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REVIEW

Fifteen years on: a review of the Cam-CAN study of the cognitive neuroscience of ageing

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Abstract The Cambridge Centre for Ageing and Neuroscience (Cam-CAN, www.cam-can.org) was established 15 years ago to investigate the cognitive and brain bases of healthy adult ageing. Demographic, health and lifestyle data, cognitive data and a wide range of brain imaging data, were shared with other researchers around the world, resulting in many scientific findings. Here we review these findings under the broad headings of 'neuroscience of ageing', 'methodological developments' and 'clinical/translational use', and look to future longitudinal continuation and sharing of further data.

Keywords Cognition · Brain · Ageing · Neuroimaging · Reserve · Maintenance

Introduction

Cam-CAN (www.cam-can.org) started in 2010 as a virtual centre bringing together individuals from several departments within the University of Cambridge, UK, who were interested in the cognitive neuroscience of ageing. It was fortunate to obtain a grant from the UK Biotechnology and Biological Sciences Research Council, which enabled us to recruit a sample of healthy individuals across the adult lifespan who kindly contributed data on their lifestyle, and their cognitive abilities and their brains, as well as a saliva sample for genotyping. Their brain data came from multiple magnetic resonance imaging (MRI) contrasts, as well as magnetoencephalography (MEG). In 2016, these data were made available to other researchers using a managed-access system. This article reviews the main scientific findings enabled by this.

Full details of the initial Cam-CAN protocol can be found in ref. [1]. Data from the first three stages[1] have been made available so far. Subsequent funding from the European Union Horizon 2020 scheme (specifically the 'LifeBrain' project, www.lifebrain.uio.no), plus intramural funding from the UK's Medical Research Council (MRC) to the Cognition & Brain sciences Unit (CBU), has enabled Cam-CAN to continue with a further two stages of data collection, including repeat MRI and MEG [2]. Data from these two more recent stages will be made available soon.

The main scientific aim of Cam-CAN is to study the systems neuroscience of healthy ageing, in particular to understand how some people can maintain cognitive abilities into late life, often despite the

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[1] In subsequent work, we sometimes use the word "phase" rather than "stage", but these are equivalent.

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atrophy of the brain that typifies ageing. To this end, we acquired data from questionnaires, from a range of cognitive tests, from a range of MRI contrasts (T1-weighted, T2-weighted, diffusion-weighted, MT-weighted and BOLD-weighted; see Glossary) and from MEG. The BOLD-weighted fMRI data were acquired in three runs of approximately 9 min, during which participants either rested with eyes closed, watched a stimulating movie, or performed a simple, trial-based sensorimotor task. MEG data were acquired during rest and the sensorimotor task. Saliva was genotyped by colleagues in Radboud university, using the 'OmniExpressExome' chip that covers > 960,000 single-nucleotide polymorphisms (SNPs) throughout the genome. From these, collaborators in Cardiff have estimated several polygenic scores for outcomes like longevity, intelligence and Alzheimer's disease (AD).

Recruitment

The Cam-CAN team approached 7616 eligible adults living in the city of Cambridge, UK, initially contacted by letter via doctor surgeries. In the absence of a reply, we called at their home. Of these, $N = 2681$ (35%) agreed to take part, which is a reasonably high proportion for such studies. Importantly, these were not just people who respond to advertisements for research, who are often super-healthy and more affluent individuals. Thus, this sample is more representative of the population than many other neuroimaging studies of ageing. See ref. [3] for further discussion about recruitment.

The $N = 2681$ completed an interview at home that lasted around 2 h, with several structured questionnaires and some simple cognitive tests. These behavioural data are referred to as 'Stage 1' (or 'Home Interview') data. In Stage 2, we sub-sampled 100 of these people for each of the 7 decades from 18 to 88 years. These people made three visits to the MRC CBU, to acquire more detailed cognitive data, as well as undergo MRI and MEG scanning. The final number of $n = 708$ who completed at least one visit are sometimes referred to as the 'CC700' cohort.[2] These people were selected to have no signs of dementia, defined as no referral for dementia assessment, no memory complaints and a Mini-Mental State Examination (MMSE) score greater than 24. They also needed to be able to tolerate MRI and MEG scanning (see ref. [1], for full inclusion criteria). In Stage 3, a further subset of $n \sim 280$ people from Stage 2 were sampled, 1–3 years later, which entailed two more visits to the CBU for fMRI and MEG imaging of more specialised cognitive tasks.

Obtaining the dataset

The data can be requested from this website: https://opendata.mrc-cbu.cam.ac.uk/projects/Cam-CAN/. These data include questionnaire responses, and cognitive scores, as well as raw MRI and MEG data (genetic data are not available owing to their sensitivity, but formal agreements can be discussed with Cam-CAN management). The imaging data are in BIDS format (https://bids.neuroimaging.io/index.html), though a separate BIDS repository has been created for each type of imaging data (e.g. diffusion-weighted, BOLD-weighted), given that researchers typically only want a subset of the data (what we call 'BIDSsep'). In addition to details about the applicant, completion of an online Data Usage Agreement is required (which prohibits, for example, attempts to identify participants), as well as a rationale for use of the data. Though we cannot enforce specific uses of the data, a record of the original rationale would allow us to question any non-scientific or non-ethical deviation. These are reviewed by a subset of Cam-CAN PIs, typically within 2 weeks. Approximately 3000 requests have been received at the time of writing, from researchers around the world.

Brief review of scientific uses

A PubMed search for papers that cite the [1] protocol paper (https://pubmed.ncbi.nlm.nih.gov/?linkname=pubmed_pubmed_citedin&from_uid=25412575) done on 28 October 2025 revealed 311 papers, 72 of which come from members of the core Cam-CAN

[2] The CC700 cohort are in fact now called 'Arm 1', because later in 2017–2018, a separate group of $n \sim 100$ people ('Arm 2') were sub-sampled from Stage 1 and undertook very similar cognitive, MRI and MEG assessments at the CBU, approximately half of whom fell below the MMSE cut-off for dementia (the 'cognitively frail'), in order to study potential early stages of dementia.

team (https://cam-can.mrc-cbu.cam.ac.uk/publications/). In this review, we focus on empirical papers that used some Cam-CAN data (rather than reviews that just reference the study), but even then we may have missed some. In what follows, we divide the empirical publications into those about (1) the basic neuroscience of ageing, (2) methodological developments and (3) clinical/translational work. There is of course a bias towards research done by the Cam-CAN team, simply because we know that work better, but the references provide further information on other studies. Figure 1 provides a conceptual overview of the main points.

Neuroscience of ageing

This section reviews novel findings about the effect of age on cognition and the brain.

Effect of age on cognition

There are long-standing debates about how age affects various cognitive abilities. At one extreme, there are single-factor accounts that assume age detrimentally affects a single (or at least a small number of) 'domain-general' factors underpinning performance on many cognitive tests. Nonetheless, there is broad agreement that tests that measure 'fluid' abilities (such as problem-solving or learning) decline with age, whereas others that measure 'crystallised' abilities (such as language comprehension or general knowledge) show little effect of age. Shafto et al.

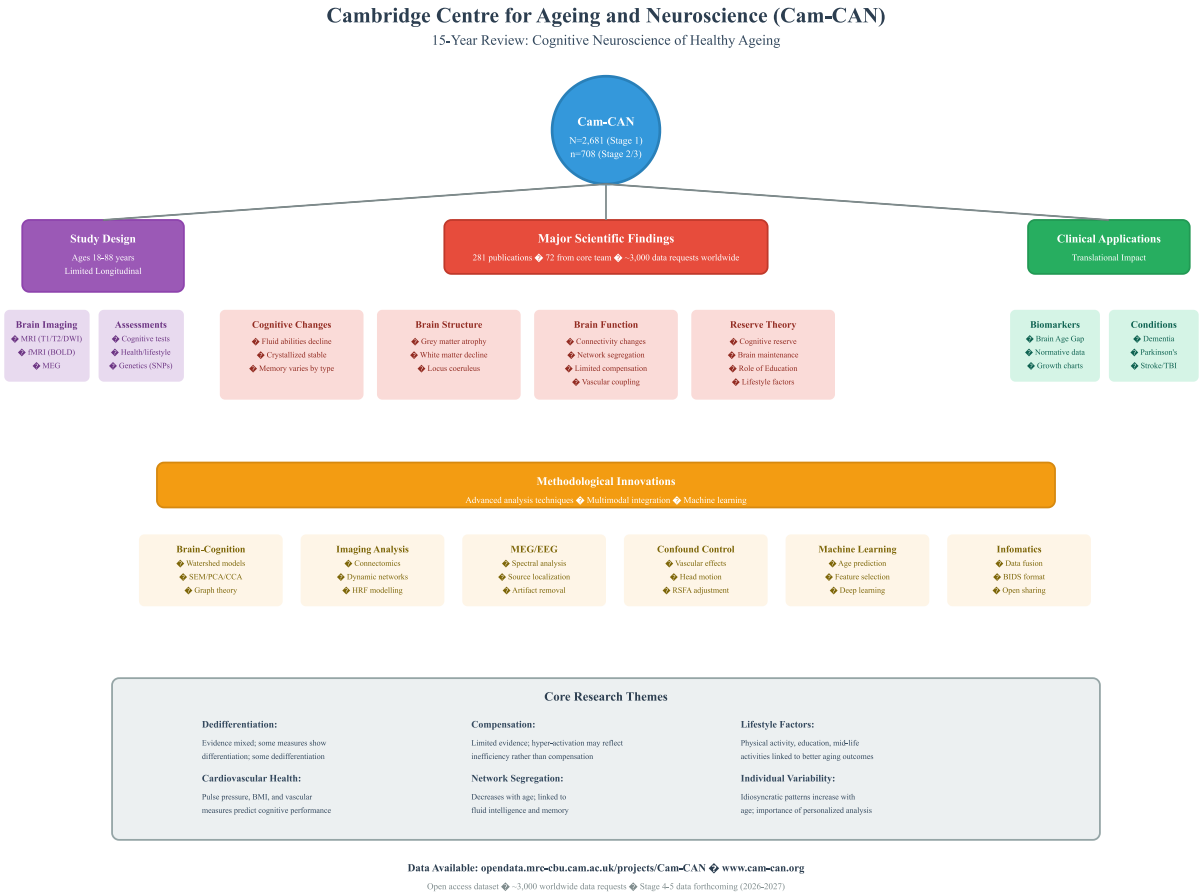

Fig. 1 Concept map of key findings in this review, created with assistance from Claude AI (Anthropic)

[4] performed principal component analysis (PCA) across 17 cognitive/affective measures from Stages 1–2 of Cam-CAN.[3] While the identification of a 'sufficient' number of principal components is always a matter of debate, the normalised eigenvalue and scree criteria agreed on 4 components (explaining 20%, 14%, 10% and 7% of the variance). The dominant component related to fluid abilities, and showed the strongest (negative) effect of age (with age capturing nearly 50% of its variance). The second component related to naming tasks (such as famous face naming, picture naming speed and tip-of-the-tongue experiences), and showed an inverted-U profile across age. The third related to crystallised abilities, which showed a small increase with age, while the fourth related to sentence comprehension, which showed no effect of age. However, it must be remembered that these components are specific to the set of cognitive tasks used (which may be biased towards language tasks in Cam-CAN, for example), and are derived from cross-sectional data, so it could be influenced by generational effects (due to differing birth years). PCA on longitudinal (within-participant) changes might reveal a different cognitive structure.

Other studies have focused on specific tasks. For example, Mitchell and Cusack [5] showed that performance of Cam-CAN's continuous report test of visual short-term memory (VSTM) decreased with age, and this could not be explained by decreases in visual and sensorimotor precision. They considered two strategies that might offset these memory declines: the use of contextual encoding, and metacognitive monitoring of performance. While both strategies were associated with better performance, they did not differ by age. This suggests that older adults retain their capacity to boost VSTM performance through attention to external context and monitoring of their performance, which could be utilised to help maintain short-term memory performance with advancing age.

Henson et al. [6] dissected the effects of age on different cognitive processes associated with longer-term memory, which is one of the most common complaints as we get older. By comparing different factor structures, they concluded that performance of Cam-CAN's 'emotional memory' task was supported by three latent factors: associative memory, item memory and (visual) priming. These factors were differentially affected by age, such that, after adjusting for fluid intelligence and education, associative memory was most adversely affected by age, while priming was not significantly affected, supporting claims that age affects different types of memory in different ways.

Shafto et al. [7] examined the 'tip-of-the-tongue' (TOT) phenomenon—the word-finding problem that we all experience as we get older. One hypothesis for this common age-related problem is greater interference between words as vocabulary size increases. However, data from the Cam-CAN TOT and picture naming tasks showed that TOT incidence actually decreased with vocabulary size. This result is more consistent with the TOT problem arising from a phonological retrieval deficit instead, in which associations between meanings and phonological forms weaken with age. On the positive side, having more phonological neighbours in one's vocabulary, as one gets older, should ameliorate this problem to some extent.

It is well-documented that face perception—including recognition of both expression and identity—declines with age, but this could be a consequence of general decline in fluid intelligence. Connolly et al. [8] showed that the age-related decreases in expression and identity recognition remained after adjusting for fluid intelligence. Furthermore, recognition of expression and identity showed unique associations with age, suggesting that age has independent effects on the dissociable pathways for identity and expression assumed in many models of face processing.

Thus, the somewhat specialised laboratory-based tasks used by Cam-CAN have generally revealed multiple, dissociable age-related factors contributing to specific abilities such as short-term memory, long-term memory, word-finding and face processing, questioning the sufficiency of single-factor accounts of cognitive ageing. At the same time, factor analysis across these tasks does reveal a common factor of fluid intelligence, which explains much of the age-related variance in each task. One way to reconcile

[3] Many of these were specialised laboratory tasks developed by Cam-CAN investigators to address specific hypotheses about ageing, rather than being more standardised neuropsychological test batteries (which are often only sensitive to brain disorders). Nonetheless, the relative dearth of standardised tests does hinder pooling of Cam-CAN cognitive data with those from other cohorts.

this psychometric tradition of identifying common factors with the cognitive psychological tradition of fractionating processes underlying individual tasks is to accept that there are many different psychological functions, but that all of them can be affected by age to some extent, e.g. in the speed with which those processes can be conducted.

Effects of age on brain structure

Grey matter

The most common metric of brain structural health is volume of grey matter, either in the cortex, or of subcortical structures ('volumetrics'). Grey matter volume can be estimated by segmenting a T1-weighted MRI into different tissue types, and assigning a (partial) grey matter volume to each voxel. Alternatively, the cortical surface can be defined by the boundaries between those tissue types, and its local thickness and surface area estimated at vertices across that surface. This cortical surface is often parcellated according to anatomical features, e.g. based on a standard brain atlas.

The basic effects of age on grey matter (as well as related measures like ventricular volume) have been well-documented for several decades. The studies using Cam-CAN data have tended to address more specific hypotheses. For example, Roe et al. [9] combined Cam-CAN's T1-weighted images with those from other cohorts to examine the effects of age on cortical hemispheric asymmetry. The left and right hemispheres are known to differ in function, and to a lesser extent, structure, but this asymmetry may change with age. They found that, whereas the asymmetry of cortical surface area is largely stable across life, the asymmetry of cortical thickness increases in childhood and peaks in early adulthood. On the basis of heritability analyses and correlations across cortical regions, they suggested that areal asymmetry arises early in life through genetic effects, whereas thickness asymmetry changes during childhood development.

