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Older Adults With Efficient Reconfiguration of Task-Positive Networks Showed Higher Cognitive Control Performance

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Abstract

Older Adults With Efficient Reconfiguration of Task−Positive Networks Showed Higher Cognitive Control Performance

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Appropriate reconfiguration of the brain functional network based on various given situations came to the fore as an important factor for the adaptive function in younger adults. Since the role of reconfiguration in older adults needs to be clarified, this study aimed to examine the relationship between brain network reconfiguration and adaptive function even in older adults who had experienced both structural and functional brain change over a lifetime. A total of 83 elderly people who participated in the Korean Social Life and Health Aging Project (KSHAP) completed the resting−state and multi−source interference task (MSIT) fMRI protocol. They underwent 10−minute resting state fMRI acquisition with their eyes open, and 6−minute MSIT state to measure their performance on the cognitive control task. Older people who reconfigured their task−positive networks less from the resting−state to the MSIT showed better performance both in the MSIT, and the neuropsychological tests measuring working memory function. These results were still significant even controlling age, sex, years of education, total gray matter volume, and the mean movement between two states. Especially, the less reconfiguration in the fronto−parietal network (FPN) was significantly associated with better performance on both the cognitive control task and the working memory tests. The MSIT performance was not affected by the individual difference in the configuration of both rest and task state. Yet, the working memory function was significantly affected by the individual difference in the configuration of task state. These results indicated that less and efficient reconfiguration was associated with better adaptive function even in elderly people. In addition, the FPN stability between two different states played a significant role in the cognitive function of elderly adults. Moreover, the cognitive control in older adults was associated with task switching rather than the optimization of the states. On the other hand, the working memory was still associated with the optimization of the task state. This study extended the analysis method of neuroimaging and suggested a novel approach to investigate the cognitive control of older adults.

keywords : Elderly Cognitive functions, Cognitive Control, Working Memory, MSIT, Reconfiguration, Functional Brain Network

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Chapter 1. Introduction

Adaptation to the environment is one of the outstanding abilities of humans. When people get older, they confront diverse life changes which require them to adapt. Retirement, death of close friends, or family members, and the senescence of body frequently occurs in late life (Serby & Yu, 2003). Also, aging-related brain changes are inevitable. They include structural changes (e.g., atrophy in the gray and white matter, white matter microstructural integrity (Raz et al., 2005), and white matter lesion (Chen et al., 2016)), functional changes (e.g., the task-related activation (Persson et al., 2007), functional connectivity (Avelar-Pereira et al., 2017), and network reconfiguration (Gallen et al., 2016)). Therefore, the cognitive decline in late life has numerous impacts on living.

1.1. Cognitive Aging in Older adults

High cognitive functions in late life are ones of the components of successful aging (Rowe & Kahn, 1997). While the objective definition of successful aging is focused on physical health such as freedom from disability and disease, the older adults themselves value well-being, social connectedness, and adaptation over the objective criteria of successful aging (Jeste et al., 2010). Cognitive aging accompanies various structural and functional changes of brain. For example, the prefrontal cortex, where the largest volume decline occurs, supports the episodic encoding and executive processes (Hedden & Gabrieli, 2004). Cognitive aging affects many different domains of function. Recent studies spotlighted three types of trajectory of normal cognitive aging (Salthouse, 2010, 2019): (1) Almost linear decline of speed across adulthood, (2) accelerating declines after age 60 in memory and reasoning, (3) improvements in vocabulary knowledge until the decade of the 60s.

However, the aging trajectory is not irreversible. In fact, there are many reports regarding protective factors against aging (Reuter−Lorenz & Park, 2014; Valenzuela et al., 2007) as well as individual difference in biological (Nyberg et al., 2012) and cognitive aging (Cabeza et al., 2018; Grady & Craik, 2000; Stern et al., 2018). It is crucial to reveal where those individual differences come from for successful aging.

Considering that cognitive control is a very vulnerable and influential function in late life (Braver et al., 2001; Jacoby et al., 2005; Paxton et al., 2008), the cognitive control function needs to be highlighted in this context. In fact, the cognitive decline in late life is prominent in the tasks associated with the cognitive control, involving time planning, working memory, multi−tasking, and inhibitory control (Kim, 2015).

1.2. Cognitive Control Function in the Cognitive Aging

The human cognitive system can configure itself for the performance of specific tasks. The processes behind such adaptability are referred to collectively as "cognitive control" (Botvinick et al., 2001). A collective set of cognitive functions includes response selection, inhibition, and task-set maintenance in the service of goal-directed behavior (Lenartowicz et al., 2010). The flexible hub regions of brain play important roles during functional adaptation, which flexibly and rapidly shifts their connectivity (Cole et al., 2013).

Impairment in cognitive control, which processes the context, can be regarded as a key mechanism to disturb multiple systems in healthy aging (Braver et al., 2001). Older people show a decline in multiple cognitive domains including episodic memory, working memory, inhibition, and attention (Braver et al., 2001). Similarly, another line of the study also suggests inhibition, which is a component of cognitive control, as a central mechanism to influence working memory and a wide array of cognitive functions (Hasher et al., 1991). Namely, cognitive control has a pervasive effect on our lives, and its disruption results in life-altering deficits such as the risk of illness (Cole et al., 2013; Urfer-Parnas et al., 2010).

The cognitive control function is traditionally associated with prefrontal brain regions (Cabeza & Nyberg, 2000). Recent studies suggest that cognitive control recruits wide brain regions through the hub area of brain including the lateral prefrontal cortex (LPFC). Also, graph-theoretical analyses suggest that at least five distinct subnetworks are associated with cognitive control (Cole et al., 2013; Dosenbach et al., 2008; Fair et al., 2009): (1) the fronto-parietal network (FPN), (2) the cingulo-opercular control network (CON), (3) the salience network (SAN), (4) the ventral-attention network (VAN), (5) the dorsal-attention network (DAN). Each network plays a slightly different role in cognitive function. FPN is a well-known task positive network anchored by LPFC. FPN regulates the distributed systems according to task goal. Alterations in the FPN could harm the adaptive function by using feedback control (Cole, Repovš, et al., 2014). CON is also a core system to implement tasks and consists of the (not ventral) anterior insula (aINS), and the adjacent frontal operculum (Dosenbach et al., 2006). The core function of the CON refers to task-set-maintenance. CON is sometimes associated with the attention-demanding task while combined with FPN (Mao et al., 2014). The cortical hub of the SAN is composed of the anterior cingulate and ventral aINS cortices. SAN has a domain-general function because SAN coactivates in response to diverse experimental circumstances (Seeley et al., 2007).

1.3. The Multi-Source Interference Task (MSIT): an

fMRI task to measure cognitive control

To identify the neural pattern of cognitive control, a reliable fMRI task is necessary. The multi-source interference task is a well-validated fMRI task to measure cognitive control (Avelar-Pereira et al., 2017; G. Bush et al., 2003; George Bush & Shin, 2006; Dwyer et al., 2014; Kim-Spoon et al., 2016). The MSIT requires the resolution of interference generated by the incompatibility of cognitive stimulus, thus measuring the cognitive control. There are numerous attempts to capture the neural signature of cognitive control utilizing the MSIT. Compared to younger adults, older adults showed activation in larger regions other than the cognitive control network, which reacted to cognitive demands. In addition, cognitive training enhances the activity during MSIT in the regions in the fronto-parietal network and diminished the connectivity between the fronto-parietal network and default mode network (Kim, 2011). Similarly, stronger activation in the regions related to cognitive control was associated with more successful task performance. The regions showing more activation included the mid orbital gyrus, supramarginal gyrus, middle temporal gyrus, postcentral gyrus, inferior frontal gyrus, insula lobe, middle frontal gyrus, and superior frontal gyrus (Kim, 2017). In sum, the previous studies pointed out the fronto-parietal network and default mode network as important network for cognitive aging. However, these results did not provide the whole picture of the changing network in older adults. Dynamic change of the default mode network, which is composed of the regions activated in the resting−state, could be fully comprehended only in consideration to the resting−state simultaneously.

1.4. Brain Network Reconfiguration and the General Cognitive Ability

The human brain plays an important role to help people adapt to environment where different changes occur. It has been well known that no brain region is working alone. A bunch of studies confirmed that brain configures several networks in the resting−state (Power et al., 2011; Shen et al., 2013; Yeo et al., 2011). Both the local and global architecture must be considered to wholly understand the particular region of the brain (Shine & Poldrack, 2018). Also, brain dynamically changes its organization of the network to different states. It is called the "network reconfiguration" of brain (Bullmore & Sporns, 2012; Cole et al., 2013). The dynamic change of brain network configuration becomes a new focus of study based on the progressive development of neuroimaging methods. To be more specific, the brain reconfiguration between states (e.g., between resting−state and cognitive state) can demonstrate the mechanism which makes the brain functionally−localized and globally−integrated at the same time (Shine & Poldrack, 2018). In this context, the relationship between adaptive mechanisms in two levels, brain reconfiguration in the brain level and cognitive control in the behavioral level, needs to be clarified.

