Cam-CAN Newsletter 2025

Reserve vs Maintenance *Rik Henson*

Theories of ageing often distinguish between "reserve" and "maintenance". Reserve refers to an invariant difference between adults (e.g. arising from different genetics or early life experience), whereas maintenance refers to a difference that emerges with age (e.g., owing to lifestyle choices throughout adulthood). Thus the "green" person in Figure 1 would have higher reserve (left panel) or better maintenance (right panel) than the "red" person. Indeed, if the horizontal dashed line in Figure 1 represents a cut-off on a test of dementia, then the red person might perform below this cut-off either because they always did poorly on such tests (the "reserve" scenario) or because they are declining faster than other people (the "maintenance" scenario) – possibly due to a neurodegenerative disease like Alzheimer's. However, if that test is only performed once, we cannot distinguish these two scenarios; only with repeated follow-up tests can one compare the "slopes" (steepness of the arrows in Figure 1). If the red person's slope is steeper than the average slope of others, then there is more reason for concern.

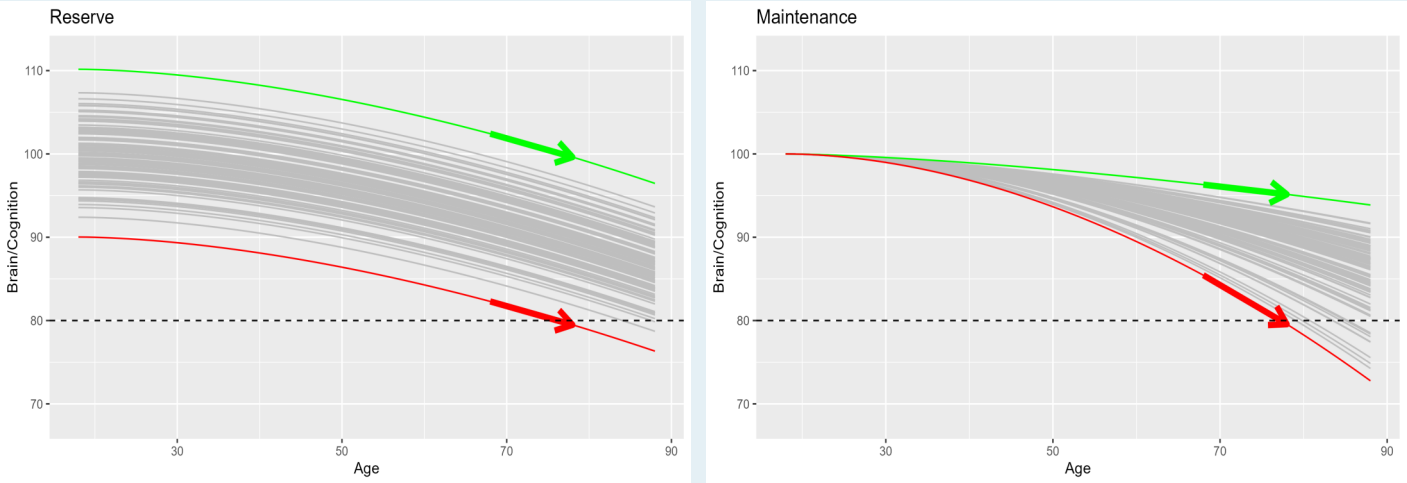


Figure 1. Reserve (left panel) versus maintenance (right panel). Y-axis could reflect cognitive ability (e.g., performance on a memory test) or a measure of brain health. Each grey line is a hypothetical trajectory of a person, with the red and green lines representing two extreme cases, while arrows indicate slopes across two measurement points. Black dashed line illustrates cut-off for a cognitive test of dementia.

This distinction between the conclusions you can draw from one timepoint (a "cross-sectional" analysis) versus multiple timepoints (a "longitudinal" analysis) is one reason why we are so keen to keep in touch with you, and repeatedly measure your cognitive abilities and your brain properties. We are very grateful to the ~150 of you to date who returned for a repeat brain scan this year or last year (and if you did not find time, but are still interested, please contact camcan-manager@mrc-cbu.cam.ac.uk).

