bipolar disorder, and healthy controls. *Neuropsychopharmacology* **44**, 898–906 (2019).

11. Tønnesen, S. *et al.* Brain Age Prediction Reveals Aberrant Brain White Matter in Schizophrenia and Bipolar Disorder: A Multisample Diffusion Tensor Imaging Study. *Biol Psychiatry Cogn Neurosci Neuroimaging* **5**, 1095–1103 (2020).

12. Kaufmann, T. *et al.* Common brain disorders are associated with heritable patterns of apparent aging of the brain. *Nat. Neurosci.* **22**, 1617–1623 (2019).

13. Ballester, P. L. *et al.* Brain age in mood and psychotic disorders: A systematic review and meta-analysis. *Acta Psychiatr. Scand.* (2021).

14. Kirkpatrick, B., Messias, E., Harvey, P. D., Fernandez-Egea, E. & Bowie, C. R. Is schizophrenia a syndrome of accelerated aging? *Schizophr. Bull.* **34**, 1024–1032 (2008).

15. Ballester, P. L. *et al.* Predicting Brain Age at Slice Level: Convolutional Neural Networks and Consequences for Interpretability. *Frontiers in Psychiatry* **12**, (2021).

16. Lombardi, A. *et al.* Brain Age Prediction With Morphological Features Using Deep Neural Networks: Results From Predictive Analytic Competition 2019. *Frontiers in Psychiatry* **11**, (2021).

17. Lombardi, A. *et al.* Extensive Evaluation of Morphological Statistical Harmonization for Brain Age Prediction. *Brain Sci* **10**, (2020).

18. Lundberg, S. M. & Lee, S.-I. A Unified Approach to Interpreting Model Predictions. in *Advances in Neural Information Processing Systems 30* (eds. Guyon, I. et al.) 4765–4774 (Curran Associates, Inc., 2017).

19. Fjell, A. M. & Walhovd, K. B. Structural brain changes in aging: courses, causes and cognitive consequences. *Reviews in the neurosciences* **21**, 187–221 (2010).

20. Hulshoff Pol, H. E. *et al.* Volume changes in gray matter in patients with schizophrenia. *The American journal of psychiatry* **159**, 244–50 (2002).

21. Gaser, C., Nenadic, I., Buchsbaum, B. R., Hazlett, E. A. & Buchsbaum, M. S. Ventricular enlargement in schizophrenia related to volume reduction of the thalamus, striatum, and superior temporal cortex. *The American journal of psychiatry* **161**, 154–6 (2004).

22. Horga, G. *et al.* Correlations between ventricular enlargement and gray and white matter volumes of cortex, thalamus, striatum, and internal capsule in schizophrenia. *European archives of psychiatry and clinical neuroscience* **261**, 467–76 (2011).

23. Sayo, A., Jennings, R. G. & van Horn, J. D. Study factors influencing ventricular enlargement in schizophrenia: a 20 year follow-up meta-analysis. *NeuroImage* **59**, 154–67 (2012).

24. Pfefferbaum, A. *et al.* Variation in longitudinal trajectories of regional brain volumes of healthy men and women (ages 10 to 85 years) measured with atlas-based parcellation of MRI. *NeuroImage* **65**, 176–93 (2013).

25. Walhovd, K. B. *et al.* Effects of age on volumes of cortex, white matter and subcortical structures. *Neurobiology of aging* **26**, 1261–70; discussion 1275-8 (2005).

26. Madsen, S. K. *et al.* Mapping ventricular expansion onto cortical gray matter in older adults. *Neurobiology of aging* **36 Suppl 1**, S32-41 (2015).

27. Voisey J. *et al.* Epigenetic analysis confirms no accelerated brain aging in schizophrenia. *npj Schizophrenia* **3**, 26 (2017).

28. McKinney B.C., Lin H., Ding Y. & Lewis D.A. DNA methylation evidence against the accelerated aging hypothesis of schizophrenia. *npj Schizophrenia* **3**, 13 (2017).

29. Franke, K. & Gaser, C. Ten Years of BrainAGE as a Neuroimaging Biomarker of Brain Aging: What Insights Have We Gained? *Front. Neurol.* **10**, 789 (2019).

30. Ball, G., Kelly, C. E., Beare, R. & Seal, M. L. Individual variation underlying brain age estimates in typical development. *NeuroImage* **235**, 118036 (2021).

31. Cole, J. H. & Franke, K. Predicting Age Using Neuroimaging: Innovative Brain Ageing Biomarkers. *Trends Neurosci.* **40**, 681–690 (2017).

32. Cole, J. H. *et al.* Brain age predicts mortality. *Mol. Psychiatry* **23**, 1385–1392 (2018).

33. Wang, J. *et al.* Gray Matter Age Prediction as a Biomarker for Risk of Dementia. *Proc. Natl. Acad. Sci. U. S. A.* **116**, 21213–21218 (2019).

34. Ribeiro, M. T., Singh, S. & Guestrin, C. "Why Should I Trust You?": Explaining the Predictions of Any Classifier. (2016).