In order to study brain reconfiguration, representative methods are readily used, and such means employ functional connectivity, which directly captures the property of the network and graph-theoretical indices which captures the topology of the network (Rubinov & Sporns, 2010; Shine & Poldrack, 2018). Individual differences in adolescent cognitive control could be attributable to the dynamic and context-dependent interplay between the networks by analyzing functional connectivity, and the resultant graph indices (Dwyer et al., 2014). On the other hand, some researchers focused on the slightly different aspect of brain reconfiguration, so-called "efficiency" (Barbey, 2018; Girn et al., 2019; Mill et al., 2017; Popov et al., 2018; Schultz & Cole, 2016; Shine & Poldrack, 2018; Zuo et al., 2018). One potential mechanism for the network-level reconfiguration is the brain's energy usage controlling system (Shine & Poldrack, 2018). A similar configuration of the network reflects the close distance in state space and is also associated with better performance (Schultz & Cole, 2016). In addition, the more intense network reconfiguration between resting and task predicts relatively poor cognitive performance (Zuo et al., 2018). In this regard, less reconfiguration between resting-state and task state could be comprehended as an efficient change of brain network. Considering the results that the network similarity is associated with general intelligence and cognitive control, the brain network reconfiguration might capture the general adaptability of humans. It would support the modularity of cognitive processes, and the dynamic reorganization of this modular architecture in the service of system-wide flexibility and adaptation (Barbey, 2018).

1.5. Brain Network Reconfiguration in the Aging

The brain network reconfiguration could also be affected by aging. There are the age-related differences in functional interactions among FPN, DMN, and DAN during resting and. The difference of FPN-DMN connectivity between states is lower in older, whereas, the difference of FPN-DAN connectivity between states was not different in both younger and older adults. (Avelar-Pereira et al., 2017). On the other hand, altered connectivity due to aging could have an influence on behavior, especially for cognitive control. Older adults present larger changes in inter-network connectivity between resting and task, and the larger change of between-network connectivity predicts the better performance of cognitive control task (N-back task) (Gallen et al., 2016). These reports raised the importance to clarify the role of reconfiguration in older adults.

The resting-state might play an important role in the brain network reconfiguration. Resting-state configuration is pointed out as the source of the effect of brain reconfiguration in younger adults (Schultz & Cole, 2016). Also, the resting−state functions as a task−general network architecture of brain. For example, a common task state network architecture exists across tasks with multiple cognitive domains and across tasks with diverse rules (Cole, Bassett, et al., 2014). However, there is still a possibility that the resting−state has a different effect on older adults. The reason is that the age−related alterations of functional connectivity in the resting−state have associations with cognitive impairment (Ferreira et al., 2013; Hausman et al., 2020).

1.6. Objectives and Hypotheses

Previous literature tried to identify the relationship between the brain network reconfiguration and human cognition. However, there are few studies to examine those relationships among older adults. This study clarifies the relationship between the efficiency of reconfiguration and cognitive control function in older adults. Despite the alterations in the functional connectivity in older adults, the less reconfiguration still can be the fundamental rules of efficient processing of brain resources. Also, it should be clarified in detail that these relationships still hold in the cognitive control networks even in the older adults. Lastly, the relationship between resting−state and reconfiguration needs to be demonstrated in older adults. Since the resting−state functional connectivity could predict the cognitive impairment in older adults, resting-state configuration altered by aging might predict the task performance.

From this background, the hypotheses in this study follow: (1) The less reconfiguration (similar configurations) between resting-state and cognitive control task state in the whole brain, and three task-positive networks will predict better task performance and cognitive control function measured by the neuropsychological tests. (2) The configuration of individual resting-state will predict better task performance and cognitive control function even in older adults.

Chapter 2. Methods

2.1. Participants & Procedures

Participants were recruited from the panel of the Korean Social Life, Health and Aging Project (KSHAP). The KSHAP has longitudinally tracked the older adults aged above 60 in the Korean rural area. The participants in this study were especially based on the township K and the township L among the panel.

Participants were excluded in the analysis of this paper based on the following screening criteria: psychiatric or neurological disorders, vision or hearing problems, possessing metals in the body that cannot be removed, hypertension or diabetes uncontrollable by drugs or insulin, history of losing consciousness due to head trauma, and history of infarction or stroke.

To examine the effect in the context of normal cognitive aging, people with the significant cognitive impairment or with neurological conditions or radiological problems were also excluded as following screening criteria: people with the significant cognitive impairment were excluded based on the Clinical Dementia Rating Scale (CDR) sum of boxes score above 0.5. CDR sum of boxes score was made through the following procedures. At first, participants who scored below 1.5 standard deviations in the Mini Mental Status Examination for Dementia Screening (MMSE-DS; (Han et al., 2010)) or two index scores in Elderly Memory-disorder Scale (EMS; Chey, 2006) were identified. Finally, participants identified by the above procedure were examined with the semi-structured interview of CDR. Furthermore, people with neurological conditions or radiological problems were excluded based on the clinical decision of the neurologists. Among the participants who could take a Magnetic Resonance Imaging (MRI) scan, those who had either diffuse infarction, subcortical lacunes, hemorrhagic lesion, or other cerebrovascular signs were also excluded from the analysis. People who had moved excessively during functional MRI (fMRI) scans and people with the missing data in the regions of interest (ROIs) were also excluded. More detailed information for excessive movements has been in the fMRI Preprocessing section. After these exclusion criteria were applied, total 83 participants who passed the criteria were included in the analysis.

At first, participants who satisfied the inclusion criteria were voluntarily recruited to the neuropsychological tests from the whole KSHAP panel. Some participants were excluded from the following procedures due to cognitive impairment based on the results of the neuropsychological tests. Among the remaining participants, those who want to participate in MRI scanning and have no metallic objects were identified. Participants are brought to the Brain Imaging Center at Seoul National University. Participants underwent the whole MRI scan in a day. All participants received the explanation for the procedure of the experiment and voluntarily provided the written format of informed consent in each procedure. The study was approved by the Seoul National University Institutional Review Board (SNU-IRB).

2.2. Multi-Source Interference Task

A Multi-Source Interference Task (Bush, Shin, Holmes, Rosen, & Vogt, 2003) was modified and used during the fMRI scan. The MSIT can regard as a task measuring cognitive control (Dwyer et al., 2014) as well as inhibitory control (Avelar-Pereira et al., 2017; Kim-Spoon et al., 2016). The task was modified for the characteristics of elderly participants (i.e., slow processing speed) to secure the validity of the task. This task has the reliability to activate the cingulo-frontal-parietal cognitive/attention network (Bush & Shin, 2006).

The MSIT is divided into two conditions, "incongruent (IC) condition" and "congruent (C) condition". Figure 1 illustrates the presented stimulus and a matched correct answer in each condition. The task requires the participants to choose one different number among three numbers using a button box as fast and accurately as possible. The three buttons in a box represent 1, 2, 3, in order, and the participants are required to press the button using the index finger, middle finger, ring finger of the right hand for each number in order. In the incongruent condition, there are numbers interfering to choose the correct answers. This requires the participants to inhibit the alternative responses in conflict. Two types of incompatibility contribute to the interference, leading to error or delayed response. The incompatibility of an item, the distinction between the right answer and the other numbers, makes the interference in selective attention, which is called a *flanker effect*. The incompatibility of position, the visuospatial gap between answer and response button, makes interference in response, which is called a *Simon effect*. Whereas, in the congruent condition, there is no incompatibility. There are two zeros instead of interfering numbers, and the answer and the correct button are visuospatially matched.

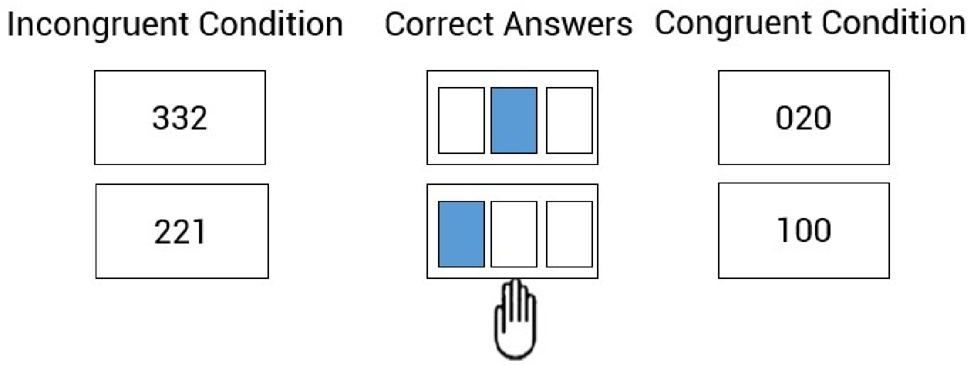


Figure 1. The illustrative conditions of the Multi-Source Interference Task
Note. The left (incongruent condition) and right (congruent condition) is the presented stimulus during each condition. The middle is the correct answer for the conditions in a same row.

All participants were required to practice before the actual task during the fMRI scan to ensure that the participant comprehends the rule of the task and how to use the button box correctly.

MSIT is a block designed fMRI task (Figure 2). Each run starts and ends with the baseline condition which appears fixation cross in the middle of the screen and lasts for 18 seconds. One run consists of 6 blocks. Each block has two conditions, 12 trials of the incongruent condition and 12 trials of congruent condition. Thus, in this task, a total of 144 trials of the task takes 6 minutes 40 seconds for a run for each participant. Only trials in incongruent conditions were extracted for the calculation of the brain reconfiguration because the congruent trials only reflect the sensory-motor function, which is not central to cognitive control function. For all participants, only the first runs of MSIT were used in statistical analysis due to the insufficient number of runs in some participants. Reaction time (RT) in incongruent condition and Interference RT (RT in IC condition - RT in C condition) were used to measure the performance of cognitive control task.

