Multiple neural pathways to successful visual short-term memory across the adult lifespan

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Abstract

Cognitive task performance can be supported through multiple neural pathways, a concept referred to as brain degeneracy. We used a novel approach to consider brain degeneracy during a visual short-term memory task (VSTM) across the adult lifespan in the Cam-CAN study (n = 113, 23-87 years old). Our main goal was to identify subgroups of participants whose VSTM performance was characterized by distinct brain activation patterns. First, we identified seven brain modules that responded similarly to the VSTM task and resembled previously identified functional networks (adjusted mutual information [aMI] = 0.45). Subsequently, latent profile analysis revealed four distinct subgroups of participants. Each subgroup was characterized by different recruitment patterns of these brain modules, predominantly in the frontal control module (FCM), visual module (VM), and default mode module (DMM). Subgroups did not differ in demographics or task performance. However, associations between brain activity and performance varied across subgroups, particularly in the FCM, suggesting that individuals may use different cognitive operations to perform the VSTM task. Further analyses revealed group differences in white matter integrity, mostly in the uncinate fasciculus, suggested that individual differences in structural brain properties may shape the different brain activation patterns. Altogether, our study contributes to our understanding of how multiple neural pathways could underlie cognitive performance.

Keywords: brain degeneracy; many-to-one mapping; fMRI; visual short-term memory; lifespan; white matter integrity

1 Introduction

Over the past decades, research sought to elucidate how the brain's functional and structural architecture gives rise to cognitive functioning (Finn et al., 2023; Genon et al., 2022; Park & Friston, 2013; Poldrack, 2006). Nevertheless, this relationship is far from straightforward. Not only do brain measures typically account for only a small portion of the variance in cognitive functioning (Hedden et al., 2016), but there are also several contradictory findings in terms of which neural mechanisms are adaptive or maladaptive for cognitive performance. For example, age-related increases in prefrontal activation have been linked to both superior and inferior performance in older adults (Grady, 2012; Nyberg et al., 2020). The complex nature of brain-cognition associations is further emphasized by previous studies showing that the extent to which brain structure or function relates to cognitive performance varies substantially across individuals (Lindenberger, 2014; Lövdén et al., 2018; Patel et al., 2022; Salami et al., 2018).

To gain a better understanding of how cognitive functions are supported throughout the lifespan, we may need to revisit the common assumption that most individuals exhibit similar patterns of neural activity to perform a certain cognitive task (one-to-one mapping) (Seghier & Price, 2018; Westlin et al., 2023). Conversely, brain degeneracy suggests that a specific task could be executed through multiple neural pathways (many-to-one mapping) (Edelman & Gally, 2001; Noppeney et al., 2004; Price & Friston, 2002). Degeneracy is evident in many neural systems, including those supporting cognitive functions (Kelso, 2012; Noppeney et al., 2004). In line with this, previous studies have identified subgroups of individuals showing unique neural activity patterns while performing the same task (Cerliani et al., 2017; Kherif et al., 2009; Seghier et al., 2008). Interestingly, this neural variability was associated with the use of different strategies to complete the task (Kherif et al., 2009; Noppeney et al., 2006), despite similar levels of task performance (Fischer-Baum et al., 2018; Noppeney et al., 2006). This illustrates how multiple neural routes can lead to successful cognitive performance. However, if we focus on similarities across individuals these possibilities are overlooked, emphasizing the need to understand brain degeneracy and what it might mean for how we study the associations between brain and cognition.

Building on the concept of many-to-one mapping, it has been suggested that secondary activation repertoires may be prompted when the primary circuit is unable to sustain successful task completion (Mason et al., 2015; Noppeney et al., 2004; Price & Friston, 2002). For instance, studies using transcranial magnetic stimulation showed that younger adults adapt to temporary functional lesions by recruiting alternative neural circuits (Lee et al., 2003; Pascual-Leone et al.,

2005). Furthermore, differential recruitment of brain regions during task performance has been related to functional recovery after acquired brain injury (Nudo, 2013). In the context of normal ageing, alterations in brain activity have been linked to the degradation of major white matter tracts (Burzynska et al., 2013; Lucas et al., 2018), and localized grey matter loss (Kalpouzos et al., 2012; Salami et al., 2012; Salami et al., 2014). Although this involves functional deterioration, older adults are able to compensate for impaired brain function by recruiting additional brain regions, particularly in the frontal lobes (Cabeza et al., 2002; Grady, 2012; Park & Reuter-Lorenz, 2009). In contrast, structural preservation in older individuals (i.e., brain maintenance; Nyberg et al., 2012) has been related to neural activation patterns more closely resembling those typically observed in younger adults (Cabeza et al., 2018; Nyberg et al., 2012). Together, these findings stress that it is important to consider interindividual variability in brain structure to understand why different neural systems may be recruited during task performance.

In the present study, we aimed to investigate brain degeneracy across the adult lifespan in the context of visual short-term memory (VSTM), using data from the Cam-CAN project (*n* = 122, 23-87 years old). VSTM is particularly interesting in the context of degeneracy, given that high performance can be achieved via different strategies (Ritakallio et al., 2024). VSTM refers to our ability to maintain visual information and is crucial for many other cognitive functions (Luck & Vogel, 2013; Pearson & Keogh, 2019). However, the precise neural mechanisms underlying successful VSTM performance are not fully understood, partially due to inconclusive findings in prior research that did not consider the possibility of different brain activation patterns (Pearson and Keogh, 2019). Our primary aim was therefore to identify subgroups of participants whose VSTM performance was characterized by distinct brain activation patterns. We first identified modules of brain regions that showed similar responses across participants during the VSTM task. Next, we applied latent profile analysis to identify sub-groups of participants that demonstrated differential recruitment patterns of the previously identified brain modules. To better understand the variability in brain activity during the VSTM task, we characterized the most significant differences in brain activity across subgroups.

Furthermore, we sought to elucidate factors contributing to the observed subgroup differences in brain activity patterns. Specifically, we investigated the extent to which these subgroups differed in demographic variables (i.e., age, sex, educational attainment) and task performance. We were particularly interested in the role of age, as this factor was previously related to both performance and neural correlates of the VSTM task (Lugtmeijer et al., 2023; Mitchell & Cusack, 2018; Morcom & Henson, 2018; Sander et al., 2012). For example, if age-related differences in brain function were the largest source of inter-individual variability in brain activation patterns

during the VSTM task, we expected to identify subgroups that differed in their age and task performance. Conversely, if age-invariant inter-individual differences were most prominent, we expected to see participant subgroups that were roughly age-matched. Additionally, we investigated whether structural brain characteristics, such as grey matter volumes and white matter integrity, would explain variations in brain activity among the subgroups, as reflected by subgroup differences in these measures.

Lastly, we assessed associations between brain activation profiles and task performance within each subgroup. For example, increased activity in brain module X might have been beneficial for performance for subgroup Y but hindered this for subgroup Z. Such unique associations would not only provide further evidence for the presence of different neural routes to facilitate successful VSTM performance, but also potentially suggest cognitive strategies that were used to succeed.

2 Methods

2.1 Participants

This study included data from 122 participants (59 female, 48.4%) who were aged 23–87 (mean age 53.9, SD = 18.1) from the healthy, population-derived cohort tested in Stage III of the Cam-CAN project (Shafto et al., 2014; Taylor et al., 2017).

A complete overview of the study procedures and inclusion criteria have been described previously (Shafto et al., 2014; Taylor et al., 2017). Briefly, in Stage I, participants engaged in home-based interviews where demographic information, cognitive measures, and other measures of health (e.g., mental and physical health) were collected. In Stage II, participants engaged in three testing sessions, including cognitive and behavioural assessments, structural MRI (e.g., T1-weighted imaging and diffusion-weighted imaging), functional MRI (e.g., resting-state), and MEG recordings. During Stage III, among other things, structural MRI (e.g., T1-weighted images) and task-related functional MRI (fMRI) data during a VSTM task were acquired. In this manuscript, we use the demographic information from Stage I, the diffusion-weighted images from Stage II, and the T1-weighted images and VSTM fMRI paradigm from Stage III. Participants were native English-speakers with normal or corrected-to-normal vision and hearing and had no neurological disorders. Additional exclusion criteria were history of drug or alcohol abuse, and poor hearing or vision.

The study was conducted in accordance with ethical approval obtained from the Cambridgeshire 2 (now East of England - Cambridge Central) Research Ethics Committee. All participants gave written informed consent prior to participation.

We excluded a total of 9 participants from our analyses due to poor VSTM task performance (*n* = 8) or data quality issues (*n* = 1*)*, leaving a final sample of 113 participants (see below for more details).

