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Effects of Working Memory Training on Cognitive Functions and Neural Systems

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SYNOPSIS

Working memory (WM) is the limited capacity storage system involved in the maintenance and manipulation of information over short periods of time. WM plays a key role in a wide range of higher order cognitive functions and its impairment is observed in a wide range of psychiatric or neurological disorders, making it clinically important. Intensive adaptive training of WM has been shown to enhance individual WM. In this article, we review the studies and describe the methodologies of WM training, along with the psychological, clinical, and neuroimaging findings related to WM training. Training of WM is associated with a wide range of cognitive improvements in non-clinical and clinical subjects, although, on certain points, the results are divided. In clinical studies, training of WM was associated with an improvement of clinical symptoms outside the laboratory. Neuroimaging studies of WM training revealed the effect of WM training on the neural systems of the fronto-parietal network, which play a key role in WM. Still, a number of important issues remain uninvestigated, and we anticipate that future studies will solve these issues.

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KEY WORDS

plasticity, cognitive function improvement, frontal lobe, parietal lobe, working memory, attention training, intervention

1. INTRODUCTION

Working memory (WM) is the limited capacity storage system involved in the maintenance and manipulation of information over short periods of time /7/. WM is a functionally important system that underlies a wide range of higher-order cognitive activities such as reasoning, thinking, reading, learning, mental calculation and conversation /7,29/. Consistent with this, individual working memory capacity (WMC) is correlated with a wide range of cognitive functions /7/. WM is also clinically important because impaired WMC is associated with normal aging /122/, as well as with neurologic and psychiatric disorders /7,40/. Diseases or disorders having impaired WMC include schizophrenia /82/, obsessive-compulsive disorder /87/, major depression /76/, chronic alcoholism /2/, attention deficit hyperactivity disorder (ADHD) /118/, schizotypal personality disorder /82/, high-functioning autism /39/, Alzheimer's disease /8/, Parkinson's disease /46/, learning disabilities /97/, Down syndrome, William syndrome /113/, phenylketonuria /120/, stroke /80/, multiple sclerosis /22/, and intellectual disabilities /109/. Previous neuroimaging studies using diverse imaging methods have investigated the neural correlates of WM and WMC /7/.

Previous findings have indicated that, together with a number of neural systems, the brain structures and functions of the fronto-parietal regions are associated with WMC and with

TABLE 1

Studies of adaptive WM training

References	Subjects (number, age y, characteristics)	Duration, total amount	Tasks	Comparison (number, characteristics, age y, intervention type)	Tests showing training effects	Tests not showing training effects
Buschkuehl et al. /18/	16, healthy (mean 80)*3	45min/ses, 23 ses, 12 w, 17h	1 basic-type (vis) WM, 2 complex (animal) WM, 2 RT tasks	23 healthy, (mean 80)*3, eccentric muscle training	Block span	Digit span, visual free recall, verbal free recall
Chein & Morrison /23/	19, healthy (mean 20)	40m/ses, 5 ses, 4 w, 13h	2 complex (vis,ver) WM	23, healthy, (mean 21), passive	Reading comprehension test, Stroop	Raven test, Verbal Reasoning test
Dahlin et al. /31/	15 healthy (mean 24)	45m/ses, 3ses/w, 5w, 11h	5 updating tasks	7, healthy (mean 23), passive	N-back task, an episodic memory test	Several tests*1
Dahlin et al. /31/	11, healthy (mean 68)	45m/ses, 3ses/w, 5w, 11h	5 updating tasks	8, healthy (mean 68), passive	none	Several tests*1, N-back
Holmes et al. 2009 /47/	22, low WM (mean 10)	35m/ses, 20-ses in 5-7 w, 11 h-	10 basic-type (vis, ver) WM, A racing game	20, low WM, (mean 10), non-adaptive	Visual, verbal simple and complex span tasks Mathematical reasoning test	VIQ PIQ (WASI), Basic reading test
Jaeggi et al. 2008 /51/	35, healthy (mean 26)*3	8 d-19 d 25 m/day	Dual N-back	35, healthy (mean 26)*3, passive	Digit span BOMAT	Reading span
Klingberg et al. /60/	27, ADHD (mean 10)	40m/ses, 27 ses, 5 w, 17 h	6 basic-type (vis,ver) WM	26, ADHD (mean 10), non-adaptive	Digit span, Span board, Stroop, Raven test, (ADHD symptoms)	(Head movements)
Klingberg et al. /61/	4, healthy (20-29)	25m/ses, 26ses, 5 w, 11 h	3 basic-type (vis,ver) WM,1 CRT*1	7, ADHD, (mean 11), non-adaptive	Span board, Stroop, Raven test	CRT
Klingberg et al. /61/	7, ADHD (mean 11)	25m/ses, 24 ses, 5-6 w, 10 h	3 basic types of (vis,ver) WM,1 CRT*1	7, ADHD (mean 11), non-adaptive	Span board, Stroop, Raven test, (Head movements)	CRT
Olesen et al. /78/	3, healthy (mean 22)	40m/ses, 25 ses, 5 w, 17 h	3 basic-type (vis,ver) WM	11, healthy (mean 26), passive	Span board, Stroop, Raven test	
Olesen et al. /78/	8, healthy (mean 29)	40m ses, 18 ses 5 w, 12 h	3 basic-type (vis) WM	11, healthy, (mean 23), passive	Stroop	Span board Raven test