Roger et al. [10] focused on the asymmetry of regions within a 'language-and-memory network', from which they extracted grey matter volumes (as well as the dominant gradient of resting-state fMRI connectivity; see Connectomics section). From these, they identified two distinct age-related asymmetry trajectories: one pattern revealed a bilateralisation of language-dominant regions, while the other showed increasing leftward specialisation in multimodal regions associated with both memory and language. These opposing patterns emerged around midlife and were associated with performance in language production tasks.

Escalante et al. [11] also focused on geometric brain changes with age, rather than individual regions. They found that increasing age was associated with global expansion across inferior-anterior gradients, global compression across superior-posterior gradients and regional expansion between fronto-temporal homologues. Some of these global patterns were further associated with deficits in various cognitive domains.

Wang et al. [12] used a multi-scale description of the brains of 11 primate species, and showed that their cerebral cortices are all approximations of the same archetypal shape with a fractal dimension of 2.5. This enables a more precise quantification of brain morphology as a function of scale, which they demonstrated on Cam-CAN data by showing that a spatial scale of approximately 2 mm produced a fourfold increase in the effect size of age compared to standard morphological analyses. Leiberg et al. [13] confirmed that scales around 2 mm produced the largest effect of age when considering entire cortical hemispheres, but lobal variations became more pronounced in lower scales around 0.7 mm.

Other studies have focused on sub-cortical regions. Yu et al. [14] compared effects of age on thickness and surface area of the hippocampus. While the cortex showed a linear decrease with age, hippocampal thickness and surface area showed an inverted U-shape. These effects were fairly uniform across the hippocampus. These findings suggest important differences in the ageing of the hippocampus and cortex. Fjell et al. [15] combined Cam-CAN with other LifeBrain cohorts to assess the degree to which subcortical regions that develop together continue to change together through life. Using graph theory, they identified five clusters of coordinated development, indexed as patterns of correlated volumetric change. These clusters tended to follow placement along the cranial axis in embryonic brain development, suggesting continuity from prenatal stages. Importantly, they were conserved through adult life, suggesting a genetic basis of this coordinated subcortical change.

One particular sub-cortical focus in Cam-CAN has been on the locus coeruleus (LC), for two main reasons. Firstly, the LC is the major origin of noradrenergic modulation, which is believed to play an important role in Parkinson's and Alzheimer's diseases. Secondly, LC noradrenergic neurons accumulate neuromelanin with increasing age, and neuromelanin affects the contrast in MT-weighted MRI. However, the LC is a small structure that is difficult to localise on a standard T1-weighted MRI. By combining MT- and T1-weighted images, and normalising MT-weighted signal relative to the pons, Liu et al. [16] found a quadratic relationship between normalised LC signal and age, with the peak occurring around 60 years. In a subsequent study, Liu et al. [17] tested the pre-registered hypothesis that those cognitive functions that are putatively noradrenergic-dependent would be more strongly associated with this LC integrity in older versus younger adults. However, a unidimensional model was a better fit, in which LC related to a single cognitive factor. Nonetheless, the relationship between LC and this single cognitive factor did significantly increase with age, as predicted. These effects of age on LC are therefore likely to have wide-ranging functional and clinical implications.

White matter

One can also estimate white matter volume from a T1-weighted image, though another approach for assaying white matter is to use a T2-weighted image to estimate white matter lesions, which appear as hyper-intensities (WMHI). Gutiérrez-Zúñiga et al. [18] used such images from Cam-CAN (and another cohort) to estimate both grey matter density and white matter lesions, and suggested that grey matter changes lead to secondary white matter degeneration in vascular border zones, whereas white matter lesions lead to secondary grey matter degeneration in cortical projection areas. They linked these findings to small vessel disease.

A third approach is to estimate myelin density from the T1:T2 ratio. Sui et al. [19] used this ratio and found a nonlinear profile of myelin across cortical depth. This profile was sensitive to age, even when adjusting for age-related changes in cortical thickness, suggesting that it offers a unique marker of microstructural alterations within the cortex.

Yet another approach uses diffusion-weighted MRI to estimate the micro-structural integrity of white matter tracts. The most common such method (DTI) uses a tensor model, in which the diffusion of water in multiple directions is measured in order to infer the dominant orientation of white matter tracts. Summary metrics of the diffusion tensor, like fractional anisotropy (FA), can be extracted to index the overall tract integrity. One can also perform tractography, i.e. estimate the strength/probability of connections between any pair of regions, and generate a white matter connectome, as discussed later.

One advantage of Cam-CANs 'multi-shell' diffusion-weighted sequence is that it allows estimation of higher-order tensor properties such as kurtosis. In Henriques et al. [20], we performed a factor analysis of six common diffusion metrics: FA (from the standard DTI model), mean signal diffusivity and kurtosis (from a higher-order tensor model), and three biophysical properties estimated from a popular compartmental model called NODDI. Factor analyses revealed that three factors were sufficient to capture these six metrics: one relating to microscopic properties (e.g. differences in fibre density/myelin), one related to configuration complexity (e.g. crossing, dispersing, fanning fibres) and one related to free-water contamination (e.g. partial-volume effects or white matter damage). These factors showed different age-related trajectories, and were expressed differently across white matter tracts.

Finally, myelin density can also be estimated from the MT-weighted images mentioned earlier. Indeed, one strength of Cam-CAN is its multiple measures of white matter (from T1-, T2-, diffusion- and MT-weighted images). In Raykov et al. [21], we added five more non-diffusion metrics to the six diffusion metrics considered by Henriques et al. [20]. While there was now a fourth white matter factor, it explained only a small amount of additional variance, and the factors were dominated by the diffusion metrics, suggesting that there is, in fact, little complementary information about white matter in the T1-/T2-/MT-weighted images. Structural equation modelling showed that these white matter factors had face validity, in that they were predicted by cardiovascular factors, and themselves predicted cognition, as considered next.

Relating brain structure to cognition

In one of the first Cam-CAN studies relating brain structure to cognitive abilities, Kievit et al. [22] compared Cam-CAN's tests of fluid intelligence (as measured by the Cattell task) and multitasking (as measured by the Hotel task), and related them to grey matter volume (from T1-weighted MRI) and white matter integrity (from diffusion-weighted MRI) within four a priori regions within prefrontal cortex (PFC). In addition to showing that multitasking and fluid intelligence are distinct executive functions with diverging age-related differences, structural equation modelling showed that they are mediated by different neural substrates, and exhibit different brain–behaviour relationships in older versus younger individuals. These results suggest that ageing in PFC is a multidimensional process with different consequences for different types of executive control.

Henson et al. [6] took a similar structural equation modelling approach to data from the emotional memory task mentioned earlier, and found that associative memory, item memory and priming had unique contributions from both grey matter and white matter associated with regions in the medial temporal lobes (MTL). However, a later study by Guardia et al. [23] found that grey matter in PFC predicted memory performance better than structures of the MTL, particularly for associative memory. These findings emphasise the additional role of PFC in control processes needed for successful memory performance.

Kljajevic and Erramuzpe [24] examined the neural correlates of the TOT phenomenon (see Cognition section) in middle-aged relative to younger Cam-CAN participants. The middle-aged group showed more TOT states, with FA values in the right superior longitudinal fasciculus being positively correlated with 'don't know' scores, implicating a dorsal white matter route for retrieval of proper nouns. Gong et al. [25] used graph-metric summaries of the diffusion-based connectome (see Connectomics section), and found that global efficiency and mean degree centrality of a phonological processing network positively predicted TOT rates. They suggested these findings suggest the 'blocking' hypothesis, viz. retrieval of target words is interfered with by phonological neighbours. Similarly, Chen et al. [26] related word-finding problems in Cam-CAN's picture-naming task to 'brain age', as estimated from white matter (see the Brain age gap section). They concluded that the phonological component of word retrieval ability declines as cerebral white matter ages, whereas the semantic component is relatively resilient to white matter aging.

Better white matter integrity has also been hypothesised to support more consistent behavioural performance by decreasing noise in neural communication. The consistency of performance can be indexed by the trial-to-trial variability in reaction times (RTs) in repetitive tasks. Using the 'simple RT' task in Stage 1 of Cam-CAN, McCormick et al. [27] showed that the standard FA measure of white matter integrity predicted the variance in RTs, even after adjusting for age, consistent with the noisy-communication hypothesis of ageing.

The studies reviewed above have provided neural evidence to support the age-related dissociations between the different types of executive function, long-term memory and word-finding processes considered earlier, as well as relating the more fundamental concept of processing speed to white matter integrity. Again, it is possible that a general factor like age-related demyelination and/or neuronal loss could cause such cognitive changes, the relative size of which can dissociate (across individuals) according to differing extents of such neural changes in different brain regions. Next we consider more specific theories of age-related cognitive and brain changes.

(De)differentiation

One prominent theme in theories of ageing is 'de-differentiation'. Differentiation refers to the reduced correlation often seen between multiple measures (e.g. of cognition) as children get older, i.e. as their cognitive abilities become more specialised. The opposite pattern of de-differentiation is believed to happen in ageing, whereby cognitive scores becomes more correlated ('when it goes, it all goes together'). However, the Shafto et al. [4] study mentioned earlier found no evidence of (de)differentiation in Cam-CAN's cognitive scores, whereas others have found differentiation instead. While several studies have examined (de) differentiation of brain measures with age (e.g. correlations between white matter integrity across different ROIs), de Mooij et al. [28] were the first to measure (de)differentiation between brain measures and cognitive measures. They found evidence for differentiation between a number of white matter factors

and the three cognitive factors of fluid intelligence, crystallised intelligence and memory. The presence of such brain-cognition differentiation could reflect ageing at different rates, or different sub-populations of participants (e.g. those with versus without early stages of neurodegenerative disease). It is less obvious why this differentiation would occur for theories like 'brain maintenance' (see later) that relate cognition more directly to brain structural health.

This age-related differentiation (rather than de-differentiation) is consistent with other evidence that people become less similar, or more 'idiosyncratic' with age. For example, Campbell et al. [29] found that the similarity between participants in their fMRI time series while watching the same movie decreased in older age groups, and that this reduced inter-subject functional correlation (ISFC) related to measures of attentional control. Geerligs and Campbell [30] went further to show that ISFC was preserved in some brain regions, particularly the language network, and that the overall ISFC declines were driven by distinct temporal activity and white matter declines. They concluded that, while regions involved in language processing might remain intact with age, those involved in attentional control show age-related differences even in situations similar to daily life.

In summary, there does not appear to be a common pattern of differentiation or de-differentiation across cognitive and/or brain measures: i.e. some measures may show age-related increases in their correlation across people, others may show decreases, and this is not necessarily surprising, given that the measures could represent fundamentally different processes. Having said this, some of these different patterns could also reflect the cross-sectional nature of the data, and more consistent (de)differentiation might emerge in longitudinal data.

Cognitive reserve

A related concept in theories of ageing is 'cognitive reserve', i.e. the observation that some people can maintain their cognition in old age (or in the presence of early neurodegenerative disease) despite showing similar structural brain atrophy as others who do suffer with cognitive impairments. West et al. [31] defined cognitive reserve for each older person in Cam-CAN by the similarity of their scores across multiple cognitive tests with those in a young group. Their scores on this 'person-based similarity index' were associated with education, with structural morphometry, but most strongly with higher functional connectivity between lower- and higher-order resting-state networks. They claimed that their results support the notion that brain network functional organisation may underlie variability in cognitive reserve in late adulthood.

Cognitive reserve is often contrasted with brain reserve and brain maintenance. Given a materialist view that cognition must derive from the brain, many feel that there is no real distinction between cognitive reserve and brain reserve (e.g. any compensatory psychological processes must have a correspondence in brain activity; see the next section). Maintenance is often distinguished from reserve within a longitudinal perspective: reserve implies that differences between individuals in cognitive or brain measures are constant across the lifespan, whereas maintenance implies an increasing divergence with age, with some people maintaining their cognition/brain better than others (a related distinction is between 'preserved differentiation' and 'differential preservation'). To test such ideas, Walhovd et al. [32] combined Cam-CAN with other LifeBrain cohorts to test whether general cognitive ability (GCA) is associated with more cortical tissue from a young age (brain reserve) and/or less cortical atrophy in adulthood (brain maintenance). Controlling for education, there were widespread cross-sectional relationships between GCA and cortical characteristics, as well as a subset of regions where higher baseline GCA was associated with less longitudinal atrophy. These findings suggest that higher GCA is associated with cortical volume via both brain reserve and brain maintenance.

Other factors that might contribute to cognitive reserve are considered later in the Environmental/lifestyle section, while one mechanism behind cognitive reserve might be functional compensation of brain activity when performing a cognitive task, to which we turn next.

Brain function measured by fMRI

The fMRI data in Cam-CAN use the blood oxygenation-level dependent (BOLD) contrast to track changes in blood oxygenation, flow and volume resulting from changes in neural activity. This is the most common type of fMRI, though it must be

remembered that it is not a direct measure of neural activity (unlike MEG considered later), so it can also be affected by age-related changes in the brain's vasculature. fMRI can be used to measure activation in response to different tasks or stimuli, or to estimate patterns over voxels associated with those tasks/stimuli (multi-voxel pattern analysis (MVPA)), or to estimate the functional connectivity between brain regions, for example based on the correlation of BOLD time series at rest, so-called resting-state fMRI (rsfMRI).

Functional activation and compensation

A prominent idea in the cognitive neuroscience of ageing is that older individuals can maintain their cognitive performance to some extent by recruiting new brain regions (or networks)—termed 'functional compensation'. This is based partly on fMRI (and PET) observations that older people often show 'hyper-activation' compared to younger people in some brain regions, across a range of tasks. This led to theories like 'posterior-to-anterior shift with ageing' (PASA), which suggests that older people engage additional anterior (frontal) regions to compensate for structural atrophy of more posterior (occipital/parietal/temporal) regions. When Morcom et al. [33] tested PASA using two fMRI memory-related tasks from Stage 3 of Cam-CAN, they replicated this increased level of frontal activation with age. However, when they used MVPA to test whether the frontal region contained additional information about the tasks beyond the posterior region—as would be expected if the frontal activation were compensatory—they found evidence against PASA. This suggests that the frontal hyper-activation in older people reflects 'inefficiency' rather than compensation (e.g. greater metabolic activity to engage the same cognitive processes).

Another common finding is a more bilateral pattern of activation in older people (i.e. less lateralisation in tasks often associated with a dominant hemisphere). This led to another theory called 'HAROLD', which stands for Hemisphere Asymmetry Reduction in OLDer adults. Knights et al. [34] replicated this pattern in two of Cam-CAN's motor tasks, in which young adults show clear lateralisation of activation to the left motor cortex when responding with their right hand, whereas older adults tend to show more bilateral motor cortex activation. Again however, when they looked at multivoxel pattern information, they found no evidence that the right (ipsilateral) motor cortex contained additional information in either of two Stage 3 tasks (e.g. about which finger was pressed), nor did activation in the right motor cortex relate to the mean or variance of RTs, which would be expected if it were compensatory. An alternative explanation is that inter-hemispheric inhibition is less effective in older people, consistent with another study by Mayhew et al. [35] that showed that the size of the negative BOLD response in ipsilateral motor cortex in younger people correlated with size of their positive contralateral response, and with a third study by Tak et al. [36] that examined effective connectivity between motor regions within and across hemispheres.

