Lifestyle and brain health determinants of word-finding failures in healthy ageing

Foyzul Rahman*1,2,3, Kamen A. Tsvetanov4,5, Jack Feron1,6, Karen Mullinger1,7, Kelsey Joyce6, Ahmed Gilani8, Eunice G. Fernandes9, Allison Wetterlin9, Linda Wheeldon9, Samuel J.E. Lucas1,6, Katrien Segaert1,2

1. Centre for Human Brain Health, University of Birmingham, UK
2. School of Psychology, University of Birmingham, UK
3. College of Psychology, Birmingham City University, UK
4. Department of Clinical Neurosciences, University of Cambridge, UK
5. Department of Psychology, University of Cambridge, UK
6. School of Sport, Exercise, and Rehabilitation Sciences, University of Birmingham, UK
7. Sir Peter Mansfield Imaging Centre, University of Nottingham, UK
8. University Hospitals Birmingham NHS Foundation Trust, UK
9. Department of Foreign Languages and Translation, University of Agder, Norway

<Correspondence address>

*f.rahman@bham.ac.uk

Foyzul Rahman, Centre for Human Brain Health, School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT, United Kingdom.

Abstract

Cognitive decline associated with healthy ageing is complex and multifactorial: vascular and lifestyle factors uniquely and jointly contribute to distinct neurocognitive trajectories of ageing. To evaluate existing accounts of neurocognitive ageing that propose mechanisms of compensation, maintenance or reserve, studies should explore how various known brain-based and lifestyle factors intersect to better understand cognitive decline. Here, we bring together brain function, structure, perfusion, and cardiorespiratory fitness to investigate a well-documented, prominent cognitive challenge for older adults: word-finding failures. Commonality analysis on 73 neurologically healthy older adults revealed that functional activation of language networks associated with tip-of-the-tongue states is in part determined by age and, interestingly, cardiorespiratory fitness levels. Age-associated atrophy and perfusion in regions other than those showing functional differences accounted for variance in tip-of-the-tongue states. Our findings can be interpreted in the context of the classic models of neurocognitive ageing, with mechanisms of compensation and reserve interacting with each other.

Keywords

Healthy ageing; Tip-of-the-tongue; Functional magnetic resonance imaging; Structural magnetic resonance imaging; Cerebral blood flow; Cardiorespiratory fitness; Commonality analysis

Highlights

- The incidence of word-finding failures is determined by brain health and lifestyle factors
- Language network activation associated with word-finding failures is determined by age and cardiorespiratory fitness levels
- Distinct contribution of brain structure and perfusion also predict this decline
- Brain health indices in concordance with lifestyle measures provide a holistic explanation of individual differences in age-related cognitive decline

The proportion of older adults in the global population is rapidly increasing, a trend most pronounced in high-income countries (WHO, 2022). Despite this, there are considerable gaps in our understanding of how we can promote maintenance of cognitive function in later life. Even in the absence of pathology in older age, cognitive decline—including difficulties with memory, processing, and communication skills—can limit everyday functioning and restrict independent living (Clouston et al., 2013; Njegovan et al., 2001). One prominent example is the increasing difficulty in older age with word finding and a related phenomenon known as tip-of-the-tongue states. These are impermanent failures to retrieve and produce intended words; lapses where we cannot call upon a word that we know. Research has shown that incidences of tip-of-the-tongue states increase with age (Huijbers et al., 2017; Salthouse & Mandell, 2013; Schwartz & Frazier, 2005). Indeed, tip-of-the tongue states are frustrating experiences and are among the most common cognitive failures self-reported by older adults (Ossher, Flegal, & Lustig, 2013). These word retrieval failures, which engender poorer verbal expression and communication, may lead to detrimental consequences such as social withdrawal. Though this type of cognitive decline is highly prevalent, the exact mechanisms underlying them are not fully understood.

Existing neurocognitive accounts show that tip-of-the-tongue states are associated with structural and functional changes in the brain (Huijbers et al., 2017; Resnik et al., 2014; Shafto et al., 2007; 2010), and behavioural performance studies have found that lifestyle factors including cardiorespiratory fitness levels modulate individuals' abilities to resolve tip-of-the-tongue states (Segaert et al., 2018). However, an integrated mechanistic explanation of these highly prevalent cognitive failures is currently lacking. To address this gap in the literature, we examined how lifestyle and brain-based factors contribute to age-related changes in tip-of-the-tongue states. We measured brain function, grey matter integrity, cerebral blood flow, alongside cardiorespiratory fitness, and employed a commonality analysis to quantify how these predictors uniquely and collectively explain variation in tip-of-the-tongue rates. Furthermore, our analyses controlled for education—an important mitigator in cognitive ageing—and other demographic variables.

Key theories of healthy ageing centre around mechanisms of maintenance, compensation, or reserve and typically assume contributions of both genetic and lifestyle influences, such as an individual's fitness level, to the neurocognitive mechanisms of healthy ageing (Cabeza et al., 2018). Theories of maintenance are established on maintaining or returning neural resources to their former levels in response to the typical "wear and tear" associated with non-pathological ageing (Habeck et al., 2017; Nyberg et al., 2012). As such, fitness levels are predicted to contribute to the dynamic process of successful maintenance through neural components such as grey matter preservation and cerebrovascular

components such as perfusion levels, which are indicative of vascular health. Theories of compensation entail functional recruitment of additional resources to meet high cognitive demands when there is an insufficiency in neural resources (e.g., brain atrophy or hypoperfusion) (Reuter-Lorenz & Cappell, 2008). Typically, observations of increased recruitment of particular neural regions in older (vs younger) adults are taken as evidence for compensation, with the presumption that these increases offset neural decline elsewhere in the brain (Knights et al., 2023). Nevertheless, a key assumption with this model is that the degree of compensatory involvement is directly related to the degree of cognitive performance, an assumption which has been tested less frequently in studies so far. Lastly, theories of reserve typically posit the idea that fitness (similarly to other proxies for reserve) can contribute to accumulated neural reserve (structural and/or functional) which is amassed over an extended period (which may be childhood, early adulthood, or, in older age) (Tucker & Stern, 2011; Whalley et al., 2004). The accumulation of reserve is thought to act as a protective shield against age-related neural pathology. Applied to the current data, this theory would predict that fitness levels would alter brain structure and/or brain function mechanisms.

Several previous neurocognitive investigations into tip-of-the-tongue states, everyday cognitive failures that older adults frequently experience, are already present in the literature. These signify difficulties with accessing phonology (i.e., sound form representations). Meaning and sound occupy different but connected nodes in the wider architecture of language (Levelt, 2001). When one produces a spoken word, first the meaning of the word is retrieved, and then the associated phonology is accessed (Abrams & Davis, 2016; Levelt, 2001). For most people, most of the time, this process is effortless. However, in older age, connections throughout the lexical system are weakened, and the transmission from meaning to phonology is thought to be compromised, resulting in increased occurrences of tip-of-the-tongue states (Burke, MacKay, Worthley, & Wade, 1991). The processes contributing to this type of cognitive failure thus involve contributions that are distinct from general cognitive slowing or memory (Salthouse & Mandell, 2013). Complementing these psycholinguistic accounts, several neuroimaging studies have demonstrated neural markers associated with tip-of-the-tongue states: lower grey matter density in brain areas implicated in phonological production, in particular the left insula, is related to greater frequencies of tip-of-the-tongue states (Shafto et al., 2007), and reduced functional activation in this same brain region has been demonstrated for older adults (Shafto et al., 2010). Several studies have demonstrated distinct neural signatures for successfully recollected responses compared to tip-of-the-tongue states (Galdo-Alvarez, Lindın, & Diaz, 2009), including recruitment of the wider lateral prefrontal cortex (Huijbers et al. 2017). In addition to the

neural accounts of tip-of-the-tongue states, modifiable lifestyle factors, such as fitness, have also been shown to decrease the probability of experiencing tip-of-the-tongue states in healthy older adults (Segaert et al., 2018). However, these individual and isolated accounts have led to a fragmented picture; consequently, how different measures of brain health (structural, functional, and vascular) intersect with each other as well as with lifestyle variables in determining age-associated cognitive decline remains largely an underexplored area.

