



저작자표시-비영리-변경금지 2.0 대한민국

이용자는 아래의 조건을 따르는 경우에 한하여 자유롭게

- 이 저작물을 복제, 배포, 전송, 전시, 공연 및 방송할 수 있습니다.

다음과 같은 조건을 따라야 합니다:



저작자표시. 귀하는 원저작자를 표시하여야 합니다.



비영리. 귀하는 이 저작물을 영리 목적으로 이용할 수 없습니다.



변경금지. 귀하는 이 저작물을 개작, 변형 또는 가공할 수 없습니다.

- 귀하는, 이 저작물의 재이용이나 배포의 경우, 이 저작물에 적용된 이용허락조건을 명확하게 나타내어야 합니다.
- 저작권자로부터 별도의 허가를 받으면 이러한 조건들은 적용되지 않습니다.

저작권법에 따른 이용자의 권리는 위의 내용에 의하여 영향을 받지 않습니다.

이것은 [이용허락규약\(Legal Code\)](#)을 이해하기 쉽게 요약한 것입니다.

[Disclaimer](#)

이학석사학위논문

Cognitive control training enhances
the integration of intrinsic functional
networks in adolescence

인지 통제 훈련이 청소년의
뇌 기능적 연결성에 미치는 영향

2018년 8월

서울대학교 대학원
협동과정 뇌과학 전공
이래형

M. S. Thesis

**Cognitive control training
enhances the integration of intrinsic
functional networks in adolescence**

August 2018

Raihyung Lee

Interdisciplinary Program in Neuroscience

Graduate School

Seoul National University

Abstract

Cognitive control training enhances the integration of intrinsic functional networks in adolescence

Studies have demonstrated that the intensive cognitive training can induce sustained improvements in cognitive performance in adolescents. However, few studies have investigated the neural basis of these training effects, leaving the underlying mechanism of cognitive plasticity during this period unexplained. In this study, we trained 51 normally developing adolescents on cognitive control tasks and examined how their brain intrinsic networks changed by applying graph theoretical analysis. We hypothesized that the training would accelerate the process of network integration, which is a key feature of network development occurring throughout adolescence. We found that the training enhanced the integration of functional networks, particularly the cross-network integration of cingulo-opercular network. Moreover, the analysis of additional data from older adolescents revealed that the cingulo-opercular network was more integrated with other networks in older adolescents than in younger adolescents. These findings suggest that cognitive control training speeded up the network development, such that brain networks exhibit more mature patterns after training.

Keywords: cognitive training, adolescence, cognitive control, development, resting-state fMRI, graph theory

Student Number: 2016-28864

Table of Contents

Abstract	i
Tables of Contents	ii
List of Figures	iii
List of Tables	iii
Introduction	1
Methods	5
2.1 Participants	5
2.2 Cognitive assessments	6
2.3 Cognitive control training	7
2.4 Image acquisition and preprocessing	8
2.5 Network definition	10
2.6 Graph theoretical analysis	14
Results	17
3.1 Demographics and behavioral measures	17
3.2 Graph theoretical analysis	19
Discussion	26
Bibilography	34

List of Figures

Figure 1. Anatomical location of ROIs	14
Figure 2. Network organization of subjects	20
Figure 3. Changes in CON degree after training.....	21
Figure 4. Changes in between-CON degree after training	22
Figure 5. Brain change-Behavior change.....	25
Figure 6. Brain-behavior relationship before training	25

List of Tables

Table 1. The list of ROIs and their coordinates	12
Table 2. Participant information	18
Table 3. Pre- and post-scores for neuropsychological tests	19
Table 4. Differences in degree between young and old adolescents	24

Introduction

Cognitive control, the ability to guide behavior in a goal-directed fashion, is a key requirement for everyday tasks and continues to improve throughout adolescence (Huizinga et al., 2006; Luna et al., 2010). Given that cognitive control is a strong predictor for crucial life outcomes such as academic achievement and mental health (Moffitt et al., 2011; Paus et al., 2008), numerous studies have aimed at improving cognitive control through cognitive training interventions in adolescents (for review, see Karbach & Unger, 2014). However, despite the growing interest in cognitive training and reports on its effectiveness, relatively little is known about the neural mechanisms of these training effects. This is because of the difficulty in combining longitudinal neuroimaging analysis with controlled behavioral interventions, especially in subjects such as children and adolescents (Astle et al., 2015; Rueda et al., 2012). The goal of the present study is to examine whether and how cognitive control training alters neurophysiology during adolescence.

Cognitive control requires the coordination of executive components such as task-set switching, adaptive gating, working memory, and response inhibition, and thus it involves widely distributed brain circuitries (Cole et al., 2013; Lenartowicz et al., 2010). Similarly, researchers have found that adolescent cognitive control is not attributable to the isolated operations of single brain regions, but rather dependent on an interplay

among large-scale brain networks (Dwyer et al., 2014; Luna et al., 2015). Brain networks associated with cognitive control include the fronto-parietal (FP) and cingulo-opercular (CO) networks, which are task control networks; the cerebellar (CB) network, which provides error-related feedback to task control networks; and the default mode (DM) network, which is a task negative network (Dosenbach et al., 2008; Fair et al., 2009). Cognitive control is supported by the ability for these specialized functional networks to collaborate and flexibly integrate information (Cole & Schneider, 2007). This fact also suggests that the training of higher-order cognitive skills such as cognitive control is likely to have a broader impact on brain at a systematic network level, which cannot be fully captured by inspecting single brain regions or tracts (Taya et al., 2015).

Existing studies have demonstrated the changes in brain functional networks among adults with a variety of cognitive trainings, such as working memory training (Takeuchi et al., 2013), reasoning training (Mackey et al., 2013) and mnemonic training (Dresler et al., 2017). It should be noted, however, that the same training could have different outcomes in adolescents and adults, depending on the current stage of development in which the changes take place. While training in adults largely modifies the existing neural architecture, training in adolescents may still influence the ongoing construction of neural structure (Galván, 2010). Thus, training effects in adolescents are best understood in the context of the developing brain, because they result from an interaction between learning and brain maturation (Jolles & Crone, 2012). One possible mechanism of how training affects the developing brain is that it may accelerate maturational changes, such that brain structure and function are more similar to those of adults after

training. In one study, for example, young adolescents exhibited a more mature pattern of fronto-parietal brain activation after intensive working memory practices (Jolles et al., 2012). A similar effect was observed for children who showed a more adult-like scalp distribution of event-related potentials after participating in executive attention training (Rueda et al., 2005). However, since few studies have examined the impact of training on brain in children or adolescents, more work is needed to explain the process by which the cognitive training rewires the developing brain.

Developmental changes in brain functional networks have been investigated using a powerful graph theoretical approach applied to intrinsic connectivity at rest (Vértes & Bullmore, 2015). The maturation of functional networks during adolescence is primarily characterized by refinements of network structure that is already present in infancy and childhood (Grayson & Fair, 2017). Multiple reports have found that basic network topologies are evident early in development, but continue to evolve during adolescence in ways that support the emergence of more complex cognitive abilities (Cao et al., 2014; Gu et al., 2015). One core principle of network maturation, which is particularly critical to the development of cognitive control, is greater integration among networks (Luna et al., 2015). Children display specialized networks that have similar organization structure to those of adults (Fair et al., 2013; Power et al., 2012), but the integration between those networks continues to strengthen during adolescence (Hwang et al., 2013). A recent study directly investigating the neural basis of cognitive control development has also found that the foundational organization of brain functional networks does not change from children to adults (Marek et al., 2015). However, the process of network integration,

particularly the integration of cingulo-opercular network with other brain networks, has shown to continue throughout adolescence. Importantly, this increased cross-network integration of CO network underlies behavioral improvements in cognitive control (Marek et al., 2015).

Here, we trained typically developing adolescents on cognitive control tasks and examined how their resting-state functional networks changed by applying graph theoretical analysis. Our hypothesis was based on consideration of brain developmental trajectory during adolescence. Specifically, we hypothesized that cognitive control training would accelerate the typical development of adolescents, and thereby promote the integration of functional networks. This reflects previous studies showing that the cognitive training lead to changes in neurophysiology in a way that seemingly speeds up the brain maturation (Jolles et al., 2012; Rueda et al., 2005). Fifty-one young adolescents were randomly assigned to a training or control condition, and they underwent resting-state functional magnetic resonance imaging (rs-fMRI) before and after training. To test the hypothesis, we analyzed the *degree* of brain functional networks, which is a commonly used graph theoretical measure. We examined how the degree of brain functional networks changed as a result of training. Additionally, we used ADHD-200 data set consisting of rs-fMRI scans from 47 typically developing older adolescents to serve as a contrast group. The network degree of these older adolescents were compared to that of our young adolescents to support the hypothesis. Finally, we examined how changes in brain networks after training relate to gains in behavioral performances measured outside the scanner.

Methods

2.1. Participants

Sixty-four healthy participants in the first or second year of middle school enrolled in the study. Participants were recruited through e-mails and online posting to community schools and private educational institutes located in Seoul metropolitan region. A phone screen was used to assess medical history at the time of recruitment. Participants previously diagnosed with a neurological or psychiatric illness were excluded. All participants were right-handed, free from prior head injury, and eligible for the magnetic resonance imaging environment. Before participation, all subjects provided informed written consent approved by the institutional review board of Seoul National University.

Participants underwent magnetic resonance imaging (MRI) and neuropsychological tests followed by 6 weeks of training with follow-up assessments. Three participants dropped out of training and those who failed to complete the 80% of required training schedule were excluded from analysis ($n = 11$). Regarding fMRI assessments, two additional participants were excluded due to acquisition problems (i.e., scanner malfunction and poor visual acuity). We found no subject whose head motion exceeds 3mm translation or 3 degrees rotation. Final data are reported for 25 participants (11 females) in the training group and 26 participants (11 females) in the control group.

