Functional changes in the brain associated with differences in cognitive performance

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ABSTRACT

Aging is associated with multiple changes in cognitive performance and brain function. Longitudinal studies show that interindividual differences in cognitive performance increases from early to late adulthood. However, it is less clear how these inter-individual differences in cognition are linked to differences in brain function. In the current study, we used fMRI to link differences in cognitive performance of a visual short-term memory task to differences in activation at a whole-brain level. We used a modularity maximization algorithm to identify brain networks that show similar inter-subject variability. Based on the activity patterns obtained in each of the networks, we used latent-profile analyses to identify subgroups with different profiles of brain activation. The modularity algorithm identified a set of 8 brain networks with different distinct levels of activation across subjects. We distinguished three subgroups of participants with different profiles of brain activation and different level of performance in the task. The first group (n=21) showed significantly lower activation in brain networks involving mostly regions associated with FPCN and FEN, and higher activation in regions involving the visual cortex and the cerebellum. A second group (n=15) showed an opposite pattern of results, displaying higher levels of activation in areas associated with FPCN and FEN and lower activation in visual processing areas and the cerebellum. Finally, the third group (n=66) showed a uniform pattern of brain activation across all the networks. Collectively, these data might suggest the use of different cognitive strategies by each subgroup. These changes in strategies might reflect an adaptation to a working memory cognitive system that is less able to manage representations in a top-down manner.

Keywords: fMRI, inter-individual variability, working memory, fronto-parietal control network, visual networks, cognitive strategies.

INTRODUCTION

Life expectancy over the last decades has increased as a result of advancements in medicine in new treatments, biomedical equipment, and a better understanding of the biological underpinnings of diseases. However, such an increase in life expectancy has led to an ever-growing number of different people experiencing neurodegenerative disorders and age-related cognitive deterioration. Demographic studies anticipate that there will be around one billion people older than 60 in the world by 2050 (Prince et al., 2013), with a growing proportion of humans suffering from different sorts of dementia. According to the International AD. World Alzheimer Report in 2016 the economic cost of dementia might have reached 1$ trillion in 2018, alongside a deepening burden on patients, caregivers, and health care systems.

It is well known that not everyone ages in the same way. A challenge in the field of cognitive neuroscience has been to understand the brain mechanisms underlying preserved or impaired cognitive abilities associated with aging. In this sense, to comprehend healthy aging, it is important to understand the link between brain changes and underlying cognitive changes. In this context, the degree of age-related differences and changes in the brain and cognitive performance varies considerably between individuals. Longitudinal studies (M. de Frias et al., 2007; Small et al. 2011) have shown that interindividual differences in cognitive performance increases from early to late adulthood and old age. In particular, these differences are more prominent in tasks that involve learning and retrieving both verbal and non-verbal information (Tulving, 1983) and tasks involving working memory (Zacks & Li, 2000), attention (Madden, 1990), and cognitive flexibility (Connelly et al., 1991; Allen et al 1992). It is on these interindividual differences in cognitive performance that fMRI and structural neuroimaging studies have focused their attention during the past decade.

Nonetheless, the interpretation of the results remains unclear since some experiments showed an increase of task-related brain activity for older adults relative to younger adults, while others resulted in a decrease in brain activity (Spreng et al, 2010; Eyler et al, 2011). One generalization across the results from imaging studies in aging is that brain activity in older adults show a pattern of age-related dedifferentiation, (Cabeza, 2002; Li & Sikström, (2002); Park et al., 2004) that is, brain areas that show specialized responses for a specific cognitive operation in young adults are susceptible to become less specialized and activate for a greater number of cognitive processes. This “dedifferentiation” process has been shown to be associated with alterations in the ability of different brain regions to communicate with each other, having important consequences for the level of cognitive performance (Rakesh et al., 2020; Chong et al. 2019). Further insight into the process of (de)differentiation could aid theories of cognitive development and aging to better understand the signature of cognitive impairment in the brain. Changes in the pattern of specialization of brain areas might reflect important biological processes such as compensatory reorganization (Cabeza et al., 2002; Greenwood, 2007; Park and Reuter-Lorenz, 2009), vulnerability to disease states, and the emergence of subgroups that differ in the degree to which they show these patterns (de Mooij et al., 2018).

Amidst this complex background of age-related neurocognitive changes associated with aging, it is important to take into account one important methodological issue that arises in fMRI studies that attempt to localize brain regions whose activity is enhanced or diminished during a particular task. Usually, these types of studies estimate how consistent the effect of the task is, by examining the difference from zero at each voxel in the group average parameter estimate (Holmes & Friston, 1998). This assumes that the majority of the participants performing a specific task would engage similar brain regions and that task-related activity elsewhere in the brain of a minority of people will be characterized as a confound or noise (Noppeney et al., 2004). Nevertheless, several studies (Kherif et al., 2009; Seghier et al., 2008) have shown how inter-individual variability in brain activation patterns might lead to differences in cognitive performance and changes in cognitive strategies. For instance, Noppeney et al. (2006) using a weight estimation task presented visually and auditory primed showed the existence of two distinctive subgroups with different levels of activity in occipital and posterior temporal regions, as well as in the posterior parietal cortex (PPC). This result suggested the possibility that some participants depended more on visual information whereas others relied more on auditory cues. Another study carried out by Kherif et al. (2009) from a reading aloud task showed different levels of activation in the left posterior occipito-temporal and right inferior parietal regions or in the left anterior occipito-temporal and left ventral inferior frontal regions respectively. While this variability in brain activation was not a consequence of gender, age, education or stimulus differences, it was related to behavioral outcomes such as speed reading. Finally, Salami et al. (2018) using a working memory (WM) task identified two subgroups of participants, one with normal performance and other with lower scores. The group with lower performance had weaker load-dependent BOLD modulation and worse connectivity in the fronto-parietal network (FPN) and the striatum, as well as lower connectivity within the FPN during rest. Therefore, there is evidence in the literature indicating the existence of distinct cognitive subgroups within the older population (Salami et al. 2018).

In summary, the results of the previous studies point out the importance of modelling latent profiles of brain activation, failing to do so could have important consequences on the group-level results and on their interpretation (Cerliani et al. 2017). For instance, if different groups of participants perform a task using common and different brain areas, only those areas whose activation is consistent in the whole sample will be represented, resulting in a less accurate representation of the brain areas involved in the performance of the task across participants (Noppeney et al. 2006). In the context of aging, Cabeza et al. (2016) showed a linear association between age-related changes in the brain and performance in and behavior. However, according to Burzynska et al. (2012) this link might also not be linear, and only appreciable in a determined number of people when a certain amount of brain deterioration has already occurred.

The aim of the current study is to use fMRI to relate inter-individual differences in brain activation at a whole-brain level to differences in cognitive performance in a visual short term memory task. We characterize subgroups of people that capture the variability shown in cognitive performance across the life span and in late adulthood and old age. In order to identify these subgroups, we first reduced the dimensionality of the neural data by grouping brain voxels into a set of 748 anatomically distinct regions of interest (ROIs). We analyzed the task data for each individual to select ROIs that are significantly associated with the task in at least 10% of the participants. This way, we can investigate the intersubject variability in brain activation in those ROIs that show a less consistent effect between participants. Subsequently, we applied complex network measures to identify brain networks that activate when participants perform the task.

In the context of network theory, complex networks can be considered as a graph where brain regions are considered as nodes and connections between the nodes are thought of as edges. Brain networks are organized in structures characterized by internally coherent connections (tightly-packed connection within networks) and less coherent (fewer connections) connections between networks (Bullmore and Sporns, 2012). The degree to which a system's component shows such an organization can be evaluated with a complex network measure known as modularity (Newman, 2014). Modularity is used mainly to reduce the complexity of the network by partitioning the structure of the system into varying degrees of independence and interdependence (Cole et al., 2014). Although it has been shown that modularity has a resolution limit effect (it is limited by the number of smaller networks it can detect), this approach has been proven successful in extracting meaningful communities from graph networks (Clauset et al., 2014). In addition, this method has extra advantages over other mass-univariate approaches (Geerligs et al., 2015). First it avoids the problem of multiple comparisons, and second, properties of the networks can be assessed in a more fine-grained manner.

To this end, we built a similarity matrix based on the across-subject correlation in brain activation in the ROIs that we previously selected. Specifically, the correlation coefficient between two ROIs will inform us about the degree of similarity between these two regions. Once this process is finished, we will use this similarity matrix as an input to a modularity maximization algorithm that will identify modules that show similar inter-subject variability. Once these modules are identified through the previous steps, we will compute the average brain activity of each participant within each module. Based on the activity patterns obtained we use Gaussian mixture modelling, specifically, latent profile analyses (LPA) to identify latent subgroups within our sample of participants (Vermunt & Magidson, 2002). This approach has been proven successful in capturing relevant subgroups within clinical populations such as AD (Scheltens et al. 2016) and Parkinson's disease (Flensborg Damholdt et al. 2012), and also between healthy elderly adults (Ko et al. 2007; Pruchno et al. 2010; Hayden et al. 2011; Fandako et al. 2012; Lövden et al. 2017). This approach has the advantage over other clustering methods, in that it is totally data driven and independent of other predetermined cut-offs (Salami et al. 2018).

This novel approach makes our analysis different from functional connectivity analyses. In functional connectivity analysis (FC), the temporal correlation between the time series of two brain regions are used to construct a brain map or a FC matrix, that denotes the connectivity between these 2 regions within each subject. In our analyses, we used the variability in activation in each region (ROI) across participants to construct a correlation matrix, that indicated the degree of similarity between regions. If two or more regions show a high correlation coefficient across individuals, then these areas will have a higher probability of belonging to the same cluster (network). The modularity maximization algorithm will detect community structure between the modules that show similar inter-individual variability in brain activity.

These methods will be applied to the Cam-CAN (Cambridge Centre for Ageing Neuroscience) dataset inventory. This is a large-scale collaborative effort launched in 2010, and consists of epidemiological, cognitive and imaging data to understand cognitive performance in old age (Shafto et al., 2014). We expect to see a relationship between the subgroups identified based on brain activity patterns and performance on the visual short-term memory task. By comparing differences in task performance and the task-based activation in the brain networks, we expect to distinguish neural indicators that could help us to better differentiate between declining and preserved cognitive abilities across individuals.

MATERIALS AND METHODS

Participants

122 participants from the Cambridge Centre for Ageing and Neuroscience (Cam-CAN) study (Shafto et al., 2014) were selected for the current experiment. The recruitment of the participants took place in several stages. The sample of participants willing to participate in the study consisted of a list of residents that were targeted in particular areas of the United Kingdom. In the first stage, data from over 3000 participants was collected, including interviews, health and lifestyle questionnaires, and a screening assessment of cognitive impairment. Out of those 3000 participants, only those who had no history of serious or psychiatric conditions, were MRI compatible, fluent in English, and showed no indication of cognitive impairment (MMSE <25) were invited to continue. Additional exclusion criteria were history of drug or alcohol abuse, and poor

hearing or vision. In a second stage around 700 participants attended three sessions that included MRI, MEG, blood measures, cognitive tasks and a saliva sample. Finally, a subset of 280 participants who completed the core measures in stage 2 and were still interested in participating were invited to continue to the last stage. In this last stage, more specific cognitive neuroscience tasks were performed. Specifically, 122 participants completed the visual short-term memory task (VSTM) that we analyzed in the current study. 20 participants had to be excluded due to noise and defective data, so the final sample of participants consisted of 102 participants aged between 18 years old and over. Participants gave written consent and the study was approved by the Cambridgeshire 2 Research Ethics Committee, United Kingdom. For more detailed information about the selection criteria see Shafto et al. (2014)

Visual short term memory task (VSTM)

The material and instructions for this task (see Figure 1) are based on Emrich et al. (2013). An array of three coloured dots (red, yellow and blue) were presented sequentially on each trial. The dot displays were shown in succession. Each trial began with a 5s gray fixation dot centered on the middle of the screen. Subsequently, the fixation dot disappeared for 2 s and then the coloured dot displays were shown for 500ms each with 250 ms separation between them. As a manipulation of set size, one, two, or three of the dots in the array moved in a single direction which had to be remembered. In the same display, the other dots, which functioned as a distraction (had to be ignored), rotated around a central axis. On 90% of the trials the probed dots moved in three directions (7º, 127º, or 247ºs). On 10% of the trials the probed dots moved at random directions to avoid the subjects learning the directions. The order of the presentation of the three displayed colors was randomized by trials, as was memory load. The direction for the distracting dots was alternated across trials of given loads. After the third display, there was a blank delay period of 8 s followed by the dot display. The probe display consisted of a coloured circle to indicate which of the three-dot display (red, yellow, or blue) the participant has to remember. The circle had a pointer that can be adjusted to indicate the direction of the to be remembered dot display. Participants had up to 5 s to adjust the pointer with 2 buttons until it matched the direction of the motion. Participants completed three runs of 30 trials per run (10 for each load). For each set size condition, behavioral outcomes of accuracy and precision were estimated by fitting a mixture model approach to the error distribution (Zhang & Luck, 2008).

