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Research report

# Effects of working memory training on functional connectivity and cerebral blood flow during rest

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ABSTRACT

Working memory (WM) training (WMT) alters the task-related brain activity and structure of the external attention system (EAS). We investigated whether WMT also alters resting-state brain mechanisms, which are assumed to reflect intrinsic brain activity and connectivity. Our study subjects were subjected to a 4-week WMT program and brain scans before and after the intervention for determining changes of functional connectivity and regional cerebral blood flow during rest (resting-FC/resting-rCBF). Compared with no-intervention, WMT (a) increased resting-FC between the medial prefrontal cortex (mPFC) and precuneus, which are key nodes of the default mode network (DMN), (b) decreased resting-FC between mPFC and the right posterior parietal cortex/right lateral prefrontal cortex (LPFC), which are key nodes of the EAS, and (c) increased resting-rCBF in the right LPFC. However, the training-related decreases in resting-FC between the key DMN node and the nodes of EAS were only observed when the whole brain signal was regressed out in individual analyses, and these changes were not observed when the whole brain signal was not regressed out in individual analyses. Further analyses indicated that these differences may be mediated by a weak but a widespread increase in resting-FC between the nodes of EAS and activity of multiple bilateral areas across the brain. These results showed that WMT induces plasticity in neural mechanisms involving DMN and the EAS during rest and indicated that intrinsic brain activity and connectivity can be affected by cognitive training.



## 1. Introduction

Working memory (WM) is the limited capacity storage system involved in the maintenance and manipulation of information over a short time period (Baddeley, 2003). WM is a functionally important system that underlies a wide range of higher-order cognitive activities (Baddeley, 2003; Osaka and Nishizaki, 2000). Reduced working memory capacity (WMC) is associated with

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neurological and psychiatric disorders (Baddeley, 2003; Goldman-Rakic, 1994; Rose and Ebmeier, 2006) as well as normal aging (Wingfield et al., 1988).

Some aspects of functional connectivity (or correlation of activities between different brain regions) and cerebral blood flow (CBF) during rest [resting-FC/resting-regional CBF (rCBF)] are associated with conditions with reduced WMC. Regions in the external attention system (EAS), which is dedicated to external attention (Buckner et al., 2008; Corbetta and Shulman, 2002; Laird et al., 2005), such as the lateral prefrontal cortex (LPFC) and posterior parietal cortex (e.g., the inferior/superior parietal lobule), are involved with WM and are activated during WM performance (Baddeley, 2003). The EAS is divided into two networks; the dorsal attention network and the ventral attention network (Fox et al., 2006). In contrast, regions in the default mode network (DMN), such as the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), and precuneus, are deactivated during WM performance. Activities in brain regions that belong to the same network correlate with one another during rest, and a strong anticorrelation is observed between the abovementioned two networks during rest (Fox et al., 2005). In other words, when one network is activated, the other is deactivated. The strength of resting-FC among regions in DMN is correlated with individual WMC (Hampson et al., 2006). The strength of anticorrelations between the two networks is generally reduced under conditions with reduced WMC (Broyd et al., 2009; Sambataro et al., 2010). It was shown resting-rCBF in PFC or anterior regions was decreased under conditions with reduced WMC (Martin et al., 1991; Weinberger et al., 1986) described above. These brain activities during rest are assumed to reflect brain's intrinsic activity and connectivities (Fox and Raichle, 2007).

Previous studies have shown the effects of WM training (WMT) on psychological measures and neural systems (Klingberg, 2010; Takeuchi et al., 2010b; Uchida and Kawashima, 2008). Moreover, changes in brain activity, gray/white matter structures, and dopamine D1 receptor density in LPFC and posterior parietal regions after WMT have been demonstrated (Klingberg, 2010; Takeuchi et al., 2010b). Nevertheless, to our knowledge, no previous study has investigated the effect of WMT on resting-FC and resting-rCBF. Using these analyses of rest-related neural mechanisms, we were able (a) to determine how brain regions interact not only with other brain regions to which they are directly connected structurally but also with regions to which they are not structurally connected and (b) to investigate the state of DMN and the WMN during the cognitive processes involved during rest. Given that altered resting-FC underlies conditions with reduced WMC and that resting-FC underlies individual WMC, both of which are of scientific and clinical interest, it is important to investigate the extent of plasticity in resting-FC and resting-rCBF. Our previous study demonstrated that regional gray matter volume (rGMV) in EAS was decreased after a 5-day intensive (4-h training per day) WMT program involving mental calculations (Takeuchi et al., 2011d). We previously proposed that this type of intensive and concentrated training leads to decreased rGMV, possibly after an initial increase in rGMV, whereas training that is not so extensive (e.g., up to 1 h per day for 4 weeks) leads to increased rGMV, which may be followed by a decrease in rGMV after further training (Takeuchi et al., 2011b, 2011d). This proposal is based on the observation of many studies. We further suggested usage dependent synaptic formation and reduction may underlie these rGMV changes (Takeuchi et al., 2011b, 2011d). It is unclear whether this relatively mild form of WMT leads to increased rGMV.

Here young adult subjects underwent a 4-week WMT (up to 1 h per day). Before and after the intervention, they underwent scanning sessions in which resting-FC associated with DMN and the EAS, resting-rCBF and rGMV were measured. Subjects in the WMT group completed a 4-week intensive adaptive WMT program, and subjects in the control group did not participate in any such training during the study period. The lack of an active control group (placebo training) is common to almost all imaging studies of cognitive training (Dahlin et al., 2008; McNab et al., 2009; Olesen et al., 2004; Takeuchi et al., 2010a, 2011b; Westerberg et al., 2004), while an active control group has been widely used in psychological studies of cognitive training (Klingberg et al., 2005, 2002). It is an appropriate approach for this type of study as the effects of placebo training in a cognitive training study of this type, which involves normal adults, are not known and cannot be detected statistically (Takeuchi et al., 2011d). In addition, the real effects of some cognitive intervention that can be used as an active control intervention cannot be ruled out (Takeuchi et al., 2011b). Our subjects also participated in psychological experiments in which they completed a number of cognitive tests. We hypothesized that WMT would increase resting-FC within DMN, increase anticorrelations between DMN and EAS, increase resting-CBF in PFC, and increase rGMV in EAS. The hypotheses relating to resting-FC and resting-CBF are based on the abovementioned previous studies that showed that conditions with reduced WMC are generally characterized by a decrease in resting-FC within DMN, a decrease in anticorrelations between DMN and EAS, and a decrease in resting-CBF in PFC. The hypothesis relating to rGMV is based on our previous proposition described above.

## 2. Methods

### 2.1. Subjects

We enrolled 81 healthy, right-handed university students [59 men and 22 women; mean age 21.1 years, standard deviation (SD) 1.9]. They had normal vision and no history of neurological or psychiatric illness, which was assessed using a routine questionnaire. Handedness was evaluated using the Edinburgh Handedness Inventory (Oldfield, 1971). Written informed consent was obtained from each individual for the projects in which they participated. The Ethics Committee of Tohoku University approved all procedures. This study was performed together with another intervention study involving multitask (MT) training. The different subjects underwent the different training protocols (WMT and MT training). We aimed to determine the following: (1) effects of WMT on resting-FC, resting-rCBF, rGMV and performance on the belowmentioned cognitive tests, (2) effects of WMT on social/emotional/self/behavioral variables, (3) cognitive and neural factors affecting the WMT outcome, and (4) whether polymorphism or genetic factors affects the WMT outcome. Given these