Data of older adolescents were provided by the ADHD-200 Consortium (Brown et al., 2012), an open access data set comprising resting-state fMRI data of children with and without ADHD aggregated across eight different sites. The current study used data from the Pittsburgh University site, which had the largest number of old adolescents without ADHD. Detailed descriptions of participant recruitment procedures and selection criteria are available online at http://fcon_1000.projects.nitrc.org/indi/adhd200/. The original Pittsburgh University data set consisted of resting-state data collected from 94 subjects. We restricted our analysis to typically developing adolescents whose age ranged from 14 to 18. Among those, three subjects with motion parameters of more than 3mm translation or 3 degrees and one left-handed subject were excluded. All subjects had the normal range of IQ scores. The final set of subjects consisted of 47 individuals (25 females; age = 17.08±1.56 yr).

2.2. Cognitive assessments

Neuropsychological tests were administered for pre- and post-training evaluation which included the following: [A] The Stroop task measures response inhibition and interference resolution. The outcome variables are the number of items completed in 45 s for each condition (W = word score, C = color score, CW = color-word score). The interference was quantified, as Golden (Golden, 1978) proposed, by first calculating a

predicted color–word score (PCW) on the basis of the word (W) and color (C) scores:
 $PCW = 45 / \{[(45 \times W) + (45 \times C)] / (W \times C)\} = (W \times C) / (W + C)$. This score was then subtracted from the actual color–word score (CW) to calculate the interference score ($I = CW - PCW$). Because a higher actual color-word score relative to the predicted score suggests one’s performance was better than anticipated, the higher interference score indicates the better interference control. [B] The Trail Making Test (TMT) reflects set-switching and executive control. The interference score was calculated as follows: $Interference\ score = (TMT-B\ score - TMT-A\ score) / TMT-A\ score$. Because TMT-B captures additional cost for alternating switches, the higher interference score indicates the poorer interference control. [C] The Digit Span (both forward and backward) and [D] the Symbol Span test was used to measure verbal and visual working memory, respectively. [E] The Arithmetic test assesses working memory and mathematical reasoning. [F] The Block Design and the [G] Matrix Reasoning involves perceptual organization and perceptual reasoning, both considered as adequate measures of intelligence.

Additionally, because the stress has been associated with changes in fronto-parietal connectivity (Liston et al., 2009), we collected the Perceived Stress Scale (Cohen et al., 1983) at both visits. Further, because juvenile impulsivity has also been reported to alter resting functional connectivity (Shannon et al., 2011), we collected UPPS-P Impulsive Behavior Scale (Whiteside & Lynam, 2001) at both time points.

2.3. Cognitive control training

The cognitive control training program was originally developed by Kim et al. (2017) and was modified for adolescents in this study. The training program consisted of 7 computerized tasks that could be performed via internet. Given that cognitive control comprises a set of cognitive components including task-set switching, updating, working memory, and response inhibition (Miyake et al., 2000), each task was designed to tap one or more of these components.

Both groups performed the training at home and each individual's training record was monitored online by the researchers. The training lasted for 6 weeks, with training group performing the training 5 sessions a week (30 sessions in total) and the control group 2 sessions a week (10 sessions in total). For the training group, each session comprised 3 tasks with a total duration of approximately 30 min. Task difficulty was adjusted on a trial-by-trial basis according to individual's improving performance as the session proceeds. For the control group, each session comprised 3 tasks but took less than 10 min to complete, because the tasks did not progress to more difficult levels in response to the individual's performance. We used the active control group to control for placebo effect (Klingberg, 2010).

2.4. Image acquisition and preprocessing

Anatomical and functional MRI scanning was performed on a 3T Siemens Tim Trio at the Brain Imaging Center at the Seoul National University. Subjects' heads were fixed using foam padding and a 12 channel head coil. T1-weighted structural images were collected using a magnetization-prepared rapid gradient echo (MPRAGE) sequence (TR = 2300 ms, TE = 2.36 ms, 1.0 X 1.0 X 1.0 mm voxels, FOV = 256 mm). During the 6 min resting-state scan, participants were asked to remain relaxed but not fall asleep while gradient echo EPI images were acquired (TR = 2200 ms, TE = 30 ms, 33 axial slices, 3.0 X 3.0 X 3.5 mm voxels, flip angle = 79°, FOV = 240 mm, GRAPPA factor 2). Prior to the resting-state scan, subjects underwent two sessions of a cognitive control task fMRI. Data from the task fMRI sessions will be reported elsewhere.

Image preprocessing was performed using Statistical Parametric Mapping toolbox (SPM12; www.fil.ion.ucl.ac.uk/spm/software/spm12/) running under Matlab R2017a (Mathworks). Each subject's EPI images were unwarped using field maps and were realigned using a six-parameter (rigid body) spatial transformation with the first image as a reference. Images were then corrected for differences in slice timing acquisition. Spatial normalization was achieved via the Diffeomorphic Anatomical Registration through Exponentiated Lie Algebra (DARTEL) procedure (Ashburner, 2007). EPI images were co-registered to T1 image and a sample-specific template was created using all subjects' T1 images. Then the deformation of the T1 to a sample-specific template was calculated and applied to normalize the EPI to standard space. The images were finally smoothed with an 8 mm full-width at half-maximum Gaussian kernel.

Pittsburgh University data were acquired using the similar imaging protocol to that used for Seoul National University data. MRI scanning was performed on a 3T Siemens Tim Trio at the University of Pittsburgh Medical Center Magnetic Resonance Research Center. T1-weighted images were collected using a magnetization-prepared rapid gradient echo (MPRAGE) sequence (TR = 2100 ms, TE = 3.43 ms, 1.0 X 1.0 X 1.0 mm voxels). During the 5 min resting-state scan, gradient-echo EPI images were acquired with the following parameters: TR = 1500 ms, TE = 29 ms, 29 axial slices, 3.1 X 3.1 X 4.0 mm voxels, GRAPPA factor 2. More detailed descriptions of the ADHD-200 imaging protocol can be found in the literature (Bellec et al., 2017). We applied standard preprocessing procedures to the raw fMRI data using SPM12; Images were slice-time and motion corrected, registered to MNI space using nonlinear transformation, and smoothed with an 8mm Gaussian kernel.

2.5. Network definition

We used a previously defined 34 ROIs comprising four functional networks (i.e., fronto-parietal, cingulo-opercular, cerebellar, and default networks) whose coordinates were derived from fc-mapping and meta-analytic techniques (Dosenbach et al., 2008; Fair et al., 2009). These networks were chosen for their central involvement in exerting cognitive control. ROIs were generated as 7.5 mm radius spheres around a center

coordinate. Each ROI represented a node of the network. The MNI coordinates and the corresponding regions for all sets of ROIs are listed in Table 1.

Functional connectivity analysis was performed in the CONN toolbox v17 (Whitfield-Gabrieli & Nieto-Castanon, 2012), implemented with SPM12 (www.fil.ion.ucl.ac.uk/spm/software/spm12/). For both training and ADHD-200 data sets, an exact noise reduction method called CompCor extracted the principal components from white matter and cerebrospinal fluid signals (Behzadi et al., 2007), which were entered as confound regressors in the subject-level GLM. Given the importance of reducing motion artifacts, we implemented the Artifact Rejection Toolbox (ART; http://www.nitrc.org/projects/artifact_detect/) to detect outlier image frames based on brain activation and head movement (motion scrubbing; Power et al., 2014). In addition to the six realignment parameters and their first order derivatives, invalid scans identified using ART were included as confound regressors. The data underwent linear detrending and a temporal filter of 0.009 and 0.08 Hz was applied to focus on low frequency fluctuations (Fox et al., 2005). For each participant, a time series was calculated by averaging the BOLD signal across all voxels within each ROI. Pearson correlation coefficients were computed for each pair of ROIs and were Fisher-transformed to produce normally distributed values. The resulting 34 x 34 symmetric correlation matrices represented the networks of nodes and edges that captured each participant's intrinsic functional connectivity profile. The networks were then carried forward to the graph theoretical analysis.