2.2 Data acquisition

2.2.1 Demographic information

Demographic information, including age, sex, and educational attainment, was acquired during home-based interviews during Stage I of the Cam-CAN project. Educational attainment in this study was based on the highest level of completed education (i.e., categorized in 1 = no education above the age of 16 years old; 2 = GCSEs or equivalent; 3 = A levels or equivalent; 4 = university levels or equivalent).

2.2.2 MRI data

MRI data was acquired on a 3T Siemens TIM Trio System scanner at the MRC Cognition Brain and Sciences Unit, Cambridge, UK. During each of three VSTM task runs, functional data were acquired using a multi-echo, T2*-weighted EPI sequence (TR = 2000 milliseconds, TE = 12 milliseconds, 25 milliseconds, 38 milliseconds, flip angle = 78 degrees, 32 axial slices of thickness of 3.7 mm with an interslice gap of 20%, FOV = 294mm × 294 mm, voxel-size = 3 mm × 3 mm × 3.48 mm). Each volume had 34 axial slices (acquired in descending order), slice thickness of 2.9 mm, with an interslice gap of 20%. The multiple echoes were combined by computing their average weighted by their estimated T2* contrast. The number of scans acquired varied per run, depending on reaction time, between 294 and 349.

A high-resolution 3D T1-weighted structural image was acquired using a Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence, with the following parameters: TR = 2250 ms; TE = 2.99 ms; TI = 900 ms; flip angle = 9 degrees; FOV = 256 × 240 × 192 mm; voxel size = 1 mm isotropic; GRAPPA acceleration factor = 2. This T1 image was missing for two of the participants in this sample, however for these participants T1 images were acquired during the scanning session that took place during Stage II of Cam-CAN, approximately 1-3 years earlier.

Diffusion-weighted images (DWIs) were acquired with a twice-refocused spin-echo sequence during Stage II of Cam-CAN. Thirty diffusion gradient directions were obtained for each of two

b-values: 1000 and 2000 s/mm2, plus three images acquired with a b-value of 0. These parameters were optimized for estimation of the diffusion kurtosis tensor and associated scalar metrics (Shafto et al., 2014). Other DWI parameters were TR = 9100, TE = 104 ms, FOV = 192 mm × 192 mm, voxel size 2 mm isotropic, 66 axial slices, with acquisition time 10 minutes and 2 seconds.

2.2.3 Visual short-term memory (VSTM) task

During fMRI scanning, participants performed a VSTM paradigm (see **Figure 1)**, based on Emrich et al. (2013). A detailed description of the task is provided in Lugtmeijer et al. (2023).

Briefly, three displays containing different coloured moving dots (red, yellow and blue) were presented sequentially on each trial. Each trial began with a grey fixation dot for 5 seconds. Subsequently, the fixation dot brightened for 2 seconds and was followed by the coloured dot displays. Each coloured dot display was shown for 500ms, with a 250ms black screen in between. As a manipulation of the number of items in memory, trials could contain one, two or three arrays of dots moving in a single direction (load 1, 2, and 3, respectively).

Participants were instructed to remember the direction of motion for dot displays in which all dots moved in a single direction, and to ignore any dot displays that rotated around the fixation location (the encoding phase). As three displays were shown in each trail, the memory load was manipulated by varying the number of rotating dots in relation to the number of moving dot displays. After the third coloured dot display, there was a blank display of 8 seconds (the maintenance phase), followed by a probe display. The probe display consisted of a coloured circle that indicated which of the three dot displays (red, yellow, or blue) the participant should recall. Participants had up to 5 seconds to adjust a pointer on the circle until it matched the direction of motion of the probed dot display (the response phase).

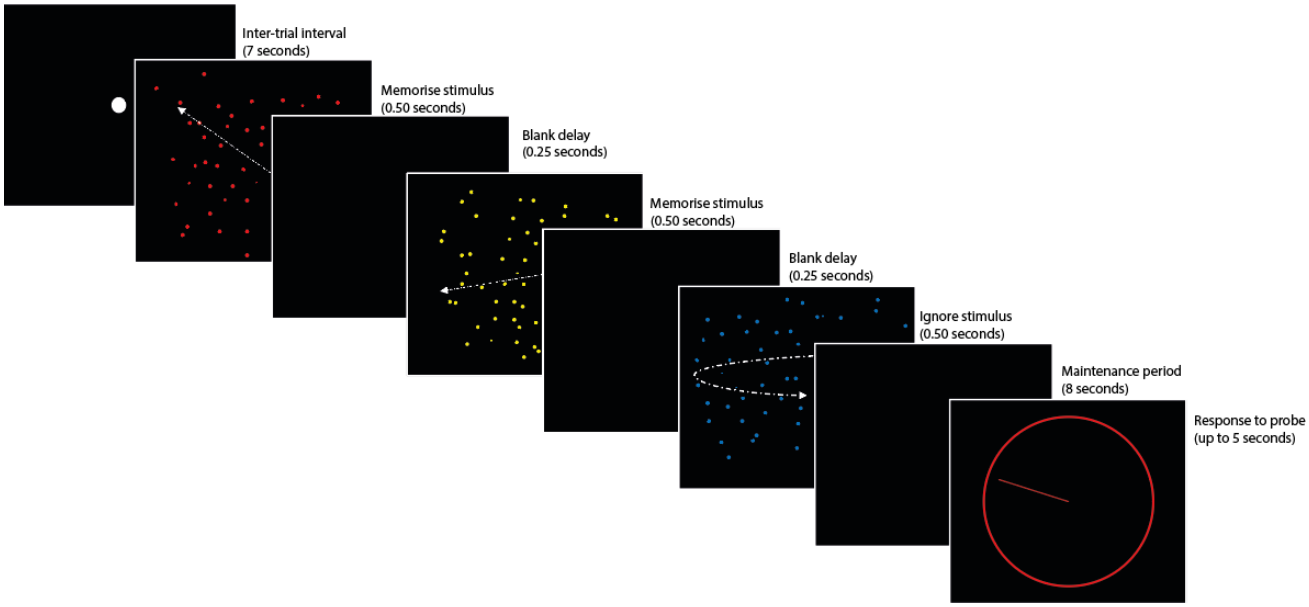


Figure 1: Adapted from Morcom and Henson (2018). An example of the VSTM task. Trials began with a fixation dot for 7 seconds. On each trial, three moving dot displays were then presented in red, yellow, and blue for 500 ms each (250 ms in between). After the last display, the screen was blank for an 8 second maintenance period and then a probe display was presented. A coloured circle indicated which dot display participants should recall (red, yellow, or blue). Participants had up to 5 seconds to adjust a pointer until its angle matched the motion direction of the probed display.

2.3 VSTM performance

Several factors can limit VSTM performance. For example, memory imprecision (e.g., uncertainty between 80 or 85 degrees), random guessing (e.g., when forgetting an item entirely), and reporting an incorrect item (mis-binding, e.g., reporting the angle of the red dots instead of the blue dots). To distinguish these different sources of error, we applied a three-component mixture model (Bays et al., 2009). A complete description of the application of the mixture model to the VSTM task is provided in previous work (Mitchell et al., 2018; Lugtmeijer et al., 2023).

For our subsequent analyses, we used the estimates of a memory item's precision (the inverse of the standard deviation in degrees) and the number of items (directions) that were stored in memory (K). Eight participants in our sample showed very poor performance for memory of a single item (>30 degrees deviation on average). This suggests that they may not have understood the task instructions and were therefore excluded from further analyses. Since there was a ceiling effect for the number of items in memory at load 1 (mean = 0.96, SD = 0.06) and to some extent at load 2 (mean = 1.76, SD = 0.24), we decided to focus on performance at load 3 (mean

229 = 2.40, SD = 0.46). The distribution of scores for the number of items in memory at each load is
230 shown in **Supplementary Figure 1**.

231 **2.4 MRI pre-processing and first level analyses**

232 All MRI data were pre-processed using SPM 12 (http://www.fil.ion.ucl.ac.uk/spm) and
233 "automatic analysis" software (Cusack et al., 2015). The T1 and T2 weighted structural images
234 were rigid body registered with a MNI template, bias corrected and segmented into six tissue
235 classes using the newer segment protocol in SPM 12 (Ashburner & Friston, 2005). Non-linear
236 transformation using DARTEL normalization was performed to match a grey matter template
237 created from the Cam-CAN stage III sample. The functional images were spatially realigned and
238 interpolated to correct for differences in acquisition times, and co-registered to the structural
239 image using rigid body transformations. Both grey matter volume images and functional images
240 were transformed to MNI space using the warps and affine transformation estimated from the
241 structural images. For grey matter volume images, this was done while preserving the total
242 amount of signal from each region in the images. The functional images were resliced to 3x3x3
243 mm voxels, while grey matter volume images were resliced to 1.5x1.5x1.5 mm voxels and both
244 were smoothed with an 8 mm full-width half-maximum (FWHM) Gaussian kernel. For the two
245 participants with missing T1-weighted scans, normalization and co-registration were performed
246 based on the T1 images collected during stage II of the Cam-CAN project. One participant was
247 excluded from further analyses due to data quality issues.