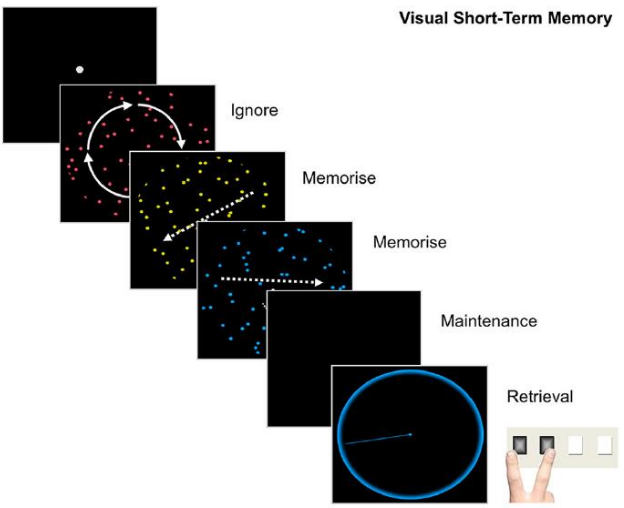


Figure 1: Adopted from Morcom & Henson, (2018). A trial example of the VSTM task. Trials began with fixation dot for 5 s. On each trial, three-dot displays were shown in red, yellow, and blue for 500 ms each (250 ms in between). After the last display, the screen was blanked for an 8 s maintenance period and then the probe display presented. A colored circle to indicate which dot display to recall (red, yellow, or blue). Participants had up to 5 s to adjust the pointer until the direction matched that of the to-be-remembered display.

Data acquisition and preprocessing

Data acquisition

MRI data was recorded on a 3T Siemens TIM Trio System scanner at the MRC Cognition Brain and Sciences Unit, Cambridge, UK. Approximately 300 volumes 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. Higher-resolution (1mm x 1mm) 3D T1 and T2 weighted structural images were acquired to aid registration across participants (Taylor el al. 2013). T1-weighted structural images were acquired using a Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence (TR =2250 ms; TE =2.99 milliseconds; TI =900 milliseconds; flip angle =9 degrees; FOV =256mm x 240mm x 192mm; voxel size =1mm isotropic; GRAPPA acceleration factor =2; acquisition time of 4 minutes and 32 seconds. T2-weighted structural images were acquired with a SPACE sequence (TR =2800 milliseconds; TE =408 milliseconds; FOV =256mm × 256mm × 192mm; resolution =1mm isotropic; GRAPPA acceleration factor =2; acquisition time of 4 minutes and 30 seconds.

Data preprocessing

Preprocessing analyses (Morcom & Henson, 2018) were carried out with the SPM 12 software (http://www.fil.ion.ucl.ac.uk/spm). The T1 and T2 weighted structural images were rigid body registered with a MNI template, bias corrected and segmented into six tissue classes using the newer segment protocol in SPM 12 (Ashburner and Friston, 2005). Non-linear transformations using DARTEL normalization was performed to match a gray matter template created from the CamCan stage 3 sample. The functional images were spatially realigned and interpolated to correct for differences in acquisition times, coregistered to the structural image using rigid body transformations, and transform to MNI space using the warps and affine transformation estimated from the structural images. The images were resliced to 3x3x3 voxels and smoothed with a 10 mm full-width half-maximum (FWHM) Gaussian kernel.

First level univariate imaging analysis

A general linear model (GLM) with three neural components was fitted for each participant. The components were: (1) encoding, modeled as an epoch of 1 s duration, at the beginning of the dot display movement. (2) maintenance, modeled as an epoch of 4s for the duration of the display. (3) response, modeled as a delta function at the time of the participant response. These three components were each split into three regressors (one for each load). Six additional regressors were added, representing the motion parameters estimated in the realignment stage. The main contrast of interest in this study was the difference between the highest and the lowest set size of items during the maintenance period.

ROI analyses and across subject correlations.

In order to make the analyses more computationally efficient in later stages, we reduced the dimensionality of the data by grouping brain voxels into a set of 748 anatomically distinct ROIs (See figure 5a) based on the parcellation created by Craddock et al. (2012). To investigate different profiles of brain activation evoked by the VSTM task, we extracted the average t-values across all voxels in each ROI for each participant. Subsequently, we threshold significant ROIs ($T > 1.96$, $p < 0.05$) and selected those that were significantly more activated in load 3 than load 1 in at least 10% of the participants. This thresholding method ensures that regions that are only active in some participants are retained for the following analyses steps. After the ROI selection step, we constructed a similarity matrix (figure 3b) based on the correlation of the load-related activity (load 3 – load 1) between ROIs across all the participants. One value in this matrix will inform us about the degree of similarity between 2 specific ROIs. In other words, a higher correlation coefficient between ROI (A) and ROI (B) will tell us that those 2 regions will have a higher probability of belonging to the same cluster.

Complex network measures

To identify modules (groups of ROIs) that showed equivalent inter-individual variability in brain activation, we used the similarity matrix from the previous step as an input for a Louvain modularity algorithm (Blondel et al., 2008) that created an initial partition of the brain into brain networks. This initial partition was further refined using an optimization of the Louvain modularity algorithm (Sun et al., 2009). The partition was performed 100 times, and all the repetitions were assembled into an ROI-by-ROI agreement matrix. Each number in the matrix indicates the proportion of repetitions in which two pairs of ROIs were assigned to the same module (node). This matrix was used again as an input for a new partitioning. This was repeated until the algorithm converged into a matrix consisting of ones and zeros, which mean that a single partition was reached. This procedure was applied for multiple resolution elements (RE) ranging from 1 to 4 with steps of 0.1 between RE. The RE indicates a penalty term that results in the size of the communities to be found. Smaller RE values will result in larger networks while higher RE values will result in smaller networks respectively. The most stable partition, calculated as the highest adjusted mutual information between the 100 repetitions that were performed (Vinh et al., 2009) was used as our final set of brain networks. Finally, to measure the intensity of brain activation associated with the task in each brain network, we computed the average brain activation of each participant within each module.

Latent profile analyses

To identify latent subgroups of participants characterized by different patterns of brain activity, we fit Gaussian mixture models, specifically LPA, to the distribution of average brain activity values per module (networks) across all the participants. A gaussian mixture model assumes a multivariate Gaussian distribution for each subgroup or class, so every observation will have a specific probability of belonging to a specific class. This probability will be specified by a probability density function determined by the average, the variance, and the covariance of each of the distributions. In a multivariate setting such as this one, different models can be specified based on the geometry (volume, variance and covariance) of the distribution to be specified. We estimated gaussian mixture models between 1 and 5 classes based on the average brain activity in each of the networks identified by the modularity maximization algorithm. For this purpose, we used the Mclust package in R (Scrucca et al., 2016), which allowed us to choose the number of components that fitted the data best. This decision was based on the Bayesian Information Criterion (BIC) and the likelihood ratio test (LRT). The BIC gives us an estimation about how well the model we fit predicts the actual data, while the LRT provides information about the degree of improvement of the classification when adding one more class to the analysis.

RESULTS

Behavioral results

The variance distribution of scores (set size load) showed a strong ceiling effect in accuracy and precision for the load conditions 1 ($M_{accuracy}$ = 0.93; $SD_{accuracy}$ = 0.11; $M_{precision}$ = 1.08; $SD_{precision}$ = 0.40) and 2 ($M_{accuracy}$ = 1.69; $SD_{accuracy}$ = 0.32; $M_{precision}$ = 0.92; $SD_{precision}$ = 0.35). Based on this distribution, we decided to restrict our behavioral and parametric analyses to the load condition 3 ($M_{accuracy}$ = 2.32; $SD_{accuracy}$ = 0.54; $M_{precision}$ = 0.87; $SD_{precision}$ = 0.35), which showed a more spread-out pattern of variance across participants. A distribution of the scores for all the load condition can be seen in figure 2. As expected, memory performance showed a strong age-related decline (Pearson's *r* [95% confidence interval]) both in accuracy (*r* (100) = -0.54, p= $3.5^{-0.9}$) and precision (r (100) = -0.26, p= 0.008) (see figure 3).

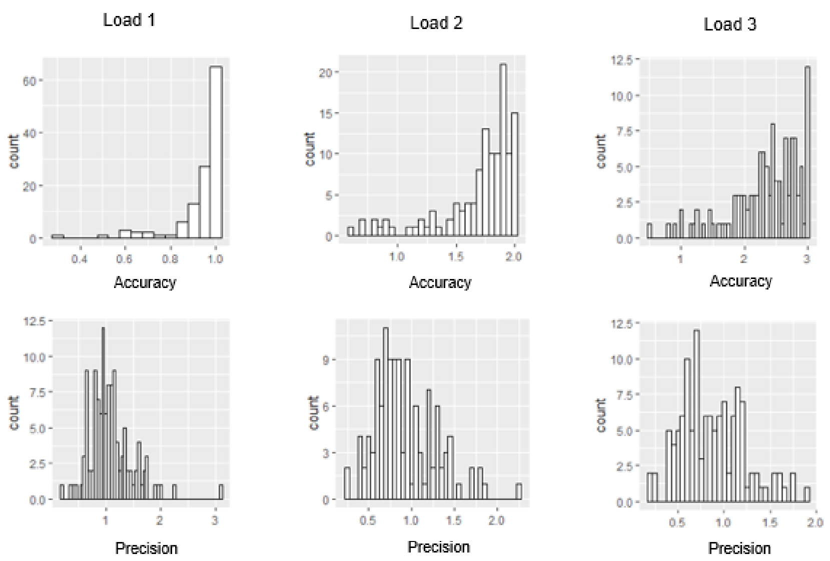


Figure 2. Variance distribution of the scores for each set size manipulation. **A** Accuracy scores for loads 1,2 and 3. **B** Precision scores for loads 1,2 and 3.

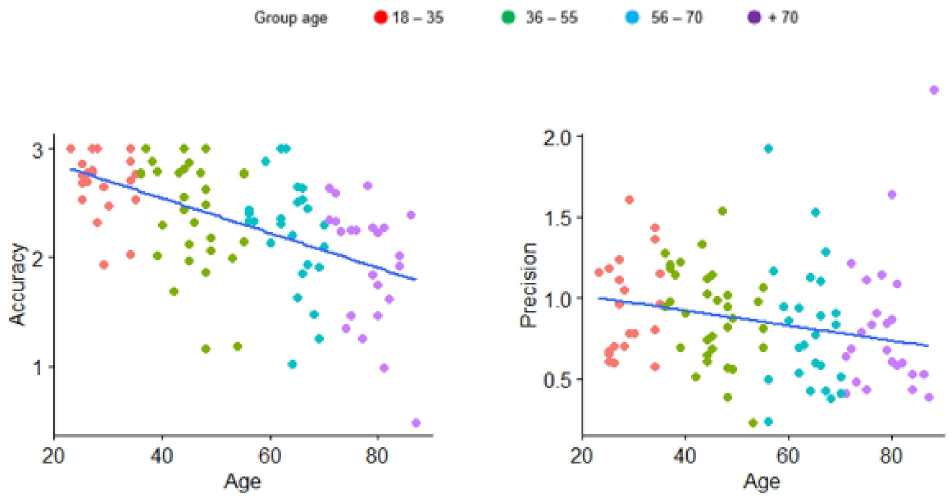


Figure 3. Correlation between memory performance scores (accuracy and precision) and age. Both behavioral measures show a strong age-related decline.

