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Normal aging modulates prefrontoparietal networks underlying multiple memory processes

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Abstract

Functional decline of brain regions underlying memory processing represents a hallmark of cognitive aging. Although a rich literature documents age-related differences in several memory domains, the effect of aging on networks that underlie multiple memory processes has been relatively unexplored. Here we used functional magnetic resonance imaging during working memory and incidental episodic encoding memory to investigate patterns of age-related differences in activity and functional covariance patterns common across multiple memory domains. Relative to younger subjects, older subjects showed increased activation in left dorso-lateral prefrontal cortex along with decreased deactivation in the posterior cingulate. Older subjects showed greater functional covariance during both memory tasks in a set of regions that included a positive prefronto-parietal-occipital network as well as a negative network that spanned the default mode regions. These findings suggest that the memory process-invariant recruitment of brain regions within prefronto-parietal-occipital network increases with aging. Our results are in line with the dedifferentiation hypothesis of neurocognitive aging, thereby suggesting a decreased specialization of the brain networks supporting different memory networks.

Keywords

working memory; episodic memory; aging; functional magnetic resonance imaging

INTRODUCTION

Memory declines with aging (Salthouse, 2003). Episodic memory (EM) and working memory (WM) show age-related differences in terms of behavioral performance (Hultsch *et al.*, 1998). Evidence from cross-sectional and longitudinal studies (Nilsson, 2003) shows that within long-term memory, EM has the largest decline in older age (Nyberg *et al.*, 2003). Although most cross-sectional studies suggest a constant memory decline from the age 20-30, longitudinal studies tend to postpone its age of onset. EM is relatively stable until the

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age of 60-65 after which performances clearly decline (Finkel *et al.*, 2003; Rönnlund *et al.*, 2005). Similarly, the age of onset of WM decline derived by reasoning tasks, which directly tap on WM function (Kyllonen & Christal, 1990), can be estimated at the age of 55 (Rönnlund *et al.*, 2001; Rönnlund & Nilsson, 2008).

Developmental models of cognition suggest that aging is associated with decreased differentiation of cognitive abilities (Baltes & Lindenberger, 1997). This process is called “dedifferentiation” as opposed to “differentiation” which takes place when children differentiate to highly specialized abilities during development (Garrett, 1946). The correlation between cognitive performances increases with age and this phenomenon is thought to reflect a decline of basic cognitive structures (Baltes & Lindenberger, 1997). Previous studies have identified cognitive task-invariant age-related differences in several cortical and subcortical regions, including increased recruitment of prefrontal (PFC) and parietal cortices, and reduced occipital, temporal and striatal activity (Cabeza *et al.*, 2004; Dennis & Cabeza, 2010; St Laurent *et al.*, 2011). The identification of increased memory task-invariant activation along with increased covariance (which indicates highly correlated response from different brain regions) is supportive of a dedifferentiation process. Both EM and WM are mediated by a common network of brain regions which include PFC and posterior parietal (PPC) cortices (Wagner, 1999). Both PFC and PPC show functional differences with aging (Buckner, 2004; Grady *et al.*, 2010). However, to our knowledge, none of these studies has investigated shared neural effects of aging on WM and the encoding phase of EM.

To identify the common neural substrate of neurocognitive aging of memory, in the current study we investigated age-related differences in brain functional activity and covariance associated with both incidental encoding of EM and WM processing within the same individuals. We studied the encoding phase of EM as alterations in this process are thought to underlie alterations in both EM and WM (Craig & Rose, 2012). We administered an incidental (vs. intentional) EM paradigm to minimize spontaneous elaborative processes (Friedman & Trott, 2000) that are known to cause *per se* a performance decline and an under-recruitment of prefrontal circuits in older relative to younger subjects (Logan *et al.*, 2002). We used joint independent component analysis (ICA), a statistical approach that estimates functional covariance maximizing the cross-information between imaging responses to different functional tasks, to identify patterns of covariance across EM and WM. We tested the following hypotheses: 1) advanced age is associated with increased PFC activity during memory processing independently of performance; 2) PFC-PPC networks show memory task-invariant age-related increases of covariance.