Supported by: BBSRC bioscience for the future; UKRI; MRC Cognition and Brain Sciences Unit; University of Cambridge

No evidence that education affects rate of decline of memory *Rik Henson*

It is well documented that people with higher levels of education have a lower incidence of dementia. In our 2021 Newsletter, we reported a study that showed that higher levels of education do not, however, affect the *rate* of decline of brain volume with age. A more recent study (Fjell et al., 2025) used data from an even larger number of international cohorts, including Cam-CAN, and found that, while more education is associated with higher levels of memory ability in old age, such education does not affect the subsequent rate of decline of memory (Figure 2).

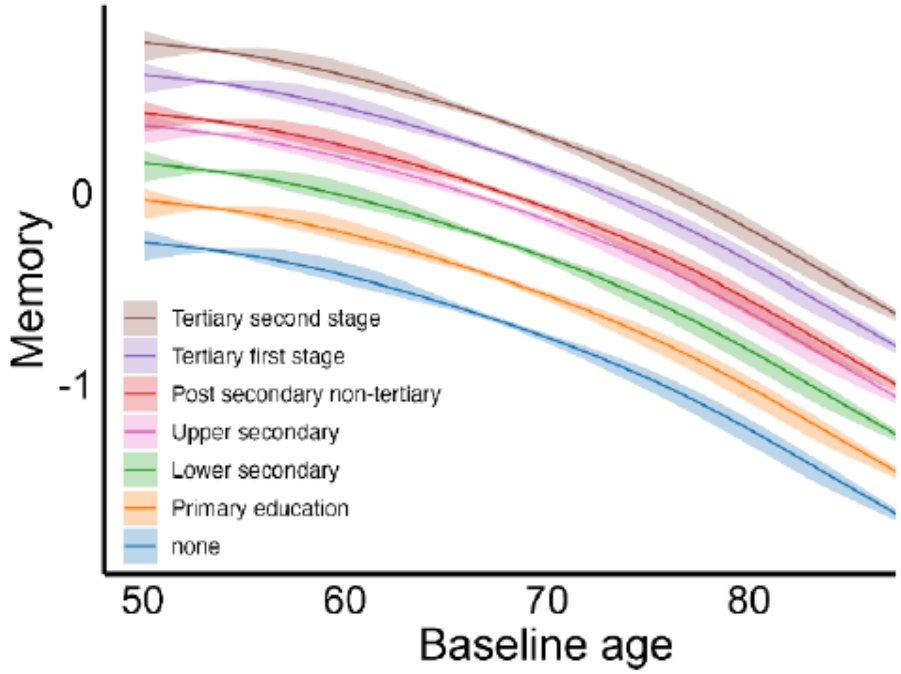


Figure 2. Results from Fjell et al: while memory at age 50 is generally better for people with higher levels of education during their youth, the subsequent rate of memory decline is the same for all levels of education, suggesting that education does not really protect against dementia.

This pattern is more consistent with reserve than maintenance (Figure 1), i.e., people with more education are likely to have had good memory throughout their life, rather than being better able to maintain memory in old age. Indeed, 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 for dementia (Figure 1). This suggests that education does not actually protect against neurodegenerative diseases that cause dementia. Instead, the pattern is consistent with the possibility that higher memory abilities in youth (e.g., owing to genetics) cause more years spent in education, rather than more years in education causing better memory in old age.

Reference: Fjell et al. (2025). Re-evaluating the role of education on cognitive decline and brain aging in longitudinal cohorts across 33 Western countries. Nature Medicine. doi: https://www.nature.com/articles/s41591-025-03828-y

No sex differences in dementia diagnosis and brain change *Rik Henson*

In another, large "mega-analysis" across multiple cohorts, Ravndal et al. (2025) asked whether the increased prevalence of dementia diagnoses in women reflects a greater extent of structural brain decline. On the contrary, men in their later years showed a greater decline of brain volume than women of the same age 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 dementia diagnosis in women, necessitating research into alternative explanations, such as survival bias, other pathological differences, or even cultural ones relating to receiving a clinical diagnosis.

Reference: Ravndal et al. (2025). Sex differences in healthy brain aging are unlikely to explain higher Alzheimer's disease prevalence in women. Proc. Natl. Acad. Sci. U. S. A. doi: https://www.pnas.org/doi/10.1073/pnas.2510486122

Using Hitchcock movies to understand the aging brain *Karen Campbell*

Alfred Hitchcock was the master of suspense. He transformed the world of cinema, and now he is helping transform our understanding of the aging brain.

