Original Article Age-related increase in brain activity during task-related and -negative networks and numerical inductive reasoning

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Abstract: Objective: Recent neuroimaging studies have shown that elderly adults exhibit increased and decreased activation on various cognitive tasks, yet little is known about age-related changes in inductive reasoning. Methods: To investigate the neural basis for the aging effect on inductive reasoning, 15 young and 15 elderly subjects performed numerical inductive reasoning while in a magnetic resonance (MR) scanner. Results: Functional magnetic resonance imaging (fMRI) analysis revealed that numerical inductive reasoning, relative to rest, yielded multiple frontal, temporal, parietal, and some subcortical area activations for both age groups. In addition, the younger participants showed significant regions of task-induced deactivation, while no deactivation occurred in the elderly adults. Direct group comparisons showed that elderly adults exhibited greater activity in regions of task-related activation and areas showing task-induced deactivation (TID) in the younger group. Conclusions: Our findings suggest an age-related deficiency in neural function and resource allocation during inductive reasoning.

Keywords: Aging, numerical inductive reasoning, fMRI

Introduction

Functional magnetic resonance imaging (fMRI) has recently been increasingly used in the study of cognitive aging [1, 2]; however, most of the studies have used perceptual or motor paradigms [3, 4] with little attention devoted to the study of age-related changes in more complex mental processes, such as inductive reasoning.

Inductive reasoning is an often-used life skill, and is considered to be an important form of higher-level thinking. In healthy, young adults, neuroimaging studies have shown that numerical inductive reasoning engages a distributed network consisting of frontal and parietal areas, as well as subcortical structures [5, 6]. Our previous study showed that patients with mild cognitive decline (MCI) had functional abnormalities of the dorsolateral prefrontal cortex (DLPFC) compared to normal aging during numerical inductive reasoning [7]; however, the differences in brain activity between elderly and young adults during numerical inductive reasoning are unclear. In the present study we applied fMRI to provide insight into the similarities and differences of cerebral activation for elderly and young adults during numerical inductive reasoning. We hypothesized that a distributed network consisting of the frontal and parietal lobes, as well as subcortical structures [5, 6], would be activated in elderly and young adults. Based on aging studies with other cognitive tasks, elderly adults were expected to exhibit more extensive and greater magnitude of activation in task-related regions, as well as regions showing task-induced deactivation (TID) in the younger group.

Materials and methods

Participants

The study was approved by the Ethical Committee of Xuan Wu Hospital. All of the participants voluntarily joined this study and signed informed consent.

Young adults were recruited from local campuses, and elderly adults were recruited from announcements posted in the community near

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	Younger group N = 15, M (SD)	Aged group N = 15, M (SD)	P-value	
Age (years)*	24.40 (3.09)	63.67 (3.29)	0.00	
Education (years)	15.80 (2.98)	15.60 (1.96)	0.83	
Gender(Male/Female)	8/7	8/7	1	
WAIS-R	116.87 (8.53)	116.20 (8.83)	0.84	

 Table 1. Participant characteristics and neuropsychological data

Note: M = mean; SD = standard deviation; MMSE = mini-mental status examination. *P < 0.05.

Xuan Wu Hospital. The inclusion criteria were years of education > 12 years, right-handedness, no history of severe head trauma and loss of consciousness, and no history of taking medications which are known to have an effect on the central nervous system in the past 6 months. In addition, participants had to score at least 91 on the Wechsler Adult Intelligence Scale-Revised [8]. For the elderly group, the Mini-mental State Examination score [9] was not < 28, the Clinical Dementia Rating (CDR) [10] score should be 0, and showed no signs of depression on the Geriatric Depression Scale (GDS) [11]. Participants with severe white matter lesions were excluded [12]. All participants had normal or corrected vision, and were defined as right-handed according to the Edinburgh Handedness Inventory [13].

