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1 **Title page**

2 Title: Predicting age using neuroimaging: innovative brain ageing biomarkers

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10

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15

16 **Abstract**

17 The brain changes as we age and these changes are associated with functional deterioration
18 and neurodegenerative disease. It is vital that we better understand individual differences in the
19 brain ageing process, hence techniques for making individualised predictions of brain ageing
20 have been developed. We present evidence supporting use of neuroimaging-based *brain age*
21 as a biomarker of an individual's brain health. Increasingly, research is showing how brain
22 diseases or poor physical health negatively impact *brain age*. Importantly, recent evidence
23 shows that having an 'older'-appearing brain relates to advanced physiological and cognitive
24 ageing and the risk of mortality. We discuss controversies surrounding *brain age* and highlight
25 emerging trends such as the use of multi-modality neuroimaging and the employment of 'deep
26 learning' methods.

27

28 **Brain scans can be used to predict age**

29 As the global population ages, the burden of age-associated functional decline and disease is
30 increasing [1]. Methods are required for predicting who is at higher risk of age-associated
31 deterioration, how this decline will progress and which treatments are most appropriate. The
32 ageing process is biologically complex [2], and despite the generally negative effects of ageing,
33 there is pronounced variation among people in the timing of manifestation of ageing effects
34 (Figure 1). This variation in brain aging may contribute to the enormous variation in human
35 lifespan, and in the varying ages at which people develop age-related diseases. Potentially, a
36 person's underlying **biological age** (see Glossary) may differ from their chronological age, and
37 could be a better indicator of future risk of experiencing age-associated health issues.

38 Ageing results in marked changes to the structure and function of the brain. Cognitive decline
39 and an increased risk of neurodegenerative diseases are a key source of the burden caused by
40 ageing. However, pronounced individual differences are also seen in measures of the brain as
41 people age [3]. While the average age-driven trajectories of brain volume, cortical thickness and
42 white matter microstructure have been characterised in healthy people [4-6], a single person
43 may differ considerably from the average. Potentially, the extent to which someone deviates
44 from healthy brain ageing trajectories could indicate underlying problems in outwardly healthy
45 people, and relate to the risk of cognitive ageing or age-associated brain disease. Hence, reliable
46 biomarkers of brain ageing could be of great neuroscientific and clinical value.

47 Using structural or functional neuroimaging data, it is now possible to predict age [7, 8]. The
48 most effective approaches to age prediction have used data from **magnetic resonance imaging**
49 **(MRI)** scans of the brain and run a type of statistical analysis on the images called **machine**
50 **learning**. By 'learning' the relationship between patterns of data from brain scans and
51 chronological age in a training dataset of healthy people, age predictions can be made using
52 brain images from people not included in the initial training. The most accurate measures in
53 adults have reported a mean absolute error (MAE) of <5 years [8-12], which can be measured
54 with high test-retest reliability [9, 13]. Moreover, in studies covering age ranges between early
55 childhood and young adulthood the most accurate predictions result in MAEs of approximately
56 only 1 year [14-16].

57 While using neuroimaging to predict age may be seen as an interesting academic exercise, it is

58 also an important proof-of-concept, showing that the information extracted from a single MRI
59 scan relates strongly to chronological age and that it can be used to make accurate age
60 estimations in new scans. Furthermore, a growing body of research is demonstrating that so-
61 called **brain age** has both clinical and broader scientific relevance. This paradigm has provided
62 a new way to explore how the brain changes during ageing and how brain diseases interact with
63 'normal' brain ageing. Potentially, *brain age* could be used as a personalised biomarker of brain
64 health during ageing, and this individual-specific nature is particularly important. The extensive
65 study of group-mean differences in case-control studies of brain diseases has yielded few clinical
66 applications. Conversely, *brain age* locates an individual within a normative ageing distribution.
67 If this location can be shown to be relevant for health outcomes, then *brain age* presents a
68 framework for applying neuroimaging clinically to characterise brain health. Here we outline the
69 methods for predicting *brain age*, evaluate evidence for its use as an ageing biomarker and
70 discuss trends in the ongoing development of the paradigm.

