Joint contributions from brain activity and activity-independent functional connectivity to working memory aging

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Abstract

Working memory (WM) impairment has been well characterized in normal ageing. Various studies have explored changes in either the regional activity or the interregional connectivity underlying the WM ageing process. We proposed that brain activity and connectivity would independently alter with ageing and affect WM performance. WM was assessed with a classical N-back task during functional magnetic resonance imaging in a community-based sample comprising 168 elderly subjects (aged 55 to 86 years old). Following the rationale of background functional connectivity, we assessed age-related alterations in brain activity and seed-based interregional connectivity independently. Analyses revealed age-related decrease in the activity of the inferior parietal lobule (IPL) and an increase in the activity of the ventral anterior cingulate cortex (ACC), and the local functional dysfunctions were accompanied by alterations in their connectivity to other cortical regions. Importantly, regional activity impairments in the IPL and ACC could mediate age-related effects on accuracy rate and reaction time, respectively, and those effects were further counterbalanced by enhancement of their background functional connectivity. We thus claimed that age-induced alterations in regional activity and interregional connectivity occurred independently and contributed to WM changes in ageing. Our findings presented the way brain activity and functional connectivity interact in the late adulthood, thus providing a new perspective for understanding WM and cognitive ageing.

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Running title:

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Abstract

Working memory (WM) impairment has been well characterized in normal ageing. Various studies have explored changes in either the regional activity or the interregional connectivity underlying the WM ageing process. We proposed that brain activity and connectivity would independently alter with ageing and affect WM performance. WM was assessed with a classical N-back task during functional magnetic resonance imaging in a community-based sample comprising 168 elderly subjects (aged 55 to 86 years old). Following the rationale of background functional connectivity, we assessed age-related alterations in brain activity and seed-based interregional connectivity independently. Analyses revealed age-related decrease in the activity of the inferior parietal lobule (IPL) and an increase in the activity of the ventral anterior cingulate cortex (ACC), and the local functional dysfunctions were accompanied by alterations in their connectivity to other cortical regions. Importantly, regional activity impairments in the IPL and ACC could mediate age-related effects on accuracy rate and reaction time, respectively, and those effects were further counterbalanced by enhancement of their background functional connectivity. We thus claimed that age-induced alterations in regional activity and interregional connectivity occurred independently and contributed to WM changes in ageing. Our findings presented the way brain activity and functional connectivity interact in the late adulthood, thus providing a new perspective for understanding WM and cognitive ageing.

Keywords

Working memory, task activity, background functional connectivity, cognitive ageing, N-back paradigm

Key Points

1. Both positive and negative brain activity during performing task were linked to age-related changes in working memory performance.

2. Age-induced changes in brain activity were accompanied by alterations in regional functional connectivity during performing tasks.

3. Brain activity and functional connectivity independently contributed to age-related changes in working memory.

1. Introduction

Working memory (WM) is the ability to efficiently maintain and manipulate temporarily available information, and provides a crucial functional backbone for complex behaviours, such as memory, learning, and problem solving (Baddeley, 2012; Diamond, 2013; D'Esposito and Postle, 2015). Motivated by the centrality of WM throughout human cognition, as well as the remarkable vulnerability of WM to ageing, most theories or hypotheses on cognitive ageing have implicated WM as one fundamental cause of more general age-related declines in cognitive performance (Park et al., 2002; Reuter-Lorenz and Sylvester, 2005; Craik and Salthouse, 2011; Anderson and Craik, 2017). Therefore, illustrating the neural mechanism of WM ageing would help untangle the cognitive ageing process and develop strategies to protect and promote cognition in old age.

Over the past decades, studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have shown that WM relies heavily on the prefrontal cortex (especially its dorsolateral part) and regions of the parietal lobes (e.g., superior parietal lobule and inferior parietal lobule) (Curtis and D'Esposito, 2003; Wager and Smith, 2003; Bledowski et al., 2009; Rottschy et al., 2012), and numerous studies have examined their alterations in ageing, linking extended patterns of neural activity and functional connectivity changes to WM impairment in old age (Spreng et al., 2010; Grady, 2012). When compared to their younger counterparts, older individuals have shown both decreased and increased WM-related activity (Rypma and D'Esposito, 2000; Grady et al., 2008; Carp et al., 2010; Piefke et al., 2012; Toepper et al., 2014), and the interpretation of these age-related changes has been a long-standing issue in the field. While decreased activity is usually considered to be a reflection of neurocognitive decline, those increases (i.e., hyperactivity or over-recruitment) have been viewed as signs of either compensation or dedifferentiation (Cabeza, 2002; Reuter-Lorenz, 2002; Reuter-Lorenz and Cappell, 2008), based on the correlations between brain activities and task performance. In addition, recent evidence from functional connectivity investigations on WM ageing, including those using task or resting-state fMRI, has revealed diverse results in older individuals as well, ranging from weakened long-range functional correlations (mainly between frontal and posterior regions) (Podell et al., 2012; Heinzel et al., 2017; Tsvetanov et al., 2018), to increased functional covariations between adjacent cortical regions during tasks (Cook et al., 2007; Sambataro et al., 2012).

