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Age differences in the fronto-striato-parietal network underlying serial ordering

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ABSTRACT

Maintaining the ability to arrange thoughts and actions in an appropriate serial order is crucial for complex behavior. We aimed to investigate age differences in the fronto-striato-parietal network underlying serial ordering using functional magnetic resonance imaging. We exposed 25 young and 27 older healthy adults to a digit ordering task, where they had to reorder and recall sequential digits or simply to recall them. We detected a network comprising of the lateral and medial prefrontal, posterior parietal, and striatal regions. In young adults, the prefrontal and parietal regions were more activated and more strongly connected with the supplementary motor area for "reorder & recall" than "pure recall" trials (psychophysiological interaction, PPI). In older adults, the prefrontal and parietal activations were elevated, but the PPI was attenuated. Individual adults who had a stronger PPI performed more accurately in "reorder & recall" trials. The decreased PPI appeared to be compensated by increased physiological correlations between the prefrontal/parietal cortex and the striatum, and by that between the striatum and the supplementary motor area.

1. Introduction

The ability to arrange thoughts and actions in an appropriate serial order (serial ordering) is crucial for cognitive processes such as planning and reasoning. Serial ordering in working memory requires actively maintaining and manipulating the serial order of items, in addition to maintaining the information about each specific item (e.g., color, location, meaning). The ability of serial ordering decreases not only following frontal lobe lesions (Petrides and Milner, 1982) or in neurodegenerative diseases (Cooper et al., 1991; Wilson et al., 2010), but also in normal aging (Blachstein et al., 2012; Wiegersma and Meertse, 1990), potentially causing difficulties in understanding temporal relations between events (Natsopoulos et al., 1991) or in planning sequential actions to solve problems (Robbins et al., 1994; Sullivan et al., 2009). In this study, we aimed to investigate how the fronto-striato-parietal network that supports serial ordering changes in older adults using functional magnetic resonance imaging (fMRI).

The cognitive mechanisms that code and retrieve the serial order of items are assumed to differ from the mechanisms that code and retrieve the information about a specific item. Most contemporary models of short-term memory for serial order use a competitive queuing mechanism in which all items in a to-be-recalled sequence are active simultaneously (e.g., Botvinick and Plaut, 2006; Burgess and Hitch, 2006; Page and Norris, 2009). The perceived order is represented in terms of a primacy gradient of node activation. Namely, the node activation of the first item is strongest and the node activations of the subsequent items decline monotonically

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toward the last item. Serial recall is accomplished via iterative processes. At each iteration, the most active item is selected for recall and then suppressed, so that the second strongest item becomes the most active at the next iteration (for a review, see Hurlstone et al., 2014). The competitive queuing model is supported by monkey electrophysiological studies (Averbeck et al., 2002; Berdyyeva and Olson, 2009, 2010; Ninokura et al., 2004) and human magnetoencephalographic studies (Kornysheva et al., 2019). These studies consistently showed that the serial order of items is coded as the rank order of the strength of the items' neural representations in the lateral prefrontal cortex. Human neuroimaging studies showed that the striatum and intraparietal sulcus are also involved for holding serial order (Attout et al., 2019; Majerus et al., 2006; Marshuetz et al., 2000; Roberts et al., 2018; Wager and Smith, 2003).

Our work has been focusing on the flexible manipulation of serial order which is even less understood. On the basis of the competitive queuing model, we hypothesize that reordering sequential items may require a precise adjustment of the items' node activations. The adjustment may be realized by inhibiting items that should be moved downward and enhancing items that should be moved upward in the rank; or by keeping constant the last item in the target order and enhancing all other items relative to the last item. In this study, we examined whether the adjustment and related neural processes were supported by the fronto-striato-parietal network. In particular, we expected a distributed network for serial ordering that comprises the medial and lateral prefrontal cortex, posterior parietal cortex, striatum, thalamus, and cerebellum (see Fig. 1 for a simplified scheme). In primates, the mid-dorsolateral prefrontal cortex (BA46, BA46/9) receives projections from the lateral and medial parietal cortex, whereas the dorsomedial prefrontal cortex (BA8) receives projections from the medial parietal cortex (Petrides, 2005; Petrides and Pandya, 1999); the dorsolateral prefrontal cortex (BA46, BA9) and posterior parietal cortex (BA7) project to adjacent territories in the striatum and thalamus (Selemon and Goldman-Rakic, 1985, 1988); the striatum and cerebellum project back to the dorsolateral prefrontal cortex (BA46, BA9) via the thalamus (Middleton and Strick, 1994, 2001).

Our recent work showed that the behavioral performance of serial ordering decreased as age increased in both healthy adults and patients with Parkinson's disease (Ma et al., 2018). Here we aimed to investigate how age compromises the neural network for serial ordering, in terms of regional activation and interregional interaction, and consequently, affects the behavioral performance. To this end, we combined fMRI with a computerized digit ordering task and contrasted a "reorder & recall" condition with a "pure recall" condition to isolate the cognitive processes of serial ordering (Fig. 2). We expected an elevation of ordering-related regional activation in the lateral prefrontal cortex (e.g., Rajah and D'Esposito, 2005; Reuter-Lorenz et al., 2000) and a reduction of ordering-dependent inter-regional interaction between the prefrontal cortex and the striatum, posterior parietal cortex, or premotor cortex in older adults (e.g., Heinzel et al., 2017; Nagel et al., 2011; Podell et al., 2012). Following previous work (Tsvetanov et al., 2018), we distinguished between the ordering-dependent inter-regional interaction (psychophysiological interaction, PPI) and the ordering-independent functional connectivity (correlation between physiological signals). More importantly, we expected a relationship between decreased performance accuracy and altered regional activation and/or interregional interaction.

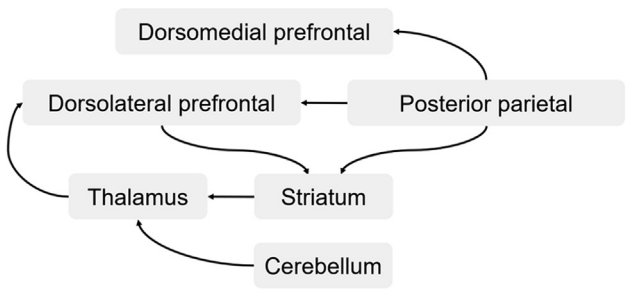

Fig. 1. Fronto-striato-parietal network.

