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Title page

Title (10/17 words)

Neuroimaging studies illustrate the commonalities between ageing and brain diseases

Subtitle (20/20 words)

Examining features common to different brain diseases and ageing could engender a greater appreciation of the importance of individual differences

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Conclusion (157/300 words)

Keywords

Ageing; Brain diseases; neuroimaging; personalised medicine

Abbreviations

AD: Alzheimer's Disease

ALE: Activation Likelihood Estimation

APOE: Apolipoprotein Epsilon gene

ASL: Arterial Spin Labelling

DTI: Diffusion Tensor Imaging

FDG: fludeoxyglucose

FLAIR: Fluid-Attenuated Inversion Recovery

MCI: Mild Cognitive Impairment

MDD: Major Depressive Disorder

MRI: Magnetic Resonance Imaging

PET: Positron Emission Tomography

Abstract

The lack of specificity in neuroimaging studies of neurological and psychiatric diseases suggests that these different diseases have more in common than is generally considered. Potentially, features that are secondary effects of different pathological processes may share common neurobiological underpinnings. Intriguingly, many of these mechanisms are also observed in studies of normal (i.e., non-pathological) brain ageing. Different brain diseases may be causing *premature* or *accelerated ageing* to the brain, an idea that is supported by a line of 'brain ageing' research that combines neuroimaging data with machine learning analysis. In reviewing this field, I conclude that such observations could have important implications, suggesting that we should shift experimental paradigm: away from characterising the average case-control brain differences resulting from a disease towards methods that place individuals in their age-appropriate context. This would also lead naturally to clinical applications, whereby neuroimaging could contribute to a personalised-medicine approach to improve brain health.

1. Introduction

Neuroimaging has provided myriad novel insights into the structure and function of the living human brain for well over two decades. The application of neuroimaging to neurological and psychiatric diseases (i.e., brain diseases) has generated swathes of information about the anatomical and functional changes associated with these disabling conditions. The canonical experimental paradigm compares a group of individuals meeting the disease' s diagnostic criteria with a group of healthy controls. Statistical analysis is then conducted on measures derived from neuroimaging data to ascertain which aspects of brain structure and function differ on average between the disease and control groups. However, there is a critical lack of specificity in these neuroimaging findings (Table 1), with similar findings appearing across a wide range of different diagnoses. These findings have been derived from various neuroimaging modalities, including T1-weighted magnetic resonance imaging (MRI), T2-FLAIR MRI, diffusion-MRI, functional-MRI, arterial spin labelling and fludeoxyglucose (^{18}F) (FDG) positron emission tomography (PET). Data from these methods can be used to infer brain volumes, cortical thickness, white matter hyperintensity volume, white matter microstructure, functional connectivity, cerebral perfusion and cerebral metabolism. It is apparent when viewing the breadth of the neuroimaging literature that changes to these different aspects of brain structure and brain function can occur in many different contexts.

The commonalities across diseases can be highlighted by taking two common brain diseases as examples. Alzheimer' s disease (AD) research has consistently documented lower grey matter and white matter volume,^[1] cortical thinning,^[2] lower fractional anisotropy (FA; reflecting white matter microstructure),^[3] higher white matter hyperintensity load,^[4] abnormal functional connectivity,^[5] and reductions in cerebral perfusion^[6] and metabolism.^[7] While this valuable research has given considerable insights into the pathological processes involved in AD, this same pattern of brain changes has also been reported in Major Depressive Disorder (MDD).^[8-13] Furthermore, going beyond these more general whole-brain changes, atrophy to the hippocampal region is commonly presented as being a characteristic hallmark of AD.^[14, 15] Ideally, focusing on specific regions using the anatomical precision provided by high-resolution techniques would improve the specificity of neuroimaging measures. However, it is notable that hippocampal atrophy is also

commonly seen in MDD,^[16] alongside a range of other conditions.^[17-20] Hence distinguishing AD from MDD using neuroimaging is not straightforward, despite the differential clinical presentation and likely treatment implications. Clearly, AD and MDD are not the same disease, nor do they have the same pathogenesis. Nevertheless, there appears to be a substantial overlap in terms of changes to the brain. This is potentially due to the common comorbidity of depressive symptoms in people with AD,^[21] which questions the validity of 'pure' (i.e., comorbidity-free) experimental groups. Another issue is more statistical; the variability within each disease group is often overlooked, with the assumption of within-group homogeneity implicitly included in experimental designs. The overlap between AD and MDD is just an example; the lack specificity between multiple pairwise combinations of diseases can be seen in Table 1.