71 **How does neuroimaging-based *brain age* prediction work?**

72 The accuracy of *brain age* prediction relies on the fact that the brain changes as we age (Box 1)
73 and that these changes are reasonably consistent between different people. Neuroimaging
74 provides a unique window into the brain ageing process, allowing precise and reliable
75 measurement of many aspects of brain structure and function. Recent advances in computing
76 and the increasing availability of large neuroimaging datasets mean that researchers have been
77 enabled to apply machine learning to the problem of age prediction (Figure 2, Key Figure; Box
78 2).

79 **How does *brain age* relate to other ageing measures?**

80 The brain can be affected by peripheral physiological changes and having a healthy brain is
81 essential for overall health. Therefore, measuring *brain age* could provide a window for general
82 biological ageing, as a potential **ageing biomarker**. To that end, it is useful to consider whether
83 *brain age* relates to other known facets of ageing. Measures of ageing typically used in
84 **gerontology** include physiological, cognitive and biological components. Physiological
85 measurements of hand-grip strength, lung function, and walking speed are used to characterise
86 general physical health as well as to predict risk of mortality in older adults [17-19]. Evidently, by
87 using robust measurements techniques as proxies of underlying physiological variability,

88 information about general health and residual lifespan can be obtained. *Brain age* appears to
89 meet these criteria, as a recent large-scale study in 73 year-olds found a significant relationship
90 between *brain age* and mortality risk, ascertained up to seven years after scanning [20]. For
91 every year that an individual's brain was predicted to be older than their chronological age, there
92 was a 6% increased risk of death. This study also showed that lower grip-strength, lower forced
93 expiratory volume and a slower walking time were all significantly associated with *brain age*, as
94 was a composite measure of fluid cognition. This supports the idea that the brain is sensitive to
95 general declines in health and suggests that *brain age* could be used as an ageing biomarker,
96 to make individualised predictions about mortality risk in older adults. The abovementioned study
97 also compared *brain age* to other putative ageing biomarkers. *Brain age* did not correlate with
98 either leukocyte telomere length or *DNA-methylation age*. Interestingly, *brain age* was a stronger
99 predictor of mortality than the other measures, though a combined model of *brain age* with *DNA-*
100 *methylation age* was the best predictor, illustrating the benefits of combining distinct ageing
101 biomarkers.

102 **Brain diseases and *brain age***

103 If *brain age* can provide information about future health outcomes in the general population, this
104 motivates research into potential causes of deviations from healthy brain ageing. As such,
105 considering how specific diseases relate to *brain age* may help isolate deleterious influences on
106 brain health in later life. Understanding how variability in *brain age* within diverse clinical samples
107 relates to other facets of non-communicable and age-related diseases could help identify
108 individuals at risk of poor health outcomes as ageing and disease processes interact. Potentially,
109 diseases result in increases to brain ageing, as a one-off 'hit' or a progressive acceleration to
110 the process. Alternatively, the presence of a disease may not cause brain ageing *per se*, but
111 occurs on top of underlying individual differences in 'normal' brain ageing. This could mean that
112 the effects of that disease are exacerbated in those with 'older' as opposed to 'younger'
113 appearing brains. Either way, measuring *brain age* in disease groups could be fruitful for
114 quantifying some of the heterogeneity within a disease, improving identification of individuals at
115 higher risk of poor health outcomes. Consequently, *brain age* could be used as general marker
116 of poorer brain health to help stratify enrolment of individuals into clinical trials of therapies aimed
117 at improving brain health in older adults, who may not have observable clinical or cognitive
118 impairments.

119 While aetiologically and pathophysiologically distinct, many diseases seem to have common,
120 secondary effects on the brain. For example, brain injury, multiple sclerosis, major depressive
121 disorder and Alzheimer's are all associated with a heightened immune response,
122 neuroinflammation, oxidative stress, mitochondrial dysfunction and epigenetic alterations [21-
123 30]. Notably, all these phenomena are also implicated in the biology of 'normal' ageing [2].
124 Furthermore, a number of diseases have been proposed to exacerbate biological ageing,
125 including Down's syndrome, HIV and traumatic brain injury [31-33]. Given the relationship
126 between ageing and disease risk, it is unsurprising that common underlying mechanisms may
127 be present. However, the availability of ageing biomarkers now allows researchers to evaluate
128 evidence of abnormal ageing in specific diseases, and in the context of brain diseases, *brain*
129 *age* is likely to be a particularly relevant measure. It is hoped that combining ageing-related
130 biomarkers with more disease-specific biomarkers will lead to further improvements in diagnostic
131 and prognostic modelling, moving closer to clinical applications of neuroimaging.