Network analyses

Overall mean activation

The mean activation between all the ROIs significantly associated with the VSTM task was computed for each participant to evaluate whether there was a link between overall brain activation, age, and behavioral performance. The results from the analyses (figure 4) showed that there were no significant effects in terms of age (r (100) = 0.17, p= 0.097), accuracy (r (100) = 0.13, p= 0.19) and precision (r (100) = 0.19, p= 0.054)

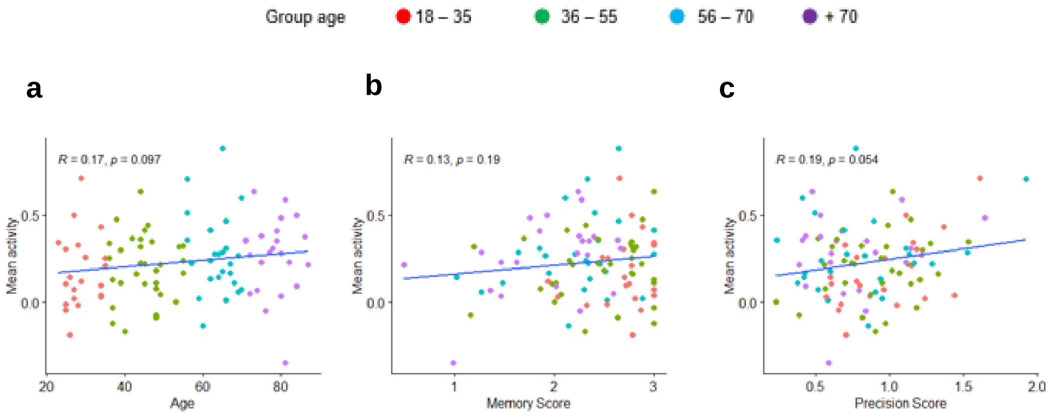


Figure 4. The mean activation between all the ROIs significantly associated with the VSTM task was computed for each participant. Correlation between overall brain activation and age **(a)**, accuracy **(b)**, and precision **(c)**

Network identification

A representation of the parcellation of all the brain voxels into ROIs and the similarity matrix used for the Louvain modularity algorithm can be seen in figure 5.

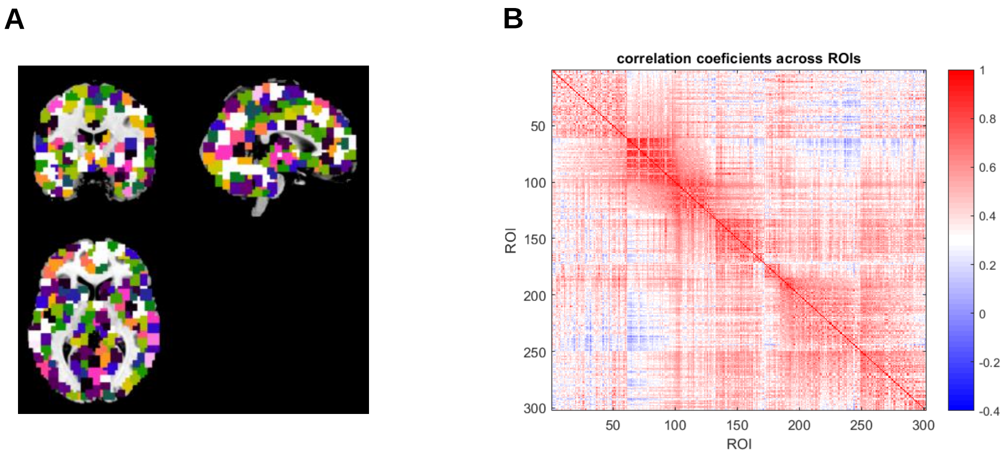


Figure 5. A Parcellation of the brain voxels into 748 anatomically distinct ROIs based on Craddock et al. (2012). **B** Similarity matrix constructed upon the correlation of the load effect sizes between ROIs across all the participants.

The most stable partition, calculated as the highest adjusted mutual information between all the partitions that were performed, was achieved with a RE of 1.2. This partition resulted in a set of 8 brain networks significantly associated with the task. The components of each of these networks were based on the large-scale networks identified and described in Geerligs et al. (2015b). We estimated the proportion of these 16 network labels on each of the networks identified in our analysis. A detailed representation of the networks significantly associated with the VSTM task can be found in figure 6. The first two brain networks were composed mainly of frontal areas and regions involved in attentional and executive processes. Specifically, brain network 1 included 37.2 % of the fronto-parietal control network (FPCN), 19.6 % of the dorsal attention network (DAN) and 17.6 % of the frontal executive network while network 2 contained 49 % of the FPCN. Brain networks 3, 4 and 5 were comprised of more sensory and somato-motor regions. In particular, brain network 3 included 33.3% of the somato-motor network and 23.3% of the auditory network. Network 4 included mainly cerebellar regions (72.4%) while network 5 was composed of visual regions (87.7%). Networks 6 and 7 included parietal brain regions involved in attentional processes. Network 6 included 76.9% of the DAN, while network 7 33.3 % of the DAN and 33% of the FPCN. Finally, network 8 included only regions of the anterior insula.

Network mean activation across participants

We computed the average brain activation across participants for each of the 8 brain networks. We observed a strong positive correlation in the mean activation between all the brain networks (see figure 7). Based on this observation, we decided to regress out the mean activation across regions to evaluate how the modulation from the average relates to age and performance. See supplementary material for further information.

Association between age and network activity

We measured the association between activation in each of the 8 brain networks identified by the modularity algorithm an age (figure 8). We observed a significant relationship between age and activation in some of the networks. Specifically, activation in networks primarily involved in executive and attentional processes such as network 1 (FPCN: 37.2%; DAN: 19.6%; FEN: 17.6%; VAN: 15.6%) and 2 (FPCN: 49%; VAN:14.5%; FEN:14.5%) showed a significant decline with age (r network 1 (100) = - 0.38, p = 7.9-5; r network 2 (100) = - 0.23, p = 0.022) while activation in networks predominantly involved in more sensory and somato-motor processes such as network 3 (Auditory: 23.3%; SMN: 33.3%), 4 (Cerebellum: 72.4%) and 5 (Visual: 87,7%) indicated an opposite pattern of results, revealing a significant increase in activation with age (r network 3 (100) = 0.32, p = 0.0011; r network 4 (100) = 0.24 p = 0.015; r network 5 (100) = 0.32, p = 0.0011).

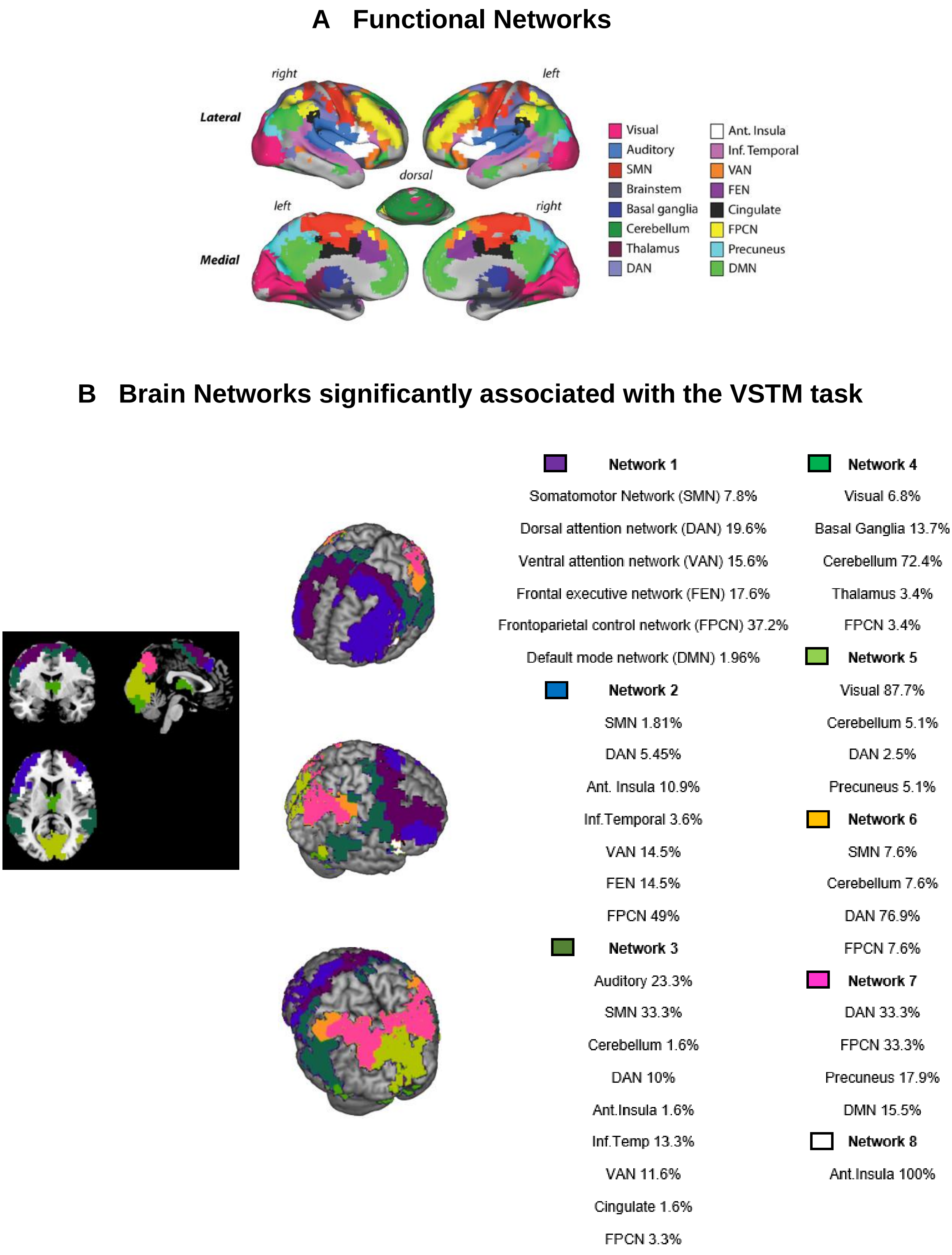


Figure 6. **A** Figure adopted from Geerligs et al. (2015b). The 16 large-scale networks identified in Geerligs et al. (2015b), displayed on inflated surface rendering of the human brain using the CARET program (Van Essen et al., 2001). **B** The 8 brain networks significantly associated with the VSTM task and the proportion of the functional networks identified in Geerligs et al. (2015b) contained in each of our brain networks.

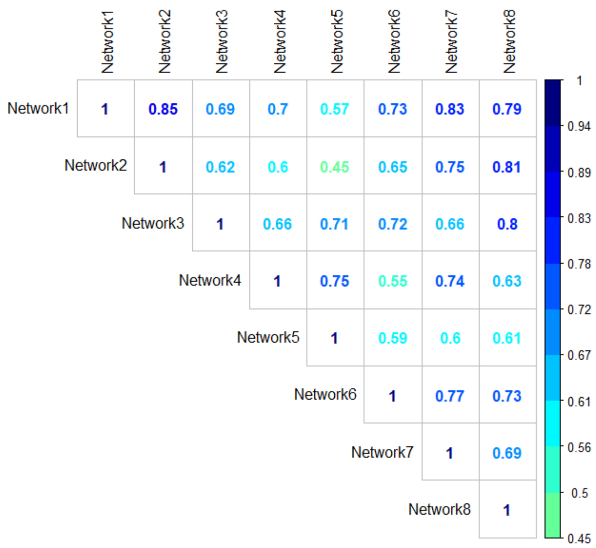


Figure 7. Correlation between the average mean activation among the 8 brain networks. A strong positive correlation between all networks can be observed.