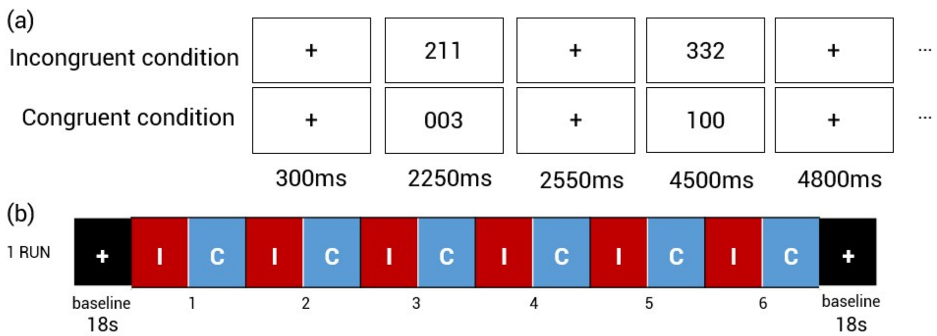


Figure 2. the order and components of the experiment conditions
Note. (a) The timelines of each condition, (b) The composition of conditions in the whole MSIT experiment. Incongruent conditions and congruent conditions are alternating in total run.

Stimuli were presented electronically using the E−Prime 1.1 software (Psychology Software Tools, Pittsburgh, PA).

2.3. Neuropsychological Tests

Neuropsychological tests were used to measure the cognitive function of participants. Using neuropsychological tests, the network similarity has been confirmed about the general effect on the cognitive function besides the fMRI task which directly measures the network similarity. Neuropsychological tests assess two different domains which are composed of cognitive control: executive function and working memory.

Working Memory.

Digit/Spatial Span test (forward/backward). In the span tests, participants are asked to repeat back the item instructed by the examiner. Digit/Spatial span tests in the Elderly Memory Disorder Scale (EMS; Chey, 2006; Song & Chey, 2006) were used in the study. The item could be the series of numbers (digit span) or the position of block (spatial span). Participants should repeat the item in reverse in the backward condition. The sum scores of 4 conditions (Digit/Span * Forward/Backward) were used in the analysis. Digit span is associated with a verbal/auditory working memory, and spatial span is associated with a visual/spatial working memory. The forward condition reflects attention and retention of stimulus in the short-term memory, and the backward condition reflects a mental manipulation which is one of the components of working memory.

Working memory could be comprehensively measured by the EMS Working memory index (WMI). WMI is based on the longest correct backward scores (span score) in the digit and spatial span test. WMI is calculated by the following equation:

Working Memory Index = (Digit Span Backward span score/8) + (Spatial Span Backward span score/8)

The denominator (8) in the equation indicates the maximum number of the span.

Executive Function.

The Modified Trail Making Test (TMT). The TMT is a test that requires drawing a line that connects all shapes in the test paper in a certain order. The TMT has several different rules according to the version. The Modified TMT used in this paper is composed of 3 conditions, TMT A, TMT B, TMT C (Park & Chey, 2003). In TMT A, there are only circles with a number, and participants have to draw a line that connects all circles in numerical order (e.g., ①-②-③-④-…). In TMT B, there are triangles and squares, and participants have to start with a triangle and connect the line alternating triangle and square (e.g., △−□−△−□−…). In TMT C, there are not only circles in a number but also triangles and squares. Participants should start with the circle of number 1 and should simultaneously alternate between number and shape and between triangle and square (e.g., ①−△−②−□−③−△−…). Time to complete in the three conditions is used in the study. TMT A measures attention, motor coordination, and processing speed. TMT C additionally needs shifting ability compared to TMT A.

Stroop test. In the Stroop test, participants received a paper with four words printed with four colors (i.e., BLACK, RED, BLUE, and YELLOW). Each word has an unmatched color with the written letter (e.g., BLUE colored with black, RED colored with yellow). Korea−Color Word Stroop Test−60 (K−CWST−60) in Seoul National Screening Battery−II (SNSB−2) was used in the study (Lee, & Kang, 2000; Kang et al., 2012). In the word reading (WR) trial, participants should read the words as written while ignoring the color. While, in the color reading (CR) trial, participants should read the colors of the word while ignoring the letter. The number of correct responses in Stroop WR and CR was used in the analysis. Stroop WR reflects the attention and processing speed of participants, and Stroop CR reflects the inhibitory control and processing speed.

Category Fluency test. Category fluency test is measuring the ability to produce the word in a specific category as many as possible in a limited time. Animal Fluency and Store Fluency in the Controlled Oral Word Association Test (COWAT; Kang et al., 2000; Kang et al., 2012) was used in the study. The number of correct responses in Animal and Store Fluency was used in the analysis. The performance of the category fluency test is determined by the updating ability, vocabulary, and semantic memory function.

2.4. MRI Acquisition and Preprocessing

MRI Acquisition Protocol

Whole-brain functional and structural MRI data of all participants were acquired on a 3T SIMENS MAGNETOM Trio TIM Syngo MR with 32 channel coil and GRAPPA. Total 160 volumes of MSIT functional images were acquired using the echo-planar imaging (EPI) sequence with the following parameters: TR=2250ms, TE=30ms, 30 slices, slice thickness=3.0mm, slice gap=1mm, FA=79° , FOV=240mm, voxel size 3x3x3mm^3 voxels.

In the resting-state, participants received instructions to lie down while relaxing and not to sleep with the eyes open. Total 300 volumes of resting-state fMRI data were also acquired using the echo-planar imaging (EPI) sequence with the following parameters: TR=2000ms, TE=30ms, 30 slices, slice thickness=3.0mm, slice gap=1mm, FA=79° , FOV=240mm, voxel size 3x3x3mm^3 voxels.

Structural images were acquired using a T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) sequence with the following parameters: TR=23000ms, TE=2.36ms, FA=9°, FOV=256mm, voxel size 1x1x1mm^3 voxels.

Defining Region of Interests (ROIs)

Regions of interests were defined using Power's functional atlas (Power et al., 2011). 255 regions of the whole brain were used in the analysis. While Power's original atlas has 264 regions including 9 cerebellar regions, some participants had missed the signal from the cerebellum due to the restricted number of image slices.

Three task-positive networks determined from atlas are respectively central to the analysis: 25 regions of Fronto-parietal Network (FPN), 18 regions of Salience Network (SAN), 14 regions of Cingulo-opercular Network (CON) (Figure 3, Table 1).

Table 1. Regions of interests, their MNI coordinates, and functional properties

Regions of Interests (ROI)	Coordinates			Functional Network	Network Color
	x	*y*	*z*		
Superior Frontal Gyrus	−23	11	64	Fronto−parietal	Cyan
Superior Parietal Lobule	−28	−58	48	Fronto−parietal	Cyan
Middle Frontal Gyrus	−34	55	4	Fronto−parietal	Cyan
Medial Frontal Gyrus	−3	26	44	Fronto−parietal	Cyan
Inferior Frontal Gyrus	−41	6	33	Fronto−parietal	Cyan
Inferior Parietal Lobule	−42	−55	45	Fronto−parietal	Cyan
Middle Frontal Gyrus	−42	25	30	Fronto−parietal	Cyan
Middle Frontal Gyrus	−42	38	21	Fronto−parietal	Cyan
Middle Frontal Gyrus	−42	45	−2	Fronto−parietal	Cyan
Middle Frontal Gyrus	−44	2	46	Fronto−parietal	Cyan
Inferior Frontal Gyrus	−47	11	23	Fronto−parietal	Cyan
Inferior Parietal Lobule	−53	−49	43	Fronto−parietal	Cyan
Superior Frontal Gyrus	24	45	−15	Fronto−parietal	Cyan
Superior Frontal Gyrus	32	14	56	Fronto−parietal	Cyan
Inferior Parietal Lobule	33	−53	44	Fronto−parietal	Cyan
Middle Frontal Gyrus	34	54	−13	Fronto−parietal	Cyan
Inferior Parietal Lobule	37	−65	40	Fronto−parietal	Cyan
Middle Frontal Gyrus	38	43	15	Fronto−parietal	Cyan
Middle Frontal Gyrus	40	18	40	Fronto−parietal	Cyan

Middle Frontal Gyrus	43	49	−2	Fronto−parietal	Cyan
Inferior Parietal Lobule	44	−53	47	Fronto−parietal	Cyan
Middle Frontal Gyrus	47	10	33	Fronto−parietal	Cyan
Middle Frontal Gyrus	48	25	27	Fronto−parietal	Cyan
Inferior Parietal Lobule	49	−42	45	Fronto−parietal	Cyan
Middle Temporal Gyrus	58	−53	−14	Fronto−parietal	Cyan
Anterior Cingulate	−11	26	25	Salience	Green
Cingulate Gyrus	−1	15	44	Salience	Green
Middle Frontal Gyrus	−28	52	21	Salience	Green
Extra−Nuclear	−35	20	0	Salience	Green
Superior Frontal Gyrus	−39	51	17	Salience	Green
Anterior Cingulate	0	30	27	Salience	Green
Anterior Cingulate	10	22	27	Salience	Green
Paracentral Lobule	11	−39	50	Salience	Green
Superior Frontal Gyrus	26	50	27	Salience	Green
Sub−Gyral	31	33	26	Salience	Green
Middle Frontal Gyrus	31	56	14	Salience	Green
Extra−Nuclear	34	16	−8	Salience	Green
Insula	36	22	3	Salience	Green
Inferior Frontal Gyrus	37	32	−2	Salience	Green
Middle Frontal Gyrus	42	0	47	Salience	Green
Inferior Frontal Gyrus	48	22	10	Salience	Green
Supramarginal Gyrus	55	−45	37	Salience	Green
Cingulate Gyrus	−11	26	25	Salience	Green