MATERIALS AND METHODS

Subjects

61 right-handed Caucasian subjects (37 younger and 24 older) were recruited for this study (see supplementary materials for details on this cohort). All subjects had normal or corrected to normal visual acuity. Handedness was assessed with the Edinburgh Questionnaire (Oldfield, 1971). Exclusion criteria included past history or the presence of any medical (including diabetes, hypertension, and hyperlipidemia), neurological or psychiatric disorders according to DSM-IV (following a Structured Clinical Interview, SCID-IV, (First *et al.*, 1996), drug treatment (except birth control pills in young women and hormonal substitution therapy in postmenopausal women and subjects with hypothyroidism), past head trauma with loss of consciousness. Older subjects underwent a thorough neuropsychological assessment to evaluate cognitive status and to exclude gross cognitive decline (Mini Mental State Examination >28, Clinical Dementia Rating = 0). All subjects gave written informed consent to take part in the study, which was approved by the Intramural Review Board of the

National Institute of Mental Health. From the initial sample, data from 44 subjects, 22 younger [mean age (SD), 32.6 (10.1); number of females, 11] and 22 older [mean age (SD), 62.37 (5.7); female, 11] matched for gender, education, handedness, as well as 1-back and episodic retrieval accuracy were selected for the analyses (see Table 1).

Tasks

Subjects performed two levels (1-back and 2-back) of the n-back parametric WM task (Callicott *et al.*, 1999) as well as an incidental EM task (Hariri & Weinberger, 2003) while in the scanner.

N-back—Briefly, N refers to the number of previous stimuli that the subject had to recall (see Figure S.2 for a more detailed description). For the WM task conditions (1-back and 2-back) the stimulus consisted of a digit, 1,2,3, or 4 being displayed at one corner of a diamond-shaped box, while the other three corners were blank. Each digit was always presented in the same location. Each trial consisted of stimulus presentation (1.8 seconds) followed by an interstimulus interval (0.2 secs) during which no digits were displayed. A non-memory guided control condition (0-back) that required subjects to indicate the stimulus (digit) they were seeing on the screen, alternated with the WM condition. The 1-back condition required subjects to recollect the stimulus seen one trial before while presented with a new trial. The 2-back condition required subjects to recollect the stimulus seen two trials previously while presented with a new trial. Performance data were recorded as the number of correct responses (accuracy) through the use of a fiber optic response box. The stimuli were arranged in a block-design, and each WM level consisted of eight 30-second blocks: four blocks of control condition (0-back) alternated with four blocks of the WM condition ($n=1$ or $n=2$). Subjects performed one run of 1-back alternating with 0-back and one run of 2-back alternating with 0-back. The order of the task combinations was counter-balanced across subjects. Subjects were asked to respond as accurately as possible pressing one of four buttons with the dominant hand thumb. Buttons were arranged in a diamond-shape configuration, which mirrored the visual presentation of the stimuli.

Incidental Encoding Phase of Episodic Memory Task (EMET)—The paradigm consisted of the incidental encoding of novel, complex scenes. Four encoding blocks were interleaved with a passive cross-hair fixation rest condition, resulting in a total of 9 blocks. During each encoding block, subjects viewed six images, presented serially for 3 sec each in the center of the screen, and responded with a button press (dominant hand thumb) whether each image represented an “indoor” (left button) or “outdoor” (right button) scene. All images were derived from a standardized set (Lang *et al.*, 1997). The order of presentation of the images was counterbalanced for emotional valence across subjects. We restricted our analyses to pictures with neutral valence to avoid age by emotion biasing effects. After the encoding scan (3 – 5 minutes), retrieval performance was evaluated using images already presented during the encoding session (50%) interleaved with new images (50%). Subjects were not told beforehand about the debriefing recognition phase thus making the encoding implicit. They were asked to indicate with a button press whether each scene was “new” (right button) or “old” (left button). Their responses were recorded and analyzed for accuracy and reaction time. BOLD fMRI was performed during the retrieval session as well, but it was not analyzed in the current study given the relatively small sample size with respect to the number of task features analyzed.

Imaging

Structural imaging acquisition and processing—Three-dimensional structural MRI scans were acquired on a 1.5-T GE scanner in a subset of subjects matched for gender, IQ, race and performance (see Table S.1) using a T1-weighted SPGR sequence (TR/TE/NEX

24/5/1, flip angle 45°, matrix size 256 × 256, FOV 24 × 24 cm) with 124 sagittal slices (0.94 × 0.94 × 1.5 mm resolution). These scans were segmented into grey matter, white matter and cerebro-spinal fluid, spatially normalized into a standard stereotactic space (MNI template) and modulated using the unified segmentation approach in SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/>).

