

Does training on higher cognitive functions change patterns of brain
connectivity at rest during middle childhood?

BY

Jingtai Liu

Supervised by

Pedro M. Paz-Alonso, PhD

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Abstract

Cognitive training can improve performance on trained abilities, and this effect can be also transferred to untrained capacities. However, the neural mechanisms supporting these behavioral improvements due to training are still unclear. The present study was aimed at investigating whether training school-aged children in cognitive control and attention could alter their involved intrinsic functional networks, and to what extent these effects can be generalized to untrained reading abilities and their brain networks. A total of 41 children (8-10 years old) underwent MRI scanning before and after being assigned to either training sessions involving games of increasing difficulty (Experimental, $n = 20$) or training sessions where children just played lower levels of difficulty of the same games (Control, $n = 21$). The two groups were carefully matched on age, gender and intelligence. After 2-3 weeks of training, the task-related networks showed important changes in terms of increasing and decreasing functional connectivity patterns in the Experimental group. Observed connection changes in cognitive control and attention were mainly concentrated on fronto-parietal networks. In contrast, changes in reading task were mainly emerged between parietal and temporal regions. These results not only provided strong evidence to support the view of neural plasticity on large-scale networks during middle childhood, but also direct neuroimaging evidence for the transfer effects of cognitive training.

Keywords: transfer effects; resting-state functional connectivity; attention; cognitive control; reading; cognitive training

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Introduction

Cognitive Training

People say practice makes you perfect. We all may have similar experience from our daily life and, in fact, researchers have also provided considerable evidence in music and motor learning to support this widely known adage. But we may want to ask if the cognitive abilities could also be improved, because, obviously, finding ways to increase cognitive abilities has significant appeal to all classes, ages, and aptitudes. Fortunately, many studies have provided positive answers to this question (Klingberg, Forssberg & Johnson, 2002; Klingberg et al., 2005). For example, Klingberg and his colleagues (2002) realized that initial ill-fated attempts of improving working memory (WM) through training may failed due to errors in selecting the appropriate training paradigms and methods (Kristofferson, 1972; Phillips & Nettelbeck, 1984), so they utilized a new type of computerized cognitive training based on two main features: (1) training tasks were performed by using an adaptive parametric system, with tasks getting progressively harder depending on participants' performance, to optimize training effects; (2) the training period and duration of the sessions were set to ensure that participants got enough practice. By means of these improvements in their new training paradigm, they found after training fourteen children with Attention Deficit Hyperactivity Disorder (ADHD) and four healthy young adult without ADHD not only performed better on the trained visuo-spatial WM tasks, and more remarkable, the training effects were transferred to untrained tasks, such as Raven's Progressive Matrices, a measure of fluid intelligence.

After this landmark study, more and more studies have emerged in the last 12 years, corroborating the view that cognitive abilities can be trained to a significant degree. Klingberg et al. (2005) replicated his prior finding including a large amount of participants. However, the real deluge of cognitive training studies started with Jaeggi et al.'s study published in 2008. In that study, Jaeggi and her colleagues (Jaeggi, Buschkuhl, Jonides & Perrig, 2008) used a newly developed training paradigm consisting of a demanding working memory task, which was called dual N-back task, to investigate the effects of training on the working memory and its transfer to fluid intelligence. Their work showed the possibility of improving fluid intelligence by working memory training, and in fact the gains in fluid intelligence critically depended on the amount of training.

Training effects have not been only characterized in working memory (Brehmer, Westerberg & Bäckman, 2012; Borella, Carretti, Riboldi & De Beni, 2010; Chein & Morrison, 2010; Green et al., 2012; Li, Schmiedek, Huxhold, Röcke, Smith & Lindenberger, 2008; Richmond, Morrison, Chein & Olson, 2011; Schmiedek, Lövdén & Lindenberger, 2010), but also extended to other cognitive functions that are assumed to form the basis of general cognitive abilities, such as attention (Rueda, Rothbart, McCandliss, Saccomanno & Posner, 2005; Tamm et al., 2010; Wass, Porayska-Pomsta & Johnson, 2011), cognitive control (Diamond, Bameitt, Thomas & Munro, 2007; Karbach & Kray, 2009), reasoning (Mackey, Miller Singley & Bunge, 2013; Mackey, Whitaker & Bunge, 2012; Mackey, Hill, Stone & Bunge, 2011),

perceptual speed (Ball, Edwards & Ross, 2007; Schmiedek, Lövdén & Lindenberger, 2010), and sensory discrimination (Mahncke et al., 2006).

Thorell (Thorell, Lindqvist, Bergman Nutley, Bohlin & Klingberg, 2009) made a brief summary of the main practice effects found on different training tasks. First, it is very reasonable to get improvements in performance on the trained tasks themselves. Second, there can be training effects on non-trained tasks that are measuring the same cognitive abilities or cognitive construct (i.e., near-transfer). Third, the training effects extend beyond particular cognitive aspects to other related cognitive and motor abilities: for example, as indicated, working memory training can transfer to fluid intelligence (i.e., far-transfer).

Among these positive and exciting results, some researchers made different voices. In one large-scale study including 11,430 participants, Owen and his colleagues (Owen et al., 2010) found no evidence for any generalized improvements in cognitive function following training on 12 different tasks, covering a broad range of cognitive functions. Redick et al. (2013) compared practice groups, who received an adaptive dual n-back training program or an adaptive visual-search training program, to a control group, overcoming common design limitations in previous studies (like no-contact control groups, single measures of cognitive constructs). Redick et al.'s study also did not find positive transfer effects. Shipstead (Shipstead, Redick & Engle, 2010) criticized the fact that researchers only appear to care about whether the training effects are present or not, while neglecting the mechanisms underlying the effects. The debate of training effects is far from settled, but advances

in functional Magnetic Resonance Imaging (fMRI), structural MRI and other neuroimaging tools, have enabled us to measure experience-dependent brain plasticity, which may help to shed further light on this debate.

Resting-State Functional Connectivity

“Our brain is a complex network of functionally and structurally interconnected regions” (van den Heuvel & Hulshoff Pol, 2010). To investigate the interconnections between brain regions, functional connectivity has been proposed to measure temporal coherence of neural activities of anatomically separated or adjacent brain regions (Friston, Frith, Liddle & Frackowiak, 1993). Regions whose blood oxygen level-dependent (BOLD) signal fluctuations show a higher degree of temporal coherence are presumed to constitute a tighter neural network. Greicius (Greicius, Krasnow, Reiss & Menon, 2003) firstly used fMRI to look at robust functional connectivities within the so-called default mode network during resting state. The existence of spontaneous neural networks indicates that even in the absence of a to-be-performed task, the exchange of information between neurons is still there. Thus it is arguable to speculate that the functional connectivity may support the intrinsic functional systems, and is always at its service to improve task performances whenever it is needed (van den Heuvel & Hulshoff Pol, 2010). Some studies also showed the relations between behavioral performance and functional connectivity strength. For example, frontoparietal brain networks are strongly associated with fluid intelligence and working memory (Cole, Yarkoni, Repovš, Anticevic & Braver, 2012),

and the creativity is positively correlated with the resting state functional connectivity (rs-FC) between medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC) regions (Takeuchi et al., 2012).

It has been shown that functional connectivity at rest may change after perceptual (Lewis, Baldassarre, Committeri, Romani & Corbetta, 2009), working memory (Jolles, Van Buchem, Crone & Rombouts, 2013; Takeuchi et al., 2013), reasoning training (Mackey et al., 2013), as well as with video game practice (Martínez et al., 2013). For example, Lewis and his colleagues (Lewis et al., 2009) demonstrated that resting-state functional connectivity between visual cortex and frontal-parietal areas, involved in the control of spatial attention, was significantly altered after intense training on a difficult shape-identification task. Moreover, Mackey et al. (2013) measured the training effects on participating in a 3-month reasoning instruction course designed to prepare the Law School Admission Test and found strengthened fronto-parietal and parietal-striatal connections after the course. Taken together, we argue that if the rs-FC is reconfigured after repeated cognitive practice, we could make the assertion with more confidence that training-specific plasticity should be exhibited.