Rather than showing people boring lists of words or objects to remember, cognitive aging researchers have started using movies, like those by the famed director, to study how age affects the brain under more lifelike conditions.

Part of the reason movies feel more lifelike to us is that they are made up of a series of meaningful events. Even though we experience the world around us in a continuous fashion, we tend to remember it as a series of separate events. For instance, your day today may have consisted of waking up to take a shower, going downstairs to eat breakfast, and then commuting to work. How are these relatively long events represented in the brain and committed to memory?

Hitchcock to the rescue! Cam-CAN scanned people aged 18-88 years with functional magnetic resonance imaging (fMRI) while they watched a short episode of Hitchcock's "Bang! You're Dead". We wanted to know how the brain represents complex, continuous events and whether these representations change with age.

Our study shows that when people watch movies, their brains move through a series of states – stable patterns of neural activity that change when one event ends and another begins (Figure 3). The boy finds a gun in his uncle's suitcase and thinks it's a toy [state change], he heads to the living room with the loaded weapon [state change], then roams through the town aiming it at people [state change].

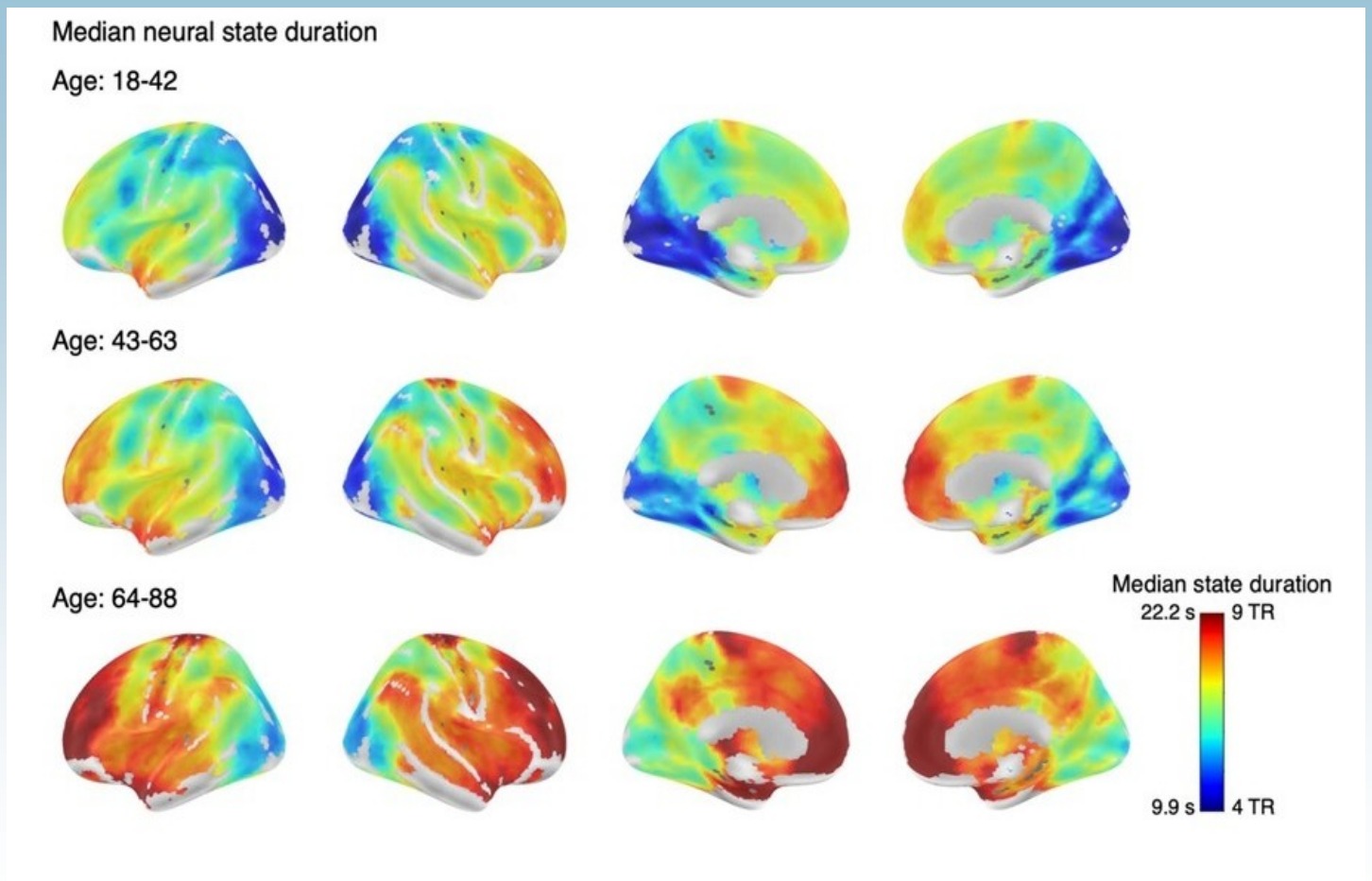


Fig 3. Durations of neural states across the cortex for the youngest (top row), middle-aged (middle row), and oldest groups (bottom row). Shorter states (indicated by cooler colours) are seen in sensory-processing regions like the visual cortex and longer states (warmer colours) are seen in higher-order regions like the prefrontal cortex. As people get older, the average duration of these states gets longer (as indicated by the warmer colours moving from top to bottom).