The present research aims for a comprehensive account of *how* and *why* ageing leads to more cognitive lapses such as tip-of-the-tongue states. From a wider cognitive ageing perspective, approaches are needed that encompass multi-domain data and examine how each explains the phenomenon of interest in a unique and combined way. A suitable approach to address this is a commonality framework (Nimon & Oswald, 2013; Nimon et al., 2008). Commonality analysis is a statistical approach used to understand the contributions of multiple predictors to the variance in a dependent variable. It helps to decompose the total variance in the dependent variable into distinct components: *unique variance* and *shared variance*. Unique variance can be attributed solely to a specific predictor in the model, while shared variance represents the variance apportioned to two or more predictors (see Wu et al. 2023 for a recent and comprehensive example of applying commonality analyses to neuroimaging data). Using this approach, we assessed the unique and shared effects of brain function (networks revealed by task-based fMRI), grey matter density, cardiorespiratory fitness via a gold-standard lab-based maximal test, cerebral perfusion, education, age, and sex to explain tip-of-the-tongue behaviour. Education was included in the modelling as prior literature has demonstrated that brain structure and fitness have been shown to vary as a function of education (Ho et al., 2011); similarly, sex has been associated with neural/volumetric (Ruigrok et al., 2014), fitness, and cerebral perfusion differences (Leidhin et al., 2021).

As explained above, different neurocognitive theories of ageing, centring around maintenance, compensation, or reserve, make different predictions about which aspects of brain health will be modulated by fitness levels in explaining older adults' abilities to resolve tip-of-the-tongue states. It is not clear if one, multiple, or indeed any of the models align with age-related changes in tip-of-the-tongue states. Our objective in the current contribution, therefore, is twofold: 1) to provide a holistic account, incorporating brain health and lifestyle factors, of tip-of-the-tongue states in ageing, and 2) to embed our findings within and provide support for existing frameworks of neurocognitive ageing. To test the suppositions of these models in a single contribution requires the capture of multi-domain data, ideally in a single design. Here, for the first time, we provide such a contribution.

Results

Participants (N = 73, age range 60–81) reported to the research centre on separate days, first for neuroimaging (structural, functional, and perfusion MRI) and then for cardiorespiratory fitness testing ($\dot{V}O_2$peak). Prior to this, they received extensive health screening (see Methods). Structural anatomical images were acquired using a T1-weighted sequence and cerebral perfusion (cerebral blood flow, CBF) was obtained using a pseudo-continuous arterial spin labelling (pcASL) protocol. Functional brain activity during a tip-of-the-tongue task—which comprised definitions where participants responded with either Know, Don't Know, or TOT (i.e., tip-of-the-tongue)—was recorded using blood-oxygen-level-dependent (BOLD) fMRI, with TOT > Know as the primary statistical contrast. Fitness testing was performed using an incremental treadmill test where respiratory gases and heart rate were continuously monitored as participants advanced through progressive stages until volitional exhaustion.

Figure 1 depicts the key bivariate relationships in our healthy older adult sample, corroborating findings from prior studies. With increasing age, the incidence of tip-of-the-tongue states increased (Panel A) and cardiorespiratory fitness levels (measured as $\dot{V}O_2$peak) decreased (Panel B). Age did not significantly impact on overall cerebral blood flow (Panel C) (see Feron et al. 2023 for more detailed discussion). FMRI-BOLD analysis of the TOT > Know contrast produced significant clusters of activation within the precuneus and angular, cingulate, and frontal gyri (Panel D, and Table 1, Huijbers et al., 2017). Voxel-based morphometry analysis of whole-brain grey matter density showed significant and widespread age-related atrophy consistent with non-pathological ageing (Panel E, e.g., see Giorgio et al., 2010).

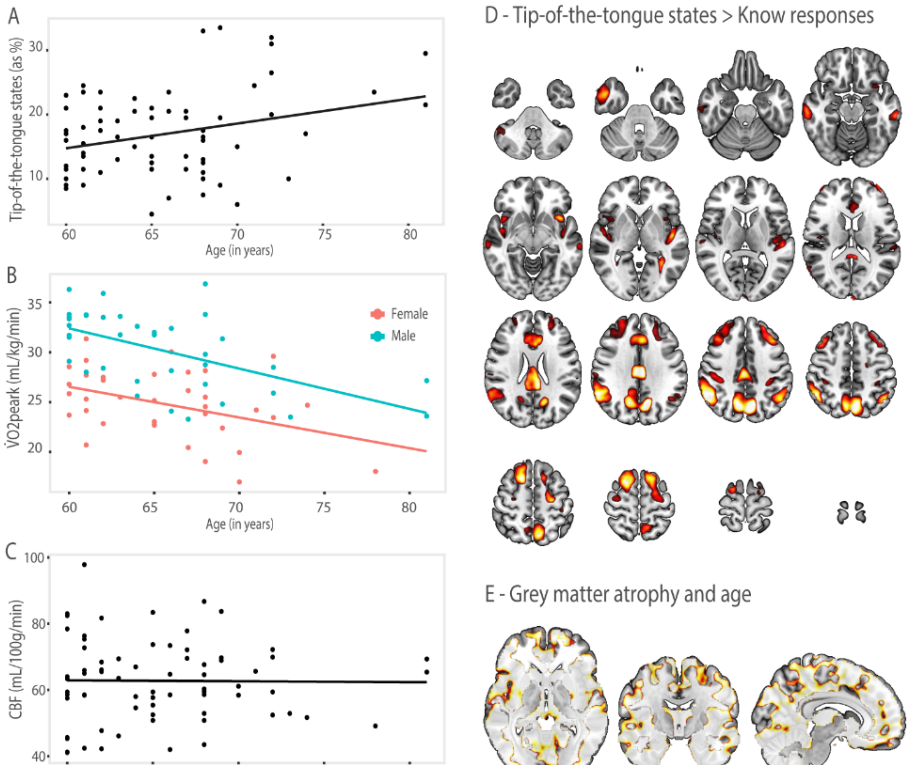

Figure 1. Bivariate analyses of the precursors to commonality analysis. A. Tip-of-the-tongue by age relationship (r = .288, p = .014). B. $\dot{V}O_2$peak by age as a function of sex (Males r = -.566, p < .001, Females r = -.407, p = .014). C. Cerebral blood flow by age (r = -.011, p = .926). D. Significant clusters (determined by Z>3.1 and a corrected cluster significance threshold of p = .05) from the Tip-of-the-tongue > Know contrast. Slices, presented in MNI space, begin (top left) at z = -40 and conclude at z = 80 (bottom right), with each progressive slice representing an increment of +8. Heatmap depict z scores ranging from 2.3 to 9, with lighter colours representing higher z scores. E. Volumetric analysis depicting grey matter atrophy by age (voxel-based morphometry analysis with 10,000 permutations using threshold-free cluster enhancement). Heatmap represents z scores ranging from 2.3 to 6, with lighter colours representing higher z scores (greater age-related atrophy). All brain images presented in radiological convention.

Table 1. Coordinates (MNI), size, and z value of brain regions showing significant tip-of-the-tongue activation (TOT > Know).

Cluster	Cluster size	Region	Z Max	Z Max X (mm)	Z Max Y (mm)	Z Max Z (mm)
1	1161	Precuneus	5.06	-8	-68	36
2	758	R Angular Gyrus	4.73	56	-56	40
3	537	P Cingulate Gyrus	5.34	-4	-22	32
4	307	L Angular Gyrus	4.86	-52	-56	46
5	184	R S Frontal Gyrus	4.37	16	16	56
6	160	L S Frontal Gyrus	4.41	-20	14	68
7	159	L Middle Frontal Gyrus	4.72	-40	24	42

L = Left hemisphere. R = Right hemisphere. P = Posterior. S = Superior. For brevity, clusters containing fewer than 100 voxels are omitted.