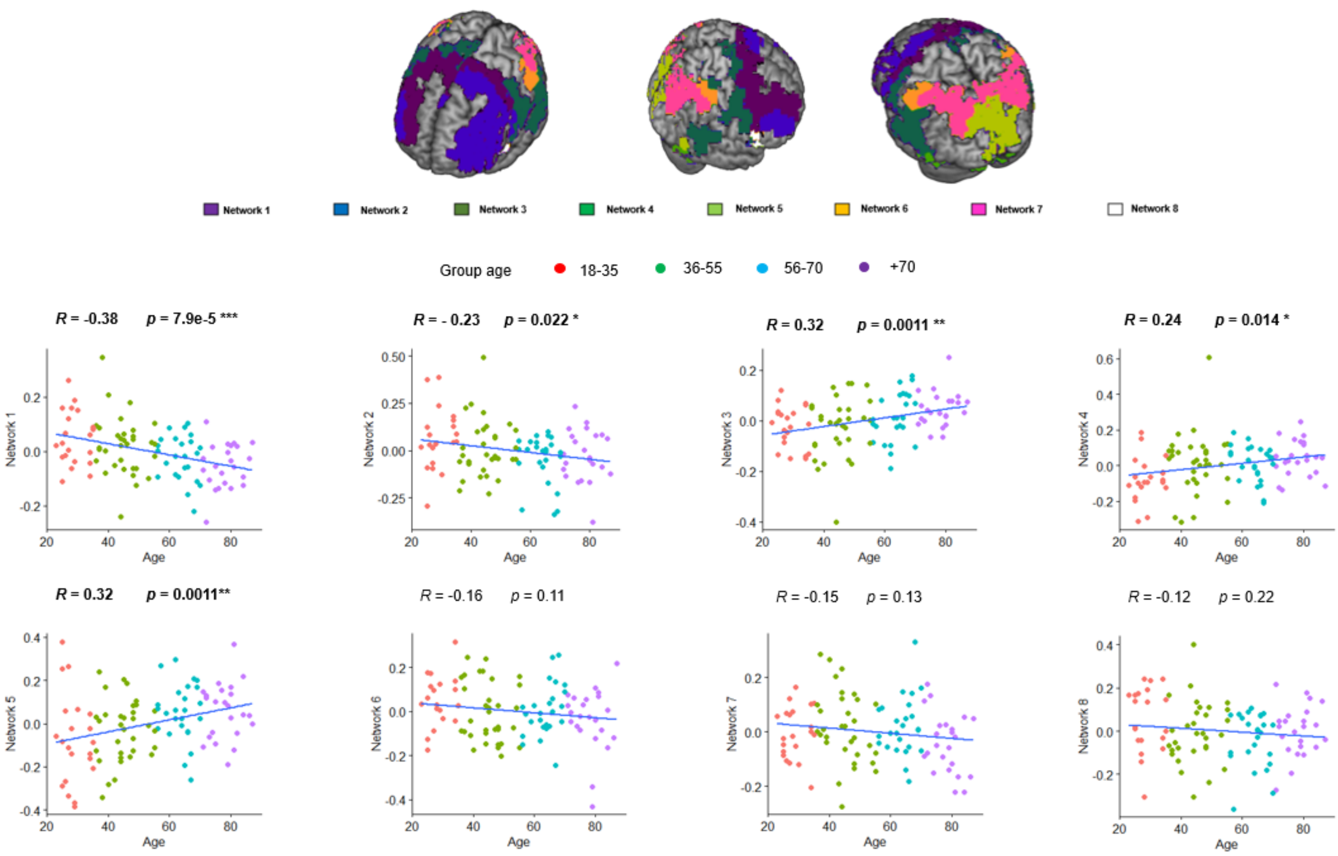


Figure 8. Correlation between activation in each of the networks and age. A significant age-related decline in activation can be observed for brain networks 1 and 2. The activity in brain networks 3, 4, and 5 showed an opposite pattern characterized by a significant age-related increase in activation

Association between performance in the VSTM task and network activity

With regards to the relationship between the activity in the networks and performance in the VSTM task (see figure 9), we found that activation in network 3 showed a negative correlation with accuracy in the task (r network 3 (100) = -0.24, p = 0.01). However, this effect disappeared when controlling for the effects of age in the interaction between network activity and memory performance (r network 3 (100) = - 0.07, p = 0.43). No significant effects were found in the resulting networks.

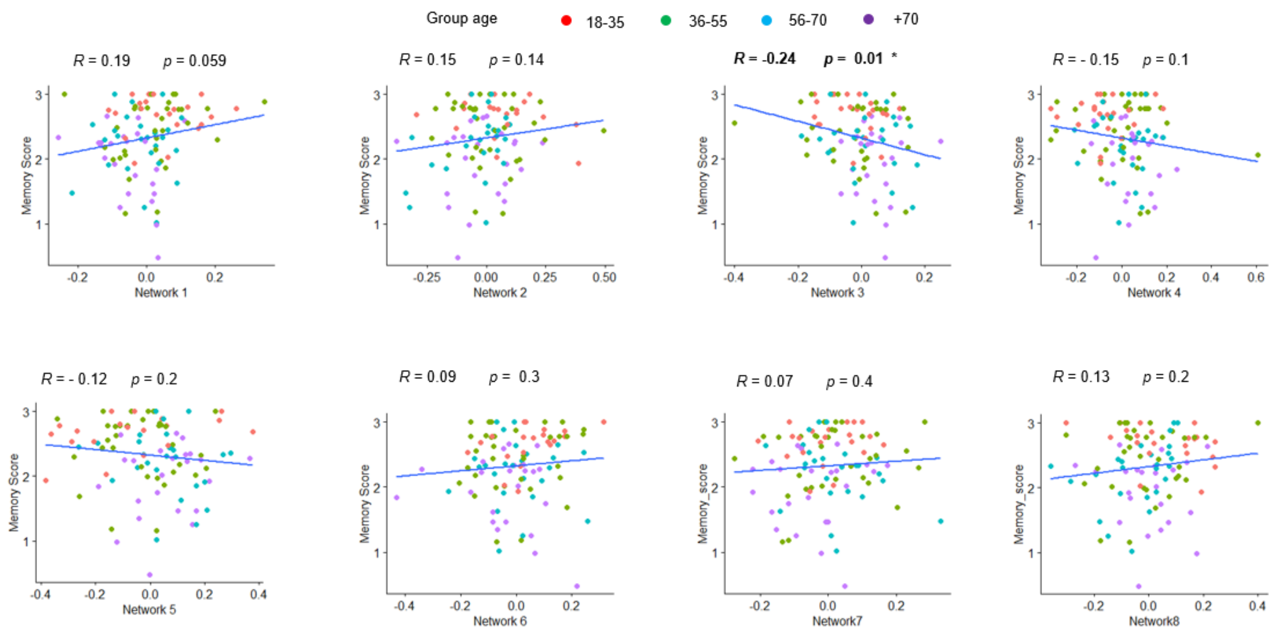


Figure 9 Correlation between activation in each of the networks and accuracy in the VSTM task. Only activation in network 3 showed a negative correlation with accuracy in the task. This effect disappeared when controlling for the effects of age in the interaction between network activity and memory performance.

Subgroup distribution in terms of brain activation

To identify latent subgroups of participants, latent profile models between 1 and 5 classes were estimated based on the average brain activity in each of the 8 networks. The fit indices obtained in the analyses are reported in table 1. The BIC and ICL indicated that a diagonal model with 3 latent subgroups of equal shape, variable volume (VII) fitted the data best (Scrucca et al., 2016) (see supplementary for further information). The likelihood ratio test (LRT) and the non-significant bootstrapping result for 4 classes (p=0.21) suggested that no further improvement was seen when adding one more class to the analysis. Figure 10 shows the distribution of subgroups in terms of the relative differences in brain activation in each of the networks identified in this study. The figure illustrates the distribution of profiles found by the LPA analyses. Group 2 was found to be the larger group (n=66), followed by group 1 (n=21) and group 3 (n=15).

A one-way between subjects ANOVA and follow-up post-hoc comparisons using the Tukey HSD tests were conducted to compare relative differences in average brain activation in each of the networks between the 3 groups. Normality and sphericity assumptions were checked using the graphical representation of Q-Q plot and Mauchly's test. A summary of the differences in brain activation between all the networks can be found in tables 2 and 3. These results suggest a pattern of brain activation in which predominantly executive and attentional networks such as network 1 (FPCN: 37.2%; DAN: 19.6%; FEN: 17.6%; VAN: 15.6%) and network 2 (FPCN: 49%; VAN:14.5%; FEN:14.5%) were over-recruited in group 3, and under-recruited in group 1. However, a reverse pattern of brain activation was revealed for networks primarily involved in somato-motor and lower and higher order sensory processes. Here, the distribution of differences showed that network 3 (Auditory: 23.3%; SMN: 33.3%), 4 (Cerebellum: 72.4%), and 5 (Visual: 87,7%) were over-recruited in group 1 and under-recruited in group 3. The largest differences between groups were found in network 5, a network mostly composed of low and higher order visual areas. A uniform average pattern of average brain activation across all the networks was found for group 2.

Solution	BIC	ICL	LRT	p-value
1 vs 2	1004.817	1004.817	74.64523	0.001
2 vs 3	1037.837	1028.217	55.40535	0.001
3 vs 4	1051.618	1036.054	19.12429	0.214

Table 1: Comparison of Gaussian mixture models based on brain network activity. BIC= Bayesian information criterion; ICL= Integrated Complete-data Likelihood criterion; LRT= Likelihood ratio test

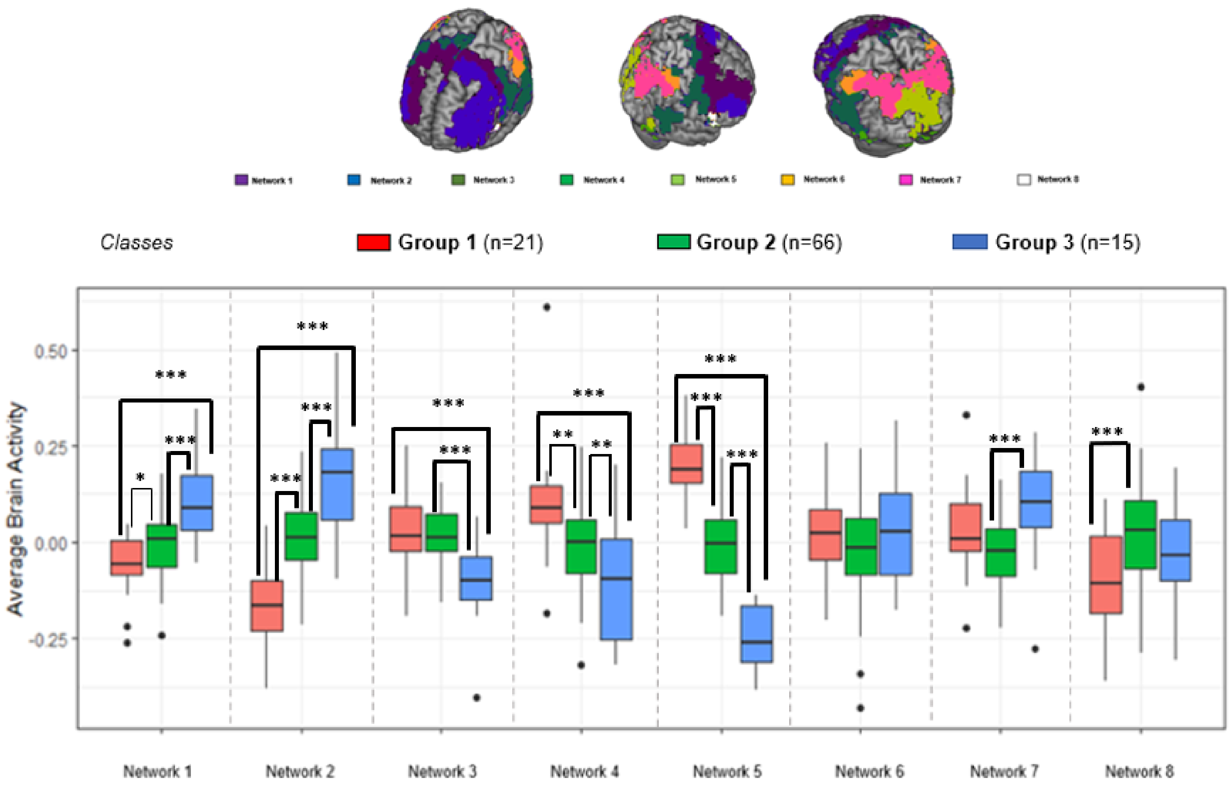


Figure 10 Gaussian mixture modelling classification. Subgroup distribution based on the relative differences in brain activation in networks 1-8. Pattern of brain activation in which predominantly executive and attentional networks such as network 1 (FPCN: 37.2%; DAN: 19.6%; FEN: 17.6%; VAN: 15.6%) and network 2 (FPCN: 49%; VAN:14.5%; FEN:14.5%) were over-recruited in group 3 and under-recruited in group 1. An opposite pattern was revealed for networks primarily involved in somato-motor and lower and higher order sensory processes. Networks 3 (Auditory: 23.3%; SMN: 33.3%), 4 (Cerebellum: 72.4%) and 5 (Visual: 87,7%) were over-recruited in group 1 and under-recruited in group 3. A uniform average pattern of average brain activation across all the networks was found for group 2.