248 For each participant and voxel, we fit a general linear model (GLM) with three phases of each
249 trial per run: encoding, maintenance, and response. The encoding phase was modelled as an
250 epoch of 2 seconds starting from the beginning of the first dot display movement. The
251 maintenance phase was modelled as an epoch of 8 seconds (i.e., the duration of the blank
252 display that was shown after all probes were displayed). The response phase was modelled as
253 an epoch of the time between the probe onset and response. These three components were
254 each split into three regressors: one for each load. Six additional regressors were added per run,
255 representing the motion parameters estimated in the realignment stage. The means of each run
256 were also modelled separately. The main contrast of interest in this study was the difference
257 between the highest and the lowest memory load during the maintenance period (load 3 vs.
258 load 1). This contrast allows us to equate the amount of visual information that was presented
259 just before the maintenance period as well as the motor response that was required just after,
260 while maximizing the difference in memory load.

261

262 **2.5 Identifying modules with similar inter-individual variability**

263 To make the analyses more computationally efficient in later stages, we reduced the
264 dimensionality of the data by grouping voxels into a set of small regions of interest (ROI).
265 Specifically, we used the 748 (out of 840) regions from the Craddock atlas (2012) that had
266 sufficient coverage in our recent paper (Geerligs et al., 2015), allowing us to use the network
267 labels defined in our previous study. To select ROIs that might be involved in task-performance
268 in a subset of participants, we first extracted the average t-values for the contrast of interest
269 (i.e., load 3 vs. load 1 during the maintenance period) across all voxels in each ROI for each
270 participant. To further reduce the dimensionality of the data, we only included ROIs that showed
271 increased or reduced activation in load 3 versus load 1 in at least 10% of the participants at a
272 liberal significance threshold ($T > 1.96$, $p < 0.05$). This resulted in the final inclusion of 418 ROIs.

273 For each included ROI, we extracted the average beta-values. Subsequently, we calculated the
274 correlation values between ROIs for load 3 vs. load 1 across participants (i.e., ROI-by-ROI
275 correlation matrix). A high correlation coefficient between two ROIs suggests that these regions
276 show similar inter-individual variability in load-dependent modulation of the BOLD response,
277 and therefore may contribute to the same brain module.

278 In the next step, we used the Brain Connectivity Toolbox to identify groups of ROIs, or brain
279 modules, that showed similar brain activity patterns across participants (Rubinov & Sporns,
280 2010). Specifically, we applied consensus partitioning based on the Louvain modularity
281 algorithm (Bassett et al., 2013; Lancichinetti & Fortunato, 2012). The ROI-by-ROI correlation
282 matrix was used to create an initial partition of the ROIs into distinct modules with the Louvain
283 modularization algorithm (Blondel et al., 2008), and was further refined using an optimization
284 procedure (Sun et al., 2009). This partitioning procedure was repeated 500 times, and all the
285 repetitions were assembled into an ROI-by-ROI agreement matrix, where each number indicates
286 the proportion of repetitions in which a pair of ROIs were assigned to the same module. The
287 ROI-by-ROI agreement matrix was then used as an input for consensus partitioning, where a
288 permuted version of the agreement matrix was used for thresholding. This was repeated until
289 the algorithm converged into a matrix of ones and zeros, indicating that a single partition was
290 reached.

291 The complete partitioning procedure was performed for multiple values of the resolution
292 parameter γ, ranging from 1 to 1.5 with steps of 0.05. The γ parameter is a penalty term that
293 biases the size of the communities to be found. Smaller values of γ will result in larger modules,

while higher values will result in smaller modules. As an γ value of 1.5 already resulted in 49 modules, we did not explore a wider range of this parameter space.

Next, we selected the partition with the highest resemblance to a previously defined set of age-representative networks (Geerligs et al., 2015b), as measured with the adjusted mutual information (aMI), as our final set of brain modules. The optimum we identified was at γ = 1.25, resulting in 13 distinct modules (aMI = 0.45). However, as many modules consisted of only one ROI or a few ROIs, we only included modules with at least 15 ROIs in our analyses. This resulted in the exclusion of 6 brain modules, comprising of 28 ROIs in total. The final set of 7 brain modules was used for further analyses (see "Results").

Within each brain module and for each participant, we computed the average brain activity for load 3 vs. load 1. However, we observed strong correlations between the average brain activity values across all brain modules (ranging from r=0.39 to 0.77). This is consistent with prior research which demonstrated that overall network responsivity, rather than module-specific activation patterns, were related to age and task performance (Samu et al., 2017). To be able to look beyond this general factor in our subsequent analyses, we computed the residual activity within each brain module after regressing out the mean activity across the 418 ROIs. To be able to retain information about the engagement of each network during the task, the mean activity across all subjects was added back after computing the residuals. The extent to which the mean activity across these ROIs explained the variance within each brain module varied between 0.61-0.75, as indicated by the adjusted R^2 values.

2.6 Brain activity profiles

To identify latent subgroups of participants characterized by different patterns of brain activity, we applied latent profile analysis (LPA) using the Mclust package in R (Scrucca et al., 2016). Briefly, LPA is a data-driven Gaussian mixture modelling method to identify hidden subgroups in a population (Vermunt & Magidson, 2002). A Gaussian mixture model assumes a multivariate Gaussian distribution for each subgroup. Therefore, every observation (here, participant) will have a specific probability of belonging to a specific subgroup, as specified by a probability density function determined by the average, the variance, and the covariance of each of the subgroup distributions.

We applied LPA using both the residual activity in each brain module and the overall responsivity across all networks, specifying between 1 and 5 subgroups. This allowed us to look at module-specific variations in responsivity in addition to the overall responsivity across brain modules. We restricted the model space to models that do not allow for covariance between modules

327 within subgroups of participants (i.e., models with a spherical or diagonal distribution of the
328 within-group covariance matrix). This way, our model assumes that any correlations between
329 modules must be caused by participants with different brain activity profiles (similar to Lövdén
330 et al., 2018). The Bayesian Information Criterion (BIC), Integrated Completed Likelihood (ICL)
331 and bootstrapped Likelihood Ratio Test were used to select the most optimal model and class
332 solution (i.e., the number of subgroups).

333 **2.7 Structural brain characteristics**

334 To investigate subgroup differences in grey matter, we extracted grey matter volumes for each
335 of the 418 ROIs that were included in our main analysis and subsequently averaged the grey
336 matter volumes within each module. The two participants with the missing T1-scan at Stage III
337 were excluded from this analysis, resulting in a sample of 111 participants for the grey matter
338 data.

339 To investigate subgroup differences in white matter microstructure, we used the diffusion data
340 to estimate mean kurtosis. Mean kurtosis is influenced by changes in organelles, cell membranes
341 and the ratio of intracellular to extracellular water compartments (Falangola et al., 2008). It
342 provides a sensitive metric to determine how aging affects the complexity of white matter
343 microstructure, and typically decreases in late-life (Benitez et al., 2018).

344 Diffusion data were pre-processed and analysed as described in a previous paper (Geerligs et
345 al., 2018). Briefly, the data were co-registered, normalized to MNI space and smoothed with a
346 1-mm FWHM Gaussian kernel to reduce residual interpolation errors. Subsequently, we
347 calculated the average mean kurtosis values for 18 tract-based regions of interest defined by
348 the Johns Hopkins University white matter tractography atlas (Hua et al., 2008). These included
349 the uncinate fasciculus, superior longitudinal fasciculus, inferior fronto-occipital fasciculus,
350 anterior thalamic radiations, forceps minor, forceps major, cerebrospinal tract, the inferior
351 longitudinal fasciculus, ventral cingulate gyrus, and the dorsal cingulate gyrus. All tracts were
352 split into their left and right hemisphere sections, except for the forceps minor and forceps
353 major.

354 Participants with severe head motion during the DWI scan, as revealed by an automated striping
355 detection method on the diffusion data, were excluded (Neto Henriques and Correia, 2015). In
356 addition, for each tract, participants with mean kurtosis values of 3 SDs above or below the
357 group average were excluded. This resulted in a final sample of 96 participants for all tracts,
358 except for the inferior longitudinal fasciculus (n = 95), superior longitudinal fasciculus (n = 95),
359 cerebrospinal tract (n = 94), and ventral cingulate gyrus (n = 86).