But due to the small body of literature, it is still difficult to say if the rs-FC changes are accounted for by training. The present study is aimed at examining whether intensive cognitive training in higher cognitive functions exerts influence over the inherent functional connectivity associated with cognitive control and attentional networks, and if so, to what extent these changes may transfer to other non-trained functional neural networks, such as the ones supporting reading.

Cognitive Control

Cognitive control refers to the ability of shifting among a variety of novel situations and flexibly adapting behavior to the demands of particular goals. This ability, includes two fundamental subcomponents-interference suppression (the ability to filter out irrelevant information) and response inhibition (the ability to override improper but prepotent response tendency) (Bunge, Dudukovic, Thomason, Vaidya & Gabrieli, 2002). And cognitive control has been found to serve some high-level cognitive functions, such as working memory, second language study, and problem solving (Braver, Gray & Burgess, 2007; Passolunghi & Siegel, 2001; Rodriguez-Fornells, De Diego Balaguer & Münte, 2006).

Cognitive control could also make contributions to some more complex achievements and social topics, like academic success (Blair & Razza, 2007), the improvement of citizen's health and wealth and the reduction of crime (Moffitt et al., 2010), and the moral judgment (Greene, Nystrom, Engell, Darley & Cohen, 2004). Specifically, Blair's (2007) study showed that cognitive control ability accounts for unique and prominent variance in the academic success of childhood independent of intelligence quotient (IQ) scores. And compared with more self-control children as adults, Moffitt et al. (2010) found that when the children with less self-control grow up, they usually had worse health, less wealth, and commit more crimes. Thus, improving cognitive control abilities may not only benefit children immediately, but

also benefit their future careers and lives; possibly reducing the needs for special education and public costs for regulating antisocial behavior (Diamond et al., 2007).

The dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC) (Botvinick, Nystrom, Fissell, Carter & Cohen, 1999; Botvinick, Cohen & Carter, 2004; van Veen, Cohen, Botvinick, Stenger & Carter, 2001), and parietal cortex (Brass, Ullsperger, Knoesche, Von Cramon & Phillips, 2005) are mostly involved in cognitive control. Evidence has shown that positive correlations exist between brain activity in these regions and the cognitive control abilities (MacDonald, Cohen, Stenger & Carter, 2000). For example, MacDonald and his colleagues (2000) found that more activations in the left DLPFC in color naming task was associated with smaller interference effects. The DLPFC may be selectively involved in the preparatory period for cognitive control, through representing and actively maintaining the attentional demands of the task (MacDonald et al., 2000). The ACC, have a dissociable function with DLPFC, functions as part of a “control loop” (Solomon, Ozonoff, Ursu, Ravizza, Cummings, Ly & Carter, 2009), being more involved in the evaluative processes and in detecting cognitive conflicts. According to the proposed conflict-monitoring hypothesis, the ACC monitors the occurrence of conflicts in information processing and therefore engage other complementary systems to properly adjust the conflicts (Botvinick et al., 2004). The parietal cortex is engaged when attention must be switched between tasks (Ravizza & Carter, 2008; Yeung, Nystrom, Aronson & Cohen, 2006). Some researchers also argued that the

processing in posterior brain regions might be biased by prefrontal cortex because of its role in updating task representations (Brass et al., 2005; Miller & Cohen, 2001).

Research has showed that cognitive control abilities can be modulated by different training paradigms, such as video games (Anguera et al., 2013), go/no-go tasks (Thorell et al., 2009), flanker tasks (Thorell et al., 2009), Wisconsin Card Sorting task (Dowsett & Livesey, 2000), stroop tasks (Davidson, Zack & Williams, 2003), stop-signal tasks (Berkman, Kahn & Merchant, 2014), and even the acute cardiovascular exercise (Colcombe et al., 2004; Hillman, Snook & Jerome, 2003). Training effects have also been found by studies with older adults (Anguera et al., 2013; Davidson et al., 2003) and preschool children (Diamond et al., 2007; Dowsett & Livesey., 2000; Thorell et al., 2009). However, it is still largely unclear to what extent training induces neural changes in the brain networks supporting cognitive control abilities. To our knowledge, so far only few studies have investigated the neural changes associated with cognitive control training. For example, by using stop-signal task, Berkman and his colleges (2014) found that, after training, activity in the inferior frontal gyrus decreased during the stopping phase (i.e., inhibitory control implementation) and increased during cues phase (i.e., inhibitory control preparation) that preceded the stopping phase. However, among the limited amount of neuroimaging studies looking at the effects of training, no study has focused on middle childhood, which is an important period in terms of plasticity and development of high cognitive functions. So, part of the aim of our study was trying to fill the gap through studying the resting-state functional connectivity changes in

children aged 8 to 10 years among abovementioned regions supporting cognitive control abilities. All the regions involved in cognitive control in our study are presented in Table 1.

Table 1.

Regions implicated in cognitive control

Anatomical Group	Region	Hemisphere	Brodmann Area	MNI Coordinates		
PFC	Middle Frontal Gyrus	L	46	-45	38	31
	Middle Frontal Gyrus	R	10	39	47	28
	Inferior Frontal Gyrus	R	44	45	17	7
	Insula	L	13	-36	11	10
	Insula	R	13	33	20	10
Cingulate	Anterior Cingulate Cortex		24	3	29	25
Parietal	Superior Parietal Cortex	L	7	-33	-61	52
	Superior Parietal Cortex	R	7	33	-64	52
	Inferior Parietal Cortex	L	40	-45	-40	46
	Inferior Parietal Cortex	L	40	-48	-40	46
	Inferior Parietal Cortex	R	40	48	-46	55
Occipital	Lingual Gyrus	L	18	-12	-88	-14
	Lingual Gyrus	R	18	12	-91	-11

Note. MNI= Montreal Neurological Institute. L=Left, R=Right.

Attention

Attention is considered as one of the most important cognitive functions and has been widely examined in psychological research. It refers to the cognitive process that

selectively concentrating on certain aspects of our environment while ignoring distractors, or refers to some ideas in our mind that are stored in memory (Raz & Buhle, 2006). Posner and Petersen (1990) argued that the attention system could be divided into three subnetworks that perform different, but interrelated, functions. The *Alerting* network is involved in achieving and maintaining an alert state (when the target will occur); the *Orienting* network refers to the selection of information from the sensory inputs (where the target will occur); and the *Executive control* network, is defined as the network in charge of resolving response conflicts and regulating thoughts and feelings (Fan, McCandliss, Sommer, Raz & Posner, 2002).

Fan et al. (2002) have devised a simple attention network test (ANT), which is a combination of the cued reaction time (Posner, 1980) and the flanker task (Eriksen & Eriksen, 1974), and that can be used to separate the three attention networks (i.e., alerting, orienting and executive control) and measure them independently. Fan (Fan, McCandliss, Flombaum & Posner, 2001) collected fMRI images from 16 healthy adults performing the ANT and found that different anatomic regions subserved these distinct attention networks. Specifically, the alerting network showed the involvement of fronto-parietal regions along with the thalamic activation; the orienting network showed bilateral superior parietal activation; and the executive network showed anterior cingulate cortex and bilateral frontal activation.

Even though previous studies mainly showed that frontal and parietal regions in the right hemisphere are required to maintain the alert state (Coull, Frith, Frackowiak & Grasby, 1996), more recent studies also supported the involvement of left

hemispheric regions in the specific presentation of warning signals (Coull, Nobre & Frith, 2001). Some reviews (Posner, Sheese, Odludas & Tang, 2006; Raz & Buhle., 2006) further summarized that subcortical areas like the pulvinar, superior colliculus, and cortical areas such as superior parietal lobe, temporoparietal junction, superior temporal lobe and frontal eye fields are often activated in studies examining orienting network. Since, in the previous section on cognitive control, we have already reviewed and mentioned that the executive control network mainly involves the anterior cingulate and lateral prefrontal areas, here we will not discuss this again in the present section.