A final study of functional compensation in Cam-CAN examined fMRI data while people performed the Cattell task of fluid reasoning. This study by Knights et al. [37] is the only Cam-CAN study to date to find some suggestion of compensation: activation in a cuneal region (1) increased with age, (2) was more positively correlated with performance of the task in older than younger people and (3) contained additional multivoxel information beyond that in the main task-related network (the so-called multiple-demand network (MDN)). Moreover, the age-related effects remained after adjusting for possible age-related vascular changes using RSFA (see later section on neurovascular coupling). However, the specific compensatory role of this largely visual region remains unclear: it could, for example, reflect more eye movements between the elements of the Cattell stimuli in older participants who perform better.

Brain activation while performing the Cattell task was also examined by Mitchell et al. [38]. They found that fMRI activation in many parts of the MDN mediated the effect of age on performance of the task. They also found that this mediation effect was moderated by the variety of regular physical activities participants perform in their daily life, whereby more physical activities meant that the MDN activation was less strongly associated with task performance. This suggests that physical exercise may support cognition by improving the efficiency of neural function.

A study by Samu et al. [39] compared functional activation across three of the Stage 3 fMRI tasks: two that show age-related decline in performance (Cattell

and picture naming) and one that does not (sentence comprehension). Simultaneous independent component analysis (ICA) across tasks revealed common task-positive brain components that predicted performance in each task. Only the two tasks showing age-related cognitive decline also showed age-related decreases in task-positive components, along with decreasing suppression of the default mode network (DMN). These results suggest that maintenance of distributed, multi-component brain responsivity, along with maintained DMN deactivation, characterise successful ageing.

Other studies of functional activation during Cam-CAN tasks are covered in later sections on specific behavioural outcomes, but in regard to functional compensation, at least as measured by fMRI, the CamCAN data provide only limited evidence, and so the search for more generic (task-independent) evidence of functional compensation continues.

Functional connectivity

fMRI functional connectivity can be measured during three brain 'states' in Stage 2 of Cam-CAN: resting, movie-watching and a sensorimotor task. Geerligs et al. [40] showed that the effects of age on fMRI functional connectivity differed according to brain state, implying that conclusions about age effects (or other individual differences) drawn from the most common resting-state (rsfMRI) may not generalise.

The connectome of connectivity between every pair of brain regions normally reveals a number of networks (communities/modules), where regions within the same network are more highly correlated than regions in different networks (these often have names like DMN, the 'dorsal attention network', the 'salience network'). The networks can be summarised by graph-theoretic metrics like 'functional segregation': the mean within-network connectivity minus the mean between-network connectivity. Higher segregation means the networks are better separated, and this is normally viewed as healthier. Indeed, Raykov et al. [41] replicated previous studies in showing that functional segregation declines with age (in all three Cam-CAN brain states), and is positively related to fluid intelligence and episodic memory, even after removing effects of age. Jiang et al. [42] also examined functional segregation, and found that both age and cognition are associated with decreased within-network connectivity (especially within DMN and ventral attention networks) and increased between-network connections, with the exception of the dorsal attention network, which was predictive of cognitive ability but only weakly related to age. This suggests that network segregation is an important functional brain characteristic of ageing.

Guardia et al. [43] explored the role of the ascending arousal system (ARAS) in functional segregation. They found that rsfMRI connectivity between ARAS and cortex decreased with age, and mediated some of the age-related differences in connectivity within and between association networks (e.g. within the DMN, and between the DMN and salience networks). Connectivity between the ARAS and association networks also predicted cognitive performance over and above the effects of age and connectivity within the cortical networks themselves. These findings suggest that age differences in cortical connectivity and cognition may be driven, in part, by altered arousal signals from the brainstem. Bernard et al. [44], on the other hand, focused on cerebellar connectivity, and showed that age reduced rsfMRI connectivity in both the dorsal and ventral dentate networks that are connected to motor and prefrontal cortices respectively.

Niu et al. [45] explored the role of the thalamus in functional connectivity during movie-watching. Here they used a variant of ISFC, in which the correlation between the time course of a network in one participant was correlated with that of each voxel in the thalamus in all other participants, and then averaged over corresponding correlations for remaining participants. They found significant effects of age on ISFC between the posterior thalamus and the dorsal attentional network, sensorimotor network and visual networks, and between the mediodorsal and ventral thalamic nuclei and other higher-order cortical networks, including the DMN, salience network and frontal control networks. These alterations in thalamo-cortical ISFCs were correlated with fluid intelligence, suggesting they play a role in age-related cognitive decline.

Other studies have examined connectivity during a task. For example, Lugtmeijer et al. [46] used fMRI data from the VSTM task in Stage 3 of Cam-CAN. When testing whether the functional connectivity differed according to VSTM load, they found that the connections most strongly modulated were within the dorsal attention and visual networks, but

that this modulation decreased with age. They suggested that older adults may have already exhausted their neural resources at the lowest level of VSTM load, and were therefore less able to further increase connectivity with increasing task demands. A related study by Neudorf et al. [47] showed that VSTM performance was related to transitions from a visual/somatomotor network state to an attention network state, and that these transitions were related to structural connectivity as measured by the diffusion-weighted MRI data. The authors suggested that structural connectivity supports flexible, functional dynamics that enable better VSTM with age.

Some studies have looked at dynamic changes in functional connectivity across successive time windows. For example, Antal et al. [48] showed that the 'instability' in functional networks across time was greatest in mid-life, while Sastry et al. [49] compared an entropy-based measure of dynamic connectivity across Cam-CAN's resting-state, movie-viewing and sensorimotor fMRI data. The latter found higher stability in young than older participants in the movie and sensorimotor sessions, but that stability was a U-shaped function of age in the resting state. This again demonstrates that the effects of age on functional connectivity depend on the brain state; i.e. it may be unwise to collect only resting-state data and assume that any individual differences will generalise.

Yao et al. [50] examined how nodes transitioned from one module to another across time windows, and found that this variability increased with age, while Petrican et al. [51] analysed dynamic connectivity during movie-watching, and found that changes in connectivity aligned with critical points in the movie, and this alignment was stronger in people with higher fluid intelligence. Nonetheless, care must be taken when examining the effects of age on dynamic fMRI connectivity, as explained in the Methodological developments section.

In summary, age has clear effects on functional connectivity, and it is possible that focusing on large-scale networks of highly correlated brain regions, or at least graph-theoretic summaries of those networks (like segregation), rather than activation in individual regions, will reveal a closer correspondence with age-related changes in cognition. Nonetheless, functional connectivity during states like rest or even movie-watching may not relate as closely to cognitive functions as does connectivity during tasks that emphasise those functions.

Neurovascular coupling

One problem with using BOLD-weighted fMRI to investigate age-related changes in neural activity is that the neurovascular coupling may also change with age, meaning that the same change in neural activity may not translate to the same change in BOLD signal. In one of the first Cam-CAN studies, Tsvetanov et al. [52] tested the ability of a voxel-wise metric called 'Resting-State Fluctuation Amplitude' (RSFA) to adjust fMRI data for age-related changes in neurovascular coupling. RSFA is simply the standard deviation of the amplitude of band-passed BOLD data from an independent resting-state scan. When scaling fMRI data from Cam-CAN's sensorimotor task by RSFA, we found that most of the effects of age on the magnitude of task-related activation in sensory regions were no longer significant, suggesting that they had a vascular rather than neural origin. However, one danger with this approach is that RSFA could also contain age-related variance in neural activity at rest (rather than being a pure measure of vascular reactivity), such that scaling task data by RSFA could remove true neural effects of age on a task. This is where the Cam-CAN MEG data on the same people were invaluable, because we found no evidence that resting-state MEG data mediated the effect of age on RSFA (using a wide range of MEG metrics). By contrast, we did find that various cardiovascular measures (derived from blood pressure and the electrocardiogram (ECG)) mediated the effect of age on RSFA. These results suggest that RSFA is a reasonable proxy for the vascular component of BOLD, and therefore that it is safe to scale fMRI task data by RSFA in order to better isolate age-related differences in neural activity. In a later paper, Tsvetanov et al. [53] showed that RSFA relates both to cardiovascular and cerebrovascular measures, but not to grey matter atrophy.

Rather than adjusting task fMRI data by a surrogate measure of neurovascular coupling like RSFA, an alternative is to employ more sophisticated models of fMRI data, which allow age to moderate multiple stages along the neural-to-BOLD pathway. For example, Henson et al. [53] showed marked variation across age in the shape of the haemodynamic response function (HRF) to brief stimuli using the

Cam-CAN sensorimotor task (the timing of which was optimised for estimation of the HRF). Importantly, using nonlinear, biophysical modelling, they found that most of the effects of age on the HRF in sensory regions could be explained by an increased rate of vasoactive signal decay and decreased transit rate of blood, rather than changes in neural activity per se (consistent with the results of RSFA adjustment in ref. [52]).

Other MRI contrasts can also be used to measure vascular components. In particular, cerebral blood flow (CBF) can be estimated with arterial spin labelling (ASL), which was acquired in Stage 3 of Cam-CAN. Wu et al. [54] applied commonality analysis to the Cattell fMRI data to show that age-related differences in CBF explained not only performance-related BOLD responses, but also performance-independent BOLD responses. This suggests that, while non-neuronal contributions to BOLD signals reflect an age-related confound, maintaining CBF is also important for maintaining cognitive function.

In an impressive analysis of the stability of functional networks across four large datasets including Cam-CAN, the aforementioned study by Antal et al. [48] showed that brain networks destabilise with age, but in a nonlinear fashion, with a transition in midlife. They argued that metabolic, vascular and inflammatory biomarkers implicate dysregulated glucose homeostasis as the driver of such transitions, supported by correlations between the regional pattern in aging and expression of genes related to insulin and neuronal ketone transport. Consistent with these results, an interventional study of 101 participants showed that ketones exhibit robust effects in re-stabilising brain networks from ages 40 to 60, suggesting a midlife 'critical window' for metabolic intervention.

Park et al. [55] characterised fMRI data in terms of the 'spectral slope' of slow versus fast activity. They found that the relative proportion of fast activity increased with age (flattening the spectral slope) and that the regional distribution of this effect was correlated with that of cerebral glucose metabolism (from another dataset). They suggested that BOLD spectral slope flattening is a biomarker of age-associated neurometabolic pathology.

In summary, CAN has provided compelling evidence that age affects the vascular component of the BOLD signal used by fMRI. This requires adjustments of the fMRI data by other measures (e.g. RSFA/CBF), or more sophisticated biophysical modelling, before claims can be made that age affects neural activity. Furthermore, estimates of the vascular component may themselves provide an indirect measure of brain health and cognitive performance.

Brain function measured by MEG

Though it cannot localise neural activity as precisely as fMRI, the electrophysiological technique of MEG (and EEG) has the major advantage of much higher temporal resolution (milliseconds), opening a window on the brain's rich repertoire of oscillatory activity (typically from 1 to 100 Hz). Moreover, MEG signals are not directly confounded by effects of age on the neurovascular coupling described above. Cam-CAN is one of very few shared datasets with MEG data on hundreds of people.

Evoked responses

Ageing is known to increase the latency of stimulus-evoked responses measured by EEG/MEG, consistent with a general slowing of neural processing. However, rather than estimating the latency of individual evoked components (e.g. 'N1', 'P3'), Price et al. [56] fit template waveforms to MEG data from Cam-CAN's sensorimotor task, which were parameterised by a temporal 'shift' (constant delay) and a temporal 'stretch' (cumulative delay). Interestingly, the effect of age on these two types of latency differed in visual and auditory cortices: age increased the shift but not stretch of visual responses, and increased the stretch but not shift of auditory responses. Moreover, the visual shift parameter related to white matter integrity in the optic radiations, consistent with delayed transmission from thalamus to visual cortex, whereas the auditory stretch parameter related to grey matter volume in auditory cortex, consistent with slower dynamics of local computation. This demonstrates that the effect of age on the dynamics of sensory processing is not uniform across the brain. In future work, we are fitting these evoked responses using dynamical, neurophysiological models.

Bruffaerts et al. [57] examined evoked responses in the picture-naming task in Stage 3 of Cam-CAN, and found that the capacity to represent semantic information was correlated with higher fluid intelligence, whereas the latency of visual processing did not relate

to measures of cognition. Ghosh Hajra et al. [58] examined activity locked to blinks, which is assumed to reflect environmental monitoring as the brain evaluates new visual information following spontaneous blinks. They found that blinks were associated with increases in theta and alpha power within the precuneus, and exhibited an inverted-U relationship with age.

Power spectra

Stier et al. [59] reconstructed the MEG resting-state data onto the cortical surface, and found age-related increases in power in most frequency bands (theta, alpha, beta, low gamma) except for delta, which showed a decrease. They also found frequency-specific effects of age on functional connectivity, as measured with imaginary coherence. In the delta and beta bands, these age effects correlated with the effects of age on cortical thickness, shedding light on how age-related differences in brain structure relate to differences in fast oscillatory activity. Ustinin et al. [60] estimated electric power in the brain and also found age-related increases in beta but decreases in delta.

Whereas Stier et al. focused on cortical activity, Hinault et al. [61] estimated sub-cortical sources of Cam-CAN's resting MEG, and found increased delta and decreased gamma power in these deeper brain regions, including the hippocampus, striatum and thalamus. This pattern of 'sub-cortical slowing' appears to be the opposite of the pattern found on the cortex by Stier et al. This observation deserves further validation, given the different analysis procedures used by these two studies.

The power in human MEG/EEG tends to decline with frequencies (f) from 1 to100 Hz, in a manner approximately proportional to 1/f. This is called the 'aperiodic' component, and has been attributed to 'brain noise', or more interestingly, to the excitatory-inhibitory balance in the brain. Thuwal et al. [62] found that the 1/f power in Cam-CAN resting-state MEG data increased with age (i.e. power declined more slowly with frequency), and this increase related to performance of Cam-CAN's VSTM task. They also found effects of age on alpha peak frequency and the ratios of power in various bands, which related to more specific components of VSTM performance.

However, the effects of age on some spectral features need careful examination, since the 1/f slope is also influenced by age-related cardiac differences (see the Methodological developments section). Furthermore, the frequency ranges of standard spectral bands (delta, theta, alpha, beta, gamma) may vary across individuals, and the power in those bands may not always be truly rhythmic. Karvat et al. [63] developed a method to test rhythmicity. This can be used to define bands for each individual, as well as reveal bands in which power is not rhythmic (e.g. 'bursting' activity in a subset of the beta bands). Using Cam-CAN data, they showed that age decreases the frequency ranges of nearly all bands, rhythmic and arrhythmic, independent of any power changes.