Next, we analysed all data modalities with one joint approach using commonality analysis, to determine a parsimonious combination of factors—which were all individually theoretically-motivated, as shown above—in explaining healthy older adults' tip-of-the-tongue rates. Figure 2 summarises the main components of the present multi-domain dataset, feeding into a commonality analysis. The term *functional* refers to functional MRI data derived from the contrast in BOLD signal between TOT and Know responses, *structure* or *grey matter* are used interchangeably to refer to the quantification of whole-brain grey matter density/integrity, and *fitness*, *cardiorespiratory fitness*, and $\dot{V}O_2$*peak* are used to refer to cardiorespiratory fitness. Our core model of interest included the three brain-based datatypes, a measure of cardiorespiratory fitness, and age. As sex and in-scanner head

motion can affect brain measures (Ruigrok et al., 2014), these variables were additionally entered into the model as covariates of no interest.

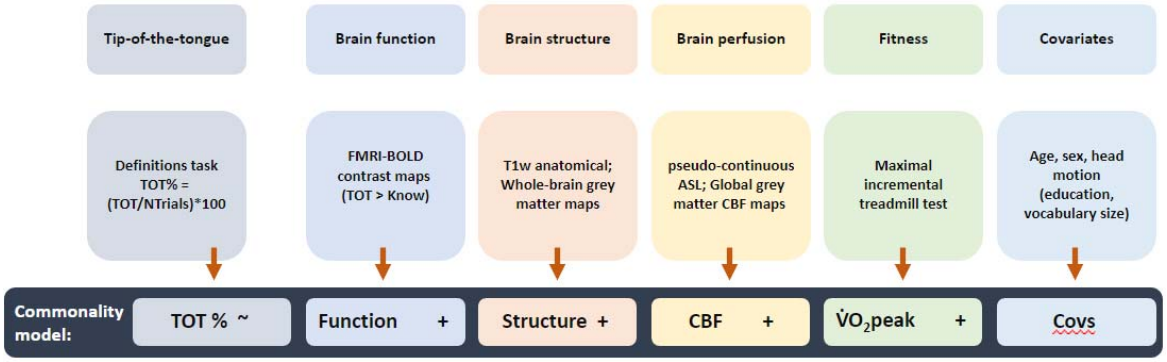

Figure 2. Summary of the main components of the commonality analysis used to analyse the present multi-domain data.

Complementing the bivariate functional analyses, commonality was found between age and function in explaining variance of tip-of-the-tongue rates in regions including the cerebellum, middle temporal gyrus, inferior frontal gyrus (pars triangulars), and superior frontal gyrus (medial part). See Table 2 and Figure 3B for details of significant contrasts and their associated coefficients. Note that the regions reported for the age and function common effect show some degree of dissimilarity relative to the regions reported previously in the pre-commonality analysis. The reasons for this are twofold. First, only regions that expressed commonality in age *and* function and survived stringent thresholding are reported for the commonality analyses; and second, clusters containing fewer than 150 voxels were not reported in the pre-commonality analyses for the sake of brevity but are reported here due to overall smaller effects. Please refer to Figure 3 for conceptualisation of significant contrasts against the dependent variable, three-dimensional visualisation of results, and the associated region of interest analysis.

Table 2. Coordinates (MNI), size, *t,* and *p* values of significant commonality effects and their respective brain regions.

Contrast	Cluster size (k)	Cluster	*t*	*p*	x	y	z
Age.Function	67	R. Cerebellum Crus VI	1.897	.009	32	-56	-24
	55	L. Middle Temporal Gyrus	1.921	.009	-56	-4	-20
	40	L. Inferior Frontal Gyrus - pars	1.848	.010	-50	16	0

		triangulars					
	45	R. Superior Frontal Gyrus - Medial Part	1.944	.009	10	64	4
Age.Function.VO_2peak	27	L. Lingual Gyrus	-1.842	.002	-6	-64	0
Age.Structure	9	R. Middle Temporal Pole	2.196	.001	46	12	-38
Age.CBF	46	L. Cerebellum Crus I	1.810	.025	-24	-70	-28
	12	L. Cerebellum Crus IX	2.077	.015	-18	-42	-48
	10	R. Cerebellum Crus IX	2.047	.014	8	-50	-44

A unique effect of age was also present but not reported in the above table because an isolated age effect is uninformative and was not hypothesised. Note: R = Right. L = Left. CBF = Cerebral blood flow.

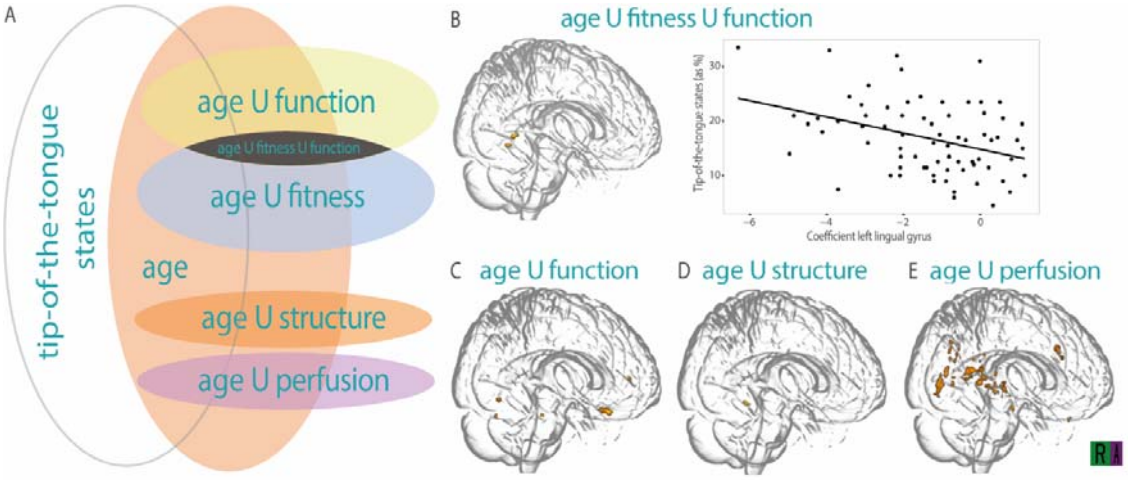

Figure 3. A: Venn diagram depicting the relationships, as established by the commonality analysis, where, for example, the intersection tip-of-the-tongue states on the one hand with age and function on the other hand, depicts that the commonality between age and functions explains a significant portion of the variance in tip-of-the-tongue states. The size of the ellipses is only illustrative, it is not indicative of the size of an effect. Our key finding is the common effect of age, fitness and function (i.e., black intersection) accounted for a significant portion of variance in tip-of-the-tongue states (which is depicted further in Panel B). B. Three-dimensional render depicting the age, function, and fitness common effect including a scatter presenting the relationship between this contrast and its intensity in the region of interest analysis (lingual gyrus). C. Age by function common effect. D: Age by structure common effect. Age and structure common effect did not converge with function or fitness. A significant age by fitness common effect was observed but is not visualised here. Heatmaps are indicative of *t* values, with brighter colours representing stronger effects (*t* range 1.80 – 3.00). U = unison (commonality).

Interestingly, and key to the present research question, we also found commonalities between age, function, and $\dot{V}O_2$peak in explaining age-related tip-of-the-tongue variability. While these effects were not widespread, with the effect being localised to the left lingual gyrus, the finding was robust across multiple iterations of commonality modelling (see

Additional Models below). Building on age and function above, the concomitant effect of age, function, and $\dot{V}O_2$peak suggests that age-related functional recruitment of processing tip-of-the-tongue states is linked to differences in cardiorespiratory fitness. It is worth noting, however, function did not produce a shared effect with brain structure or perfusion, suggesting that the functional effects are over and above any differences in atrophy and/or perfusion.

Further, a shared effect of age and structure in the right middle temporal pole also emerged as significant in explaining ageing tip-of-the-tongue states, which suggests a link between age-related atrophy and age-related increases in tip-of-the-tongue rates. Finally, a shared effect of age and perfusion emerged as significant in explaining ageing tip-of-the-tongue states, implying a link between age-related vascular changes and age-related increases in tip-of-the-tongue rates. The distinct effects of brain structure, perfusion, and function suggest that the mechanisms by which these three indices of brain health contribute to tip-of-the-tongue in healthy ageing are unrelated.