35. Wachter, S., Mittelstadt, B. & Russell, C. Counterfactual Explanations without Opening the Black Box: Automated Decisions and the GDPR. *Harvard Journal of Law & Technology* (2018).

36. van Gestel H. *et al.* Brain age in bipolar disorders: Effects of lithium treatment. *Aust. N. Z. J. Psychiatry* **53**, 1179–1188 (2019).

37. Franke, K. & Gaser, C. Longitudinal changes in individual BrainAGE in healthy aging, mild cognitive impairment, and Alzheimer's disease. *GeroPsych: The Journal of Gerontopsychology and Geriatric Psychiatry* **25**, 235 (2012).

38. Aine, C. J. *et al.* Multimodal Neuroimaging in Schizophrenia: Description and Dissemination. *Neuroinformatics* **15**, 343–364 (2017).

39. Aine, C. J. *et al.* Multimodal Neuroimaging in Schizophrenia: Description and Dissemination. *Neuroinformatics* **15**, 343–364 (2017).

40. Gollub, R. L. *et al.* The MCIC collection: a shared repository of multi-modal, multi-site brain image data from a clinical investigation of schizophrenia. *Neuroinformatics* **11**, 367–388 (2013).

41. Gorgolewski, K. J., Durnez, J. & Poldrack, R. A. Preprocessed Consortium for Neuropsychiatric Phenomics dataset. *F1000Research* **6**, 1262 (2017).

42. Poldrack, R. A. *et al.* A phenome-wide examination of neural and cognitive function. *Scientific data* **3**, 160110 (2016).

43. Chen, T. & Guestrin, C. Xgboost: A scalable tree boosting system. in *Proceedings of the 22nd acm sigkdd international conference on knowledge discovery and data mining* 785–794 (2016).

44. Glasser, M. F. *et al.* A multi-modal parcellation of human cerebral cortex. *Nature* **536**, 171–178 (2016).

45. Beheshti, I., Nugent, S., Potvin, O. & Duchesne, S. Bias-adjustment in neuroimaging-based brain age frameworks: A robust scheme. *Neuroimage Clin* **24**, 102063 (2019).

46. Shapley, L. S. A value for n-person games. *Contributions to the Theory of Games* (1953).

47. Huber, P. J. Robust Regression: Asymptotics, Conjectures and Monte Carlo. *The Annals of Statistics* **1**, (1973).

Tables

Table 1. Demographic characteristics of participants from included databases.

Database		Control	Treatment	Total	*p-value*
COBRE*	**N**	93	90	183	
	Age				0.99
	Mean (SD)	37.63 (11.66)	37.61 (13.66)	37.62 (12.65)	
	Range	18 - 65	18 - 65	18 – 65	
	Sex				0.28
	Female	26 (27.96%)	18 (20.00%)	44 (24.04%)	
	Male	67 (72.04%)	72 (80.00%)	139 (75.96%)	
MCIC	**N**	109	94	203	
	Age				0.47
	Mean (SD)	32.64 (11.97)	33.81 (11.20)	33.27 (11.55)	
	Range	18 - 60	18 - 60	18 – 60	
	Sex				0.26
	Female	30 (31.91)	26 (23.85)	56 (27.59)	
	Male	64 (68.09)	83 (76.15)	147 (72.41)	
UCLA	**N**	125	50	175	
	Age				< 0.01
	Mean (SD)	31.53 (8.80)	36.46 (8.88)	32.94 (9.07)	
	Range	21 – 50	22 – 49	21 – 50	
	Sex				0.01
	Female	59 (47.20)	12 (24.00)	71 (40.57)	
	Male	66 (52.80)	38 (76.00)	104 (59.43)	