The novel finding from this study is that neural states last longer in older adults. Put another way, older adults' brains stay in the same configuration for longer before they transition to a new configuration. And even when they do change, the change is less pronounced. This may be because older adults are still processing the previous event as the next one begins. Alternatively, increased knowledge and experience of older adults might allow them to form stronger links between distinct events and only mark the most meaningful changes. Indeed, we found that older adults still show neural state transitions when there are important changes in the storyline.

What does this mean for memory? In a related study we showed that bigger changes between states relate to better memory in both younger and older adults. When a new event starts, you want your brain to say, "hey, there is something new happening here, let's pay attention". If you don't do this updating process very well, it can affect your ability to remember the movie later on.

We are now using this knowledge to develop an intervention aimed at improving event memory in older adults exhibiting the first signs of dementia. Ultimately, we want to help people remember what the doctor said or what happened at yesterday's bridge game, not just the details of Hitchcock Presents.

Reference: Selma Lugtmeijer, Djamari Oetringer, Linda Geerligs & Karen L. Campbell (2025). Temporal dedifferentiation of neural states with age during naturalistic viewing. Communications Biology **8**, Article number: 1390. doi: https://www.nature.com/articles/s42003-025-08792-4

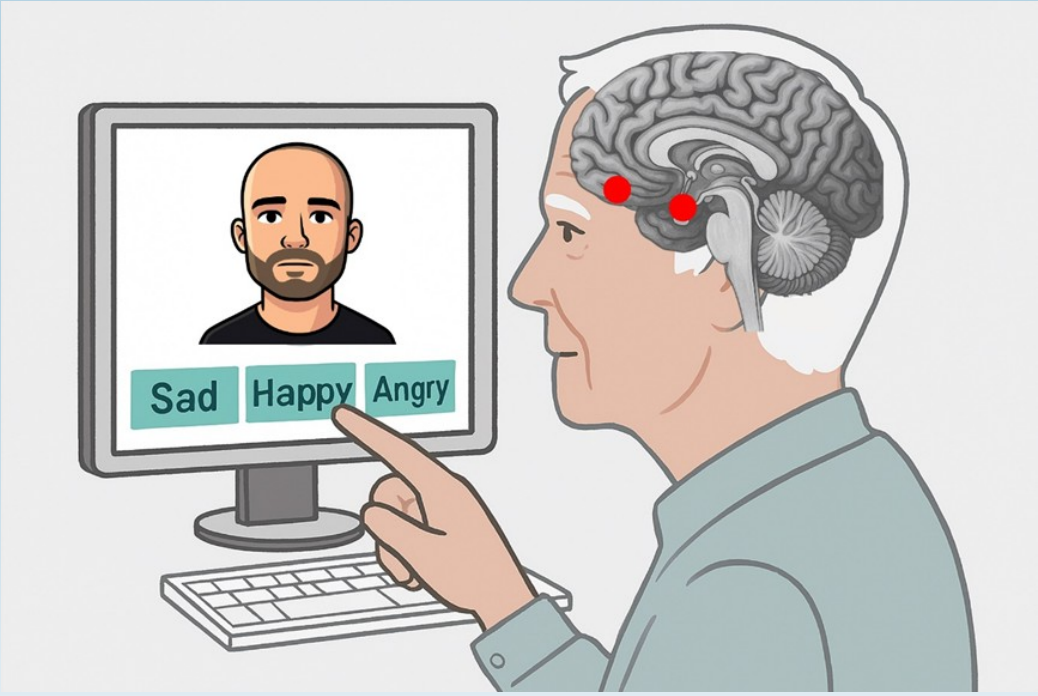
The Positivity Twist: Facial Emotion Bias as a Window Into Brain Aging