Neuroimaging's lack of specificity has important consequences for research into brain diseases. Quantifying the parameters on which patients of a given brain disease differ from healthy people is insufficient to either definitively make diagnoses nor explain the symptoms associated with that disease. This fact has limited the application of neuroimaging in clinical contexts, and it is rare that insights from quantitative neuroimaging have resulted in patient benefit (pre-neurosurgical planning using diffusion-MRI is an exception). Given the increasingly high burden of brain diseases on our ageing society and the manifest potential of neuroimaging, these limitations to its clinical application need to be overcome.

There are contrasting explanations behind this general lack of specificity in neuroimaging studies of brain diseases. The relatively small sample sizes generally used in neuroimaging, due to the financial and logistical challenges of expensive scanning studies, may be a contributor. Arguably, larger samples could lead to more precise localisation of neuroanatomical signatures, a concept that is supported by the results of activation likelihood estimation (ALE) meta-analyses.^[22, 23] In theory, this should enable better separation between diseases; however, ALE meta-analyses have also highlighted neuroanatomical overlap between neuropsychiatric disorders.^[24, 25] Greater numbers may in fact decrease specificity even further. Another potential explanation is the spatial resolution of neuroimaging methods, which is somewhat coarse relative to the size of brain cells (mm versus μm). This may mean that present technology is insufficient to wholly discriminate

brain diseases and that the key distinguishing signatures are not yet visible. A third possibility is that the diagnostic process of brain diseases is flawed. This may well be the case in psychiatric diseases, where diagnosis is often imperfect and symptomatic overlap between diagnostic categories is pronounced.^[26, 27] However, this is less likely to be true of neurological diseases, where the cause of pathology is often better understood.

Here, I would like to propose an alternative explanation for the commonalities across diseases. Potentially, despite disparate aetiologies, these diseases could share common secondary neurobiological effects. These secondary effects, occurring downstream to the primary pathogenesis, result in changes detectable with neuroimaging, leading to the observed overlap in profiles of neuroimaging measures. Furthermore, these deleterious changes to the health of the brain can also be caused by the accumulation of subtle damage that may not manifest as a diagnosable disease. Such a build-up of minute damage is also observed in, and may well be the driver of, brain ageing.

2. Changes in neuroimaging measures commonly observed in brain diseases are also seen in ageing

Neuroimaging has been used frequently in the study of ageing.^[28] Intriguingly, the patterns of age-associated changes detected using neuroimaging overlaps substantially with those observed in the brain diseases. Ageing in this context refers to 'normal' ageing. While this may well be a misnomer given the individual differences observed in brain ageing,^[29] normal differs from 'healthy' in that normal refers to ageing in the absence of clinically-diagnosed pathology, whether the individuals in question are particularly healthy or not.

Research into the characteristics of the ageing brain have used the full gamut of biological techniques to assess changes at molecular, cellular, tissue and organ levels. Post-mortem research has associated older brains with decreased weight, larger ventricles and thinner cortices.^[30-32] There is also evidence of the gradual breakdown of the blood-brain barrier during ageing, such as the accumulation of blood-derived proteins (e.g., albumin, fibrinogen).^[33] Alongside this, retinal imaging studies have reported retinopathy and microvascular narrowing,^[34, 35] suggesting that the cerebrovascular system deteriorates with increasing age. Histopathology has shown that axons degenerate, glial numbers change, synapses are pruned, and eventually neuronal loss occurs.^[32, 36-38] Gene expression changes