Network	Sum of squares (residuals)	df	Mean square (residuals)	F	p	η²
Network 1	0.246 (0.752)	2,99	0.123 (0.008)	16.217	8.09^{-7}	0.247
Network 2	1.085 (1.073)	2,99	0.542 (0.011)	50.036	9.62^{-16}	0.503
Network 3	0.189 (0.804)	2,99	0.094 (0.008)	11.620	2.93^{-5}	0.190
Network 4	0.367 (1.485)	2,99	0.184 (0.015)	12.24	1.78^{-5}	0.198
Network 5	1.780 (0.809)	2,99	0.890 (0.008)	108.9	2^{-16}	0.687
Network 6	0.058 (1.609)	2,99	0.029 (0.016)	1.78	0.174	0.035
Network 7	0.200 (1.132)	2,99	0.100 (0.011)	8.75	3.15^{-4}	0.150
Network 8	0.248 (1.566)	2,99	0.124 (0.016)	7.84	6.86^{-4}	0.137

Table 2. One-way between subjects ANOVA tests conducted in each network. From left to right: Sum of squares, and in between brackets the square of the residuals. Degrees of freedom, mean square, F values, p values, and the eta squared values (effect size).

	Groups	Mean difference	SE	t	p_{tukey}	Cohen's d
Network 1	1 vs 2	- 0.055	0.022	- 2.535	0.034 *	- 0.679
	1 vs 3	- 0.166	0.029	- 5.643	< 0.001 ***	- 1.727
	2 vs 3	- 0.111	0.025	- 4.448	< 0.001 ***	- 1.247
Network 2	1 vs 2	- 0.189	0.026	- 7.255	< 0.001 ***	-2.084
	1 vs 3	- 0.344	0.035	- 9.775	< 0.001 ***	-2.561
	2 vs 3	- 0.155	0.030	- 5.197	< 0.001 ***	-1.508
Network 3	1 vs 2	0.005	0.023	0.235	0.970	0.062
	1 vs 3	0.125	0.030	4.114	< 0.001 ***	1.139
	2 vs 3	0.120	0.026	4.654	< 0.001 ***	1.420
Network 4	1 vs 2	0.108	0.031	3.524	0.002 **	0.959
	1 vs 3	0.201	0.041	4.854	< 0.001 ***	1.295
	2 vs 3	0.093	0.035	2.650	0.0025 **	0.797
Network 5	1 vs 2	0.208	0.023	9.185	< 0.001 ***	2.281
	1 vs 3	0.450	0.031	14.717	< 0.001 ***	5.328
	2 vs 3	0.242	0.026	9.348	< 0.001 ***	2.626
Network 6	1 vs 2	0.043	0.032	1.331	0.381	0.346
	1 vs 3	- 0.015	0.043	- 0.358	0.932	- 0.115
	2 vs 3	- 0.058	0.036	- 1.589	0.255	- 0.449
Network 7	1 vs 2	0.058	0.027	2.154	0.084	0.583
	1 vs 3	- 0.063	0.036	- 1.756	0.190	- 0.489
	2 vs 3	- 0.121	0.031	- 3. 962	< 0.001 ***	- 1.163
Network 8	1 vs 2	- 0.122	0.032	- 3.883	< 0.001 ***	- 0.983
	1 vs 3	- 0.065	0.043	- 1.531	0.281	- 0.488
	2 vs 3	0.057	0.036	1.592	0.254	0.463

Table 3. Post hoc comparisons between the 3 groups using the Tukey HSD test. Mean difference between groups. SE= standard error, t values, p-value adjusted for comparing a family of 3, and Cohen's d effect size values.

Behavioral differences in the VSTM performance between groups.

Behavioral analyses were conducted to evaluate how the differences in brain activation between groups were related to cognitive performance in the VSTM task (figure 11b). The mean age of each of the groups showed that the groups were composed of people with different age distributions (figure 11a). While group 2 contained people with ages normally distributed across the lifespan (M age = 56, SD age = 17.4), the ages of participant in group 1 (M age = 58; SD age = 19) was significantly higher than participants in group 3 (M age = 36; SD age = 10.7). The result from a one-way ANOVA on the behavioral performance on the VSTM task did not show significant differences between groups in accuracy ($F_{accuracy}$ (2,99) = 2.133, p = 0.12) nor in precision ($F_{precision}$ (2,99) = 1.5, p = 0.214). However, when comparing individually each of the group with a Welch two sample t-test, and Bonferroni correcting the p value, we showed that the accuracy in the task was significantly higher (t (33) = -2.44, p = 0.03) in group 3 ($M_{accuracy}$ = 2.56, $SD_{accuracy}$ = 0.37) compared to group 1 ($M_{accuracy}$ = 2.194, $SD_{accuracy}$ = 0.52). The differences between group 2 ($M_{accuracy}$ = 2.31, $SD_{accuracy}$ = 0.56) and group 3 did not survive multiple comparison correction (*p* = 0.08). No significant differences were found in accuracy between groups 1 and 2. No significant differences between groups were found in precision. Taken together, these results seem to suggest that participants who showed greater activation in fronto-parietal and executive networks, and less activation in sensory and somato-motor regions, showed higher accuracy scores in the VSTM task, whereas participants who exhibited an opposite pattern of brain activation (greater activity in sensory and somato-motor networks and reduced brain activity in fronto-parietal and executive networks) showed worse accuracy performance in the task. However, it should be noted that these differences in brain activation must be high to see an effect in cognitive performance as shown by the lack of significant effects in group 2, who showed a uniform average pattern of average brain activation across all the networks and no differences in performance with the other groups.

Network activity and memory performance in older participants

To investigate whether the differences in the profile of activation and cognitive performance were a result of age differences between the groups, we decided to perform the same gaussian mixture modeling approach we used before, but this time only considering the older participants in the sample (n = 51). An arbitrary cut-off (+55 y/o) was used to select the participants.

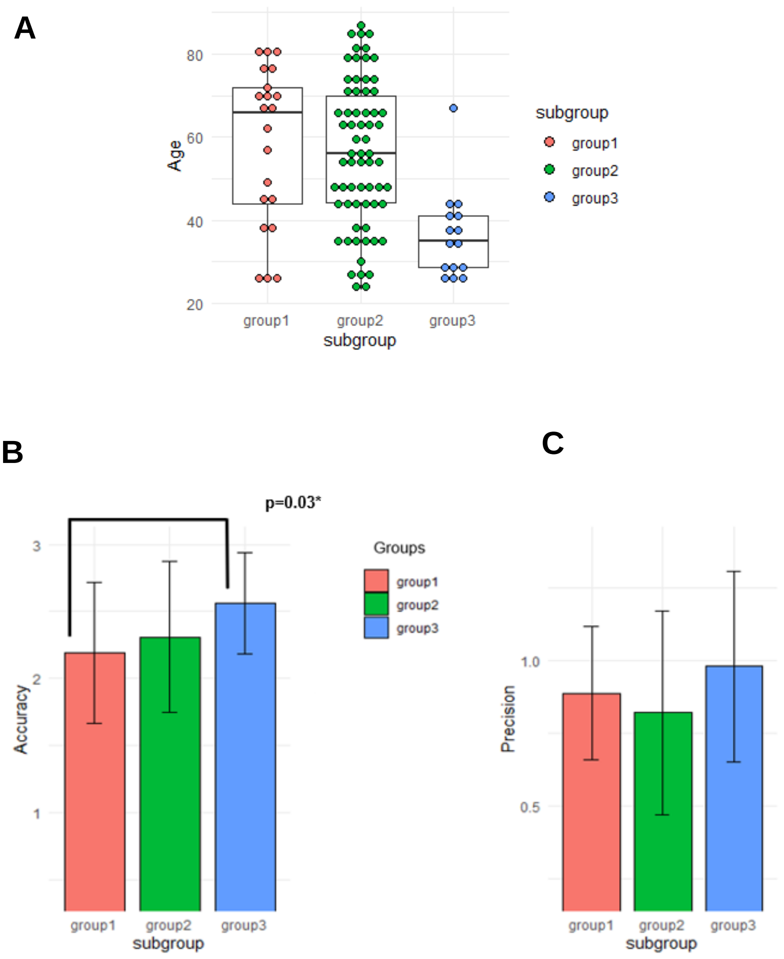


Figure 11 **A** Age differences between the 3 subgroups. **B** VSTM accuracy differences between the 3 groups. Accuracy in the task was significantly lower in group 1 compared to group 3. No significant differences were found for group 1 compared to group 2, and for group 2 compared to group 3.

Subgroup distribution in older participants in terms of brain activation

As before, latent profile models between 1 and 5 classes were estimated based on of the average brain activity in each of the 8 networks. The fit indices obtained in the analyses are reported in table 4.

Solution	BIC	ICL	LRT	p-value
1 vs 2	616.6387	614.3083	60.6202	0.001
2 vs 3	612.4416	599.4965	31.1893	0.006

Table 4. Comparison of Gaussian mixture models on the basis of brain network activity considering only the participants older than 55 years old. BIC= Bayesian information criterion; ICL= Integrated Complete-data Likelihood criterion; LRT= Likelihood ratio test.

This time, the BIC and ICL indicated that a spherical model with 2 latent subgroups of equal volume and shape (EII) fitted the data best (Scrucca et al., 2016) The likelihood ratio test (LRT) and the non-significant bootstrapping result for 3 classes ($p = 0.006$) compared to two classes ($p = 0.001$) suggested that no further improvement was seen when adding one more class to the analysis. Figure 12 shows the subgroup distribution in terms of the relative differences in brain activation. Group 1 consisted of 40 participants while group 2 comprised 11 participants respectively. An independent t-test was conducted in each network to compare the relative differences in brain activation between the 2 groups. Table 5 summarizes the statistical results of the analysis. The results of the analyses are more in line with the pattern of results we found in the previous stage, which showed an under recruitment of executive and attentional networks for one group compared to the other (subgroup 2 vs subgroup 1) and over recruitment of somato-motor and lower and higher order sensory networks by the very same group.