Cingulate Gyrus	−10	−2	42	Cingulo−opercular	Yellow
Superior Frontal Gyrus	−16	−5	71	Cingulo−opercular	Yellow
Claustrum	−34	3	4	Cingulo−opercular	Yellow
Medial Frontal Gyrus	−3	2	53	Cingulo−opercular	Yellow
Precentral Gyrus	−45	0	9	Cingulo−opercular	Yellow
Superior Temporal Gyrus	−51	8	−2	Cingulo−opercular	Yellow
Cingulate Gyrus	−5	18	34	Cingulo−opercular	Yellow
Superior Frontal Gyrus	13	−1	70	Cingulo−opercular	Yellow
Middle Frontal Gyrus	19	−8	64	Cingulo−opercular	Yellow
Insula	36	10	1	Cingulo−opercular	Yellow
Insula	37	1	−4	Cingulo−opercular	Yellow
Superior Temporal Gyrus	49	8	−1	Cingulo−opercular	Yellow
Inferior Parietal Lobule	54	−28	34	Cingulo−opercular	Yellow
Medial Frontal Gyrus	7	8	51	Cingulo−opercular	Yellow
Precentral Gyrus	−45	0	9	Cingulo−opercular	Yellow

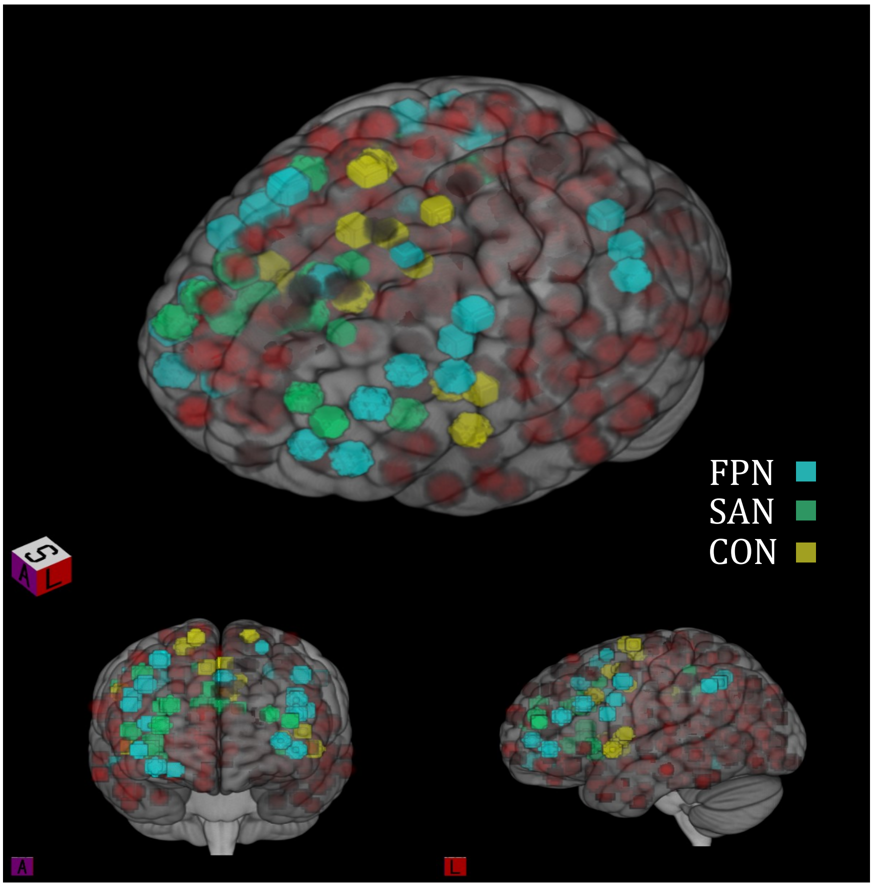


Figure 3. ROIs of Three Task-Positive Networks.
Note. FPN: Fronto-parietal Network, SAN: Salience Network, CON: Cingulo-opercular Network. Cyan regions represent ROIs of FPN. Green regions represent ROIs of SAN. And yellow regions represent ROIs of CON. Red colored ROIs represent the other network except for the three task-positive networks. Detailed information for each node was provided in the Table 1.

Brain Connectivity Analysis

Preprocessing. Each functional image was preprocessed by the same procedure, respectively. First, the motions between successive frames were realigned. The frame−wise displacement (FD) was estimated by using the parameters in the realignment and then used in the statistical analysis as a covariate. Participants with excessive head motions were excluded based on the estimated FD (resting-state mean FD > 0.3mm, MSIT mean FD > 0.2mm, n=30) (Power et al., 2012, 2014). Participants tended to move more in the resting-state compared to the task state. Slightly different criteria were applied to secure the appropriate number of subjects. Then, timings between slice acquisition were corrected and all functional images were co-registered to the anatomical image. Anatomical images were spatially normalized to the standard atlas and were segmented to gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). After co-registration of functional images to anatomical images, the nonlinear deformation of anatomical images to standard space was used for spatial normalization of functional images to standard space. Gaussian filter with 8mm full-width half maximum (FWHM) were applied to smooth the functional images. The Artifact Detection Tools (ART) was used to identify motion and signal intensity outlier images. Images with global mean intensity Z-value > 5 and movement > 0.9mm were identified as outliers. Identified outlier images were used as nuisance covariates in the time-series linear regression. To exclude the irrelevant physiological noise signal, band-pass temporal filtering (0.0008-0.09) was applied to and the effects of CSF and WM were regressed out.

Brain Connectivity Matrix. A time-series correlation of the average BOLD (blood-oxygen-level-dependent) signal across voxels in each ROI was calculated. Pearson correlation coefficients were calculated for each pair of ROIs, and fisher-transformed correlation was made to assume normally distributed data. 255*255 weighted symmetrized matrices in incongruent condition and resting-state were computed by this procedure and then used to calculate the brain network reconfiguration.

All preprocessing procedures mentioned above were done by using SPM12 (Statistical Parametric Mapping 12; Wellcome Trust Centre for Neuroimaging, London, UK) and CONN18.B toolbox (Whitfield-Garbrielli & Nieto-Castanon, 2012) implemented in the MATLAB 2018b.

Brain Activation Analysis

To identify the effect of the task, brain activation was analyzed with the general linear model (GLM) using incongruent and [incongruent > congruent] contrasts within ROIs. To identify the regions contributing to behavioral performance, a one-sample *t*-test was carried out, while using the RT difference between conditions as an independent variable and controlling age, sex, and years of education. The preprocessing is done by the same procedure with brain connectivity analysis except for the band-pass temporal filtering and the usage of the ART.

2.5. Calculating the Network Similarity Index of the Brain Network

Network Similarity Index. Similarity of functional connectivity (FC) is regarded as a measure of functional network updates, and the inverse of network reconfiguration (Schultz & Cole, 2016). One of the synonyms for similarity is proximity and antonym would be the distance from the scientific and mathematical point of view (Cha, 2007). The single continuous value for the update of the whole brain network is made with Pearson' s correlation for each participant. To calculate the correlation between connectivity matrices, only lower triangles of the matrix were extracted and then were vectorized. The correlation between the two vectors from the connectivity matrix in the MSIT/resting-state was computed and stands for the network similarity index (Figure 4). Fisher-transformed correlation of network similarity was made to assume normally distributed data. As a result, two network similarity indices for each condition was made and then was used for statistical analysis across participants.

Calculating the Network Similarity Index of the Sub-networks. The reconfiguration of some task-positive sub-network of the brain was also measured. In the connectivity matrices, only the connectivity value of ROIs in target networks was left before the calculation of the network similarity index. The left matrices targeting specific networks included intra-network connections (target to target connection) and inter−network connections (target to remaining connection). For example, if the target network is FPN which includes 25 regions (nodes) inside, intra−network connections include 300 (25*24/2) connections (edges) and inter−network connections include 5750 (25*230) connection. As a result, FPN has a total 6050 of connections. The single FC similarity between resting−state and MSIT state were calculated on those connections, which represented the network similarity index of FPN. This network similarity index of sub−networks was processed with the fisher−transformation, and then was used for statistical analysis across participants.

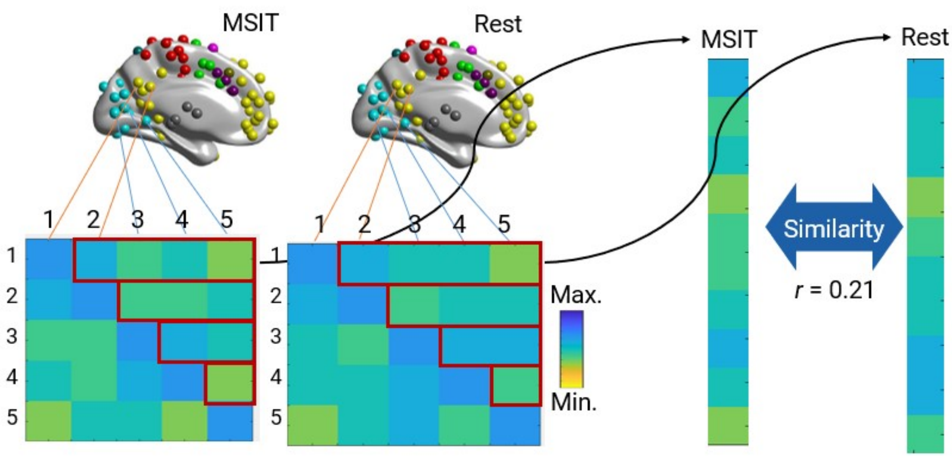


Figure 4. Schematic illustration of Calculating the network similarity index between MSIT and resting.
Note. The original brain connectivity matrices were made to vectors to calculate the correlation coefficients. The single correlation coefficient between two states means the similarity between two states and the less reconfiguration from one state to the other state.