A developmental study conducted by Rueda et al.(2004) revealed the different developmental trajectories in these three attention networks with the alerting network maturing stably during middle childhood, but improving significantly from age 10 to adulthood; the orienting network showing no changes from 6 years to adulthood; and the executive attention network showing a strong development from 6 to 7 years of age and then keeping stable. Although several studies suggest the development of attention networks is highly determined by biological factors, it is still relevant to training, because important interactions between genetic and environmental factors still influence these networks. In their review, Petersen and Posner (2012) concluded that there are two main forms of intervention methods that have been used in the literature to train attention. One involves practice of a particular attention network, especially the executive control network. For example, several studies have found improvements in executive attention function and association between these changes

and brain responses (Rueda, Rothbart, McCandliss, Saccomanno & Posner, 2005).

The another one method used to train attention is meditation, which is also demonstrated that could produce important benefit in executive attention (Tang et al., 2007). Though the results from these studies have suggested that executive attention function is susceptible to training-induced changes, it is still hard to consider that the alerting and orienting networks can be also changed by interventions, especially considering that the three networks are independent (Fan et al., 2002; Rueda et al., 2004).

Therefore, another aim of our present study is trying to test if attention training can influence the rs-FC among regions involved in alerting and orienting networks. For doing so, the method of choosing ROIs for our analyses related to attention was the same one that we used to examine training effects in cognitive control. Based on functional activation during an attentional task involving alerting and orienting networks, we identified the local maximas within the main regions of interest and drawn 5-mm radius spheres centered at this local maximas. For the rs-FC analyses related to attention, we selected ROIs in the frontal (bilateral inferior frontal gyrus, left frontal eye field and right Precentral), parietal (bilateral inferior parietal lobe and bilateral supramarginal gyrus), temporal (right fusiform gyrus and right superior temporal gyrus), as well as other subcortical regions of interests (bilateral putamen and left thalamus) (see Table 2 for more details).

Table 2.

Regions implicated in attention (alerting and orienting attention)

Anatomical group	Region	Hemisphere	Brodmann Area	MNI Coordinates		
Frontal	Inferior Frontal Gyrus	L		-60	8	22
	Inferior Frontal Gyrus	R		66	5	10
	Frontal Eye Field	L	6	-27	-4	49
	Precentral Gyrus	R	4	36	-19	52
Parietal	Precuneus		7	0	-58	49
	Inferior Parietal Lobe	L	7	-42	-37	40
	Inferior Parietal Lobe	R	7	42	-64	37
	Inferior Parietal Lobe	R	7	36	-67	46
	Supramarginal Gyrus	L		-48	-52	28
	Supramarginal Gyrus	R		51	-55	25
Temporal	Fusiform Gyrus	R	37	39	-49	-23
	Fusiform Gyrus	R	37	36	-58	-17
	Superior Temporal Gyrus	R		48	-40	13
Occipital	Inferior Occipital Gyrus	L	17	-21	-94	-8
	Inferior Occipital Gyrus	R	19	36	-67	-17
	Inferior Occipital Gyrus	R		42	-79	-14
	Middle Occipital Gyrus	L	19	-42	-70	-14
	Middle Occipital Gyrus	R	18	30	-88	1
	Middle Occipital Gyrus	R	18	24	-97	-2
Subcortical	Putamen	L		-24	5	-5
	Putamen	L		-24	-7	7
	Putamen	R		24	5	7
	Putamen	R		27	2	-5
	Medial Dorsal Nucleus	L		-12	-19	10

Note. MNI= Montreal Neurological Institute. L=Left, R=Right.

Transfer Effects and Reading

There are several ways of evaluating the effectiveness of cognitive training. The most obvious criterion is the to examine the performance on the trained task.

Nevertheless, improvements on the trained task can just owe to the practice and familiarity effect. For that reason, it is important to find training effects in near-transfer tasks, even far-transfer tasks, before we claiming that the specific training task is effective. Several studies have demonstrated the increased performance could emerge on tasks that were highly similar to trained tasks or on tasks within the same cognitive domain (Bergman Nutley, Söderqvist, Bryde, Thorell, Humphreys & Klingberg, 2011; Holmes, Gathercole & Dunning, 2009; Thorell et al., 2009). Also, other studies, found the generalization of training effects to some other seemingly disparate domains (Chein & Morrison, 2010; Houben, Wiers & Jansen, 2011; Jaeggi et al., 2008; Thorell et al., 2009). One interpretation of the transfer effect is that training may target some domain-general mechanisms which could be utilized to support different functions (Chein & Morrison, 2010). For example, Dahlin (Dahlin, Neely, Larsson, Bäckman & Nyberg, 2008) found that transfer effects could occur on an untrained 3-back task, but not on an untrained Stroop task after five weeks of training with updating tasks (a test of letter memory). The authors explained that the differences of specific overlapping processing components (updating) and engaged brain regions (striatum) between trained task and transfer tasks may be the cause of the differences in transfer. Because the 3-back task requires updating processes, but not the Stroop task; the 3-back task and updating task both activate the striatum, which is not the case of Stroop task. To date, it is still not clear to what extent the overlap, of the cognitive domains or the regions supporting functions, between

training and transfer task should be to result in transfer effects (Buschkuehl, Jaeggi & Jonides, 2012).

There are a few studies have showed that the training effect of working memory can transfer to the reading performance (Chein and Morrison, 2010; Horowitz-Kraus & Breznitz, 2009; Karbach, Strobach & Schubert, 2014; Loosli, Buschkuehl, Perrig & Jaeggi, 2011). Nevertheless, to date no study has investigated the transfer effects from cognitive control and attention training to reading performance. However, executive skills have been proposed by early researcher (Brown, 1980) that it could contribute to reading performance by means of monitoring and controlling reading processing.

With respect to attention, a 3 year longitudinal study revealed that pre-reading attentional orienting in preschoolers can predict future reading acquisition after controlling for age, nonverbal IQ and other confounding variables (Franceschini, Gori, Ruffino, Pedrolli & Facoetti, 2012). Even, research on cognitive neuroscience has indicated that cognitive control and reading may share some common neural areas.

For example, the left inferior frontal gyrus (IFG), which is critical for successful implementation of inhibitory control (Swick, Ashley & Turken, 2008), is also involved in both phonological awareness and phonological naming ability, and activity in this region could be a good predictor of the reading ability (Turkeltaub, Gareau, Flowers, Zeffiro & Eden, 2003). Thus combined with Dahline et al's hypothesis (2008), it makes intuitive sense that training cognitive control and attention may contribute substantially to the improvements on the transfer task: reading.

To test if the transfer effect could occur on the rs-FC of reading, we chose the regions activated in our prior fMRI reading task as seeds, and included the left inferior frontal gyrus, bilateral superior parietal, bilateral middle cingulum, left temporal lobe, left superior temporal gyrus and visual word form area (see Table 3 in for all the regions used), which were corresponded with most areas discovered in other publications.

In summary, our study is trying to fill the gap of training effects on resting state functional connectivity in healthy middle school children by investigating changes in coactivation among a broader set of brain regions engaged in cognitive control, orienting and alerting attention, and to examine the extent to which the trained tasks may account for changes in interconnections among regions involved in reading performance.

Table 3.