360 **2.8 Statistical tests**

361 All statistical tests were performed using R (version 4.3.1).

362 Given that overall responsivity (i.e., average activity across all included ROIs) explained most of
363 the variability in brain module activity, we first explored how this factor related to age and task
364 performance using Pearson correlations. To investigate whether associations between overall
365 responsivity and task performance were age-independent, we additionally calculated the partial
366 correlations between these two variables while accounting for age.

367 Next, we performed several between-group comparisons to better understand the diverse brain
368 activity profiles associates with the VSTM task that were identified with the latent profile
369 analysis. To assess which brain modules showed the most pronounced differences across
370 subgroups we statistically compared brain module activity between groups. We also tested
371 whether subgroups differed in demographic characteristics (age, sex, educational attainment),
372 VSTM task performance (the number and precision of items in memory at load 3), grey matter
373 volumes (i.e., average grey matter volumes in each of the brain modules), and white matter
374 microstructure (i.e., average mean kurtosis in each of the 18 tracts). These comparisons were
375 performed to understand which factors contributed to the differences in brain activity profiles.

376 We applied a two-step approach to determine between-group differences. First, Welch's
377 ANOVA was used to determine if there were differences between subgroups in the variable of
378 interest. This was used instead of the regular Fisher's one-way ANOVA because of unequal sizes
379 and variances between groups. Second, each significant ANOVA was followed by pairwise
380 Welch's t-tests between groups (i.e., using non-pooled standard deviations to consider the
381 unequal variances between groups). Chi-squared tests were used in case of categorical data (i.e.,
382 comparing sex or educational attainment across groups). As educational attainment had less
383 than < 5 observations in certain categories, this variable was split into a dichotomous category
384 prior to performing the comparisons (university level vs. other educational categories), however
385 for descriptive purposes all categories are reported.

386 Analyses on grey matter volumes were corrected for intracranial volume. All analyses were
387 repeated while additionally correcting for the effects of age, except for the comparisons on
388 demographic characteristics. Specifically, we regressed the covariate(s) on the variable of
389 interest and used the residuals of that regression for the ANOVA and subsequent t-tests.

390 To further investigate the extent to which different neural routes facilitated successful VSTM
391 performance, we investigated the associations between brain module activity and task

performance within each subgroup. If certain associations are present in one subgroup but not in another, this could suggest that these subgroups relied on different cognitive operations to successfully complete the task. To test this, we calculated Pearson correlations between brain module activity and task performance within each subgroup, adjusting for the effects of age (i.e., partial correlations). The difference between coefficients were statistically compared using Fisher's z-tests.

We used false discovery rate (FDR) corrections (Benjamini & Hochberg, 1995) to adjust for multiple comparisons across different brain modules, white matter tracts or pairwise tests. In addition to reporting (FDR-corrected) p-values, we computed Bayes Factors (BF) for the alternative hypothesis using the *BayesFactor* package (https://cran.r-project.org/web/packages/BayesFactor/index.html). Effects were considered as strongly supported in case of both FDR-adjusted $p < 0.05$ and $BF > 3$ (Buades-Rotger et al., 2023; Driessen et al., 2018). In addition, we calculated Bayesian R^2 to evaluate the fit of each model (Gelman et al., 2019), using the *performance* package (https://easystats.github.io/performance/index.html).

3 Results

3.1 Brain modules with similar brain activity patterns across participants

We identified seven distinct modules of brain regions with similar patterns of inter-individual variability in terms of their brain activity while performing the VSTM task (**Figure 2**). The brain activity metric utilized to define these modules (and used in all subsequent analyses) is based on load 3 vs. load 1 during the maintenance period.

The modules included a frontal control module (FCM), which overlapped largely with the traditional fronto-parietal control network. This module encompasses the lateral prefrontal cortex and the anterior cingulate but did not include parietal areas. A distinct temporo-parietal module (TPM) included parietal areas that typically fall within the default mode and fronto-parietal control network, predominantly in the left hemisphere, but also included temporal areas. The cerebellum and thalamus module (CTM) covered the cerebellum and thalamus, and the visual module (VM) included the occipital cortex. Another module overlapped with the dorsal attention network, covering the frontal eye fields and the intraparietal sulcus, which we refer to as the dorsal attention module (DAM). The motor module (MM) covered the bilateral precentral gyrus but also extended into the right posterior temporal cortex. Lastly, one module

largely overlapped with the default mode network, covering the medial prefrontal cortex, precuneus, and temporal areas, which we refer to as the default mode module (DMM).

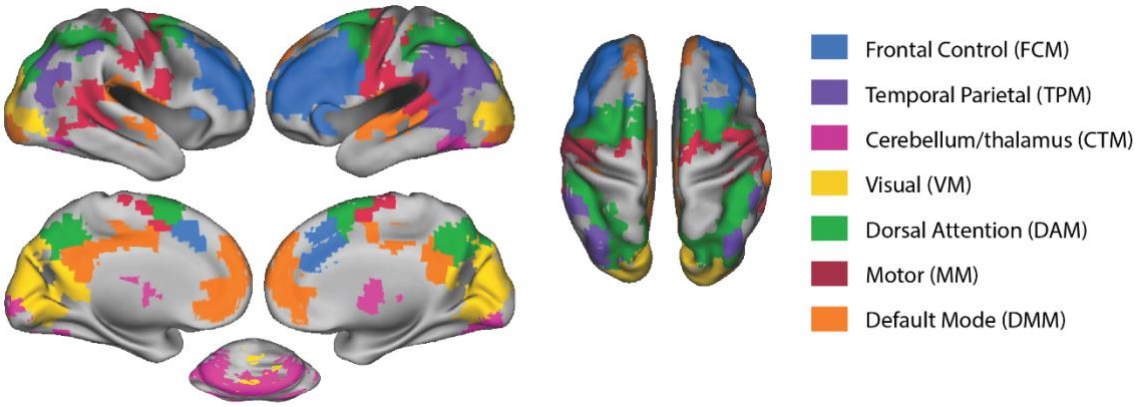


Figure 2: An illustration of the seven brain modules we identified.

3.2 Overall responsivity increases with age and accounts for module-specific brain activity

As previously described, the average activity across all included ROIs explained a substantial proportion of the variance in brain activity within each module (R^2 = 0.61-0.75).

We explored how the overall responsiveness related to age and task performance. Average activity across all brain modules increased with age (r = 0.37, 95% CI = [0.19; 0.52], uncorrected p < 0.001, BF = 338.96). However, we did not observe significant associations between overall activity and memory precision (r = 0.04, uncorrected p = 0.688, BF = 0.15) or number of items in memory (r = -0.07, uncorrected p = 0.460, BF = 0.18).

3.3 Latent profile analysis identifies subgroups with distinct activation signature across modules

To look beyond overall responsivity, this factor was regressed out of the seven identified brain networks. To account for all variance in brain activity, the LPA grouped participants based on the residual brain activity within each brain network, in addition to the overall responsivity across all ROIs. The BIC and ICL values suggested that the most optimal fit was acquired with a model of four latent subgroups with equal shape, variable volume and assumed diagonal covariance matrix (n = 35, n = 24, n = 42, and n = 12 in groups 1-4, respectively). The distributions of BIC and ICL values for the different latent profile models are shown in **Supplementary Figure 2 and 3.** A more detailed description of the decision on the number of classes, as well as the corresponding fit indices, is provided in **Supplementary Methods.**

An overview of the brain module activation profiles across subgroups is displayed in **Figure 3.** To investigate which networks were the strongest drivers of the subgroup differences, we

statistically compared the brain activity profiles across subgroups **(Table 1).** It should be noted that the LPA was designed to produce subgroups with distinct brain activity profiles. Therefore, these significance values are only meaningful in relation to each other as a comparison of the relative contributions of different modules and subgroups, but not in isolation. A complete overview of the between-group statistics for the brain module activity is depicted in **Supplementary Table 1**.

The most substantial differences in residual brain activity were observed for the FCM, VM, DAM, and DMM, as reflected by the corresponding Bayes Factors and values of Bayesian R^2 (all ≥ 0.26, indicating substantial effect size; Cohen, 2013). Focusing on four most influential modules, subgroup 1 is characterized by less FCM activity compared to subgroups 3 and 4, the lowest DAM activity across all groups, and the least DMM deactivity. Subgroup 2 demonstrates the least FCM activity but the highest VM activity across all subgroups. In contrast, group 3 shows higher FCM activity than subgroups 1 and 2, but lower VM activation than subgroup 2. Subgroup 4 shows a similar pattern as subgroup 3 with even higher FCM and lower VM activity. We observed no significant differences for the TPM and overall responsivity of brain activity to the task load manipulation. These results remained consistent after applying age corrections.