2.6. Testing the influence of individual Resting/Task State Functional Connectivity Configuration on the Cognitive Performance through the Network Reconfiguration

The network similarity index reflects the shift between task state and resting-state. This index includes three sources of variance, the effect of the individual configuration of task state and resting-state, and interaction between them. In other words, if the network similarity index is associated with the cognitive performance, the results could be caused by three sources, task state FC, resting-state FC, and/or the similarity/distance between them itself. To examine the effect of each state separately, the association between the network similarity index and the cognitive performance was analyzed with the FC of either one state-controlled (Schultz & Cole, 2016). If we want to examine the effect of resting-state, the correlation between cognitive performance and the network similarity index with the task state FC controlled was examined, and vice versa. For the controlling procedure, the resting FC and task FC was averaged. The correlation between the averaged resting FC and the individual task FC was computed when we focused on the effect of task FC variance (task state configuration). Similarly, the correlation between the averaged task FC and the individual resting FC was also computed when we focused on the effect of resting FC variance (resting-state configuration). Using a leave-one-out approach, the averaged resting/task state FC was calculated for each subject with his/her own resting/task state FC not included.

2.7. Statistical Analysis

All analyses were conducted using R 3.5.3 (2020) using a multiple linear regression model, controlling for age, sex, years of education, total gray matter volume, and the mean movement. Also, the false discovery rate (FDR) was applied to correct for the independent multiple comparisons. First, the relationship between the MSIT performance and the network similarity index was tested. The relationship between the neuropsychological tests and the network similarity index was also tested to identify the general effect. Second, the network similarity index which was controlled in either resting or MSIT state was replaced with the original network similarity index. And then, the relationship between the index and the MSIT performance was tested.

Chapter 3. Results

3.1. Behavioral Results

Demographic variables and Cognitive performance. The descriptive statistics of demographic variables and cognitive functions in this study were in Table 1. The mean age of the total 83 participants was 70.86 (SD=6.73), the number of female participants was 54 (65.06%), and the mean years of education was 6.71 (SD=3.75).

Table 2. Demographic variables and Cognitive performance

Variables	Mean	SD
Sex (M: 29, F: 54)	–	–
Age	70.86	6.73
Years of Education	6.71	3.75
EMS Digit Span Forward	7.59	1.94
EMS Spatial Span Forward	6.73	1.45
EMS Working Memory Index	1.01	0.24
SNSB-II Stroop CR Correct Answers	34.31	11.90
TMT C completion time	134.12	80.41
Animal Fluency Correct Answers	13.80	3.82
MSIT Interference RT	403.05	84.32
MSIT Incongruent Condition RT	1295.88	162.02

MSIT Congruent Condition RT	892.83	132.3

Bivariate correlations between variables. MSIT Interference RT performance was not associated with age, sex, and years of education (*p*>.05). Slower RT in the both conditions of MSIT were significantly associated with the age (Incongruent (IC): *r*=0.27, *p*<.05; Congruent (C): *r*=0.29, *p*<.01), female sex (IC: *r*=−0.31, *p*<.01; C: *r*=−0.35, *p*<.01). EMS Digit Span (DS) forward (*r*=0.45, *p*<.001), and EMS working memory index (WMI) (*r*=0.31, *p*<.01) were significantly associated with the years of education.

Between MSIT behavioral indices, MSIT IC RT performance was significantly associated with the MSIT Interference RT (*r*=0.58, *p*<.001), and the MSIT C RT (*r*=0.85, *p*<.001). MSIT Interference RT and MSIT C RT were not associated with each other (*p*>.05). There were some significant associations between MSIT RT and neuropsychological measures. MSIT Interference RT performance was associated with the EMS Digit Span forward (*r*=−0.51, *p*<.001), Spatial span forward (*r*=−0.31, *p*<.01), EMS working memory index (*r*=−0.43, *p*<.001), and Stroop CR correct answer (*r*=−0.34, *p*<.001). MSIT IC performance was associated with the EMS Digit Span forward (*r*=−0.48, *p*<.001), Spatial span forward (*r*=−0.22, *p*<.05), EMS working memory index (*r*=−0.43, *p*<001), Animal fluency (*r*=−0.36, *p*<.001), and Stroop CR correct answer (*r*=−0.26, *p*<.05). MSIT C RT performance was associated with the

EMS Digit Span forward (r=0.26, p<.05), EMS working memory index (r=0.26, p<.05), Animal fluency (r=−0.38, p<.001), and Stroop CR correct answer (r=−0.39, p<.001).

The network similarity indices of FPN, CON, and SAN were not significantly associated with age, sex, years of education, and total gray matter volume (p>.05).

Table 3. Table of Correlations between the Main Dependent Variables

		1	2	3	4	5	6	7	8	9	10	11	12	13
1	Age	1.00												
2	Edu	−0.22*	1.00											
3	Sex	0.09	0.45**	1.00										
4	nGMv	−0.57***	0.02	−0.38***	1.00									
5	Movement	0.24*	−0.10	−0.02	−0.10	1.00								
6	RT Incongruent	0.27*	−0.31**	−0.14	−0.03	0.27*	1.00							
7	RT Congruent	0.29**	−0.35**	−0.14	0.03	0.28*	0.85***	1.00						
8	RT interference	0.13	−0.18	−0.05	0.10	0.10	0.58***	0.07	1.00					
9	Digit Span F	−0.07	0.45***	0.14	−0.07	−0.09	−0.48***	−0.26*	−0.51***	1.00				
10	Spatial Span F	−0.08	−0.04	−0.02	0.03	−0.16	−0.22*	−0.07	−0.31**	0.16	1.00			
11	EMS WM Index	−0.12	0.31**	0.16	0.06	−0.18	−0.43***	−0.26*	−0.43***	0.53***	0.41***	1.00		
12	Stroop CR	−0.40***	0.45***	0.02	0.23*	−0.16	−0.26*	−0.39***	−0.34***	0.45***	0.13	0.33**	1.00	
13	TMT C	0.17	−0.37***	−0.16	−0.02	0.33***	0.19	0.28*	0.25	−0.40***	−0.24	−0.40***	−0.33**	1.00
14	Animal Fluency	−0.27*	0.53***	0.15	0.16	−0.13	–	–	−0.18	0.37***	0.11	0.29**	0.32**	0.46***

0.36***	0.38***

Note. * indicates $p<.05$; ** indicates $p<.01$; *** indicates $p<.001$. nGMv stands for the normalized Gray Matter volume. 'F' in 9th and 10th variables mean forward. 'CR' in 12th variable means color reading. TMT C means the completion time of TMT C. Stroop CR and Animal Fluency measures the number of correct answers in each test.

3.2. Brain Network Similarity Index & Cognitive Control Functions

The effect of brain network similarity index was examined in the whole brain, FPN, CON, & SAN. For RT in the incongruent condition, there was no significant effect of the brain network similarity index in any regions (p>.05). For RT difference between IC and C conditions, network similarity index of FPN and SAN had a significant effect (FPN: r=−0.24, p=.050, SAN: r=−0.28, p=.031) (Table 4, 5, Figure 5).

When examining the results of the neuropsychological tests, the network similarity index had a significant effect only in performances of working memory tasks. Specifically, the working memory index, a reliable index for measuring working memory ability, was significantly affected only by the network similarity index in the FPN (r=0.30, p=.021), and marginally affected by the network similarity index in the whole brain (r=0.21, p=.065) (Table 6, 7, Figure 6). EMS DS forward was affected by the network similarity index in the FPN (r=0.30, p=.009) and SAN (r=0.34, p=.006). EMS SS forward was affected by the network similarity index in the SAN (r=0.28, p=.042), and the whole brain (r=0.29, p=.009).

Table 4. Regression Analysis Summary for Interference RT in FPN.

Variable	Unstandardized Coefficients		Standardized Coefficients	*t*	*p*
	B	SE	Beta(β)		
(Constant)	−175.93	318.30		−0.55	0.580
Age	2.85	1.71	0.01	1.67	0.100
Sex	20.03	23.23	−0.03	0.86	0.390
Years of Education	−3.32	2.82	0.11	−1.18	0.240
Mean movement	301.01	247.81	0.34	1.22	0.230
nGMv	1040.99	545.67	−0.03	1.91	0.060
Network Similarity	−324.93	149.88	−0.24	−2.17	0.050*

Note. * indicates $p<.05$. $F(6,75)=2.209$, $p>.05$ R^2 adjusted = 0.08.
nGMv is normalized Gray Matter volume. *p* was corrected for the network similarity.

Table 5. Regression Analysis Summary for Interference RT in SAN.

Variable	Unstandardized Coefficients		Standardized Coefficients	*t*	*p*
	B	SE	Beta(β)		
(Constant)	−104.88	317.50		−0.33	0.740
Age	2.79	1.69	0.02	1.65	0.100
Sex	11.79	23.27	−0.16	0.51	0.610
Years of Education	−2.49	2.83	0.19	−0.88	0.380
Mean movement	247.05	236.09	0.21	1.05	0.300
nGMv	890.66	544.77	−0.11	1.64	0.110
Network	−363.03	138.04	−0.28	−	0.031

Similarity	2.63

Note. $F(6,75)=2.617*$, $p<.05$ R^2 adjusted = 0.11.
nGMv is normalized Gray Matter volume. p was corrected for the network similarity.