Regions implicated in reading

Anatomical group	Region	Hemisphere	Brodmann Area	MNI Coordinates		
Frontal	Inferior Frontal Gyrus, triangular	L	45	-48	35	4
	Inferior Frontal Gyrus, triangular	L	45	-48	26	22
	Inferior Frontal Gyrus, opercular	L	44	-42	5	28
Parietal	Superior Parietal Gyrus	L	7	-27	-61	49
	Superior Parietal Gyrus	R	7	33	-58	49
	Supramarginal Gyrus	L		-54	-64	31
Cingulate	Angular Gyrus	L	39	-48	-70	34
	Median Cingulate	L		-3	5	25
	Median Cingulate	R	24	6	-1	28
Temporal	Temporal Pole	L	38	-54	2	-8
	Temporal Pole	L	38	-54	11	-11
	Superior Temporal Gyrus	L	22	-48	-40	7
	Superior Temporal Gyrus	L	22	-57	-34	4
	Visual Word Form Area	R	37	-42	-61	-14
	Fusiform Gyrus	L	37	-45	-52	-17
	Fusiform Gyrus	L	37	-39	-52	-14
	Fusiform Gyrus	L	37	-39	-40	-17
Occipital	Inferior Occipital Gyrus	L	17	-18	-94	-8
	Inferior Occipital Gyrus	L	18	-27	-88	-11
	Inferior Occipital Gyrus	L	18	-39	-79	-14
	Inferior Occipital Gyrus	R		30	-82	-8
	Inferior Occipital Gyrus	R		36	-85	-8
	Inferior Occipital Gyrus	R		24	-91	-8
Subcortical	Putamen	L		-21	-1	10
	Putamen	L		-24	5	1
	Thalamus	L		-12	-13	13
	Hippocampus	L	28	-18	-13	-17

Note. MNI= Montreal Neurological Institute. L=Left, R=Right.

Methods

Participants

Participants were recruited through schools in San Sebastian, Spain. The study was approved by the Basque Center on Cognition, Brain and Language (BCBL) Ethics Committee. Participants received small toys and educational materials for their participation in the study.

The final study sample consisted of 41 right-handed children aged 8 to 10 years ($M = 9.41$ years; $SD = .49$ years; range = 8.10-10.12 years) distributed in two groups: the experimental group included 20 children (11 females), and the control group included 21 children (12 females). A chi-square test confirmed that sex distribution did not differ between the two groups ($\chi^2(1)=0$, $p>0.05$). Data from 9 additional participants were excluded due to excessive head motion (6 participants) or coregistration problems due to participants' motion during the acquisition of the T1-weighted structural sequence (3 participants).

Participants had no history of psychiatric or neurological disorder, and no history of attention or learning disorders. All participants were fluent in Spanish. The Kaufman Brief Intelligence Test (K-BIT; Kaufman & Kaufman, 1990) was administered to the participants to measure their general intelligence. The test provides a measure of crystallized (Verbal) intelligence and a measure of fluid reasoning (Matrices) as well as a composite intelligence (total IQ) score. In order to avoid differences in the general IQ between the two study groups, participants were initially assigned to the control or the experimental groups controlling for differences

in these measures. As expected, in the final study sample, the trained group and the control group did not differ significantly in any of these measures, including the K-BIT raw and standardize Vocabulary and Matrices measures as well as in total IQ score ($F(1,40)<1$, $p>.05$) (see table 4 for more demographic information about the final study sample).

Table 4

Participants' information

	Trained (n=20)	Control (n=21)
Gender	11F/9M	12F/9M
Age	9.39 (0.36)	9.43 (0.59)
K-BIT		
Vocabulary (raw)	43.9 (6.29)	47 (4.13)
Vocabulary (normalized)	100.15 (14.23)	106.95 (8.43)
Matrices (raw)	29.1 (5.03)	30 (5.50)
Matrices (normalized)	106.4 (13.43)	108.29 (14.60)
Total IQ	101.4 (13.72)	106.38 (11.95)

Note. Means and SDs in two groups are reported for individual variables and K-BIT measures at pre-training. No statistically significant differences between groups were observed in any of these measures and individual variables with student's t test (all $p>.05$).

Training paradigm

The training program was the same as the one used by Rueda et al. (Rueda et al., 2005, Rueda, Rothbart, Saccomanno & Posner, 2007) adapted for their use with

middle childhood children. The program consists of a total of 12 computerized exercises divided in 4 categories: (1) Tracking/Anticipatory, (2) Attention Focusing/Discrimination, (3) Conflict Resolution, and (4) Inhibitory Control. All the exercises were programmed in a child-friendly manner and involved giving responses with a keyboard. All exercises required completion of a number of trials organized in increasing levels of difficulty. Children in the experimental group progressed up to the highest levels of the difficulty of all the games. The control group was only presented with the lower levels of difficulty of all the games, spending approximately the same time with the experimenter as children in the experimental group.

Exercises in the Tracking/Anticipation category were designed to teach children to track a cartoon cat on the computer screen by using the mouse, and monitor the position of other cartoons in the screen. In the Side exercise the child is asked to take the cat to the grass while avoiding going into the mud. As the child achieves higher levels, the mud area gets progressively bigger and the grass area gets smaller, increasing the difficulty to control the movement of the cat. In the Maze exercise, children help the cat to get food by navigating it through a maze to where the food is. Finally, in the Chase exercise children must anticipate the location where a duck that swims across a pond in a straight line will come across in order to chasing it. In a second version of the exercise (Chase Invisible), the duck becomes invisible when it goes into the pond, as if diving, so that its trajectory remains invisible.

The exercises in the Focusing/Discrimination category have two types. The first type consists on matching-to-sample games, in which children have to click on the

one of two pictures that looked exactly the same as a sample picture. Similarities between the two options increased progressively, requiring the child to pay closer attention. There are two versions of the exercise. In this first version (Portraits), the sample picture remains on the screen while the child selects the matching item. In the second version (Portraits Delay), the sample picture disappears forcing the child to keep in mind the attributes of the sample picture.

The second type of exercises on Attention Focusing/Discrimination consist of the presentation of a number of overlapping figures (Shapes) and the child's task is to determine which are the ones presented by clicking on the appropriate buttons displayed on the sides of the screen. Difficulty is augmented in successive levels by increasing the number of overlapping shapes and the complexity of the patterns.

The Conflict Resolution exercises consisted of Stroop-like games with numbers. In the first one (Number of Numbers), children are presented with two sets of items. Their job is to click in the group composed by the larger amount of items. In the first levels of the exercise, sets consist of pictures of fruits and the number of items in each group differs by a large amount (e.g., two compared to eight). As the difficulty levels increase, the two sets are made of digits, and therefore trials can be congruent (when the larger set of digits is formed by digits of higher value, for example four numbers 8 vs. two numbers 1) or incongruent (when the larger set of digits is formed by digits of smaller value, for example six numbers 2 vs. four numbers 9). The second Stroop-like exercise (Value-Not-Size) also involves numbers, but in this case the conflicting dimensions are value and size. In successive trials, various numbers (either two, three

or four), which differ in size, are presented and children are asked to click on the number of higher value disregarding the size. Again, there can be congruent (the larger number is the one with higher value) or incongruent (the larger number is not the one with higher value) trials (Figure 1). To go on from one difficulty level to the next, children must correctly perform three incongruent trials in a row. Before performing these exercises, children completed another exercise in which their knowledge of Arabic digits was practiced.