In summary, while subgroup 2 exhibited the lowest frontal activation paired with higher visual activation, subgroups 3 and 4 displayed the opposite pattern. In contrast, subgroup 1 was characterized by having the least DAM activity and DMM deactivation. This may suggest that different neural mechanisms were used to complete the VSTM task.

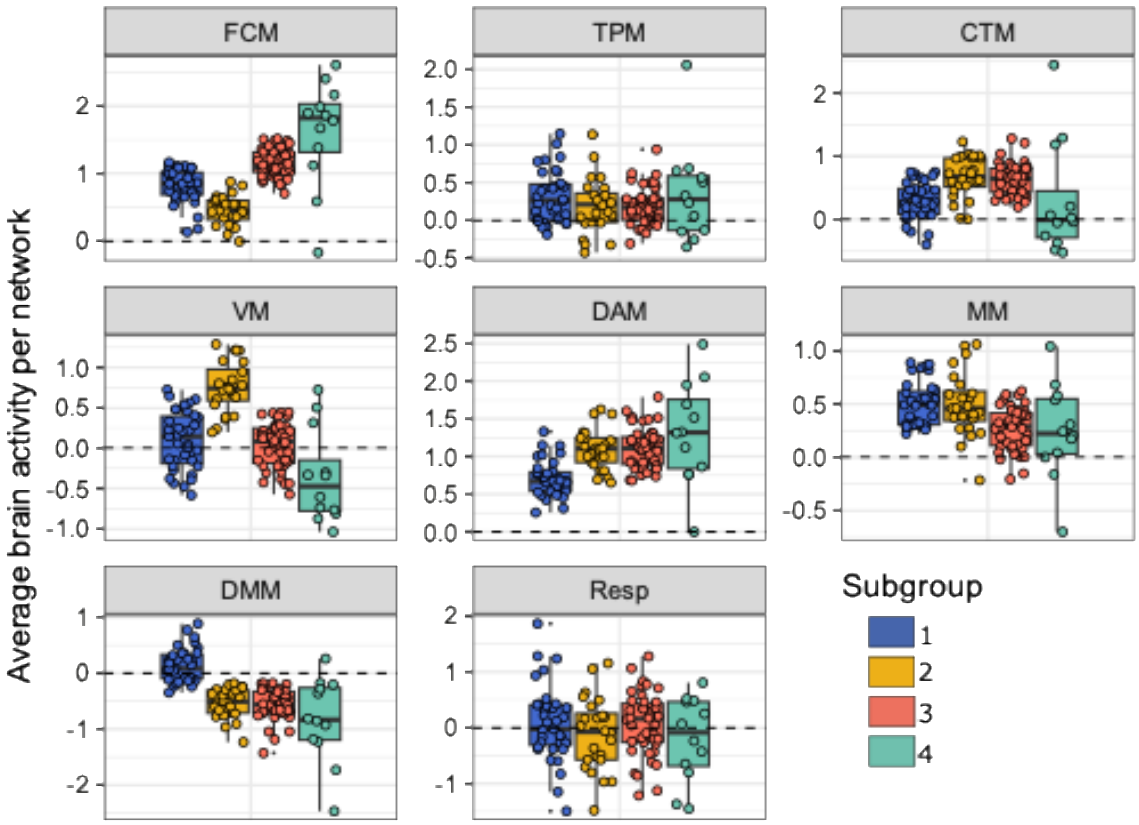


Figure 3: *For each of the four identified subgroups this figure shows the mean-regressed average brain activity in each of the seven identified brain networks as well as the overall responsivity across all ROIs (Resp). The most influential brain modules were the FCM, VM, DAM, and DMM. FCM = frontal control module; TPM = temporal parietal module; CTM = cerebellum/thalamus module; VM = visual module; DAM = dorsal attention module; MM = motor module; DMM = default mode module.*

Table 1. *Comparing residual network activity across subgroups*

	F	Bayesian R^2	t 2>1	t 3>1	t 4>1	t 3>2	t 4>2	t 4>3
FCM	54.29**	0.51†	-5.37**	4.82**	3.43**	12.45**	4.98**	2.00
TPM	1.05	0.00						
CTM	10.92**	0.15	4.42**	5.33**	-0.03	-0.45	-1.42	-1.32
VM	33.93**	0.46†	7.48**	-0.89	-2.54*	-9.43**	-6.22**	-2.23
DAM	20.00**	0.28†	5.69**	7.01**	3.06*	0.30	1.11	1.03
MM	9.45**	0.15	-0.05	-4.97**	-1.91	-3.29*	-1.75	-0.17
DMM	42.56**	0.47†	-8.99**	-10.49**	-4.32*	-0.37	-1.31	-1.21
Resp	0.77	0.00						

*FDR-corrected p-value < 0.05 & BR > 3;

**=FDR-corrected p-value < 0.001 & BR > 3.

†$R^2 \geq 0.26$.

482 **3.4 Subgroups showed no differences in demographics or VSTM task performance**

483 Subgroup characteristics are displayed in **Table 2.** No significant between-group differences
484 were found for age, sex, education (all $p > 0.05$, BF < 3). We found a trend level age difference
485 between the subgroups ($F_{3,40.8}$=2.79, $p = 0.053$, BF = 0.43), with subgroup 4 tended to be younger
486 than the other participant groups (subgroup 1: $t_{23.6} = 2.83$, $p = 0.009$, BF = 3.70; subgroup 2: $t_{27.7}$
487 = 2.29, $p = 0.030$, BF = 1.74; subgroup 3: $t_{18} = 2.01$, $p = 0.059$, BF = 1.49). VSTM performance did
488 not significantly differ across subgroups (precision and number of items in memory at load 3, all
489 $p > 0.05$, BF < 3). These results were unaffected by age corrections. A complete overview of the
490 between-group statistics for the subgroup characteristics can be found in **Supplementary Table**
491 **2**.

492 ***Table 2.*** *Subgroup characteristics.*

	All participants	**Subgroup 1**	**Subgroup 2**	**Subgroup 3**	**Subgroup 4**
N	113	35	24	42	12
Age, mean (SD)	53 (18.0)	57 (19.1)	55 (19.8)	51 (15.6)	41 (15.4)
Sex					
Male, n (%)	59 (52%)	14 (40%)	15 (63%)	24 (57%)	6 (50%)
Female, n (%)	54 (48%)	21 (60%)	9 (38%)	18 (43%)	6 (50%)
Highest education					
University, n (%)	82 (73%)	21 (60%)	19 (79%)	32 (76%)	10 (83%)
A' levels, n (%)	17 (15%)	6 (17%)	3 (13%)	7 (17%)	1 (8.3%)
GCSE grade, n (%)	9 (8%)	4 (11%)	1 (4.2%)	3 (7.1%)	1 (8.3%)
None > 16, n (%)	5 (4.4%)	4 (11%)	1 (4.2%)	0 (0%)	0 (0%)
Number of items in memory (load 3), mean (SD)	2.40 (0.46)	2.35 (0.50)	2.38 (0.47)	2.43 (0.47)	2.49 (0.34)
Memory precision (load 3), mean (SD)	0.12 (0.05)	0.10 (0.04)	0.12 (0.04)	0.12 (0.05)	0.13 (0.04)

493 **3.5 Subgroups revealed distinct associations between brain activity and VSTM task**
494 **performance**

495 Next, we investigated the association between brain activity and task performance within each
496 subgroup, while correcting for age. Since this concerned within-group analyses, we excluded
497 subgroup 4 because of its small number of participants (*n* = 12). To limit the number of
498 comparisons, we focused on the brain modules with the most pronounced differences between
499 the subgroups: the FCM, VM, DAM, and DMM. A complete overview of the associations between
500 brain module activity and performance on the VSTM task for each of the subgroups is displayed
501 in **Supplementary Table 3.**

For the FCM, we found that the subgroups 1 and 2 showed negative associations between FCM activity and memory precision (subgroup 1: r = −0.37, 95% CI = [−0.62; −0.04], uncorrected p = 0.030, BF = 2.36; subgroup 2: r = −0.41, 95% CI = [−0.70; 0.01], uncorrected p = 0.045, BF = 1.93, see **Figure 5A**). However, this association was absent in subgroup 3 (r = 0.11, p = 0.465, BF = 0.30). When we compared the slopes between subgroups 1 and 3, we found that they were significantly different (z = -2.11, 95% CI = [-0.87; -0.03], uncorrected p-value = 0.035), the same was true for the comparison between subgroups 2 and 3 (z = -2.05, 95% CI = [-0.94; -0.02], uncorrected p-value = 0.040). Notably, subgroups 1 and 2 were characterized by having relatively low FCM recruitment than subgroup 3 and 4. Therefore, these results suggest that the low recruitment of the FCM within subgroups 1 and 2 may have been beneficial to their memory precision. No association was observed between FCM activity and number of items in memory in any of the subgroups.