BOLD fMRI - Acquisition and processing—Each subject was scanned on a GE Signa (Milwaukee, WI) 3T scanner. A gradient echo BOLD-EPI pulse sequence was used to acquire 120 images per each N-back run and 170 images for the EMET. Each functional image consisted of 24 (N-back: 6-mm-thick; EMET: 5-mm-thick) axial slices covering the entire cerebrum and most of the cerebellum (N-back: TR/TE= 2000/30 ms, field of view= 24 cm, flip angle= 90; EMET: TR/TE= 2000/28 ms, field of view= 24 cm, flip angle= 90).

Images were processed using SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/>). Briefly, images were realigned to the first image of the scan run using INRIalign, spatially normalized to a 3x3x3 mm³ voxel size into a standard stereotactic space (MNI template) using an affine and nonlinear transformation, and smoothed using a 8 mm full width half maximum isotropic 3D Gaussian kernel. The data were temporally high pass-filtered with a cut-off frequency of 1/120 Hz for N-back tasks and 1/84 Hz for EMET to remove the effects of scanner signal drifts. For each experimental condition, a box car model convolved with the hemodynamic response function (HRF) at each voxel was modeled. Subject-specific movement parameters obtained from the realignment procedure were included in the model as covariates, taking into account the effects of subject motion. In the first level analyses, linear contrasts were computed producing t-statistical parameter maps at each voxel for 1-back as well as 2-back relative to 0-back for N-back, and visual stimulus encoding relative to fixation for EMET, respectively.

These statistical images were entered in a second-level random effects model to identify age-related differences of brain activation (repeated measures ANCOVA with WM accuracy as a nuisance variable for N-back and a two sample t-test for EMET). Statistical threshold was set at $p < 0.05$ corrected for the false discovery rate (FDR). Small volume correction (SVC) for lateral PFC including BAs 9 and 46, and hippocampal formation including hippocampus and parahippocampal gyrus was implemented using WFU Pick Atlas for N-back and EMET respectively. Previous reports have demonstrated robust task-related activations that show relevant age-related modulation in these regions (Mattay *et al.*, 2006; Murty *et al.*, 2009).

To assess common areas of age-related differences in activation across memory tasks, we created conjunction maps of the contrast images showing age-related effects for both older>younger and younger>older comparisons. Contrast images were masked inclusively for the main effect of the task ($p < 0.05$) and thresholded with $p < 0.1$ so that the resulting conjoint probability of the conjunction maps was $p < 0.001$ (Allan *et al.*, 2000; Cabeza *et al.*, 2004).

Joint Independent Component Analysis (joint-ICA)—A joint Independent Component Analysis was performed on the data using the Fusion ICA Toolbox [FIT; http://icatb.sourceforge.net/fusion/fusion_startup.php]. This technique presents several advantages in data fusion analysis over traditional techniques used in the analysis of functional connectivity. Compared to seed-based connectivity, joint-ICA is a multivariate analysis, which decomposes patterns of brain signals into spatially independent sources that are not confined single regions of interest. Compared to standard spatial group ICA, joint-ICA allows the identification of brain networks recruited during each individual task maximizing the estimation of shared pattern of covariance over subjects and not the identification of

independent components that are specific per task. Although the shared dependence of brain responses to EM encoding and WM across subjects could be detected by other multivariate techniques (e.g., Partial Least Squares), joint-ICA allows the estimation of networks of brain regions that are functionally covariant and are not necessarily anatomically overlapping across tasks (Calhoun *et al.*, 2006). Furthermore, the use of second level analysis indices ('features') increases the sensitivity for the detection of canonical brain responses as well as the computation of covariance matrices with a smaller dimensionality compared to voxel-wise 4D matrices that are required in first level analysis techniques (see Calhoun *et al.*, 2009 for a review).