Connectivity/criticality

The rich temporal information in MEG allows a wide range of connectivity measures, including time-/phase-lagged measures that can distinguish the direction of information flow between two regions (unlike fMRI, where such time-lagged effects are confounded by potential differences in the neurovascular coupling of the two regions). One such directional measure is 'transfer entropy', which Jauny et al. [64] applied to detect frequency-specific, directed connectivity in a subset of Cam-CAN's resting-state MEG. Several effects of age were found, including a reversal of the direction of information transfer in the DMN in the delta frequency band, as well as increased variability over time of overall brain synchronisation. These changes in functional connectivity were associated with cognitive impairments. The authors suggest that advancing age is accompanied by a functional disorganisation of dynamic networks, with a loss of communication stability and a decrease in information transmitted.

Another way to characterise time series is in terms of the frequency of extreme values. Vakorin et al. [65] showed that older age is associated with a greater tendency for the brain to produce extreme neuromagnetic events. This skewed nature of brain activity is commonly overlooked in traditional neurophysiological studies, which typically emphasise average values, but is expected from theoretical conceptions of 'criticality' within dynamical systems, in which peaks in healthy brain activity are believed to occur at phase transitions between states. This illustrates

an interesting approach to using dynamical systems analysis to characterise the effects of age on brain function.

In summary, MEG offers a much richer window on functional connectivity and brain dynamics, being able to resolve potential differences across a range of frequencies 1–100Hz, unlike fMRI for which the HRF means it can only detect slow changes from 0.01 to 0.1Hz (and confounded by vascular effects of age). While MEG cannot offer the same spatial resolution, it still has the potential to provide complimentary information about brain function beyond fMRI, so should be utilised to greater extent in future to address theoretical questions about functional compensation, differentiation, cognitive reserve, etc.

Connectomics

Connectomes are matrices encoding the strength of connection between every pair of a large number of brain regions. Structural connectomes can be estimated by the covariance across participants for a single brain feature (e.g. grey matter volume) in each pair of regions. Alternatively, single-participant connectomes can be estimated by the similarity between distributions of a single feature across voxels/vertices within each pair of regions, or by the 'morphological' similarity between multiple features (e.g. thickness, area, curvature, fractal dimension, gyrification index, sulcal depth). A third type of connectome is the functional connectome, defined by functional rather than structural connectivity, such as the correlation between time series while people rest in the scanner (rsfMRI or rsMEG). Connectomes can then be summarised by various graph-theoretic measures like small-worldness, efficiency and clustering.

Using individual connectomes based on morphological similarity, Ruan et al. [66] found age-related differences in global network properties such as small-worldness, particularly for the feature of cortical thickness and particularly in PFC. The age-related differences also affected 'hubs'—key regions with high similarity to many other regions—which may have a particularly strong effect on connectivity and cognition. Using individual connectomes based on distributions of grey matter volume, Yu et al. [67] employed partial least squares (PLS) to relate them to Cattell test scores. Using the graph-theoretic measure of 'degree centrality' for each node (region), the first PLS component explained 32% of the variance in fluid intelligence. Particularly high weights were found for the degree centralities of several nodes within the MDN, suggesting that the structural stability of MDN might contribute to the maintenance of fluid intelligence.

Neudorf et al. [68] also examined graph-theoretic correlates of fluid intelligence, but using connectomes based on tractography from Cam-CAN's diffusion-weighted data instead. Some age-related reorganisations of the connectome were associated with poorer cognitive outcomes, while others were associated with spared cognitive ability. The positive changes included strengthened intra-hemispheric connectivity and increased nodal efficiency of the ventral occipital-temporal stream and hippocampus for older adults. Khalilian et al. [69] also used diffusion-based connectomes, as well as those from rsfMRI, to examine the effect of age on the 'rich club' properties of the connectomes. The 'rich club' are a densely connected set of hubs in a network that efficiently link multiple other sub-networks (communities). Both structural and functional connectomes showed age-related decreases in rich club connectivity. Given that network function is particularly vulnerable to damage to rich club nodes, the authors suggested that network vulnerability increases in ageing, particularly over 70 years of age.

Levakov et al. [70] focused on the face-processing network defined by rsfMRI and diffusion-weighted MRI, and its relationship to performance on Cam-CAN's facial recognition test (matching the identity of unfamiliar faces). The modularity of this network was positively correlated with face recognition abilities even when controlled for age. This correlation was not found in the place network or spatially permuted null networks, and the strongest correlation to behaviour was found in edges in the right hemisphere, consistent with other evidence that the right hemisphere tends to be specialised for face processing.

Liu et al. [71] examined the relationship between the functional connectome and the structural (white matter) connectome, where the latter was estimated using diffusion-based tractography. They found that cognitive function was increasingly dependent on the convergence between functional and structural connectivity as age increased. This suggests that brain functional network integrity sustains cognitive

functions in old age, in a manner dependent on the integrity of the brain's structural connectivity.

McPherson and Pestilli [72] used Canonical Correlation Analysis (CCA) to relate 334 behavioural/cognitive scores to the nodal degree of 376 brain regions from tractography of diffusion-weighted MRI data. They found that a single axis of covariation was sufficient to relate cognition/behaviour to their structural connectome ($r=0.58$). Individual variability along this axis closely predicted individuals' ages ($r=0.63$), which they interpreted in terms of a coherent pattern of degradation that affects both structural brain networks and behaviour.

By framing the white matter connectome as a 'computing reservoir', Mijalkov et al. [73] showed that the computational memory capacity (the ability to replicate random time-dependent input signals) depends on connectome density, and correlates with age, cognitive performance, grey matter atrophy and functional connectivity, as well as the integrity of the LC. Zhang [74] introduced an index called 'hemispheric similarity of functional connectivity', based on the similarity between the functional connectomes of each hemisphere, and showed that it was affected by age, differentially for different sub-networks, e.g. primary, subcortical and paralimbic.

Connectome-based predictive modeling (CBPM) uses the full, individual-level connectomes to predict a cognitive/behavioural outcome. Gbadeyan et al. [75] combined Cam-CAN fMRI data with other cohorts to predict variation in reaction times. While the coefficient of RT variability could be predicted by task-based CBPM, this did not generalise to resting-state CBPM. Interestingly, the movie-watching study by Kurkela and Ritchey [76] mentioned above also used CBPM, and only this way were they able to predict episodic memory ability from the fMRI data, and surprisingly, most of the predictive connections were outside the MTL.

Another approach decomposes the connectome using dimension reduction techniques to reveal 'gradient' maps. Bethlehem et al. [77] identified three gradients (explaining > 50% of variance): (1) sensory-to-transmodal, (2) visual-to-insula and (3) somatomotor-to-insula. They detected a shift of the visual network with age towards a more central location within this 3-dimensional gradient space. Whereas the location of most transmodal networks did not differ by age, they became more dispersed with age, reflecting more dissimilar functional connectivity. Increasing dispersion of frontoparietal, attention and default mode networks, in particular, was negatively associated with fluid intelligence, suggesting that functional gradients can provide insights into age-related cognitive decline.

In sum, there are numerous studies that employ connectomics to examine the effects of age in a range of CamCAN neuroimaging modalities, though they tend to be largely descriptive, and few offer a mechanism or relevance to major theories of ageing. One future potential direction is to simulate different mechanisms of ageing (e.g. random node or edge deletion, or trophic deletion of connected nodes) and see which mechanism reproduces graph-theoretic properties that best match the effect of age in the data (see Bougacha et al. [78], in later section on Clinical Uses, for an example of this).

Specific topics of interest

Motor and inhibitory control

The control of voluntary movement changes markedly with age. Using fMRI data from Cam-CAN's 'force-matching' task, Wolpe et al. [79] showed that sensorimotor attenuation—the reduction in perceived intensity of sensations from self-generated compared with external actions—increased with age. This attenuation was associated with differences in the structure and functional connectivity of the pre-supplementary motor area (pre-SMA). The results suggest that ageing alters the balance between the sensorium and predictive models.

In a second study using instead Cam-CAN's visuomotor learning fMRI task, Wolpe et al. [80] showed that the age-related reduction in motor adaptation to a visual distortion was associated with reduced volume in striatum, prefrontal and sensorimotor cortical regions, but not cerebellum. Somewhat surprisingly, the association between hippocampal volume and adaptation became stronger with age, as did the association between adaptation and measures of long-term memory. These results suggest that cerebellar learning is largely unaffected in old age, and the reduction in motor adaptation with age is driven by a decline in explicit memory systems.

Using MEG data associated with button presses in the sensorimotor task, Bardouille et al. [81] found

that peak rebound frequency and amplitude of beta oscillations decreased with age, as did the peak motor-evoked response amplitude, but the peak beta suppression amplitude increased with age, as did movement-related gamma burst amplitude. They suggested that these reflect age-related changes in the neurophysiology of both thalamo-cortical loops and local circuitry in the primary somatosensory and motor cortices.

There has been much interest in the hypothesis that older people have reduced inhibitory control in general, and that this can explain many cognitive as well as motor problems in ageing. One way to measure inhibitory control is the stop-signal reaction time (SSRT) from the Stop-Signal/No-Go Task in Stage 3 of Cam-CAN. Using fMRI data recorded during this task, Tsvetanov et al. [82] showed that individual differences in SSRT correlated with both activity and connectivity in a distributed network, comprising prefrontal, premotor and motor regions. Importantly, the relationship between connectivity and SSRT depended on age, but the relationship with activity did not, suggesting that age-related differences in inhibitory control are best characterised by the joint consideration of activity and connectivity within distributed brain networks. The degree of inhibitory control is believed to be modulated by noradrenaline, which is controlled by the LC. Tomassini et al. [83] tested this hypothesis, and found that better response inhibition (SSRT) was correlated with integrity of the LC (from the magnetisation-weighted MRI data discussed earlier).

Mental health/affective control

While Cam-CAN was not designed to directly address mental health questions, and excluded individuals with current major psychiatric conditions, there was some natural variation in anxiety and depression. This included both self-reports of any history of anxiety/depression, and measures of current levels using the Hospital Anxiety and Depression Scale (HADS). Interestingly, increasing age was associated with a reduced likelihood of reporting a history of depression. This could reflect either poor recall of historical diagnoses or a generational effect of lower rate of incidence, diagnosis or self-report in the older participants.

In terms of current symptoms, Harlev et al. [84] applied network analysis to the HADS scores, and showed that the overall network structure, which included anxiety and depressive symptoms as two communities, remained stable with age. However, older adults showed fewer connections between symptoms within the depression community, suggesting greater heterogeneity in how depression manifests in older populations. They also showed fewer connections between depression and anxiety communities, with a shift in the 'bridging' symptoms from cognitive (rumination) in young adults to somatic (restlessness) in older adults. This suggests subtle yet clinically important differences in how depression and anxiety are linked across the lifespan, reinforcing the need for age-informed assessment and diagnosis of them.

Kirk et al. [85] tested whether those Cam-CAN participants scoring high in self-reported anxiety would have greater engagement of a well-documented amygdala-dorsomedial prefrontal circuit associated with 'threat vigilance', even in the absence of anxiogenic stimuli. However, they found no evidence for this in rsMRI. In an exploratory analysis, they did see a relationship with connectivity between amygdala and the periaqueductal grey region, suggesting that this subcortical circuitry may be chronically engaged in hyper-vigilant individuals, but that amygdala-prefrontal circuitry may only be engaged in response to anxiogenic stimuli.

Kirk et al. [86] extended this to Cam-CAN's movie-watching data, and found a relationship between anxiety, amygdala-prefrontal dynamics and anxiogenic features of the movie (canonical suspense ratings): amygdala-prefrontal circuitry was modulated by suspense in low-anxiety individuals, but was less sensitive to suspense in high-anxiety individuals. They suggested that this could reflect habituation or amplified anticipation.

Bätz et al. [87] examined the functional integration of four functional networks previously associated with emotional regulation, and how this related to mental health measures in two cohorts (using the HADS in the case of Cam-CAN). Integration of the 'emotional control' network increased with age, whereas that of a network associated with 'emotion generative and regulative processes' decreased with age, suggesting complex effects of age on affective processing in the brain.

Using Stage 3 fMRI data from an implicit 'Emotional Expression Recognition' task, which involved judging the gender of neutral and angry faces, Nagrodzki et al. [88] showed that the attentional bias towards angry faces related to self-reported history of depression, and to brain activation in bilateral insula/inferior frontal gyrus and bilateral parietal cortex. This bias in emotional engagement may therefore persist even after a depressive episode.

Katsumi et al. [89] correlated rsfMRI connectivity with the degree of affective advantage in Cam-CAN's Stage 3 'Emotional Memory' task (i.e. positive or negative vs neutral) and found widespread correlations across the brain. Nonetheless, when Kandaleft et al. [90] combined these rsfMRI connectivity estimates to predict individual differences, they were unable to predict more subtle emotional differences in the emotional memory task, despite being able to predict age and fluid intelligence.

Positivity bias

A more specific effect of age on affective processing is the 'positivity bias': the observation that older people tend to attend less to negatively valenced information, and more to positive information. For example, in the aforementioned emotional memory task, the detrimental effect of age on memory for the association between an object and a scene was greater when the scene was negative than when it was neutral or positive [6]. One explanation is based on socioemotional theory: that older people shift their attention away from negative information because they perceive their future as limited. This might be why Schweizer et al. [91] found that the poorer memory performance for negative trials, but not neutral trials, was associated with (sub-clinical) depressive symptoms. However, using Cam-CAN's Stage 2 explicit facial expression judgment task, Wolpe et al. [92] found that the positivity bias in this context—reduced recognition of negative expressions, and a bias in labelling expressions as positive—was not associated with depressive symptoms, as might be expected from socioemotional theory, but was associated with general cognitive decline instead.

Wolpe et al. [92] also found that the positivity bias in expression recognition was associated with reduced grey matter volume in bilateral anterior hippocampus-amygdala, and increased functional connectivity between these regions and orbitofrontal cortex. Orlando et al. [93] found that more general behavioural performance on this facial expression task was positively correlated with greater volume in the superior parietal lobule, higher white matter integrity in the corpus callosum and greater functional connectivity in the mid-cingulate area. Relating data across Cam-CAN affective tasks, Hamlin et al. [94] found that greater negative reactivity was associated with better facial expression recognition in older adults, but worse for young adults. They suggested that older adults with higher negative reactivity may be able to integrate their negative emotions effectively in order to recognise other's negative emotions more accurately, whereas young adults may experience interference from negative reactivity, lowering their ability to recognise other's negative emotions.

Indeed, it is important to distinguish *reactivity* to affective stimuli from *regulation* of emotional responses to them. Using Cam-CAN's Stage 2 'Emotional Reactivity and Regulation' task, Stretton et al. [95] found that people's ability to positively *regulate* their responses to negative movies (i.e. derive positive affect from negative material) significantly increased with age (and this ability was associated with grey matter volume in several brain regions). However, this regulation ability did not correlate with depression history, and participants' net positive *reactivity* (adjusted for reactivity to neutral stimuli) actually decreased with age. In the Stage 3 fMRI version of this task, Schweizer et al. [96] found that this age-related decrease in positive reactivity was associated with reduced activation in middle frontal gyrus. These data are consistent with the positivity bias deriving from improved emotion regulation with age, rather than reactivity per se, though the relationship with mental health remains unclear.