References	Subjects (number, age y characteristics	Duration, total amount	Tasks	Comparison (number, characteristics, age y, intervention type)	Tests showing training effects	Tests not showing training effects
Takeuchi et al. /105/	18, healthy (mean 11)	4 h/ses, 5 ses, 1w, 20h	2 WM tasks using mental calculation	37, healthy (mean 22), non-adaptive or passive*2	A creativity test, stroop performance, letter span, complex arithmetic task,	Raven test, arithmetic (WAIS-III), digit symbol, simple arithmetic task, letter mental rotation, Trail making B-A,
Thorell et al. 2008 /107/	17, healthy (mean 5)	15m/ses, 23ses, 5 w 6 h	5 b basic-type visuospatial WM	30, healthy, (mean 5), passive or computer game*2	Word span, Span board go/no go omissions	Block design, Stroop-like test, Go/no-go commissions and RT, auditory CPT
Van der Molen et al. 2010 /110/	41, low IQ (mean 15)	6m/ses, 3ses/w, 5 w 2 h	1 (vis) complex WM	27, low IQ (mean 15), no intervention	Visual and verbal simple span, Visual complex span tasks a story recall test arithmetic test	Stroop Raven test Fast reading test
Van de Molen et al. 2010 /110/	41, low IQ (mean 15)	6m/ses, 3ses/w, 5 w -2 h	1 complex (vis) WM	27, low IQ (mean 15), non-adaptive	none	
Vogt et al. 2009 /111/	15, multiple sclerosis (mean 43)	45m/ses 4ses/w, 4 w, 12h	2 basic-type (vis, ver) WM, 1 complex (ver) WM, 1 updating task	15, multiple sclerosis (mean 46), passive (4w	PASAT, Digit span, SDMT, FST, Fatigue measures	Corsi blocks, 2back, SDMT, Depression measure QOL measure
Vogt et al. 2009 /111/	15, multiple sclerosis (mean 43)	45m/ses, 2ses/w, 8w 12h	2 basic-type (vis, ver) WM, 1 complex (ver) WM, 1 updating task	15 multiple sclerosis (mean 46), passive (4w)	Corsi blocks, Digit span, 2back, PASAT, FST, Fatigue measures	SDMT, Depression measure QOL measure
Westerberg et al. 2007 /119/	9, stroke patients (mean 54)	40m/ses, 23 ses, 5 w, 15 h	7 basic-type (vis, ver) WM,	9, stroke patients (mean 55), passive	Digit span, Span board, PASAT, RUFF 2&7, CFQ	Raven test, Stroop Declarative memory tests

Studies in the table are limited to published studies that used adaptive procedures and controlled the practice effects seen in outcome measures in some ways. Popular tests were called by popular names.

Vis = visual, ver = verbal, w = week, d = day, h = hour, m = minute.

*1, See the Factors that affect the effects of training section for details.

*2, The passive control group and the active control group were combined after confirming there were no differences in the effects of the intervention between the two groups,

*3, This mean age is mean age of the all the subjects (intervention group + control group).

Test battery

Test name	Cognitive function
Auditory continuous performance task (CPT) /62/	Attention
Bochumer Matrizen-Test (BOMAT) /50/	Non-verbal reasoning
Cognitive failure questionnaire (CFQ; /15/)	Cognitive functioning in daily life
Choice reaction time task (CRT)	Processing speed
Block design /116/	Spatial problem solving (non-verbal reasoning)
Digit span /116/	Basic type of verbal WM
Digit symbol /116/	Processing speed
Faces symbol test (FST /96/)	Processing speed (and attention)
Go/nogo commission error /108/	Inhibition
Go/nogo omission error /108/	Attention
Go/nogo reaction time (RT) /108/	Inhibition (and processing speed)
Paced auditory Serial Addition Test (PASAT /43/)	Sustained attention (and WM)
Raven matrices tests /88/	Non-verbal reasoning
Reading span /32/	Complex WM
RUFF 2&7 /92/	Selective attention
Span board /114/	Basic-type visual WM
Stroop /65/	Inhibition
Symbol digit modalities test (SDMT; /98/)	Processing speed
Raven's matrices tests /88/	Non-verbal reasoning
Wechsler Abbreviated Scales of Intelligence (WASI /117/)	IQ scale, yielding measures of verbal IQ (vIQ) and performance IQ (pIQ)
Word span /106/	Basic type of verbal WM

