

# 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.

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## 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,  $tD[(tiv(.3165iv)511.5(367)-42.1(ve)-306ed)-42$

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; Berdyeva 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

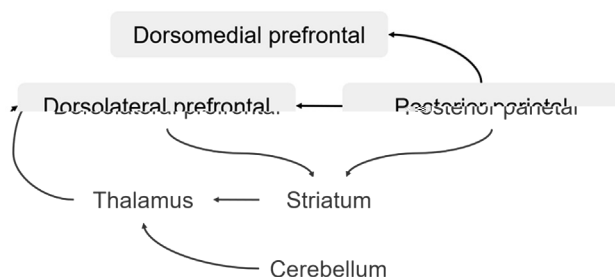


Fig. 1. Fronto-striato-parietal network.

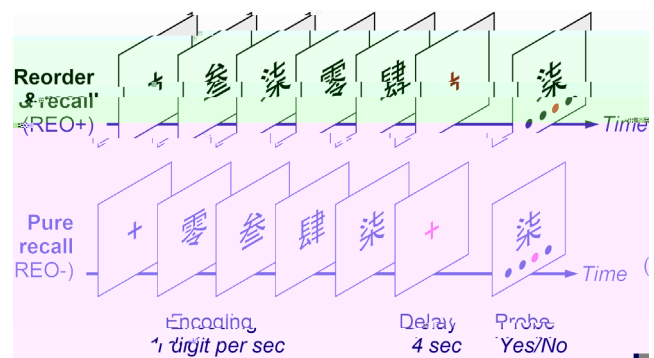


Fig. 2. Digit ordering task.

cortex and the striatum, posterior parietal cortex, or premotor cortex in older adults (e.g., Heinzl 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.

## 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 ≥26/30). Table 1 presents demographic features and neuropsychological measures of the 2 age groups.

### 2.2. Experimental design

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).

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 ( $\geq 85\%$ ).

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

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](#))

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  $[-3, 9, 54]$ ,  $p = 10.48$ , 1218 voxels), dorsolateral prefrontal cortex (BA9/46: left  $[-48, 12, 30]$ ,  $p = 8.29$ , 217 voxels; right  $[45, 33, 24]$ ,  $p = 6.66$ , 83 voxels), ventrolateral prefrontal cortex (BA44/45:

left  $[-54, 9, 12]$ ,  $p = 7.03$ , 139 voxels; right  $[57, 9, 18]$ ,  $p = 6.10$ , 60 voxels), posterior parietal cortex (BA7/40: left  $[-36, -45, 36]$ ,  $p = 9.38$ , 780 voxels; right  $[45, -45, 45]$ ,  $p = 9.14$ , 684 voxels), thalamus (left  $[-12, -3, 12]$ ,  $p = 9.83$ , 96 voxels; right  $[12, -3, 12]$ ,  $p = 6.59$ , 45 voxels), globus pallidus (left  $[-15, -3, 9]$ ,  $p = 7.15$ , 32 voxels; right  $[15, 0, 9]$ ,  $p = 6.21$ , 23 voxels), subthalamic nucleus ( $[-12, -15, -9]$ ,  $p = 4.43$ , 5 voxels), substantia nigra ( $[-9, -18, -12]$ ,  $p = 5.24$ , 6 voxels), and cerebellum (VI/Crus I:  $[-27, -63, -36]$ ,  $p = 9.51$ , 655 voxels; VIIIa/VIIb:  $[3, -72, -33]$ ,  $p = 6.15$ , 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 ( $[6, 51, 12]$ ,  $p = 7.19$ , 1245 voxels), posterior cingulate cortex ( $[-6, -54, 12]$ ,  $p = 6.65$ , 509 voxels), and Rolandic operculum (left  $[-42, -18, 18]$ ,  $p = 4.93$ , 33 voxels; right  $[48, -27, 21]$ ,  $p = 5.25$ , 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 con-293.3([9Tc3122(e)0(d)-60-r1F11Tf1.1d38.2888)T]/F31[(ol

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 the default mode network

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 the 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 the PPI