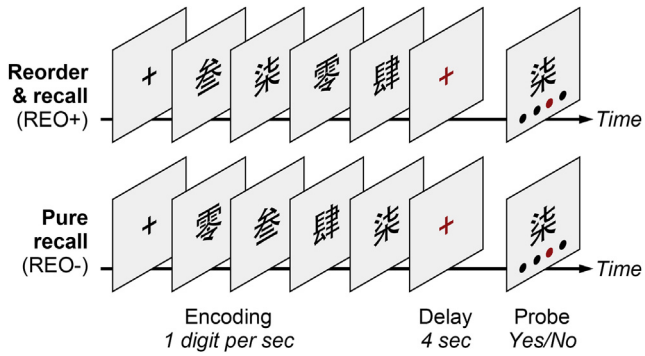

Fig. 2. Digit ordering task.

2. Materials and methods

This study was approved by the ethical committee of Peking University Third Hospital in accordance with the Declaration of Helsinki. Each participant signed a written informed consent before participating in this study.

2.1. Participants

We recruited 25 young (18–22 years) and 27 older healthy native Chinese speakers (50–74 years). They were right-handed (Chinese handedness classification criteria, Li, 1983) and had a normal or corrected-to-normal vision. None of them had a history of significant neurologic or psychiatric disorders. All participants were screened for possible current depression (Beck Depression Inventory-II <7). Older participants were additionally screened for possible dementia or mild cognitive impairment (Montreal Cognitive Assessment $\geq 26/30$). Table 1 presents demographic features and neuropsychological measures of the 2 age groups.

2.2. Experimental design and procedure

All participants completed the computerized digit ordering task during scanning and 2 classical neuropsychological tests of working memory (the adaptive digit ordering test and digit span forward test) outside of the scanner.

Fig. 2 illustrates the computerized digit ordering task which used a slow event–related design (trial duration 14–16 seconds, intertrial interval 0.5–2 seconds). The "reorder & recall" trials (REO+, 32 trials) and "pure recall" trials (REO–, 30 trials) were presented in an m-sequence to maximize the efficiency of estimating the shape of hemodynamic responses in fMRI (Buracas and Boynton, 2002). In the encoding phase, 4 different digits written in Traditional Chinese were presented sequentially at a speed of one digit per second. Participants were asked to remember the digits in ascending order through a short delay of 4 seconds. In "reorder & recall" trials, the digits were fully randomized and participants had always to reorder them (e.g., *3-7-0-4*). In "pure recall" trials, the digits were presented in ascending order and there was no need to reorder (e.g., *0-3-4-7*).

Table 1
Demographic features, neuropsychological measures and task performance (means, standard deviations, and group differences)

Features/measures	Health young (N = 25)	Health older (N = 27)	Group differences (corrected p)
Male: female	12:13	12:15	n.s.
Age (y)	20.1 (1.1)	57.0 (6.1)	$p < 0.001$
Education (y)	14.0 (1.1)	13.3 (1.6)	n.s.
Beck Depression Inventory-II	1.2 (1.5)	1.5 (1.3)	n.s.
Montreal Cognitive Assessment	–	28.7 (1.2)	–
Digit span forward test (span)	9.4 (1.5)	7.9 (0.9)	$p < 0.001$
Adaptive digit ordering test (span)	6.9 (1.0)	6.4 (1.1)	
Digit ordering task (with fMRI)			
Accuracy (%)			
Pure recall	98.1 (2.9)	96.5 (3.6)	n.s.
Reorder & recall	97.6 (3.8)	95.9 (4.4)	
Reaction times (ms)			
Pure recall	1442 (299)	1728 (377)	$p = 0.004$
Reorder & recall	1452 (343)	1738 (387)	

Group differences, p values of one-way ANOVAs, Kruskal-Wallis one-way ANOVAs, or repeated-measures ANOVAs as appropriate, thresholded at $p < 0.007$ (Bonferroni correction).
Key: n.s., not significant.

In the probe phase, one of the digits occurred on the screen, together with 4 dots indicating 4 ordinal positions from left to right. Participants were asked to judge whether the digit matched the ordinal position indicated by the red dot in the target output order. They had up to 5 seconds to respond with their right hand by pressing the left or right buttons of an MRI compatible button response pad (Shenzhen Sinorad Medical Electronics Inc). The mapping between yes/no responses and left/right buttons was counterbalanced across participants and groups. The trial sequence was pseudorandomized to ensure that (1) the regularity with which the 2 conditions followed each other was evenly balanced; (2) there was no repetition of digits or ordinal positions in any 2 consecutive trials; and (3) there were no more than 3 repetitions of yes/no responses in consecutive trials. Participants completed 2 experimental blocks (8 minutes each) after practice (4 minutes). Both age groups reached high accuracy in practice (≥85%).

We examined whether task performance differed between age groups, in terms of accuracy (percentage of correct trials) and reaction time (mean reaction time of correct trials). For each parameter, the ANOVA had a within-subject factor condition (REO+ vs. REO−) and a between-subject factor group (older vs. young).

Participants also completed the adaptive digit ordering test and digit span forward test (Werheid et al., 2002) outside of the scanner. The neuropsychological tests measured the longest digit sequences one can remember correctly (span) in the "reorder & recall" and "pure recall" conditions. The 2 tests were used to ensure that no participant had a span shorter than 4 in either condition. In the adaptive digit ordering test, 3 to 8 digits were presented sequentially at a speed of one digit per second and participants were asked to immediately recall the digits in ascending order. In the digit span forward test, they were asked to recall the digits in the original order. Both tests were adaptive regarding the sequence length.