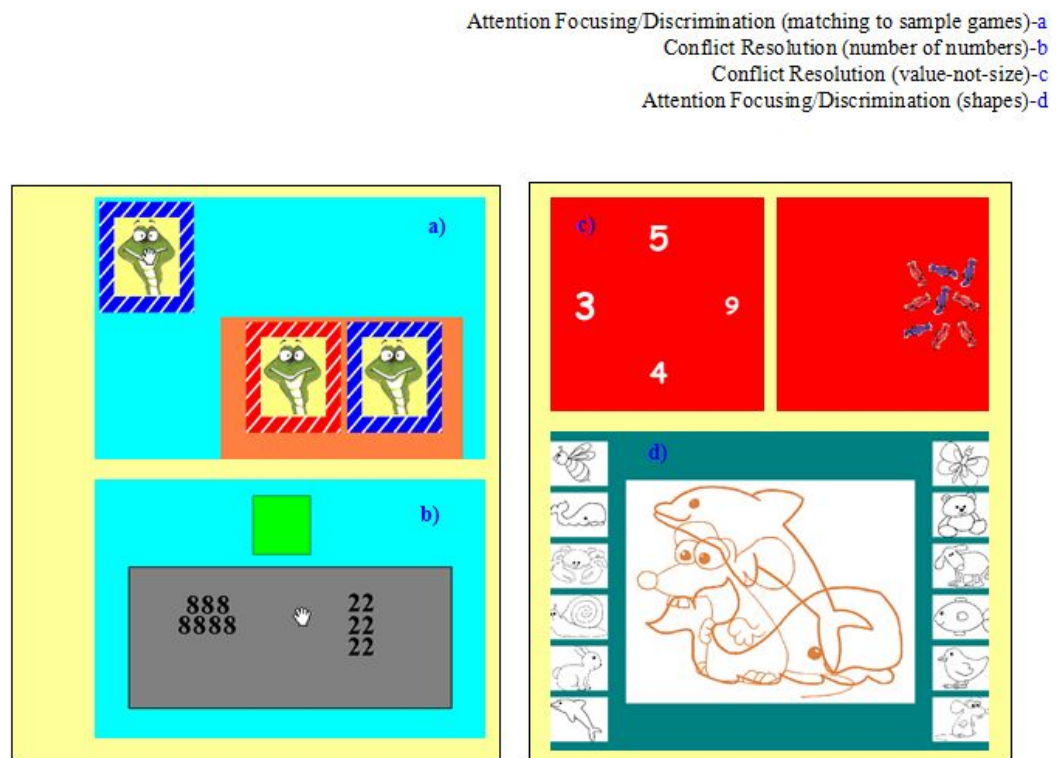


Figure 1. Examples of the games used in the Attention Focusing/Discrimination and Conflict Resolution training dimensions.

The exercise (Farmer) included in the Inhibitory Control category consisted of a Go/No-Go game in which the child's job is to help a farmer taking sheep inside a fence. The picture of a bale of hay is displayed in the middle of the computer screen.

Children click on the bale of hay to find out whether the animal behind it is a sheep or a wolf. If the animal is a sheep the child is asked to click as quick as possible to make it go inside the fence, whereas the response must behold to the wolf. In advanced levels, the wolf dresses-up as a sheep and only after a short interval it losses its mask and reveals its identity, making the response inhibition more challenging. Finally, a category of Sustained Attention was included. This consists of one exercise (Frog) in which children are asked to help a frog catch flies that come out of a bottle at a particular time rate. The child must press a key as fast nas possible in order to unroll the frog's tongue and catch the fly. In some trials, the fly makes a noise before coming out of the bottle. The requirement of sustaining attention is increased across blocks of trials by enlarging the interval of time between flies.

Procedure

Children underwent two separated MRI sessions where functional and structural data were acquired. Between these MRI sessions, participants attend to a total of 8 individual behavioral sessions of 30-40 minutes of duration each distributed in 2-3 weeks. During these behavioral sessions, children either received the complete training program progressing on the different levels of difficulty of the games (i.e., experimental group), or just kept playing at the lower levels of difficulty of the same games (i.e., control group).

The MRI sessions were separated by no more than 4 weeks. At the scanner children perform three different functional tasks in both sessions: 1) The Dots task

(Davidson, Amso, Anderson & Diamond, 2006) intended to measure cognitive control;

2) A variation of the ANT task specifically intended to measure the alerting and orienting attention networks; and, 3) a semantic decision reading task including words, pseudowords, and consonant strings. All these tasks require button presses to all the trials and examine accuracy and reaction times.

Imaging acquisition

Functional and structural images were acquired on a Siemens 3-T whole-body MRI scanner with a 32-channel headcoil at the BCBL. The resting-state functional sequence used a gradient echo EPI with TR=2s, TE=25ms, 35 descending 3-mm cubic axial slices, FOV=240mm, flip angle=78°, matrix=64 × 64, slice thickness/gap=3/0.75mm, and 180 volumes. During the resting-state scans, the participants were instructed to passively lay in the scanner while fixing their eyes on small cross on the screen. Each participant was scanned for approximately 7 mins. Prior to time-series acquisition, a 6.5 minutes' T1-weighted (MPRAGE) anatomical scan (TR=2530ms, TE=2.97ms, matrix=256 × 256, effective voxel resolution of 1 × 1 × 1 mm, flip angle=7°, slice number=176) was acquired to aid spatial normalization to standard atlas space. In order to minimize motion, subjects' heads were stabilized in the head coil using foam pads over each ear and also over the top of the head. All participants were scanned twice before and after the behavioral training.

fMRI Data Analyses

Preprocessing

fMRI data were preprocessed with DPARSF (Data Processing Assistant for Resting-State fMRI) version 2.3 (Yan & Zang, 2010). The software is a plug-in software based on SPM8 (<http://www.fil.ion.ucl.ac.uk>) and REST version 1.8 (http://www.restfmri.net/forum/REST_V1.8) (Song et al., 2011). The following preprocessing steps were performed by DPARSF by calling functions in SPM8 at the single-subject level. We first discarded the first 6 volumes (174 volumes left) out of the consideration of steadiness of MRI signal and the adaptation of subjects. The remaining images were preprocessed with the following steps: slice-timing correction; head motion correction and followed by spatial smoothing with 4mm full-width at half maximum (FWHM). Studies have shown that head motion exerts substantial and systematic effects on resting-state functional connectivity estimates (Satterthwaite et al., 2012; Van Dijk, Sabuncu & Buckner, 2011). Since in-scanner head motion is significantly related to age (Satterthwaite et al., 2012), young children tend to move more than adults in the scanner and it was more necessary to control for the effect of head motion on connectivity in our study.

To quantify the effect of head movement on the quality of the data, we inspected the data using the ArtRepair toolbox for SPM8 (Mazaika, Whitfield-Gabrieli & Reiss, 2007), and the realignment parameters used in ArtRepair were generated after the SPM8 head motion correction procedure. Of particular interest is the scan-to-scan (incremental) motion during the scanning, i.e., the change in position between two

successive images. The criteria for exclusion were that 20% of volumes in one participant were showing inter-volume movements greater than 2.0 mm, and based on this criterion, we excluded 5 participants from the control group and 1 participant from the experimental group. The remaining 44 participants were corrected with linear interpolation from the nearest unrepaired volumes to ensure no incremental motion was above 2.0 mm.

Then the T1 images were coregistered to the mean fMRI scans got from realignment. After that, the T1 images were transformed to the coordinates of the Montreal Neurological Institute (MNI) standard space and resampled to $3 \times 3 \times 3 \text{ mm}^3$ voxels. This transformation was applied to the Artifact repaired resting state fMRI images to convert them to MNI space. After the coregistration, we visually checked the registration results and excluded 1 subject from the control group and 2 subjects from the experimental group. After spatial normalization, we smoothed the remaining 41 subjects with a 3mm FWHM Gaussian kernel, since our first smoothing kernel was 4mm, the two smoothing had a similar effect with a 5mm Gaussian kernel in one time. A linear trend correction (Tanabe, Miller, Tregellas, Freedman & Meyer, 2002) was applied to all smoothed images by calling functions in REST to remove any residual drift, followed by using band-pass filter with cutoff frequencies of 0.009 and 0.08Hz to remove high-frequency noise and very low-frequency signals from the images.

Before the functional connectivity analysis, 9 nuisance signals were regressed out from the time series of each voxel via multiple linear regression, including white matter (WM) signal, cerebrospinal fluid (CSF) signal, the whole-brain signal, and the

6 head motion parameters. The WM and CSF signal were generated by averaging the times series of all voxels within the WM and CSF masks produced by the T1 image segmentation procedure. Even after controlling for the 6 motion parameters, the motion artifacts remains in the data, so we used the scrubbing method proposed by Power (Power, Barnes, Snyder, Schlaggar & Petersen, 2012) to further damp the influences of motion on following rs-fMRI functional connectivity analyses (a minimum of 1 mm frame displacement, 1 volume before displacement, 2 volumes after displacement). The volumes did not meet the threshold were deleted.

Selection of seed regions

Data from the abovementioned functional tasks on cognitive control, attention and reading were used to identify the local maximas showing task-related increases and decreases in activity within regions of *apriori* interest. To make all the ROIs uniform in size and more anatomically precise, we build 5-mm radius spheres surrounding the coordinates of maximal activation values (for all the regions we used, see table 1, 2 and 3 in Appendix). Then we used a ROI-wise correlation approach to examine functional connectivity changes within three networks that were involved in the cognitive control, alerting and orienting attention, and reading, respectively. For each network, we extracted the time courses from one ROI and defined the correspondence of time courses between this region and all other ROIs within the network.