Noham Wolpe

As we get older, our ability to recognise emotions in other people's faces subtly changes. In our recent Cam-CAN study, we found that older adults tend to interpret ambiguous or hard-to-read facial expressions more positively than younger adults do. For example, when shown a face that is partly angry or partly happy, older adults need much more evidence to decide that the person looks angry, but very little to conclude that they look happy. This shift toward "seeing the positive" is known as a positivity bias.

One popular idea is that this bias might help support emotional wellbeing in later life. But our results suggest a different interpretation. We tested more than 600 Cam-CAN participants using a sensitive facial-morph task and compared their performance with measures of thinking and memory. Those who showed a stronger positivity bias also tended to show lower cognitive performance, particularly among older adults. This link remained even after controlling for general face-recognition ability and was not explained by depressive symptoms. In other words, the positivity bias appears to be more closely related to subtle cognitive decline than to mood.

To understand why this might be, we looked at brain structure and functional connectivity using the MRI data collected as part of Cam-CAN. We found that greater positivity bias in older adults was associated with reduced grey-matter volume in the anterior hippocampus–amygdala region, which are areas important for processing emotional information and making sense of social cues.



These same individuals also showed stronger connectivity between this region and the orbitofrontal cortex, a frontal area involved in evaluating emotional signals and guiding decisions. This pattern resembles changes seen in the early stages of certain neurodegenerative conditions, raising the possibility that positivity bias could serve as an early behavioural marker of brain changes that precede dementia.

Although emotion-recognition tests are not ready for clinical use, they may eventually complement existing cognitive assessments. We are now examining whether the individuals who showed a stronger positivity bias at their first Cam-CAN visit are more likely to show cognitive decline 12 years later. In parallel, we are developing more naturalistic ways to measure emotional responses,

including using a virtual-reality environment where we observe how long people look at emotionally meaningful scenes. Early results suggest that people with subtle cognitive difficulties spend more time looking at negative emotional stimuli, consistent with the patterns we observed in the current study.

Overall, our findings suggest that the way we interpret other people's emotions, particularly when those expressions are uncertain, may reveal important information about how the ageing brain is changing beneath the surface. Understanding these early behavioural and neural signals could eventually help improve early detection of cognitive decline and guide more timely interventions.

Reference: Wolpe et al. (2025) Age-Related Positivity Bias in Emotion Recognition Is Linked to Lower Cognitive Performance and Altered Amygdala–Orbitofrontal Connectivity.
doi: https://www.jneurosci.org/content/45/39/e0386252025.abstract

Use of Cam-CAN Data

Finally, we would value your thoughts on the following issue. We have been approached by several companies over the years who want to use the Cam-CAN data. In the past, we have always declined, because we told you the data would never be used for purposes other than research, i.e., not-for-profit. However, we are wondering what you would think about their potential use in healthcare, because more and more companies want such data to train algorithms that can then make predictions, e.g., about the cognitive or brain health of a new patient. We would never share personal details like your name, address, email etc. Your data would just be numbers, such as scores on a cognitive test, or volumes of your brain, mixed in with numbers from many others. These combined data would allow, for example, a fairly accurate "control" or "normative" description of what the healthy brain should look like, for a certain age and sex. This has potential benefits for diagnosis in others, e.g., following traumatic brain injury or early Alzheimer's Disease, though of course the companies seek to charge for this service.

Please email camcan-manager@mrc-cbu.cam.ac.uk with your thoughts. We are very keen to hear from volunteers who do, or do not, support whether their data should be used in this way.

Please do keep in touch

If your contact details have changed, or you do not want to participate in further studies, please let us know via:

E-mail: camcan-manager@mrc-cbu.cam.ac.uk

Tel: 01223 769442

Post: Cam-CAN, Medical Research Council Cognition and Brain Sciences Unit, University of Cambridge, 15 Chaucer Road, Cambridge, CB2 7EF