In addition to the core model of interest outlined above, we ran additional analyses which included the variables education and vocabulary size. We considered these variables as indicators of crystallised intelligence and found a moderate-to-strong positive correlation between them (r = .638, p <.001). However, neither education nor vocabulary were significant—uniquely or jointly with other predictors—in explaining variance in tip-of-the-tongue occurrences.

Discussion

Here, for the first time, we bring together multiple brain-health and lifestyle factors to explain the differences of word-finding difficulties and more broadly cognitive decline in older adults. Commonality analyses revealed that functional recruitment of language networks associated with resolving tip-of-the-tongue states differed with age. Crucially, functional activation of these language networks was also determined by individuals' fitness levels. Finally, age-associated loss of brain structure (or atrophy) and age-related cerebrovascular differences in brain regions other than those showing functional differences accounted for the variance in tip-of-the-tongue state incidence.

Our findings can be interpreted in the light of key neurocognitive models of ageing centring around mechanisms of maintenance, compensation or reserve. We did not observe evidence of fitness contributing to maintenance: fitness levels did not determine grey matter preservation or cerebrovascular components, at least not in a way that predicted tip-of-the-tongue behaviour. We did, however, see evidence for mechanisms of compensation and/or reserve at play: there was a shared effect of functional recruitment, cardiorespiratory fitness,

and age predicting tip-of-the-tongue incidence. The unison of these factors in explaining variance in age-associated tip-of-the-tongue states suggests that fitness modifies the functional recruitment of word finding areas in the brain. It is difficult, however, to distinguish between mechanisms of compensation and reserve based on observations solely for one specific task. This is because mechanisms of reserve imply that our findings could also be observed for other aspects of cognition in future research, since mechanisms of reserve are assumed to manifest like trait-like effects (Cabeza et al. 2018). Mechanisms of compensation on the other hand are assumed to depend on the nature and degree to which cognitive demand is challenged. While previous studies have found evidence of fitness levels contributing to altered brain function (Douw et al., 2014; Prakash et al., 2011; Voss et al., 2016; Wong et al., 2015), these studies did not make explicit and robust links with cognitive performance levels. Future studies could use our present holistic approach integrating over different brain-health measures to examine other domains of cognition. As a final note, while the processes underlying compensation and reserve have traditionally been purported to be distinct, it is worth considering that these mechanisms may interact with each other (Cabeza et al., 2018). Our findings may imply that highly fit older individuals show differential brain activity compared to low fitness individuals because fitness offers reserve, allowing fitter individuals to implement more effective compensatory processes.

Experiencing tip-of-the-tongue states was associated with clusters within well-established word retrieval and language production networks, including the middle temporal and inferior frontal gyri (Huijbers et al., 2017; Shafto et al., 2010). These findings extend existing literature by showing adjustments according to individual differences in cardiorespiratory fitness, with the implication that in older adults, differential age-dependent recruitment was associated with variation in fitness levels. Functional activity, indexed by the BOLD signal, represents—in response to neuronal metabolic demand—fluctuations in deoxyhaemoglobin effected by regional changes in brain blood flow, volume and blood oxygenation. The mechanism by which these changes are coupled to underlying neuronal activity is known as neurovascular coupling, and the vascular system of fitter (and often, younger) individuals can replenish depleted neuronal resources more effectively relative to their less fit counterparts. Further, ageing brings about deterioration of these processes while simultaneously being associated with variance in tip-of-the-tongue states; a strong age-related deterioration of $\dot{V}O_2$peak is also typically observed. The present findings provide a brain-based explanation for the bivariate relationship observed in previous research between fitness and tip-of-the-tongue states (Segaert et al. 2018), outlining a potential pathway for how cardiorespiratory fitness might downstream into cognitive processes.

Our findings also build upon previous work which has found that atrophy (Shafto et al., 2007) was associated with age-related tip-of-the-tongue rates. Specifically, age-related increases in tip-of-the-tongue states have been associated with atrophy in the left insula, a region implicated in phonological production (Shafto et al., 2010). Similarly, in the current contribution, we report commonality between age and brain structure, albeit not in the insula region but in the right middle temporal pole. Further to functional and structural brain effects, we also observed that individual differences in cerebral perfusion, as a function of age, explained variation in tip-of-the-tongue states. The literature on the association between age-related changes in cerebral blood flow, cognition, and wider brain health is unresolved (for a review on perfusion and cognition in ageing, see Ogoh, 2017): while some accounts report perfusion maintenance in old age supporting brain function and cognition (De Vis et al., 2018; Wu et al., 2023), others have shown mixed results (Espeland et al., 2018; Leeuwis et al., 2018; Poels et al., 2008). With our data, we bring further clarity by extending the literature to show that cerebral blood flow is an important contributor to age-related tip-of-the-tongue states.

We focused on tip-of-the-tongue variability as an example of cognitive decline in older age. Failure to produce known words is a common human experience; it often leads to frustration and disrupts the natural flow of verbal communication. While it is not unique to ageing, healthy older adults tend to display more tip-of-the-tongue occurrences relative to their younger counterparts. This age-related pattern cannot be explained by memory deficits alone—indeed, semantic and phonological features of the intended yet elusive word can often still be articulated (Brown, 1991; Brown & McNeill, 1966; Miozzo & Caramazza, 1997). Moreover, previous work has shown the independence of memory and word retrieval/production systems (Salthouse & Mandell, 2013). We demonstrate that, for the first time, tip-of-the-tongue variability in ageing can be explained by variability in brain function, structure, and perfusion in addition to fitness, in one mechanistic explanation, and provide a theoretical and methodological step forward in bringing together seemingly disparate streams of data to profile a recognisable, everyday age-related irritation. Our approach could be applied to other aspects of cognitive function which are relevant to characterising age-related cognitive decline.

There are several other potential extensions to the present work. Firstly, while the study included participants aged 60 to 81, 84% of participants were aged 60-69, 13% were aged 70-79, and only 3% were aged 80 or above. While this inequality in age distribution is understandable given the stringent nature of our inclusion criteria, it nonetheless means that the current analysis perhaps lacked sensitivity at the highest bands of age in our sample, and we were unable to test whether the reported effects differed across older age groups.

We do, however, contend that chronological age is only one component that determines cognitive ageing; here, a much wider perspective on how the effect of ageing is potentially modified by lifestyle factors, and how this then downstreams into cognition, is provided. Nevertheless, sampling more widely in the future would be an improvement on the current work. Additionally, a more comprehensive understanding of cerebral perfusion could be achieved by incorporating arterial transit time, i.e., the time it takes blood to travel from an arterial input to a brain region, to supplement the standard cerebral blood flow measure (Feron et al., 2023). The inclusion of arterial transit time may highlight potential commonality with functional BOLD signal (e.g., if blood takes longer to reach an 'activated' area due to a prolonged arterial transit time, it may delay the onset of, and therefore distort, the BOLD signal response). In addition, education—which is widely thought to be a proxy for cognitive reserve—was modelled as a covariate of no interest in the current analysis because of a suboptimal method of recording the education data (self-reported categorical data with low variability). Our lack of effect with education does not suggest that education is an unimportant variable in the characterisation of cognitive decline, instead, we posit that better, more sensitive measures of education and crystallised intelligence are needed. Lastly, the data presented in this work are cross-sectional in nature. An interventional design, with repeated assessment of neurocognitive and cardiorespiratory function, could build on the current findings to provide an account of how these processes adjust in line with a change in lifestyle; for example, through increased physical activity. We believe that the work set out in the current contribution provides a sound theoretical basis and analytical framework to motivate future interventional designs.

In sum, we report unique and shared effects of multi-modal data to offer a useful framework that helps the cognitive ageing field move away from siloed approaches. The current contribution is the first of its kind to examine a widespread and recognisable feature of language processing with a multi-domain design, showing how brain function, structure and perfusion contribute to cognitive performance levels in older age in concordance with lifestyle factors such as fitness.