Functional connectivity statistical analysis

The averaged time courses were extracted from each seed region in each volume, Pearson correlations coefficients for each pair of regions were calculated with the REST software, then the correlation maps were converted into z map by Fisher's r-to-z improve the normality of these coefficients. Paired t tests comparing pre-training and post-training data were performed for both experimental and control groups. We also used independent t test to compare the group connectivity intensities on pre- and post- training. The correlations showing significant differences between experimental and control group at the pre-training were excluded from the analysis. We used the false discovery rate (FDR) with an alpha level of 0.05 to correct the multiple comparisons.

To visualize the spatial distribution of correlation changes, we projected the correlation strength of paired areas, showing significant increased and decreased connections, onto the brain surface using the BrainNet viewer (www.nitrc.org/projects/bnv) (Xia, Wang & He, 2013).

Results

We used resting-state functional connectivity to examine if training higher cognitive functions lead to changes in pair-wise connectivity among the brain regions involved in cognitive control, orienting and alerting attention, and reading functions.

Since our main interest was to examine changes resulted from cognitive training, the pair-wise comparisons that showed significant differences between pre- and post-training in the Experimental group were considered the changed pairs, after controlling for the changes between pre- and post-training in the Control group. Moreover, we further excluded the pairs showing significant differences between the two groups in pre-training to minimize the interferences of potential differences between these two groups. We conducted this control procedure across every function network analysis here examined: Cognitive Control, Attention, and Reading.

Cognitive Control Network

We extracted time series from 13 structural regions (listed in Table 1), and constructed a correlation matrix with 78 pairs. The paired t test was applied in both Experimental and Control groups, to compare the correlation values between pre- and post-training. Four pairs showed significant changes in the Experimental group (all $p < 0.05$) and only 1 pair had a p -value of < 0.05 in the Control group. Among the four pairs showing changes in Experimental group, all of them survived to the rigorous abovementioned control procedure to examine for training-related changes. Within these pairwise correlations, the correlation coefficients of left IFG and right inferior parietal cortex (IPC), right IFG and bilateral superior parietal cortex (SPC) increased from pre- to post-training (all $p < 0.05$), whereas, the correlation value of anterior cingulate cortex (ACC) and right middle frontal gyrus (MFG) decreased from pre- to post-training ($p < 0.05$) (see Figure 2).

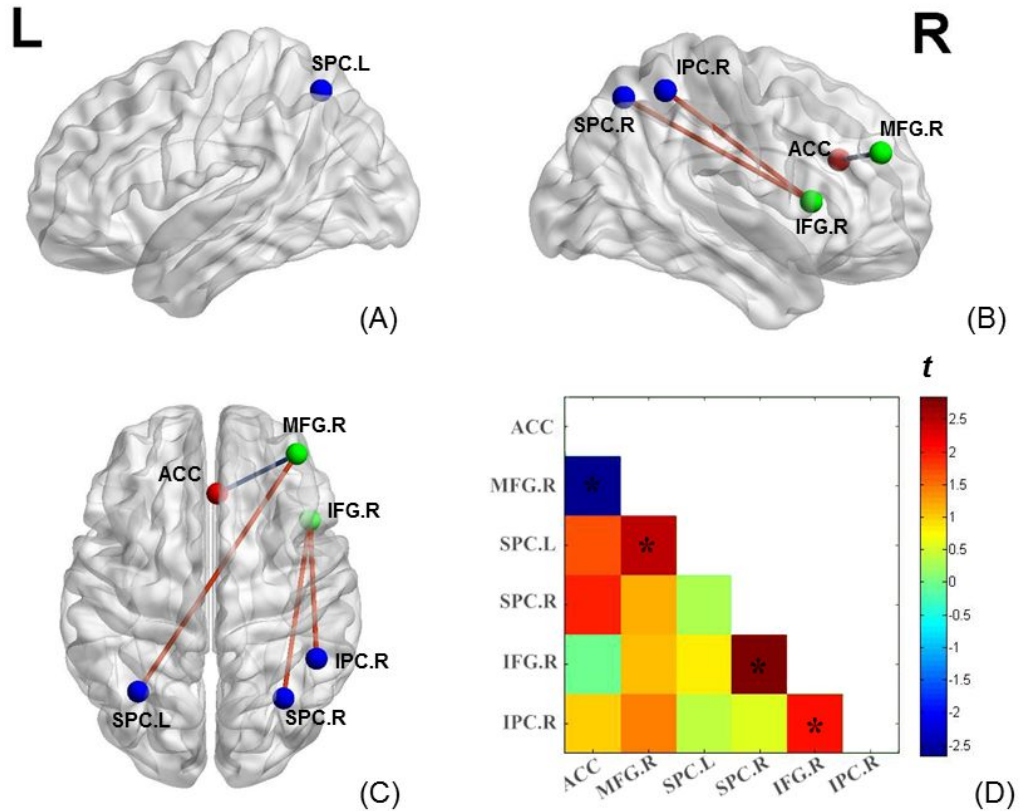


Figure 2. Significant changes in pairwise correlations between pre- and post-training in the Experimental group within the cognitive control network. (A) (B) and (C) sections show results (nodes and edges) in left and right sagittal and axial views, respectively. For the nodes, frontal regions were colored in green, cingulate cortex in red, and parietal regions in blue. For the edges, red indicates a significant increase in the strength of correlation from pre- to post-training, and blue indicates a significant decrease. (D) Correlation matrix showing the magnitude of change for all pairwise comparisons among nodes. The color bar on the right indicates the t values distribution of these pairs in the form Post-training > Pre-training. Asterisks denote statistically significant changes.

Alerting and Orienting Attention Networks

We extracted time series from a total of 24 structural regions (see Table 2).

Nevertheless, since in this case several local maximas were found within the same big regions, we just selected some of them to report in the analyses, and ended up with a correlation matrix of 18 regions. In this simplified matrix, we used the same control procedure used in the cognitive control analyses (i.e., excluding changes between pre- and post-training in the Control group and pairs showing significant differences between the two groups at pre-training), and found that significant differences in the strength of coactivation before and after training were detected in 14 pairs. Half of these changes corresponded to significant increases in the correlation strength among nodes, and the half remaining corresponded to significant decreases in correlation strength (Figure 3).

The functional connectivity of the left frontal eye field (FEF) and left IFG, the left FEF and right putamen (PUT), the left inferior parietal lobe (IPL) and bilateral IFG, the right FFG and right PUT, the right FFG and right inferior occipital gyrus (IOG), and the left PUT and left thalamic medial dorsal nucleus decreased after training.

Compared with the widely distributed decreased correlations in brain, the increased ones mostly involved connections with the selected parietal lobe regions [precuneus (PCUN), right IPL, left supramarginal Gyrus (SMG)], including connections with the frontal lobe [right IPL-left IFG, right IPL-precentral (PreCG)], with the temporal lobe [left SMG- right FFG], with the Occipital lobe [PCUN-left IOG], and with subcortical regions [right IPL-right PUT, right IPL-left thalamic medial dorsal

nucleus]