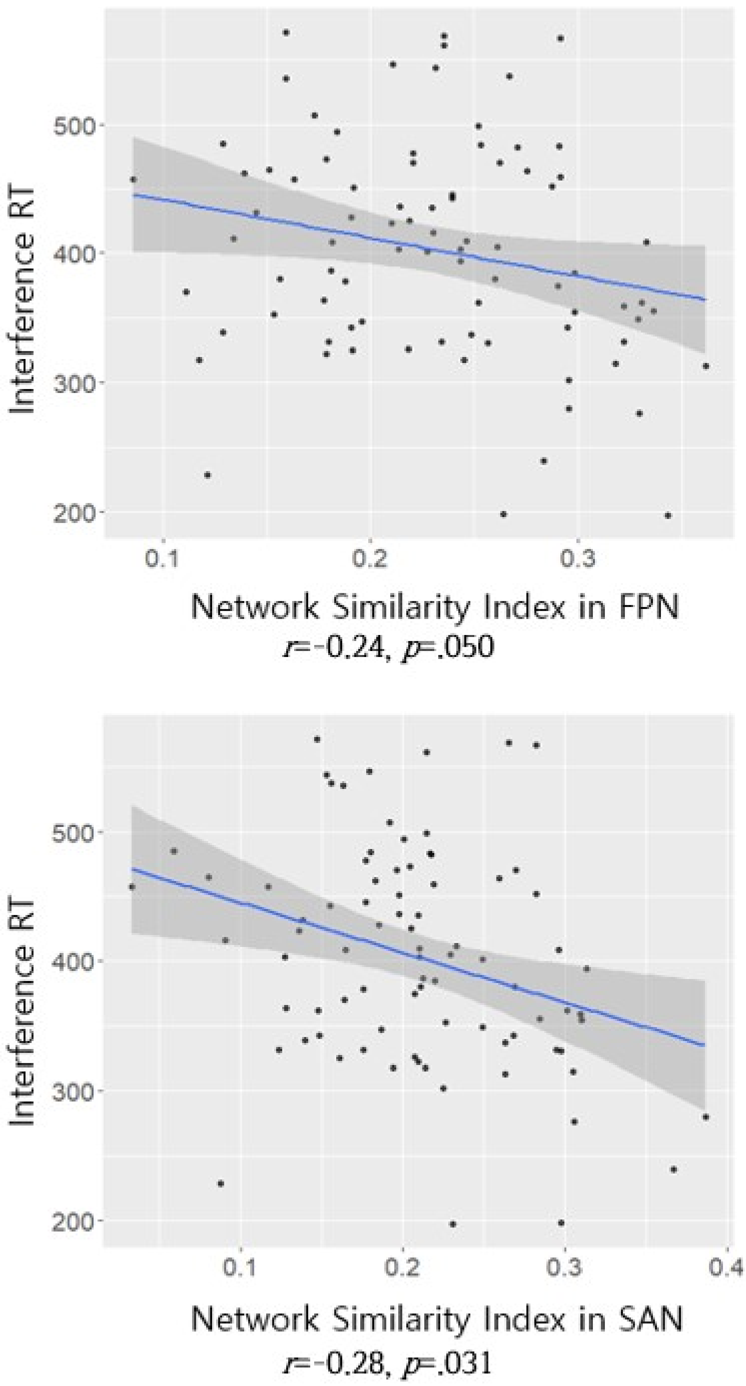


Figure 5. Regression plots of Interference RT and the reconfiguration
Note. (Top) The effect of the Network Similarity Index in FPN on the Interference RT. (Bottom) The effect of the Network Similarity Index in SAN on the Interference RT.

Table 6. Regression Analysis Summary for WMI in FPN.

Variable	Unstandardized Coefficients		Standardized Coefficients	*t*	*p*
	B	SE	Beta(β)		
(Constant)	0.27	0.87		0.31	0.760
Age	0.00	0.00	−0.06	0.06	0.950
Sex	0.04	0.06	−0.22	0.64	0.520
Years of Education	0.01	0.01	0.15	1.73	0.080
Mean movement	−1.48	0.67	0.27	−2.15	0.031
nGMv	1.13	1.50	−0.19	0.75	0.450
Network Similarity	1.16	0.41	0.30	2.81	0.006

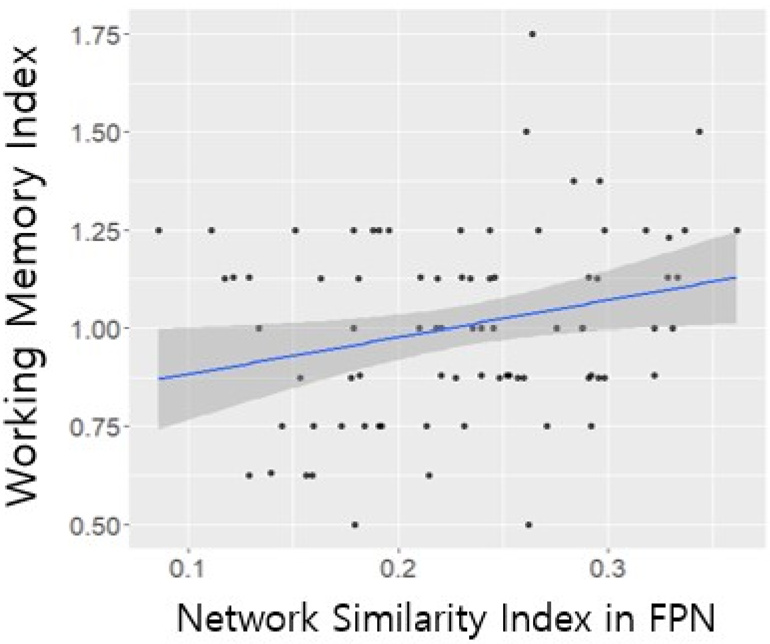
Note. $F(6,75) = 3.176^{**}$, $p<.01$, R^2 adjusted =.139
nGMv is normalized Gray Matter volume. p was corrected for the network similarity.

Table 7. Regression Analysis Summary for WMI in whole brain.

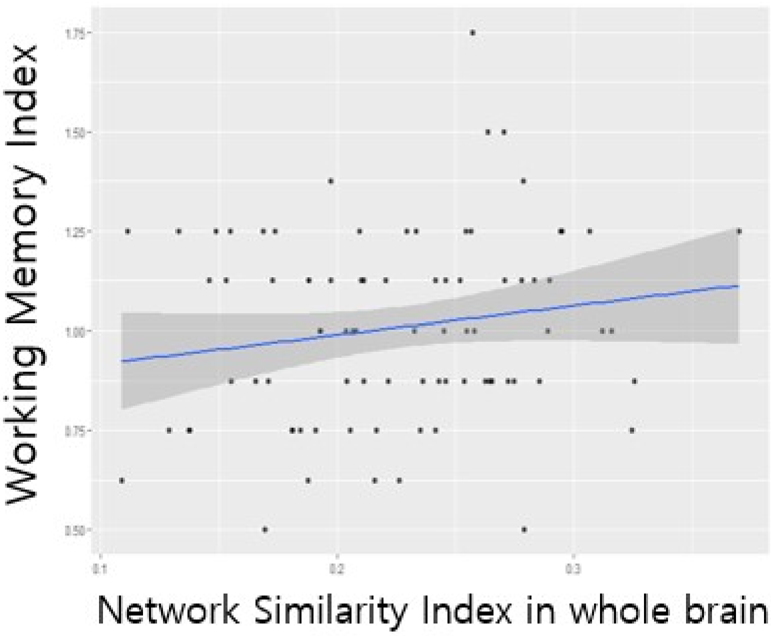
Variable	Unstandardized Coefficients		Standardized Coefficients	*t*	*p*
	B	SE	Beta(β)		
(Constant)	0.22	0.92		0.24	0.812
Age	0.00	0.00	−0.04	0.11	0.913
Sex	0.06	0.07	−0.08	0.85	0.399
Years of Education	0.01	0.01	0.07	1.66	0.101
Mean movement	−1.16	0.69	0.37	−1.69	0.094

nGMv	1.28	1.56	−0.04	0.82	0.416
Network Similarity	0.92	0.50	0.21	1.85	0.068

Note. $F(6,75) = 2.331*$, $p<.05$, R^2 adjusted =.090
nGMv is normalized Gray Matter volume. p was corrected for the network similarity.



r=0.30, p=.021



r=0.21, p=.065

Figure 6. Regression plots of WMI and the reconfiguration
Note. (Top) The effect of the Network Similarity Index in FPN on the WMI. (Bottom) The effect of the Network Similarity Index in whole brain on the WMI.

3.3. Impact of Resting−State and Task Configuration on Brain Reconfiguration

To clarify the source of the effect of the reconfiguration, the effect of the configuration of each state was examined for the network similarity which had a significant effect on the behavior.

The network similarity (reconfiguration) was significantly correlated with the resting−state configuration of the FPN (r=0.36, p<.001), SAN (r=0.42, p<.001), and the whole brain (r=0.53, p<.001). Also, the reconfiguration was significantly correlated with task state configuration of the FPN (r=0.55, p<.001), SAN (r=0.49, p<.001), and the whole brain (r=0.69, p<.001). However, the correlations between each configuration across each network were only significant for the whole brain (r=0.22, p=.047) (Table 8).

There was no significant effect of the configuration of resting− & task states for the RT difference between IC and C conditions. On the other hand, the working memory index had been significantly affected by the task state configuration in FPN (r=0.29, p=.011), and the whole brain (r=0.25, p=.028) (Table 9, 10).

Table 8. Correlations between the reconfiguration, the configuration of resting, and the configuration of MSIT state

r	Whole Brain	1	2
1	Reconfiguration	1.00	
2	Resting Configuration	0.53***	1.00
3	Task Configuration	0.69***	0.22*

r	FPN	1	2
1	Reconfiguration	1.00	
2	Resting Configuration	0.36***	1.00
3	Task Configuration	0.55***	0.07

r	SAN	1	2
1	Reconfiguration	1.00	
2	Resting Configuration	0.42***	1.00
3	Task Configuration	0.49***	0.03

Note. * indicates $p<.05$; ** indicates $p<.01$; *** indicates $p<.001$.
FPN: Fronto−parietal Network, SAN: Salience Network.