Sleep

Ageing is known to affect sleep patterns. Sleep quality in Cam-CAN was measured using the Pittsburgh Sleep Quality Index (PSQI) questionnaire. Gadie et al. [97] applied latent class analysis to PSQI data to reveal four sleep types: 'good sleepers' (68%, most frequent in middle age), 'inefficient sleepers' (14%, most frequent in old age), 'delayed sleepers' (9%, most frequent in young adults) and 'poor sleepers' (8%, most frequent in old age). They found a

U-shaped association between sleep duration and self-reported depression and anxiety, such that both short and long sleep were associated with poorer outcomes. However, they did not observe associations between self-reported sleep quality and white matter integrity. They argued that lifespan changes in sleep are not captured well by summary measures, but instead should be viewed as partially independent symptoms that vary in prevalence across the lifespan.

A subsequent study by Fjell et al. [98] pooled Cam-CAN data with many others in the EU LifeBrain consortium to examine the effects of sleep on hippocampal volume. No cross-sectional effects were found, but worse sleep quality and efficiency, as well as more sleep problems and daytime tiredness, were all related to greater hippocampal volume loss over time. In a subsequent study, Fjell et al. [99] focused on 'short-sleepers' (those sleeping < 6 h per night, but who did not experience sleep problems or daytime drowsiness). Interestingly, these people showed significantly larger regional brain volumes relative to short-sleepers with sleep problems/daytime drowsiness, and relative to people sleeping the recommended 7–8 h, after controlling for BMI, depression symptoms, income and education. These results suggest that some people can cope with less sleep without obvious negative associations with brain morphometry.

Tibon et al. [100] used multivariate methods to relate PSQI data to MEG resting-state data, analysed with Hidden Markov Models (HMMs). They replicated their previous findings (Tibon et al. [101]) of an age-related 'neural shift', expressed as decreased occurrence of 'lower-order' brain networks coupled with increased occurrence of 'higher-order' networks: a shift that was associated with decreased fluid intelligence. Furthermore, they showed that the shift was associated with increased sleep dysfunction, even after accounting for age and other covariates. These results suggest that poor sleep quality, as evident in aging, results in a shift in resting (but awake) neural dynamics.

Language

While some language functions like word production are impaired with age (e.g. the TOT state considered earlier), other language functions like comprehension tend to be resilient to ageing (as examples of crystallised intelligence). Campbell et al. [102] compared functional networks (revealed by ICA) during passive listening to spoken sentences, versus those during an overt task of judging the 'acceptability' of comparable sentences. Only auditory and frontotemporal networks were implicated during natural listening, while the overt task recruited many additional networks. Importantly, the functionality of frontotemporal networks was maintained across age, showing no difference in within-network connectivity or responsivity to syntactic processing demands, despite it showing grey matter loss and reduced connectivity to task-related networks. Nor was there evidence for reduced specialisation or compensation with age in the fMRI data. Nonetheless, overt task performance related to crystallised knowledge in older, but not younger, adults, suggesting that decreased between-network connectivity may be compensated by older adults' richer knowledge base. This study also illustrates important differences in brain activity when performing explicit tasks (as often the case in fMRI experiments) relative to more naturalistic and implicit tasks (like hearing speech or watching movies).

Guichet et al. [103] used CCA to relate language abilities to graph-theoretic properties of the rsfMRI 'language connectome'. CCA revealed two canonical variates: One was associated with domain-general components of language tasks (such as executive function), which declined linearly with age, and was related to functional deactivation in peripheral nodes and functional integration in connector nodes; the second was associated with semantic processing, which peaked in mid-life, and was associated with stronger peripheral-to-connector paths. The authors suggested that decline in some language tasks with age may reflect a lessened ability to deactivate the DMN, leading to difficulties suppressing irrelevant semantic associations. In a subsequent study, they found similar results using rsMEG [104]. In a more focused analysis, Wu and Hoffman [105] examined rsfMRI connectivity between left and right anterior temporal lobes. This inter-hemisphere connectivity was weaker for participants with greater semantic knowledge, an effect that was independent of age (even though connectivity generally increased with age).

Naturalistic stimuli

Continuing the discrepancies between fMRI findings from passive (natural) and active (task-based) language processing considered above, there has been much recent interest in brain activity during more naturalistic conditions, such as watching a movie. Such situations engage multiple cognitive functions in a continuous fashion, in contrast with the more typical, trial-based laboratory tasks designed to isolate a specific cognitive function. Cam-CAN's movie fMRI data have proved to be valuable in this respect, particularly in comparison to resting-state data: Not only do movies 'engage' many regions of the brain (rather than relying on endogenous activity, or unconstrained thought processes, at rest); they also provide a common reference signal for phase-locking the data across participants (e.g. ISFC). Indeed, the same Cam-CAN movie (a shortened version of Hitchcock's movie 'Bang! You're Dead') has been used by other studies, e.g. EEG in older people [106] and intracranial EEG in patients [107].[4]

One opportunity afforded by more continuous stimuli like movies is to relate transient brain states to people's subjective boundaries between when one meaningful event ends and another begins ('event boundaries'). For example, Ben-Yakov and Henson [108] showed that activation in the hippocampus closely tracks such subjective event boundaries. Reagh et al. [109] examined how age affects such event boundaries. Boundary-locked responses in the hippocampus reduced with age, whereas those in medial prefrontal cortex and middle temporal gyrus increased with age. Using an independent sample, they found no evidence of subjective differences in boundary placement between young and old, suggesting similar segmentation, but possibly less effective and/or requiring greater effort in older people. They also found that individual differences in the hippocampal boundary response correlated with their scores on Cam-CAN's independent 'logical memory' test of verbal, episodic memory. Indeed, this correlation was only found in the hippocampus, suggesting that hippocampal boundary activations relate to memory encoding, whereas other boundary activations related to general segmentation of the movie.

Cooper et al. [110] focused on fMRI connectivity while movie-watching, and dissociated two sub-networks of the posterior medial network (PMN), which includes regions connected with posterior MTL regions: a ventral PMN and a dorsal PMN. Whereas both dorsal and ventral PMN connectivity tracked the movie content, only the ventral PMN connections increased in strength at event transitions. However, Kurkela et al. [76] found that functional connectivity in this ventral network did not correlate with Cam-CAN's episodic memory test, regardless of whether this connectivity was measured during rest, movie-watching or the sensorimotor task.

Sun et al. [111] found a close correspondence between functional connectivity, particularly within DMN, to variations in the 'tension' within the movie (as defined by independent watchers). A similar approach was taken by Brandman et al. [112], who found that DMN activity correlated with periods of surprise in the movie, compared to periods of high emotion or vividness. They suggested that the DMN acts as a major hub in signalling high-level prediction errors. Indeed, Yazin et al. [113] applied a model that distinguished contextual predictions, social predictions and abstract action predictions, and suggested that these predictions are integrated in the precuneus, part of the DMN. Indeed, movies even provide the opportunity to 'discover' the functions associated with a given brain region, by identifying periods when that region shows high neural activity, and trying to find a consistent pattern/theme in the movie content during those periods.

Methodological developments

Cam-CAN data have also been useful for developing/validating novel analysis approaches.

Relating brain to cognition

Kievit et al. [114] introduced a generic conceptual and statistical framework to relate brain and cognitive measures, based on a 'watershed model'. This model implies that causality 'flows' from many 'upstream' measures (such as brain, or even genetics) to fewer 'downstream' consequences (such as cognition).

[4] It was unfortunate that we did not record MEG during movie-watching in Stages 2–3 of Cam-CAN, but we did recently for Stage 5, using comparable clips from other Hitchcock movies [2].

Using Cam-CAN data, an example watershed model was tested for white matter contributions through processing speed to fluid intelligence. The model was supported in terms of (i) greater upstream dimensionality, (ii) partially independent downstream contributions and (iii) hierarchical dependence.

Jacobucci et al. [115] used Cam-CAN data to illustrate the value of regularised structural equation models for relating multiple brain measures to multiple cognitive measures (when sample sizes are relatively small for the number of such measures), while van Kesteren and Kievit [116] demonstrated how theoretically driven constraints can be placed on exploratory factor analysis (e.g. based on the known hemispheric symmetry in structural covariance matrices) to improve fits and interpretability (e.g. of lateralisation effects).

Yu and Fischer [117] used machine-learning methods to map brain-behaviour associations as a function of the age of the participants used for training (predicting 11 of Cam-CAN's behavioural measures from structural and resting-state functional connectivity, and grey matter volume/cortical thickness). Interestingly, training on a young group meant poorer generalisation to older groups, whereas training on the old group did not impair generalisation to younger groups. In a similar approach, Xiao et al. [118] focused on Cam-CAN's VSTM task, and showed that combining voxel-wise data across different modalities (e.g. grey matter volume, resting-state fluctuation amplitudes, fractional anisotropy) increased prediction accuracy, emphasising the importance of multimodal measures in understanding cognitive functions.

Brain structure

Head motion during an anatomical MRI scan can blur the image, and older people tend to move more during MRI scanning (e.g. as evidenced from fMRI, where head motion is more easily tracked). Indeed, Geerligs et al. [119] provided evidence that head motion is a trait characteristic that might itself be associated with grey matter loss in the cerebellum. Madan [120] showed that this age-related increase in head motion can influence estimates of cortical morphology, but suggested this can be attenuated by using an engaging task, such as movie-watching, during the structural scan. Another way to minimise motion confounds is to utilise recent 'AI' techniques for improving image resolution. These allow lower-resolution images to be acquired, saving time and reducing motion confounds. For example, Fiscone et al. [121] used Cam-CAN's T1- and T2-weighted images to test their Enhanced-Deep-Super-Resolution model, and showed that it outperformed standard up-sampling using conventional cubic spline interpolation.

Segmenting a T1-weighted image into grey and white matter is a nontrivial (and underdetermined) problem, and Cam-CAN data have been used to compare segmentation strategies. For example, we showed that combined segmentation of both T1- and T2-weighted images improved results using the SPM software [unpublished], while Kim et al. [122] used Cam-CAN T1-weighted data to evaluate segmentation of human habenula. Wang et al. [123] used estimates of cortical thickness, total surface area and exposed surface area from Cam-CAN's T1- and T2-weighted images, and showed that these were better combined, e.g. using a morphological scaling law, than analysed independently. For example, they were able to show that the effects of age are distinct from the effects of temporal lobe epilepsy, despite their similarity according to individual cortical measures.

Doucet et al. [124] introduced a 'person-based similarity index' for brain morphometry, which considers all relevant morphometric measures of each individual as a vector, and then calculates the average correlation of that vector with those from all other individuals. They showed that this index differs between men and women, is heritable, is robust to variation in neuroimaging parameters and sample composition, and correlates with age, BMI and fluid intelligence. Madan et al. [125] used white matter measures from some Cam-CAN participants in a computational framework for examining how information flows through brain networks, while Correia et al. [126] used Cam-CAN's diffusion-weighted data to evaluate a nonlinear-least-squares approach to fitting a tensor model and showed it more robust to free-water contamination.

Grødem et al. [127] combined Cam-CAN data with others to fit a computational model of the effect of ageing on grey matter volumetrics. A stochastic dynamical model was used to estimate both the variability and persistence of longitudinal changes across adulthood. This model predicted that, up to 60 years, inter-individual differences almost exclusively reflect stable differences between individuals, and

only afterwards did systematic differences in rate-of-change emerge. The implications are that empirical studies will have a low reliability to detect inter-individual brain change before age 60, while after 60, reliability increases sharply with longer intervals between scans, but more modestly with additional intermediate observations.

Brain Age Gap

There has been much recent interest in using machine-learning of large datasets to predict age from high-dimensional brain data. Once trained, one can predict the age of a new participant from their brain scan, and then subtract that person's actual (chronological) age to produce a 'Brain Age Gap' (BAG). This metric has been proposed as a useful biomarker, with a more positive value (i.e. higher-than-expected brain age) being linked to neurodegeneration or even mental health conditions. Several of Cam-CAN's image modalities have be used to estimate BAG (often combined with other cohorts), and for multiple purposes, as described in the later Clinical/translation section. More relevant to present concerns, the Cam-CAN data have also been used to identify novel features for predicting BAG. For example, Li et al. [128] showed that mutual information can be used to identify those brain regions important for predicting age, while Massett et al. [129] used ridge regression and found strong contributions from the nucleus accumbens, inferior temporal gyrus, thalamus and brainstem, among others. Richie-Halford et al. [130] developed a method based on sparse group lasso that takes into account multiple diffusion properties along white matter bundles. Interestingly, the weights were distributed throughout the brain, indicating that many regions of white matter differ across the lifespan. Richard et al. [131] compared age prediction based on various features from T1- and diffusion-weighted images, and showed that combining features from both modalities did best. Rosell et al. [132] used higher-order, scale-dependent statistics as features (inspired from cosmological techniques), while Zhang et al. [133] predicted age from functional connectivity, and showed that a support vector machine with recursive feature elimination was robust to choices such as global signal regression and parcellation atlas.

However, there are also methodological caveats with BAG. One is a well-known statistical bias, which results in overestimation of brain age for young participants and an underestimation for older participants. Wang et al. [134] introduced a new loss function for calculating a less biased-estimation of BAG, and evaluated this with Cam-CAN data. Another bias comes from the nature of the training data, such as demographic differences, but also the age range, which warns against comparisons across different cohorts (de Lange et al. [135]), particularly different ethnic groups (Irajpour et al. [136]).

Yet another source of variance is the precise pre-processing of the images (e.g. Antonopoulos et al. [137], Dular et al. [138]). For example, pre-processing of T1-weighted scans for age prediction often involves normalisation to a common template and resampling to a common voxel size. Lancaster et al. [139] showed that Bayesian optimisation of such resampling parameters significantly improved brain-age prediction accuracy, while Zeighami and Evans [140] showed important effects of smoothing levels and parcellation scheme on predicting BAG from cortical thickness.

Another important factor is the precise machine-learning algorithm. Han et al. [141] showed that regularised linear regression methods achieved similar performance to nonlinear and ensemble methods, while Lee et al. [142] compared six different algorithms on grey matter estimates, and found comparable training performance, but even so, their BAG predictions varied from 4.5 to 11.7 years in one patient group. Dular et al. [143] compared five deep learning methods on data from several cohorts, and found all methods predicted a heightened BAG for patients with AD and those with multiple sclerosis, as expected, with a particular artificial neural network predicting the largest group differences. However, they raised important caveats regarding estimation biases due to survival bias, disease progression, adaptation and therapies in the patients.

A more fundamental caveat with BAG is that it is normally estimated from cross-sectional data, so it can include individual differences due to (epi) genetics, childhood development or even generational changes in nutrition, which may be unrelated to the ageing process per se. Indeed, a large study by Vidal-Pineiro et al. [144] showed no association between cross-sectional brain age and the rate of brain change

measured longitudinally. Rather, brain age in adulthood was associated with the congenital factors of birth weight and polygenic score (PGS) for brain age. These results suggest that cross-sectional BAGs reflect a constant, lifelong influence on brain structure, questioning their utility as markers of within-person brain changes.

fMRI analysis

Another methodological strength of Cam-CAN is having two resting-state datasets (for both fMRI and MEG) on $N \sim 280$ participants across Stages 2 and 3. These have proved useful for testing of the reliability of various metrics (assuming negligible age-related change across the 1–3 years between Stages 2 and 3), such as those for assessing functional connectivity.