132 Indeed, a growing number of neuropsychiatric diseases have been associated with increases in
133 *brain age* (Table 1). These include traumatic brain injury [34], schizophrenia [12, 35, 36], epilepsy
134 [37], Down's syndrome [38], HIV [39], mild cognitive impairment and Alzheimer's [13, 40-42].
135 Similar results have also been seen in peripheral conditions and non-communicable diseases,
136 such as mid-life obesity [43] and diabetes [44], suggesting again that the brain is also sensitive
137 to deteriorations in general physical health. These outwardly disparate conditions may share
138 some common pathological neurobiological components, effects secondary to the disparate
139 primary pathological processes, that result in an increase in age-associated loss of brain volume.
140 Interestingly, *brain age* was more sensitive in showing differences between groups, when
141 compared to total and regional brain volumes [40]. Methodologically, the variance in *brain age*
142 is largely explained by a composite of brain volume, age and sex, though also contains unique
143 variance not captured by commonly used measures. Thus, analysing *brain age* in these contexts
144 provides a novel way to capture individual differences within the general population as well as
145 disease groups, which relate to additional facets of various diseases or even predict future
146 outcomes. For example, increased *brain age* in people with mild cognitive impairment has been
147 associated with greater risk of developing Alzheimer's within three years [40, 42].

148 Despite the many different causes of neuropathology, response mechanisms of the brain seem
149 to be relatively limited, whether the causes are infectious, traumatic or genetic. Hence, the *brain*

150 age studies can be seen as evidence that common secondary mechanisms, observed across
151 diseases, may relate to those seen in healthy ageing and may be important for some of the
152 neurological, cognitive and behavioural consequences of brain diseases. In line with this,
153 cognitive performance has also been assessed in studies of *brain age*. In general, there are
154 significant relationships between global cognitive performance and *brain age*, being more
155 pronounced in disease samples [10, 13, 15, 20, 34, 39, 40, 42]. This supports the idea that brain
156 ageing and cognitive ageing are linked, though the modest strength of these associations
157 suggests that further methods development is needed to better capture the variation in brain
158 structure and cognitive performance.

159 **Improving individual brain health**

160 While there may be many deleterious influences on *brain age*, there is also evidence of
161 protective factors. Significant associations with decreased *brain age* and markers of good health
162 in cognitively healthy elderly [45] and the general population [46] have been reported.
163 Furthermore, the number of years of education and a self-reported measure of physical activity
164 (number of stairs climbed daily) were reported to be significantly associated with a lower *brain*
165 *age* in individuals aged 19-79 years [47]. Alongside this, recent studies have observed a
166 reduction in *brain age* in long-term practitioners of meditation [48] and in amateur musicians [49].

167 Although only cross-sectional, such results are promising. They suggest that interventions could
168 be effective in slowing or potentially even reversing brain ageing, reducing the risk of future
169 cognitive decline and age-associated disease. However, prospective longitudinal studies of
170 positive influences on *brain age* are yet to be conducted. This represents the next, and crucial,
171 step in developing a framework for evaluating potential treatments of age-associated brain
172 deterioration.

173 **Controversies around *brain age***

174 While the *brain age* paradigm offers a powerful approach to investigating brain ageing, it has
175 attracted some criticisms, either technical or philosophical. For instance, some consider the only
176 factor that affects age to be time, thus ageing *per se* cannot deviate from its chronological
177 course. This criticism applies to all potential ageing biomarkers, instead suggesting that in fact
178 there is limited biological variability in ageing and that deviations are due to specific pathological
179 processes, not reflecting an extension of 'normal' ageing. However, there is strong support for

180 the hypothesis that ageing results from cumulative biological damage [50]. It follows from this
181 that variable exposure to the causes of this cumulative damage would result in individual
182 differences in rates of underlying biological. Furthermore, the very fact that ageing is the major
183 risk for numerous diseases strongly suggests that biological ageing and disease are intrinsically
184 linked. Beyond this, we argue that whether or not an increased *brain age* indicates that a brain
185 is actually 'older' is not the chief consideration. If *brain age* (or other biologically-predicted ages
186 for that matter) can be a useful neuroscientific and clinical tool then it warrants further
187 exploration.