conditions having impaired WMC. Regions in the lateral prefrontal cortex (LPFC) and parietal cortex, especially the inferior parietal lobule (IPL) and the intra-parietal lobule, are involved with the WM system and are activated during WM performance /7,58/. Further, the structural integrity of the white matter in the fronto-parietal white matter regions is correlated with WMC /58,77/. Previous anatomical studies revealed that regional gray matter and white matter volume in the PFC and the parietal regions are correlated with WM performance among clinical samples /3,4,69,99/. Additionally, several neurologic and psychiatric disorders are associated with impaired WMC as well as with normal aging, characterized by impaired WMC and impaired structural integrity of fronto-parietal white matter regions and reduced rGMV in the fronto-parietal regions /24,57,74/. The dopamine system is also important for WM as WM performance is affected by dopamine in the PFC /94/. Cortical dopamine release has been observed during the performance of WM tasks /1/. Among the dopamine receptors, D1 receptors have been known to be the most associated with WM, and among the dopamine receptors, D1 receptors exist most in the PFC /95/. Furthermore, there is an optimal level of dopamine for WM performance and too much or too little stimulation of D1 receptors results in reduced WM performance /5,75/. So, can WMC and the associated cognitive functions, disabilities or neural systems be improved by any means?

Recently, intensive adaptive training of WM has been shown to improve or alter WMC, associated cognitive functions, disabilities, and neural systems /61,78/. In intensive adaptive training of WM, training was performed at a capacity similar to that of an individual by using an adaptive staircase method that adjusted the difficulty on a trial-by-trial basis. Training was performed intensely in a concentrated period (such as at least 20 minutes per day, 4-6 days a week). In experiments in which subjects perform WM tasks without adapting the difficulty level, this intensity typically does not increase WMC /63,84/. In addition, teaching rehearsal strategies to subjects typically does not increase performance on non-trained WMC or other tasks /16,19/. Contrary to that, intensive adaptive training of WM leads to improvement on the performance of non-trained WM tasks, a reasoning task, and a response inhibition task in children with ADHD /61/. Since then, numerous studies have been performed to investigate the effects of WM training on WMC, the associated cognitive functions, disabilities, and neural systems. In this article, we review the studies of WM training and describe the methodologies of WM training and the psychological, clinical, and neuroimaging findings of WM training.

2. INTENSIVE ADAPTIVE TRAINING OF WM

As described, in intensive adaptive training of WM, training was performed intensely in an adaptive way. In existing studies, computerized training has made it possible to adjust the task level automatically. However, now many studies on intensive adaptive training of WM have been published, as shown in Table 1. The methodology varies much on several points such as length (1w–10w), the total training time (2h to 20h), the task used in training, the number of training tasks that are used (1 task-10 tasks), the subjects' characteristics (age, cognitive functions, normal or clinical), the measures used to investigate the effect of training, etc.

As for the task used in training, basically, we classified these tasks into four categories.

(1) *Basic types of WM.* Training tasks that we refer to as basic-type have been used in many studies as shown in Table 1. Basically, in these tasks, the stimuli are presented and subjects must remember them. After the presentation of the stimuli, subjects have to reproduce the task (as in a digit span), or compare the presented stimuli with the subsequently presented second set of stimuli and respond based on a particular rule (such as by indicating the difference between the sets of stimuli). In some tasks, the stimuli to be remembered have to be manipulated in a simple way after the presentation of the stimuli (such as by reversing the order of the stimuli as in the digit span backward task). Whether there is a difference between the psychometric properties of the span task with manipulation of the remembered stimuli after the presentation of the stimuli (such as a backward digit span) or in the span task without such manipulation (such as a forward digit span), is a matter of debate /42/. We placed both span task types in the same category in this study for the sake of convenience, without going in to the details of this debate because both task types are usually used as training tasks in one study at the same time in the studies of WM training. We included the WM tasks in which subjects had to remember instructions in this category. For example, in the verbal version of the City Map task /111/, instructions such as "turn left after the library" are presented to the participant and have to be remembered, and then, based on the remembered instructions, participants have to find the path using given arrows along a virtual city map.