Table 9. The effect of Task Configuration in the FPN on the WMI

Variable	Unstandardized Coefficients		Standardized Coefficients	*t*	*p*
	B	*SE*	Beta(β)		
(Constant)	0.27	0.88		0.31	0.756
Age	0.00	0.00		0.33	0.75
Sex	0.08	0.07		1.19	0.24
Years of Education	0.01	0.01		1.57	0.120
Mean movement	−1.23	0.67		−1.85	0.069
nGMv	1.16	1.51		0.77	0.445
Task Configuration	1.24	0.47	0.29	2.62	0.011

Note. $F(6,75) = 2.978*$, $p<.05$, R^2 adjusted =.128
nGMv is normalized Gray Matter volume.

Table 10. The effect of Task Configuration in the whole brain on the WMI

Variable	Unstandardized Coefficients		Standardized Coefficients	*t*	*p*
	B	*SE*	Beta(β)		
(Constant)	0.14	0.91		0.15	0.881
Age	0.00	0.00		0.46	0.649
Sex	0.08	0.07		1.20	0.235
Years of Education	0.01	0.01		1.03	0.308
Mean movement	−1.32	0.00		−1.91	0.060
nGMv	1.11	1.53		0.72	0.472
Task Configuration	1.06	0.48	0.25	2.23	0.029

Note. $F(6,75) = 2.621*$, $p<.05$, R^2 adjusted =.107
nGMv is normalized Gray Matter volume.

3.4. MSIT activation & Cognitive Control Functions

Significant brain activation in incongruent condition compared to congruent (Interference; IC−C) condition was reported in Figure 7 and Table 11. Left inferior parietal lobule, superior parietal lobule, right frontopolar cortex showed positive associations with interference RT. Left middle orbital gyrus, superior frontal gyrus, superior medial gyrus, angular gyrus, superior orbital gyrus, right posterior cingulate cortex showed negative associations with interference RT. These regions were widely overlapped with functional atlas including the FPN, CON, SAN, and DMN.

When the lenient criterion (p<0.001, uncorrected) was applied, some regions showed a significant positive association with interference RT in MSIT interference of conditions. Positive associations were reported in the left (x: −10, y: 50, z: 36; DMN), and right superior medial gyrus (x: 2, y: 42, z: 6; DMN). Also, there are some regions showing a significant positive association with WMI in MSIT interference of conditions (p<0.001, uncorrected). These included right middle temporal gyrus (x: 66, y: −8, z: −18; undefined network), left superior temporal gyrus (x: −58, y: −12, z: 8; DMN), and right middle temporal gyrus (z: 66, y: −8, z: −18; DMN).

There is no region showing significant activation associated with behavioral indices in MSIT incongruent condition, which satisfied the multiple comparison correction (FDR). Although the lenient criterion ($p<0.001$, uncorrected) was applied to identify the trend, there is no region showing a significant correlation on the atlas of ROIs.

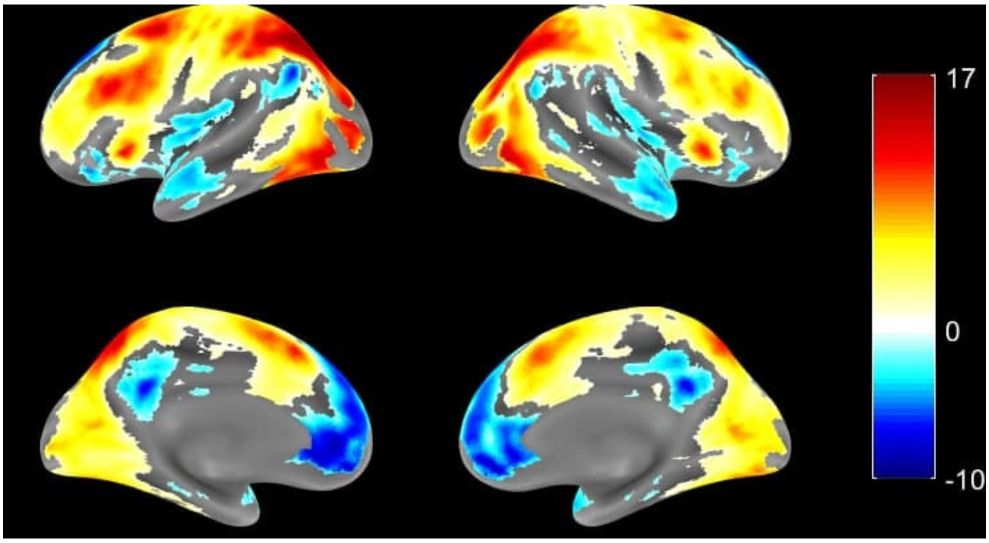


Figure 7. Activated Brain Regions in MSIT Interference condition
Note. Incongruent Condition > Congruent Condition. FWE Corrected (p<.05)

Table 11. Activated Brain Regions in MSIT Interference condition

Regions	k	hemisphere	MNI coordinates			*t* value
			x	y	z	
Positive activation						
IPL	47665	L	−30	−56	48	17.72
*SPL		L	−24	−62	52	16.72
*SPL		L	−24	−62	42	16.66
FPC	209	R	24	44	12	6.44
*FPC		R	34	58	18	5.92
Negative activation						
MOG	3485	L	−6	46	−8	−10.17
*SFG		L	−14	42	50	−7.89

*SMG		L	−6	48	18	−7.15
AG	187	L	−50	−66	38	−8.43
PCC	437	R	6	−50	32	−7.60
SOG	149	L	−24	8	−8	−7.57

Note. k means the cluster size (p<.05, FWE corrected). '*' means included areas in the above cluster. L is the left hemisphere and R is the right hemisphere. IPL is the inferior parietal lobule. SPL is the superior parietal lobule. FPC is the frontopolar cortex. MOG is the middle orbital gyrus. SFG is superior frontal gyrus. SMG is superior medial gyrus. AG is the angular gyrus. PCC is the posterior cingulate cortex. SOG is superior orbital gyrus.

Chapter 4. Discussion

In the present study, it was found that less reconfiguration of resting-state and task-related activation of brain was indeed associated with better performance on cognitive control tasks and working memory ability tests. Interference RT was associated with the less reconfiguration of the fronto-parietal network (FPN) and the salience network (SAN). Working Memory Index (WMI) was associated with the less reconfiguration of the FPN and the whole brain. Working memory subtests were associated with the less reconfiguration of the FPN, the SAN, and the whole brain.

Furthermore, in the analysis to identify the role of each state in the reconfiguration, interference RT was not affected by any state. However, the working memory index was affected by the task state in the FPN and whole brain.

Performance of Interference RT and the network reconfiguration

Higher network similarity in FPN and SAN between resting and MSIT was significantly associated with the faster interference RT. This result is consistent with the previous studies with other datasets (Schultz & Cole, 2016; Zuo et al., 2018). Zuo et al. (2018) divided the brain networks into two groups: FPN-group (FPN, SAN, DAN, and visual network) and DMN-group (DMN and VAN). The researchers insisted that the reconfiguration of certain networks (i.e., FPN, DMN, and SAN) was core factor, explaining the better performance. In other words, such core networks involved in the specific mental process showed significant behavior-similarity correlations. In this regard, the FPN and SAN were core networks to process the interference of MSIT. The FPN is widely activated in mental simulation, visuospatial attention, and working memory tasks. The FPN is the most dominant, but the least flexible network in responses to changes in the state (Zuo et al., 2018). The FPN already showed its protective effect on clinical symptoms. For example, Cole et al (2014) denoted the FPN as an "immune system of the mind" due to two reasons. The first reason is that the several major mental illnesses involve altered brain-wide connectivity of this control system. Also, it regulates the anxiety symptoms using a feedback 'control' system. The "immune system" analogy could apply to the cognitive system. The intact and stable FPN is crucial to cognitive system.

The SAN generally coordinates the executive role of the FPN (Zuo et al., 2018). The SAN and CON are similar in terms of position and function. Both networks are composed of the insular regions and cingulate regions and involved in the attentional control. However, these two networks also have differences. While the CON is involved in the tonic alertness or sustained attention (Sadaghiani & D'Esposito, 2015), the SAN is involved in the more complex and delicate process in attentional control. Recently, the role of the SAN was clearly revealed. The SAN responds to the homeostatic system engaging partly in the task–control network to maintain the most relevant task set for as long as the salient stimulus complex remains. Also, the SAN arranges the network to switch to a new task set and relevant configuration of the network in response to shifts in the salience landscape (Seeley, 2019). In this context, MSIT, which mainly measure the interference resolution in conflicting stimulus, might require responding salient stimuli, rather than tonic alertness. There could be some reasonable rejection in this conclusion. The alternative hypothesis would be that the reconfiguration of CON has a different relationship when compared with the reconfiguration of other networks. However, the relationship between the network similarity and the interference RT in the whole brain and CON was still in a positive direction for performance. Thus, having less reconfiguration does not mean being harmful.

The reconfiguration of whole brain was also not significant to predict better performance. We assumed that the efficiency of reconfiguration in the whole brain was too weak to make a significant effect, unlike the CON which was assumed not to involve in the core process in MSIT. Because the reason is that the reconfiguration of the whole brain was at least associated with the working memory. The network similarity of the whole brain is lower than the similarity of FPN ($t=-31.51$, $p<.001$) and SAN ($t=-29.70$,

p<.001). On the other hand, the SAN and CON were not significantly different in the network similarity (t=−0.68, p=0.495). The more reconfiguration of the whole brain could be due to the age−related alteration of other networks other than the FPN and SAN. DMN, which constitutes a great portion of the whole−brain functional network, was already pointed out as one of the most flexible networks (Vatansever et al., 2015). The reconfiguration of the whole brain would be discussed more in the later section about working memory.