This multivariate technique allows the analysis of covariance of all the brain features (activation maps in our study) across subjects by decomposition into joint spatially independent components and a common mixing matrix, which includes subject-specific weights for each component (see Figure S.1). Features are biological indices measured in individual subjects such as functional and structural imaging data, electroencephalographic data, genetic data, etc. (Calhoun *et al.*, 2009). All features are assumed to have similar linear covariation across subjects. Also, imaging features are estimated from first levels analysis and thus have low dimensionality and are more computationally tractable. For this analysis, the individual subject contrast images with both positive and negative activations for 1-back, 2-back and EMET were used as features. Joint ICA identifies sources associated with features from each of the datasets included (e.g. 1-back, 2-back and EMET in our study) that modulate the same way across all the subjects. Although theoretically these covariance patterns may vary spatially across modalities or tasks, in our study they overlap in the PFC-PPC network. This spatial overlap supports our hypothesis of age-related change of a core cognitive process common to all the administered tasks. Initially, brain features undergo spatial concatenation, which combines all of the data from each subject into a single dataset. The ICA model is completely blind of which voxels belong to which task and therefore the identified joint components span across multiple tasks. Since the patterns of covariance are estimated across subjects and not across tasks they may not overlap spatially. Indeed, each spatial component identifies a spatial mode, which includes the three spatial maps, one for each task, which is present in all subjects at various levels and measured by a mixing coefficient. Mixing coefficients are a measure of each subject's contribution to the joint independent component reflecting shared covariance of regional activity within networks (Calhoun *et al.*, 2006), and can be interpreted as individual subject's measures of network activity. Features were normalized across all subjects and all voxels using the square root of the mean of the contrast images to obtain the same average sum-of-squares for each task, which allows a similar weighting of each task. A feature matrix including features for each task stacked side by side across all the participants was computed. The dimensionality of the functional data of this matrix was reduced using Principal Component Analysis to 11 principal components as estimated by minimum description length criteria (Li *et al.*, 2007). A spatial ICA decomposition using the extended-Infomax algorithm was used to extract a common mixing matrix and 11 joint independent components including three spatial maps, one for each task. These spatial maps identify network covariance patterns within and across tasks. After 100 runs of ICA, averaged estimated sources were group back-reconstructed. The estimated joint ICA mixing coefficients, which represent the degree of contribution of each individual subject to the joint component across the entire sample, were compared across age groups using a two sample t-test. Only the joint components that show significant age-related differences ($q\text{-FDR} < 0.05$) in mixing coefficients were considered for further analysis (joint independent component of interest, jCOI). Joint independent components were calibrated using Z-scores and reconverted into spatial images. Each joint independent component included networks of brain regions that correlate directly (positive network) or inversely (negative network) with the mixing coefficients.

Mixing coefficients were correlated with performance in the whole group as well as in each age group separately.

Structural analysis—To ensure that these differences were not unduly driven by age-related structural differences in the brain, we analyzed the normalized, modulated grey matter images across age. Structural MRI data were available only in a subsample of 25 subjects (9 younger and 16 older subjects). Grey matter volumes were calculated within the mask $|Z| > 1.5$ of the jCOIs for each task. These measures were entered in a general linear model to compare mixing matrix loadings across age groups covarying out grey matter volumes.

Demographics and behavioral data—Two sample t-tests and chi-square tests were used to compare continuous and categorical variables respectively. Correlation analyses were performed with Pearson's r test.

RESULTS

Behavioral results

Age groups were matched for accuracy (percent correct) on the 1-back WM and on the recognition phase of the episodic memory task (see Table 1, all $p > 0.2$). At 2-back older subjects showed decreased accuracy relative to younger subjects ($t_{42} = 4.75$, $p < 0.001$).

GLM results

Contrast images were also analyzed using second level analyses in SPM5. For the N-back tasks, a two way repeated measures ANCOVA reported greater DLPFC ($p < 0.05$ FDR-SVC corrected for PFC) activation in older relative to younger subjects. Both groups showed a task-load (2-back > 1-back) related increased activation of a network of brain regions that included bilateral DLPFC, VLPFC, posterior parietal cortex, anterior cingulate and putamen ($p < 0.05$ FDR). During the EMET, older subjects showed relatively lower activation in the left hippocampus ($p < 0.05$ FDR-SVC) along with an increased activation in bilateral prefrontal cortical regions ($p < 0.005$) when compared to younger subjects.

Task-induced deactivations during N-back were lower in medial prefrontal cortex, posterior cingulate as well as in the left lateral posterior parietal cortex in older relative to younger subjects ($p < 0.05$ FDR). During the EMET, task-induced deactivations were greater in precuneus and lower in bilateral temporo-parietal junction and posterior cingulate regions ($p < 0.005$) in older subjects relative to younger subjects. Conjunction analysis showed greater activation in left DLPFC ($x = -51$, $y = 27$, $z = 21$; BA45/46) (Figure 1.A) and lower activation in bilateral superior parietal lobule (left, $x = -24$, $y = -69$, $z = 39$; right, $x = 21$, $y = -72$, $z = 57$) and SMA ($x = 0$, $y = 12$, $z = 48$) in older compared to younger subjects across all three tasks. Additionally, older subjects showed greater task-induced deactivation in posterior cingulate ($x = -6$, $y = -66$, $z = 15$; $x = -9$, $y = -51$, $z = 24$), left posterior parietal ($x = -48$, $y = -66$, $z = 21$) and BA8 ($x = 21$, $y = -36$, $z = 63$) relative to younger subjects (Figure 1.B).