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

Regions of Interest (ROI)	Abbreviations	Coordinates			Functional Network	Network Color
		x	y	z		
dorsolateral prefrontal cortex	dIPFC	-45.04	28.22	31.49	Fronto_Parietal	Yellow
dorsolateral prefrontal cortex	dIPFC	47.88	28.55	29.87	Fronto_Parietal	Yellow
Frontal	frontal	-42.77	8.23	35.67	Fronto_Parietal	Yellow
Frontal	frontal	45.82	8.54	34.13	Fronto_Parietal	Yellow
mid cingulate cortex	mCC	1.57	-26.27	31.60	Fronto_Parietal	Yellow
inferior parietal lobule	IPL	-53.35	-49.24	41.54	Fronto_Parietal	Yellow
inferior parietal lobule	IPL	56.91	-43.97	45.86	Fronto_Parietal	Yellow
intraparietal sulcus	IPS	-31.63	-57.05	48.66	Fronto_Parietal	Yellow
intraparietal sulcus	IPS	34.24	-59.26	44.40	Fronto_Parietal	Yellow
Precuneus	Precun	-7.88	-71.31	44.07	Fronto_Parietal	Yellow
Precuneus	Precun	12.67	-67.84	45.61	Fronto_Parietal	Yellow
anterior Prefrontal Cortex	aPFC	-29.21	57.15	7.07	Cingulo_Opercular	Black
anterior Prefrontal Cortex	aPFC	30.32	57.13	15.02	Cingulo_Opercular	Black
anterior insula/frontal operculum	al/fO	-36.76	16.73	-0.01	Cingulo_Opercular	Black
anterior insula/frontal operculum	al/fO	39.92	19.03	-2.67	Cingulo_Opercular	Black
dorsal anterior cingulate	dACC	0.56	16.87	45.28	Cingulo_Opercular	Black
anterior thalamus	ant thal	-11.77	-13.81	4.83	Cingulo_Opercular	Black
anterior thalamus	ant thal	12.01	-13.63	5.52	Cingulo_Opercular	Black
anterior medial prefrontal cortex	amPFC	2.19	61.08	12.87	Default	Red
ventromedial prefrontal cortex	vmPFC	-2.39	42.72	-11.01	Default	Red
superior frontal cortex	sup frontal	-13.52	47.22	49.24	Default	Red
superior frontal cortex	sup frontal	19.98	46.28	48.76	Default	Red

inferior temporal	inf templ	-64.94	-35.43	-16.78	Default	Red
inferior temporal	inf templ	71.12	-17.93	-20.83	Default	Red
parahippocampal	parahippo	-22.84	-27.94	-19.36	Default	Red
parahippocampal	parahippo	27.96	-27.55	-18.02	Default	Red
posterior consulate cortex	pCC	-0.46	-33.00	40.15	Default	Red
lateral parietal	latP	-48.96	-66.24	43.14	Default	Red
lateral parietal	latP	59.07	-65.86	41.27	Default	Red
retro splenial	retro splen	4.60	-51.94	9.44	Default	Red
lateral cerebellum	lat cereb	-33.67	-71.87	-29.40	Cerebellar	Blue
lateral cerebellum	lat cereb	34.38	-66.31	-31.11	Cerebellar	Blue
inferior cerebellum	inf cereb	-19.63	-85.00	-32.82	Cerebellar	Blue
inferior cerebellum	inf cereb	20.35	-86.99	-33.30	Cerebellar	Blue

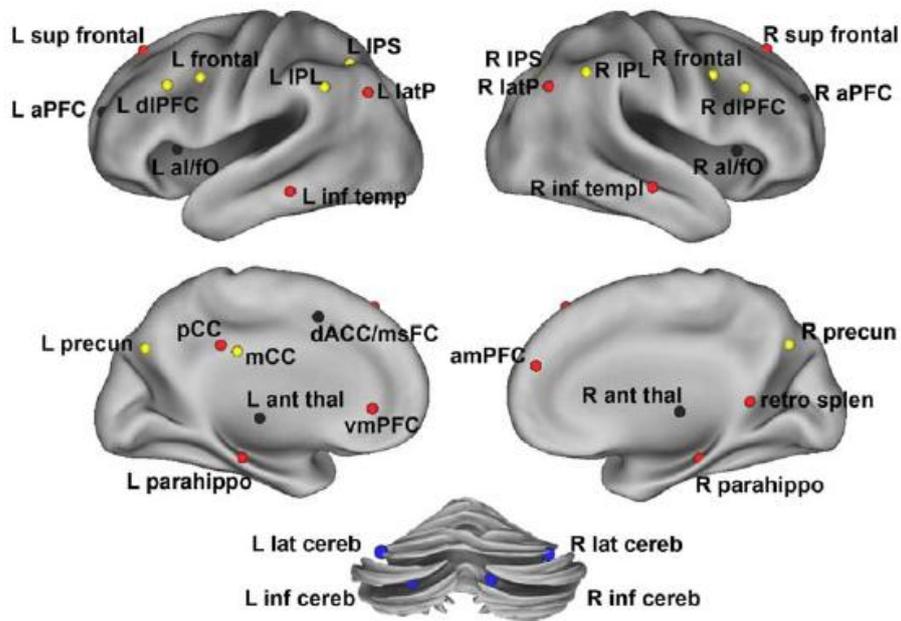


Figure 1. Anatomical location of ROIs. Regions are colored by network membership (yellow – fronto-parietal network; black – cingulo-opercular network; red – default mode network; blue – cerebellar network) and overlaid on an inflated cortical surface. The Figure was adopted from Fair et al. (2009).

2.6. Graph theoretical analysis

In this study, we sought to test the hypothesis that cognitive control training would facilitate the integration of functional networks. Recent studies have found that canonical network structure is observable early in development and stabilizes prior to adolescence (Doria et al., 2010; Gao et al., 2014), whereas the integration of those networks continues

to strengthen into adulthood (Hwang et al., 2013). Importantly, the increased integration of networks has been associated with behavioral improvements in cognitive control in adolescence (Marek et al., 2015). We hypothesized that our training intervention would accelerate this developmental change, such that brain networks are more integrated after training. To define network integration, we used a basic and important graph measure, *degree*. The degree of an individual node is equal to the number of links connected to that node. The neurobiological interpretation of the degree is straightforward: brain regions with a high degree are interacting, structurally or functionally, with many other regions (Rubinov & Sporns, 2010). In the context of network integration, a network whose nodes have many links across other networks (a network containing nodes with a high degree) is interacting vigorously with other networks, and thus are interpreted as a highly integrated network. To examine the changes in network integration after training, we calculated the mean degree for each of four networks (fronto-parietal, cingulo-opercular, cerebellar, and default networks) for each subject. We took the absolute value of all negative weights, and thresholded each subject's connectivity matrices by network densities ranging from the strongest 15% to 60% of pairwise connections. Connections above the threshold were binarized, and the average number of links connected to nodes in each network was calculated. Group X Time ANOVA was then conducted to examine whether the increases in the mean degree of networks were greater in the trained group compared with the control group after training.

To calculate the degree for each of four networks as described above, nodes were grouped by the network to which they were assigned in the predefined ROIs parcellation

(Table 1). However, it is possible that network organization of our subjects does not follow the current ROIs parcellation scheme. Thus, to ensure that our subjects' networks are organized in the same way as current ROI sets are partitioned into four networks, we performed a modular analysis. A modular analysis decomposes the whole-brain network into several distinct modules. Modules are characterized by nodes that work more closely together than with nodes belonging to other modules (Newman & Girvan, 2004). When applied to brain functional connectivity matrices, modules correspond to collections of strongly interconnected brain regions sub-serving common functions, and therefore are regarded as brain functional networks (Meunier et al., 2009; Stevens et al., 2012). To perform a modular analysis, we first averaged all 51 subjects' 34 x 34 connectivity matrices. We then partitioned average connectivity matrices into modules using a popular greedy modularity-maximization algorithm known as Louvain algorithm (Blondel et al., 2008) across network densities. Louvain algorithm has been verified to be one of the most accurate module detection algorithms among many other methods (Lancichinetti & Fortunato, 2009). The resulting modular structure represents the functional network organization of our subjects. The similarity between the network organization of our subjects and the predefined ROI partition was then examined.

Next, to interpret the meaning of changes in network degree followed by training, we calculated the mean degree of each network in old adolescents from ADHD-200 dataset. We conducted paired t-tests to examine whether there was any difference in network degree between old and young adolescents before training.

Finally, to examine brain-behavior correlations, we tested whether the increases in

the mean degree of networks were correlated with the improvements in neuropsychological tests. We performed Pearson correlation analysis investigating whether the improvements in neuropsychological tests were associated with the increases in the mean degree of networks that were found significant in the abovementioned Group X Time ANOVAs.

Results

3.1. Demographics and behavioral measures

The training group and the control group were well matched for age, sex, scores on neuropsychological tests before training, and the number of days between tests. Subjects were within a tight age range, which reduced the effects of maturation on cognitive control and resting-state connectivity patterns. Both groups were also matched on stress and impulsivity levels, and neither group displayed a change in either of these variables before and after training (Table 2). Given that head motion confounds analyses of resting-state connectivity (Power et al., 2012; van Dijk et al., 2012), we confirmed that neither mean relative head displacement nor number of frames with >0.5mm displacement changed between time points for either group or differed between groups at either time point (Mackey et al., 2013).

Table 2. Participant information

	Training group (n = 25)	Control group (n = 26)	t / χ^2	p
	Mean (SD)	Mean (SD)		
Age	13.22 (0.74)	13.15 (0.58)	-0.33	0.741
Sex (Female)	11	11	<0.01	1.000
Test-retest interval	64.5 (9.81)	65.92 (10.03)	-0.51	0.612
Perceived stress				
Time 1	20.23 (6.87)	19 (5.34)	0.72	0.478
Time 2	19.5 (7.66)	18.28 (5.83)	C [‡] 0.6	0.556
			T [‡] 0.71	0.484
Impulsivity				
Time 1	136.42 (16.26)	132.24 (18.13)	0.87	0.391
Time 2	138.04 (18.66)	127.72 (21.76)	C [‡] -0.63	0.533
			T [‡] 1.72	0.100

‡ Paired t-test to assess the changes between time 1 and time 2 in control and training groups.

The Group X Time ANOVA analyses revealed that, compared to the control group, the training group showed significantly greater improvement on the Block Design ($F(1,49)=6.69, p=.013$). Subsequent paired t-tests found that, although both training and control groups showed significant improvement on the Block Design, improvement in the training group was greater. Paired t-tests also demonstrated that the training group improved significantly on Stroop interference score ($t=2.974, p=.007$) and Symbol Span ($t=2.426, p=.023$). By contrast, there was no such change in the control group. Results for all neuropsychological tests are presented in Table 3.

Table 3. Pre- and post-scores for neuropsychological tests.