Performance of Working Memory and the network reconfiguration

Higher similarity in FPN and the whole brain between resting and MSIT was significantly associated with the higher working memory index. Subtests that were not involved to produce the WMI measure another aspect of the working memory domain and yield similar results. EMS digit span forward, measuring retention of auditory short−term memory, was significantly associated with the less reconfiguration of FPN and SAN. Also, EMS spatial span forward, measuring retention of visual short−term memory, was significantly associated with the less reconfiguration of SAN and whole brain. The better working memory associated with the less whole−brain reconfiguration (Schultz & Cole, 2016) and less FPN reconfiguration (Zuo et al., 2018) is consistent with the previous literature. The reconfiguration of SAN was involved in the subtests measuring more direct retention of auditory/verbal and visuospatial working memory, but not involved in the working memory index. The component of working memory gives an answer to this phenomenon. The construct of working memory involves two psychometric properties, domain-specific stores, and domain-general attentional control (Engle, 2010). The working memory index reflects attentional control and mental manipulation because it only considers the backward working memory test. In conclusion, the reconfiguration of SAN only reflects the capacity of domain-specific stores in the working memory.

Influence of the Resting and Task state on the behavioral performance

The significant brain activation in the interference of MSIT conditions (Incongruent - Congruent condition) showed wide regions included in the FPN, CON, and SAN from the atlas. The regions showing significant association in the interference of MSIT with the interference RT or working memory are primarily in the sensory and default mode network. These results suggest that the mechanisms explaining cognitive function through the reconfiguration of networks are not in line with the traditional brain activation analysis (Dwyer et al., 2014).

The network similarity index between resting- and MSIT state was significantly correlated with the configuration index of each state. It implies the reconfiguration validly reflected the configurations of both states. If the less reconfiguration were the mere result of the non-activation of task state due to subjective task difficulty, the resting- and MSIT states had primarily similar configuration at the first place. However, the configuration of MSIT and resting state in the networks except for the whole brain did not correlate with each other, suggesting the results is not simply affected by the only one state. In this context, the reconfiguration of whole brain network could be affected in part by the primary similar configuration of each state. The better performance behind the less reconfiguration of the whole brain might be based on the optimization for efficiency, requiring less changes to achieve better task performance, of network in task-state (Schultz & Cole, 2016).

Both individual differences in the resting and task state configurations were not associated with faster interference RT in any networks. It seems inconsistent with the previous results of younger adults who show the significant association between the behavior and resting (or task) state configuration (Schultz & Cole, 2016). On the other hand, the individual difference in the task state configuration was associated with the working memory index in the whole brain and FPN.

There could be two hypotheses to explain such result. The first is that the age-related alterations in the functional connectivity could impair the behavior-configuration correlation. Aging alters not only the task state connectivity but also the resting–state connectivity. Some older individuals show inter–individual differences while performing a task in the brain activation, which are the results of dedifferentiation or compensation for the aging or pathological change (Cabeza et al., 2018; Reuter–Lorenz & Cappell, 2008; Stern, 2009; Stern et al., 2018). This age–related heterogeneity in the network configuration could form a different direction in forming the configuration of older and younger adults. Also, age–related variation in the intensity of the BOLD signal might impact the result. There is a report that the degree of network anticorrelation during the task was associated to resting cerebral blood flow (CBF). It suggests that the reduced DMN neural activity during resting might impair achieving anticorrelation during a task (Avelar–Pereira et al., 2017). This implies the age–related reduction of neuronal activity in the resting–state might change the reconfiguration between the networks.

The second hypothesis is that the brain mechanism of cognitive control may not be based on the similar configuration between states, but solely on the change or reorganization of the network itself. Older adults present reduced processing resources (Salthouse, 1988, 1990). Such reduction makes it important to assign the resources or to process efficiently a task rather than the optimization of performance. Thus, the ability to switch the mode between states of older adults becomes more important than younger adults (Adrover−Roig & Barceló, 2010; Schapkin et al., 2014; Tsai & Wang, 2015). This interpretation is reasonable if we consider the configurations of FPN and the whole−brain task state showed significant association with the WMI. Attention and cognitive control were regarded as "emergent properties" of information representation in working memory (Courtney, 2004), which requires more processing resources. Both components mentioned here possibly contribute partly to the result.

Limit and Future Considerations

This study has three implications. This study revealed the relationship between reconfiguration and cognitive control in elderly people. This result demonstrates that the efficient reconfiguration still maintains the association with better performance within the normal aging population. This could be the foundation of the reconfiguration research in clinical studies. Especially, the role of task−positive networks in the reconfiguration was highlighted in elderly people. The different role of resting and task configuration in the reconfiguration was also demonstrated in older population. Finally, this study suggests another approach to research the cognitive control function. Some limited points in this study should be noted for future considerations. First, the longitudinal, or experimental design complements the explanation of the brain reconfiguration in older adults. This study is an observational study that recruits only older adults. If the FPN stability of reconfiguration is a key factor to maintain the cognitive function, it can be examined in the longitudinal measurement or in comparison with the younger adults. It is well known that there are many discrepancies between cross-sectional and longitudinal aging trajectories (Salthouse, 2010). Fortunately, the discrepancy was more pronounced in the memory and reasoning measures than speed and vocabulary measures (Salthouse, 2014, 2019), which is not directly associated with measures used in this study.

Second, more fMRI tasks could support this result. Schultz & Cole. (2016) reported the relationship between the brain reconfiguration and the cognitive performance in younger adults based on the fMRI signal of three different tasks. If there is a relationship between the modular reconfiguration and the cognitive domain, matching the cognitive domain to the other network would be more helpful of clarifying the rule of modular reconfiguration.

Third, similarly, the relationship between modular reconfiguration and the task-negative network (DMN), attentional network, or sensory network could be subject to study. In reality, the DMN is regarded as an important agent network other than FPN in several kinds of literature (Vatansever et al., 2015; Zuo et al., 2018). But they were not included in this paper due to the scope of the study. If the networks were included, the full picture behind the network reconfiguration would be provided.

Finally, the graph theory indices might give detailed information about the state of the network in reconfiguration. Dwyer et al. (2014) reported the robust modular affiliation of the node in the network between resting and task makes adolescents perform better in the cognitive control task. The modularity used in the study, which is one of the graph-theoretical indices, gave information about the dynamic state of the brain region. The utilization of diverse graph theory measures could enrich the result and interpretation of the reconfiguration. Despite the several limitations, this study provides a robust index and new approach to adapt to the clinical field utilizing neuroimaging.

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국문초록

노년기 과제 관련 뇌 연결망의 효율적 재조직화와 연관된 인지 통제 수행

뇌의 기능적 연결망 (brain functional network)을 상황에 따라 효율적으로 재조직화하는 능력 (network reconfiguration)은 젊은 인구에서 적응적인 기능과 연관성이 있는 것으로 알려져 있다. 본 연구는 뇌의 구조적, 기능적 변화가 발생하는 노년기에도 그러한 연관성이 나타날 수 있는지 탐구하는 것을 목적으로 하였다. Korean Social Life and Health Aging Project (KSHAP) 연구에 참여한 농촌지역 L 지역과 K 지역의 참가자 83명을 대상으로 아무 과제도 수행하지 않는 휴지기와 인지 통제를 요구하는 다중간섭과제 (MSIT) 기능적 자기공명영상 (fMRI)을 얻었다. 휴지기에서 인지적 통제를 요구하는 과제로의 뇌 기능적 연결망의 재조직화가 적은 사람일수록 (효율적일수록) 과제 수행 속도가 빨라지며, 높은 작업기억 지수 및 작업기억 소검사에서 뛰어난 수행을 보였으며, 이러한 결과는 연령, 성별, 교육 연한에 더불어 뇌의 노화를 반영하는 뇌 구조적 변수들을 통제하고도 유의미하게 나타났다. 특히, 전두두정 네트워크 (FPN)의 적은 재조직화를 보이는 사람들은 인지 통제 기능과 작업 기억 기능 모두에서 뛰어난 수행을 나타내었다. 한편, 노년기 인지통제 기능에는 휴지기나 과제 수행 상태 각각의 연결망 조직화 (configuration)의 개인차는 영향이 없었지만, 작업기억 기능에는 과제 수행 상태 연결망 조직화의 개인차의 영향이 확인되었다. 이러한 결과는 노년기에도 적은,

효율적인 재조직화가 적응 기능과 연관이 있음을 드러내며, 상황에 따른 전두두정 네트워크의 안정성이 노년기 인지기능에서 중요한 역할을 하고 있음을 입증한다. 또한, 노년기 인지 통제 기능에는 휴지기 연결망 조직화의 최적화가 아니라 과제 간 전환이 보다 적응적인 기능과 연관되어 있음이 확인되었으며, 작업 기억 기능에서는 과제를 수행할 때의 연결망 조직화의 최적화가 중요한 역할을 하고 있음을 확인했다. 본 연구 결과는 뇌 연결망 재조직화가 정상적인 노화를 포함하는 일반적인 발달 과정 내에서 수행과 맺는 관계를 확인하여 추후 임상 연구의 기틀이 될 수 있다. 또한, 기존의 뇌 영상 분석법을 확장하여 인지 통제 기능을 연구할 또다른 관점을 제시한다. 추후 연구에서는 그래프 이론 지수를 활용하여 뇌의 다양한 상태의 구성방식(topology)과 재조직화 간의 관계를 연구한다면, 적응 기능과 연결망 재조직화의 관계가 더욱 분명하게 밝혀질 것이다.

주요어 : 노년기 인지기능, 인지통제기능, 작업기억,
다중간섭과제(MSIT), 재조직화, 기능적 뇌 연결망
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