Figures

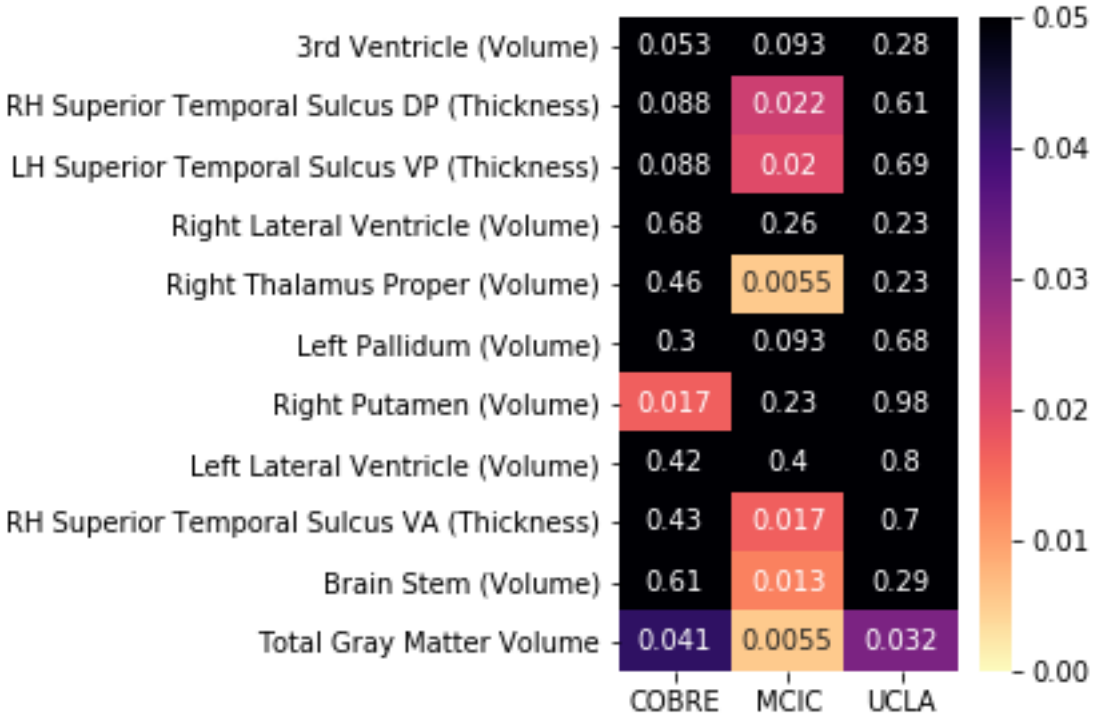

Figure 1. P-values for the difference in SHAP between SCZ and HC groups across datasets for the top 10 most relevant features of each source (11 in total, ranked in descending order of importance) after correcting for age and sex. P-values are corrected by the false discovery rate method. DP=dorsal posterior, VP=ventral posterior, VA=ventral anterior, RH=right hemisphere, and LH=left hemisphere.

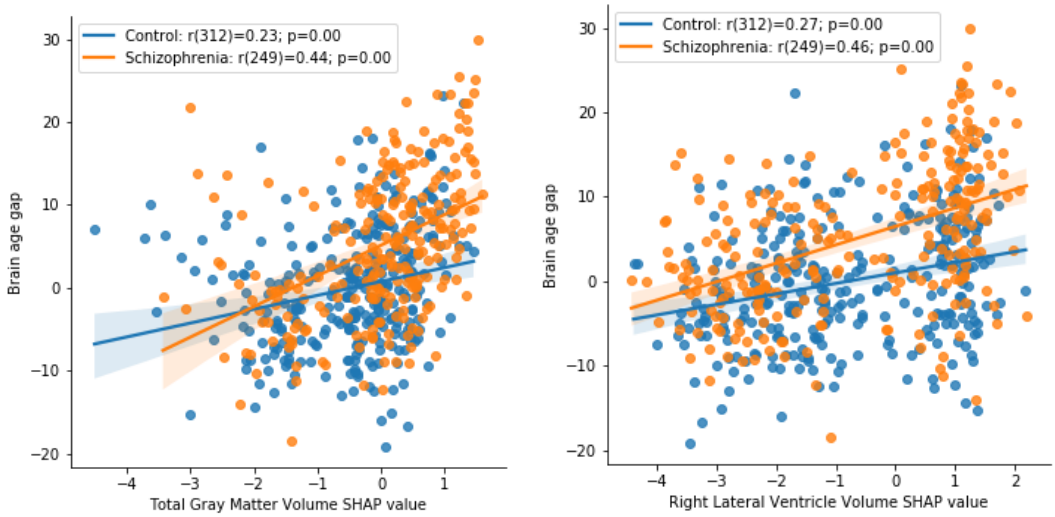

Figure 2. Univariate association between age-corrected brain age gap and total gray volume SHAP values (left) and univariate association between age-corrected brain age gap and right lateral ventricle volume SHAP values (right).

Chapter 6: Discussion

6.1 Summary of Findings

The brain age gap is a phenomenon observed in MRI scans of individuals with mood and psychotic disorders, but findings thus far have been heterogeneous. Our systematic review and meta-analysis is consistent with the presence of a brain age gap in SCZ, BD, and MDD. We also took steps to analyze the clinical utility of brain age. In our study, the brain age gap was not a predictor of antidepressant treatment response in MDD. We also identified that the brain age gap is mostly driven by total gray matter volume reduction and ventricle enlargement in SCZ.

In chapter 2, we systematically reviewed three publication databases and conducted a meta-analysis on studies of brain age in MDD, BD, and SCZ. A total of 18 studies were included. Each of the included studies used machine learning for brain age prediction with MRI data and reported the brain age gap as their main outcome. This was calculated by subtracting brain age predictions from chronological age. We identified a significant brain age gap in all three disorders, with SCZ presenting the highest gap, followed by BD and MDD. Additionally, we demonstrated a significant and positive correlation between the mean age of each study sample and the reported brain age gap for both SCZ and MDD. This association was not significant for BD, arguably due to a power issue.