VSTM group behavioral differences between subgroups

As in the previous stage, we evaluated how the differences in the pattern of brain activation for each subgroup were related to cognitive performance in the VSTM task. As figure 13a shows, both groups were composed of participants with similar ages ($M_{group\ 1} = 69$ $SD_{group\ 1} = 9.6$; $M_{group\ 2} = 71$ $SD_{group\ 2} = 6.9$). The differences in accuracy and precision between the two groups were evaluated using a Welch two sample t-test. The result from this analysis suggests that the differences in accuracy and precision were somewhat similar to the results we obtained when participants of all ages were taken into account. However, the differences in accuracy between group 1 ($M_{accuracy} = 2.18$, $SD_{accuracy} = 0.55$) and group 2 ($M_{accuracy} = 1.88$, $SD_{accuracy} = 0.45$) were not big enough to be considered significant ($t(49) = 1.610$, $p = 0.11$). There were no significant differences in precision between group 1 ($M_{precision} = 0.76$, $SD_{precision} = 0.36$) and group 2 ($M_{precision} = 0.90$, $SD_{precision} = 0.245$). These results suggest that in a certain number of older participants, there might be a shift towards less activation in brain networks involved in executive and attentional processes, and more activation in brain networks involved in primarily involved in somato-motor and lower and higher order sensory processes. This shift in the profile of brain activation might be associated with performance differences in the VSTM task.

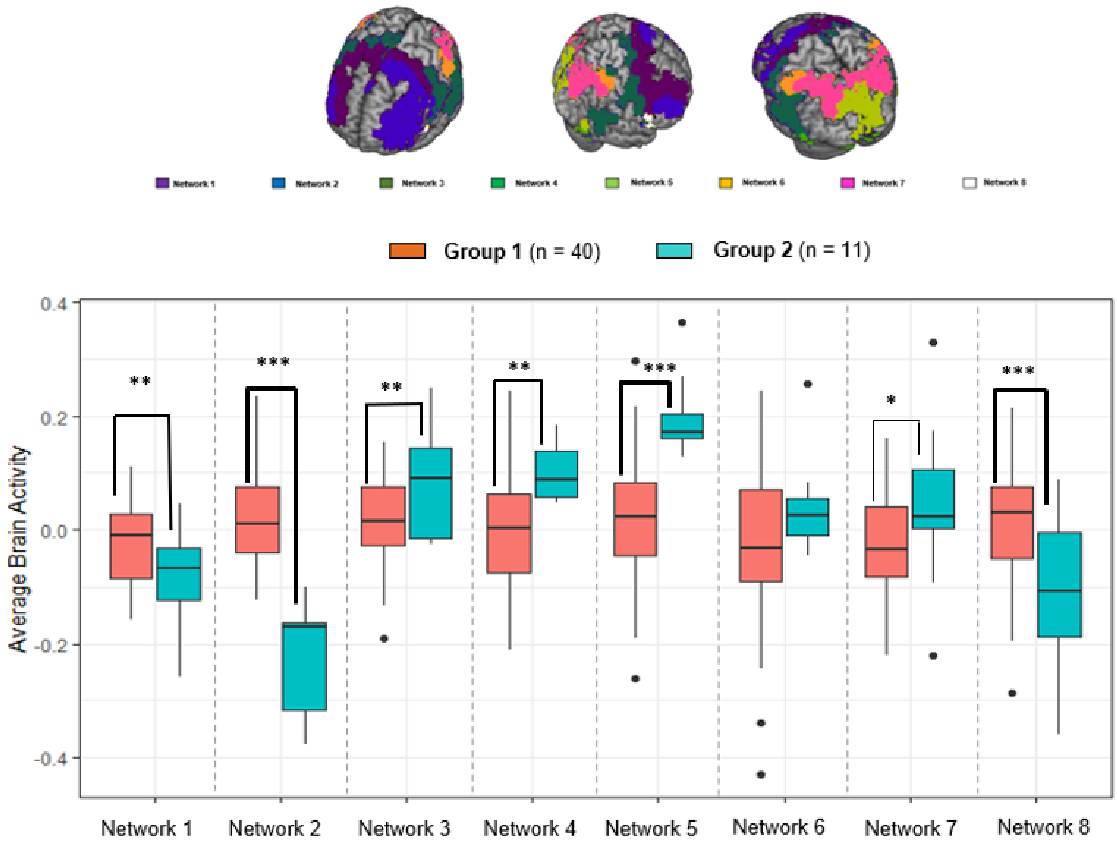
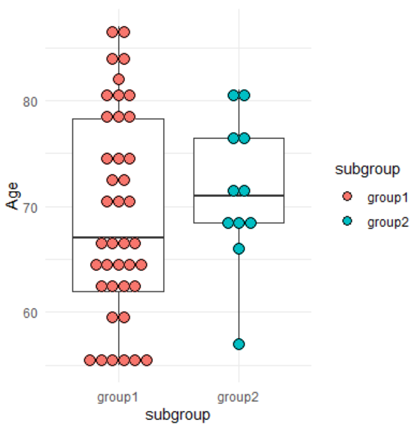


Figure 12 Gaussian mixture modeling classification in participants aged 55 and over. Subgroup distribution based on the relative differences in brain activation in networks 1-8. The largest differences were found in network 2 (comprised of areas involved in executive and attentional processes), network 5 (low and higher visual areas), and network 8 (ant. Insula).

	t	df	p	Cohen's d
Network 1	2.497	49	0.016**	0.850
Network 2	9.097	49	< 0.001***	3.097
Network 3	- 2.482	49	0.017**	- 0.845
Network 4	- 3.062	49	0.004 **	- 1.042
Network 5	- 5.725	49	< 0.001***	- 1.796
Network 6	- 1.489	49	0.143	- 0.507
Network 7	-2.093	49	0.042*	- 0.713
Network 8	3.558	49	< 0.001***	1.211

Table 5. Independent t-test in each network. The biggest differences in brain activation between the 2 groups were found for network 2, network 5 and network 8.

A



B

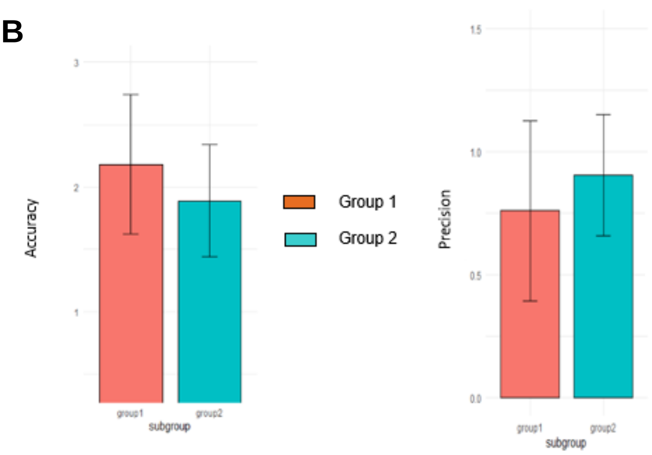


Figure 13. **A** Age differences between both groups. **B** VSTM accuracy and precision differences between the 2 groups. No significant differences both in accuracy and precision were found between the groups**.**

DISCUSSION

The primary goal of this study was to examine how inter-individual variation in the pattern of brain activation was related to changes in the cognitive performance of a VSTM task. We aimed to distinguish neural indicators that could help us better differentiate the spectrum of cognitive performance across the lifespan. However, in order to study the inter-individual variability in brain activation, we needed a different methodological approach than the ones used by standard fMRI analyses. This is an important limitation that we had to overcome since these types of studies usually consider brain activation that is not highly consistent between individuals as a confound or noise. Therefore, we aimed to address this issue by taking an innovative approach to the study of brain activation evoked by cognitive tasks. In order to do so, we grouped brain voxels into a set of ROIs and then selected those that were significantly active in at least 10% of the participants. This allowed us to characterize brain regions that showed less consistent effects between individuals. Subsequently, we correlated the BOLD effect sizes of the ROIs that survived the selection across subjects. If the inter-subject variability is highly correlated between two ROIs, this might suggest that these two areas could belong to the same module. Once we had a matrix with the correlation coefficients between all the ROIs, we applied complex network measures, specifically, an optimization of a Louvain modularity algorithm to identify modules that showed equivalent inter-individual variability in brain activation. Finally, we used latent profile analyses to identify latent subgroups of participants characterized by different levels of brain activation in each module.

One of the most important results of this study is that by using this novel approach, we were able to capture the inter-individual variability in brain activation shown by the subjects when they performed the VSTM task. The output of the modularity maximization algorithm resulted in a set of 8 different brain networks with distinct levels of activation across subjects. By applying latent profile analyses we could describe three subgroups of participants with different profiles of brain activation and different level of performance in the task. While there was one group that showed a uniform pattern of brain activation across all the networks, there were also two subgroups that showed striking differences in the level of activation in some of the networks. In particular, one of the groups showed significantly lower activation in brain networks involving mostly regions associated with FPCN and FEN, and higher activation in regions involving the visual cortex and the cerebellum. Remarkably, the other group showed an opposite pattern of results, displaying higher levels of activation in areas associated with FPCN and FEN and lower activation in visual processing areas and the cerebellum. In addition, the group of participants who displayed higher levels of activation in executive and attentional networks also showed higher accuracy scores in the VSTM task. It is important to note that these effects were highly correlated with age. Activation in brain networks involved in attentional and executive processes showed a strong age-related decline, while brain networks involved in processing somato-motor and low and higher sensory information showed a high age-related increase in activation.

These changes in brain activation between the groups might suggest the use of different cognitive strategies to perform the VSTM task. In this sense, previous research has outlined 2 factors that might be playing an important role in the storage of representations in visual working memory (VWM). First, it is possible that the relative bottom-up perceptual salience of the items determines what is active in VWM and thus guiding attention to the perceptual properties of the stimuli (Fan et al. 2021). However, another factor that might be modulating the storage of information in VWM is the use of semantic coding. In this context, better recall performance is achieved when associating stimulus meaning with the perceptual properties of the stimuli (Brown & Wesley, 2013). Therefore, semantic knowledge may automatically be activated by the perception of a previously encoded stimulus, which in turn, might be sufficient to boost performance (Logie, 2011).

Therefore, these different working memory mechanisms might be related to the result of our study where we showed that in a certain number of participants, and especially when a certain age is reached, there seems to be a shift in activation from frontal and executive areas towards more visual areas. Specifically, some older adults might show greater reliance on external information and perceptual salience rather than in executive processes supporting semantic processing (Lindenberger and Mayr, 2014). For instance, while some might associate the movement of the dots in our task with a particularly known shape, others might guide their attention only to the movement and position of the dots. Lindenberger and Mayr (2014) suggested two possible mechanisms that could be causing this shift from executive processes supporting semantic processing to the over-reliance on the perceptual properties of the environment. The first explanation was grounded within the framework of biased competition (Desimone & Duncan, 1955). This theory postulates that there is some degree of competition between bottom-up representations and top-down signals representing more abstract representations. From this point of view, impairment in the systems that support top-down down processing will result in a greater contribution of bottom-up representations to behavior. However, this account is not entirely accurate as it does not explain why some individuals who show normal abstract thinking, still rely more on the perceptual saliency of the task. Therefore, Lindenberger and Mayr (2014) proposed a second mechanism that might be reflecting a long-term adaptation to a cognitive system that is less able of directing information in a top-down manner. The interaction between both mechanisms might partially explain the differences in activation and cognitive performance that we found between the groups. Current research suggests that as the attentional load of a task increase, older adults are less able to meet the increasing demands of the task, probably as a result of deterioration of frontal-based brain networks such as the FPCN (Campbell et al., 2012) In particular, this network is assumed to implement cognitive control through working memory, attentional selection and error monitoring (Cole & Schneider., 2007; Vincent et al., 2008; Spreng et al., 2010). Hence, when deterioration in networks like the FPCN reaches a certain level, the working memory system which now is less able to manage information in a top-down manner might adapt to maintain similar levels of performance. This adaptation might be reflecting the increases in activation that we observed in sensory regions such as the visual cortex.

Finally, due to some of the limitations of the current study, we could not provide a full picture of the contributing factors that could be causing these differences in activation between the groups. Specifically, the cross-sectional approach of the cam-CAN study did not allow us to evaluate whether the observed changes were a result of compensatory mechanisms or functional dedifferentiation of specialized brain regions. Furthermore, the strong ceiling effects that we found for the VSTM task limited our ability to relate the changes in activation to changes in cognitive performance. In this sense, acquiring longitudinal and ample cognitive data would allow for a more detailed investigation of age-related changes in cognition and neural activation over the lifespan. For instance, what is the time frame in which we are more readily able to observe this shift in activation? What are the factors that might be driving these changes, even when there is no sign of cognitive impairment? In conclusion, future research needs to address the factors contributing to these differences in a more detailed manner, ensuring that the results generalize to intraindividual changes over the life span.