188 Another criticism of *brain age* is that by condensing whole-brain **voxel**-wise information into a
189 single number it is overly 'black box'. By not scrutinising exactly which **features** of a brain scan
190 are used for predicting age, important neuroscientific information may be disregarded and it is
191 unclear precisely what information age prediction is based on. However, there are several
192 important reasons why interpreting the '**weight maps**' derived from machine learning is
193 complicated and does not offer a straightforward interpretation in the context of brain ageing
194 [51]. First, no one part of the brain is the sole driver of ageing; brain ageing is a global
195 phenomenon. Second, age-related changes to the brain are subtle, non-linear, spatially
196 distributed and vary between individuals [4, 6, 52]. The advantage of the *brain age* paradigm is
197 that, by using machine learning, the model can learn a range of different brain structures that
198 may be healthy. This avoids reductively focusing on the average, which likely is unrepresentative
199 of any single individual.

200 A final criticism of *brain age* is that it relies on using the resulting error in prediction (i.e., the
201 difference between the predicted age and chronological age) as a metric for further analysis.
202 Statistically, this is equivalent to using the residuals for an individual from a linear regression
203 model. Basing clinical or neuroscientific interpretations on error may be semantically dubious,
204 as in theory more accurate models would reduce this error. Crucially, however, the key to
205 determining the validity of *brain age* lies in external validation with other characteristics
206 measured in the same individuals. For example, the fact that the error metric (e.g., brain-
207 predicted age difference) relates to cognitive performance, ageing fitness and subsequent
208 survival [13, 15, 20, 40, 42, 47], strongly supports the idea that by quantifying this error, clinically
209 and biologically meaningful insights can be derived.

210 **Concluding remarks**

211 The emerging field of *brain age* prediction is evolving rapidly and an increasing number of
212 researchers are employing *brain age* analysis to explore brain ageing in health and disease. A
213 number of promising trends are developing. These include the combination of multiple
214 neuroimaging modalities, for example combining structural and functional MRI data, or multiple
215 structural MRI modalities (T2*, diffusion-MRI), resulting in improved prediction performance [10,
216 53]. Combined predictors potentially better capture the various facets of brain ageing, including
217 brain atrophy, iron deposition and alterations to white matter microstructure (see Outstanding
218 Questions).

219 Another development is the increasing availability of large datasets. Key to accurate machine
220 learning is having a sufficient number of examples to learn from. Initiatives such as the
221 International Neuroimaging Data-Sharing Initiative (INDI; http://fcon_1000.projects.nitrc.org/)
222 and NeuGrid4U (<https://neugrid4you.eu/>) encourage sharing existing datasets. Ground-breaking
223 projects like the Human Connectome Project and UK Biobank have been explicitly designed to
224 share data and are making unprecedented amounts of neuroimaging data accessible.

225 Important for leveraging these larger and more complex datasets is innovation in computational
226 statistics, to optimise algorithms for predicting *brain age* [54]. In particular, **deep learning**
227 methods show particular promise [9]. The ‘hidden’ layers in deep learning allow data-driven
228 representation of different global and local data features, meaning that hitherto unknown
229 relationships can be more accurately identified. One benefit particular to neuroimaging is the
230 removal the reliance on data pre-processing to extract meaningful features. Such features are
231 automatically encoded by the deep neural network, avoiding the model-dependent decisions
232 used in image pre-processing (e.g., registration algorithm, template selection). While the
233 computational demands for deep learning are high, the added benefits likely outweigh the costs,
234 and deep learning might enjoy increasing interest in *brain age* analysis, as in other neuroimaging
235 research.

236 The ability to predict a person’s *brain age* using neuroimaging data is increasingly providing
237 insights into both positive and negative effects on age-associated brain changes, and is
238 shedding new light on how diseases affect the ageing brain. Furthermore, *brain age* has the
239 potential to identify individuals at risk of experiencing advanced biological ageing, and thus could

240 provide a biomarker of age-associated health problems. As the technical aspects of *brain age*
241 analysis are further developed, the possibility that neuroimaging-based measures of *brain age*
242 could be used to evaluate neuroprotective preventions and therapeutics comes closer to being
243 realised.

244

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365

366 **Glossary**

367 (411/450 words)

368 **Ageing biomarker:** A biological measurement that gives an estimate of an organism’s biological
369 age, based on the biological age of an organ, tissue or cell.