Methods

Participants

The sample comprised 73 (36 female, 37 male) community-dwelling, right-handed, healthy older adults aged 60-81 (M = 65.51, SD = 4.94). Participants were recruited as part of the wider Fitness, Ageing, and Bilingualism (FAB) project (www.fab-study.com) that was publicly preregistered on OSF (https://osf.io/d7aw2/). Neuroimaging data were collected in a single session; a cardiorespiratory fitness measure was performed on a different day (on average 9 days after the neuroimaging data). Data and stimulus materials as relevant to the present report can be found here: https://osf.io/d7aw2/files/osfstorage.

Participants underwent physical and cognitive screening which included a 12-lead resting electrocardiogram (ECG), blood pressure measures at rest, and the Montreal Cognitive Assessment (MoCA, Nasreddine et al., 2005). Participants were excluded if they presented with an abnormal ECG trace, were hypertensive, and/or scored ≤23 on the MoCA (Carson, Leach, & Murphy, 2018). We only included participants who reported to partaking in less than 150 minutes of exercise per week, did not suffer from a severe health condition (e.g., cancer, dementia, cardiorespiratory disease, etc.), and were non-smokers. All participants provided informed consent and were compensated £10.00 (GBP) per hour of participation. All were British-English monolinguals with no speech or language disorders. The research was conducted at the Centre for Human Brain Health and School of Sports, Exercise, and Rehabilitation Sciences, both at the University of Birmingham, UK. The study was granted institutional ethics approval (University of Birmingham, ERN 20_1107) and complied with the Declaration of Helsinki.

Tip-of-the-tongue states as measured by a definition task

Participants completed a task whereby definitions were presented in text format alongside three response options: (1) Know, (2) Don't Know, and (3) Tip-of-the-tongue (TOT). Respondents were instructed to select *Know* if they knew the word to which the definition was referring, *Don't Know* if they did not know, and *TOT* if they had a tip-of-tongue experience. The proportion of tip-of-the tongue responses was calculated by dividing the number of true tip-of-the-tongue states (indication and verification of a TOT state, see below) by the total number of trials observed. See Table 3 for example stimuli and Figure 4 for a task schematic.

Table 3.

Examples of definitions and their respective target words

Definition	Correct Answer	Noun Class
The termination of the existence of a particular kind of organism or species	Extinction	Common
A word borrowed from German that means the “spirit of the times”	Zeitgeist	Common
The boy king of Egypt whose tomb was discovered largely intact in 1922	Tutankhamun	Proper

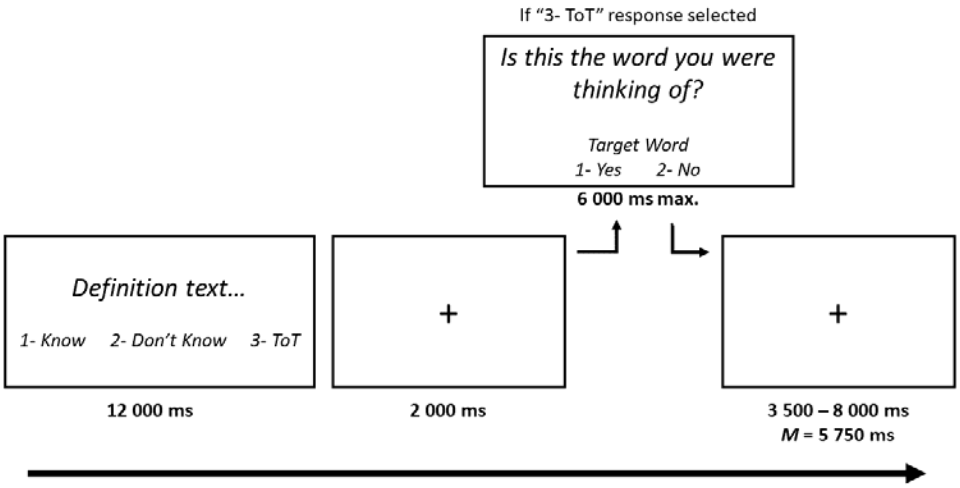

Figure 4. Schematic of the tip-of-the-tongue task. Trial lengths varied depending on the volume of tip-of-the-tongue responses (which triggered an additional verification slide that was not included for Know or Don’t Know responses). TOT = tip-of-the-tongue.

A true TOT was recorded only when participants indicated they were experiencing a tip-of-the-tongue state *and* pressed Yes when asked “Is this the word you were thinking of?” in a subsequent verification slide (where participants pressed No in response to the verification slide, these trials were considered in the same manner as Don’t Know responses). The definition texts were presented for a fixed duration of 12000 ms which was followed by a 2000 ms ISI and, in the case of TOT responses, verification slides were presented for a maximum of 6000 ms (or sooner with button press). A jittered ITI was presented for an average of 5750 ms (range 3500 – 8000 ms; 500 ms increments). A total of 200 unique definitions were presented across four scanning blocks (50 per block); correct answers (targets) pertaining to definitions were arranged so that the number of proper and common nouns, syllable, phoneme, and letter count, as well as word frequency were

counterbalanced across the four experimental blocks. The task was written in PsychoPy (v2021.1.4) and text was presented in white Open Sans font on a grey (normalised RGB 0.5, 0.5, 0.5) background projected onto a screen using a ProPixx visual projector system (1440 Hz refresh rate) and viewed by a mirror-system attached to the MRI headcoil. An MRI-compatible button box was used to register Know, Don't Know, and TOT responses. Before entering the scanner, participants performed a practice run of the TOT task with 12 definitions not included in the experimental stimuli—during this practice phase, an explanation of TOT states was provided to ensure participants understood the task. There was no limit on practice; participants could repeat the practice task as many times as they wished. The set-up and parameters of the out-of-scanner practice task was identical to the in-scanner experimental task.

Behaviourally, from 200 stimuli presented across four fMRI runs, an average of 59.94% (SD = 13.52) of responses were recorded as Know, 23.19% as Don't Know (SD = 10.98), and 16.87% (SD = 6.62) as TOT.

Cardiorespiratory Fitness

Participants completed an incremental exercise test on a treadmill (Pulsar 3p, H/P/Cosmos, Germany). Respiratory gases ($\dot{V}O_2$; oxygen consumption, $\dot{V}CO2$; carbon dioxide production) were recorded continuously using a facemask (7450 V2, Hans Rudolph, USA) and metabolic cart (JAEGER Vyntus CPX, Vyaire, USA), as was heart rate and rhythm using a 12-lead ECG (Cardiosoft, Vyaire, USA). Participants warmed up on the treadmill before completing 4-min walking stages with a 1-min rest period between each stage. Treadmill speed started and remained at 3.8 km/h until either all elevation stages were completed (7 possible stages: 4, 7, 10, 13, 16, 19, and 20%) or individual lactate threshold was reached. Finger-prick blood lactate was measured during each rest period (Biosen C-Line, EKF Diagnostics, United Kingdom). If all elevation stages were completed, 4-min stages continued with speed increasing 0.5 km/h per stage until lactate threshold was reached or until volitional exhaustion. If lactate threshold was reached, participants immediately began 1-min stages where just the speed increased 0.5 km/h per stage until volitional exhaustion (rest periods were removed).

Participants were asked to exercise to volitional exhaustion unless halted by the researcher due to ECG abnormalities, injury, or the presence of a plateau in heart rate or $\dot{V}O_2$. Cardiorespiratory fitness was measured as peak oxygen consumption ($\dot{V}O_2$peak) recorded during the treadmill test, determined as the mean of the two highest 30 s $\dot{V}O_2$ intervals recorded. For participants who only completed a sub-maximal test (N = 8),

$\dot{V}O_2$peak was predicted using sub-maximal $\dot{V}O_2$ and heart rate data acquired from three of the first possible six stages using a linear regression where y = HRage-pred (age-predicted maximal HR, 220-age) (for more information, see Feron et al. 2023).

Neuroimaging data acquisition and analyses

All neuroimaging data were acquired using a 3-T Siemens PRISMA system with a 32-channel head-coil at the Centre for Human Brain Health, University of Birmingham, UK. The scan sequence comprised T1-weighted anatomical, TOT task-based fMRI, and pseudo-continuous arterial spin labelling (pcASL) scans. The total session lasted approximately 150 minutes (with ~100 minutes in-scanner time).