(2) *N-back task and other updating tasks.* In the N-back task, stimuli are presented one by one and the participants are asked to memorize a series of presented stimuli and their temporal order, update a list of recent items, and select the appropriate responses based on the previously observed (N stimuli ago) stimuli, according to the N-back rule. There are two types of response patterns. One version of the N-back asks the subjects to push the button that corresponded to the previously observed

stimuli presented N stimuli ago was 4) /104/. Another version of the N-back task asks subjects to judge whether the currently presented stimuli and the stimuli presented N stimuli ago are the same and to indicate the results of the judgments by pushing buttons /51/. Other updating tasks different from the N-back task are used in the study by Dahlin et al. /30/. In one task, lists of items were randomly presented sequentially, and the task was to recall the four last presented words after the presentation was unexpectedly stopped. "Find Pairs" is another updating task used in Vogt et al. /111/'s study. In this task, subjects have to remember the location of cards that have been turned over and back again and find pairs of cards with the same image.

(3) *Complex WM tasks*. In complex WM tasks, subjects have to remember the presented stimuli as basic types of WM tasks, but in addition they have to perform other processing tasks during or between the presentation of each stimulus to be remembered. For example, in the spatial complex WM task of the Chein et al. /23/ study, subjects have to remember the location of the presented spatial stimuli, but between the presentation of each spatial stimuli, subjects have to perform the other task in which they have to judge whether or not the presented picture is symmetrical.

(4) *Other types*. In recent studies, other various types of WM tasks have been used. For example, in the Dash et al. /29/ study, the dual WM task is used. In this task, subjects have to perform two basic types of WM tasks simultaneously. Similarly, the Jaeggi et al. /51/ study used a dual N-back task in which subjects have to perform simultaneously two N-back tasks. In our recent study /104/, an operation N-back task is used. In this task, subjects are presented with an equation of simple addition, and subjects have to calculate and remember the answer to the equation and perform the N-back task using the answer to the equation. In another of our recent studies /105/, WM training tasks using mental calculations were used. In these tasks, subjects had to perform computerized mental calculations (mental multiplication or successive 2-digits mental addition). The difficulty of the mental multiplication task was adjusted by changing the number of digits used in the equations of the task, while the difficulty of 2-digit mental addition was adjusted by changing the speed of the presentation of the digits.

3. FACTORS THAT AFFECT THE EFFECTS OF TRAINING

Previous studies have indicated several factors that may affect the effects of training as described below.

3.1 Adaptive training (adjustment of the difficulty of the task)

From early studies of WM training, it has been stressed that an adaptive procedure (adjusting the difficulty of the task, based on the subjects' performance) is important for improving training. In experiments during which subjects perform WM tasks without adapting the difficulty level, WMC typically does not increase /63,84/ indicating that any negative findings of non-adaptive WM training effects should be taken cautiously. Thus, most studies have used adaptive training in the experimental WM training group, and the non-adaptive training (with low WM demand) has been used in the control group in some studies /60,61/.

However, some studies did not use adaptive procedures in the WM training group for a few reasons. Although, the number of studies is limited, a lack of far transfer in WM training groups in these studies as opposed to the studies described above may indicate that non-adaptive training fails to cause far transfer. For example, Li et al. /66/ investigated the effect of non-adaptive WM training (a spatial N-back and a spatial N-back task with mental manipulation of retained information) in elderly healthy adults. The training in this study affected the performance of the more demanding spatial N-back task and numerical N-back task (similar task rules, stimuli of different modalities). However, the training did not impact the performance of complex span WM tasks. In the

Persson and Reuter-Lorenz /83/ study, as described in detail below, demand on WM itself was not the focus, and non-adaptive high WM demand training was used in one of the control groups. This training did not cause any transfer to non-trained tasks in young adults. Also, in the Dahlin et al. /31/ study, training on the updating of information in young and old healthy adults was the study's focus, and demand on WM itself was not focused on in this study. The difficulty of the task was adjusted, however, by increasing the number of trials in 4 out of 5 updating tasks and demand on memory load was not directly modulated (the number of stimuli subjects had to remember was kept the same). In this study, as opposed to other studies of updating (N-back) in which demand on memory load was modulated /51,52/, no training-related far transfer was observed (except in an episodic memory test among a number of tests), while transfer to the non-trained updating task (N-back task; near transfer task) was observed in young healthy adults (but not in old healthy adults). The tasks that did not show training-related improvement in this study included measures for general cognitive control, processing speed, basic type of WM, complex WM, verbal fluency, verbal ability (a word synonym test), mental flexibility, non-verbal reasoning and inhibition.