2.3. MRI acquisition and preprocessing

Neuroimaging data were acquired on a GE Discovery MR750 3.0 T scanner with an 8-channel head coil. Functional images used a standard echo-planar imaging sequence (33 interleaved ascending axial slices, 2000-ms time of repetition, 30-ms time of echo, 90° flip angle, 224 × 224 mm^2 field of view, 4.2-mm thickness, no gap, and 3.5 × 3.5 mm^2 in-plane resolution). High-resolution T1-weighted images used an inversion recovery prepped-fast spoiled gradient recalled echo imaging sequence (192 sequential sagittal slices, 450-ms time of inversion, 7-ms time of echo, 12° flip angle, 256 × 256 mm^2 field of view, 1-mm thickness, and 1 × 1 mm^2 in-plane resolution).

fMRI data were preprocessed and analyzed with SPM12 (revision 7219, www.fil.ion.ucl.ac.uk/spm). The first 5 volumes of each experimental block were discarded to allow magnetization equilibration. fMRI data were realigned to the mean functional image, corrected for slice acquisition time difference, normalized to the Montreal Neurological Institute and Hospital (MNI) coordinate system using a segmentation function that segments, bias-corrects, and spatially normalizes images in the same model (Ashburner and Friston, 2005), smoothed with a Gaussian kernel of 6-mm full-width half-maximum, and filtered with a 128-second high-pass filter.

We controlled the quality of fMRI data using 6 motion parameters estimated in the realignment. First, we excluded 2 participants (one from each age group) who had excessive head motion (translation >3 mm, or rotation >3°). The motion parameters of the included participants were shown in the supplemental Table S1. Second, we combined the 6 motion parameters into a more comprehensive indicator (total displacement) using the equation of Wilke (2012) and included total displacement as a nuisance regressor in general linear models (GLMs) to minimize motion effects (see section 2.4).

2.4. Statistical analysis of fMRI data

First, we applied a whole-brain analysis to detect the distributed network for serial ordering that was common to older and young participants. At the subject level, the GLM convolved a design matrix with a canonical hemodynamic response function. The design matrix included correct and error REO+ and REO− trials as separate regressors, and total displacement as a nuisance regressor. Each trial was modeled as a mini-block of 14–16 seconds. Note that there was a variable interval (0.5–2 seconds) between consecutive trials but not between consecutive phases within a trial. For the sake of statistical power, we did not separate the encoding, delay, and probe phases in the design matrix. Classical parameter estimation was applied with a one-lag autoregressive model. We defined the ordering-related activation using the contrast of REO+>REO−, and the ordering-related deactivation using the opposite contrast. At the group level, we conducted 2-sample t-tests to detect the distributed network across age groups (voxel-level $p < 0.001$, cluster-level $p < 0.05$ familywise-error-corrected).

Second, we applied a region-of-interest analysis to examine whether the ordering-related regional activation differed between age groups, focusing on the prefrontal cortex (BA8, BA9/46, BA44/45) and posterior parietal cortex (BA7). We overlapped the atlas of Brodmann area with the contrast map of REO+>REO− to create a study-specific, anatomically clear, ordering-related, and unbiased mask. The mask definition was independent of the group effect. The

percentage signal change relative to the whole-brain mean signal was extracted from the mask with MarsBaR 0.44 and entered into an ANOVA with a within-subject factor condition (REO+ vs. REO−) and a between-subject factor group (older vs. young). Significance was considered at $p < 0.013$ (Bonferroni-corrected for 4 regions). Given the presence of the subcortical regions (see section 3.2) and the default mode network (see section 3.3), we also explored the group effect on the thalamus, globus pallidus, subthalamic nucleus, substantia nigra, ventromedial prefrontal cortex, posterior cingulate cortex, and Rolandic operculum.

Third, we applied a separate GLM to detect the ordering-dependent inter-regional interaction (PPI) and ordering-independent functional connectivity (correlation between physiological signals), using the 4 regions of interest defined previously as seeds (BA8, BA9/46, BA44/45, BA7). We reported the results of the study-specific seeds in the main text and replicated the results using alternative seeds derived from Neurosynth (see Supplementary Information). For each seed, time courses were extracted from all voxels of the seed, averaged to crease a representative time course, demeaned and deconvolved to create the PPI variable. At the subject level, the GLM included a PPI regressor, a physiological signal regressor, and a psychological contrast regressor (REO+>REO−) (Friston et al., 1997). The estimated parameter of the PPI regressor indicated the degree to which the influence of the seed on the voxel was modulated by serial ordering. The estimated parameter of the physiological signal regressor indicated the degree to which the time course of a voxel correlated with the time course of the seed. At the group level, we conducted 2-sample *t*-tests, separately for the PPI and the ordering-independent functional connectivity (voxel-level $p < 0.001$, cluster-level $p < 0.05$ familywise-error-corrected).

Fourth, we used a linear regression model to examine whether individual differences in the accuracy of REO+ trials can be