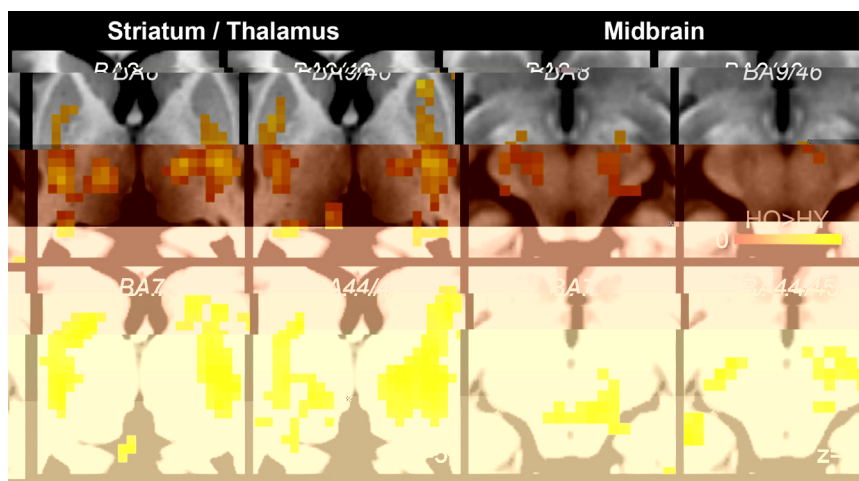
Fig. 6A shows the group effect (young > older) on the PPI. In young participants, the 4 cortical seeds were more strongly connected with the supplementary motor area/cingulate cortex (BA6/32) for REO+ than REO- trials, indicating a positive psychological modulation of the functional connectivity. However, 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. Prediction of REO+ accuracy by PPI and regional activation

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 ( $p < 1$ ).

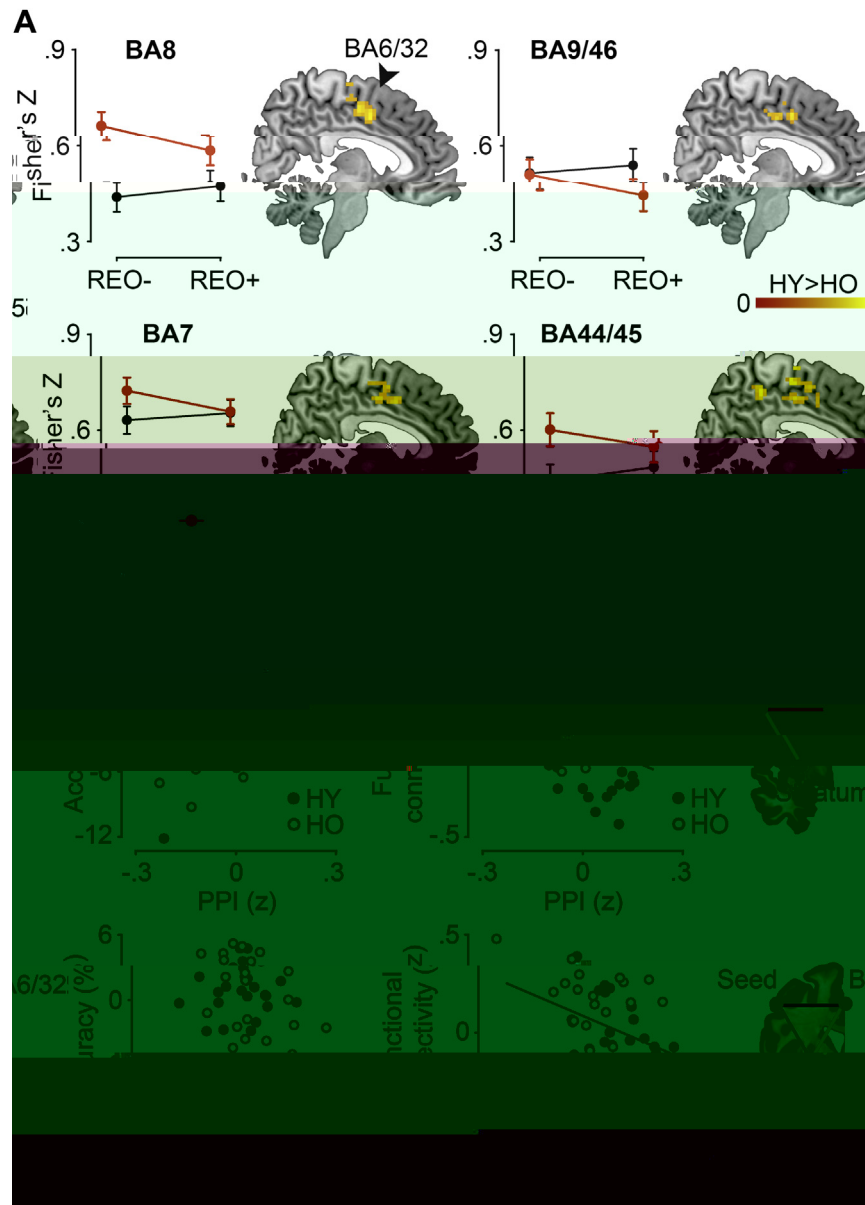
### 3.9. Relationship between PPI and ordering-independent functional connectivity

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.



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.,

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