3.2 Contents of training

There are various types of WM training tasks. Some of the characteristic of the WM training tasks are known to affect the effects of WM training and others may affect the effects of WM training, too.

3.2.1 Resolving Interference. Persson and Reuter-Lorenz /83/ reported that 8 sessions of 40 minute "training" (over 2 weeks, resulting in 5 hours total) on high-interference versions of the WM tasks, including item-recognition tasks and the N-back task, led to improved performance on non-trained WM tasks (the item recognition task), semantic memory (verb-generation), and episodic memory tasks (paired-associates learning), compared with training on low-interference versions of WM tasks or training on low demand WM tasks. In each trial of these tasks, stimuli were presented and subjects had to judge whether subsequently presented probes were presented stimuli or not. In the high-interference version, probes were confusing because when the probes are not presented stimuli in the current trial, often they were stimuli presented in previous trials, while in the low-interference version, that was not the case. In this study, the training task was not adaptive (and thus not included in Table 1), however, the results should be taken into consideration to make training effective.

3.2.2. Dual WM. A study by Jaeggi et al. /51/ showed the most robust effects of WM training on young healthy adult's fluid intelligence (performance of nonverbal reasoning tests) using a dual N-back task with a relatively large sample size. However, the effect of WM training on fluid intelligence is inconsistent across studies (see Table 1), making it a matter of interest to know whether the dual task component or the dual N-back task is crucial for WM training on fluid intelligence.

Recently, Dash and colleagues /29/ answered this problem. The researchers reported that training that uses a dual WM task, in which subjects have to remember two types of stimuli at the same time, is more effective in improving the performance of non-verbal reasoning tests [Bochumer's matrizen-test (BOMAT) or the fluid intelligence] than is training which uses two single WM tasks. In this study , training that used single WM tasks did not improve performance on these tests at all.

However, Jaeggi et al. /52/ recently reported seemingly contradictory results. In their study, both training which used a dual WM task and that using a single N-back task were equally effective in improving young adults' performance on the fluid intelligence task (Raven's matrix test and the BOMAT). The difference in results between the two dual WM task /29,52/ studies could be due to differences in the WM tasks used. In the Dash et al. /29/ study, the trained WM tasks were basic-type visual and verbal WM tasks, while in the Jaeggi et al. /52/ study, the trained WM tasks were N-back tasks. In N-back tasks, subjects have to simultaneously recall, encode, and update information. But, Dahlin et al. /31/ reported that adaptive training which used updating tasks that did not include N-back tasks did not improve fluid intelligence. This could be due to the method used for adjusting the difficulty of the tasks, which may have focused on the function of updating and not on memory capacity in WM (see the *Adaptive training* paragraph). Furthermore, although the sample sizes were small, Olesen et al. /78/ and Klingberg et al. /61/ reported that training that used single WM tasks resulted in improved fluid intelligence (performance evaluated on Raven's matrix test). Thus, these problems remain to be solved. We can ask ourselves the following questions: Under what conditions can basic-type WM training impact fluid intelligence? Is a single N-back task more effective for improving fluid intelligence than other WM tasks?

3.2.3. Other WM training tasks. As described, other types of WM training tasks have been used in previous studies. These WM training tasks include WM tasks using mental calculation and complex WM tasks in which subjects have to remember the presented stimuli and perform a processing task simultaneously. WM tasks using mental calculation were used for the reason that mental calculation is typical of WM, requiring not just the maintenance of information but also strong manipulation of the maintained information. Performance of complex WM tasks, such as the reading span task, is sometimes reported to correlate more with the performance of tasks other than WM tasks, such as the forward/backward digit span /32/. Such tasks might be assumed to be more effective for WM training. However, although training that used these tasks induced an improve-ment in the performance of tasks other than the WM tasks, both tasks failed to induce a transfer effect to nonverbal reasoning tests (fluid intelligence) /23,104/.

Additionally, direct comparisons between the effects of training that use these WM tasks and the effects of training that use other WM tasks have not been performed. Whether these WM training tasks are more effective than other WM training tasks remains to be investigated. Among the basic types of WM tasks, there are WM tasks that use visual stimuli, auditory verbal stimuli, visual verbal stimuli, and so on. WM tasks using verbal and visual stimuli engage brain regions differently /112/, and WM tasks using visual-verbal and auditory-verbal stimuli engage brain regions differently /27/. Whether differences in the modality of WM training tasks affect WM training effects remains to be investigated.