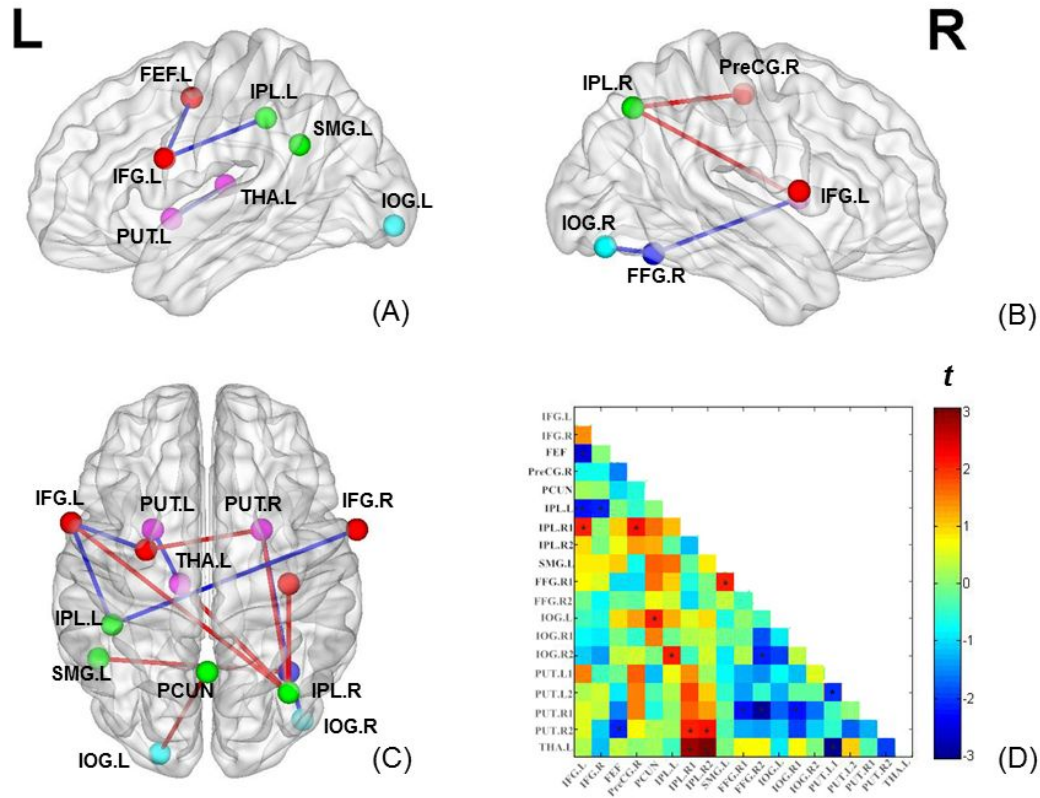


Figure 3. Significant changes in pairwise correlations between pre- and post-training in the Experimental group within the alerting and orienting attention networks. (A) (B) and (C) sections show results (nodes and edges) in left and right sagittal and axial views, respectively. For nodes, frontal regions were colored in red, parietal regions in green, temporal regions in deep blue, occipital regions in light blue, and subcortical regions in pink. For the edges, red indicates a significant increase in the strength of correlation from pre- to post-training, and blue indicates a significant decrease. (D) Correlation matrix showing the magnitude of change for all pairwise comparisons among nodes (including subregions). The color bar on the right indicates the t values distribution of these pairs in the form Post-training > Pre-training. Asterisks denote

statistically significant changes.

Reading Network

Similar to the previous attention networks analyses we extracted time series from a total of 27 local maximas identified from the reading task (see Table 3) and constrain our correlation matrix to 25 regions. Interestingly, we found that the effects of training higher cognitive functions did transfer to untrained reading-related regions. After training, we observed a significant decrease in functional connectivity among 12 pairs and a significant increase in functional connectivity among 8 pairs (see Figure 4). More specifically, the bilateral middle cingulate cortex (MCC) exhibited several of the decreases in strength of coactivation, showing that pattern in relation to its connections with right Visual Word Form Area (VWFA), left IOG, and right IOG. In addition, trainings also weakened the functional connectivity between left IFG and left PUT, left IFG and Left hippocampus, left temporal pole (TPO) and left PUT, left TPO and left thalamus (THA), left superior temporal Gyrus (STG) and left PUT, and left STG and left THA.

On the other hand, training strengthened functional connectivity among parietal lobe regions [connectivity between left superior parietal gyrus (SPG) and left IFG, left SPG and left STG, left SMG and left FFG, left angular gyrus and left MCC] and temporal lobe regions [connectivity between left TPO and bilateral IOG, left TPO and right VWFA, left STG and left FFG].

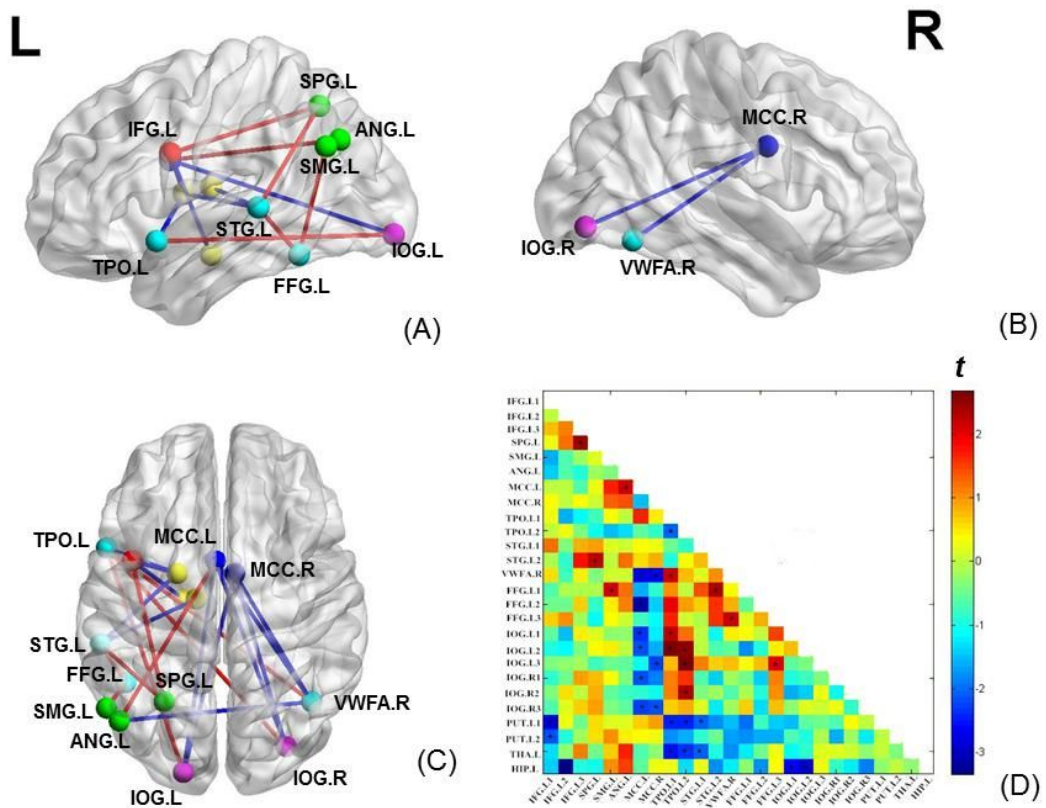


Figure 4. Significant changes in pairwise correlations between pre- and post-training in the Experimental group within the reading network. (A) (B) and (C) sections show results (nodes and edges) in left and right sagittal and axial views, respectively. For nodes, frontal regions were colored in red, parietal regions in green, temporal regions in light blue, occipital regions in pink, cingulate cortex in deep blue, and subcortical regions in yellow. For the edges, red indicates a significant increase in the strength of correlation from pre- to post-training, and blue indicates a significant decrease. (D) Correlation matrix showing the magnitude of change for all pairwise comparisons among nodes (including subregions). The color bar on the right indicates the t values distribution of these pairs in the form Post-training > Pre-training. Asterisks denote statistically significant changes.

Discussion

The present study revealed that practice on tasks requiring high-level cognitive functions are associated with changes of intrinsic brain connectivity within functional networks related to the trained functions (i.e., cognitive control, attention), and that these practice effects can also be transferred to the underlying connectivity pattern of untrained functions (i.e., reading). Across the three different networks here examined, we found connectivity changes mainly occurred on frontal, temporal and parietal regions. Interestingly, based on prior evidence, networks involving these regions are known to be implicated in a wide variety of complex cognitive functions, including the ones we trained in the present study and also other fundamental functions such as working memory (Jolles et al., 2013), reasoning (Mackey et al., 2013) and visuospatial abilities (Lewis et al., 2009). Thus, it is reasonable to speculate that the frequent coactivation of these regions during training resulted in the functional connectivity changes we observed in the present study (Martinez et al., 2013).