370 **Biological age:** The hypothetical underlying age of an organism, defined by measuring some
371 aspect of the organism’s biology. Biological age may differ from the organism’s chronological
372 age and be a better indicator of residual lifespan, functional capacity and risk of age-associated
373 changes.

374 **Brain age (or brain-predicted age):** The predicted age of an individual, derived using high-
375 dimensional neuroimaging data in a machine-learning framework. *Brain age* potentially
376 represents a biomarker of the underlying ‘age’ of the brain, whereby an ‘older’ brain in adults
377 indicates increased risks for neurodegenerative diseases and mortality.

378 **Brain ageing:** Changes to the human brain that generally accompany ageing. These changes
379 occur at molecular, cellular and tissue levels, and have characteristic functional and behavioural
380 consequences (Box 1).

381 **Deep learning:** An extension of machine learning, based on artificial neural networks. ‘Deep’
382 refers to the multiple layers of neural networks used, including one or more ‘hidden’ layers. Each
383 layer is used to transform input data into a different format that encodes something salient about
384 the features contained in the data.

385 **Feature:** A variable used in a machine learning algorithm, or an aspect of a dataset that is of
386 some relevance. In the context of *brain age*, features are local measures of brain structure or
387 function (e.g., grey matter volume).

388 **Gerontology:** The scientific study of the old and the ageing process.

389 **Machine learning:** A statistical approach derived from the study of artificial intelligence, based
390 on the concept that statistical models should be able to make accurate predictions from new
391 ‘unseen’ data (either categorical, e.g., group membership, or continuous, e.g., age, IQ).

392 **Magnetic Resonance Imaging (MRI):** A medical imaging technique that capitalises on the
393 inherent physical properties of biological tissues when inside powerful magnetic fields.

394 Particularly, hydrogen atoms contained in water within biological tissue behave in characteristic
395 ways when the magnetic fields are manipulated and release energy in the form of radiofrequency
396 (RF) pulses that can be recorded. These RF pulses can be transformed into three-dimensional
397 images that give information on brain volume, blood flow, brain function, white matter
398 microstructure to name but a few biological characteristics.

399 **Voxel:** A volume-element, the three-dimensional equivalent of a pixel. Voxels are the unit of
400 resolution for MRI scans of the brain.

401 **Weight maps:** Voxel-wise maps of the brain, where each voxel contains a numeric
402 representation of the statistical model learned by a machine learning algorithm.

403

404 **Text Boxes**

405 **Box 1. Brain ageing and its consequences**

406 (292/400 words)

407 Age-related changes in the human brain are characterised by region-specific and non-linear
408 patterns of highly coordinated and sequenced events of progressive (e.g., cell growth and
409 myelination) and regressive (e.g., synaptic pruning) processes during development [55] and
410 wide-spread atrophy during ageing [56]. In fact, grey matter volume decreases steadily
411 throughout adulthood, while white matter volume follows an inverted ‘U-shape’ curve, peaking
412 in midlife [56, 57]. Underlying these macroscopic atrophic changes are a whole host of molecular
413 and cellular events. These include altered calcium signalling, genomic alterations, reductions to
414 synaptogenesis and neurite outgrowth, demyelination, microglial activation and subsequent
415 inflammatory responses, changes to cellular metabolism and mitochondrial dysfunction and
416 eventual astrocytic hypertrophy and reduced neuronal activity [58]. These biological changes
417 have behavioural consequences. Most characteristic is the decline in cognitive function
418 commonly observed across adulthood (i.e., cognitive ageing). While memory impairments are
419 most recognised, performance decrements are seen in the majority of cognitive domains, with
420 only crystallised intelligence spared [59]. While the precise relationship between cognitive
421 ageing and the neurophysiological changes in the brain is still unclear, the presence of some
422 link between the two is intuitive [60]. Beyond cognitive ageing, advanced brain ageing is also
423 associated with an increased prevalence of brain diseases, particularly neurodegenerative
424 diseases, including Alzheimer’s, Parkinson’s and Amyotrophic Lateral Sclerosis, to name a few.
425 In fact, age is the biggest risk factor for many of these diseases, and the progressive nature of
426 these conditions means that severity worsens with age. The dementia that results from many of
427 these diseases causes a high burden on society and on individuals, both financially and socially.
428 Currently, there are limited options for modifying or treating these diseases, and even evaluating
429 potential therapeutics is difficult as the relatively slow rates of disease progression make long-
430 term interventional studies challenging.