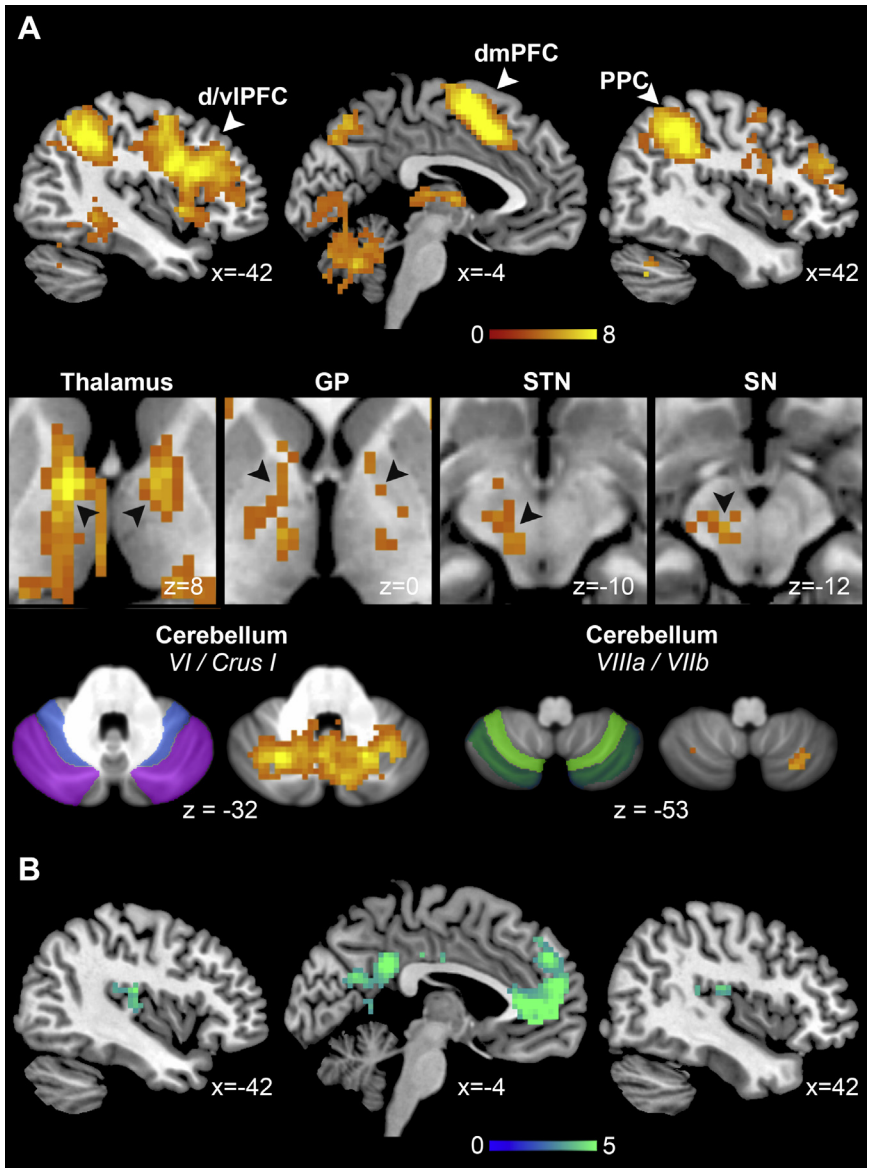

Fig. 3. Ordering-related regional activation and deactivation across age groups. (A) Regional activations were greater for "reorder & recall" than "pure recall" trials in the dorsolateral and ventrolateral prefrontal cortex (d/vlPFC), dorsomedial prefrontal cortex (dmPFC), posterior parietal cortex (PPC), thalamus, globus pallidus (GP), subthalamic nucleus (STN), substantia nigra (SN), and cerebellum. Subregions of the cerebellum are labeled in color (blue: VI, purple: Crus I, light green: VIIIa, dark green: VIIb). (B) Regional deactivations in the default mode network were greater for "reorder & recall" than "pure recall" trials. Color scales indicate *t* values. Coordinates are in MNI space. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

predicted by the PPI or the regional activation. The independent variables were the mean Fisher-transformed PPI between the 4 seeds and the BA6/32 (which showed a significant age difference in the PPI analysis, see section 3.7) and the mean percentage signal change of the 4 seeds. Significance was considered at $p < 0.05$.

Last but not least, we examined the relationship between the PPI and the ordering-independent functional connectivity. We correlated the mean Fisher-transformed PPI between the 4 seeds and the BA6/32 with the mean Fisher-transformed correlation coefficient between the 4 seeds and the striatum, and with that between the striatum and the BA6/32, controlling for the mean percentage signal change of the seeds. Significance was considered at $p < 0.025$ (Bonferroni-corrected for 2 correlations).

3. Results

3.1. Task performance

Table 1 shows demographic features, neuropsychological measures, and task performance of older and young participants. The 2 age groups were matched in sex ratio, education, and depression score. All participants had a span higher than 4 in the adaptive digit ordering test and digit span forward test. The ANOVA with 2 factors, condition (REO+ vs. REO−) and group (older vs. young), revealed a main effect of group in reaction time ($F(1,50) = 8.95$, $p = 0.004$, $\eta^2 = 0.15$) but not in accuracy ($F(1,50) = 3.41$, $p = 0.071$, $\eta^2 = 0.06$). Older participants were as accurate as but slower than young participants in the computerized digit ordering task.

3.2. Ordering-related regional activation

Fig. 3A shows the ordering-related regional activation common to older and young participants. The whole-brain 2-sample t-test (voxel-level $p < 0.001$, cluster-level $p < 0.05$ familywise-error-corrected) revealed greater activations for REO+ than REO− trials in the dorsomedial prefrontal cortex (BA8/6: peak in MNI coordinates [−3, 9, 54], $t = 10.48$, 1218 voxels), dorsolateral prefrontal cortex (BA9/46: left [−48, 12, 30], $t = 8.29$, 217 voxels; right [45, 33, 24], $t = 6.66$, 83 voxels), ventrolateral prefrontal cortex (BA44/45: left [−54, 9, 12], $t = 7.03$, 139 voxels; right [57, 9, 18], $t = 6.10$, 60 voxels), posterior parietal cortex (BA7/40: left [−36, −45, 36], $t = 9.38$, 780 voxels; right [45, −45, 45], $t = 9.14$, 684 voxels), thalamus (left [−12, −3, 12], $t = 9.83$, 96 voxels; right [12, −3, 12], $t = 6.59$, 45 voxels), globus pallidus (left [−15, −3, 9], $t = 7.15$, 32 voxels; right [15, 0, 9], $t = 6.21$, 23 voxels), subthalamic nucleus ([−12, −15, −9], $t = 4.43$, 5 voxels), substantia nigra ([−9, −18, −12], $t = 5.24$, 6 voxels), and cerebellum (VI/Crus I: [−27, −63, −36], $t = 9.51$, 655 voxels; VIIIa/VIIb: [3, −72, −33], $t = 6.15$, 19 voxels).

3.3. Ordering-related regional deactivation

We also observed the ordering-related regional deactivation across age groups (Fig. 3B). The whole-brain 2-sample t-test (voxel-level $p < 0.001$, cluster-level $p < 0.05$ familywise-error-corrected) revealed greater deactivations for REO+ than REO− trials in the default mode network, including the ventromedial prefrontal cortex ([6, 51, 12], $t = 7.19$, 1245 voxels), posterior cingulate cortex ([−6, −54, 12], $t = 6.65$, 509 voxels), and Rolandic operculum (left [−42, −18, 18], $t = 4.93$, 33 voxels; right [48, −27, 21], $t = 5.25$, 61 voxels).