Joint-ICA results

One jCOI had a significant age-related difference in joint-ICA loadings (another jCOI showed uncorrected significance for an age effect but did not survive the correction for multiple comparisons, see supplementary material), which reflect differences in the degree of functional covariance between the brain regions identified by the joint component across tasks. Two sample t-test showed that older subjects had significantly greater mixing coefficients for the jCOI compared to younger subjects ($t_{42} = 3.304$, $p = 0.002$ FDR corrected;

Figure 2.A). Mixing coefficients for the jCOI were negatively correlated with accuracy at 2-back ($r=-0.47$, $p=0.001$; Figure 2.B), but not at 1-back and EMET. To exclude that this correlation was driven by the effect of age, we entered these data in a multiple regression model with the mixing coefficients as dependent variable, and age and accuracy at 2-back as predictors. The results of this analysis confirmed the significant negative relationship between the mixing coefficients and the accuracy ($R^2=.2667$, $F(2,41)=7.456$ $p<0.001$: beta of accuracy= -0.34 , $p=0.031$; beta of age= 0.24 , $p=0.119$). We did not find any mixing coefficient performance correlation in within-age group analyses. The jCOI identified a positive functional covariance network (see Table S.2) that encompasses the following regions for N-back (Figure 3.A, B): bilateral VLPFC, DLPFC as well as inferior parietal lobule and visual cortex; and for the EMET (Figure 3.C): bilateral DLPFC, inferior parietal lobule as well as secondary visual cortex. For N-back, the negative covariance network (see Table S.3) included the precuneus and right superior parietal cortex, and for the EMET this included midline regions including medial PFC, posterior cingulate and precuneus.

The intersection of positive network maps identified left DLPFC (BA45/46), left SMA, and bilateral ventral PPC extending into extrastriate visual cortex (Figure 4.A). The intersection of negative maps included the precuneus and ventromedial PFC (Figure 4.B).

Structural results

Grey matter volumes of the brain regions within the jCOI networks were reduced in older compared to younger subjects (all $p<0.001$). A multiple regression on the mixing coefficients with age group as predictor and grey matter volumes within the jCOI mask as covariates of no interest confirmed increased mixing coefficients in older relative to younger subjects ($p<0.001$, FDR corrected).

DISCUSSION

In this study we investigated age-related differences of activity and functional covariance across multiple tasks in the brain regions subserving WM and EM encoding. During both types of tasks, older subjects showed greater prefronto-cortical activation along with lower deactivation of the default mode network (DMN) relative to younger subjects. We found a functionally covariant network of brain regions across both WM and EM encoding that was modulated by age, with older subjects recruiting this network to a greater extent. Analysis using a spatial conjunction of the brain networks revealed a positive covariance network, which included prefrontal, parietal and occipital regions, and a negative covariance network which spanned across the DMN regions. Older subjects showed greater engagement of these covariance networks irrespective of the memory task at hand when compared to younger subjects.

In older subjects, functional covariance was greater relative to younger subjects within higher-order brain networks that included the bilateral PFC, parietal and occipital cortices for WM and bilateral DLPFC, SMA and bilateral posterior cortex and occipital cortex for EM encoding. The spatial conjunction of these circuits identified a common positive functional covariance network including left DLPFC, SMA and ventral PPC extending to visual cortex. These regions have been implicated in memory for their individual contribution as well as in the context of large brain networks. DLPFC has been shown to subserve domain non-specific cognitive processing with a specific role in contextual control. This process involves maintaining contextual signals or task sets to flexibly perform cognitive tasks, including WM and EM encoding (Koechlin *et al.*, 2003). Ventral PPC plays an important role in regulating the focus of attention. According to Corbetta's dual-attention model of PPC (2008), the ventral part of this region mediates reflexive reorienting of attention with a bottom-up mechanism (Ciaramelli *et al.*, 2008). Salient and behaviorally