Taken together, these findings highlight the important roles for both neural activity and functional connectivity in the WM ageing process, consistent with the idea that the two functional measurements provide complementary information on the brain physiology underlying cognition (Friston, 2011; Turk-Browne, 2013; Misic and Sporns, 2016). However, to the best of our knowledge, limited studies have applied the two methods in concert to better understand cognitive functions or their ageing (Murphy et al., 2016; Tsvetanov et al., 2018). This lack of integration might be partly because most connectivity studies have been conducted based on resting-state fMRI data, which lacks cognitive measurements during data acquisition, and for methods to examine connectivity in task fMRI data, such as psychophysiological interactions (PPI) (Friston et al., 1997) and dynamic causal models (DCM) (Friston et al., 2003), task-evoked activations have been incorporated into the modelling of time series (Friston, 2011), thus without clear distinctions between brain activity and connectivity. Hence, we proposed that the distinction and joint evaluation of brain activity and connectivity would improve the understanding of how the brain was functionally shaped for higher cognitive function and how cognitive ageing occurred in the brain.

We therefore applied a recently introduced approach, background connectivity, to process task-induced blood oxygen level-dependent (BOLD) signals. The background connectivity could be thought of as an extension of resting connectivity, where one does not need to assume a stable default state, and the logic of background connectivity emphasizes that the BOLD signals during performing cognitive tasks carry two components of task-related information, one is the task stimuli reaction (task-evoked activity) and the other one is the current cognitive status maintenance (state-related activity) (Al-Aidroos et al., 2012; Norman-Haignere et al., 2012; Turk-Browne, 2013; Duncan et al., 2014); therefore, the connectivity among regions could be assessed independently by regressing out the task-evoked activity. In the present cross-sectional research, we aimed to characterize those two functional components with a classical visual N-back WM task and to then examine their contributions to age-related changes in WM.

2. Materials and Methods

2.1 Subjects

All procedures and ethical aspects of this study were approved by the institutional review board of Beijing Normal University Imaging Center for Brain Research. Written informed consent was obtained from each subject.

Subjects in this study were from the Beijing Aging Brain Rejuvenation Initiative (BABRI), which is an ongoing cohort project to investigate the cognitive ageing and impairment of urban residents in Beijing and to identify neuroimaging biomarkers for normal ageing and AD (Yang et al., 2021). In this cross-sectional study, one hundred and sixty-eight (168) subjects from Wave 1 and 2 of the BABRI cohort were included per the following criteria: (a) aged 55 years old and above; (b) had at least 6 years of education; (c) scored 24 or higher on the Chinese version Mini-Mental State Examination (MMSE); (d) had valid N-back task performance data and N-back task fMRI data; and (e) had no history of neurological, psychiatric, or systemic illness known to influence cerebral function.

2.2 fMRI Experimental Paradigm

A blocked periodic design that incorporated alternating 0-, 1- and 2-back conditions was used during the N-back WM task. Each condition contained three blocks and were pseudo-randomly shown to subjects. During the 0-back condition, subjects were asked to press a button when a preassigned digit (e.g., 1) appeared on the screen. In the 1- or 2-back condition, subjects pressed a button when the digit on the screen matched the digit presented one or two items prior, respectively. Every block started with a 10-s cue presentation that indicated the 0-, 1- or 2-back, which was followed by 20 consecutive trials of single-digit stimuli (1000 ms duration and 1000 ms interstimulus interval). The whole experiment ended with 20-s cue presentation that the task was over, and he or she could have a rest. The responses and reaction time from each subject were recorded by an MRI-compatible response button box. The stimuli were presented using E-Prime (version 1.0, Psychology Software Tools Inc., Pittsburgh, PA).

To ensure that subjects understood the instructions and performed the tasks correctly, they were asked to practice a simplified version of the tasks for 10-15 min before the experiment.