3.3 Motivation, arousal, feedback

The effects of motivation, arousal, and feedback on the learning effect have not been examined in studies of WM training, but their importance has been thoroughly examined in studies of learning and neuroplasticity (for example, see /41/). In the studies of WM training, feedback on performance is normally given automatically through computer programs. Various methods have been taken to motivate subjects and maximize the effect of training including making the training program more attractive and rewarding, giving positive and negative feedback based on compliance with the training protocol and allowing subjects to play a game after the training /47/. These measures may be especially important when subjects have low motivation.

3.4 Variability of the training tasks

The importance that increasing the variability of the training tasks has on learning has been thoroughly examined in studies of learning and neuroplasticity /41,103,123/. Variability refers to the diverseness and novelty of the tasks, stimuli, and the situation where training is done. The variability of training may force subjects to extract the more general principles of the tasks or to improve their general abilities in the trained domain rather than focusing on specific features of a task or learning specific strategies which cannot be applied to tasks other than the trained task.

Increasing the variability of training tasks has been practiced in studies of WM training. Most studies (see Table 1) use multiple training tasks rather than single training tasks for WM training. These measures may be important when training is used for practical purposes because different WM training tasks may yield different effects, as indicated in this paper. On the other hand, using multiple training tasks makes it difficult to know the difference between the effects of the training tasks used. One interesting study topic is to investigate the difference between the effects of various training tasks, as was reported in a recent study that compared the effect of a single N-back task training and that of dual N-back task training /52/.

3.5 The schedule and total amount of training

The total amount of time spent training is another factor that is considered to affect the training effects. This matter has not been thoroughly examined in studies of WM training, though recent studies have shown that the effects of WM training on fluid intelligence /51/ and white matter structural integrity /104/ are training time dependent. Furthermore, these studies seem to reveal that groups or subjects with less training (in the case of a former study, WM training was performed on 8 or 12 days for 25 min/day) show few or no training-related effects on the above measures. These results may underscore the importance of insisting that subjects set aside a particular amount of time for training to see the effect WM training has on certain measures.

The intensity of the training protocol may also be important. We define "intensity" here as how the same amount of training is massed in to shorter time periods or distributed in to longer ones. In clinical rehabilitation, massed interventions are usually performed based on the results of such training in patients after stroke /86/. However, evidence gathered from studies of normal subject learning suggests that the material learned under distributed practice is generally retained longer than the material learned by massed practice /9/. Some studies also suggested that distributed practice enhances skill acquisition more so than massed practice /e.g., 73/. Although, 12 hours of WM training performed over 4 week and 8 week periods in patients with multiple sclerosis did not reveal any difference in training protocol effects /111/, more drastic differences in training protocols may be able to reveal what kind of training protocol is effective in WM training.

3.6 The amount of time after the training begins and after the training ends

The amount of the time after training begins may be another factor that affects WM training effects. Some studies show that the effect of WM training, on some measures, becomes apparent sometime after the training has ended (in the follow-up test), but it is not seen soon after the training has ended. Comparisons between the amounts of time after training ends are also interesting from the perspective of how long WM training can affect cognitive functions even after WM training has ended. It was reported that training related improvement has been maintained even 18 months after training. However, as was described just above, how long the training effects continue may depend on a number of factors including the intensity of the training.

In the study by Holmes et al. /47/, WM training using basic-type WM tasks performed 35 minutes each session for at least 20 sessions over 5-7 weeks, resulting in at least 11 hours of training time total in children with low WM, resulted in an improvement on the performance of various types of WM tasks and an improvement in most of the tasks was even evident 6 months after the training had ended. Not only that, in this study, the effect training had on mathematical abilities appeared 6 months after the training, though the effect was not evident soon after the training had ended. A similar finding was obtained in the study by Van der Molen et al. /110/, in which adolescents with a low IQ performed WM training using complex WM tasks 6 minutes a day, 3 times per week over a 5 week period which resulted in less than 2 hours of training in total. The results included improvement in the performance of a simple arithmetic task, a story recall test, and a visual basic-type WM task, that was not seen 10 weeks after training but not soon after the training. On the other hand, improvement in the performance of the verbal basic-type WM task seen soon after the training was substantially maintained 10 weeks later.

Klingberg et al. /60/ used basic-type WM tasks to examine the effects of WM training in children with ADHD. Their training protocol lasted 40 minutes/day, for about 27 training days over a course of 5 weeks and resulted in 17 hours as a whole. WM training effects were seen in 4 cognitive tasks, as well as in the symptoms of ADHD, both soon after and 3 months after the training (follow-up). The effect sizes of these measures in the follow-up study were 99%-55% of the effect sizes obtained soon after training. In the Dahlin et al. /31/'study, improvement in the performance of the N-back task was seen after 5 weeks of a training program which lasted 45 minutes/per day and was performed 3 days per week, resulting in 11 hours of total training. Improvement using updating tasks (not including the N-back task) in young adults, was maintained even 18 months later. On the contrary, in the Buschkuehl et al. /18/ study, the effects of training were seen soon after the training, but were not evident 1 year after training completion. The study had used healthy elderly adult subjects for a training protocol which consisted of visual basic-type WM tasks, including basic- and complex-type WM tasks and reaction time tasks. Training was performed 45 minutes per day for 23 training days over a period of 12 weeks, resulting in 17 hours of training time in total.