relevant environmental stimuli can reorient the focus of attention thus contributing to EM encoding and WM (stimulus-driven attention(Corbetta *et al.*, 2008)).Moreover,the PFC-PPC network is involved in parallel-distributed processing across different types of memory (Diwadkar *et al.*, 2000; Babiloni *et al.*, 2004; Babiloni *et al.*, 2006). The activity of this circuit could be associated with the attentional regulation that is crucial for maintaining a representation required for delayed response tasks as well as for the episodic encoding of the memoranda (Rossi *et al.*, 2006).Additionally, the positive functional covariance network identified in our study was negatively correlated with the medial PFC, the posterior cingulate and the precuneus. These brain regions spatially overlap with the default mode network (DMN)(Raichle *et al.*, 2001), which is a large-scale interacting brain system whose activity has been shown to attenuate during an active task. The DMN is involved in monitoring external as well as internal environment (Raichle *et al.*, 2001)along with mentation and attention(Buckner *et al.*, 2008). Alterations of DMN function have been implicated in aging and in severe neuropsychiatric disorders with cognitive impairments(Sambataro *et al.*, 2010a; Sambataro *et al.*, 2010b). Greater recruitment of DMNregions in the older subjects compared to younger subjects may reflect an increased allocation of attentional resources to the task at hand in older subjects (Sambataro *et al.*, 2010a).

Notably, the positive functional covariance network also included sensory-motor regions, primary visual and pre-SMA that are not part of a classical cognitive network in younger subjects. Previous neuropsychological and neuroimaging studies have demonstrated age-related decline in sensory-motor systems as indicated by increased reaction time, reduced visual and auditory acuity(Lindenberger & Baltes, 1994), and increased brain activation in the brain regions underlying those processes(Carp *et al.*, 2011a; Van Impe *et al.*, 2011).Furthermore, age-related differences in sensory-motor function are strongly correlated with cognitive function thus supporting a shared mechanism (Lindenberger & Baltes, 1994; Baltes & Lindenberger, 1997). Consistently, our finding of increased covariance of responses of brain regions within the executive and sensory systems may reflect a non-specific recruitment of these brain regions.

Previous imaging studies of memory have reported age-related differences in lateral PFC function (Mattay *et al.*, 2006; see Spreng *et al.*, 2010 for a metaanalysis). In our study, older subjects have greater activation in DLPFC (especially in the left hemisphere) relative to younger subjects irrespective of the type of memory process at hand.Older subjects were matched for 1-back, episodic retrieval performance thus reflecting a selected cohort of super-performing individuals. Increased DLPFC activation during memory processing has been frequently reported in older subjects when maintaining performance at the levels of younger subjects (Cabeza *et al.*, 2002; Rajah & D'Esposito, 2005). In particular, increased PFC activation in older subjects has been associated with better performances (Rypma & D'Esposito, 2000; Grady *et al.*, 2003; Persson *et al.*, 2004; Rypma *et al.*, 2007), and a recent review identified this finding in 35% of older subjects with successful cognitive aging (Eyler *et al.*, 2011). Other studies suggest that the age-related increase of PFC activation during memory processing may reflect a necessary response for better performance only in super-performing older subjects (Nyberg *et al.*, 2010). Further studies with lower performing older subjects or with task difficulty titration to individual subjects are needed to ascertain the effect of the performance selection bias.

Dedifferentiation is a model of brain aging that interprets cognitive impairment as resulting from a decrease in differentiation of specialized cognitive abilities (Baltes & Lindenberger, 1997). Previous studies have identified age-related differences in functional activation and deactivation across hemispheres and within the same hemisphere, predominantly in prefrontal, occipital and temporal regions as supportive of this model, with older subject