2.3 MRI Data Acquisition and Preprocessing

The MRI data were acquired by scanning on a 3.0 T Siemens scanner at the Imaging Center for Brain Research at Beijing Normal University. With the head snugly fixed by straps and foam pads, subjects were asked to refrain from head movement. The functional images were acquired using an echo-planar imaging (EPI) sequence as follows: 33 axial slices, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, slice thickness = 3.5 mm, flip angle = 90°, field of view = 200 mm×200 mm, acquisition matrix = 64×64, 235 volumes. The T1-weighted structural data were also collected for spatial normalization using three-dimensional (3D) magnetization prepared rapid gradient echo (MP-RAGE) sequences as follows: 176 sagittal slices, repetition time = 1900 ms, echo time = 3.44 ms, slice thickness = 1 mm, flip angle = 9°, field of view = 200 mm×200 mm, acquisition matrix = 256×256.

Functional imaging data were preprocessed using the Statistical Parametric Mapping toolbox (SPM12, http://www.fil.ion.ucl.ac.uk/spm) run within MATLAB software (Mathwork, Inc., Natick, MA). The images were spatially realigned to the iteratively generated (over the realignment procedure) mean image from the series and then resliced, followed by slice-time correction for acquisition order (referenced to the first slice). Based on the transformation parameters from the segmentation of co-registered structural images, the functional images were spatially normalized to the Montreal Neurological Institute (MNI) space at 3 mm isotropic voxel resolution. Together with the six realignment paraments, the mean signals of the brain ventricle and white matter were extracted in the naive space and regressed out from the data. The functional images were then smoothed with a 6-mm full-width half-maximum Gaussian kernel. After preprocessing, six subjects were excluded due to excessive head motion (larger than 3 mm or degree), resulting in 162 subjects included in the final analyses.

For each subject, the preprocessed time series was modelled using GLMs. Task-evoked neural effects were estimated using separate block regressors representing 4 task conditions (fixation/cues, 0-back, 1-back, and 2-back) convolved with the canonical haemodynamic response function (HRF) plus its temporal and dispersion derivatives, and contrast images of interest (i.e., "1back - 0back" and "2-back - 0-back") were attained by subtracting the 0-back from the 1-/2-back. To acquire task-based background brain activity images, residual images from the GLM were high-pass filtered with a cut-off frequency of 0.01 Hz.

2.4 Voxel-wise Task-evoked Activity Analyses

Group-level one-sample t tests were first conducted to identify regions with task-evoked positive and negative activity in the contrasts of 1back - 0back and 2-back - 0-back, and binary masks of positive and negative regions during both contrasts were generated, under which age-related changes in task-evoked activity were then separately calculated for positive and negative regions in each contrast via multiple regression models in SPM12 toolbox, with gender and years of education as covariates.

For the above analyses, the Gaussian random field (GRF) correction was used for multiple comparison corrections on the results with voxel-level $p < 0.001$ and cluster level $p < 0.05$. Brain regions showing significant age-related effects were identified as seed regions for further functional connectivity analyses.

2.5 Task-based Background Functional Connectivity Analyses

The background functional connectivity examined the functional correlations among brain regions that occurred in the background of stimulus-locked changes, that is, independent of the evoked responses to individual stimuli during the tasks. To assess such correlations, for each subject, based on the acquired background brain activity images, the strength of connectivity was evaluated through Pearson's correlations between the averaged time series of voxels in each seed region (significant regions in *2.4 Voxel-wise Task-evoked Activity Analyses*) and the time series of each voxel in the rest of the brain. Then, Fisher's r to z transformation was applied to normalize the original correlation maps, followed by whole-brain z score standardization to rescale the functional connectivity using Data Processing & Analysis for Brain Imaging (DPABI) (Yan et al., 2016).

Next, multiple regression models were performed on the standardized FC maps using the SPM12 toolbox to determine regions where FC showed significant age-related changes, with gender, years of education, and mean task-evoked activity of the seed region included as covariates, and all the results were corrected for multiple comparisons using the same method in *2.4 Voxel-wise Task-evoked Activity Analyses* . The mean functional connectivity of the resulting areas was then extracted for subsequent analyses.

2.6 Statistical Analyses

Relationships between N-back task performance and task-evoked activity, as well as task-based background FCs, were separately estimated via linear regression models using SPSS (version 22.0, IBM Inc., New York, NY), with gender, years of education, age, and task-evoked activity as covariates, and a statistical significance level of $p < 0.05$ was applied.