431 **Box 2. How brain age prediction works**

432 (396/400 words)

433 The general analytic ‘pipeline’ for predicting the biological age of individual brains uses structural

434 neuroimaging from a large sample of healthy people, screened to exclude those with
435 neuropsychiatric or physical health conditions. The chronological age of these individuals is
436 known and they should represent the adult lifespan. These individuals comprise the so-called
437 'training set'. The following stages are carried out: 1) Neuroimaging data from the training set
438 then usually undergoes image pre-processing to derive meaningful features that relate to ageing,
439 for example spatial registration to a template, to quantify brain volume at each voxel. 2) These
440 features are then used as predictors or independent variables in a regression model, with
441 chronological age as the outcome or dependent variable. This is the inverse to conventional
442 statistical approaches that aim to understand which brain regions may have a linear relationship
443 with age, as in voxel-based morphometry. Ordinary least-squares (OLS) regression models are
444 inappropriate for such high-dimensional neuroimaging datasets, where each individual is
445 characterized by several hundred or thousand datapoints. Hence, multivariate machine-learning
446 methods (e.g., support vector, relevance vector or Gaussian Processes regression) are used,
447 as they were designed to cope with high-dimensional types of data. 3) The accuracy of the
448 machine learning regression model is assessed using a cross-validation procedure. Popular
449 variations of this include k-fold and split-half cross-validation. The idea behind cross-validation
450 is that some proportion of the individuals in the training set is left out of the initial 'learning' stage.
451 The parameters of the learned model (analogous to OLS beta estimates) are then applied to the
452 pre-processed data of the left-out individuals, resulting in brain-derived predictions of age. This
453 age prediction is then compared to the known chronological age of each left-out individual.
454 Accuracy metrics, including the Pearson correlation between the predicted and chronological
455 ages, the R^2 (i.e., variance explained) of the prediction model and the mean absolute error
456 (MAE), are then generated to evaluate the specific age prediction model. 4) Assuming the *brain*
457 *age* prediction model reaches a desired level of accuracy, entirely new individuals ('test set') can
458 now be run through the model, generating individual predictions of *brain age*. The difference
459 between predicted and chronological age quantifies the acceleration or deceleration in individual
460 brain ageing. For example, if the *brain age* of a 70 year-old results in a difference of +5 years,
461 this individual shows the typical atrophy pattern of a 75 years old.

462

463 **Figure Legends**

464 **Figure 1. Trajectories of biological ageing**

465 As chronological age increases, there is a trend towards a higher risk of diseases and the onset
466 of cognitive decline. This trend is thought to have a biological basis, relating to the cumulative
467 damage to cells and tissues acquired over time. While people who are generally healthy (grey
468 arrow) reach the threshold for symptoms to appear at approximately a similar age, other people
469 may follow different trajectories of biological ageing. This could be due to genetic differences, or
470 exposure to environmental effects that subtly increase the rate at which age-associated damage
471 accumulates (blue arrow). Potentially, people may experience pronounced environmental
472 influences, such as a brain injury or cerebral infection, leading to a marked acceleration of the
473 rate of biological ageing (red line). In the current context, *brain age* may represent a measure of
474 the underlying biological age of the brain. By measuring how far an individual is from the healthy
475 brain ageing trajectory, researchers hope to be able to quantify advanced and decelerated brain
476 ageing and use this to predict individual's future trajectories and subsequent risk of age-
477 associated health deterioration.

478 **Figure 2. How brain age prediction works**

479 Overview of the *brain age* prediction process, using 'supervised' machine learning. A)
480 Neuroimaging data, usually T1-weighted structural MRI scans, from healthy individuals (training
481 set) are labelled with the participants' chronological age and put into a machine learning
482 regression model. B) To validate the accuracy of the model, a proportion of participants' images
483 are left out of the model. For example, ten-fold cross-validation involves training the model on
484 90% of participants and predicting age values on the left-out 10%. This is then iterated through
485 all participants, and predicted values are compared with real values (i.e., chronological age) to
486 assess accuracy. C) Assuming the model is sufficiently accurate, the model is trained using the
487 entire training set and the resulting model coefficients applied to new participants' brain scans
488 (test set) to generate unbiased individual *brain age* predictions, in this example 61.7 years. D)
489 The predicted *brain age* can then be compared with the chronological age of test set participants,
490 with 'older' appearing brains assumed to reflect advanced brain ageing and 'younger' appearing
491 brains to reflect decelerated or healthy brain ageing. The discrepancy between *brain age* and
492 chronological age (brain-predicted age difference) can then be used as a metric to statistically

493 relate to other measured characteristics of the participants.