For the VM, no significant associations with items in memory or memory precision were observed.

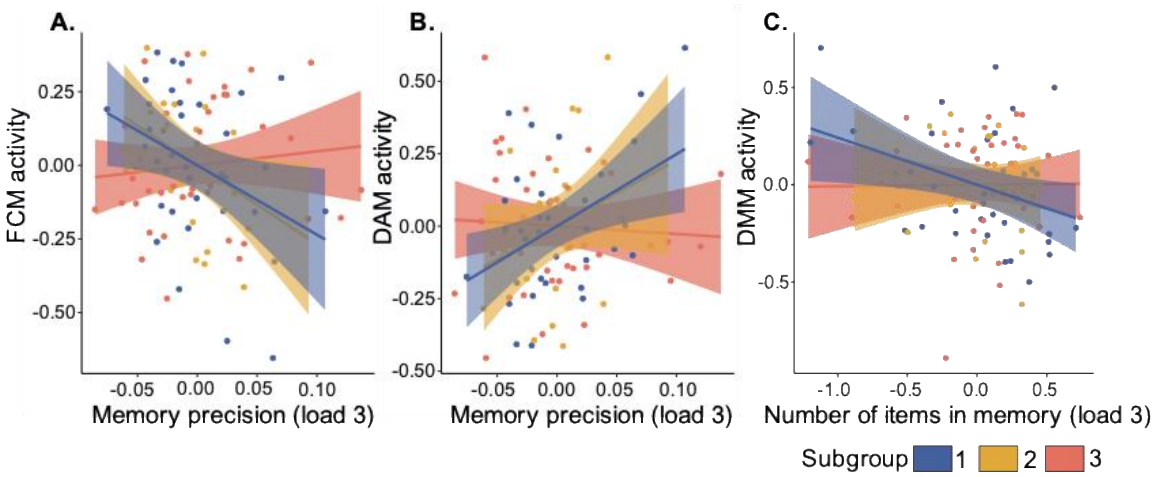
In the DAM, we observed that subgroup 1 demonstrated a positive association between DAM activity and memory precision (r = 0.42, 95% CI = [0.10; 0.66], uncorrected p = 0.012, BF = 4.97, see **Figure 5B).** In subgroup 2, this association tended in a similar direction; however, this was not significant (r = 0.30, uncorrected p = 0.15). The slope from subgroup 1 significantly differed from subgroup 3 (z = 2.14, 95% CI = [0.04; 0.86], uncorrected p = 0.032). Subgroup 1 was characterized by having the least DAM recruitment. This suggests that for subgroup 1, their low DAM activity may have negatively impacted their memory precision. There were no significant associations between DAM activity and number of items in memory.

In the DMM, no associations were observed between DMM activity and memory precision. A negative association was observed between reduced DMM deactivation and the number of items in memory in subgroup 1 (r = -0.38, 95% CI = [-0.63; -0.05], uncorrected p = 0.026, BF = 2.65), however no associations were found in subgroup 2 (r = -0.11, p = 0.597, BF = 0.35) or subgroup 3 (r = 0.01, p = 0.942, BF = 0.23; see **Figure 5C**). The slopes did not significantly differ between groups. These results suggest that the increased activity (or reduced suppression) of the DMM in subgroup 1 may have hindered the number of items participants in that subgroup could recall.

Taken together, we observed several unique associations between brain module activity and VSTM performance that were subgroup-specific, even though task performance did not differ across groups. This further supports the notion that these distinct brain activity profiles reflect

535 different yet equally effective pathways to perform the task. It should be noted that after
536 applying FDR-corrections for multiple testing across the three subgroups and four networks,
537 none of these associations remained significant, and therefore should be interpreted with
538 caution.

539



540

541 ***Figure 4:*** *Associations between brain module activity in the frontal control module (FCM), visual*
542 *module (VM), dorsal attention module (DAM), and default mode module (DMM) and*
543 *performance on the visual short-term memory task. All analyses were corrected for age.* ***A.***
544 *Subgroups 1 and 2 showed negative associations between FCM activity and memory precision*
545 *(uncorrected p = 0.030, uncorrected p = 0.045).* ***B.*** *Subgroup 1 demonstrated a positive*
546 *association between DAM activity and memory precision (uncorrected p = 0.012).* ***C.*** *Subgroup 1*
547 *demonstrated a negative association between reduced DMM suppression and the number of*
548 *items in memory (uncorrected p = 0.026).*

549 **3.6 Subgroups differ in white matter integrity**

550 Next, we investigated whether structural brain characteristics differed between groups. First,
551 we compared grey matter volumes within each of the modules between groups while correcting
552 for total intracranial volume. Grey matter volume in the TPM significantly differed across
553 subgroups ($F_{3,39.84}$ = 5.67, FDR-adjusted p-value = 0.017, BF = 5.10), however this effect
554 disappeared after additionally correcting for age (unadjusted p = 0.048; BF = 0.72).

555 We also investigated whether the different subgroups showed significant differences in white
556 matter microstructure, as measured by mean kurtosis (MK). We found significant differences
557 between subgroups for four white matter tracts (**see Figure 5**). These included the left inferior
558 frontal occipital fasciculus (IFOF; $F_{3,37.8}$ = 4.73, FDR-adjusted p = 0.030, BF = 5.04), right IFOF

($F_{3,36.10}$ = 4.08, FDR-adjusted p-value = 0.049, BF = 3.49), left inferior longitudinal fasciculus ($F_{3,35.09}$ = 6.71, FDR-adjusted p-value = 0.011, BF = 28.10) and the left uncinate fasciculus ($F_{3,35.43}$ = 6.60, FDR-adjusted p-value = 0.011, BF = 16.93).