in astrocytes and neurons, [39, 40] and the epigenetic signature of brain tissue changes, particularly DNA methylation at CpG sites across the genome.[41] Neuroimaging itself has provided many insights into brain ageing. MRI has shown reduced brain tissue volume, cortical thinning, leukoaraiosis (i.e., white matter hyperintensities on T2-weighted MRI), altered white matter microstructure, changes to structural and functional connectivity, reduced cerebral perfusion, microbleeds and greater blood-brain barrier permeability.[42-48] PET has been used to show reduced cerebral metabolism, the deposition of beta-amyloid and signs of neuroinflammation.[49-51] As can be seen in Table 1., these age-related changes to the brain also tally with those seen across multiple brain disorders. While the tabulated studies are a rather selective representation, with levels of evidence varying considerably, this overlapping pattern of findings supports both a lack of disease specificity and the absence of a clear distinction between ageing and disease when viewed through the lens of the neuroimaging literature. Even relatively uncommon techniques like dynamic contrast-enhanced MRI, that have yet to be applied in psychiatric disorders, are likely to evince more commonalities, given evidence for the involvement of blood-brain barrier integrity in psychosis and related conditions.[52]

3. Neurobiological commonalities are seen in ageing and disease

Whether ageing itself is a disease or not is a highly contentious and controversial subject of debate. On one hand, authorities such as Hayflick,[53] contend that ageing is driven by fundamentally different processes to any known disease, while others assert that ageing is best understood as a pathology.[54] I support the conclusion proposed by Gladyshev and Gladyshev,[55] that: *"aging is neither a disease, nor a non-disease."* In other words, the overlap between ageing and disease is sufficient that they should not be considered entirely separate entities, yet at the same time ageing does not fall neatly into commonly accepted definitions of disease. In particular, the ageing process does not necessarily require clinical intervention, at least for the majority of the lifespan. Nevertheless, ageing is the leading risk factor for many different diseases, and even when ageing is not a risk factor, ageing co-occurs with all chronic diseases, by their very definition. However, from the perspective of brain ageing, I contend that arguments over whether or not ageing truly is a disease are somewhat academic. What is more important is that if common mechanisms can be

identified in different states, then it is reasonable to consider common therapies for treating those states if they are pathological or increase the risk of pathology.

Alongside the neuroimaging commonalities outlined above, there also appear to be neurobiological commonalities across disease. Though different brain diseases are often defined and distinguished by contrasting aetiological and pathophysiological factors, there is evidence that suggests a range of common effects on the brain across disease states. For example, traumatic brain injury, AD, MDD and multiple sclerosis have all been linked to neuroinflammation, oxidative stress, a heightened immune response, mitochondrial dysfunction and epigenetic alterations.^[56-65] As mentioned, these phenomena have also been associated with neurobiology of normal ageing.^[41, 66-69] The neurobiological overlap between ageing and disease is paralleled outside the brain, with mechanistic commonalities observed in other bodily systems (see Franceschi and colleagues for review).^[70]

So how to reconcile these observed commonalities between ageing and disease? That diseases may differ only *quantitatively* from ageing, as measured by neuroimaging, is an important consideration. This view implies that brain diseases represent one end of a spectrum that also contains 'healthy' and 'normal' ageing. If true, this calls into question the common conception that diseases are *qualitatively* different from health. It also means that the lines drawn to distinguish disease and health, or between two diseases, are likely to be more or less arbitrary; casting into doubt the classic univariate case-control design used in biomedical research.

Potentially, the fact that certain biological states lead to clinical pathology and others do not, may be more due to underlying individual differences rather than qualitative differences in neurobiological mechanisms. Thus, understanding how a patient's biological state compares to the spectrum of similarly aged people provides an alternative and promising approach to putting chronic brain diseases properly in the context of ageing-related changes. One way of achieving this is to consider measurements of underlying biological ageing and how these can be affected in disease states.