For example, the standard Pearson correlation coefficient measure of functional connectivity is well-known to be prone to artifacts such as head motion and non-neural biorhythms (e.g. respiratory and cardiac), which limits inferences about underlying neural connectivity. Some of these artifacts vary with age. Furthermore, age-related changes in the neurovascular coupling (see earlier section) can affect the temporal autocorrelation in fMRI time series, in turn affecting the correlation coefficient. Indeed, Geerligs et al. [119] showed that fMRI measures of functional connectivity correlate with independent measures of vascular health. When they compared various preprocessing options to address these confounds, they found that high-pass filtering and pre-whitening increased reliability, and that adjusting for mean-connectivity reduced confounding effects of vascular health.

Geerligs et al. [145] introduced a multivariate measure of functional connectivity based on distance correlation (estimated across voxels within a region) and showed that it was more reliable that the Pearson correlation coefficient (averaged across voxels within a region). It was also less affected by vascular health, and had a closer correspondence with structural covariance of grey matter volumes. These benefits did not seem to reflect its ability to capture nonlinear as well as linear dependencies, but rather its robustness to the possibility that the regions (parcels) themselves vary spatially with age.

Rather than adjusting the data post hoc, another way to address age-related vascular confounds in fMRI connectivity is to explicitly model such factors. Tsvetanov et al. [146] did this by using dynamic causal modelling (DCM) to estimate effective connectivity within and between key networks during the resting state. DCM can separate the effects of age on neural, haemodynamic and connectivity parameters, and revealed effects on the haemodynamic and connectivity parameters, but not the neural parameters (that control the 1/f neural spectrum assumed at rest). Interestingly, when the connectivity parameters from DCM were related to multiple cognitive measures, CCA revealed a much stronger relationship than when performed on conventional Pearson correlation measures.

Liu et al. [147] extended dynamic functional connectivity by allowing for individual differences in brain parcellation and in sliding window length, which is likely to be important in ageing. However, Lehmann et al. [148] demonstrated that dynamic connectivity in fMRI can be distorted by age-related differences in neurovascular coupling. It would be interesting to replicate findings about dynamic fMRI connectivity using models like DCM that can incorporate age-related variation in haemodynamic parameters.

Considering the above issues, we recommend that fMRI studies of the effects of age on functional activation or connectivity either adjust their data (e.g. using RSFA for activations or mean-connectivity for connectivity), or use more sophisticated models (e.g. biophysical modelling for activations, or DCM for connectivity), or switch to more direct neural measures like MEG/EEG.

Geerligs et al. [149] used Cam-CAN's movie-watching data to validate a new method for defining brain states from fMRI data that they called Greedy State Boundary Search (GSBS). In addition to being much faster, GSBS outperformed more conventional HMMs on simulated data and Cam-CAN data. GSBS also showed better agreement of neural states with subjective event boundaries in movies (see earlier section on Naturalistic stimuli). In a later paper, Geerligs et al. [150] used GSBS to show that brain state boundaries are organised temporally along a cortical hierarchy, with short states in primary sensory regions, and long states in lateral and medial prefrontal cortex. Importantly, subjective event boundaries tended to occur when neural boundaries co-occurred across large parts of this cortical hierarchy. Most

recently, Lugtmeijer et al. [151] examined the effects of age on these states, and found they become longer with increasing age, particularly in visual and ventromedial prefrontal cortices, even though the relationship between state changes and event boundaries was unaffected by age. The authors interpreted these results in terms of reduced temporal differentiation of successive neural states.

Finally, Doucet et al. [152] combined rsfMRI data from older folk in Cam-CAN with those from two other cohorts in order to develop an atlas ('Atlas55 + ') of resting-state networks, which showed high spatial reproducibility, but differed reliably from those from a young group, reinforcing the importance of age-appropriate atlases. Olszowy et al. [153] used Cam-CAN's event-related sensorimotor fMRI data to demonstrate how more accurate modelling of temporal autocorrelation improves reliability of task activations, while Shinn [154] used Cam-CAN rsfMRI data to demonstrate the dangers of interpreting PCA components, given that smoothness across features (e.g. in space or time) can result in oscillatory behaviour in PCA loadings that do not exist in the data.

MEG analysis

As mentioned earlier, the power of brain activity measured by MEG/EEG declines with frequency in an 1/f fashion. However, a similar decline is seen for the spectral slope of cardiac activity in the ECG, raising the possibility that some effects of age on MEG/EEG power spectra have a cardiac origin. Indeed, Schmidt et al. [155] demonstrated that common artifact rejection settings (i.e. for ICA) may not be sufficient to separate cardiac from neural activity (and more liberal thresholds for identifying cardiac components are needed). Moreover, they showed that the flattening of the spectral slope with age is dependent on the recording site and frequency range, highlighting the complexity of interpreting aperiodic activity. This type of bias is less pertinent to the mass univariate approach of Quinn et al. [156], who extended the general linear model to estimate full-frequency, whole-head power spectra after adjusting for potential confounds within and between participants, and showed that some (cross-sectional) effects of age, but not others, are robust to adjustment for grey matter volume.

An interesting new discovery from van Es et al. [157] is that MEG data (from several cohorts including Cam-CAN) suggest a cyclic pattern of occurrence of large-scale, functional networks. This cyclical structure grouped states associated with similar cognitive function and spectral content at specific phases of the cycle, occurring over timescales of 300–1000 ms. Moreover, metrics that characterise the cycle strength and speed were shown to be heritable, and relate to age and cognitive performance. These results demand an overarching theoretical framework.

In terms of practical guidelines, Wiesman et al. [158] reported that both rhythmic and arrhythmic spectral properties of intrinsic brain activity can be robustly estimated in most cortical regions even from relatively short segments of 30 to 120 s of resting-state MEG data. They also showed that the stability of spectral features over time was unaffected by age, sex, handedness and general cognitive function, suggesting that short MEG sessions are sufficient to yield robust estimates of frequency-defined brain activity during rest, which may be particularly important for patient studies. Bailey and Bardouille [159] used Cam-CAN's MEG sensorimotor data to show that the change in beta power induced by a key press takes 4–5 s to return to baseline, suggesting that future studies of this effect should use long inter-stimulus intervals of 6–7 s. Wainio-Theberge et al. [160] used the same data to investigate the relationship between spontaneous and evoked neural activity. They found that high pre-stimulus amplitudes led to greater event-related desynchronisation for high-frequency activity, and greater synchronisation for low frequencies. This again has implications for experimental design and analysis of electrophysiological data.

In terms of various MEG metrics, the existence of two MEG sessions (across Stages 2–3) enabled Krieger et al. [161] to examine the test–retest reliability of various novel metrics, while Stier et al. [162] compared a wide range of metrics for characterising resting-state MEG data, and found that autocorrelation was one of the best predictors of cross-sectional age (better than, for example, more convention 1/f slope and alpha peak frequency). It would be interesting to see if the same is true in terms of predicting longitudinal changes.

The Cam-CAN MEG data have also been used to (i) validate harmonisation of MEG covariance matrices across scanners using a Riemannian framework

(Mellot et al. [163]); (ii) test an automated version of an algorithm ('Zapline') that combines spectral and spatial filtering to effectively remove line noise from electrophysiological data (Klug & Koosterman [164]); (iii) illustrate an iterated masking, empirical mode approach to automatically decompose electrophysiological data into distinct non-sinusoidal oscillatory modes (Fabus et al. [165]); (iv) show that signal-space separation increases the correlation between data from magnetometers and planar gradiometers, suggesting that analysis of just one sensor type is sufficient after such signal-space separation (Garcés et al. [166]); (v) to evaluate a new method for inferring directed connections that caters for instantaneous and non-Gaussian effects (Zhu et al. [167]); (vi) to evaluate statistics for comparing a single (TBI) patient with a large group (Zhang and Green, [168]); and (vii) to compare results from DCM of Cam-CAN's Stage 3 auditory mismatch task with those in patients with intracranial EEG recordings (Phillips et al. [169]). Clearly, the provision of a large MEG dataset has helped develop many new methods for MEG analysis.

Head modelling

Cam-CAN's T1-weighted MRIs have been used to inform computational modelling of the head, e.g. in terms of the distribution of tissue types with different electrical conductivities. One application of these models is for source reconstruction ('inversion') of MEG/EEG data. For example, Sommariva et al. [170] used these MRIs to test a method that divides the cortex into 60–120 parcels, based on clustering the leadfields of a head model, such that activity can be faithfully represented by a single dipolar source while minimising inter-parcel crosstalk. Cho et al. [171] compared the resting-state networks derived from MEG (Cam-CAN) and EEG (from another cohort) using HMMs, and found comparable static and dynamic network descriptions, though MEG offered increased reproducibility and increased sensitivity to age. Interestingly, for dynamic networks at least, age prediction was comparable with versus without individual MRI images (relative to a common template MRI). Indeed, Jaiswal et al. [172] showed that source localisation based on warping a template head model based on digitised head points was sufficient for MEG source localisation, obviating the need for obtaining an MRI.

Another application of head models is for optimising transcranial neurostimulation. For example, Kashyap et al. [173] simulated the dose-target determination index to optimise focality of transcranial direct current stimulation (tDCS), while Kashyap et al. [174] showed how the CSF channels the flow of electrical current. Importantly, Bhattacharjee et al. [175] found sex differences in simulated tDCS current density that depended on age and stimulation locations, and Zhang et al. [176] showed that the variability of electric field distribution patterns was highest at the extremes of the age range, and this depended on local anatomical parameters (such as scalp or skull thickness below the electrode). These results suggest that it is necessary to consider age and sex when using transcranial electrical stimulation to modulate or treat individuals.

Graph/network analysis

Lehmann et al. [177] developed a Bayesian framework based on exponential random graphs to characterise the distribution of a population of networks, and used it to compare functional connectivity across young and old groups from CamCAM's resting-state fMRI data. Levakov et al. [178] explored 'connectome embedding' on diffusion-weighted and rsfMRI data, which is a way of characterising the role of brain nodes within a global network topology. Connectome embedding substantially improved the correspondence between structural to functional connectivity, and enhanced the effects of age on this structure–function mapping. Razban et al. [179] used an Isling model from physics to relate functional integration and segregation to ordered and disordered states, and tested on rsfMRI data including those from Cam-CAN. They found that integration decreased, and segregation increased, with age, but these effects were consistent with weakened connection strength among regions, rather than change in topological connectivity based on T1- and diffusion-weighted MRI data.

St-Onge et al. [180] tested whether the functional connectome can be used as a 'fingerprint' to match individuals across fMRI tasks. They defined identifiability as when the within-individual correlation across resting-state and sensorimotor tasks was higher than

the maximum between-individual correlation across these tasks. Identifiabilty was close to 100%, despite the fact that both within-individual and between-individual similarity followed a U-shaped distribution, being highest in youth and old age. Connectome edges contributing to self-identifiability were not restricted to specific brain networks, and were different between individuals. These findings indicate that individual participants across the adult lifespan have unique connectomes preserved across tasks. Similarly, Taimouri and Ravindra [181] used leverage scores to identify a small subset of fMRI connectivity features that minimised inter-individual similarity while maintaining intra-individual consistency across Cam-CAN's tasks, and argued that these features can help differentiate normal ageing from neurodegenerative processes.

Finally, there is interest in the metabolic costs associated with various connectomes, given the hypothesis that the brain evolved an optimal trade-off between these costs and the benefits of communication efficiency. For example, Ma et al. [182] used Cam-CAN's diffusion-weighted data to argue for a three-way model that trades-off cost, integration and segregation. Castelluzzo et al. [183] on the other hand used Cam-CAN's resting-state MEG data to examine the dependence of functional connectivity on geometric distance between sources, and identified three regimes of distance that each showed a specific pattern of connectivity.

Multimodal integration

As mentioned earlier, a strength of Cam-CAN is the multimodal nature of the brain data, from multiple MRI contrasts to MEG. There are dependencies between these modalities during preprocessing, such as using the T1-weighted image to define transformations to a common space for the other modalities, or to build a head-model for the MEG (see previous section). Taylor et al. [184] addressed this complexity of preprocessing using a Matlab-based batching tool called 'Automatic Analysis' (AA), though there have been many improvements since, in addition to a move to the free programming language Python instead. For example, Cam-CAN data have been used to help illustrate the BIDS app 'micapipe', specialised for generating connectomes from T1-, diffusion- and BOLD-weighted MRI data (Cruces et al. [185]), as well as more general decentralised and open-source cloud platforms for multimodal analysis such as brainlife.io (Hayashi et al. [186]).

A major interest is whether information about the brain is shared versus complementary across modalities. For example, Liu et al. [187] demonstrated the value of linked ICA to combine grey matter volume estimates from T1-weighted MRI, cerebrovascular estimates from ASL and functional network topographies from fMRI in relation to measures of fluid intelligence. Jauny et al. [188], on the other hand, used multilayer network analysis to relate structural (diffusion-weighted) and functional (MEG) networks. The multiplex participation coefficient indicated that the similarity between structural and functional connectivity in the alpha frequency band, at least within parietal and temporal regions, was associated with cognitive performance in healthy older individuals. They suggested that the association between structure and function could represent a marker of individual variability, potentially including pathological changes. Other examples of multimodal integration include Karahan et al. [189], who related MEG and diffusion-weighted data in terms of inter-subject variability of connectivity, and Wodeyar and Srinivasan [190], who showed how the MEG functional connectome (based on partial coherence) can be improved with knowledge of the structural connectome.

Naskar et al. [191] used Cam-CAN's diffusion-weighted and rsfMRI data to test a multiscale, dynamic mean-field computational model of spontaneous brain activity, consisting of coupled differential equations for capturing synaptic gating dynamics in excitatory and inhibitory neural populations as a function of neurotransmitter kinetics. They demonstrated that an optimal range of glutamate and GABA neurotransmitter concentrations is important for the metastability observed in rsfMRI data. In subsequent work, they claimed that glutamate, rather than GABA, is the principle cause of the topological variation of functional connectivity along the adult lifespan (Saha et al. [192]). The same group also built a computational model based on diffusion-based tractography to reproduce phase-locking of alpha oscillations in Cam-CAN MEG data (Pathak et al. [193]). They showed that enhancing inter-areal coupling can overcome the effect of increased axonal transmission delays associated with age-related degeneration of white matter tracts, and argued that frequency

slowing with age (frequently observed in the alpha band) may be an epiphenomenon of an underlying compensatory mechanism.

Finally, Engemann et al. [194] used machine-learning to examine the improvements in age prediction when adding fMRI and MEG to T1-weighted data. Adding fMRI or MEG alone reduced the mean error from 6 years to 5.2 years, while combining all three reduced it to 4.7 years. Indeed, there was little correlation between the mean error from fMRI and that from MEG, suggesting that they provide complementary information about age. Liu et al. [195] meanwhile showed good age prediction using a novel, low-rank tensor fusion algorithm to combine Cam-CAN's T1-weighted MRI, diffusion-weighted MRI and resting-state MEG data.

Clinical/translational use

Cam-CAN data have also been used for clinical purposes, particularly in providing normative ('healthy') data on various brain and cognitive measures across the adult lifespan.