showing increasing widespread activity (Dolcos *et al.*, 2002). These effects were shown in all types of working memory (verbal vs spatial, Reuter-Lorenz *et al.*, 2000), visual processing (objects vs faces and places, Grady *et al.*, 1994; Park *et al.*, 2004; Park *et al.*, 2012), in learning (implicit vs explicit, Dennis & Cabeza, 2010), and more recently in motor systems (Carp *et al.*, 2011a). Our study extends the findings of previous literature on age-related dedifferentiation to memory systems. Within the positive functional covariance network, the brain regions that showed greater task-invariant covariance in older relative to younger subjects included left DLPFC and bilateral ventral PPC extending to extrastriate cortex. This network plays a crucial role in executive processing and as such, alteration of its function may impact on multiple cognitive domains. The age-dependent increase in the recruitment of this network may reflect dedifferentiation (Lövdén & Lindenberger, 2005) where increased functional covariance non-specifically supports both memory functions indicating less distinct processing pathways (Li & Sikstrom, 2002). Increased functional covariance indicates greater correlation and hence decreased specialization of prefrontal and parietal activity during performance of a cognitive task (Li & Sikstrom, 2002). The engagement of the occipital cortex together with the prefrontal and the parietal regions also add further support to dedifferentiation of visual systems with aging (Carp *et al.*, 2011b). Alternatively, the recruitment of this network may reflect attempted compensation (Rajah & D'Esposito, 2005). Older subjects may recruit this network in a non-memory specific manner to compensate for age-related decline of cortical efficiency that is evident already at low WM loads (Mattay *et al.*, 2006). As WM load increases, memory representations become more fragile and task demands become greater thus making the recruitment of a non specific network not beneficial and this may represent failed compensatory overactivity.

Consistent with these imaging findings, behavioral studies show strong correlations between performance on multiple cognitive tasks of processing speed, fluid intelligence, and crystallized intelligence as measured using psychometric batteries such as Woodcock-Johnson Psycho-Educational Battery -Revised, category-fruit task, The Wechsler-Bellevue intelligence scale (Balinsky, 1941; Ghisletta & Lindenberger, 2003; Li *et al.*, 2004).

Altered local function with less distinctive neural representations may be associated with age-related deficits in neurotransmission (Li & Sikstrom, 2002) and specifically, dopaminergic signaling (Nagel *et al.*, 2008; Backman *et al.*, 2010; Sambataro *et al.*, 2012). Aging is associated with decline in multiple dopamine system markers within the nigrostriatal system as well in the cortex, particularly in the frontal, parietal and temporal areas (Ota *et al.*, 2006). Studies investigating the effect of genetically determined levels of dopamine in PFC support a role for an age-related decrease of this neurotransmitter in network function. We have shown that carriers of a more active variant of the enzyme responsible for cortical dopamine metabolism, Catechol-O-methyl transferase (COMT), and therefore have relatively lower cortical dopaminergic signaling, show increased activity and connectivity in PFC-PPC networks during WM processing, (Sambataro *et al.*, 2009). As expected older subjects, who already have lower dopaminergic signaling, showed an exaggeration of these COMT effects relative to younger subjects. Interestingly, PFC dopamine levels are important also for episodic encoding (Wittmann *et al.*, 2005). Pharmacological studies with drugs acting on D2 receptors confirm the age by dopamine level interaction on PFC networks during this cognitive process. Older subjects show a reverse pattern of PFC responses, with D2 agonists eliciting decreased responses and D2 antagonists resulting in increased responses relative to younger subjects (Morcom *et al.*, 2009). PFC levels of dopamine have been shown to modulate the cortical signal-to-noise ratio and regulate neural efficiency both at the level of brain activity and connectivity. Dopamine signaling modulates pyramidal neurons and inhibitory interneurons in PFC, thus focusing and stabilizing PFC response during a cognitive task (Seamans & Yang, 2004). Age-related reduction in dopamine levels can result in increased spiking of the cortical

neurons that receive temporally dispersed synaptic input, and suboptimal and relatively less focused response in multiple cortical regions, which may result in increased correlation of brain activations. Our results add to evidence that this response is invariant to the memory task at hand.

Since aging is associated with structural changes in the brain (Raz *et al.*, 2004), it is possible that our functional covariance measures may have been confounded by differences in brain morphology. To control for this effect we studied a subsample of subjects in whom we had structural data and computed grey matter differences within the jCOI regions between the two groups. Although this subsample was small, we found similar significant results as outlined above even after covarying for this variable, thus ruling out the possibility that they could have been driven by age-related structural differences in the brain.

Several studies have shown that task performance can also influence activation measures. In our attempt to reduce this bias, we matched subjects' performances on the easier levels of the task (1-back and EMET). To exclude the possibility that the difference in spatial extent of the jCOI between the two groups we found was driven by the performance difference on the 2-back task we repeated the analyses on just 1-back and EMET and found a similar jCOI. Nevertheless, aging can non-linearly affect the relationship between brain activity and task difficulty (Mattay *et al.*, 2006; Nagel *et al.*, 2009) or performance levels (Duvernoy *et al.*, 2009; Nagel *et al.*, 2009).