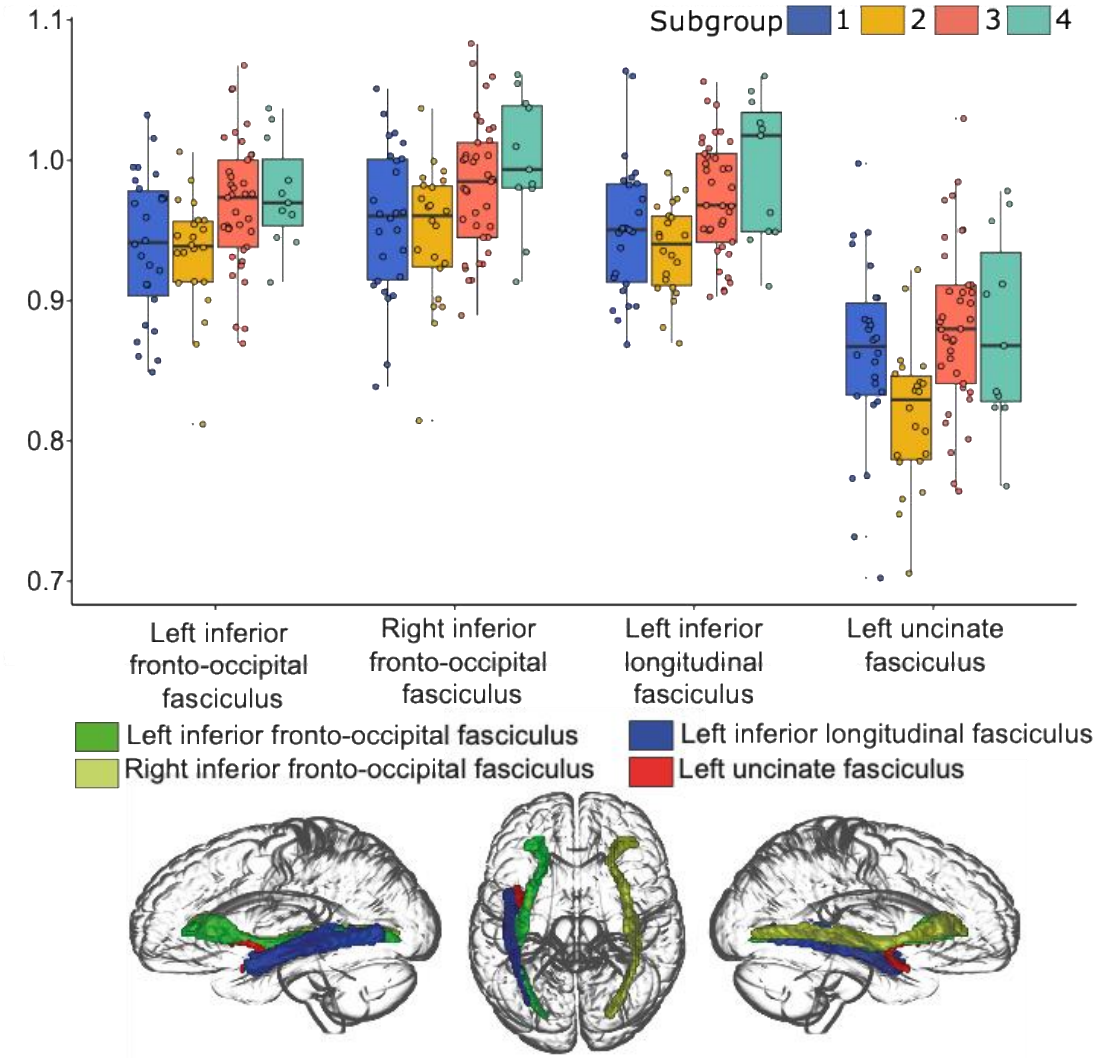


Figure 5: *The upper part of the figure shows the average mean kurtosis values in each subgroup for the white matter tracts that displayed significant between-group differences (FDR-corrected p-value < 0.05 and Bayes Factor > 3). The bottom part visualizes the white matter tracts in a glass brain, generated with MRIcroGL (https://www.nitrc.org/projects/mricrogl). Only the effects in the left inferior longitudinal fasciculus and left uncinate fasciculus survived additional age corrections.*

Only the effects in the left inferior longitudinal fasciculus and the left uncinate fasciculus remained significant after correcting for age ($F_{3,34.8}$ = 5.42, FDR-adjusted p-value = 0.033, BF = 5.81; $F_{3,35.4}$ = 6.64, FDR-corrected p-value = 0.020, BF = 17.32, respectively). The left inferior fasciculus showed lower MK in subgroup 2 relatively to subgroup 3 ($t_{53.56}$ = 3.71, FDR-correct p =

0.003, BF = 30.24) and subgroup 4 ($t_{13.37}$ = 2.65, unadjusted p = 0.019, BF = 11.23), however the latter effect did not survive FDR-corrections.

The left uncinate fasciculus showed lower mean kurtosis in subgroup 2 relatively to subgroup 1 ($t_{45.50}$ = 2.58, FDR-corrected p-value = 0.039, BF = 3.49), subgroup 3 ($t_{50.46}$ = 4.37, FDR-corrected p-value < 0.001, BF > 100), and subgroup 4 ($t_{15.49}$ = 2.60, FDR-corrected p-value = 0.039, BF = 6.62). So, subgroup 2, which is the subgroup with the least FCM activity but the highest VM activity across all subgroups, specifically shows lower MK in the left uncinate fasciculus and the left inferior longitudinal fasciculus. Notably, the low recruitment of the FCM within this subgroup appeared to be beneficial to their memory precision.

A complete overview of the between-group statistics for grey matter volumes and MK is provided in **Supplementary Tables 4 and 5.**

4 Discussion

While we often assume that similar patterns of neural activity are engaged to complete a cognitive task across individuals, accumulating evidence suggests that this is not necessarily the case, even in the absence of brain injury or disease (Noppeney et al., 2004; Price & Friston, 2002; Seghier & Price, 2018). Instead of discarding inter-individual variability in task-related functional activity, we leveraged it in our analyses to investigate brain degeneracy or many-to-one mapping in the context of VSTM performance. We identified four participant subgroups with distinct brain activity profiles, particularly within the FCM, VM, DAM, and DMM. Despite substantial differences in brain activity, these subgroups showed no difference in task performance or age, suggesting that these profiles may reflect different yet equally effective pathways to perform the task. This was further supported by the small, albeit distinct associations between task performance and brain modular activity across subgroups. Individual differences in brain structure may partly account for differences in brain activity, as subgroups showed age-independent differences in white matter integrity for the left inferior longitudinal fasciculus and the left uncinate fasciculus. Here, we first discuss our findings in relation to many-to-one mapping. Subsequently, we describe the modules and subgroups that we identified in more detail as well as the role of global versus local inter-individual variability in brain activity. Finally, we highlight the factors that contributed to subgroup variations in brain activity.

Degeneracy suggests that there can be multiple neural pathways leading to the same behavioural outcome (Edelman & Gally, 2001; Mason et al., 2015; Price & Friston, 2002; Westlin

605 et al., 2023). We identified four subgroups with marked differences in recruitment of various
606 brain modules during the VSTM task, after accounting for differences in overall network activity.
607 These results add to previous studies that revealed subgroups with distinct profiles of task-
608 related functional activity (Cerliani et al., 2017; Fischer-Baum et al., 2018; Kherif et al., 2009;
609 Noppeney et al., 2006; Noppeney et al., 2005; Seghier et al., 2008; Seghier & Price, 2016).
610 Similarly to previous findings (Fischer-Baum et al., 2018; Noppeney et al., 2006), these
611 subgroups demonstrated similar levels of performance. These findings illustrate how different
612 patterns of brain activity can lead to the same functional outcome, providing support for the
613 notion of brain degeneracy. Additionally, we observed several unique associations between
614 brain modular activity and task performance. This finding suggests that there is not a single route
615 to successful cognitive performance, and the optimal route may vary from person to person.
616 This finding highlights the individual-specific nature of brain-cognition relationship, where
617 diverse neural mechanisms can yield similar outcomes (Noppeney et al., 2006; Seghier & Price,
618 2018).

619 As a first step toward identifying subgroups, we reduced the dimensionality of our data,
620 identifying seven brain modules that showed similar between-participant variability in their
621 activity patterns during the maintenance period of the VSTM task (load 3 vs. load 1). Strikingly,
622 these modules show strong correspondence to brain networks that are typically identified using
623 functional connectivity analyses, such as the frontoparietal control network and default mode
624 network (Power et al., 2011; Yeo et al., 2011). This happens even though functional connectivity
625 is typically based on temporal correlations in activity within participants while we investigated
626 correlations in activity between participants, suggesting that there is a shared underlying source.
627 These results corroborate the idea that there is a stable intrinsic network architecture that is
628 largely uniform across individuals but also shows reliable individual differences (Finn et al., 2015;
629 Fox & Raichle, 2007; Gratton et al., 2018). This intrinsic architecture manifests itself both in how
630 networks are functionally connected within a single person (within-subject) and in the
631 differences in network activity among individuals (between-subjects). In line with this, previous
632 studies demonstrated that functional connectivity can be used to predict task-activation, and
633 that individual differences in connectivity are related to variability in task-related activation
634 (Cole et al., 2014; Cole et al., 2021; Finn et al., 2015; Tavor et al., 2016).

635 We observed that the brain activity across the seven brain modules was highly correlated,
636 corroborating previous findings where the global recruitment of task-related functional activity
637 explained most inter-individual variability, both in relation to performance and age (Chen et al.,
638 2022; Mitchell et al., 2023; Samu et al., 2017). Consistent with prior studies, the average activity

across all modules explained 60-75% of the variability in activity observed within each brain module. To be able to look beyond this general factor, we used module-specific activity for our subsequent analysis, where the average activity within each module was corrected for the average activity across all modules. Results from the latent profile analysis suggests that there is meaningful inter-individual variability beyond this general factor, by revealing subgroups with differences in white matter integrity and unique associations between brain activity and performance. These findings illustrate how individual differences in task-related brain activation arise from both overall responsivity to the task (Samu et al., 2017), and the specific recruitment patterns of brain regions, highlighting the importance of individual-specific factors in shaping task-related brain activity (Cole et al., 2021; Finn et al., 2015; Gratton et al., 2018).

Of the seven modules we identified, four showed the most significant differences in activity across subgroups: the FCM, VM, DAM, and DMM. These brain modules largely overlap with the frontoparietal network, visual network, dorsal attention network, and default mode network, respectively (Power et al., 2011; Yeo et al., 2011). With increasing task load, activity typically increases in the frontoparietal and dorsal attention networks, whereas the default mode network becomes more suppressed (Huang et al., 2016; Nagel et al., 2009; Salami et al., 2019; Salami et al., 2018; Zuo et al., 2019). This reflects a shift away from internally focused processes to task-oriented activity (Fox et al., 2005; Seeley et al., 2007; Smith et al., 2009). Notably, this pattern was weaker for subgroup 1, suggesting that this subgroup might have been less attentive during the maintenance phase (Anticevic et al., 2012; Berry et al., 2017). Surprisingly, this subgroup showed task performance comparable to the other subgroups, despite the positive association between DAM activity and memory precision, and the negative association between DMM activity and the number of items in memory. One possibility is that VSTM performance was sustained in this subgroup through increased engagement during the encoding or retrieval phase (Linke et al., 2011; Magen, 2017). Stimulus information might also have been preserved in a passive state, where maintenance is facilitated by neural mechanisms not characterized by increased activity (i.e., activity-silent mechanisms), such as short-term synaptic plasticity (Lewis-Peacock et al., 2014; Stokes, 2015).