Consistent with prior studies showing tighter coupling between regions after training, overall, almost half of the observed changes in functional connectivity in the present study involved increased connectivity. This pattern was more evident in the cognitive control network. Among the three pairs showing an increase, two pairs were related to the right IFG, which is consistently activated in task-switching and set-shifting paradigms as showed by quantitative meta-analyses (Derrfuss, Brass, Neumann & Von Cramon, 2005). Studies also demonstrated that the IFG is involved in the activation of task representations, a process that allows to adjust behavior in

advance in the context of changing environmental demands (Brass, Derrfuss, Forstmann & Cramon, 2005). In the present study, right IFG showed correlational increases with parietal lobe, including the right IPC and right SPC. SPC is thought to play as a domain-independent locus of cognitive control, initiating shifts in spatial attention, and switches in categorization rules (Chiu & Yantis, 2009), and IPC is also activated in multiple control processes (Fassbender et al., 2006).

Buschkuehl et al. (2012) summarized four classes of activation patterns as a consequence of training. In these patterns, one is commonly observed with increased activation after training, which could be explained as an expansion of the neural structures involved in processing (Buschkuehl et al., 2012), or a stronger neural response in existing areas (Kelly, Foxe & Garavan, 2006). Another common pattern is related to the fact that activation still occurs in the same regions after training, but these regions show a decreased activation. In our study, the correlation between ACC and right MFG decreased after training, which is congruent with Berkman et al.'s (2014) study results. In their study, dorsal ACC and the posterior right MFG showed decreases in activation during inhibitory control implementation when comparing pre- and post-training in the Experimental group.

One of the possible interpretations for the decreases in connectivity and activations is related to the neural efficiency hypothesis (Haier et al., 1988; Neubauer & Fink, 2009; Sayala, Sala & Courtney, 2006). According to this hypothesis, with practice, the information processing is more efficient: less neurons are needed to maintain the same, or even better, performance. However, it is still unclear why after

training some regions show increased activation and connectivity, whereas other regions show decreased activation and connectivity.

Another explanation for the decreased coactivation found in training studies is practice time. Hempel et al. (2004) reported an inverted U-shaped activation pattern after training over time. In their study they found that relevant regions showed activation increases with improved performance after 2 weeks of training, but also activation decreases after 4 weeks of training. Similarly, Ma et al. (2011) tested whether rs-FC would change after 4 weeks of motor skill learning, and found that the strength of the connectivity between some pairs increased from Week 0 to Week 2, and decreased from Week 2 to Week 4; at the same time that other coactivations among regions increased throughout the entire period of time (Ma, Narayana, Robin, Fox & Xiong, 2011). Therefore, it is possible that regions have different plasticity in response to the effect of training, reflected different changes in connectivity patterns.

Our results suggest that increased connectivity mainly occurred among pairs of nodes in parietal regions. This finding is in agreement with prior evidence indicating that the parietal cortex controls the ability to orient attention in space (Bisley & Goldberg, 2003; Han et al., 2004; Rushworth, Ellison & Walsh, 2001). Also, in relation to Neubauer and Fink's (2009) study results, our findings are partially consistent with their findings that decreased connectivity after training mainly occurred in frontal areas, but not in parietal areas.

The relationship between alerting and orienting is still not clear (Raz & Buhle, 2006), but the bulk of evidence suggests that both attention networks are functionally

distinct (Fernandez-Duque & Posner, 1997; Fan et al., 2002) and anatomically disperse (Fan, McCandliss, Fossella, Flombaum & Posner, 2005). Based on previous studies, we are curious about if the orienting and alerting networks would show different connectivity patterns after training, unfortunately, they did not show strong differences in the neural dynamics between the main nodes related to each of these networks.

Transfer effects on training can occur on some far-related functions, indicating that something fundamental may have changed other than only task-specific strategies or stimulus-specific representations (Kundu, Sutterer, Emrich & Postle, 2013). As expected, after training, the connectivity within reading-related brain regions changed. Since the reading-related network has extensive overlap with the networks of the other two trained functions, especially in parietal and frontal regions; it is not surprising that we found changes in pairwise correlations involving these areas. But, what is more interesting, for the reading network analysis we found some functional connectivity changes in regions in the cingulate and temporal cortex, which are not typically implicated in attention and cognitive control. For example, the VWFA in the left fusiform gyrus, a region widely known for its involvement in reading words and word-like orthography (Cohen et al., 2000), showed increased connectivity with left STG after training. The left STG is included in Wernicke's area and it is typically involved in speech perception (Scott & Wise, 2004). The left temporal pole, another region that is not typically involved in attention and cognitive control, but is linked to the level of specificity of word retrieval and combinatorial semantics (Grabowski,

Damasio, Tranel, Ponto, Hichwa & Damasio, 2001), also showed coactivation changes (in both directions: increasing and decreasing correlations), specifically with occipital cortex and subcortical regions.

Why these untrained areas were also affected? The model of human brain connectome may help us to interpret this result. In this model, some areas have different weights in their implication in the complex whole brain network, such as regions along cortical midline, the temporo-parietal junction, and frontal areas (Alstott, Breakspear, Hagmann, Cammoun & Sporns, 2009). In fact, the lesion of these regions may have an strong impact in many relevant dimensions. Probably, the training induced changes in some of these highly relevant regions, such as parietal and frontal areas, would also impact the whole brain connectivity. As previous researches indicated, not only regional changes with learning, changes on a more global level would also happen as a result of practice/learning (Bassett, Wymbs, Rombach, Porter, Mucha & Grafton, 2013). Thus, we hypothesize that the trained tasks we used here may changed the configuration of the whole brain network, determining also to some extent the transfer effects we observed.

Although our study provides strong neuroimaging evidence to support training effects and their transfer to untrained reading-related network, it has several potential limitations. First, since all the participants were trained by means of different games focused on several higher cognitive functions, it remains to be determined if these tasks have different weights in regard to their influence in the observed changes in cognitive control and attention networks, and the transfer to the reading network.

Second, one might argue that changes in functional connectivity after training could be related to reduced scanner-related anxiety during the post-training scans. Although we can not rule out this possibility, in our study we tried to minimize the anxiety and stress of participants in our experiment across both pre- and post-training MRI sessions. Given that the effects of anxiety and sleep could possibly affect rs-FC (De Havas, Parimal, Soon & Chee, 2012; Seeley et al., 2007), it is recommended that these physiological variables should be reported in future work to control for potential individual and group differences. Third, evidence linking the observed changes in connectivity to behavioral improvements in this study is lack. Further analyses should be conducted to confirm correlations between the observed changes in rs-FC and behavior. Fourth, when we applied FDR multiple comparisons corrections to the statistical analyses performed in this study, no result remained significant. This may increase the risk of type-I errors and undercut the credibility of our results in some extent. In addition, these pairwise correlations, which are considered specifically related to training tasks, did not differ significantly in the comparison between Experimental and Control groups at post-training, which suggests that despite the fact training effects did exist, they did not survive this comparison between groups at post-training. Lastly, it is unknown for how long these functional connectivity changes will remain after training. Some behavioral studies have shown that cognitive training can be effective and long lasting (Günther, Schäfer, Holzner & Kemmler, 2003; Jaeggi, Buschkuhl, Jonides & Shah, 2011). According to the interactive specialization hypothesis (Johnson, 2011), which predicts more plasticity in a less

specialized brain, the connectivity changes we observed in middle childhood ages are very likely to last for a long period of time, but this statement needs to be confirmed by future studies.

Despite of these limitations, the present research provides important evidence about the underlying neural mechanisms of cognitive training and transfer effects of this training during middle childhood. These changes, which are not limited in either their decreasing or increasing directions, emphasize the complex mechanisms underlying how practice impacts our brain. The transfer to untrained functions suggest that cognitive training may have effects on distributed regions, and even overall effects on the whole-brain network. Cognitive training programs and interventions, like the one used here, may have many practical applications. They may allow typically developing children to get better performance in their cognitive abilities, and more importantly, children with developmental deficits could benefit even more from such training interventions with the significant and proved beneficial changes of intrinsic brain connectivity.

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