In chapter 3, we proposed a new method for brain age prediction that tackles some of the issues of model interpretability. In our proposed model, each brain scan is first divided into independent slices of coronal, sagittal, and axial planes. Then, three independent models, one for each plane, predict the brain age for each of their designated

slices. For example, a scan with a resolution of 255x255x150 would lead to 255 coronal predictions, 255 sagittal predictions, and 150 axial predictions, or a total of 660 individual predictions of brain age. Each of these three models is a convolutional neural network based on a ResNet-18 (He et al., 2016). From the individual predictions, a fourth model is applied with all predictions as input and generates a single final value. As a first step, we used a linear regression model, as this allows for easy interpretation. Thus, the predictive performance capabilities of convolutional neural networks were preserved, while the regression model allowed for the inspection of coefficient magnitudes. The strongest coefficients belonged to the areas closer to the ventricles, which are widely known to be ageing markers (Peters, 2006).

In chapter 4, we investigated the relationship between the brain age gap and treatment response in a well characterized cohort of individuals with MDD (Lam et al., 2016; MacQueen et al., 2019). In the clinical context, the brain age gap is often associated with worse results on clinical scales, such as the Positive and Negative Syndrome Scale (PANSS) in SCZ and the Mini-Mental State Examination (MMSE) in mild cognitive impairment and dementia (Kaufmann et al., 2019). It is also associated with medication use (van Gestel H. et al., 2019), likely due to their neuroprotective properties (Castrén & Kojima, 2017). Given these associations with clinical scales, medication use, and the consistent finding of the brain age gap in MDD (Ballester et al., 2021; Han et al., 2020), we sought to understand if antidepressant treatment response could be predicted by the brain age gap. We hypothesized that a larger brain age gap would be associated with a worse treatment response. However, the brain age gap at baseline was not predictive of

treatment response at weeks 8 or 16. A secondary analysis identified that the older participants in the MDD group presented a larger brain age gap than the younger ones from the same group. This replicated previous findings that the brain age gap increases with age in MDD (Ballester et al., 2021; Christman et al., 2020).

In chapter 5, we examined brain age predictions in SCZ using a model explanation method called SHAP (Lundberg & Lee, 2017). Thus far, the literature on brain age had explored both the presence of a brain age gap in mental health disorders and the most relevant predictors of brain age models. However, SHAP allows us to understand model behaviour at the prediction level instead of at the model level, which opens the possibility for group comparisons. Consequently, we observed how predictions changed between HC and SCZ. We noticed that model behaviour differed in many brain structures, both cortical and subcortical, but that these differences depended on the database being used. Notably, a group x feature interaction demonstrated that the brain age gap of SCZ was significantly associated with changes in feature importance of two variables: total gray matter volume and third ventricle volume. These findings indicate that individuals with SCZ present higher levels of gray matter volume reduction and ventricle enlargement compared to HC of their corresponding age; those are thus the main drivers of the observed brain age gap in SCZ.

6.2 Significance and General Discussion

The significance of each study is discussed in-depth in their respective chapters. Taken together, our studies have significantly contributed to two major areas of brain age

research: 1) interpretation of brain age and the brain age gap, and 2) the clinical significance of the brain age gap in mood and psychotic disorders.

In chapter 2, we conducted the first systematic review and meta-analysis of MRI-derived brain age findings in mood and psychotic disorders, confirming the presence of a brain age gap. This was an important milestone for research on accelerated brain ageing, as we detailed the consistency of the findings alongside estimating the extent of the gap. We have also demonstrated how age is a significant variable in the determination of the brain age gap in clinical populations. The results from chapters 4 and 5 are also aligned with the meta-analysis. In chapter 4, older participants with MDD displayed signs of a brain age gap, while younger individuals did not. This is an expanded finding of previous studies in MDD and suggests a significant link between the brain age gap and age (Christman et al., 2020). Whether this link can be better explained or modulated by other clinical factors, such as illness duration, number of episodes, severity, medication use, and others remains to be investigated in more depth in future studies. In chapter 5, participants with SCZ also presented signs of a brain age gap. The total brain age gap identified in chapter 5 was also larger than the one in chapter 4, corroborating that SCZ presents stronger effects of accelerated brain ageing than MDD, also in accordance with our meta-analysis.

In chapter 3, we discussed the interpretability of the brain age gap, and the ability of models to yield more region-specific brain age predictions instead of a single brain age value. The necessity of region-specific brain age reflects the possibility that the brain age gap does not develop uniformly in all areas of the brain, with some areas being more

affected than others. In this sense, we also proposed to leverage the individual predictions of each region and generate a 3D map of brain age, one for each voxel. We found that more recent work has proposed the use of 3D-UNets for the same purpose (Çiçek et al., 2016; Popescu et al., 2021), however, the predictive performance of these methods is still below the performance of single brain age value prediction models (Niu et al., 2020; Peng et al., 2019). With a similar goal, we proposed in chapter 5 a way to shift brain age model-level interpretations to participant-level explanations of predictions. This time, the proposal was model-agnostic, applicable to both traditional machine learning and deep learning, unlike chapter 3's technique that relied on regression coefficients. Until this study, there were no propositions for understanding how the brain age gap differed between groups. Instead, interpretations of the brain age gap were solely guided by the feature importance of the models used (Ball et al., 2021). We demonstrated in this study that feature importance in brain age models does not translate into brain age gap influence, and that the brain age gap in SCZ is mostly driven by changes in total gray matter volume and ventricle volume.