	Training group (n=25)				Control group (n=28)				t [†]	F	P
	Pre	Post	t [‡]	p	Pre	Post	t [‡]	p			
Stroop	10.18 (7.22)	14.2 (8.26)	2.97	0.007	9.77 (6.35)	10.93 (10.52)	0.58	0.564	-0.21	1.395	.243
TMT	1.35 (0.65)	1.48 (0.81)	0.714	0.482	1.62 (0.58)	1.47 (0.84)	-0.8	0.432	1.57	1.144	.29
SSP	27.92 (4.25)	31.16 (6.16)	2.43	0.023	28.12 (4.13)	29.15 (4.86)	1.54	0.137	0.17	2.213	.143
DS	23.48 (3.87)	24.52 (4.03)	1.67	0.108	23.31 (3.06)	23.96 (4.04)	1.1	0.282	-0.18	0.201	.656
AR	29.28 (1.74)	29.16 (2.49)	-0.32	0.749	28.73 (2.31)	29 (1.88)	0.65	0.521	-0.96	0.488	.488
BD	55.56 (7.75)	61.48 (4.81)	6.84	<0.001	55.08 (7.99)	57.42 (6.57)	2.2	0.038	-0.22	6.693	.013
MR	28.84 (2.88)	29.44 (2.99)	0.86	0.4	28.73 (2.86)	29.38 (2.42)	1.07	0.296	-0.13	0.003	.954

Stroop: Stroop interference score, TMT: Trail Making Test interference score, SSP: Symbol Span, DS: Digit Span, AR: Arithmetic, BD: Block Design, MR: Matrix Reasoning.

† Independent t-test to check group differences in baseline performances.

‡ Paired t-test to assess the changes between pre- and post-performances.

3.2. Graph theoretical analysis

In this study, we sought to test whether the cognitive control training promotes the integration of functional networks. To this end, we calculated the mean degree for each of four networks and examined whether the increases in degree of networks were greater in the trained group compared with the control group. The modular analysis revealed that networks of our subjects are similarly organized to the predefined network organization

across network densities (Fig 2), which allowed for the grouping of nodes according to the current ROI parcellation scheme.

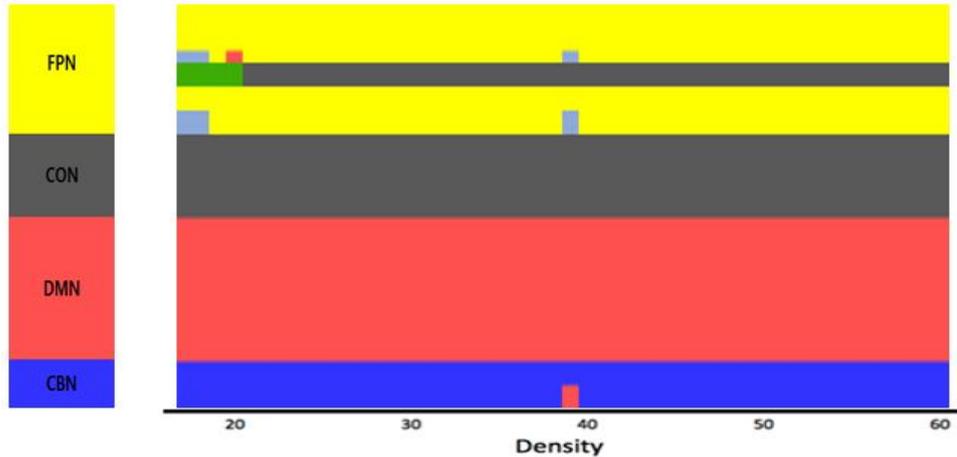


Figure 2. Left: Predefined ROI parcellation (Table 1). Nodes are colored by network membership. **Right:** Network organization of our subjects. Nodes that were grouped together are coded by the same color. Subjects showed the similar network organization to the predefined ROI parcellation. Since the predefined parcellation reflects adult network organization (Dosenbach et al., 2008), this result is also consistent with previous findings that adolescents exhibit adult-like network organization.

Group X Time ANOVA revealed that among four networks, the degree of the cingulo-opercular network (CON) significantly increased in the trained group compared with the control group (Fig 3, left). However, as shown in figure 3, the statistical significance of this training effect fluctuated according to varying network thresholds. To overcome the arbitrary bias in thresholding and acquire representative statistics, we averaged the degree of each network across the range of network densities and used these mean values in subsequent analyses. Even with this method, degree of all nodes was

significantly positively correlated with the degree of all nodes at each network density, suggesting that our results were robust to any biases in thresholding. Group X Time ANOVA was performed again with the density-averaged degree of each network, which confirmed that degree of CON significantly increased in the trained group compared with the control group ($F=4.1$, $p=.043$; Fig 3, right). Following paired t-test showed that CON degree significantly increased in the trained group ($t=-2.01$, $p=.028$, one-tailed), whereas no change was observed in the control group.

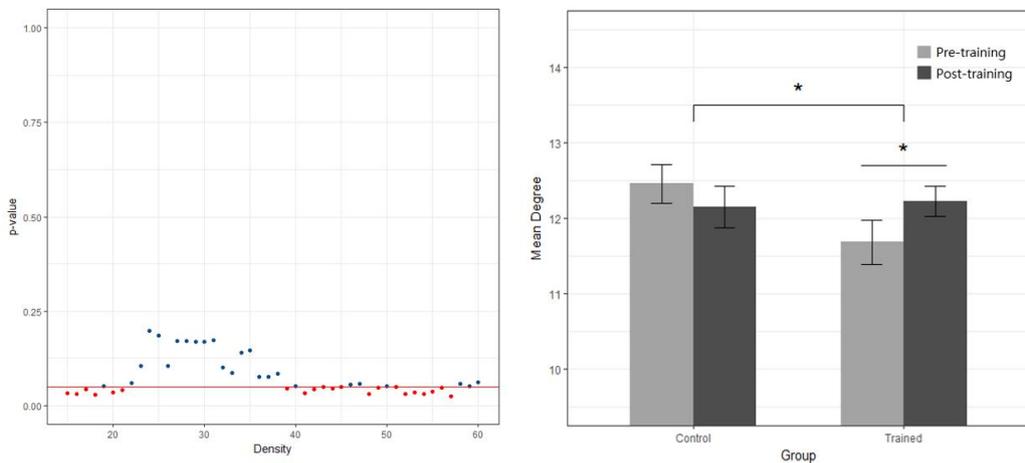


Figure 3. **Left:** P -value distribution for Group X Time ANOVA of the CON degree across network densities. A red line marks a p -value of 0.05. **Right:** Density-averaged CON degree in both groups, before and after training. There was no significant difference between the two groups in initial CON degree ($p=.054$). Error bars indicate the SEM.

Since we found that CON degree significantly increased after training, we further investigated whether it was due to the increase in the number of links within CON, or links between CON and other networks. To this end, Group X Time ANOVA was conducted separately for the change in within-CON degree (the number of links between

nodes of CON) and the change in between-CON degree (the number of links between nodes of CON and those of other three networks). We found a clear, strong trend toward the increase in between-CON degree in the trained group compared with the control group, whereas there was no difference between two groups in the change in within-CON degree (Fig 4, left). Again, to remove the bias in network thresholding, we performed Group X Time ANOVA with the density-averaged degree. We found that between-CON degree nearly significantly increased in the trained group compared with the control group ($F=3.25$, $p=.072$; Fig 4, right). Paired t-test showed that between-CON degree significantly increased in the trained group ($t=-2.01$, $p=.027$, one-tailed), whereas no change was observed in the control group. Therefore, the increased degree of CON in the training group was attributed to the increase in between-network links, not within-network links.

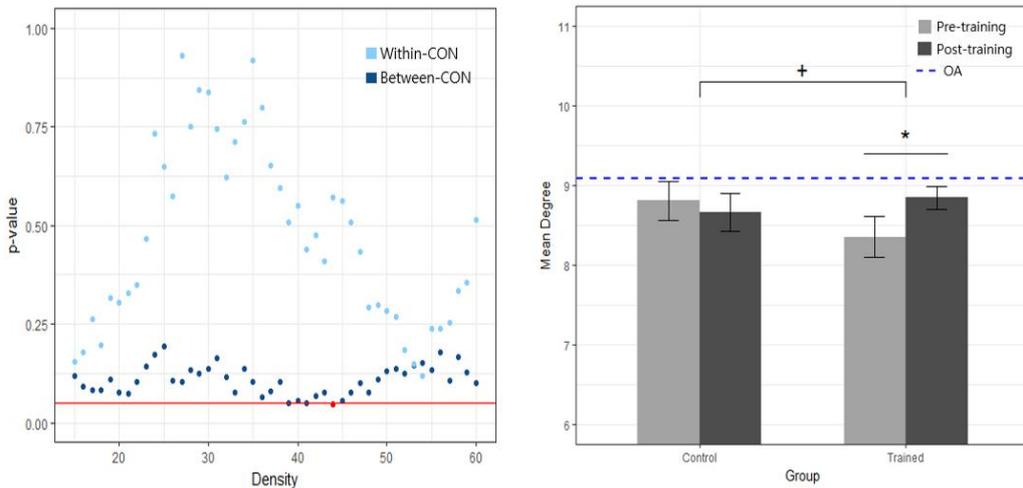


Figure 4. **Left:** *P*-value distribution for Group X Time ANOVA of the CON within- and between-degree across network densities. A red line marks a *p*-value of 0.05. **Right:** Density-averaged between-CON degree in both groups, before and after training. There was no significant

difference between the two groups in initial between-CON degree ($p=.201$). A dotted line represents between-CON degree of older adolescents. Error bars indicate the SEM.