To test how task-evoked activity and task-based background FC mediated age effects on N-back task performance, mediation analyses were further conducted using Mplus 7.11 (Muthen and Muthen, 2012), and bootstrapped 95% confidence intervals (CIs) were reported alongside parameter estimates (Preacher et al., 2007; MacKinnon, 2008).

3. Results

3.1. Demographic, neuropsychological and N-back task measurements

Table 1 presents the demographics, general cognitive status, and WM task performances of current study cohort. As shown in the table, the cohort showed relatively intact general cognitive function, with no significant age-related decline in MMSE scores ($|r| < 0.1$, $p > 0.1$). The WM task performances were remarkably affected by ageing, as significant age-related decreases in accuracy rate (AR) were found in all three task conditions ($r = -0.325$, 0.343, and 0.310 for 0-, 1-, and 2-back condition, respectively, all $ps < 0.001$), along with significantly longer reaction time (RT) in 0- and 1-back conditions ($r = 0.222$ and 0.208, and $p = 0.003$ and 0.008, respectively) in advanced age (Table 1).

3.2. Age effects on N-back task-evoked brain activity

Brain activities typically associated with WM tasks were found in the contrasts of "2-back - 0-back", with positive regions mainly clustered in the lateral prefrontal and parietal lobes and negative areas located around the cingulate cortex and temporal lobe (Figure 1). Further regression models identified regions showing significant age-related alterations within the positive and negative areas, respectively. As the right inferior parietal lobule (rIPL, peak voxel coordinates: 48, -51, 45) presented an age-related decline in activity, the right anterior cingulate cortex (rACC, peak voxel coordinates: 3, 36, -3) showed an age-related increase (Figure 1, Table 2).

3.3. Age effects on the N-back task-based background functional connectivity

With the task-based background brain activity, task-based background FC maps were separately computed using the rIPL and rACC as seed regions (Figure S1). Significantly enhanced connectivity was then observed between the rIPL and those clustered in the right posterior cingulate cortex (rPCC, peak voxel coordinates: -3, -57, 30) with increasing age (Figure 2, Table 2). On the other hand, background connectivity between the rACC and the right precentral gyrus (rPreCG, peak voxel coordinates: 48, 9, 30), the left IPL (lIPL, peak voxel coordinates: -39, -48, 42) and the right angular gyrus (rAG, peak voxel coordinates: 42, -57, 54) were also found to be strengthened with ageing (Figure 2, Table 2). There were no other regions showing significant age-related alterations in functional connectivity with either ROI.

3.4. Brain activity, functional connectivity, and WM task performance

Relationships between brain activity, FC, and WM task performance were explored by linear regression models, controlling for the effects of age, gender, and years of education. As both AR and RT of 0-back were significantly associated with rIPL and rACC activities (for AR, $| r | > 0.266$, both $p < 0.001$; for RT, $| r | > 0.174$, $p = 0.002$, 0.028, respectively), only AR of 2-back was correlated with these activities ($| r | > 0.241$, $p = 0.002$, < 0.001, respectively). Then, after regressing out the effects of the activity in seed regions, we identified specific relationships between the rACC-lIPL connectivity and RT of 0-back ($r = -0.170$, $p = 0.032$), and between the rIPL-rPCC connectivity and AR of 2-back ($r = 0.166$, $p = 0.037$).

Since the AR of the 2-back and the RT of the 0-back were affected by both activity and connectivity, we subsequently conducted mediation analyses to inspect their roles in mediating ageing effects on task performance. The results showed that age-related impacts on the AR of 2-back were partly mediated by rIPL activity (indirect effect [IE] = -0.105, 95% CI [-0.173, -0.037]), as well as a trend of mediation of the AR of 2-back by the rIPL-rPCC connectivity (IE = 0.047, 95% CI [-0.002, 0.096]). Similarly, alterations in RT of 0-back during ageing were also fully mediated through the activity of the rACC (IE = 0.045, 95% CI [0.005, 0.085]) and partially mediated by the rACC-lIPL connectivity (IE = -0.057, 95% CI [-0.111, -0.002]). More importantly, the total of indirect effects of ageing on AR and RT, mediated by the two different functional measurements, were not significant (for AR of 2-back, sum of IE = -0.059, 95% CI [-0.143, 0.026]; for RT of 0-back, sum of IE = -0.012, 95% CI [-0.080, 0.056]; Figure 3).