Stimuli and procedures

For the numerical inductive reasoning task (target task), 3 sequential numbers (13, 15, and 17) were presented on a screen. The subjects were required to identify the algorithm/rule (i.e., +2) underlying the series of numbers, and calculate the next number in the series (i.e., 19) according to the rule. The correct answer was selected by pressing a button, and the response of the left and right hands was balanced. All numbers involved in the series of numbers and answers were in the range of 1-99. The magnitude of the arithmetic operation ranged from 2-9. Interferential tasks were designed to avoid the possibility that subjects acquired the answer based on the first two numbers without consideration of the third number [5].

During resting conditions, the participants were asked to relax and passively view a cross presented on the middle of the screen.

A total of 32 target tasks, including 2 interferential tasks, were created and evenly distribut-

ed on 8 clocks. The blocks of target tasks and resting conditions were alternated and each block lasted 48 s. At the beginning of the experiment a fixation cross was presented for 14 s.

fMRI data acquisition

All MR imaging was acquired with a 3.0 T MRI system (Siemens Trio Tim; Siemens Medical System, Erlanger, Germany) using a 12-channel phased array head coil. Three-dimensional (3D) high-

resolution structural images were acquired using a T1-weighted MPRAGE sequence, as follows: TR, 2300 ms; TE, 2.93 ms; TI, 900 ms; 176 sagittal slices; field of view, 270 × 270 mm²; flip angle, 9°; and voxel size, $1 \times 1 \times 1$ mm³. Functional imaging was performed using a T2* gradient-echo EPI sequence, as follows: TR, 2000 ms; TE, 30 ms; flip angle, 90°; 64 × 64 matrix size; and field of view, 240 × 240 mm². Fluid attenuated inversion recovery (FLAIR) imaging was performed for evaluation of white matter lesions, as follows: TR, 9000 ms; TE, 90 ms; field of view, 220 × 220 mm²; and voxel size, 0.9 × 0.9 × 5 mm³. Before scanning began, head phones and foam padding were applied to reduce head motion and noise.

Data preprocessing

fMRI analysis was carried out using SPM8 software (Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk). The first four images were discarded to allow for stabilization of the MR signal. Pre-processing began with correction for timing differences between slices, after which rigid body motion correction to the median image was carried out. The functional images of each subject were co-registered with the high resolution structural image. Then, normalization parameters were applied to the EPI images and all volumes were normalized into 3 × 3 × 3 mm³ voxels. Head movement was limited within 1 mm in all cases. Finally, normalized images were smoothed with an 8 mm FWHM isotropic Gaussian kernel.

fMRI analysis

A voxel-by-voxel comparison according to the general linear model and *t*-statistics were used to calculate differences of activation between numerical inductive reasoning and rest in young and elderly subjects. The differences within



Figure 1. Regions of significant activation or deactivation for numerical inductive reasoning in young and elderly adults (uncorrected P < 0.001, cluster size ≥ 15 voxels, in MNI space). Warm color bar indicates the t-scores of task-induced activation, while the winter color bar indicates the t-score of the TID. Blue circles indicate region overlap with the age-related increases in the elderly group. Left in this map is right in the human brain.

groups were based on one-sample t-tests. Task-induced activation was acquired by the contrast of numerical inductive reasoning versus rest, and TID was acquired by the contrast of rest versus numerical inductive reasoning. The differences between two groups were based on two-sample *t*-tests. Conjunction analysis was used to reveal regions common to both groups by using the contrast of the elderly group (numerical inductive reasoning > rest) in conjunction with the contrast of the young group (numerical inductive reasoning > rest). All of the results survived an uncorrected voxellevel intensity threshold of P < 0.001 with a minimum cluster size of 15 contiguous voxels.

Results

Demographics of participants

The demographics of the participants are provided in **Table 1**. Fifteen young subjects (age range, 18-28 years; mean age, 24.40 ± 3.09 years; 8 males) and 15 elderly subjects (age

range, 60-70 years; mean age, 63.67 ± 3.29 years; 8 males) were included in this study. The young and elderly adults did not differ in gender, years of education, or scores on the Wechsler Adult Intelligence Scale-Revised.