Successful VSTM performance is further facilitated through interactions between the frontoparietal and visual networks (D’Esposito & Postle, 2015; Eriksson et al., 2015; Scimeca et al., 2018). The sensory recruitment hypothesis of working memory suggests that the same brain regions responsible for encoding the stimulus are also essential for maintaining this information (D'Esposito, 2007; D’Esposito & Postle, 2015). In line with this, in the context of VSTM, visual regions have been shown to maintain detailed sensory representations of the stimuli (Emrich et

al., 2013; Postle, 2015; Serences, 2016). The frontoparietal network is thought to exert top-down control over these areas and support the maintenance of more abstract representations of the stimuli, such as verbal descriptions (Christophel et al., 2017; Gayet et al., 2018; Scimeca et al., 2018; Serences, 2016). Interestingly, subgroup 2 demonstrated the highest VM activity and lowest FCM activity. The reduced FCM recruitment in this subgroup was beneficial to VSTM performance, as reflected by the negative associations between FCM activity and memory precision in these participants. In contrast, subgroups 3 and 4 demonstrated relatively high FCM activity and lower VM activity. The use of different strategies to complete the task is an important source of variability for task-related brain activity (Miller et al., 2012; Sanfratello et al., 2014). Consistently, previous studies that identified subgroups with distinct brain activity profiles during task engagement attributed this variability to the adoption of different strategies (Kherif et al., 2009). It is possible that subgroup 2 might have relied more on visual representations, while subgroup 3 and 4 maintained stimulus information through more abstract forms, thereby relying more on the FCM. This would also align with the two most commonly reported strategies to perform VSTM tasks: maintaining visual representations of the stimuli (e.g., picturing the red dots moving to the left corner) and translating salient stimuli features into verbal representations (e.g., mentally repeating "the red dots moved to the left corner") (Berger & Gaunitz, 1979; Pearson & Keogh, 2019).

Subgroup 2 also showed decreased white matter integrity in the inferior longitudinal fasciculus and the uncinate fasciculus, whereas this was preserved in subgroups 3 and 4. The inferior longitudinal fasciculus is involved in modulating visual information and semantic-lexical processing (Herbet et al., 2018; Shekari & Nozari, 2023). The uncinate fasciculus is associated with associative learning and semantic retrieval (Olson et al., 2015; Von Der Heide et al., 2013). This suggests that the use of a visually oriented strategy in subgroup 2 may be linked to the reduced microstructural integrity in two white matter tracts that play a role in creating and retrieving verbal representations (Duffau et al., 2013; Herbet et al., 2018; Shekari & Nozari, 2023). However, we did not find any direct association between brain activity and performance in subgroup 3, which makes it challenging to interpret how this brain activity profile precisely facilitated task performance in this group.

The age-independent differences in white matter integrity across subgroups were consistent with our expectation that structural brain characteristics would contribute to the variability in brain activity among the subgroups (or vice versa). This also aligns with previous research linking white matter microstructure to the recruitment of different brain regions during task performance (Burzynska et al., 2013; Burzynska et al., 2015). We did not observe any differences

in grey matter across subgroups, suggesting that white matter integrity may be relatively more important to explain inter-individual variability in brain activity in our sample (Miller et al., 2012). Typically, white matter degradation is associated with declines in cognitive performance, including working memory (Bennett & Madden, 2014; Oschwald et al., 2020). Our results suggest that this is not necessarily the case when different neural pathways can be used to perform a task (Madden et al., 2009), corresponding to the notion of brain degeneracy (Noppeney et al., 2004; Price & Friston, 2002). It should be noted that the differences in white matter integrity between subgroups were relatively small, emphasizing the need to further investigate these associations in future studies. Nevertheless, our findings underscore that individual differences in structural brain characteristics are an important source of variability in brain activity and cognitive performance (Genon et al., 2022; Kanai & Rees, 2011; Miller et al., 2012; Seghier & Price, 2018).

Although prior research has demonstrated strong age-related differences in brain activity and performance during VSTM tasks, including the one used here (Lugtmeijer et al., 2023; Morcom & Henson, 2018; Sander et al., 2012), we did not observe any differences in age or performance between the subgroups. This suggests that other factors beyond age or task performance were the primary drivers behind the distinct brain activation patterns observed across subgroups (Finn et al., 2015; Gratton et al., 2018). These factors may have included the extent to which participants were engaged throughout the task (Linke et al., 2011; Magen, 2017; Rose, 2020), the strategies adopted to complete the task (Kherif et al., 2009; Miller et al., 2012), and variations in white matter integrity (Burzynska et al., 2013; Burzynska et al., 2015), as discussed above. Nonetheless, age was positively correlated with the global recruitment of brain activity, consistent with prior research showing that that variability in overall responsivity was primarily due to age-differences (Mitchell et al., 2023; Samu et al., 2017). Therefore, the lack of age differences between subgroups might also be explained by our approach of clustering participants based on the residual brain activity in each module (i.e., after regressing out the overall responsiveness). In contrast, task performance was not associated with overall responsivity, suggesting that this factor is not the most substantial driver of inter-individual variability in brain activity. Therefore, studies that are interested in explaining performance metrics would benefit from distinguishing individuals based on performance itself rather than brain activity (e.g., Lövden et al., 2018; Salami et al., 2018).

There are several limitations that should be considered when interpreting these findings. First, we explored how the brain activity differences across subgroups may be associated with different cognitive processes. Although the use of different strategies has been recognized an

important source of task-related functional activity (Kherif et al., 2009; Miller et al., 2012; Noppeney et al., 2006; Sanfratello et al., 2014), we note that this interpretation remains speculative as we do not have any information about which strategies participants used when they performed the task. Therefore, the evidence here should be taken as proof of principle, showing that when we use a different approach to look at task-related brain activity, interesting dimensions of inter-individual variability are revealed that may otherwise remain hidden (Cerliani et al., 2017; Fischer-Baum et al., 2018; Kherif et al., 2009; Noppeney et al., 2006; Seghier et al., 2008; Seghier & Price, 2016; Seghier & Price, 2018). Second, our dataset consists of a relatively small number of participants, which may have limited our ability to observe within-group associations with performance. Lastly, although we have discussed the role of several factors in explaining the variability in brain activity between subgroups, this does not rule out the possibility that other variables that were not considered here could also contribute, such as other early-life factors, genetic factors or brain development (Walhovd et al., 2023). We hope that future studies focusing on this subject will include larger samples and a more extensive characterization of individual-specific factors that could further explain this variability.

Taken together, the novel approach introduced here allowed us to uncover distinct subgroups with marked differences in neural activity during the VSTM task, associations between brain module activity and VSTM performance, and white matter microstructural properties. However, these subgroups did not significantly differ in their demographic characteristics or VSTM performance. The identification of distinct subgroups illustrates how multiple neural pathways may underlie successful VSTM performance. This further highlights the importance of considering brain degeneracy to understand variability in brain-cognition associations (Edelman & Gally, 2001; Mason et al., 2015; Price & Friston, 2002; Westlin et al., 2023). Recognizing this possibility provides us with a more comprehensive understanding of the different ways in which our brains support cognitive functions and how this may vary from person to person. Consequently, these insights may help to unravel new ways in which structure and function interact, and how complementary routes can lead to the same cognitive outcomes.

Data and code availability

Data availability is provided via the Cam-CAN data portal (https://camcan-archive.mrc-cbu.cam.ac.uk/dataaccess/). The scripts and analysis pipeline are made available via Github (https://github.com/michellegjansen/neural_pathways_VSTM).

Author contributions

Michelle G. Jansen: Conceptualization, methodology, software, investigation, visualization, validation, data curation, formal analysis, writing – original draft. Alireza Salami: Conceptualization, methodology, writing – review & editing. Fernando-Ruiz Martínez: Methodology, software, investigation, data curation, formal analysis. Daniel J. Mitchell: Methodology, data curation, formal analysis, writing – review & editing. Joukje M. Oosterman: Supervision, writing – review & editing. Linda Geerligs: Conceptualization, methodology, software, investigation, visualization, validation, data curation, formal analysis, supervision, writing – original draft.

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Declaration of Competing Interests

The authors declare no competing interests.

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