The brain age gap has been previously shown to be a biomarker of conversion from mild cognitive impairment to Alzheimer's disease and a predictor of mortality risk (Cole et al., 2018; Gaser et al., 2013), but its clinical utility for mood and psychotic disorders is still unclear. Recent findings in MDD suggest a link between the brain age gap and impulsivity and symptom severity (Dunlop et al., 2021). An association between the brain age gap and symptom severity was also previously identified in SCZ (Kaufmann et al., 2019). Although these are significant links between clinical presentation and the brain age

gap, symptom severity and symptom profiles are still more easily observed through questionnaires than through MRI. Therefore, more practical applications of the brain age gap beyond a deeper understanding of illness neurobiology are necessary. In chapter 4, we conducted the first study to investigate a practical use of the brain age gap in MDD: a predictor of antidepressant treatment response. The findings of this study do not support the hypothesis that the brain age gap is associated with treatment response prediction. Beyond the specific findings of this study, significant associations between clinical outcomes and the brain age gap need to be taken lightly in terms of clinical utility. As associations are usually measured in terms of correlations, it is difficult to estimate how effective they would be at the individual level, a problem known as the ecological fallacy (Robinson, 2009). That is, the brain age gap is still far from being used to inform clinical decisions.

6.3 Limitations

Beyond the specific limitations of each study, as described in detail at each chapter, there are also general aspects that should be considered. Overall, any study that builds on top of machine learning models suffer from the consequences of a limited understanding of model behaviour. We attempted to tackle this problem in chapters 3 and 5 by developing a more interpretable model and by using SHAP with XGBoost (Chen & Guestrin, 2016; Lundberg & Lee, 2017). There are also limitations concerning the meaning of brain age predictions and whether they are properly capturing the process of ageing. As the underlying mechanisms of ageing and the characteristics of brain ageing

are still being studied, the current interpretation of brain age findings needs to match this uncertainty. For instance, ventricle enlargement is a known predictor of brain age (Ball et al., 2021), but ventricle size may be modulated by other factors. Familial risk for SCZ is associated with cortical thinning and increased ventricle size (de Zwarte et al., 2019), known markers of an ageing brain (Peters, 2006). This means that brain age prediction methods can be mistakenly overestimating the age of individuals with specific genetic markers, leading to skepticism surrounding what is the utility of the brain age gap. Beyond the genetics of brain development, the brain age in psychiatrically healthy volunteers could be affected by other factors, such as BMI, smoking, and mindfulness practices (Luders et al., 2016; Ning et al., 2020).

In chapter 2, the meta-analysis may have been affected by study heterogeneity. Although differences in the methods for brain age estimation have been shown to lead to similar predictors (Ball et al., 2021), the predictive capability of each model varies. This heterogeneity concern is augmented by the varying training set sizes among studies, which are not considered in the meta-analysis. Beyond modelling differences, age-dependency of findings may also have impacted both the effect sizes of the brain age gap and the association between age and the brain age gap (Beheshti et al., 2019). We employed age-dependency correction methods to remove the effect of overestimation of brain age below the training mean and underestimation above it. Among the studies included in the meta-analysis, some pre-dated the first age-dependency correction methods, which means they did not account for this potential issue. Other studies simply do not apply the corrections. In the studies that a correction is applied, different available

correction procedures were chosen, which may also have contributed to the heterogeneity of the findings.

In chapter 3, the attempts of stitching brain age results for independent voxels and generating an accurate depiction of brain age were flawed due to high noise. Also, our proposed method did not surpass the existing state-of-the-art predictive performance. However, Bashyam and colleagues (2020) have demonstrated that models with the best predictive performance are not the same models that lead to the best separation of the brain age gap between HC and clinical groups (Bashyam et al., 2020). This finding highlights that model interpretability and understanding model behaviour may be of more relevance than generating tightly fit models.

In chapter 4, there are limitations derived from the CAN-BIND database (Lam et al., 2016; MacQueen et al., 2019). The clinical characterization of participants was extensive, however, some relevant variables, such as illness duration, were not entirely reliable. Additionally, the distribution of age in HC was visually distinct from the distribution of age in MDD, which may have affected the results. In terms of the conducted analyses, we believe that there might have been a power issue in finding associations between the brain age gap and clinical scales due to the small effect size of the brain age gap in MDD (Ballester et al., 2021). Finally, more power would have allowed us to be more certain of the findings in individual item changes of the MADRS, such as the correlation between reported sadness and the brain age gap.

In chapter 5, the use of SHAP creates difficulties for group comparisons. Although SHAP values are linear components of a prediction, the behaviour of the SHAP values in

tree-based models is highly nonlinear, since the underlying model is nonlinear. Therefore, hypothesis testing for this type of data is complicated, thus most of our findings had to be represented by statistical tests with less power. Additionally, there are some limitations surrounding the feature importance from SHAP and the association with the brain age gap. Some of the variables that did not present significant findings might have been overshadowed by a larger signal. Total gray matter volume, due to its much larger scale, might limit the contribution of other variables that are at least in part dependent on gray matter. For instance, cortical thickness features may have been ignored due to the relevance of total gray matter volume.