Behavior analysis

Under numerical inductive reasoning conditions, the accuracy of the young and elderly groups was 92.45% \pm 9.04% and 82.67% \pm 11.28% (*P* = 0.01), respectively, and the reaction time (RT) for the 2 age groups was 3839.27 \pm 904.32 ms and 4639.13 \pm 870.55 ms (*P* = 0.02), respectively. There were significant differences in task performance between the two groups, with a better performance in the young group.

fMRI analysis

Task-induced activation in the young and elderly groups: Numerical inductive reasoning, relative to rest, yielded multiple frontal and



Figure 2. Regions commonly activated by young and elderly adults for numerical inductive reasoning to rest (uncorrected P < 0.001, cluster size ≥ 15 voxels, in MNI space). Color bar indicates the t-scores of common activation. Red circles indicate region overlap with the age-related increases in the elderly group. Left in this map is right in the human brain.

participants. As depicted in **Figure 1**, the regions of activation were comparable for the elderly and young participants; however, the elderly adults recruited a larger and more distributed network compared to the young adults (see <u>Supplementary Tables 1</u> and 2 for anatomic coordinates).

Task-induced deactivation in the young and elderly groups: As depicted in **Figure 1**, contrasting rest versus inductive reasoning, the whole-brain analysis for the young participants revealed significant regions of deactivation, including the bilateral posterior cingulate cortex/precuneus (PCC/PrC), medial frontal cortex (mFC), and angular gyrus (AG) in the classic default mode network areas, as well as the bilateral pre-/post-central gyrus (PrCG/PoCG; BA 3) and superior temporal gyrus (STG; see Supplementary Table 1 for anatomic coordinates). No deactivation during inductive reasoning was observed in elderly adults at a threshold of P < 0.001: however, when the threshold was reduced to P <0.005, task-induced deactivation was found in posterior regions, including the bilateral PCC/PrC and AG (data not shown).

Areas commonly activated in both age groups: We next examined areas commonly recruited by the young and elderly adults (task-related regions). As depicted in Figure 2, conjunction analysis of fMRI data revealed a distributed network consisting of frontal, parietal, temporal, and subcortical areas (see Supplementary Table 3 for anatomic coordinates). A large area in the inferior and superior parietal lobule (IPL and SPL, respectively), dorsolateral prefrontal cortex, mFC, as well as some subcortical areas, such as the caudate, were activated bilaterally in both groups. These regions of activation are consistent with the results reported in previous studies of numerical inductive reasoning [5, 6].

Age-related differences in brain activity: **Table 2** and **Figure 3** show the agerelated differences in brain activity for numerical inductive reasoning relative

to rest. Consistent with our predictions, elderly adults exhibited increased activation as compared with young adults in the right IPL with extension to the PCC and PoCG, left SPL, left AG, bilateral superior frontal gyrus (SFG), right middle frontal gyrus (MFG), left PoCG, right caudate, and left middle occipital gyrus (MOG). No region demonstrated a greater activity in the young group at the chosen threshold.

By comparing the maps of common activation in both age groups and deactivation in the

Table 2. Comparison between two age groups in the contrast
of numerical inductive reasoning related to rest (P < 0.001;
Extent of cluster size \geq 15)

Brain regions	BA	Cluster size	MNI		t-score	
			Х	у	Z	
Older > Younger						
Rt-Inferior Parietal Lobule	40	1357	36	-51	48	7.49
Lt-Superior Frontal Gyrus	6	899	-3	6	63	6.27
Lt-Angular Gyrus	39	140	-39	-69	33	5.23
Rt-Middle Frontal Gyrus	6	34	33	-3	69	5.45
Lt-Middle Occipital Gyrus	18	32	-27	-87	0	4.32
Lt-Superior Temporal Gyrus	22	27	-57	-9	6	4.24
Lt-Superior Parietal Lobule	7	16	-12	-69	54	4.17
Lt-Postcentral Gyrus	2	16	-54	-27	45	4.41
Rt-Caudate	СВ	15	12	-3	18	4.29
Younger < Older						
-	-	-	-	-	-	-

Note: BA = Brodmann area; Lt = left; Rt = right; CB = caudate body.

young adults, the age-related increases were further divided into *increases in task-related regions* (i.e., regions commonly activated by two age groups, but increased in the elderly group), and *increases in TID regions* (i.e., regions deactivated in young adults, but deactivation was reduced in elderly adults). Increases in the task-related regions included the right MFG, bilateral SFG, right IPL, and bilateral caudate. Increases in the TID regions included the right PCG, right PCC, and left AG.