3.4. Age difference in regional activation

Fig. 4A shows the age difference in the prefrontal and parietal regional activation. The ANOVA with 2 factors, group (older vs. young) and condition (REO+ vs. REO−), revealed a main effect of group in the BA8 ($F(1,48) = 8.62$, $p = 0.005$, $\eta^2 = 0.16$) and BA7 ($F(1,48) = 6.82$, $p = 0.012$, $\eta^2 = 0.13$), and a group-condition interaction in the BA44/45 ($F(1,48) = 7.15$, $p = 0.010$, $\eta^2 = 0.14$) and marginally in the BA9/46 ($F(1,48) = 4.15$, $p = 0.047$, $\eta^2 = 0.08$), in addition to a main effect of condition (BA8: $F(1,48) = 65.20$, $p < 0.001$, $\eta^2 = 0.59$; BA7: $F(1,48) = 95.52$, $p < 0.001$, $\eta^2 = 0.68$; BA9/46: $F(1,48) = 103.69$, $p < 0.001$, $\eta^2 = 0.69$; BA44/45: $F(1,48) = 107.61$, $p < 0.001$, $\eta^2 = 0.70$). Older participants showed greater regional activations than young participants in the dorsomedial prefrontal cortex and posterior parietal cortex regardless of the condition, and in the lateral prefrontal cortex for REO− trials.

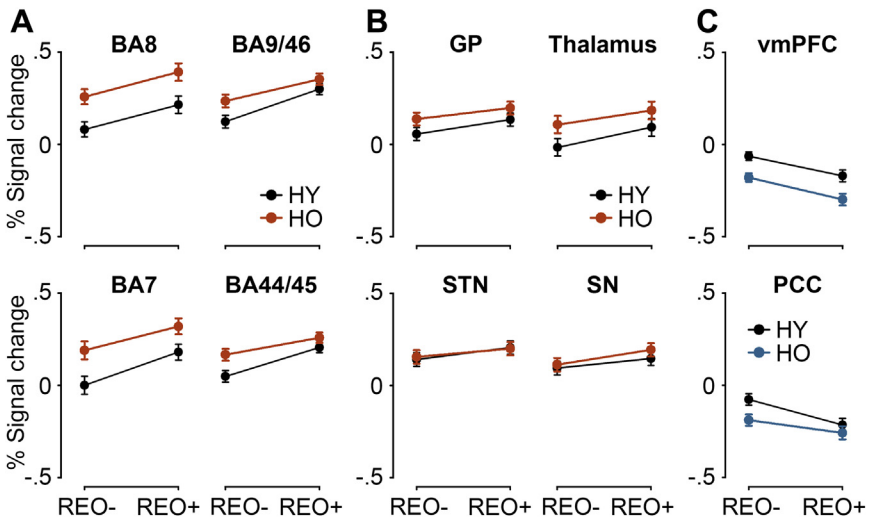

Fig. 4. Means and standard errors of the percent signal change for "reorder & recall" (REO+) and "pure recall" trials (REO−) in healthy older (HO) and young participants (HY). (A) Older participants showed greater regional activations than young participants in the dorsomedial prefrontal cortex (BA8) and posterior parietal cortex (BA7) regardless of the condition, and in the dorsolateral (BA9/46) and ventrolateral prefrontal cortex (BA44/45) for "pure recall" trials. (B) No age difference was observed in the globus pallidus (GP), subthalamic nucleus (STN), thalamus, or substantia nigra (SN). (C) Older participants showed greater regional deactivations than young participants in the ventromedial prefrontal cortex (vmPFC) regardless of the condition, and in the posterior cingulate cortex (PCC) for "pure recall" trials.

We explored the group effect in the globus pallidus, subthalamic nucleus, thalamus, and substantia nigra (Fig. 4B). There was no group effect at a Bonferroni-corrected threshold ($p < 0.013$).

3.5. Age difference in regional deactivation

We explored the group effect in the default mode network (Fig. 4C) and considered significance at $p < 0.016$ (Bonferroni-corrected for 3 regions). The ANOVA revealed a main effect of group in the ventromedial prefrontal cortex ($F(1,48) = 11.23$, $p = 0.002$, $\eta^2 = 0.20$) and a marginal group-condition interaction in the posterior cingulate cortex ($F(1,48) = 4.21$, $p = 0.046$, $\eta^2 = 0.08$), in addition to a main effect of condition (ventromedial prefrontal: $F(1,48) = 53.16$, $p < 0.001$, $\eta^2 = 0.54$; posterior cingulate: $F(1,48) = 40.62$, $p < 0.001$, $\eta^2 = 0.47$). There was no group effect in the Rolandic operculum. Older participants showed greater deactivations than young participants in the ventromedial prefrontal cortex regardless of the condition, and in the posterior cingulate cortex for REO− trials.

3.6. Age difference in ordering-independent functional connectivity

Fig. 5 shows the group effect (older>young) on the ordering-independent functional connectivity. For each cortical seed (BA8, BA9/46, BA44/45, BA7), the whole-brain 2-sample t-test (voxel-level $p < 0.001$, cluster-level $p < 0.05$ familywise-error-corrected) revealed stronger correlations between the time course of the seed and the time courses of the subcortical regions for older than young participants. The age difference in the ordering-independent functional connectivity was consistent across the seeds. Namely, the bilateral putamen/thalamus were more strongly connected with the BA8 (left [−27, −18, 6], $t = 5.81$, 92 voxels; right [27, −12, 6], $t = 5.87$, 126 voxels), BA7 (left [−21, 3, 9], $t = 5.39$, 100 voxels; right [27, −12, 9], $t = 6.57$, 168 voxels), BA9/46 (left [−27, 0, 9], $t = 5.26$, 136 voxels; right [27, −12, 9], $t = 6.20$, 112 voxels), and BA44/45 (left [−27, 0, 12], $t = 5.19$, 156 voxels; right [24, −12, 3], $t = 5.78$, 249 voxels) in older than young participants. The midbrain (substantia nigra or red nucleus) was more strongly connected with the BA8 (left [−9, −24, −3], $t = 4.29$, 13 voxels; right [9, −21, −3], $t = 4.50$, 28 voxels), BA7 ([9, −21, −3], $t = 4.84$, 62 voxels), BA9/46 ([9, −21, −3], $t = 3.97$, 12 voxels), and BA44/45 (left [−15, −21, −6], $t = 3.66$, 5 voxels; right [6, −18, −3], $t = 4.36$, 25 voxels) in older than young participants. No other regions were significant for older than young participants. No regions were significant for young than older participants.