4. Discussion

Reduced WM performance in old age is associated with changes in both local neural dysfunction and functional connectivity. In the current study, alterations in task-evoked activity and task-based functional connectivity were independently examined by applying the background connectivity approach, and the major and novel findings are that: (1) a decline in the magnitudes of task-evoked activity was accompanied by increased seed-based background functional connectivity with posterior parietal regions, and both were tightly correlated with WM performance; and (2) while task-evoked activity mediated age-related WM impairment, task-based connectivity, on the contrary, has contributed to better WM performance in old age.

Standard univariate analyses on task-evoked activity revealed an age-related decrease in activity of the right IPL and an increase in activity of the right ACC. Although alterations in the IPL activities of older individuals have been repeatedly identified in previous studies (Cabeza et al., 2004; Carp et al., 2010), the involvement of the ACC has been relatively rarely reported in WM ageing. Some studies have identified special changes in the ACC related to WM performance (Bush et al., 2000; Lenartowicz and McIntosh, 2005). There was evidence from developmental studies that neural responses (negative activity during task) in the ventral ACC could predict between-subject differences in WM (Huang et al., 2016; Vogan et al., 2016), and several training programs on WM also highlighted the importance of modulations in ACC activities (Olesen et al., 2004; Brehmer et al., 2011). All these reports linked a more deactivated ACC (especially ventral) to better WM performance, possibly due to the successful inhibition of irrelevant information during tasks (Jonides et al., 1998; Vogt, 2009). It should also be noted that as previous investigations into WM ageing mainly focused on regions with task-evoked positive activity (as detailed in recent meta-analyses (Wager and Smith, 2003; Rottschy et al., 2012)), our findings of ACC with negative activity during task, along with a few recent investigations into task-negative areas (Sambataro et al., 2010; Anticevic et al., 2012a), thus implied that those negatively activated regions were as important as the positively activated regions in supporting human cognitions, especially for externally oriented cognitive functions such as working memory and executive function. Moreover, our studies failed to find any pattern of increased activity in frontal and parietal regions, and it was possible that the age-related regression analysis method based on a single group of older individuals, rather than a typical comparison between young and older individuals, was the reason that no increases were identified in activated regions.

Along with the alterations in local cortical processing, subsequent seed-based functional connectivity analyses on the background activity derived from the WM task also showed that, regions with increased and decreased task-evoked activity were more functionally connected to other regions, as the ACC was connected to the bilateral lateral parietal area and the IPL was coupled with the posterior cingulate gyrus, and these patterns of a more connected brain were linked to better performance on the N-back task. The associations between functional connectivity and WM performance have been well-characterized in previous studies. Consistent evidence from resting state neuroimaging data has identified that regions activated in the WM task, such as DLPFC, PreCG, and IPL, were highly connected (Fox et al., 2005; Power et al., 2011) and that connections among task-deactivated regions (such as the medial PFC and PCC) also made considerable contributions to WM (Hampson et al., 2006; Hampson et al., 2010; Sambataro et al., 2010). Furthermore, task fMRI studies, which modelled task-induced BOLD signals using methods such as PPI and DCM, provided further evidence on how information flow was modulated during WM tasks, depicting more details on frontoparietal interactions in different conditions (Ma et al., 2012; Heinzel et al., 2017; Jung et al., 2018).

In addition to the well-documented relationships between local task-evoked brain activity and WM, we found seed-based connectivity closely associated with task performance after regressing out the local activity of seed regions. These results fairly agreed with the basic logic of the background connectivity approach, that the task-induced BOLD signals contained two sources of variance (i.e., stimuli-related and state-related), with distinct and complementary information on cognitive processes (Otten et al., 2002; Rissman et al., 2004). Classic FC estimated by resting-state fMRI data has been best suited to studying the latent functional architecture of the brain at rest, however, it still lacks the ability to well depict the relationship of brain interactions to specific cognitive tasks (Friston, 2011; Turk-Browne, 2013; Misic and Sporns, 2016). In contrast, there have been several studies showing that during cognitive tasks such as visual attention and memory, background connectivity could selectively respond to specific stimulus types or cognitive processes (Summerfield et al., 2006; Al-Aidroos et al., 2012; Norman-Haignere et al., 2012; Wimmer and Shohamy, 2012; Duncan et al., 2014), and changes in connectivity could be detected even when cognitive demands were modulated by diseases (Lou et al., 2015) or drugs (Anticevic et al., 2012b). Thus, our results provided more evidence that brain activity and connectivity played independent but complementary roles in the process of WM ageing, and since age-related changes in WM made critical contributions to the ageing of other higher cognition such as memory and decision-making, this evidence could also be one possible neural mechanism underlying the ageing of broader cognitive functions.