We further examined which networks increased their links with CON after training, and no individual network was found to significantly increase their links with CON in the training group paired t-test (FPN, $p=0.447$; DMN, $p=0.222$; CBN, $p=0.824$). Therefore, increase in between-CON degree was not driven by increased links of CON with any single network, but by increase in overall connection with other networks.

Also, in order to examine the contribution of single region to network integration, which is ignored when averaging at the network level, we tested each ROI in the network for increases in between-network links after training. Among 34 ROIs, only one ROI (right inferior cerebellum) were found significant in both the Group X Time ANOVA ($F=5.14$, $p=0.014$) and the training group paired t-test ($t=2.26$, $p=0.032$). Notably, ROIs belonging to CON did not show any training-related increases in between-network links. This result again indicates that increase in between-CON degree was not driven by increased links of any single brain region, but by increase in connection of network as a whole.

Next, we examined whether there was any difference in network degree between old and young adolescents before training. We performed independent t-test to compare the total, within, and between degree of each network between young and old adolescents. Compared with young adolescents, old adolescents showed smaller within-CON degree ($t=5.93$, $p<.001$) and greater between-CON degree ($t=-2.06$, $p=.045$; Figure 4, right, dotted line). There was no difference in degree of other networks between young and old

adolescents (Table 5).

Table 4. Difference in network degree between young and old adolescents

	Total degree			Within degree			Between degree		
	YA	OA	<i>p</i>	YA	OA	<i>p</i>	YA	OA	<i>p</i>
FPN	13.52 (1.23)	13.72 (1.22)	0.437	5.60 (0.93)	5.53 (0.94)	0.72	7.92 (0.71)	8.18 (0.64)	0.059
CON	12.08 (1.44)	11.82 (1.33)	0.37	3.49 (0.7)	2.74 (0.58)	<.001	8.59 (1.27)	9.09 (1.16)	0.045
DMN	11.83 (1.23)	11.70 (1.23)	0.618	4.53 (0.95)	4.49 (0.99)	0.851	7.3 (0.66)	7.21 (0.56)	0.482
CBN	11.38 (1.83)	11.67 (2.32)	0.498	1.97 (0.65)	2.03 (0.74)	0.637	9.42 (1.76)	9.64 (1.90)	0.555

YA: Young adolescents, OA: Old adolescents

Finally, we tested whether the observed changes in total-CON degree and between-CON degree were associated with the improvements in neuropsychological tests. We found that the change in between-CON degree was significantly positively correlated with the improvement in Block Design test in both groups combined ($r=0.36$, $t=2.67$, $p=.01$; Fig 5, right, black line) as well as in the training group alone ($r=0.43$, $t=2.29$, $p=.03$; Fig 5, right, blue line). The change in total-CON degree also showed the moderately positive correlation with the improvement in Block Design in both groups combined ($r=0.25$, $t=1.80$, $p=0.078$; Fig 5, left, black line) as well as in the training group alone ($r=0.38$, $t=1.98$, $p=0.06$; Fig 5, left, blue line), but it was barely not statistically significant. Furthermore, we tested whether the total-CON degree and between-CON degree were associated with performance in Block Design *before* training.

We found that both the total-CON degree ($r=0.332$, $t=2.463$, $p=0.017$; Fig 6, left) and between-CON degree ($r=0.42$, $t=3.25$, $p=0.002$; Fig 6, right) were significantly positively correlated with the Block Design scores before training. Other neuropsychological tests showed no such correlations with total-CON degree and between-CON degree.

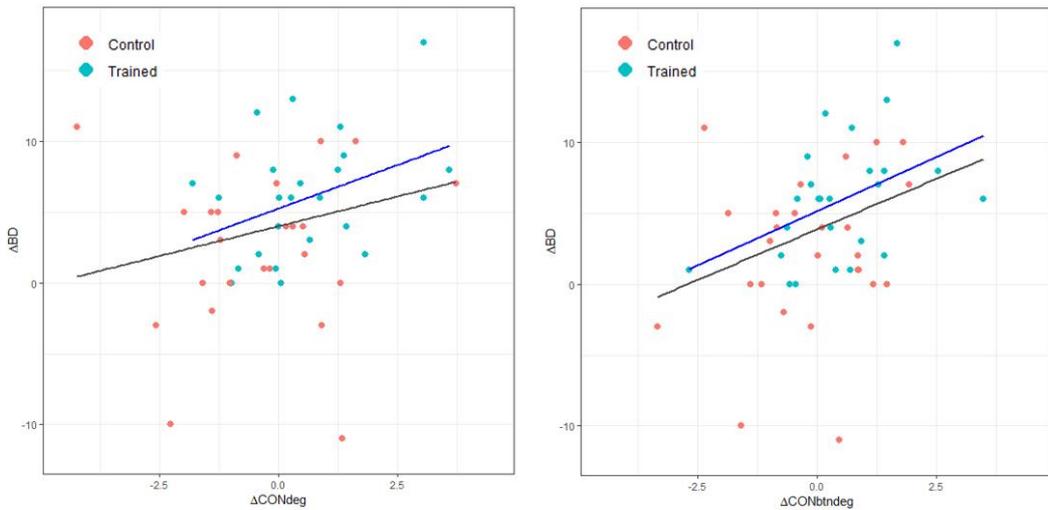


Figure 5. Left: Changes in total con degree for individual subjects across both groups plotted against changes in block design performance after training. **Right:** Changes in between-con degree plotted against changes in block design performance after training. A black line indicates the regression line for both groups, while a blue line indicates the regression line for the training group only.

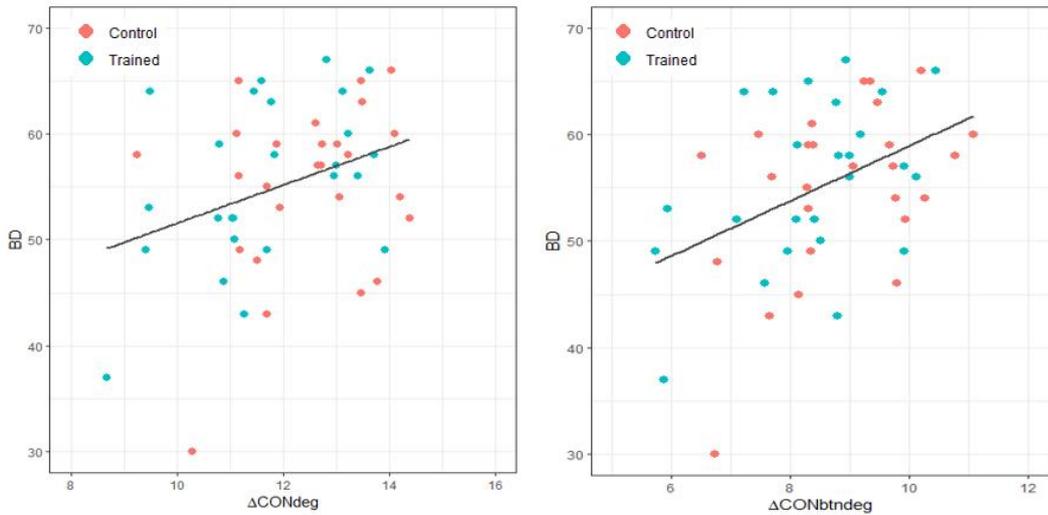


Figure 6. **Left:** Total con degree for individual subjects across both groups plotted against block design performance before training. **Right:** Between-con degree plotted against block design performance before training.

Discussion

Adolescence is a unique period when brain undergoes dynamic changes at many different levels to support the transition to adult-level cognition. At the systems level, brain networks become more involved in the integration of information from widely distributed regions, yielding more complex cognitive abilities such as cognitive control (Grayson & Fair, 2017; Stevens, 2016). Although these changes are thought to be driven

by the interplay between developmental programs and environmental inputs (Greenough et al., 1987), how those two factors interact with one another are poorly understood. In this study, we sought to test the hypothesis that the cognitive control training would accelerate the typical network development during adolescence, such that networks are more integrated after training. To this end, we applied graph theoretical analysis to rs-FC data of young adolescents who undertook 6 weeks of cognitive control training, and to independent data set from typically developing old adolescents. We found that the integration of functional networks was enhanced as a result of cognitive control training, captured by the increases in total- and between-CON degrees. The increase in between-CON degree was not attributed to increased connection of any specific network or single CON region. In addition, the analysis of network degree of old adolescents revealed that old adolescents had smaller within-CON degree and greater between-CON degree than young adolescents. Regarding the brain-behavior relationship, increases in CON degree after training were associated with the improvements in Block Design performance.

Our findings are consistent with previous characterization of major changes in functional networks occurring throughout development. Studies have shown that fundamental properties of functional networks such as network organization is established early in development, while the capacity for networks to integrate continues into adulthood (Menon, 2013; Shaw et al., 2008). It is noteworthy that smaller within- but greater between-links of CON observed in old adolescents are closely matched by the previous report demonstrating the continuous integration of CON with other networks during adolescence (Marek et al., 2015). This increased integration of CON has been

shown to play a critical role in age-related improvements in cognitive control. Functionally, CON is involved in set-maintenance, sustained alertness, and adjustments for feedback during task performance (Coste & Kleinschmidt, 2016; Dosenbach et al., 2008). Given that cognitive control is underlain by the interaction among separable cognitive components, the integration of CON with other networks may facilitate stable communication among these components, boosting the behavioral performance in cognitive control (Velanova et al., 2008). Our results suggest that this process of integration could be further advanced by extra training. Also, the fact that training only had impact on CON, but not other networks, strongly suggest that this enhanced integration was driven by the interaction between the developmental process and learning. It is well known that greater neuronal plasticity in children and adolescents allow their neuronal networks to reorganize more readily in response to environmental stimulation and to better adopt new skills and information (Johnston, 2009). In this regard, the effect of training is considered to build upon and benefit from greater neuronal plasticity (Qin et al., 2004), supposedly making CON more susceptible to learning-related changes during adolescence.