Brain structure. A T1-weighted 3D-structural MRI (GRAPPA) was acquired with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 2.01 ms, inversion time (TI) = 880 ms, flip angle = 8 deg, FOV = 256 x 256 x 208 mm, voxel dimension (resolution) = 1 mm isotropic, GRAPPA factor = 2; with a total acquisition time of 4 min and 54 s. Brain extraction was initially performed using FSL's brain extraction tool (BET v2.1) but the standard Robust method performed poorly. Therefore, each participant's anatomical image was manually extracted using the bias field and neck cleanup utility within FSL-BET (see Popescu et al., 2012); fractional intensity threshold, threshold gradient, and centre of gravity values were manually adjusted (where necessary) for optimal results. Brain-extracted images were then preprocessed with a mixture of tools found within the standard FSL-VBM and FSL-ANAT pipelines. First, all images were segmented into grey matter, white matter, and CSF, while also correcting for spatial intensity variations (bias field or RF inhomogeneities), using FMRIB's Automated Segmentation Tool (FAST). Grey matter images were then non-linearly registered to standard space using FMRIB's Nonlinear Image Registration Tool (FNIRT).

Cerebral Perfusion. To measure CBF, a pcASL sequence with 3D GRASE readout (Wang et al., 2013) was used, see also Acknowledgements. ASL imaging parameters were: echo time (TE) = 30.56 ms, repetition time (TR) = 4100 ms, in-plane resolution = 3.5 mm^2, slice thickness = 3.5 mm, transversal slices = 32, field of view (FOV) = 224 mm, labelling duration = 1508 ms, no background suppression or vascular crushing, and post-label delays (PLDs) = 200, 975, 1425, 1850, 2025, 2150, 2250, and 2300 ms. Four volumes of data were acquired for PLDs of 200 – 2250 ms and 12 volumes for 2300 ms. PLD times and number of volumes acquired were optimised according to Woods, Chappell, and Okell (2019). Slices were positioned axially from the motor cortex and angled anterior-posterior in line with the participant's anterior-posterior commissure (ACPC). A base equilibrium, M_0, scan was

acquired using these same parameters with the PLD set to 2000 ms and no inversion pulses. Acquisition time was ~17 minutes. The previously described T1-weighted anatomical images were used for differentiation and segmentation of grey and white matter so that resting CBF in only grey matter could be assessed.

ASL data were processed using the Oxford ASL toolbox (https://oxasl.readthedocs.io/en/latest/) which uses the FSL FABBER ASL package and Bayesian Inference to invert the kinetic model for ASL MRI (BASIL) to compute CBF and ATT maps (Chappell et al., 2008; Groves et al., 2009; Woolrich et al., 2006). Parameters input to the kinetic models to estimate CBF and ATT were: bolus duration = 1.508 s, tissue T1 = 1.3□s, arterial blood T1 = 1.65□s, labelling efficiency = 0.85, inversion times = 1708, 24838, 29338, 33588, 35338, 36588, 37588, and 38088 ms; all other input parameters were kept with default settings appropriate to pcASL acquisition. Partial volume error correction and adaptive spatial smoothing of the perfusion maps was performed using default settings in oxford_asl (Chappell et al., 2011; Groves et al., 2009).

Participants with abnormal post-label delay maps, often caused by motion but also due to incidental findings such that perfusion in part of the brain could not be detected, were excluded (N = 6). Grey matter masks were thresholded to ensure only voxels containing primarily grey matter were included. Areas within masks containing incorrect assignment to grey matter, primarily around the eyes and nasal cavity, were manually removed (N = 7). Global grey matter CBF was then calculated for each subject, correcting for individual and regional differences in ATT. Per-participant ATT measures were calculated but are less common in MRI perfusion measures (as often only one PLD is used) and therefore only CBF measures were used in this study with the ATT measures the subject of another paper (Feron et al. 2023).

Brain function. Four fMRI blocks (50 definitions per block) were run with an echo-planar imaging sequence with the following parameters: TR = 1500 ms, TE = 35 ms, slice thickness = 2.5 mm (2.5 mm isotropic voxel size), FOV = 210 mm, flip angle = 71 deg, phase encoding direction = A >> P, and interleaved slices. The total number of volumes per run varied according to the number of tip-of-the-tongue states reported; typically, ~610 volumes were collected per run (~16 min/run).

Both individual- and group-level data were processed using FEAT (fMRI Expert Analysis Tool) in FMRIB's Software Library (FSL, www.fmrib.ox.ac.uk/fsl) v6.0.1. Registration to the high-resolution T1-weighted structural (BBR [Boundary-Based Registration, Greve & Fischl, 2009]) and standard space images (MNI152 T1 2mm; 12 DOF transformation) was performed using FLIRT. Registration from high-res structural to

standard space was then further refined using FNIRT nonlinear registration. After registration, the following pre-statistics processing was applied: motion correction using MCFLIRT (Jenkinson, 2002), slice-timing correction (interleaved) using Fourier-space time-series phase-shifting, spatial smoothing using a Gaussian kernel of FWHM 5 mm, grand-mean intensity normalisation of the entire 4D dataset by a single multiplicative factor, highpass temporal filtering (Gaussian-weighted least squares straight line fitting, with sigma = 50.00 s). The time-series were analysed using FMRIB's Improved Linear Model tool with local autocorrelation correction (Woolrich et al., 2001) and Z (Gaussianised T/F) statistics images were thresholded non-parametrically using clusters determined by Z>3.1 and a corrected cluster significance threshold of p = .05. Whole-brain functional univariate analyses were computed within the general linear model using a multi-level mixed-effects design. Each fMRI run was modelled separately at the single-participant level. Trial-by-trial modelling commenced at trial onset and concluded at participant button press within only the definition presentation phase of the task. Participant responses, and therefore statistical modelling, were not captured once definitions disappeared from screen (BOLD signal during ISI/TOT verification slide was not modelled). Trials where participants failed to make a response were discarded. Each condition of interest or exploratory variable (TOT, Know, Don't Know) was convolved using a double-gamma hemodynamic response function. A second-level analysis combined first-level contrast estimates per participant using a fixed-effects model, and higher-level activation (third-level analysis) was computed using a mixed-effects model using FSL's FLAME (FMRIB's Local Analysis of Mixed Effects) tool.

Commonality Analysis

To explore the unique and shared contribution of TOT-related functional activity, grey matter density, cerebral blood flow (CBF), cardiorespiratory fitness ($\dot{V}O_2$peak) and age on behavioural TOT rates, we conducted a commonality analysis (Kraha et al., 2012; Nimon et al., 2008). Commonality analysis partitions the variance accounted for by all predictors in multiple linear regression into variance unique to each predictor and common variance shared between each possible combination of predictors. As such, unique effects specify the (orthogonal) variance accounted for by one predictor above and beyond that accounted for by other factors in the model, while common effects show the combined variance shared between correlated predictors. Coefficients of common effects can show how much variance is accounted for in the outcome variable mutually by two or more correlated predictors. For a more comprehensive account of subjecting neuroimaging and behavioural data to commonality analysis, please refer to Wu et al. (2023). The commonality toolbox used in the present analysis is available at https://github.com/kamentsvetanov/CommonalityAnalysis.

Significant clusters related to effects of interest (as outlined above) were reported, as identified with nonparametric testing using 1000 permutations and threshold-free cluster enhancement (TFCE) with significance level of a = .05 (Smith & Nichols, 2009).

Sex differences were not of primary interest in the current contribution but are controlled for because they may covary with multiple components of our data set, including total brain volume (which affects grey matter quantification) and cardiorespiratory fitness levels (males typically show higher $V\square O_2$ scores). Sex was included in the modelling as a binary covariate of no interest. Head motion has been shown to lead to spurious outcomes in functional neuroimaging data (e.g., Power et al., 2012) and has been linked with out-of-scanner demographic and lifestyle factors such as age (Madan, 2018) and BMI (Beyer et al., 2021), which in turn correlate with fitness. To control for this, head motion was included as a covariate of no interest in the modelling. Head motion data were derived from the TOT-fMRI task where mean displacement (in mm) was calculated as the relative movement from the middle volume per run, and then averaged across runs to compute overall head motion. Recall, however, that the initial pre-commonality fMRI analysis was already motion corrected as part of the standard pre-processing of functional MRI data.