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501 **Tables**502 **Table 1. Studies assessing *brain age* in neurological and psychiatric diseases**

Clinical group	N	Age mean (SD)	Features for <i>brain age</i>	Mean <i>brain age</i> difference (years)	References
Alzheimer's disease	102	76 (8)	GM	10.0	Franke, 2010 [8]
Alzheimer's disease	150	75 (8)	GM	baseline: 6.7 follow-up (2y): 9.0	Franke, 2012 [13]
Alzheimer's disease (APOE ε4 carriers/non-carriers)	101 / 49	74 (7) / 76 (9)	GM	baseline: 5.8 / 6.2 follow-up (2y): 8.3 / 7.7	Löwe, 2016 [42]
Alzheimer's disease	411	75 (7)	Hippocampus	7	Li, 2017 [61]
At-risk mental states for psychosis	89	25 (6)	GM	1.7	Koutsouleris, 2013 [35]
Bipolar disorder	22	38 (11)	GM	-1.3 (males: -1.9 / females: -0.8)	Nenadic, 2017 [36]
Borderline personality disorder	57	26 (7)	GM	3.1	Koutsouleris, 2013 [35]
Diabetes mellitus type 2	98	65 (8)	GM	4.6	Franke, 2013 [44]
Diabetes mellitus type 2	12	63 (7)	GM	baseline: 5.1 follow-up (4y): 5.9	Franke, 2013 [44]
Down's syndrome	46	42 (9)	Whole brain	2.5	Cole, 2017 [38]
Epilepsy (medically-refractory/newly-diagnosed)	94 / 42	32 (14) / 31 (11)	Whole brain	4.5 / 0.9	Pardoe, 2017 [37]
HIV	162	56	Whole brain	2.2	Cole, 2017 [39]
Major depression	104	42 (8)	GM	4.0	Koutsouleris, 2013 [35]
Mild cognitive impairment, progressive	112	74 (7)	GM	baseline: 6.2 follow-up (3y): 9.0	Franke, 2012 [13]

Mild cognitive impairment, progressive (early/late)	58 / 75	74 (7) / 75 (7)	GM	8.7 / 5.6	Gaser, 2013 [40]
Mild cognitive impairment, progressive (APOE ε4 carriers / non-carriers)	78 / 34	74 (6) / 75 (9)	GM	baseline: 5.8 / 5.5 follow-up (3y): 8.7 / 7.3	Löwe, 2016 [42]
Mild cognitive impairment, stable	36	77 (6)	GM	baseline: -0.5 follow-up (3y): -0.4	Franke, 2012 [13]
Mild cognitive impairment, stable (APOE ε4 carriers/non-carriers)	14 / 22	77 (6) / 77 (6)	GM	baseline: -0.9 / -0.9 follow-up (3y): 0.0 / -0.6	Löwe, 2016 [42]
Obesity	227	58 (17)	WM	10	Ronan, 2016 [43]
Objective cognitive impairment (mild/major)	632 / 251	58 (15) / 58 (16)	Whole brain (multimodal)	0.7 / 1.7	Liem, 2017 [10]
Schizophrenia	141	28 (12)	GM	5.5	Koutsouleris, 2013 [35]
Schizophrenia	341	34 (12)	GM	baseline: 3.4 follow-up (4y): 4.3	Schnack, 2016 [12]
Schizophrenia	45	34 (10)	GM	2.6 (males: 3.4 / females: 1.1)	Nenadic, 2017 [36]
Traumatic brain injury	99	38 (12)	GM / WM	4.7 / 6.0	Cole, 2015 [34]

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Features for *brain age* are reported as the aspect of brain structure used predictors in the *brain-age* model. GM = grey matter, WM = white matter. Data formats include voxelwise 3D images or summary measures of cortical thickness and subcortical volumes. Multi-modal refers to a combination of structural and function MRI.