6.4 Future Directions

There are many avenues for future research in the field of brain ageing in neuropsychiatric disorders. First, brain age prediction inherits an issue from the field of neuroimaging by presenting a high heterogeneity in preprocessing steps. On the one hand, the standardization of preprocessing steps would mitigate this issue and allow for easier comparison and reproduction of findings. On the other hand, neuroimaging data processing is a fast-developing field, and standardization might damage the speed at which developments in that area affect the field of brain age and other adjacent research fields. More effort in code sharing and virtual containers would facilitate the comparisons of results and the proposal of new, validated and compared brain age prediction methods.

Several studies have been employing the state-of-the-art of brain age prediction (Lombardi et al., 2021; Niu et al., 2020). Models are now much better at predicting brain

age than they were in the early stages of the field (Gaser et al., 2013; Koutsouleris et al., 2014). The goal of these studies is to ultimately use brain age predictions as a biomarker of relevant clinical outcomes. However, a recent study by Bashyam and colleagues (2020) suggests that the brain age gap in neuropsychiatric disorders is better captured by using models that are less fit to the training data (Bashyam et al., 2020). How this impacts the other outcomes that are known to be associated with the brain age gap is yet to be researched. Therefore, the field would benefit from systematic search for combinations of best matches between model fitness and specific outcomes of interest. Identifying what models best capture each outcome and explaining these models may help us understand what are the key factors that are contributing to the brain age gap and how they differ across outcomes (e.g., brain age gap in different psychiatric disorders or correlates between the brain age gap and measures of functioning and cognition).

In chapters 4 and 5, we analyzed how treatment response correlated with the brain age gap in MDD and how each brain feature contributed to the brain age gap in SCZ, respectively. The reasons for choosing MDD and SCZ were not specific to these disorders, as the same rationale could be applied for other neuropsychiatric disorders. The choice of MDD was based on access to data of a clinical trial with extensive clinical characterization, treatment response and neuroimaging data. The choice for SCZ was based on the effect size of the brain age gap in this population, which tends to be larger than other common neuropsychiatric conditions, and the access to large public datasets of neuroimaging data. Therefore, the natural next steps are to independently replicate these

findings across mood and psychotic disorders and investigate other important clinical outcomes, such as risk of relapse and psychosocial and cognitive functioning.

In chapters 3 and 5, we have developed methods for the interpretation of the brain age gap. However, future work needs not only to interpret the brain age gap at the feature level, but to understand its biological underpinnings. As the literature of the brain age gap in clinical populations expand, explaining the brain age gap in these populations becomes a priority. This comes with a set of challenges, since many variables may have an interplay with the brain age gap and should be interpreted under a model explanation lens (e.g., using SHAP). These variables may include sex, gender, ethnicity, socioeconomic status, etc. Importantly, to accurately investigate the brain age gap in heterogenous populations, one must train the model with heterogenous samples. Currently, the largest database used for training brain age models (UK Biobank) is of predominantly white individuals (94.6% of the sample) (Fry et al., 2017). Thus, new efforts on more heterogeneous data acquisition for modelling are paramount. Other variables such as smoking status, BMI, mindfulness, could also play a role in model behaviour and should be properly investigated, both in and out of the context of mood and psychotic disorders (Kolenic et al., 2018; Luders et al., 2016; Ning et al., 2020). Understanding exactly how these factors affect the brain age gap is a direct and logical extension of our work on brain age gap and SHAP in chapter 5.

We focused on investigating the brain age gap based on MRI data. However, as we move closer to understanding the meaning of the brain age gap, we should also analyze what is being captured by other methods such as the epigenetic clock and telomere length.

It is possible that a combination of these measures may lead to a clearer picture of ageing in the body. Additionally, studies that compare the brain age gap with the epigenetic clock extracted from different brain regions may also shed light on the differences and similarities of these measures.

6.5 Conclusion

The results of this thesis have advanced the field of brain age in mood and psychotic disorders by: 1) systematically synthesizing existing studies and confirming the brain age gap in MRI studies of MDD, BD, and SCZ through a meta-analysis; 2) proposing a new method of brain age prediction that is more interpretable while preserving good predictive capabilities; 3) showing that the brain age gap is not a good predictor of pharmacological response in MDD; and 4) identifying ventricle enlargement and total gray matter volume reduction as the two most robust factors driving the brain age gap in SCZ.

References

1. Ball, G., Kelly, C. E., Beare, R., & Seal, M. L. (2021). Individual variation underlying brain age estimates in typical development. NeuroImage, 235, 118036. https://doi.org/10.1016/j.neuroimage.2021.118036
2. Ballester, P. L., Romano, M. T., de A Cardoso Taiane and Hassel, S., Strother, S. C., Kennedy, S. H., & Frey, B. N. (2021). Brain age in mood and psychotic disorders: A systematic review and meta-analysis. Acta Psychiatr. Scand.