4. Neuroimaging can be used to model brain ageing in health and disease

4.1 Measuring underlying ‘biological age’, using neuroimaging

Independently from neuroscience, the field of biogerontology has long sought to find measures of ‘biological age’, thought to represent the ‘true’ age of an individual more accurately than chronological age alone. There are a plethora of different approaches to measuring biological age, and the search for ageing biomarkers is gathering pace.^[71] These ageing biomarkers are conventionally based on blood-derived or physiological measures, and measurements of brain ageing are seldom considered. However, neuroscientists have begun to adopt this biogerontological approach and methods for generating ageing biomarkers have been developed using neuroimaging data.^[72, 73]

The idea of generating a “brain-predicted age”, in other words a biological-age prediction derived using measurements of the brain (commonly structural neuroimaging), is becoming increasingly common.^[74] This is thanks to the adoption of sophisticated machine learning methods for statistical analysis. These methods allow extremely high-dimensional datasets, such as those derived from MRI scans (with tens of thousands of voxels as data points), to be analysed in an efficient and principled manner. This development has been enabled by both the continual improvements in computing performance and the proliferation of publicly-available datasets, providing sufficiently large sample sizes for machine learning methods to generate accurate predictions. By learning the relationship between patterns of neuroimaging data and chronological age in groups of healthy people (i.e., the training set), a predictive model can be built whereby accurate estimations of chronological age can be made from data not used to train the model (i.e., the test set). Such models are able routinely to generate predictions with an accuracy of within five years of actual chronological in adults.^[72, 73, 75, 76]

4.2 What can ‘brain-predicted age’ tell us about how diseases interact with the ageing brain?

In attempts to better understand the effects of diseases on the ageing brain, models of brain-predicted age have been applied in a range of different contexts. This includes a number of neurological conditions: Added brain ageing has been reported after a traumatic brain injury,^[75] in people with treatment-resistant epilepsy,^[77] and to a lesser extent, in older adults with HIV that is successfully treated with anti-retroviral therapy.^[78] Cognitive

performance was assessed in these disease samples, showing moderate, but consistent relationships between brain-predicted age and neuropsychological test performance in both patients and controls. Individuals with older-appearing brains tended to perform worse across different cognitive domains and more globally. This is in line with behavioural studies that show that ageing is generally associated with declining cognitive performance.^[79]

A crucial next step for research using brain-predicted age will be to conduct longitudinal follow-up of clinical samples. This will help establish whether the apparent increases in brain ageing remain constant or whether the gap increases over time, suggesting an accelerating process. The distinction between a static and an accelerating process is crucial. This will tell us whether the disease processes are adding to those seen in normal ageing (i.e., the accumulation of more damage) or whether there is an interaction between disease-specific pathogenic factors and normal ageing processes. The latter scenario is likely to be deleterious as progressive damage will result in a more rapid onset of cognitive decline, other disease symptoms and in some cases, dementia.

With regard to specific risk factors for dementia, brain-predicted ageing has been assessed in people with mild cognitive impairment (MCI) and AD. Individuals diagnosed with AD have been shown to have greater apparent brain ageing, observed in several analyses utilising the data from the Alzheimer's Disease Neuroimaging Initiative (ADNI).^[72, 80, 81] In people with MCI, brain-predicted age was a significant predictor of progression to dementia within three years from a baseline MRI scan.^[80-82] This is important as it demonstrates that brain-predicted age is sensitive to subtle underlying brain changes that occur prior to outward disease manifestation. In a slowly progressing neurodegenerative condition like AD, methods for identifying those at greater risk of future decline will be particularly useful. They can inform clinical practice and aid in the design of clinical trials of neuroprotective therapeutics by stratifying trial enrolment or serving as surrogate outcome measures to reduce trial duration making them more feasible.