Discussion

To test age differences in inductive reasoning, we used a paradigm appropriate for both age groups. The current study yielded two main findings. First, this paradigm can activate brain regions associated with numerical inductive reasoning in the young and elderly groups. Second, compared with young adults, the elderly participants showed increases in task-related activation and reduced deactivation.

Arithmetic inductive reasoning induced activation in the young and elderly groups

As predicted, elderly participants activated comparable networks to young participants in numerical inductive reasoning. Task-related activation included a distributed network consisting of frontal and parietal areas, as well as subcortical structures. These activations have been consistently identified in prior studies of numerical inductive reasoning in young adults [5, 6]. Additionally, consistent with our findings, aging studies in other cognitive domains also showed similarities in the patterns of activation across age groups [1, 14]. Thus, the present results indicate our paradigm activated brain regions associated with numerical inductive reasoning in both age groups. Moreover, the similarities in activation patterns between the two age groups indicate that basic neural mechanisms underlying numerical inductive reasoning are maintained into old age.

Greater activity in task-related regions in the elderly group

In the group comparison, some increased brain activity was found in the task-related regions. Greater cortical recruitment with increasing age has been noted in a variety of tasks [1, 3, 4]. Some studies have reported that increased activation combine with decreased activation in other regions [15, 16], and has been interpreted as compensatory neural plasticity [17]. The concomitant age-related reductions in brain activity, however, were not observed in the current study. Thus, the age-related changes demonstrated in the current study do not support a compensatory pattern. In agreement with our findings, Morcom et al. [18] reported that elderly adults used more retrieval-related neural resources to achieve similar levels of performance without an apparent decrease in brain areas. The same age-related pattern of change was also reported by Cappell et al. [19], the findings of which suggested that the overrecruitment of task-related areas in older people may indicate an age-related inefficiency in these regions [20]. Based on our previous study [5], regions near the intra-parietal sulcus play an important role in the rule identification component of inductive reasoning, whereas the MFG/SFG (BA 6) and caudate are more specific to rule extrapolation. Thus, the findings in the present study suggest that elderly adults have brain inefficiency in both rule induction and extrapolation processes during inductive reasoning.



Figure 3. Results of direct group comparisons for numerical inductive reasoning to rest (uncorrected P < 0.001, cluster size ≥ 15 voxels, in MNI space). Color bar indicates the t-scores of group differences. Red circles indicate region overlap with common activation in the two age groups, and blue circles indicate region overlap with the TID in young adults. Left in this map is right in the human brain.

Increased activity in the TID regions in the elderly group

Not all of the age-related changes were due to group differences to which regional activity was associated with the task. In the young participants, several regions, such as the midline areas and bilateral AG, demonstrated decreased activity in the task condition relative to resting conditions. The TID in the midline areas and bilateral inferior parietal cortex (IPC) has consistently been reported to have decreased activity, irrespective of the task being performed [21, 22]. The midline areas and IPC are thought to reflect a task-negative network. In addition, recent evidence also demonstrated a linear increase in the degree of TID with increasing task difficulty [23, 24]. These findings suggest that depression of task-negative regions reflect reallocation of attentional resources to the brain areas actively involved in ongoing tasks. Recent evidence also suggests that advancing age can modulate the degree of TID. Lustig et al. [25] reported decreased deactivation in elderly adults relative to young adults during a semantic classification task compared with rest. These results were further confirmed by Grady et al. [26] who reported linear increases in activity with age in areas normally decreased during memory tasks. In addition, the ability to suppress task-negative regions is further impaired in patients with MCI [27] and Alzheimer's disease [28]. In the present study, increases in right PCG, right PCC, and left AG overlapped with the regions showing TID in the young group, and reflected a reduction in deactivation in elderly adults. These findings were consistent with the observation that young adults showed widespread deactivation in task conditions relative to rest; however, no deactivation was noted in elderly adults at the same threshold. The increases in TID regions can reflect the inefficiency of transforming resources to task-related regions in elderly adults. In contrast, it is also possible to lead to reductions in the signal-to-noise ratio, which as a consequence interferes with the task at hand. Thus, we propose that a loss of regulation or functional inhibition in the elderly group may contribute to the age-related decline in inductive reasoning.