3.7. Age difference in ordering-dependent interregional interaction

Fig. 6A shows the group effect (young>older) on the PPI. In young participants, the 4 cortical seeds were more strongly connected with the supplementary motor area/cingulate cortex (BA6/32) for REO+ than REO− trials, indicating a positive psychological modulation of the functional connectivity. However, the psychological modulation was consistently reversed in older participants. The whole-brain 2-sample t-test (voxel-level $p < 0.001$, cluster-level $p < 0.05$ familywise-error-corrected) revealed a consistent age difference in the PPI across the seeds. Namely, the BA6/32 showed weaker PPI with the BA8 ([3, −3, 51], $t = 4.80$, 160 voxels), BA7 ([−6, 0, 45], $t = 5.45$, 117 voxels), BA9/46 ([9, −15, 45], $t = 5.22$, 48 voxels), and BA44/45 ([9, −15, 45], $t = 5.50$, 245 voxels). No other regions were significant for young than older participants. No regions were significant for older than young participants. We replicated the results of 3.6–3.7 using alternative seeds derived from Neurosynth (see Supplementary Information).

3.8. Predicting performance accuracy with ordering-dependent interregional interaction

We used the linear regression model to examine whether individual participants' accuracy in REO+ trials can be predicted by the mean percentage signal change of the cortical seeds (regional activation) or the mean PPI between the cortical seeds and the BA6/32 (Fig. 6B). The linear regression model was significant ($F(2,49) = 4.35$, $p = 0.019$, $R^2 = 0.16$). The accuracy in REO+ trials was predicted by the PPI (beta = 13.83, $t = 2.93$, $p = 0.005$) but not by the regional activation ($t < 1$).

3.9. Relationship between ordering-dependent interregional interaction and ordering-independent functional connectivity

Having observed the age difference in both PPI and ordering-independent functional connectivity, we then investigated their relationship (Fig. 6C). The mean PPI between the cortical seeds and the BA6/32 was negatively correlated with the mean correlation coefficient between the cortical seeds and the striatum ($r = −0.37$, $p = 0.012$) and with the mean correlation coefficient between the

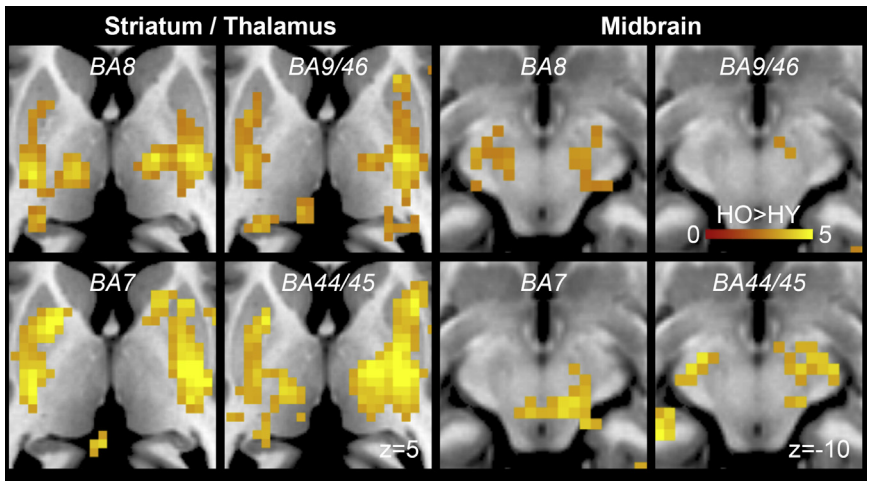

Fig. 5. Age difference in the ordering-independent functional connectivity. Healthy older participants showed a greater physiological correlation between the cortical seeds (BA8, BA7, BA9/46, and BA44/45) and the striatum, thalamus, and midbrain than young participants (HO>HY). Color scales indicate t values. Coordinates are in MNI space. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