4. THE EFFECT OF WM TRAINING ON COGNITIVE FUNCTIONS.

The effects of WM training on cognitive functions have been investigated in both non-clinical and clinical samples. As described below, the results of these studies have shown that WM training affects not only the performance of non-trained WM tasks, but also a wide range of cognitive functions that are associated with WM, although WM training has not always been shown to affect these cognitive functions.

4.1 WM

Improvement on the performance of non-trained WM tasks following WM training can be divided into different categories based on the WM task used for the outcome measures and the modality of the stimuli. The results of these studies have shown that, at least in certain cases, WM training can improve performance on non-trained WM tasks even when the tasks to measure training effects use stimuli from different modalities than the ones used in WM training tasks, or when the task types of training and the tasks to measure training effects are very different.

It has been consistently shown that there are transfer effects from WM training to WM tasks which share the same task type (simple span task, complex span task, updating tasks such as the N-back task) and the same modality of stimuli (numerical, verbal or spatial). These tasks, nevertheless, often differ in some aspects such as the use of a computer, the method used to indicate an answer, or the response presentation methods. Transfer effects of WM training to basic-types of WM with the same modality of stimuli have been seen when basic-type WM tasks are used in healthy adults /78/, in children with ADHD /61/, in children with low WM /47/, in stroke patients /119/ and so on (See Tables 1,2). The same transfer effects have also been seen in young healthy adults (but not in elderly healthy adults /30/) for updating tasks (the N-back task) that share stimuli modality with other updating tasks used in training.

As for transfer effects from WM training to WM tasks that share the same task type but not the same modality of stimuli, such effects were seen in the verbal span task when basic-type visuospatial WM tasks were used in the training of healthy preschool children /107/. Furthermore, non-adaptive WM training using a spatial N-back task and a spatial N-back task with manipulation of maintained information improved the performance of numerical (verbal) N-back tasks in young and elderly healthy adults /66/. However, training which included a basic-type WM task and two complex span tasks using pictures of animals as stimuli failed to improve subject's performance on a digit span task (a basic-type verbal WM task) in elderly healthy adults /18/.

Transfer effects from WM training to WM tasks that do not share task type have also been shown in some studies. WM training which uses a dual N-back task (letter stimuli and visuospatial stimuli) is shown to improve subject's performance on a digit span task, but not on a complex WM span task or a reading span task /51/, in young healthy adults. Transfer effects of WM training from basic-type WM tasks to complex WM span tasks have been seen in children with low WM /47/ and in adolescents with mild to borderline intellectual disabilities /110/.

4.2 Non-verbal reasoning

WMC and non-verbal reasoning ability are highly correlated /64/. Whether WM training has an impact on non-verbal performance tasks continues to be matter of interest as performance on this task is known to have a very high correlation with general intelligence /36/. Additionally, non-verbal reasoning tasks are treated as measures of general or fluid intelligence. General intelligence refers to the *g* factor /100/ which contributes to one's success on diverse forms of cognitive tests regardless of whether the tests are verbal or nonverbal. Though there are a number of studies that have investigated the effects of training on non-verbal reasoning tests, the results of these studies have been divided and the cause of this division remains largely unknown.

Both training on a single N-back task and training on a dual N-back task have been shown to improve performance on non-verbal reasoning tests (Raven's matrices tests and BOMAT, a difficult variant of the Raven's matrices test in young healthy adults) /51,52/. Training of WM using basic-type WM training has been shown to improve performance of the Raven's matrices tests in young healthy adults /61,78/ and in children with ADHD /60,61/.

On the other hand, WM training that uses basic-type WM tasks has failed to improve subject's performance on any of the following: Raven's matrices tests in stroke patients /119/, a Block design test, a different non-verbal reasoning test (or a spatial problem solving task) that has high correlation with general intelligence in pre-school children /107/, or performance IQ from Wechsler Abbreviated Scales of Intelligence (WASI), which is based on block design and matrix reasoning tests, in children with low WM /47/. Recently it has been reported that dual WM task training, in which subjects have to perform two basic types of WM training tasks concurrently, improves performance on BOMAT in young healthy adults /29/, whereas, single basic-type WM task training has failed to improve performance on either BOMAT or Raven matrices test in this study.