In summary, similarities and differences were observed in brain activation for the elderly and young groups during inductive reasoning. The up-regulation of brain activity in the elderly group is not only associated with brain inefficiency, but also reflect a deficit of inhibition. These findings indicate deficient neural function and neural resource allocation in elderly adults.

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Disclosure of conflict of interest

None.

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Brain regions	BA	Cluster size		MNI		t-score	
			х	у	Z		
Task > rest							
Rt-Inferior Parietal Lobule	40	5260	36	-51	42	19.10	
Rt-Middle Frontal Gyrus	10		33	54	15	11.77	
Rt-Precuneus	19		33	-66	42	11.75	
Lt-Inferior Parietal Lobule	40	959	-42	-45	39	9.82	
Lt-Superior Parietal Lobule	7		-27	-66	51	9.36	
Lt-Superior Parietal Lobule	7		-27	-66	42	9.27	
Lt-Middle Occipital Gyrus	19	87	-48	-57	-12	5.44	
Lt-Parahippocampal Gyrus	19		-39	-51	-9	4.52	
Lt-Cuneus	30	35	-27	-75	6	4.90	
Rest > task							
Lt-Medial Frontal Gyrus	11	5118	-3	48	-9	-11.72	
Rt-Superior Temporal Gyrus	48	401	36	-21	18	-7.95	
Lt-Cuneus	19	114	-15	-90	33	-7.6	
Lt-Angular Gyrus	39	410	-42	-69	33	-9.83	
Rt-Precentral Gyrus	3	122	39	-27	66	-6.29	
Lt-Postcentral Gyrus	3	140	-39	-21	51	-5.62	
Lt-Precentral Gyrus	6	17	-15	-21	78	-5.39	

Supplementary Table 1. Regions of Activation and Deactivation in Younger Adults for Numerical Inductive Reasoning. (p < 0.001; Extent of Cluster Size ≥ 15)

Note: BA = Brodmann area; Lt = left; Rt = right.

Supplementary Table 2. Regions of Activation and Deactivation in Aged Adults for Numerical Induc-
tive Reasoning. (p < 0.001; Extent of Cluster Size \geq 15)

Brain regions	BA Clus	Cluster size		MNI		t-score
			Х	у	Z	
Task > rest						
Rt-Caudate	CB	8747	21	6	27	14.94
Rt-Inferior Parietal Lobule	40		33	-51	45	13.10
Rt-Angular Gyrus	39		30	-60	39	11.30
Lt-Sub-Gyral	37	1717	-45	-54	-9	8.76
Rt-Fusiform Gyrus	19		45	-69	-15	8.02
Rt-Lingual Gyrus	18		12	-78	-15	7.84
Rt-Inferior Frontal Gyrus	44	22	60	18	18	6.51
Rest > task						
-	-	-	-	-	-	-

Note: BA = Brodmann area; Lt = left; Rt = right; CB = Caudate body.

Neural basis of aging effect on inductive reasoning

Brain regions	BA	Cluster size	MNI			t-score
			х	у	Z	
Rt-Inferior Parietal Lobule	40	10932	33	-51	42	11.70
Rt-Angular Gyrus	39		30	-63	36	10.78
Lt-Superior Parietal Lobule	7		-30	-60	48	10.58
Lt-Middle Temporal Gyrus	37	1653	-48	-54	-9	8.67
Rt-Fusiform Gyrus	19		39	-69	-21	6.28
Rt-Fusiform Gyrus	37		51	-51	-9	6.23
Rt-Cingulate Gyrus	23	35	6	-27	30	4.59

Supplementary Table 3. Regions Commonly Activated by Younger and Aged Adults for the Numerical Inductive Reasoning Relative to Rest. (p < 0.001; Extent of Cluster Size ≥ 15)

Note: BA = Brodmann area; Lt = left; Rt = right.