Having trisomy 21 (i.e., Down's syndrome) is another a risk factor for dementia and specifically AD. In fact, as many as 80% of people with Down's syndrome will develop dementia,^[83] invariably at an earlier age than would be expected in a non-Down's group (i.e., below 65 years of age). During a recent study, I analysed brain-predicted age in adults

with Down' s syndrome. The results showed that on average people with Down' s syndrome had brains appearing 2.5 years older than their chronological age, which was significantly greater than a local healthy control group. This indicates that some changes to brain structure in Down' s resemble those seen in normal ageing, but appear at an earlier age, akin to the physiological phenotype of the syndrome (e.g., presbyopia, hair loss, sarcopenia). Interestingly, when analysing the variability in brain-predicted age in this Down' s syndrome group, people who had a greater brain-predicted age difference also had higher levels of beta-amyloid deposition (measured using Pittsburgh-compound-B [PiB] PET) and were more likely to show signs of cognitive impairment. It seems that in Down' s people who exhibited signs of these pathological facets of brain ageing also had older-appearing brains. This indicates that measures of brain-predicted age are potentially useful to characterise individual differences in brain ageing in Down' s, which may in turn help better predict subsequent development of dementia.

Psychiatric disorders have also been investigated using brain-predicted age. In schizophrenia, reports indicate that not only is greater brain ageing observed, particularly in males,^[84, 85] but that this is accelerating over time.^[86] In the context of psychosis (e.g., bipolar disorder, at-risk mental states), increased brain ageing is less apparent.^[84, 85] The study by Koutsourleris and colleagues' also included patients with MDD, finding a mean added brain ageing of 4.0 years.^[84] People diagnosed with borderline personality disorder were also assessed, having a mean added brain ageing of 3.1 years. These studies indicate that psychiatric disorders are associated with premature age-related changes to the structure of the brain. Nevertheless, further work in larger samples is required to validate this. In particular, focus on how brain-predicted age relates to long-term outcomes of psychiatric diseases or to treatment response will be especially valuable.

4.3 Genetic influences on brain-predicted ageing

Brain-predicted age appears to be heritable,^[73] as would be expect given the known heritability of brain volumes.^[87] This motivates research into candidate genes for the brain-predicted age phenotype, which may shed light on specific biological pathways implicated in brain ageing, in turn presenting possible targets for novel therapeutics aimed at maintaining brain health during ageing. Currently, only *APOE* has been considered. One report showed that *APOE* genotype is associated with increased brain ageing in patients

with AD,^[81] whereby AD patients carrying the e4 allele showed greater longitudinal changes in brain-predicted age compared to AD patients without the e4 allele. This was despite there being no cross-sectional differences based on APOE genotype AD patients, people with MCI and cognitively-normal controls. Other cross-sectional studies also did not observe effects of *APOE* in people with Down' s syndrome or in the general population.^[88, 89] That the effects of APOE genotype on brain-predicted age are only detected longitudinally suggests the e4 allele may have subtle effects on trajectories of brain health, that only become pronounced as disease progression accelerates. Currently, further research is needed in order to identify specific genetic factors that influence the brain ageing process. Moving beyond *APOE* to consider other candidates or panels of candidate genes may well prove fruitful, if sufficiently large sample sizes can be employed to detect these likely subtle genetic effects.

4.4 Different insults, common consequences?

The growing body of brain-predicted age neuroimaging research is providing new insights into the relationship between brain diseases and the ageing process. It seems that different insults to the brain, in the form of trauma, infection or genetic abnormality, can cause changes to brain structure that in effect, shift people along the brain ageing trajectory. In light of the commonalities in neurobiological and neuroanatomical processes outlined above, this apparent added ageing resulting from disease has some face validity. The range of brain-age predicted age studies published currently supports the idea that there are commonalities between ageing and disease. Potentially, such measures of individual differences in brain health could be more relevant for future health outcomes than a specific diagnosis is. Although further validation is absolutely necessary, brain ageing findings in different diseases support a shift of research emphasis towards clinically-relevant neuroimaging measures of individual differences across diagnoses, rather than within.