Subsequent memory paradigms are better suited to study incidental encoding (Wagner *et al.*, 1999). Subsequent memory effect allows the estimation of brain responses that are predictive of subsequent memory retrieval by comparing the neural responses associated with stimuli that are later remembered vs. the responses that are forgotten. Given the low number of forgotten items in both age groups, we could not reliably estimate the neural responses associated with forgotten items and the subsequent memory effect. We cannot therefore reliably exclude that some of the variance in brain activity is not related to differences in non-memory functions. Future studies with a task paradigm that allows testing of subsequent memory are warranted to explore this issue in greater detail.

Furthermore, we investigated the effects of age on brain activity and functional covariance using a cross-sectional design. Brain differences estimated with this type of studies may reflect differences other than the effects of age per se. On the other hand longitudinal neuroimaging studies can estimate trajectories of age-related changes of brain function over time. However, these studies can be confounded by technical and practical limitations brought about by variation in scanner performance over time, upgrades in scanning hardware and software. Imaging studies combining longitudinal and cross-sectional approaches are needed.

In conclusion, our study shows that aging modulates activity and functional covariance in regions of the prefronto-parietal-occipital network underlying working memory as well as episodic memory encoding. Although older subjects tend to over recruit this network relative to younger subjects, this engagement is associated with poorer performance suggesting neural dedifferentiation across memory domains.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

DLPFC	dorsolateral prefrontal cortex
DMN	default mode network
EM	episodic memory
EMET	episodic memory encoding task
FDR	false discovery rate
ICA	independent component analysis
jCOI	joint independent component of interest
PFC	prefrontal cortex
PPC	posterior parietal cortex
SVC	Small volume correction
WM	working memory

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Figure 1. Conjunction of the age-related contrasts across 1-back, 2-back and EMET. Older subjects showed greater left DLPFC activation (BA45/46) (A) along with decreased posterior cingulate and superior parietal deactivation (B) across all three tasks
Brain renderings are overlaid on a T1 template ($p < 0.001$). Bar plots indicate signal changes across 1-back, 2-back and EMET in left DLPFC (A) and posterior cingulate (B) extracted from conjunction clusters split by age groups (Young are indicated in white, older adults are indicated in black). Signal change is indicated as mean and expressed in arbitrary units (a.u.). Error bars indicate standard error of the mean.

Figure 2. jCOI Mixing Coefficients and performance. Older adults showed greater loadings relative to younger subjects (A; $p < 0.05$ FDR corrected). Accuracy at 2-back was negatively correlated with the mixing coefficients (B; $r = -0.47$, $p = 0.001$)

Mixing coefficients are expressed in arbitrary units (a.u.). 2-back accuracy is indicated as percent correct. Error bars indicate standard error of the mean. Young are indicated in white, older adults are indicated in black.

Figure 3. Prefrontoparietal covariance network jCOI across 1-back (A), 2-back (B) and EMET (C). This component included bilateral ventral and dorsal prefrontal cortex along with ventral and dorsal parietal cortex

Axial sections thresholded at $|Z| > 1.5$ are overlaid on a T1 template and illustrate the spatial pattern of functional covariance across the three tasks. The color bar indicates Z-scores.

Figure 4. Conjunction of the brain areas within the jCOI across 1-back, 2-back and EMET. Left prefrontal cortex, left SMA and bilateral ventral posterior parietal cortex spanning into the extrastriate cortex show positive covariance in all the task subcomponents of the jCOI (A). Precuneus and medial prefrontal cortex showed negative covariance across the tasks (B). Axial sections thresholded at $|Z| > 1.5$ are overlaid on a T1 template

Table 1
Demographics and behavioral data of the sample

	Younger	Older	Difference
n	22	22	n.s.
Gender (F)	11	11	n.s.
Age (M±SD, years)	32.6±10.1	62.37±5.7	
Handedness (EHI, M±SD, years)	78.4±27.2	64.3±66.0	n.s.
NB01 Accuracy (M±SD, %)	94.9±6.9	91.0±13.5	n.s.
NB02 Accuracy (M±SD, %)	91.6±10.8	69.1±19.5	p<0.001
Recognition Accuracy (M±SD, %)	85.5±10.7	88.3±7.1	n.s.

n= sample size; M=Mean; SD=standard deviation; EHI= Edinburgh Handedness Inventory.