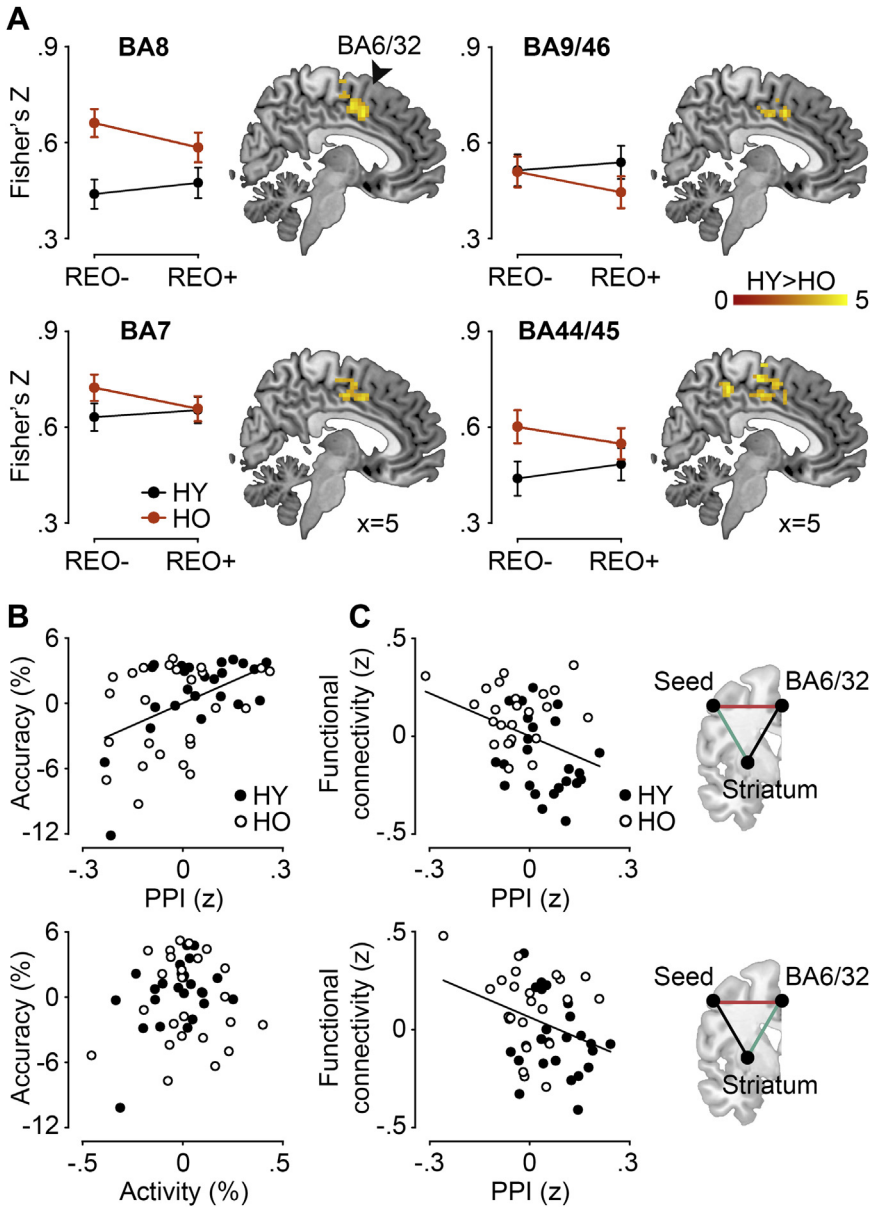

Fig. 6. Age difference in the ordering-dependent interregional interaction. (A) Healthy older participants showed a weaker psychophysiological interaction (PPI) between the cortical seeds (BA8, BA7, BA9/46, and BA44/45) and the supplementary motor area/cingulate cortex (BA6/32) than young participants (HY>HO). Line graphs show means and standard errors of the Fisher-transformed correlation coefficient for "reorder & recall" (REO+) and "pure recall" trials (REO−). Color scales indicate *t* values. Coordinates are in MNI space. (B) For "reorder & recall" trials, individual participants' performance accuracy was predicted by the mean PPI (top) but not by the mean regional activation of the cortical seeds (percent signal change, bottom). Values are demeaned. (C) For "reorder & recall" trials, the mean PPI between the cortical seeds and BA6/32 (red lines) was negatively correlated with the mean correlation coefficient between the cortical seeds and the striatum (top, green line), and with that between the striatum and the BA6/32 (bottom, green line). Values are demeaned. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

striatum and the BA6/32 ($r = -0.34$, $p = 0.020$) when the mean percentage signal change of the cortical seeds was controlled.

4. Discussion

Existing models of short-term memory for serial order have been focusing on the behavioral pattern of healthy young adults (for a review, see Hurlstone et al., 2014). We are more interested in the neural network that supports the flexible manipulation of serial order and how the neural network changes in older adults. In this study, we demonstrated a distributed network for serial ordering, comprising the dorsomedial prefrontal cortex, dorsolateral and ventrolateral prefrontal cortex, posterior parietal cortex, globus pallidus, subthalamic nucleus, thalamus, substantia nigra, and cerebellum (Fig. 3). Regional activation and interregional interaction within the network were modulated by serial ordering and age. In young adults, the dorsomedial prefrontal (BA8), lateral prefrontal (BA9/46, BA44/45), and posterior parietal regions (BA7) were more activated and more strongly connected with the supplementary motor area (BA6/32) for "reorder & recall" than "pure recall" trials. Compared with young adults, older adults showed greater regional activations in the dorsomedial prefrontal and posterior parietal regions regardless of the condition, and in the dorsolateral and ventrolateral prefrontal regions for "pure recall" trials (Fig. 4A). Moreover, older adults showed a weaker ordering-dependent interregional interaction between the prefrontal/parietal regions

and the supplementary motor area than young adults (PPI, Fig. 6A). Across age groups, participants who had a stronger PPI tended to perform more accurately in "reorder & recall" trials (Fig. 6B). By contrast, older adults showed a stronger physiological correlation between the prefrontal/parietal regions and the striatum, thalamus, and midbrain than young adults (Fig. 5). Across age groups, the decreased PPI appeared to be compensated by the increased ordering-independent functional connectivity between the prefrontal/parietal regions and the striatum, and by that between the striatum and supplementary motor area (Fig. 6C).

Our primary finding is that individual adults' performance accuracy in serial ordering can be predicted by their PPI strength between the prefrontal/parietal regions and the supplementary motor area, rather than the regional overactivation (cf. Huang et al., 2012). The involvement of the supplementary motor area is consistent with a recent proposal that the supplementary motor area plays a role in integrating items into a structured sequence, regardless of the nature of the items (e.g., verbal, motor; see Cona and Semenza, 2017). It is assumed that the supplementary motor area encodes 2 primary properties of the sequence: ordinal properties which indicate the serial order of the items and temporal properties which indicate the serial order of the time intervals between items. In this study, the supplementary motor area may operate as a hub, interacting with other cortical regions to update the serial order of the items. Moreover, the decreased PPI was likely compensated by the increased functional connectivity between the prefrontal/parietal regions and the striatum, and between the striatum and the supplementary motor area, leading to the absence of a group-level difference in performance accuracy. The observation of the increased functional connectivity between the prefrontal/parietal regions and the putamen in older adults is consistent with the previous finding that the structural connectivity of the bilateral putamen increased with age (Bhagat and Beaulieu, 2004; Càmara et al., 2007). But it is unclear how the loss of putamen neurons in normal aging (Bugiani et al., 1978) leads to the connectivity increase in this region.

We observed a general elevation of regional activation in the prefrontal and parietal regions, but not in the subcortical regions, when older adults rearranged sequential items successfully. Despite different working memory processes, the prefrontal overactivation in this study looked similar to the prefrontal overactivation in previous studies where older adults held item information as accurately as young adults (e.g., at lower memory load, Reuter-Lorenz et al., 2000). By contrast, when older adults performed less accurately than young adults in the same item memory task, they showed underactivation in the lateral prefrontal cortex (e.g., at higher memory load, Cappell et al., 2010; Rypma and D'Esposito, 2000). Previous studies seldom reported overactivation beyond the lateral prefrontal cortex (Cappell et al., 2010; Reuter-Lorenz et al., 2000; Rypma and D'Esposito, 2000). Here we observed a more widely spreading overactivation in older adults, extending from the lateral prefrontal cortex to the dorsomedial prefrontal cortex and posterior parietal cortex.