The fact that the cognitive training produces changes in intrinsic connectivity in a manner that facilitates developmental processes can also be illuminated by considering the relationship between development, learning, and intrinsic connectivity. When we engage in certain behaviors, evoked neural activity causes perturbations to intrinsic connectivity by coupling different neural components, perturbations that persist across multiple timescales (Han et al., 2008; Harmelech et al., 2013). Thus, an individual's

intrinsic network configuration at one time point reflects a history of past behavior and the statistics of environmental inputs (Sadaghiani & Kleinschmidt, 2013; Tambini et al., 2010). From this perspective, developmental changes in brain networks can be understood as emerging from the online dynamics of the child's experience that involves active sampling of the external world over the course of development (Berkes et al., 2011; Byrge et al., 2014). Importantly, most training studies are designed to enhance cognitive skills whose contents largely overlap with natural environmental inputs, or whose function is to satisfy environmental demands commonly experienced by all children (Jaeggi et al., 2011; Rapport et al., 2013). In this regard, trainings on developing children and adolescents can be viewed as providing them with age-linked experiences more precociously and intensively (James, 2010; Needham et al., 2002). This fact explains why training-induced and growth-associated changes in intrinsic networks are likely to converge to a large degree, generating the additive effect between the two. Crucially, none of this can be fully understood by studying brain regions in isolation. Developmental and learning-induced changes emerge in a dialog between brain regions, necessitating a shift toward more network-based approach (Bressler & Menon, 2010). Our findings that the training-related increase in CON degree is not captured by changes in single brain region stresses the importance of analyzing information in the brain conveyed at the network level.

Yet, questions remain as to why the training interacted with one aspect of the developmental change, namely the increase in between-CON degree, but did not have impact on the other aspect, namely the decrease in within-CON degree as observed in

this study. A plausible explanation may come from the nature of cognitive control, the particular cognitive domain on which the current training was designed to focus. As described above, cognitive control relies on a coordination of several cognitive components, which is supported by the dynamic cooperation between diverse brain networks. Thus, the ability for the brain to transfer and integrate information across networks may be more pivotal than the local communication within networks to the effective implementation of cognitive control (Cocchi et al., 2013). Indeed, it has been shown that within-network communication is important for simple cognitive tasks such as motor execution, whereas between-network communication is critical for more complex cognitive skills requiring the engagement of multiple functions, such as working memory (Cohen & D'Esposito, 2016). Also, researchers have proposed that CON serves as a mediator for competitive interactions between FPN and DMN, playing a crucial role in facilitating the crosstalk between networks (Sridharan et al., 2008; Bressler & Menon, 2010). In this regard, it is likely the between-network communication involving CON that was more strongly recruited in the course of the current training, rather than the interaction within CON which likely remained relatively separate from the demands of the training. In line with this, many training studies have found that the most relevant changes in rs-FC occur between, rather than within, networks after training (Lewis et al., 2009; Astle et al., 2015; Dresler et al., 2017). Similarly, in this study training-induced interaction between CON and other networks seems to have coincided with the developmental change, leaving a stronger trace in the increasing between-CON links.

It is worth noting that we found the strong association between brain changes and behavioral changes following the training. This proves that the observed changes in CON degree was induced by training, not by some unknown factors, with hints of individual differences in neural changes reflecting individual differences in behavioral gains. More surprisingly, CON degree was associated with performance in Block Design before training, but not with other behavioral tests. This result may provide account for the weaker training effects observed in other behavioral tests than Block Design. It has long been known that the improvement of certain cognitive skills could be constrained by the level of brain maturation. For example, the speed of information processing is modulated by the maturation of white matter (Fields, 2008; Nagy et al., 2004), which could in turn, for instance, constrain practice-related gains on higher level cognition such as working memory (Fry & Hale, 1996). In the similar vein, subjects in our study are at a developmental point when CON becomes more integrated with other networks. Thus, our findings that this developmental process could be accelerated by training may set limits on which cognitive performance is prone to be affected by training. In other words, the interaction between brain development and training is likely to alter more developmentally responsive network, in this case CON, and the change in CON could in turn affect associated cognitive performance, in this case Block Design performance. The fact that training-related behavioral gains could be limited by the current level of brain maturation may shed some light on the debate on the effectiveness of cognitive training (Melby-Lervåg & Hulme, 2013).

The results of the current study have broad theoretical and practical implications. To

our knowledge, this study is the first to demonstrate that cognitive training augments intrinsic brain connectivity in typically developing adolescents. Since we examined the resting brain, this training effect is not attributable to differences in motivation or strategy. Plus, most training studies with developing children or adolescents to date have not evaluated the training effects in the light of subjects' developmental trajectory. However, in analyzing and interpreting the training outcomes, a developmental perspective is crucial given that childhood and adolescence are a special period featuring a brain's greater yet systematic malleability when training may have unique effects. In addition, this line of basic research may be informative for designing education programs for normally developing children (Posner & Rothbart, 2005). For example, to build efficient education programs, it is useful to know how different types of learning is implemented in the brain, and whether the learning-induced changes reflect temporary adaptation in brain function or more enduring reorganization of the underlying neuronal structure (Goswami, 2006, Carew & Magsamen, 2010). Furthermore, adolescence is characterized by certain psychological traits such as increases in sensation and novelty seeking that are linked to specific brain maturational changes (Casey et al., 2008; Steinberg, 2004). Also, cognitive control is impaired in many psychiatric disorders, which also appear in the adolescent period (Paus et al., 2008). Thus, elucidating whether and how cognitive control training alters the adolescent brain may aid in targeting intervention to ameliorate adolescent maladaptive behaviors and remediate the emergence of psychopathology.

This study was not without limitations. One caveat is that resting-state scan was

preceded by a task fMRI scan. Indeed, some studies have shown that a task before an rs-fMRI scan can alter the resting-state FC over the short term (Waites et al., 2005; Stevens et al., 2010). However, since the order of scans was the same for both groups, it is unlikely that the task influenced resting-state FC of the training group disproportionately. Second, Korean children already experience much practice with cognitive control in school and everyday lives, and this might have blurred the training effect. This explanation relates to the time displacement hypothesis, which states that training should be evaluated in relation to the activities it displaces (Bavelier et al., 2010). However, there is no reason to assume that the training group received greater environmental inputs tapping cognitive control except for the required training. Also, the task difficulty of training was adapted to tax a great deal of cognitive resources for adolescents, creating significant differences in cognitive demands between two groups. One interesting future direction is to unravel the structural basis of documented changes in functional networks. The changing dynamics of functional network during adolescence is accompanied by a series of structural alterations including gray matter thinning (Gogtay et al., 2004), synaptic pruning (Petanjek et al., 2011), and the increase in white matter integrity (Lebel et al., 2008). Particularly, the increase in integrity of white matter tracts allows for faster neuronal transmission, which is thought to underlie integration of functional networks (Simmonds et al., 2014). Thus, the increased CON links observed in the current study should be paralleled by concomitant changes in white matter networks. Indeed, recent studies have demonstrated alterations of structural networks as a result of cognitive training (Caeyenberghs et al., 2016; Román et al., 2017). It remains our future work to

combine analysis of structural data to explain how recorded changes in intrinsic connectivity relate to changes in white matter networks.

References

- Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage*, *38*(1), 95–113.
- Astle, D. E., Barnes, J. J., Baker, K., Colclough, G. L., & Woolrich, M. W. (2015). Cognitive Training Enhances Intrinsic Brain Connectivity in Childhood. *Journal of Neuroscience*, *35*(16), 6277–6283.
- Bavelier, D., Green, C. S., & Dye, M. W. G. (2010). Children, Wired: For Better and for Worse. *Neuron*.

- Behzadi, Y., Restom, K., Liao, J., & Liu, T. T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *NeuroImage*, *37*(1), 90–101.
- Bellec, P., Chu, C., Chouinard-Decorte, F., Benhajali, Y., Margulies, D. S., & Craddock, R. C. (2017). The Neuro Bureau ADHD-200 Preprocessed repository. *NeuroImage*, *144*, 275–286.
- Berkes, P., Orbán, G., Lengyel, M., & Fiser, J. (2011). Spontaneous cortical activity reveals hallmarks of an optimal internal model of the environment. *Science*, *331*(6013), 83–87.
- Blondel, V. D., Guillaume, J. L., Lambiotte, R., & Lefebvre, E. (2008). Fast unfolding of communities in large networks. *Journal of Statistical Mechanics: Theory and Experiment*, *2008*(10).
- Bressler, S. L., & Menon, V. (2010). Large-scale brain networks in cognition: emerging methods and principles. *Trends in Cognitive Sciences*.
- Brown, M. R. G., Sidhu, G. S., Greiner, R., Asgarian, N., Bastani, M., Silverstone, P. H., ... Dursun, S. M. (2012). ADHD-200 Global Competition: diagnosing ADHD using personal characteristic data can outperform resting state fMRI measurements. *Frontiers in Systems Neuroscience*, *6*.
- Byrge, L., Sporns, O., & Smith, L. B. (2014). Developmental process emerges from extended brain-body-behavior networks. *Trends in Cognitive Sciences*.
- Caeyenberghs, K., Metzler-Baddeley, C., Foley, S., & Jones, D. K. (2016). Dynamics of the Human Structural Connectome Underlying Working Memory Training. *Journal of Neuroscience*, *36*(14), 4056–4066.
- Cao, M., Wang, J. H., Dai, Z. J., Cao, X. Y., Jiang, L. L., Fan, F. M., ... He, Y. (2014). Topological organization of the human brain functional connectome across the lifespan. *Developmental Cognitive Neuroscience*, *7*, 76–93.
- Carew, T. J., & Magsamen, S. H. (2010). Neuroscience and Education: An Ideal Partnership for Producing Evidence-Based Solutions to Guide 21st Century Learning. *Neuron*.
- Casey, B. J., Jones, R. M., & Hare, T. A. (2008). The adolescent brain. *Annals of the New York Academy of Sciences*.
- Cocchi, L., Zalesky, A., Fornito, A., & Mattingley, J. B. (2013). Dynamic cooperation and competition between brain systems during cognitive control. *Trends in Cognitive Sciences*.
- Cohen, J. R., & D’Esposito, M. (2016). The Segregation and Integration of Distinct Brain