Normative data

Normative data can be used to characterise, for example, how the brain of a typical 55-year-old, female should look. Such stratified comparison data can help interpret MRI scans from patients who have suffered brain damage or disease. For example, Cam-CAN data were a (small) part of the data used to produce 'brain growth charts' by Bethlehem et al. [196], based on T1-weighted MRIs. Zhu et al. [197] and Conte et al. [198] took a similar approach to estimate lifespan reference curves for white matter metrics from diffusion-weighted MRI. Cam-CAN data have also been used for the development of software for normative modelling, e.g. the PCNToolkit (https://pcntoolkit.readthedocs.io/en/latest/) and BrainMonocle https://cnnplab.shinyapps.io/BrainMoNoCle/ [199]. Similar efforts are planned for 'cognitive growth curves', which may help to identify development of, for example, psychoses (Marquand et al. [200]).

Using a so-called Mosaic Approach, normative (age and sex stratified) grey matter volumetrics from Cam-CAN have been used to examine the effects of motor neuron diseases, amyotrophic lateral sclerosis and poliomyelitis survivors (Tahedl et al. [201]) and Parkinson's disease (Tahedl et al. [202]). The use of Cam-CAN MRI data as 'healthy controls' has also been used to investigate single cases of fronto-temporal dementia (FTD) (McKenna et al. [203]), former athletes with multiple concussions (Misquitta et al. [204]), substance use disorder (Shi et al. [205]) and transdiagnostic patterns across schizophrenia, bipolar disorder and attention-deficit hyperactivity disorder (Lawn et al. [206]). Huang et al. [207] examined individual variability in structural connectivity from diffusion-weighted MRI, after combining Cam-CAN with other cohorts, while Janssen et al. [208] combined Cam-CAN with other cohorts to produce normative data on 'morphometric similarity' (across cortical measures like thickness, area, curvature), and showed that patients with schizophrenia showed reduced morphometric similarity within the DMN.

Brain Age Gap

Several studies have used Cam-CAN data (particularly T1-weighted MRIs), often combined with data from other cohorts, to train a model to predict age, and then used that model to predict BAGs (see the Methodological developments section) in a new, clinical sample, where a more positive BAG normally implies brain damage. In a sample of 372 patients with Parkinson's disease, Eickhoff et al. [209] showed that the patients' brains appeared approximately 3 years older than those of healthy controls. While this effect was already present in newly diagnosed patients, advanced brain age correlated with disease duration, and worse cognitive and motor impairment. Besson et al. [210] used deep learning of several cohorts to show that BAG was higher for patients with MCI and AD, while Kim et al. found similar results after using deep learning to transfer from research-grade, 3D MRIs to more typical, 2D clinical MRIs [211]. Ahmai et al. [212] applied deep learning across several cohorts to show that BAG was higher for AD patients who also showed evidence of Lewy bodies, indicating that they amplify AD-related neurodegeneration. Mohajer et al. [213] also found higher BAGs in MCI and AD, as expected, but no effect of sleep-disordered breathing on BAG. Navarro-González et al. [214] predicted age from various grey matter properties from the T1-weighted scan and

showed that individuals with chronic, but not episodic, migraine have a higher BAG.

In stroke research, Richard et al. [215] tested whether stroke patients with lower BAGs performed better on cognitive tests and benefited more from cognitive training. However, in a double-blind study in which 54 stroke patients received intensive cognitive training either with active or sham tDCS, there was no significant association between BAG and either baseline cognitive performance, nor response to cognitive training, with or without tDCS.

Kuhn et al. [216] predicted age from various white matter properties from the diffusion-weighted scans, and then used a clinical cohort to show that individuals with HIV had higher BAGs. Their BAGs also correlated with HIV RNA viral load (as well as cognitive impairment), suggesting accelerated white matter ageing (see also Petersen et al. [217]). Levkov et al. [218] combined BAGs from volumetrics and rsfMRI in a randomised controlled trial of a dietary intervention for weight loss, and found that a 1% loss of body weight after 18 months was associated with an 8.9 months reduction in brain age. Beck et al. [219] found correlations between higher BAG and various cardiovascular risk factors, such as systolic blood pressure, smoking, pulse, C-reactive protein levels and waist-to-hip ratio.

Dias et al. [220] combined Cam-CAN's T1-weighted images with other cohorts to create voxel-wise sensitivity maps (i.e. influenced by grey matter, white matter and CSF), which reflect the importance of each voxel for the age prediction, and showed that these differ across AD, schizophrenia and T2 diabetes. They argued that this method provides biological explanation to BAG models as well as helping to understand the pathophysiology of chronic brain conditions.

One can predict properties other than age, such as sex for example. Dibaji et al. [221] used a convolutional neural network to predict sex from T1-weighted images in a number of cohorts including Cam-CAN, and reported importance maps to identify particularly strong sex-predictive brain regions. This information could be used to address biases in other AI applications. Haas et al. [222] trained a model to predict impaired social outcome in a sample with clinical-high-risk states for psychosis, and tested on non-clinical populations, including Cam-CAN. They could not predict adverse social outcomes or higher psychopathology levels in the non-clinical samples, though could predict cognitive impairment.

Thus BAG has found use in studies of many different clinical populations, though the caveats listed in the Methodological developments section should always been kept in mind.

Other dementia studies

In addition to the studies above that used BAG to investigate dementia, other studies have performed more focused comparisons of patient groups versus (Cam-CAN) controls. For example, Tsvetanov et al. [223] used Cam-CAN data to define a subset of brain regions for investigation of differences in functional and structural connectomes in presymptomatic genetic mutation carriers for FTD versus family members. Their results suggested that integrity of functional connectivity between those regions can maintain cognitive function in the carriers despite structural atrophy. A similar approach was used to define key brain regions/networks for analysis of patient data, such as PET measures of neuroinflammation in Alzheimer's disease (Passamonti et al. [224]).

Bougacha et al. [78] compared several models of how AD pathology spreads and, using functional and structural connectomes from Cam-CAN (as well as other cohorts). They found that topological proximity to areas of maximal pathology in the functional connectome explained significant variance in hypometabolism and amyloid load, whereas atrophy and tau load were mainly predicted by structural pathways.

Plachti et al. [225] examined the pattern of structural covariance of grey matter volume in hippocampus voxels in young, middle-aged, elderly, MCI and dementia. In the healthy and MCI participants, the hippocampus was robustly divided into anterior, lateral and medial subregions reminiscent of cytoarchitectonic division, whereas in established dementia patients, the pattern of subdivision differed, being closer to known functional differentiation into anterior, body and tail subregions, suggesting important structural consequences of neurodegeneration in the hippocampus. Flaherty et al. [226] compared MTL structures in those in Cam-CAN over 55 years who indicated subjective memory problems versus those who did not. Those with subjective problems had thinner grey matter in bilateral entorhinal cortex,

but no differences in the white matter microstructure of the lower cingulum. Nonetheless, the cingulum microstructure correlated with delayed story recall in those with subjective problems, but not in those without. They interpreted their results in terms of mixed neuroinflammatory and neurodegenerative pathologies.

In some cases, cognitive data from Cam-CAN have been used as normative data with which to compare patient data from the same task. In Wolpe et al. [227], for example, 18 patients with Parkinson's disease (PD) performed the same force-matching task used in Cam-CAN, and were compared to 175 matched controls. Despite changes in sensitivity to different forces, overall sensory attenuation did not differ between medicated PD patients and controls. Importantly, the degree of attenuation was negatively related to PD motor severity, but positively related to levodopa dose. The results suggest that dopamine regulates the integration of sensorimotor prediction with sensory information to facilitate the control of voluntary movements.

Finally, Cam-CAN resting-state MEG data were used to form part of the control participants in the BioFIND dataset (Vaghari et al. [228]), which was the world's first publically-available MEG dataset to study MCI (available from DPUK; https://www.dementiasplatform.uk/research-hub/data-portal/featured-cohort-biofind).

Other stroke/TBI/glioma studies

In the case of stroke, Khalilian et al. [229] showed that structural disconnection maps from diffusion-weighted data were strong predictors of post-stroke motor and cognitive deficits, while Kim and Kang [230] compared Cam-CAN diffusion data with those from 27 patients with middle cerebral artery infarction after stroke, and found many bilateral tracts with differences in FA, even in patients with mild motor impairment.

Like for the MRI norms considered above, Krieger et al. [231] used the Cam-CAN data to establish MEG norms, with a view to facilitate investigation of traumatic brain injury (TBI). Given that APOE ε4 is associated with poor outcome following TBI, Hellstrøm et al. [232] looked for any neural correspondence of this. However, no significant differences in BAGs were found between ε4 carriers and non-carriers in 123 patients, whether BAG was trained on grey or white matter data in Cam-CAN. Nor were differences found in conventional brain measures, except a trend towards lower FA in the hippocampal cingulum.

Tinney et al. [233] used rsfMRI to claim that a prior TBI resulted in hyperconnectivity in short-range connections and hypoconnectivity in long-range connections, particularly in a frontal-parietal control network, compared to age- and sex-matched controls. Moreover, engagement in physical activity was associated with functional network connectivity in those with a TBI.

Stubbs et al. [234] used data from Cam-CAN participants to compare to those from homeless and precariously housed individuals: The latter showed more whole-brain atrophy, lower FA and higher mean diffusivity, particularly after age 35–40. Within their sample, a history of TBI or drug dependence and heroin dependence was associated with even more grey and white matter loss. Indeed, Newcombe et al. [235] showed that post-acute blood biomarkers ~8 months after TBI predicted annualised brain volume loss up to 5 years later.

Romero-Garcia et al. [236] examined rsfMRI connectivity in patients with glioma. They found that the spatial correlation between regional and global BOLD signals (also known as 'global signal topography'), identified in Cam-CAN data, was associated with tumour occurrence in their patients during a recovery period. Moreover, they found that this coupling was associated with cognitive recovery.

Physical health

Ronan et al. [237] used BMI in Cam-CAN to show that increased adiposity modulates the relationship between white matter volume and age, such that the brains of overweight and obese individuals can appear up to 10 years older in middle age. Interestingly, there was no effect of adiposity on cortical grey matter. The susceptibility of cerebral white matter to adiposity-related influences may be related to the biology of oligodendrocytes, which continue to differentiate into the fifth decade and are particularly vulnerable to insults. Spindler and Thiel [238] focused on the hypothalamus, using Cam-CAN's magnetisation-, diffusion- and BOLD-weighted data. Hypothalamic microstructure was relatively stable across age, and there was no association between any

depressive symptoms or cognitive performance. Its microstructure was however affected by BMI, which also modulated its functional connectivity with limbic regions including the hippocampus, amygdala and nucleus accumbens, suggesting alterations in the metabolic and reward systems.

Physical exercise is a factor long-known to influence physical health. By using Cam-CAN's physical activity energy expenditure (PAEE) questionnaire, Strömmer et al. [239] demonstrated that higher self-reported daily physical activity was associated with greater preservation of white matter FA in several frontal tracts, and that age-related cognitive slowing was mediated by FA in some of those tracts. Ai et al. [240] found that age-related reductions in physical activity were mediated by changes in rsfMRI connectivity, consistent with their hypothesis that aspects of executive function support engagement in physical activity. These findings support a growing body of evidence that a physically active lifestyle may protect against age-related structural disconnection and cognitive slowing. However, a more recent and larger study by Demnitz et al. [241] found no relationship between self-reported physical activity and grey matter volume in hippocampus or prefrontal cortex, regardless of sex. This raises the question of whether self-report questionnaires of physical activity are sufficiently sensitive to capture a—presumably modest—association between physical activity levels and grey matter outcomes (though such associations might be stronger for measures of white matter or functional activity/connectivity).

Parrotta et al. [242] reported that physical frailty was associated with reduced cerebellar grey matter volume, reduced diffusion-based connectivity in the corticospinal tract and increased functional connectivity in the DMN. Physical frailty was also correlated with cognitive frailty, consistent with the idea of 'cognitive and physical stability'—i.e. the importance of maintaining both cognitive and physical abilities—which has been associated with differences in graph-theoretic properties of the structural connectome (Zhou et al. [243]). Indeed, cognitive frailty (in data from Arm 2 of Cam-CAN), as defined by repeated MMSE/ACER performance below conventional cut-offs of dementia in the absence clinical assessment, was not associated with striking grey matter loss nor atypical MEG responses to associative mismatches (Kocagoncu et al. [244]).

Cardiovascular health

An important component of physical health (and brain health) is cardiovascular health. Fuhrmann et al. [245] estimated the number and volume of WMHI lesions from Cam-CAN's T2-weighted MRI images and related them to blood pressure. While systolic blood pressure was positively related to WMHI lesions, diastolic blood pressure was negatively related. This suggests that the critical factor may be 'pulse pressure'—the difference between systolic and diastolic pressures. This association was robust across sexes, antihypertensive medication, cardiovascular risk factors (e.g. diabetes, elevated cholesterol levels), alcohol consumption and smoking. BMI and physical exercise were also associated with white matter health, both directly and indirectly via cardiovascular health.

The importance of pulse pressure for cognition, particularly in older people, was confirmed by King et al. [246]. These authors identified three distinct 'latent vascular factors' from six measures in Cam-CAN: pulse pressure and mean pressure, BMI, heart rate, and high- and low-frequency components of heart rate variability. The factor that was related to pulse pressure predicted the 'cognitive discrepancy score' (the difference between fluid relative to crystallised intelligence, indicative of cognitive decline), though only in older adults.

In a subsequent study, King et al. [247] united the above two papers by integrating pulse pressure, white matter and cognition. In this case, white matter integrity was estimated from diffusion-weighted data via a metric called Peak-width of Skeletonised Mean Diffusivity, which appears particularly sensitive to age and speed measures (Raykov et al. [21]). This measure mediated the effect of pulse pressure on processing speed, which in turn predicted fluid intelligence, but again only in older people. These papers suggest that controlling pulse pressure (e.g. via medication or lifestyle) may be important to preserve cognition in older adults.

Finally, Ruffle et al. [248] examined heart-rate variability from Cam-CAN's ECG data to estimate function of the sympathetic and parasympathetic systems. They then related individual estimates of these functions to graph-theoretic analysis of grey matter volumetrics, white matter FA and functional connectivity from rsfMRI. While conventional structural

and functional maps only identified regions jointly modulated by parasympathetic and sympathetic systems, their graphical analysis discriminated between them, revealing that the cardinal roles of the autonomic system are mediated by high-level distributed interactions.

Sex differences and genetics

Some studies have explored sex differences in Cam-CAN and related cohorts, such as hormone changes in the menopause. For example, while Hicks et al. [249] found few differences in cerebellar lobular volumes, Ballard et al. [250] reported that post-menopausal females had lower functional connectivity within the cerebellum, as well as lower cerebello-striatal and cerebello-cortical connectivity, compared to reproductive females and age-matched males. A subsequent study of whole-brain functional networks found that the well-known effects of age on segregation of those networks depended on sex, and reproductive stage, though the latter could not be distinguished from effects of age [251].

A large mega-analysis across multiple cohorts by Ravndal et al. [252] asked whether the increased prevalence of AD diagnoses in women reflects a greater extent of structural brain decline. On the contrary, men showed greater decline of cortical thickness and surface area compared to women in many brain regions, with only a few regions showing greater decline in women. These results suggest that sex differences in age-related brain decline are unlikely to contribute to the higher frequencies of AD diagnosis in women, necessitating research into alternative explanations, such as survival bias, other pathological differences or even cultural ones.