3. Bashyam, V. M., Erus, G., Doshi, J., Habes, M., Nasralah, I., Truelove-Hill, M., Srinivasan, D., Mamourian, L., Pomponio, R., Fan, Y., Launer, L. J., Masters, C. L., Maruff, P., Zhuo, C., Völzke, H., Johnson, S. C., Fripp, J., Koutsouleris, N., Satterthwaite, T. D., … Davatzikos, C. (2020). MRI signatures of brain age and disease over the lifespan based on a deep brain network and 14 468 individuals worldwide. Brain, 143(7), 2312–2324.

4. Beheshti, I., Nugent, S., Potvin, O., & Duchesne, S. (2019). Bias-adjustment in neuroimaging-based brain age frameworks: A robust scheme. Neuroimage Clin, 24, 102063.

5. Castrén, E., & Kojima, M. (2017). Brain-derived neurotrophic factor in mood disorders and antidepressant treatments. Neurobiology of Disease, 97(Pt B), 119–126. https://doi.org/10.1016/j.nbd.2016.07.010

6. Chen, T., & Guestrin, C. (2016). Xgboost: A scalable tree boosting system. Proceedings of the 22nd Acm Sigkdd International Conference on knowledge Discovery and Data Mining, 785–794.

7. Christman, S., Bermudez, C., Hao, L., Landman, B. A., Boyd, B., Albert, K., Woodward, N., Shokouhi, S., Vega, J., Andrews, P., & Taylor, W. D. (2020). Accelerated brain aging predicts impaired cognitive performance and greater disability in geriatric but not midlife adult depression. Transl. Psychiatry, 10(1), 317.

8. Çiçek, Ö., Abdulkadir, A., Lienkamp, S. S., Brox, T., & Ronneberger, O. (2016). 3D U-Net: Learning Dense Volumetric Segmentation from Sparse Annotation (pp. 424–432). https://doi.org/10.1007/978-3-319-46723-8_49

9. Cole, J. H., Ritchie, S. J., Bastin, M. E., Valdés Hernández, M. C., Muñoz Maniega, S., Royle, N., Corley, J., Pattie, A., Harris, S. E., Zhang, Q., Wray, N. R., Redmond, P., Marioni, R. E., Starr, J. M., Cox S R and Wardlaw, J. M., Sharp, D. J., & Deary, I. J. (2018). Brain age predicts mortality. Mol. Psychiatry, 23(5), 1385–1392.

10. de Zwarte, S. M. C., Brouwer, R. M., Agartz, I., Alda, M., Aleman, A., Alpert, K. I., Bearden, C. E., Bertolino, A., Bois, C., Bonvino, A., Bramon, E., Buimer, E. E. L., Cahn, W., Cannon, D. M., Cannon, T. D., Caseras, X., Castro-Fornieles, J., Chen, Q., Chung, Y., … van Haren, N. E. M. (2019). The Association Between Familial Risk and Brain Abnormalities Is Disease Specific: An ENIGMA-Relatives Study of Schizophrenia and Bipolar Disorder. Biological Psychiatry, 86(7), 545–556. https://doi.org/10.1016/j.biopsych.2019.03.985

11. Dunlop, K., Victoria, L. W., Downar Jonathan and Gunning, F. M., & Liston, C. (2021). Accelerated brain aging predicts impulsivity and symptom severity in depression. Neuropsychopharmacology.

12. Fry, A., Littlejohns, T. J., Sudlow, C., Doherty, N., Adamska, L., Sprosen, T., Collins, R., & Allen, N. E. (2017). Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. American Journal of Epidemiology, 186(9), 1026–1034. https://doi.org/10.1093/aje/kwx246

13. Gaser, C., Franke, K., Klöppel, S., Koutsouleris, N., Sauer, H., & Alzheimer's Disease Neuroimaging Initiative. (2013). BrainAGE in Mild Cognitive Impaired Patients:

Predicting the Conversion to Alzheimer's Disease. PloS One, 8(6), e67346. https://doi.org/10.1371/journal.pone.0067346