CONCLUSIONS

By taking a whole brain level approach we were able to capture the inter-individual variability in brain activation shown by the subjects when they performed the VSTM task. We found a set of 8 brain networks with different levels of activation across subjects. On the basis of the differences in activation in each of these networks, we identified three subgroups of participants with different levels of activation in these brain networks. We showed two subgroups that revealed opposite patterns of brain activation evoked by the task. One group was characterized by more activation in frontal-based networks and less activation in sensory regions, while the other group showed more activation in sensory regions and less activity in frontal-based networks. A third group showed a uniform pattern of activation across all the networks. This differences in activation between groups might be a result of different cognitive strategies used by the participants. These changes in strategies might reflect an adaptation to a WM cognitive system that is less able to manage representations in a top-down manner.

ACKNOWLEGMENTS

I would like to thank Linda for her constant support during this year and for her effort to keep a great and stimulating work environment. I would also like to

thank Alireza Salami for his feedback and ideas. Finally, I would like to thank my family, who, despite the distance, have always been there.

SUPPLEMENTARY MATERIAL

Second level analyses

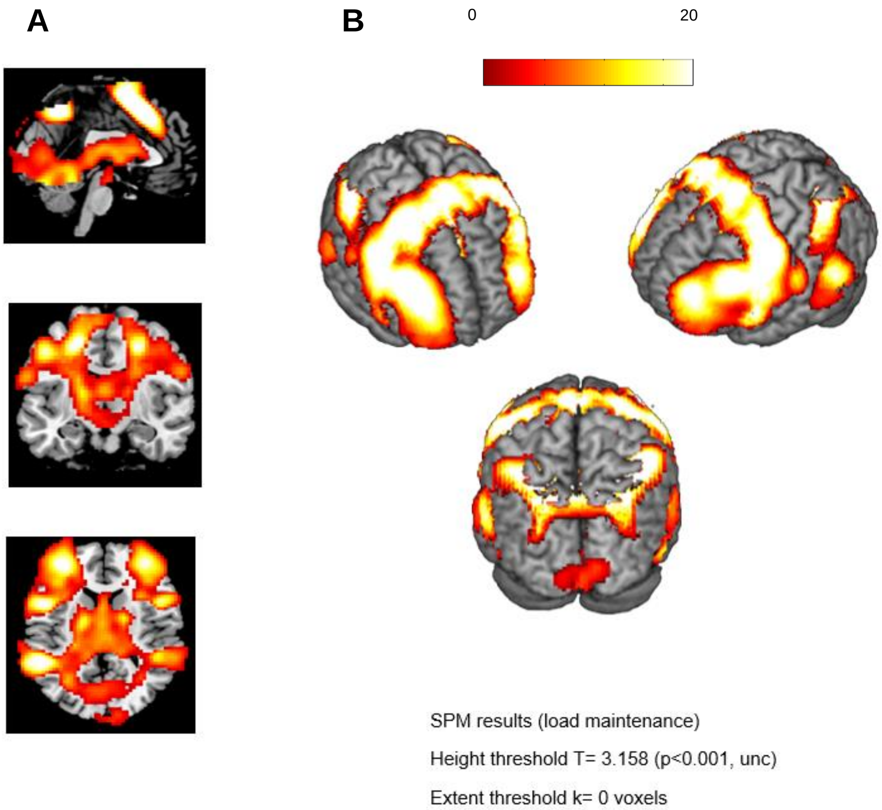


Figure 1 T-contrast derived from the maintenance load condition (difference between the highest and lowest item set size). Significant voxels associated with the VSTM task (T= 3.158, p<0.001 uncorrected). A 2D representation of the cortical and subcortical voxels significantly associated the VSTM task. B 3D representation of cortical areas associated with VSTM.

Network mean activation across participants

Average brain activation

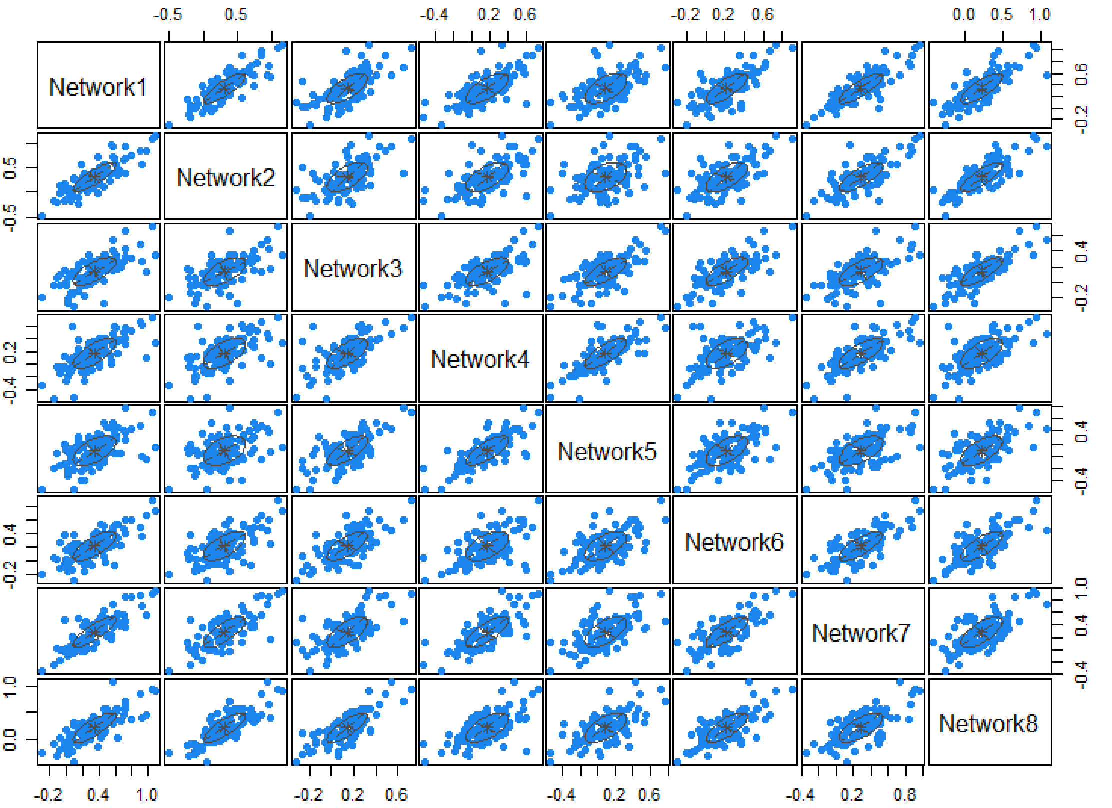
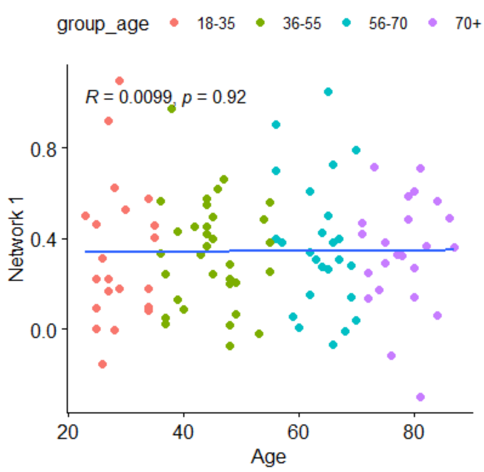
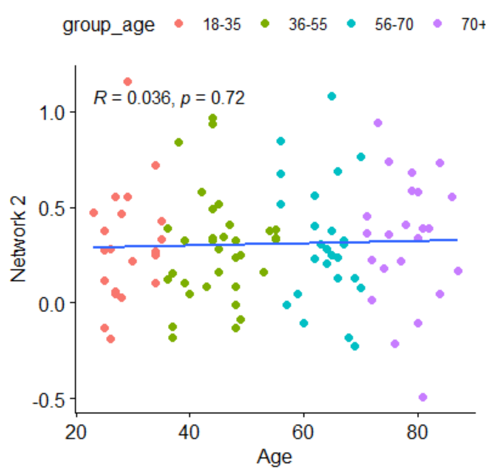


Figure 2. Correlation between the average mean activation among the 8 brain networks. A strong positive correlation between all the networks can be observed.