The prefrontal and parietal overactivations have been interpreted as dedifferentiation of function or functional compensation (Cabeza and Dennis, 2013; Huang et al., 2012; Rajah and D'Esposito, 2005; Spreng et al., 2016; Turner and Spreng, 2015). The dedifferentiation and compensation views both assume the existence of age-related functional deficits but they differ in how to interpret the rise of the functional deficits. The compensation view links the functional deficits with age-related changes in prefrontal gray-matter volume (Tisserand et al., 2002) and white-matter integrity (Yap et al., 2013). Increased prefrontal activation is assumed to reflect the development of alternative neural circuits to achieve behavioral goals (Park and Reuter-Lorenz, 2009). In this study, the additional prefrontal and parietal activations were unlikely compensatory, given the absence of a relationship between individual adults' task performance and their cortical regional activation. The lack of the performance-brain relationship has also been observed in the short-term memory for item information (Cappell et al., 2010; Reuter-Lorenz et al., 2000; Rypma et al., 2007). The dedifferentiation view proposes that the functional deficits originate from deficient neurotransmission, which causes a higher level of neural noise, a lower signal-to-noise ratio, and a less-distinct neural representation (Li et al., 2001). Increased prefrontal activation is considered as a consequence of generalized activity spreading due to the loss of neural specificity, which may or may not be compensatory. The dedifferentiation view is consistent with a recent meta-analysis, finding that dopamine receptors in the prefrontal cortex decrease with age (Karrer et al., 2017). This view can be directly tested in psychopharmacological studies. For example, elevating brain dopamine levels or stimulating dopamine D1 receptors may enhance the cortical signal-to-noise ratio and stabilize neural representations (Winterer et al., 2006), which may, in turn, improve differentiation and normalize prefrontal activation.

Beyond the task-positive neutral network, we observed ordering-related deactivations in the default mode network and a general elevation of ventromedial prefrontal deactivation in older adults. The involvement of the default mode network may reflect the suppression of self-reflection or mental state attribution when people direct their attention to a cognitively demanding task (Jenkins, 2019). Our findings of the greater ventromedial prefrontal deactivation in older adults contradict previous findings. For example, some researchers reported an age-related reduction of deactivation within the default mode network, especially for more demanding working memory tasks (e.g., 2-back vs. 1-back, see Prakash et al., 2012; Sala-Llonch et al., 2012). Other researchers found no age-related changes in the functional connectivity of the default mode network in a population-based cohort ($N = 711$, see Jockwitz et al., 2017).

Serial ordering might be a type of strategic recoding operation in working memory. In a series of fMRI studies, Owen et al investigated neural correlates of strategic reorganization (e.g., chunking, see Bor et al., 2003, 2004; Bor and Owen, 2007). Their chunking tasks included 2 types of trials. In structured trials, a mathematical association existed between sequential items (e.g., *21-32-43-54*, increasing each time by 11). Participants could use the mathematical strategy to store the sequence in a more compact representation. In unstructured trials, there was no potential association between the items (e.g., *18-63-90-47*). Participants had to memorize the sequence without the strategy. Successful chunking facilitated serial recall, leading to a higher memory span and more accurate performance. Chunking was accompanied by greater activations in the dorsolateral and ventrolateral prefrontal cortex, posterior parietal cortex, and inferior temporal cortex. A recent clinical trial further suggested that chunking-based training had the potential to improve verbal working memory and general cognition in patients with mild Alzheimer's disease (Huntley et al., 2017). But it is still unclear how chunking is cognitively or biologically realized in working memory.

This study has limitations. First, in the digit ordering task, the specific digit or ordinal position probed at a particular trial might affect working memory load. We evenly balanced the probability of a specific digit or ordinal position to be probed across trials and conditions. However, working memory load may be greater for items presented at position 3 than items presented at position one (Kalm and Norris, 2017; see an exploratory analysis of the effect of ordinal position as Supplementary Information), and be lower for digits such as "zero" and "nine" (e.g., easily matched to position one and 4). Second, we did not control the exact time when reordering

was initiated. Participants might initiate reordering when all digits have been perceived, or as soon as the first digit was perceived. The process of reordering may share some of the brain resources (e.g., prefrontal and parietal activations) with the processes of encoding and retrieval. This may be difficult to depict with the current approach. Fourth, the current results are descriptive. The ultimate goal is to propose a computational or biological model of serial ordering in working memory.

5. Conclusions

We detected a distributed network for serial ordering, functionally connecting the medial and lateral prefrontal cortex with the posterior parietal cortex, globus pallidus, subthalamic nucleus, thalamus, substantia nigra, and cerebellum. Within the network, regional activation and interregional interaction were modulated by serial ordering and age. In young adults, the prefrontal and parietal regions were more activated and more strongly connected with the supplementary motor area for serial ordering (ordering-dependent interregional interaction). In older adults, the prefrontal and parietal activations were elevated in a nonspecific manner but the ordering-dependent interregional interaction was attenuated. Meanwhile, the ordering-independent functional connectivity was enhanced between the prefrontal/parietal regions and striatum, which may play a compensatory role in the face of serial ordering. This study suggests that the impact of age goes beyond the prefrontal cortex and includes adaptive connectivity changes in the fronto-striato-parietal network. These results have the potential to extend existing models of short-term memory for serial order, which lack an account of the decline of serial ordering in older adults.

Disclosure

The authors declare no competing financial interests.

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Authors' contributions: ZY and TFM designed the research; ZY, GZ, SL, YZ, WX, and XZ performed the research; ZY analyzed the data; ZY and TFM wrote the paper. All authors approved the submitted version.

This study was approved by the ethical committee of Peking University Third Hospital in accordance with the Declaration of Helsinki. Each participant signed a written informed consent before participating in this study.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2019.12.007.

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