5. Focusing on commonalities could lead to a paradigm shift

As outlined above, the conventional experimental design for neuroimaging research into brain diseases is to compare a disease group with a healthy group and establish facets of the brain that differ on average. While this approach to comparing and contrasting different diseases can provide highly informative, its cogency relies on the validity and relevance of

diagnostic groups. Solely relying on measures of central tendency to tell us about diagnostic group differences is a reductive strategy and it makes the key assumption of homogeneity within experimental groups. However, this assumption is seldom valid. The alternative is to not merely focus on where groups differ, but to model where individuals differ. The illustration that many of tools we use for measuring aspects of biology provide little or no diagnostic specificity and the evidence of commonalities across diagnostic categories reinforces the value of considering the individual instead of the group.^[90] Furthermore, given the similarities between brain diseases and ageing I described earlier, then it is even more important to consider the individual in the context of what would be expected given their age. To return to the example of hippocampal atrophy, while it is a phenotypic ‘hallmark’ of AD,^[14, 15] it is commonly observed in MDD, and appears to be a facet of normal ageing. Thus, stating that hippocampal atrophy is the result of a disease is imprecise. If AD is characterised by a greater degree of hippocampal atrophy than normal ageing, then this does become more informative. However, even brief scrutiny of the distributions of hippocampal atrophy rates shows that many individuals with a diagnosis of AD have lower atrophy rates than the mean in age-matched healthy controls.^[91] This begs the question, is attempting to characterise the average phenotypes of a disease even the correct approach? Perhaps a better focus would be on predicting health outcomes, irrespective of how neatly someone fits into a diagnostic category.

The initial evidence from brain-predicted age neuroimaging studies clearly shows the effects are not uniform within disease groups. Interestingly, the variability in disease groups is generally similar to that observed in healthy control groups. That makes understanding the variability of individual differences in brain ageing of particular interest. As well as being related to cognitive performance, this variability also relates to physiological markers of ageing and to risk of mortality in older adults.^[89] This means that by focusing on what measures of individual differences can tell us about a person’s health, we may well be better placed to accurately predict what may happen to them in the future. This type of paradigm shift, from characterisation to prediction, will be essential if quantitative neuroimaging is to have clinical impact. By focusing on predicting prognosis or treatment response (or even non-response), we could potentially build powerful statistical models that incorporate neuroimaging alongside other sources of data (e.g., genetics, epigenetics,

biochemical, physiological) that can make precise medical predictions at a personalised level, substantially augmenting current clinical practice for brain diseases and for improving brain health during ageing.

Already, signs of this paradigm shift are appearing. There is a small, but important, body of research that is developing sophisticated models of the trajectories of different facets of brain ageing, using a range of neuroimaging modalities.^[92-96] These models, often using longitudinal data, have the potential to map out an individual's future brain health. These anatomical trajectories are of key importance as dramatic changes can occur to the brain long before behavioural symptoms appear. By assessing an individual's personalised brain ageing trajectory, in the context of known healthy and degenerative trajectories, we stand to be much better informed than by simply knowing their disease diagnosis, particularly if they are asymptomatic. Given the overlapping neurobiological, neuroanatomical and symptomatic profiles of these diseases with the ageing process, following this approach may well shed light on the breadth of different brain diseases and how those diseases relate to subtle age-related changes to the brain.

6. Conclusions and outlook

Here, I have outlined my view on the neuroimaging literature, concluding that there is substantial overlap between different brain diseases and also with ageing. This is supported by evidence from behavioural studies and from neurobiological research and indicates that the commonalities between ageing and disease have much to tell us about disease processes. Moreover, the presence of these ageing and disease commonalities should lead us to design better ways to study these phenomena to deliver benefits for patients. The key to delivering research that can make clinically useful predictions using neuroimaging is to shift away from merely characterising the average difference between a disease group and a healthy group. Instead we should consider the individual, attempt to define the status of their brain health using multi-modal neuroimaging and then model their personalised future trajectory. This should help us better establish if and when they are at risk of suffering from cognitive decline, neurodegeneration and manifest brain disease.

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