Analysis made without regressing the mean activation

Association between age and network activation





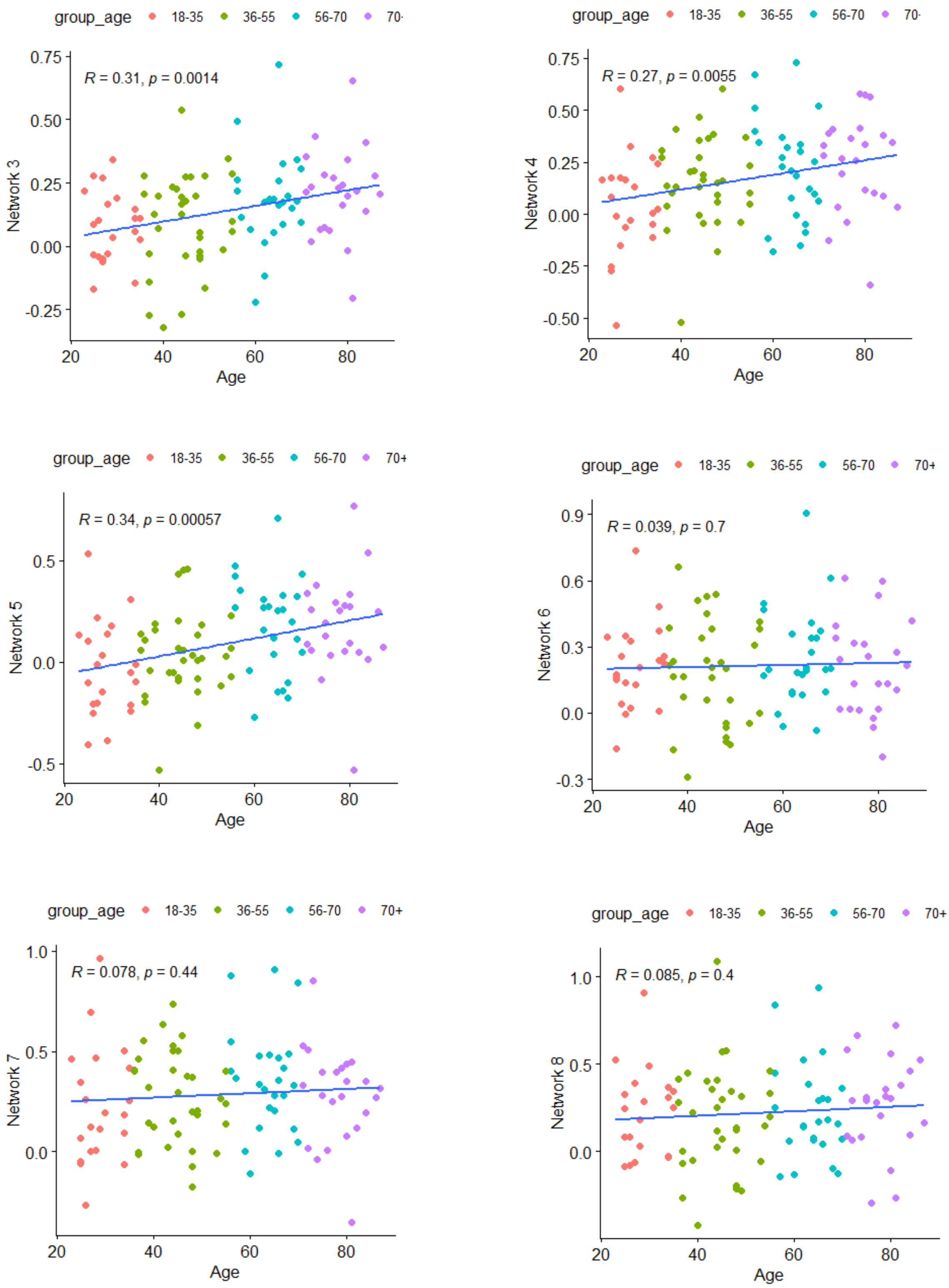
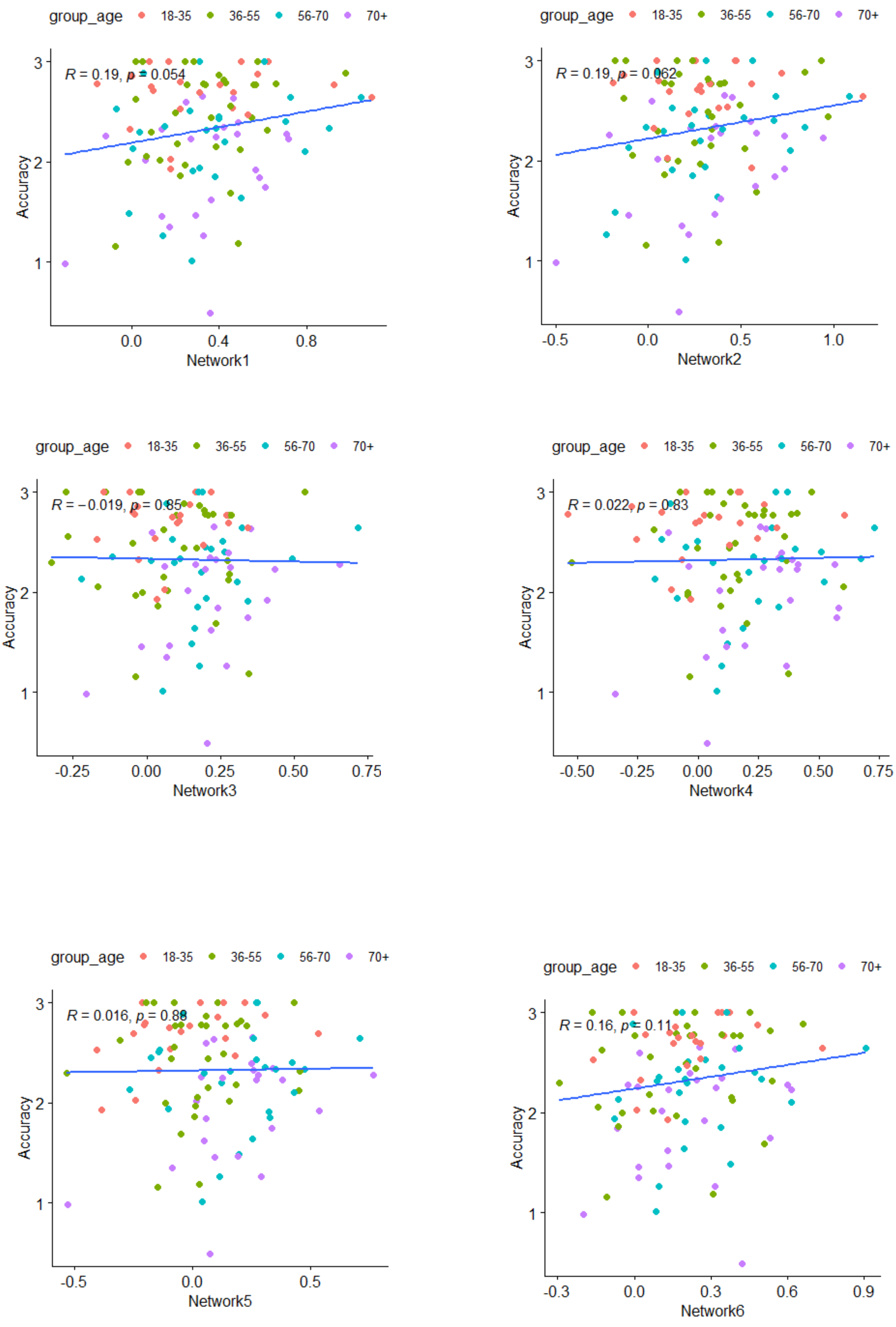


Figure 3. Association between age and brain activation in each of the 8 brain networks. A age related-increase in activation can be observed in brain networks 3, 4 and 5.

Association between network activation and accuracy in the VSTM task



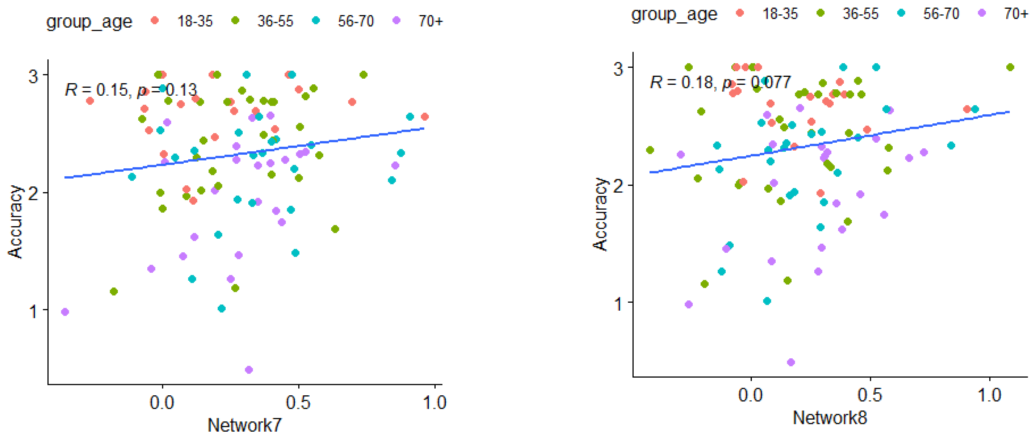


Figure 4. Association between accuracy in the task and brain activation in each of the 8 brain networks. No significant effects were found.

Subgroup distribution in terms of the relative brain activation (modulation from the average)

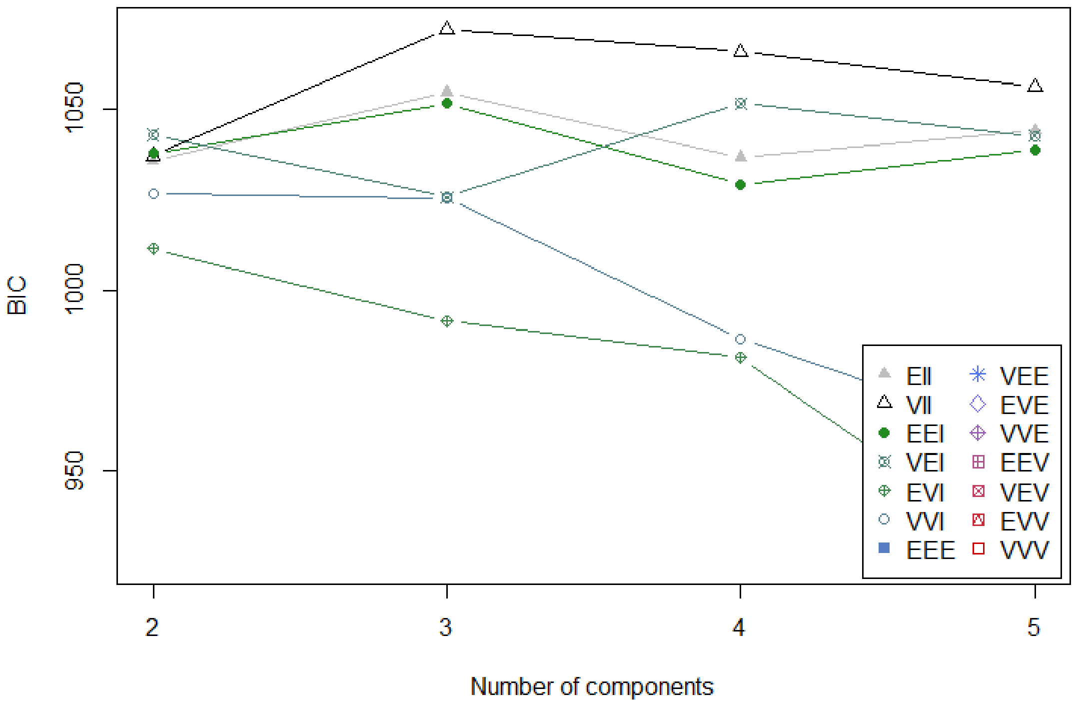


Figure 5. BIC indices obtained in the analyses. The BIC indicated that a diagonal model with 3 latent subgroups of equal shape, variable volume (VII) fitted the data best (Scrucca et al., 2016).

Subgroup distribution

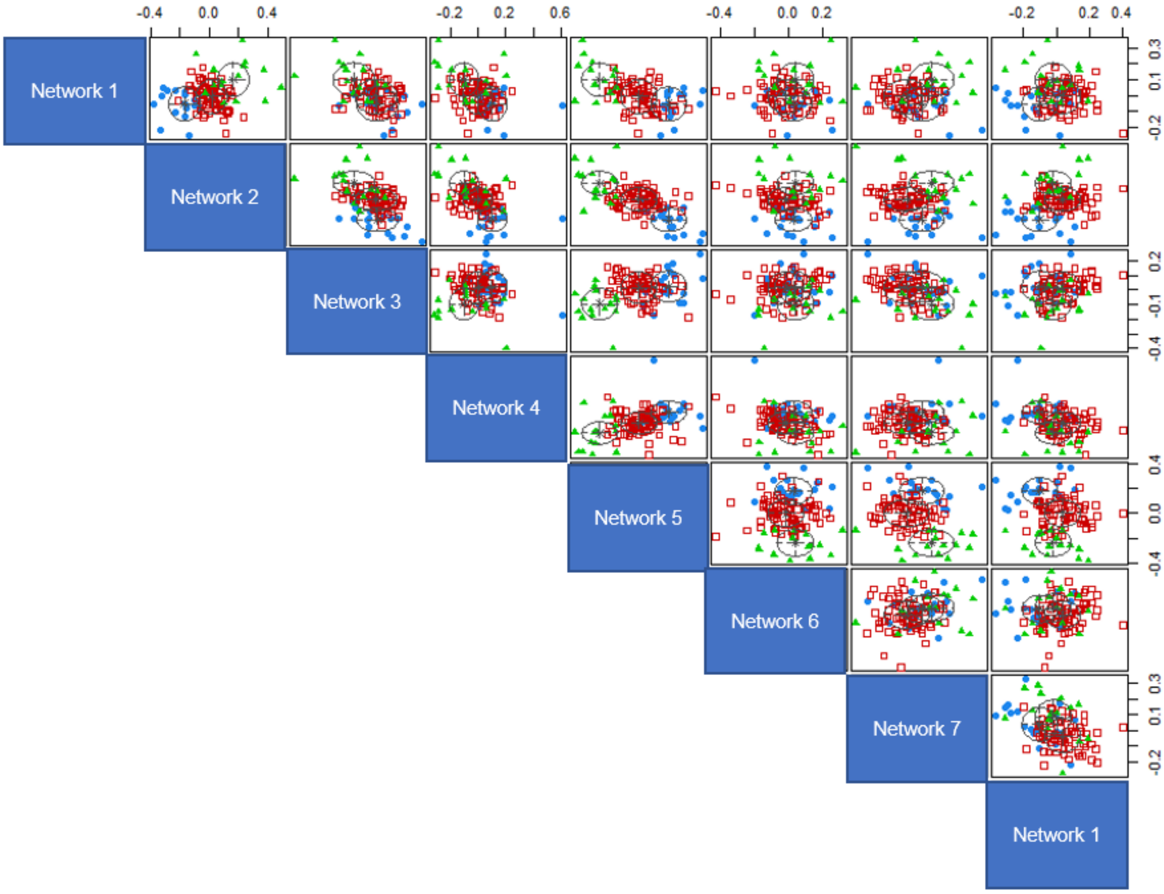


Figure 6. Subgroup distribution according to the VII model. 3 latent subgroups of equal shape and variable volume are identified.

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