In addition to the primary model, a further model was run where the following variables were included as covariates: education and vocabulary size (depicted in Figure 1 is the primary model with initial covariates, as well as the additional model with two added covariates listed between brackets). Education data were captured as part of the initial screening procedure and vocabulary was captured via an online task where participants were required to select the correct synonym or antonym of a target word. Education was categorised according to the British (English) education system: “Compulsory” = Schooling completed up to and including the age of 16 (N = 21); “College/FE” = Post-16 education including A-Levels and Further Education (N = 25); “Undergraduate” = Undergraduate qualification at university level (N = 14); “Postgraduate” = Postgraduate qualification at university level (N = 13). As education has widespread influences in linguistic and non-linguistic cognitive function (Zahodne, Stern, & Manly, 2015), is a purported component of cognitive reserve (Tucker & Stern, 2011), and is associated with cardiovascular health in ageing (Schultz et al., 2018), education was included in the modelling.

Acknowledgements

This work was funded by the Norwegian Research Council (FRIPRO 300030). We thank Sue Sandys for help with creating the tip-of-the-tongue stimulus lists. We also thank Caroline Ratcliffe, Charnjit Sidhu, Dagmar Fraser, and Jan Zandhuis for structural and technical

support. Bethany Skinner, Consuelo Vidal Gran, Nicolas Hayston, Rupali Limachya, Amelie Grandjean, Aoife Marley, Shi Miao, and Samuel Thomas helped with data collection. Finally, we thank the wonderful and committed participants that contributed to the FAB project. KAT was supported by the Guarantors of Brain (G101149) and the Alzheimer's Society (Grant Number 602). We thank Danny Wang and the University of Southern California's Steven Neuroimaging and Informatics Institute for the provision of the pcASL sequence used in this work which was provided through a C2P agreement with The Regents of the University of California.

References

Abrams, L., & Davis, D. K. (2016). The Tip-of-the-Tongue phenomenon: Who, what, and why. In H. H. Wright (Eds.), *Cognition, Language and Aging* (pp. 13-53). John Benjamins Publishing Company.

Beyer, F., Zhang, R., Scholz, M., Wirkner, K., Loeffler, M., Stumvoll, M., ... & Witte, A. V. (2021). Higher BMI, but not obesity-related genetic polymorphisms, correlates with lower structural connectivity of the reward network in a population-based study. *International Journal of Obesity, 45*(3), 491-501.

Brown, A. S. (1991). The tip of the tongue experience: A review and evaluation. *Psychological Bulletin, 10,*204-223.

Brown, R., & McNeill, D. (1966). The "tip of the tongue" phenomenon. *Journal of Verbal Learning & Verbal Behavior, 5*(4), 325–337. https://doi.org/10.1016/S0022-5371(66)80040-3

Burke, D. M., MacKay, D. G., Worthley, J. S., & Wade, E. (1991). On the tip of the tongue: What causes word finding failures in young and older adults?. *Journal of Memory and Language, 30(*5), 542-579.

Cabeza, R., Albert, M., Belleville, S., Craik, F., Duarte, A., Grady, C., ... & Rajah, M. N. (2018). Cognitive neuroscience of healthy aging: Maintenance, reserve, and compensation. *Nature Reviews. Neuroscience*, *19*(11), 701.

Carson, N., Leach, L., & Murphy, K. J. (2018). A re-examination of Montreal Cognitive Assessment (MoCA) cutoff scores. *International Journal of Geriatric Psychiatry, 33*(2), 379-388.

Chappell, M. A., Groves, A. R., Whitcher, B., & Woolrich, M. W. (2008). Variational Bayesian inference for a nonlinear forward model. *IEEE Transactions on Signal Processing, 57*(1), 223-236.

Chappell, M. A., MacIntosh, B. J., Donahue, M. J., Jezzard, P., & Woolrich, M. W. (2011). Partial volume correction of multiple inversion time arterial spin labeling MRI data. *Magn Reson Med, 65*(4), 1173-1183.

Clouston, S. A., Brewster, P., Kuh, D., Richards, M., Cooper, R., Hardy, R., ... & Hofer, S. M. (2013). The dynamic relationship between physical function and cognition in longitudinal aging cohorts. *Epidemiologic Reviews, 35*(1), 33-50.

De Vis, J. B., Peng, S. L., Chen, X., Li, Y., Liu, P., Sur, S., ... & Lu, H. (2018). Arterial-spin-labeling (ASL) perfusion MRI predicts cognitive function in elderly

individuals: a 4-year longitudinal study. *Journal of Magnetic Resonance Imaging, 48*(2), 449-458.

Douw, L., Nieboer, D., van Dijk, B. W., Stam, C. J., & Twisk, J. W. (2014). A healthy brain in a healthy body: brain network correlates of physical and mental fitness. *PLoS One, 9*(2), e88202.

Espeland, M. A., Luchsinger, J. A., Neiberg, R. H., Carmichael, O., Laurienti, P. J., Pi-Sunyer, X., ... & Action for Health in Diabetes Brain Magnetic Resonance Imaging Research Group. (2018). Long term effect of intensive lifestyle intervention on cerebral blood flow. *Journal of the American Geriatrics Society, 66*(1), 120-126.

Galdo-Alvarez, S., Lindín, M., & Díaz, F. (2009). The effect of age on event-related potentials (ERP) associated with face naming and with the tip-of-the-tongue (TOT) state. *Biological Psychology, 81*(1), 14-23.

Giorgio, A., Santelli, L., Tomassini, V., Bosnell, R., Smith, S., De Stefano, N., & Johansen-Berg, H. (2010). Age-related changes in grey and white matter structure throughout adulthood. *Neuroimage, 51*(3), 943-951.

Greve, D. N., & Fischl, B. (2009). Accurate and robust brain image alignment using boundary-based registration. *Neuroimage, 48*(1), 63-72.

Groves, A. R., Chappell, M. A., & Woolrich, M. W. (2009). Combined spatial and non-spatial prior for inference on MRI time-series. *Neuroimage, 45*(3), 795-809.

Habeck, C., Razlighi, Q., Gazes, Y., Barulli, D., Steffener, J., & Stern, Y. (2017). Cognitive reserve and brain maintenance: orthogonal concepts in theory and practice. *Cerebral Cortex, 27*(8), 3962-3969.

Ho, A. J., Raji, C. A., Becker, J. T., Lopez, O. L., Kuller, L. H., Hua, X., ... & Thompson, P. M. (2011). The effects of physical activity, education, and body mass index on the aging brain. *Human Brain Mapping, 32*(9), 1371-1382.

Huijbers, W., Papp, K. V., LaPoint, M., Wigman, S. E., Dagley, A., Hedden, T., ... & Sperling, R. A. (2017). Age-related increases in tip-of-the-tongue are distinct from decreases in remembering names: a functional MRI study. *Cerebral Cortex, 27*(9), 4339-4349.

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage, 17*(2), 825-841.

Knights, E., Henson, R. N., Morcom, A. M., Mitchell, D. J., & Tsvetanov, A. K. (2023). Neural Evidence of Functional Compensation for Fluid Intelligence in Healthy Ageing. [Preprint]. https://doi.org/10.1101/2023.09.29.560099 .

Kraha, A., Turner, H., Nimon, K., Zientek, L. R., & Henson, R. K. (2012). Tools to support interpreting multiple regression in the face of multicollinearity. *Frontiers in Psychology, 3*, 44.

Leeuwis, A. E., Smith, L. A., Melbourne, A., Hughes, A. D., Richards, M., Prins, N. D., ... & Barkhof, F. (2018). Cerebral blood flow and cognitive functioning in a community-based, multi-ethnic cohort: the SABRE study. *Frontiers in Aging Neuroscience, 10*, 279.