In terms of other genetic differences, while the sample size in Cam-CAN is insufficient for GWAS, one can focus on candidate SNPs with high effect sizes. One such gene is 'APO-E', the 'e4' variant of which is known to increase dementia risk (up to tenfold if both e4 alleles are carried). One reason why the e4 variant persists in the population may relate to 'antagonistic pleiotropy', viz if this variant provides health benefits earlier in life. This hypothesis predicts an interaction between age and APO-E variant. However, in a registered report, Henson et al. [253] found evidence against such an interaction using Bayes Factors on six key cognitive and brain measures implicated in previous studies, including hippocampal grey matter, mean diffusion within white matter and resting-state connectivity measured by both fMRI and MEG. Similarly, Raykov et al. [254] found evidence against e4-carriers differing in boundary-locked activation, functional segregation or DMN connectivity during movie-watching.

Cam-CAN's sample size may also be sufficient when using polygenic scores (PGS), which predict certain phenotypic properties (e.g. longevity) from a weighted combination of SNPs, where those weights are estimated from large, independent datasets. In Raykov et al. [21], we confirmed that a PGS for intelligence was positively associated with several cognitive measures in Cam-CAN, but adjusting for this PGS did not remove all significant associations between white matter factors and those cognitive measures. This suggests that some associations between WM and cognition are partly due to environmental factors (see next section).

Environmental/lifestyle factors

As noted earlier, cognitive reserve refers to the observation that some older people can be less prone to cognitive decline than others, despite comparable structural brain changes. Education has often been cited as a source of cognitive reserve, given that it is well-established that people with higher levels of education have a lower incidence of a dementia diagnosis. Together with a number of larger cohorts (totalling over 15,000 people), Fjell et al. [255] replicated previous findings that more years in education is associated with higher levels of memory ability and brain volume in old age, but importantly found no evidence that education affected the subsequent rate of decline of either memory or brain volume. This pattern is more consistent with reserve than maintenance, i.e. people with higher education are likely to have had higher cognitive abilities/brain volumes throughout their life, rather than being specifically able to maintain them into old age (and the lower incidence of dementia in highly-educated individuals may arise simply because it takes longer for their cognitive abilities to fall below conventional cut-offs on cognitive tests). This pattern is also consistent with higher cognitive abilities/brain volumes in youth (e.g. owing to genetics or early development) leading to more years spent in education, rather than vice versa.

Walhovd et al. [256] used Cam-CAN as part of a much larger study (54,000 people with MRI) to investigate the effects of socio-economic status (SES) on brain and cognition. They found intracranial volume (ICV), but not total grey matter volume (TGM), was related to household income (a proxy for SES). The ICV association, as well as that with cognition, was stronger in US than European cohorts, possibly reflecting different societal norms. Importantly, the ICV-income association occurred regardless of age, and the fact that this was stronger than the TGM-income association implies that SES-cognition relations in adulthood are more likely to reflect early-life differences (since ICV stabilises in childhood), rather than SES being neuroprotective.

Nonetheless, there are likely to be other lifestyle choices that increase cognitive reserve, and are potentially modifiable. Using Cam-CAN's retrospective lifestyle questionnaire, Chan et al. [257] found that reports of past, mid-life activities (physical, social and/or intellectual), outside the workplace, made a unique contribution to the cognitive abilities in those in late-life (over 65), over and above education and current (late-life) activities. Furthermore, these mid-life activities attenuated the relationship between TGM and fluid intelligence, as would be expected if they establish cognitive reserve. Other work combining even more lifestyle measures (though only current activities, and across all Cam-CAN ages) suggested that physical and social activities make independent, positive contributions to cognitive ability (Borgeest et al. [258]). Thus, public health interventions that nudge the behaviour of middle-aged people might pay dividends later in life by increasing the cognitive health span. Nonetheless, in a subsequent study, Raykov et al. [41] found no relationship between mid-life activity and the segregation of functional networks, so the functional brain correlates of this type of cognitive reserve currently remain unknown.

Advantages and limitations

One likely reason for the popularity of Cam-CAN is the broad (and approximately uniform) range of ages across the adult lifespan, and the more representative nature of the sample, at least of a certain geographic region within the UK, than many other neuroimaging studies and cohorts (e.g. that tend to recruit by advertisement). Another reason is the broad range of cognitive and demographic variables, and the multimodal nature of the neuroimaging data, particularly the inclusion of MEG. However, there are of course important limitations of the Cam-CAN dataset. Foremost, Cam-CAN is not diverse in terms of ethnicity or sociocultural environment, so it should be combined with cohorts from other countries. It is also relatively small (100s of participants), at least relative to other cohorts with MRI data like the UK BioBank (100,000s of participants). Cam-CAN is also limited in its scarcity of standardised neuropsychological tests, and lack of fluid (e.g. blood) samples. Most importantly, however, it has relatively small numbers of people with longitudinal data: only ~ 150 have been recruited for Stage 5 to date, and these are likely to be biased by attrition/survivor effects. Nonetheless, the data from Stage 5 were collected 12 years after those from Stage 2 (on average), which is a relatively large lag for neuroimaging cohorts (improving the statistical power for longitudinal effects [259]).

Future

In terms of the future of CamCAN, data from Stages 4–5 of Cam-CAN have not yet been shared. Stage 4 was run online, and contains repeated and new questionnaire and cognitive data. Stage 5 started in 2024, and is still running. This includes MRI and MEG data from repeat visits to the CBU, as well as further online questionnaire and cognitive tests. We hope to share data from Stages 4–5 in 2026/2027, though ideally with a more searchable portal, such as one based on RedCap (https://project-redcap.org/), given the complexity of the longitudinal data. In future, we hope to assess brain and cognitive health again in another 5–6 years, though obtaining funding for such longitudinal follow-up is always difficult.

In terms of the future of neuroimaging cohorts more generally, there is a pressing need to recruit from more ethnically, geographically and culturally diverse populations—to avoid the bias of neuroscientific conclusions based only on 'WEIRD' participants (participants from Western, Educated, Industrialized, Rich and Democratic societies [260])—which clearly applies to Cam-CAN. These cohorts need to track individuals longitudinally across many years, if not decades, given that cognitive/brain changes may be

negligible over just a few years (except perhaps in late life), and that longitudinal data allow much clearer conclusions about the ageing process [261]. As this review hopefully illustrates, such longitudinal cohorts will benefit from recording multiple brain measures, as well as multiple cognitive and lifestyle measures, allowing, for example, more comprehensive assessment of the brain correlates of cognitive reserve [262], and the factors contributing to it, ideally using prospective rather than retrospective tracking of lifestyle factors. Indeed, effects of lifestyle choices on brain and cognition may require decades of practice, and only emerge decades later.

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Data availability The data from Stages (Phases) 1–3 of Cam-CAN are available here: https://opendata.mrc-cbu.cam.ac.uk/projects/Cam-CAN/. More details about the Cam-CAN project can be found here: www.cam-can.org.

Declarations

Competing interests The authors declare no competing interests.

Ethics and consent to participate The Cam-CAN study was conducted in compliance with the Helsinki Declaration, and was approved by Cambridgeshire 2 Research Ethics Committee (reference: 10/H0308/50).

Glossary

AD	Alzheimer's Disease – the most common of several neurodegenerative diseases that can cause dementia
ARAS	Ascending Arousal system - a complex network extending from the brainstem to cortex, responsible for regulating arousal, wakefulness, consciousness and attentional processes
ASL	Arterial Spin Labelling – an MRI contrast that measures blood flow
BAG	Brain Age Gap – brain age predicted from neuroimaging data minus chronological age, with larger BAGs hypothesised as a biomarker for brain damage/disease.

BMI Body-Mass Index – ratio of body mass to (squared) height.

BOLD Blood Oxygenation-Level Dependent contrast – an MRI contrast that can detect metabolic consequences of neural activity (one type of fMRI, q.v.).

CBF Cerebral Blood Flow – as measured for example by ASL (q.v.).

CBPM Connectome-Based Predictive Modelling – a machine-learning approach that predicts phenotypic properties (e.g., cognitive ability) from all connections within a connectome. Because there are typically fewer participants than connections, these predictions normally need regularisation/feature selection.

CCA Canonical Correlational Analysis - a multivariate statistical technique to identify linear combinations (components) of one set of measures that correlate maximally with linear combinations of another set. Similar to PLS.

DCM Dynamic Causal Modelling – a state-space method to model the dynamics implied by a set of connected ROIs, e.g., to infer effective connectivity.

DMN Default Mode Network – a network of brain regions (including medial temporal, medial parietal and medial frontal regions) that are highly connected and active during rest (i.e., tend to be deactivated during tasks).

DTI diffusion tensor imaging, one way to model diffusion-weighted MRI data, from which summary measures like FA (of the tensor) can be extracted, or tractography used to estimate the likely path of fibres via the principal axis of nearby tensors.

EEG Electroencephalography – a topographic brain-scanning technique that measures tiny changes in the electrical fields caused by electrical currents in the brain (cf MEG)

ECG electrocardiogram – a timeseries of voltage differences across two electrodes placed either side of the heart.

FA Fractional Anisotropy – a summary measure of the diffusion tensor estimated from diffusion-weighted MRI, reflecting the degree of deviation from spherical (isodirectional) diffusion. Large, myelinated, aligned fibre bundles tend to have higher FA.

fMRI functional Magnetic Resonance Imaging – an MRI method to measure neural activity every few seconds, using BOLD-weighted contrast (q.v.) in the case of Cam-CAN.

FTD Fronto-Temporal Dementia – a type of dementia in which frontal and temporal lobes are most affected, often with symptoms and neuropathology distinct from AD (q.v.)

GCA General Cognitive Ability – a summary across multiple cognitive tests, e.g., using PCA, very similar to the notion of Spearman's g (see main text).

GSBS Greedy State Boundary Search – a method to define boundaries between states in which multivariate patterns of brain activity change significantly.

GWAS Gene-Wide Association Study – testing the relationship between a phenotypic property (e.g., fluid intelligence) and variation in a large number of genes.

HADS Hospital Anxiety and Depression Scale – a standardised questionnaire measuring anxiety and depression.

HAROLD Hemisphere Asymmetry Reduction in Older adults – the hypothesis that older people recruit the non-dominant hemisphere during cognitive tasks, resulting in a less asymmetrical pattern of activation across hemispheres.

HRF Haemodynamic Response Function – the BOLD response to a brief burst of neural activity, typically peaking 5 seconds later and lasting up to 20-30 seconds.

HMM Hidden Markov Model – a statistical model fit to timeseries data based on transitions between stable states and a measurement model linking those states to the data.

ICA Independent Component Analysis – a method for decomposing data into components that are statistically independent.

ICV intracranial volume – a measure of head-size, i.e., volume within the inner skull

ISFC Inter-Subject Functional Correlation – the correlation across participants between

timeseries from the same brain region, often while performing a common task, e.g. movie-watching.

LC Locus Coeruleus – a small nucleus in the brainstem that serves as the brain's primary source of noradrenaline (norepinephrine), believed to be affected early in ageing and AD.

MDN Multiple-Demand Network – a set of fronto-parietal regions associated with high-level cognitive function, such as fluid intelligence

MEG Magnetoencephalography – a topographic brain-scanning technique that measures tiny changes in the magnetic fields caused by electrical currents in the brain

MRI Magnetic Resonance Imaging – a tomographic brain-scanning technique that can be tuned to different brain properties or "contrasts".

MT-weighted an MRI (structural/anatomical) image whose contrast is influenced by Magnetisation Transfer, which suppresses signal from immobile protons in macromolecules such as myelin (often expressed as the magnetisation transfer ratio, MTR).

MTL Medial Temporal Lobes (MTL) – structures including the hippocampus, amygdala, rhinal cortex and parahippocampal cortex, that seem particularly important for cognitive functions like memory and imagination.

MVPA Multi-Voxel Pattern Analysis – a generic analysis method that examines dissimilarities in the patterns of activity across voxels for different stimuli/tasks, which can arise even if the mean activation in the corresponding brain region does not differ.

PASA Posterior-to-Anterior Shift with Ageing – a hypothesis that older people engage additional anterior brain regions to compensate for structural atrophy of more posterior brain regions.

PCA Principal Component Analysis – a method for decomposing data into components that are orthogonal and ranked by variance explained.

PFC Prefrontal Cortex – the most anterior part of the frontal lobe, often associated with higher cognitive functions (and particularly susceptible to ageing).

PET Positron Emission Tomography – a brain imaging technique distinct from MRI that uses a radioactive tracer to track changes in blood flow or neurotransmitters.

PGS polygenic score – prediction for the phenotypic property of an individual (e.g., longevity, AD) that is derived from the weighted combination of many of their SNPS (those weights defined by large GWAS studies, q.v.)

PLS Partial Least Squares – a multivariate statistical technique to identify linear combinations (components) of one set of measures that covary maximally with linear combinations of another set. Similar to CCA.

PMN Posterior Medial Network – a sub-division of the DMN, with strong connectivity to the posterior MTL (q.v.)

PSQI Pittsburgh Sleep Quality Index – a standardised questionnaire about sleep

RSFA Resting-State Fluctuation Amplitudes – the standard deviation across time-points of resting-state fMRI data in each voxel (after band-pass filtering to focus on haemodynamic changes).

rsfMRI resting-state fMRI – fMRI data acquired while participants are relaxed and awake in an MRI scanner (with no explicit task), sometimes with eyes open, sometimes with eyes closed (like in Cam-CAN); commonly assumed to measure intrinsic brain functional connectivity.

RT Reaction Time – the time taken to respond to a stimulus in a particular task.

SES socio-economic status – difficult to harmonise across countries/societies, but household income is one easy surrogate often used.

SNP Single Nucleotide Polymorphisms - the most common type of genetic variation in humans, when a single DNA nucleotide differs between individuals.

SSRT Stop-Signal Reaction Time – a type of RT associated with inhibitory control, e.g.,

as measured in Cam-CAN's Stop-Signal/No-Go Stage 3 Task.

T1-weighted an MRI (structural/anatomical) image whose contrast is influenced by the longitudinal (T1) magnetic relaxation time. This results in tissue with high fat content (like white-matter) appearing as bright, and areas with high water content (like cerebrospinal fluid) appearing as dark.

T2-weighted an MRI (structural/anatomical) image whose contrast is influenced by the transverse (T2) magnetic relaxation time. This results in tissue with high water content (like cerebrospinal fluid) appearing as bright, as do regions with lesions or inflammation like "white-matter hyper-intensities".

TBI Traumatic Brain Injury – a brain injury that is caused by an outside force, e.g., car accident or sport, often associated with concussion.

tDCS transcranial direct current stimulation – one type of neurostimulation using direct current passed from an anode to a cathode placed on the scalp.

TGM total grey-matter volume – the volume of all grey-matter within the brain, e.g., estimated from segmenting a T1-weighted MRI.

TOT Tip-Of-the-Tongue – a common word-finding problem that increases with age, and also the name of one of the Cam-CAN tasks used to measure this.

VSTM Visual Short-Term Memory – the ability to maintain the properties (eg color, location, orientation) of an array of visual items over a few seconds after their disappearance.

WMHI White-Matter Hyper-Intensities - abnormal bright spots seen on an MRI scan (typically T2-weighted) that indicate damage or degeneration in the white matter, often associated with aging and cerebral small vessel disease.

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