14. Han, L. K. M., Dinga, R., Hahn, T., Ching, C. R. K., Eyler, L. T., Aftanas, L., Aghajani, M., Aleman, A., Baune, B. T., Berger, K., Brak, I., Filho, G. B., Carballedo, A., Connolly, C. G., Couvy-Duchesne, B., Cullen, K. R., Dannlowski, U., Davey, C. G., Dima, D., … Schmaal, L. (2020). Brain aging in major depressive disorder: results from the ENIGMA major depressive disorder working group. Mol. Psychiatry.
15. He, K., Zhang, X., Ren, S., & Sun, J. (2016). Deep Residual Learning for Image Recognition. 2016 IEEE Conference on Computer Vision and Pattern Recognition (CVPR), 770–778. https://doi.org/10.1109/CVPR.2016.90
16. Kaufmann, T., van der Meer, D., Doan Nhat Trung and Schwarz, E., Lund, M. J., Agartz, I., Alnæs, D., Barch, D. M., Baur-Streubel, R., Bertolino, A., Bettella, F., Beyer Mona K and Bøen, E., Borgwardt, S., Brandt Christine L and Buitelaar, J., Celius, E. G., Cervenka Simon and Conzelmann, A., Córdova-Palomera, A., Dale, A. M., de Quervain, D. J. F., di Carlo Pasquale and Djurovic, S., … Westlye, L. T. (2019). Common brain disorders are associated with heritable patterns of apparent aging of the brain. Nat. Neurosci., 22(10), 1617–1623.
17. Kolenic, M., Franke, K., Hlinka, J., Matejka, M., Capkova, J., Pausova, Z., Uher, R., Alda, M., Spaniel, F., & Hajek, T. (2018). Obesity, dyslipidemia and brain age in first-episode psychosis. J. Psychiatr. Res., 99, 151–158.
18. Koutsouleris, N., Davatzikos, C., Borgwardt, S., Gaser, C., Bottlender, R., Frodl, T., Falkai, P., Riecher-Rössler, A., Möller, H.-J., Reiser, M., Pantelis, C., & Meisenzahl, E.

(2014). Accelerated brain aging in schizophrenia and beyond: A neuroanatomical marker of psychiatric disorders. Schizophr. Bull., 40(5), 1140–1153.

19. Lam, R. W., Milev, R., Rotzinger, S., Andreazza, A. C., Blier, P., Brenner, C., Daskalakis, Z. J., Dharsee, M., Downar, J., Evans, K. R., Farzan, F., Foster, J. A., Frey, B. N., Geraci, J., Giacobbe, P., Feilotter, H. E., Hall, G. B., Harkness, K. L., Hassel, S., … CAN-BIND Investigator Team. (2016). Discovering biomarkers for antidepressant response: protocol from the Canadian biomarker integration network in depression (CAN-BIND) and clinical characteristics of the first patient cohort. BMC Psychiatry, 16, 105.
20. Lombardi, A., Monaco, A., Donvito, G., Amoroso, N., Bellotti, R., & Tangaro, S. (2021). Brain Age Prediction With Morphological Features Using Deep Neural Networks: Results From Predictive Analytic Competition 2019. Frontiers in Psychiatry, 11. https://doi.org/10.3389/fpsyt.2020.619629
21. Luders, E., Cherbuin, N., & Gaser, C. (2016). Estimating brain age using high-resolution pattern recognition: Younger brains in long-term meditation practitioners. Neuroimage, 134, 508–513.
22. Lundberg, S. M., & Lee, S.-I. (2017). A Unified Approach to Interpreting Model Predictions. In I. Guyon, U. v Luxburg, S. Bengio, H. Wallach, R. Fergus, S. Vishwanathan, & R. Garnett (Eds.), Advances in Neural Information Processing Systems 30 (pp. 4765–4774). Curran Associates, Inc.
23. MacQueen, G. M., Hassel, S., Arnott, S. R., Jean, A., Bowie, C. R., Bray, S. L., Davis, A. D., Downar, J., Foster, J. A., Frey, B. N., Goldstein, B. I., Hall, G. B., Harkness, K. L., Harris, J., Lam, R. W., Lebel, C., Milev, R., Müller, D. J., Parikh, S. v, … CAN-BIND

Investigator Team. (2019). The Canadian Biomarker Integration Network in Depression (CAN-BIND): magnetic resonance imaging protocols. J. Psychiatry Neurosci., 44(4), 223–236.

24. Ning, K., Zhao, L., Matloff, W., Sun, F., & Toga, A. W. (2020). Association of relative brain age with tobacco smoking, alcohol consumption, and genetic variants. Sci. Rep., 10(1), 10.
25. Niu, X., Zhang, F., Kounios, J., & Liang, H. (2020). Improved prediction of brain age using multimodal neuroimaging data. Hum. Brain Mapp., 41(6), 1626–1643.
26. Peng, H., Gong, W., Beckmann, C. F., Vedaldi, A., & Smith, S. M. (2019). Accurate brain age prediction with lightweight deep neural networks. In Cold Spring Harbor Laboratory.
27. Peters, R. (2006). Ageing and the brain. Postgrad. Med. J., 82(964), 84–88.
28. Popescu, S. G., Glocker, B., Sharp, D. J., & Cole, J. H. (2021). Local Brain-Age: A U-Net Model. Frontiers in Aging Neuroscience, 13, 761954. https://doi.org/10.3389/fnagi.2021.761954
29. Robinson, W. S. (2009). Ecological correlations and the behavior of individuals. International Journal of Epidemiology, 38(2), 337–341. https://doi.org/10.1093/ije/dyn357
30. van Gestel H., Franke K., Petite J., Garnham J., S. C. and, Helmick C., Johnson K., Alda M., U. R. and, & Hajek T. AO - Hajek, T. O. H. O.-0003-0281-8458. (2019). Brain age in bipolar disorders: Effects of lithium treatment. Aust. N. Z. J. Psychiatry, 53(12), 1179–1188.