- Networks and Their Relationship to Cognition. *Journal of Neuroscience*, 36(48), 12083–12094.
- Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *A Global Measure of Perceived Stress*.
- Cole, M. W., Reynolds, J. R., Power, J. D., Repovs, G., Anticevic, A., & Braver, T. S. (2013). Multi-task connectivity reveals flexible hubs for adaptive task control. *Nature Neuroscience*, 16(9), 1348–1355.
- Cole, M. W., & Schneider, W. (2007). The cognitive control network: Integrated cortical regions with dissociable functions. *NeuroImage*, 37(1), 343–360.
- Coste, C. P., & Kleinschmidt, A. (2016). Cingulo-opercular network activity maintains alertness. *NeuroImage*, 128, 264–272.
- Diamond, A. (2012). Activities and Programs That Improve Children’s Executive Functions. *Current Directions in Psychological Science*, 21(5), 335–341.
- Doria, V., Beckmann, C. F., Arichi, T., Merchant, N., Groppo, M., Turkheimer, F. E., ... Edwards, A. D. (2010). Emergence of resting state networks in the preterm human brain. *Proceedings of the National Academy of Sciences*, 107(46), 20015–20020.
- Dosenbach, N. U. F., Fair, D. A., Cohen, A. L., Schlaggar, B. L., & Petersen, S. E. (2008). A dual-networks architecture of top-down control. *Trends in Cognitive Sciences*, 12(3), 99–105.
- Dresler, M., Shirer, W. R., Konrad, B. N., Müller, N. C. J., Wagner, I. C., Fernández, G., ... Greicius, M. D. (2017). Mnemonic Training Reshapes Brain Networks to Support Superior Memory. *Neuron*, 93(5), 1227–1235.
- Dwyer, D. B., Harrison, B. J., Yücel, M., Whittle, S., Zalesky, A., Pantelis, C., ... Fornito, A. (2014). Large-scale brain network dynamics supporting adolescent cognitive control. *Journal of Neuroscience*, 34(42), 14096–107.
- Eigsti, I.-M., Zayas, V., Mischel, W., Shoda, Y., Ayduk, O., Dadlani, M. B., ... Casey, B. J. (2006). Predicting cognitive control from preschool to late adolescence and young adulthood. *Psychological Science*, 17(6), 478–484.
- Fair, D. A., Cohen, A. L., Power, J. D., Dosenbach, N. U. F., Church, J. A., Miezin, F. M., ... Petersen, S. E. (2009). Functional brain networks develop from a “local to distributed” organization. *PLoS Computational Biology*, 5(5).

- Fair, D. A., Nigg, J. T., Iyer, S., Bathula, D., Mills, K. L., Dosenbach, N. U. F., ... Milham, M. P. (2013). Distinct neural signatures detected for ADHD subtypes after controlling for micro-movements in resting state functional connectivity MRI data. *Frontiers in Systems Neuroscience*, *6*.
- Fields, R. D. (2008). White matter in learning, cognition and psychiatric disorders. *Trends in Neurosciences*.
- Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). From The Cover: The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences*, *102*(27), 9673–9678.
- Fry, A. F., & Hale, S. (1996). Processing Speed, Working Memory, and Fluid Intelligence: Evidence for a Developmental Cascade. *Psychological Science*, *7*(4), 237–241.
- Galván, A. (2010). Neural plasticity of development and learning. *Human Brain Mapping*, *31*, 879-890.
- Gao, W., Elton, A., Zhu, H., Alcauter, S., Smith, J. K., Gilmore, J. H., & Lin, W. (2014). Intersubject Variability of and Genetic Effects on the Brain's Functional Connectivity during Infancy. *Journal of Neuroscience*, *34*(34), 11288–11296.
- Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, Thompson, P. M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(21), 8174–9.
- Golden, C. J. (1978). Stroop Color and Word Test: A manual for clinical and experimental uses. *Chicago: Stoelting*, 1–46.
- Goswami, U. (2006). Neuroscience and education: From research to practice? *Nature Reviews Neuroscience*, *7*, 406-411.
- Grayson, D. S., & Fair, D. A. (2017). Development of large-scale functional networks from birth to adulthood: A guide to the neuroimaging literature. *NeuroImage*, *160*, 15–31.
- Greenough, W. T., Black, J. E., & Wallace, C. S. (1987). Experience and brain development. *Child Development*, *58*(3), 539–559.
- Gu, S., Satterthwaite, T. D., Medaglia, J. D., Yang, M., Gur, R. E., Gur, R. C., & Bassett, D. S. (2015). Emergence of system roles in normative neurodevelopment. *Proceedings of the*

National Academy of Sciences, 112(44), 13681–13686.

- Han, F., Caporale, N., & Dan, Y. (2008). Reverberation of Recent Visual Experience in Spontaneous Cortical Waves. *Neuron*, 60(2), 321–327.
- Harmelech, T., Preminger, S., Wertman, E., & Malach, R. (2013). The Day-After Effect: Long Term, Hebbian-Like Restructuring of Resting-State fMRI Patterns Induced by a Single Epoch of Cortical Activation. *Journal of Neuroscience*, 33(22), 9488–9497.
- Huizinga, M., Dolan, C. V., & van der Molen, M. W. (2006). Age-related change in executive function: Developmental trends and a latent variable analysis. *Neuropsychologia*, 44(11), 2017–2036.
- Hwang, K., Hallquist, M. N., & Luna, B. (2013). The development of hub architecture in the human functional brain network. *Cerebral Cortex*, 23(10), 2380–2393.
- Jaeggi, S. M., Buschkuhl, M., Jonides, J., Shah, P., Morrison, A. B., & Chein, J. M. (2011). Short-and long-term benefits of cognitive training. *Proceedings of the National Academy of Sciences*, 108(25), 46–60.
- James, K. H. (2010). Sensori-motor experience leads to changes in visual processing in the developing brain. *Developmental Science*, 13(2), 279–288.
- Johnston, M. V. (2009). Plasticity in the developing brain: implications for rehabilitation. *Developmental Disabilities Research Reviews*.
- Jolles, D. D., & Crone, E. A. (2012). Training the developing brain: a neurocognitive perspective. *Frontiers in Human Neuroscience*, 6.
- Jolles, D. D., Van Buchem, M. A., Rombouts, S. A. R. B., & Crone, E. A. (2012). Practice effects in the developing brain: A pilot study. *Developmental Cognitive Neuroscience*, 2(SUPPL. 1).
- H. Kim, J. Chey, S. Lee. (2017). Effects of multicomponent training of cognitive control on cognitive function and brain activation in older adults. *Neuroscience Research*, 124(November), 128-115.
- Klingberg, T. (2010). Training and plasticity of working memory. *Trends in Cognitive Sciences*.
- Kray, J., & Ferdinand, N. K. (2013). How to Improve Cognitive Control in Development During Childhood: Potentials and Limits of Cognitive Interventions. *Child Development Perspectives*, 7(2), 121–125.

- Lancichinetti, A., & Fortunato, S. (2009). Community detection algorithms: A comparative analysis. *Physical Review E*, *80*(5), 056117.
- Lebel, C., Walker, L., Leemans, A., Phillips, L., & Beaulieu, C. (2008). Microstructural maturation of the human brain from childhood to adulthood. *NeuroImage*, *40*(3), 1044–1055.
- Lenartowicz, A., Kalar, D. J., Congdon, E., & Poldrack, R. A. (2010). Towards an Ontology of Cognitive Control. *Topics in Cognitive Science*, *2*(4), 678–692.
- Lewis, C. M., Baldassarre, A., Committeri, G., Romani, G. L., & Corbetta, M. (2009). Learning sculpts the spontaneous activity of the resting human brain. *Proceedings of the National Academy of Sciences*, *106*(41), 17558–17563.
- Liston, C., McEwen, B. S., & Casey, B. J. (2009). Psychosocial stress reversibly disrupts prefrontal processing and attentional control. *Proceedings of the National Academy of Sciences*, *106*(3), 912–917.
- Luna, B., Marek, S., Larsen, B., Tervo-Clemmens, B., & Chahal, R. (2015). An Integrative Model of the Maturation of Cognitive Control. *Annual Review of Neuroscience*, *38*(1), 151–170.
- Luna, B., Padmanabhan, A., & O’Hearn, K. (2010). What has fMRI told us about the Development of Cognitive Control through Adolescence? *Brain and Cognition*.
- Mackey, A. P., Miller Singley, A. T., & Bunge, S. A. (2013). Intensive Reasoning Training Alters Patterns of Brain Connectivity at Rest. *Journal of Neuroscience*, *33*(11), 4796–4803.
- Marek, S., Hwang, K., Foran, W., Hallquist, M. N., & Luna, B. (2015). The Contribution of Network Organization and Integration to the Development of Cognitive Control. *PLoS Biology*, *13*(12).
- Melby-Lervåg, M., & Hulme, C. (2013). Is working memory training effective? A meta-analytic review. *Developmental Psychology*.
- Menon, V. (2013). Developmental pathways to functional brain networks: Emerging principles. *Trends in Cognitive Sciences*.
- Meunier, D., Achard, S., Morcom, A., & Bullmore, E. (2009). Age-related changes in modular organization of human brain functional networks. *NeuroImage*, *44*(3), 715–723.
- Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The Unity and Diversity of Executive Functions and Their Contributions to Complex “Frontal Lobe” Tasks: A Latent Variable Analysis. *Cognitive Psychology*, *41*(1), 49–100.