Meanwhile, based on results from mediation modelling, that is, while a decline in activity was linked to the age-related decrease in AR and increase in the RT, the background connectivity was enhanced to support higher AR and shorter RT, we proposed that along with local processing impairment in advanced age, more regions were involved in the current WM task as a result of functional compensation (Reuter-Lorenz and Cappell, 2008; Park and Reuter-Lorenz, 2009). Specifically, although we could not clarify which alteration happened early, the compensational mechanisms might be the situation in which the age-related decline in activity led to the decline in behavioural performance, followed by the enhancement of background functional connectivity, to reduce the impact and to help older individuals maintain behavioural performance. In addition, our findings also revealed patterns that positively activated regions (IPL) during tasks were more connected to regions that were negatively activated (PCC), and connections were enhanced between regions that were negatively activated (ACC) and those that were positively activated (IPL and PreCG). Since these regions were the core regions in the frontoparietal network (FPN) and default mode network (DMN), the pattern might also catch a glimpse of network reconfiguration among brain networks (i.e., FPN and DMN) in ageing to support higher cognitive functions (Reuter-Lorenz and Lustig, 2005).

There are several points that could be explored in future studies. First, the block design of the current experiment could not fully consider correct and failed trials during the WM task, which made the impacts of regional activity and connectivity on successful WM difficult to assess. However, based on the decent accuracy rate of WM tasks (90.91 +- 6.04%) in all subjects, it could be inferred that they were focused on the tasks, which agreed with the hypothesis of maintaining cognitive status in background connectivity analyses. Second, the computation of functional connectivity was based on seed regions derived from regional activity analyses, which could have been computed at the whole brain level to examine the network reconfiguration or reorganization. Due to the primary proposal of the present study to jointly explore and compare the roles of brain activation and connectivity in WM ageing, the seed-based analyses could provide more direct evidence on their relationships and contributions to WM ageing. Finally, we assessed functional alterations within a cross-sectional sample. Although a group of elderly subjects avoided the possible biases of strategies or patterns in WM tasks, a longitudinal design would give an improved and more detailed depiction of the regional activity and connectivity alterations as well as their contributions to the ageing of WM.

5. Conclusion

By applying the background connectivity approach, this study considered the alterations of brain activities and connectivity and their roles in WM ageing. The findings revealed independent age-related changes between two functional features and identified that they exhibited counterbalanced impacts on age-related changes in WM performance, which provided a richer repertoire of brain dynamics in ageing, a possible explanation from connectivity on the brain compensation in ageing, with implications for a comprehensive understanding of higher cognitive functions and their alterations during ageing or disease-related processes.

6. Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figure Legends

Figure 1. WM-related activation and deactivation and their age-related changes.

A: lateral and medial maps of task-evoked activity in the "2back -0back" condition, red/yellow indicates positive activity, blue/cyan indicates negative activity; B: age-related changes of task-evoked activity in the "2back -0back" condition, red/yellow indicates changes in positive regions, blue/cyan indicates changes in negative regions; C: scatter plots of brain activities of regions showing significant age-related alterations. The results were corrected for multiple comparisons at $p < 0.05$. Brain maps were generated using the BrainNet viewer toolbox (Xia et al., 2013).

Figure 2. Regions showing age-related enhanced background connectivity with dysfunctional task-evoked seed regions.

Upper: seed region in the inferior parietal lobule (IPL) and brain regions where significant age impacts on background connectivity derived from the IPL were found; Lower: seed region in the anterior cingulate cortex (ACC) and brain regions where significant age impacts on background connectivity derived from the ACC were found. The results were thresholded at corrected $p < 0.05$.

Figure 3. Mediation models on age, regional activity, background connectivity and WM performance.

A: Activation and background connectivity in the inferior parietal lobule (IPL) mediated age-related effects on the accuracy rate (AR) of the 2-back; B: Deactivation and background connectivity in the anterior cingulate cortex (ACC) mediated age-related effects on the reaction time (RT) of the 0-back. All coefficients are standardized and presented as Estimate (Standard Error). Covariates included gender and years of education and were not shown in the models. *** < 0.001, ** < 0.01, * < 0.05. CI, confidence interval.

Figure S1. Maps of background connectivity derived from seed regions.

A: Group-level connectivity map derived from the anterior cingulate cortex (ACC); B: group-level connectivity map derived from the inferior parietal lobule (IPL). Images were thresholded at uncorrected $p < 0.001$.

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