Leidhin, C. N., McMorrow, J., Carey, D., Newman, L., Williamson, W., Fagan, A. J., ... & Knight, S. P. (2021). Age-related normative changes in cerebral perfusion: Data from The Irish Longitudinal Study on Ageing (TILDA). *Neuroimage, 229*, 117741.

Levelt, W. J. (2001). Spoken word production: A theory of lexical access. *Proceedings of the National Academy of Sciences, 98*(23), 13464-13471.

Madan, C. R. (2018). Age differences in head motion and estimates of cortical morphology. *PeerJ*, 6, e5176.

Miozzo, M., & Caramazza, A. (1997). Retrieval of lexical-syntactic features in tip-of-the-tongue states. *J Exp Psychol Learn Mem Cogn, 23*(6),1410-23. doi: 10.1037//0278-7393.23.6.1410.

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., ... & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society, 53*(4), 695-699.

Nimon, K., Lewis, M., Kane, R., & Haynes, R. M. (2008). An R package to compute commonality coefficients in the multiple regression case: An introduction to the package and a practical example. *Behavior Research Methods, 40*, 457-466.

Nimon, K. F., & Oswald, F. L. (2013). Understanding the results of multiple linear regression: Beyond standardized regression coefficients. *Organizational Research Methods, 16*(4), 650-674.

Njegovan, V., Man-Son-Hing, M., Mitchell, S. L., & Molnar, F. J. (2001). The hierarchy of functional loss associated with cognitive decline in older persons. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 56*(10), M638-M643.

Nyberg, L., Lövdén, M., Riklund, K., Lindenberger, U., & Bäckman, L. (2012). Memory aging and brain maintenance. *Trends in Cognitive Sciences, 16*(5), 292-305.

Ogoh, S. (2017). Relationship between cognitive function and regulation of cerebral blood flow. *The Journal of Physiological Sciences, 67*(3), 345-351.

Ossher, L., Flegal, K. E., & Lustig, C. (2013). Everyday memory errors in older adults. *Aging, Neuropsychology, and Cognition, 20*(2), 220-242.

Poels, M. M., Ikram, M. A., Vernooij, M. W., Krestin, G. P., Hofman, A., Messen, W. J., ... & Breteler, M. M. (2008). Total cerebral blood flow in relation to cognitive function: the Rotterdam Scan Study. *Journal of Cerebral Blood Flow & Metabolism, 28*(10), 1652-1655.

Popescu, V., Battaglini, M., Hoogstrate, W. S., Verfaillie, S. C., Sluimer, I. C., van Schijndel, R. A., ... & MAGNIMS Study Group. (2012). Optimizing parameter choice for FSL-Brain Extraction Tool (BET) on 3D T1 images in multiple sclerosis. *Neuroimage, 61*(4), 1484-1494.

Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage, 59*(3), 2142-2154.

Prakash, R. S., Voss, M. W., Erickson, K. I., Lewis, J. M., Chaddock, L., Malkowski, E., ... & Kramer, A. F. (2011). Cardiorespiratory fitness and attentional control in the aging brain. *Frontiers in Human Neuroscience, 4*, 229.

Resnik, K., Bradbury, D., Barnes, G. R., & Leff, A. P. (2014). Between thought and expression, a magnetoencephalography study of the “tip-of-the-tongue” phenomenon. *Journal of Cognitive Neuroscience, 26*(10), 2210-2223.

Reuter-Lorenz, P. A., & Cappell, K. A. (2008). Neurocognitive aging and the compensation hypothesis. *Current Directions in Psychological Science, 17*(3), 177-182.

Ruigrok, A. N., Salimi-Khorshidi, G., Lai, M. C., Baron-Cohen, S., Lombardo, M. V., Tait, R. J., & Suckling, J. (2014). A meta-analysis of sex differences in human brain structure. *Neuroscience & Biobehavioral Reviews, 39*, 34-50.

Salthouse, T. A., & Mandell, A. R. (2013). Do age-related increases in tip-of-the-tongue experiences signify episodic memory impairments?. *Psychological Science, 24*(12), 2489-2497.

Schultz, W. M., Kelli, H. M., Lisko, J. C., Varghese, T., Shen, J., Sandesara, P., ... & Sperling, L. S. (2018). Socioeconomic status and cardiovascular outcomes: challenges and interventions. *Circulation, 137*(20), 2166-2178.

Schwartz, B. L., & Frazier, L. D. (2005). Tip-of-the-tongue states and aging: Contrasting psycholinguistic and metacognitive perspectives. *The Journal of General Psychology*, 132(4), 377-391.

Segaert, K., Lucas, S. J., Burley, C. V., Segaert, P., Milner, A. E., Ryan, M., & Wheeldon, L. (2018). Higher physical fitness levels are associated with less language decline in healthy ageing. *Scientific Reports, 8*(1), 6715.

Shafto, M. A., Burke, D. M., Stamatakis, E. A., Tam, P. P., & Tyler, L. K. (2007). On the tip-of-the-tongue: neural correlates of increased word-finding failures in normal aging. *Journal of Cognitive Neuroscience, 19*(12), 2060-2070.

Shafto, M. A., Stamatakis, E. A., Tam, P. P., & Tyler, L. K. (2010). Word retrieval failures in old age: the relationship between structure and function. *Journal of Cognitive Neuroscience, 22*(7), 1530-1540.

Smith, S. M., & Nichols, T. E. (2009). Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage*, *44*(1), 83-98.

Tucker, A., & Stern, Y. (2011). Cognitive reserve in aging. *Current Alzheimer Research, 8*(4), 354-360.

Voss, M. W., Weng, T. B., Burzynska, A. Z., Wong, C. N., Cooke, G. E., Clark, R., ... & Kramer, A. F. (2016). Fitness, but not physical activity, is related to functional integrity of brain networks associated with aging. *Neuroimage, 131*, 113-125.

Wang, D. J., Alger, J. R., Qiao, J. X., Gunther, M., Pope, W. B., Saver, J. L., ... & UCLA Stroke Investigators. (2013). Multi-delay multi-parametric arterial spin-labeled perfusion MRI in acute ischemic stroke—comparison with dynamic susceptibility contrast enhanced perfusion imaging*. NeuroImage: Clinical, 3*, 1-7.

Whalley, L. J., Deary, I. J., Appleton, C. L., & Starr, J. M. (2004). Cognitive reserve and the neurobiology of cognitive aging. *Ageing Research Reviews, 3*(4), 369-382.

Wong, C. N., Chaddock-Heyman, L., Voss, M. W., Burzynska, A. Z., Basak, C., Erickson, K. I., ... & Kramer, A. F. (2015). Brain activation during dual-task processing is associated with cardiorespiratory fitness and performance in older adults. *Frontiers in Aging Neuroscience, 7*, 154.

Woods, J. G., Chappell, M. A., & Okell, T. W. (2019). A general framework for optimizing arterial spin labeling MRI experiments. *Magnetic Resonance in Medicine*, *81*(4), 2474-2488.

Woolrich, M. W., Chiarelli, P., Gallichan, D., Perthen, J., & Liu, T. T. (2006). Bayesian inference of hemodynamic changes in functional arterial spin labeling data. *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine, 56*(4), 891-906.

Woolrich, M. W., Ripley, B. D., Brady, M., & Smith, S. M. (2001). Temporal autocorrelation in univariate linear modeling of FMRI data*. Neuroimage, 14*(6), 1370-1386.

World Health Organisation. (2022). *Ageing and health*. https://www.who.int/initiatives/decade-of-healthy-ageing.

Wu, S., Tyler, L. K., Henson, R. N., Rowe, J. B., & Tsvetanov, K. A. (2023). Cerebral blood flow predicts multiple demand network activity and fluid intelligence across the adult lifespan. *Neurobiology of Aging, 121*, 1-14.

Zahodne, L. B., Stern, Y., & Manly, J. J. (2015). Differing effects of education on cognitive decline in diverse elders with low versus high educational attainment. *Neuropsychology, 29*(4), 649–657. https://doi.org/10.1037/neu0000141