- Moffitt, T. E., Arseneault, L., Belsky, D., Dickson, N., Hancox, R. J., Harrington, H., ... Caspi, A. (2011). A gradient of childhood self-control predicts health, wealth, and public safety. *Proceedings of the National Academy of Sciences*, *108*(7), 2693–2698.
- Nagy, Z., Westerberg, H., & Klingberg, T. (2004). Maturation of white matter is associated with the development of cognitive functions during childhood. *Journal of Cognitive Neuroscience*, *16*(7), 1227–1233.
- Needham, A., Barrett, T., & Peterman, K. (2002). A pick-me-up for infants' exploratory skills: Early simulated experiences reaching for objects using "sticky mittens" enhances young infants object exploration skills. *Infant Behavior and Development*, *25*(3), 279–295.
- Newman, M., & Girvan, M. (2004). Finding and evaluating community structure in networks. *Physical Review E*, *69*(2), 1–16.
- Paus, T., Keshavan, M., & Giedd, J. N. (2008). Why do many psychiatric disorders emerge during adolescence? *Nature Reviews. Neuroscience*, *9*(12), 947–957.
- Petanjek, Z., Judas, M., Simic, G., Rasin, M. R., Uylings, H. B. M., Rakic, P., & Kostovic, I. (2011). Extraordinary neoteny of synaptic spines in the human prefrontal cortex. *Proceedings of the National Academy of Sciences*, *108*(32), 13281–13286.
- Posner, M. I., & Rothbart, M. K. (2005). Influencing brain networks: Implications for education. In *Trends in Cognitive Sciences* (Vol. 9, pp. 99–103).
- Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage*, *59*(3), 2142–2154.
- Power, J. D., Mitra, A., Laumann, T. O., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2014). Methods to detect, characterize, and remove motion artifact in resting state fMRI. *NeuroImage*, *84*, 320–341.
- Qin, Y., Carter, C. S., Silk, E. M., Stenger, V. A., Fissell, K., Goode, A., & Anderson, J. R. (2004). The change of the brain activation patterns as children learn algebra equation solving. *Proceedings of the National Academy of Sciences of the United States of America*, *101*, 5686–5691.
- Rapport, M. D., Orban, S. A., Kofler, M. J., & Friedman, L. M. (2013). Do programs designed to train working memory, other executive functions, and attention benefit children with ADHD? A meta-analytic review of cognitive, academic, and behavioral outcomes. *Clinical Psychology Review*.

- Román, F. J., Iturria-Medina, Y., Martínez, K., Karama, S., Burgaleta, M., Evans, A. C., ... Colom, R. (2017). Enhanced structural connectivity within a brain sub-network supporting working memory and engagement processes after cognitive training. *Neurobiology of Learning and Memory*, *141*, 33–43.
- Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *NeuroImage*, *52*(3), 1059–1069.
- Rueda, M. R., Checa, P., & Cómbita, L. M. (2012). Enhanced efficiency of the executive attention network after training in preschool children: Immediate changes and effects after two months. *Developmental Cognitive Neuroscience*, *2*(SUPPL. 1).
- Rueda, M. R., Rothbart, M. K., McCandliss, B. D., Saccomanno, L., & Posner, M. I. (2005). Training, maturation, and genetic influences on the development of executive attention. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(41), 14931–6.
- Sadaghiani, S., & Kleinschmidt, A. (2013). Functional interactions between intrinsic brain activity and behavior. *NeuroImage*, *80*, 379–386.
- Shannon, B. J., Raichle, M. E., Snyder, A. Z., Fair, D. A., Mills, K. L., Zhang, D., ... Kiehl, K. A. (2011). Premotor functional connectivity predicts impulsivity in juvenile offenders. *Proceedings of the National Academy of Sciences*, *108*(27), 11241–11245.
- Shaw, P., Kabani, N. J., Lerch, J. P., Eckstrand, K., Lenroot, R., Gogtay, N., ... Wise, S. P. (2008). Neurodevelopmental Trajectories of the Human Cerebral Cortex. *Journal of Neuroscience*, *28*(14), 3586–3594.
- Simmonds, D. J., Hallquist, M. N., Asato, M., & Luna, B. (2014). Developmental stages and sex differences of white matter and behavioral development through adolescence: A longitudinal diffusion tensor imaging (DTI) study. *NeuroImage*, *92*, 356–368.
- Sridharan, D., Levitin, D. J., & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceedings of the National Academy of Sciences*, *105*(34), 12569–12574.
- Steinberg, L. (2004). Risk taking in adolescence: What changes, and why? In *Annals of the New York Academy of Sciences* (Vol. 1021, pp. 51–58).
- Stevens, A. A., Tappon, S. C., Garg, A., & Fair, D. A. (2012). Functional brain network modularity captures inter- and intra-individual variation in working memory capacity. *PLoS ONE*, *7*(1).

- Stevens, M. C. (2016). The contributions of resting state and task-based functional connectivity studies to our understanding of adolescent brain network maturation. *Neuroscience and Biobehavioral Reviews*.
- Stevens, W. D., Buckner, R. L., & Schacter, D. L. (2010). Correlated low-frequency BOLD fluctuations in the resting human brain are modulated by recent experience in category-preferential visual regions. *Cerebral Cortex*, *20*(8), 1997–2006.
- Takeuchi, H., Taki, Y., Nouchi, R., Hashizume, H., Sekiguchi, A., Kotozaki, Y., Kawashima, R. (2013). Effects of working memory training on functional connectivity and cerebral blood flow during rest. *Cortex*, *49*(8), 2106–2125. <https://doi.org/10.1016/j.cortex.2012.09.007>
- Tambini, A., Ketz, N., & Davachi, L. (2010). Enhanced Brain Correlations during Rest Are Related to Memory for Recent Experiences. *Neuron*, *65*(2), 280–290.
- Taya, F., Sun, Y., Babiloni, F., Thakor, N., & Bezerianos, A. (2015). Brain enhancement through cognitive training: a new insight from brain connectome. *Frontiers in Systems Neuroscience*, *9*.
- van Dijk, K. R. A., Sabuncu, M. R., & Buckner, R. L. (2012). The influence of head motion on intrinsic functional connectivity MRI. *NeuroImage*, *59*(1), 431–438.
- Velanova, K., Wheeler, M. E., & Luna, B. (2008). Maturation changes in anterior cingulate and frontoparietal recruitment support the development of error processing and inhibitory control. *Cerebral Cortex*, *18*(11), 2505–2522.
- Vértes, P. E., & Bullmore, E. T. (2015). Annual research review: Growth connectomics - The organization and reorganization of brain networks during normal and abnormal development. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *56*(3), 299–320.
- Waites, A. B., Stanislavsky, A., Abbott, D. F., & Jackson, G. D. (2005). Effect of prior cognitive state on resting state networks measured with functional connectivity. *Human Brain Mapping*, *24*(1), 59–68.
- Whiteside, S. P., & Lynam, D. R. (2001). The five factor model and impulsivity: Using a structural model of personality to understand impulsivity. *Personality and Individual Differences*, *30*(4), 669–689.
- Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). *Conn* : A Functional Connectivity Toolbox for Correlated and Anticorrelated Brain Networks. *Brain Connectivity*, *2*(3), 125–141.

국문 초록

인지 통제 훈련이 청소년의 뇌 기능적 연결성에 미치는 영향

다수의 연구들이 인지 훈련 이후 청소년들의 인지 기능이 향상됨을 보고하고 있으나, 그러한 효과의 신경학적 기전에 대해서는 알려진 바가 적다. 본 연구에서는 51명의 청소년을 대상으로 인지 통제 훈련을 실시하고, 그에 따른 뇌의 휴지기 기능적 연결성의 변화를 살폈다. 본 연구는 인지 통제 훈련이 청소년기에 이루어지는 뇌의 기능적 네트워크 발달을 가속화해, 네트워크 간 통합을 촉진할 것이라는 가설을 세웠다. 분석 결과, 통제 집단에 비해 훈련 집단에서 훈련 이후 뇌의 기능적 네트워크, 특히

대상화-판개 네트워크와 다른 네트워크들 간의 통합이 증가함을 확인했다. 나아가 본 연구에서는 훈련으로 인한 상기의 변화가 의미하는 바를 해석하기 위해 실험 참여자들보다 연령대가 높은 청소년들의 뇌 기능적 네트워크 통합 정도를 추가로 분석했다. 그 결과 연령대가 높은 청소년들의 대상화-판개 네트워크와 다른 네트워크들 간 통합 정도가 실험 참여자들에 비해 더욱 높다는 것을 확인했다. 본 연구 결과는 인지 통제 훈련이 청소년기에 이루어지는 뇌 기능적 네트워크 발달을 가속화함을 시사하며, 이 시기 인지 가소성의 신경학적 기전에 대한 단서를 제공한다.

주요어: 인지 훈련, 청소년, 인지 통제, 발달, 휴지기 기능적 자기공명 영상, 그래프 이론

학번: 2016-28864