In addition, WM training has failed to improve subject's performance on Raven matrices tests when (1) complex WM task training was applied to young adolescents with a low IQ /110/ or to young adults /23/, (2) when WM training using mental calculation was applied to young adults /105/, or (3) when updating training, which did not include N-back tasks, was applied to young and elderly adults /31/.

Some failures to improve performance of non-verbal reasoning could be the result of ceiling effects /105,119/ or the result of reduced sensitivity to the tests in instances when the exact same test is applied as both a pre-test and post-test /17/. Incongruence among studies could be due to the training methods. At this moment, intensive adaptive WM training using N-back and dual WM tasks are improving subject's performance of non-verbal reasoning tests in young adult samples without failure. This matter will later be discussed in detail. Besides incongruence among training methods, there is also the matter of studies which lack significant results. This could be caused by number of factors such as reduced statistical power, statistical deviation, reduced training time, and so on. A lack of significant results in one study, is not evidence of a lack of effects.

4.3 Inhibition

WMC and cognitive inhibition, or the ability to inhibit unwanted responses, irrelevant information, and so on), are deeply associated /91/. The results that WM training effects had on inhibition measures are also divided. The Stroop test is usually used as a measure of inhibitions in studies of WM training. WM training-related improvements of performance on the Stroop test are reported in some studies, but not in others. The causes of these divisions remain unclear.

Performing training of WM has improved performance on the Stroop test when basic WM training tasks are used in young healthy adults and in children with ADHD /60,61,78/, or when complex WM training tasks are used in young healthy adults /23/. However, when basic WM training tasks are used in stroke patients /119/, when complex WM training tasks are used in children with low IQ /110/, when updating training that did not include N-back tasks was used in young and old healthy adults /31/, and when basic WM training tasks are used in healthy preschool children /107/, performing training of WM has failed to improve the performance of the Stroop test. Also in the Thorell et al. /107/ study, WM training did not affect the performance of the commission errors (i.e. making a response when instructed not to do so) of the go/nogo task, which is another measure for response inhibition /11/. Possible causes of the negative findings, such as subjects' characteristics and the training amount, were cited in the study by Thorell et al. /107/. However, differences in many factors between studies make it difficult to conclude the cause of these result divisions between the studies.

4.4 Attention

Attention and WM share neural substrates /6/ and it has been indicated that the two are closely related /119/. The effects WM training have on attention have been substantiated in a few studies. Westerberg et al. /119/ investigated the effect WM training had on the performance of attention tests in stroke patients when training took place 40 minutes per training day, for 23 training days over a 5 week period, resulting in 15 hours as a whole of basic-type WM tasks. In this study, the training of WM improved the performance of two attention tests: the paced auditory serial addition test (PASAT) version A /43/ and RUFF 2 & 7 /92/. Improvement in the performance of PASAT following WM training, which includes basic, complex and updating WM training tasks, has also been observed in patients with multiple sclerosis /111/. Furthermore, WM training using basic types of WM tasks significantly improved performance of the go/nogo omission error (i.e. not making a response when instructed to make a response) and substantially improved performance of the auditory continuous performance task (CPT), both of which are measures of attention.

4.5 Reading and arithmetic, mathematics

Abilities related to arithmetic, mathematics, and reading are obviously deeply related to school performance; thus, whether WM training leads to an improvement in performance is a matter of interest. A few studies have investigated this issue.

In the Chein and Morrison /23/ study, WM training lasted 30-45 minutes per day, and was performed for 5 training days a week over a period of 4 weeks. Total training time was about 13 hours. The study using complex WM tasks in young healthy adult samples resulted in improvement on a reading comprehension test. In the Holmes et al. /47/ study, WM training using basic-type WM tasks in children with low WM resulted in the improvement of subject's performance on a mathematical reasoning test 6 months after training (though, improvement was not observed soon after training). However, the training did not result in improved performance on a basic reading test /115/ which assessed decoding and word-reading abilities. In the study of Van der Molen et al. /110/, WM training using complex WM tasks in adolescents with low IQ resulted in improved performance of a simple arithmetic task in which subjects were required to do simple arithmetic tasks as quickly as possible. The training did not, however, result in improved performance of a fast reading task in which subjects were required to read words aloud as quickly as possible. The improvement was seen 10 weeks after training, but was not observed soon after the training.

As a whole, it seems that in some cases, WM training leads to the improvement of reading, mathematical, or arithmetic abilities, but improvement is not observed in other cases. Huge methodological inhomogeneity among studies make it difficult to conclude, under what conditions will or will not WM training lead to the improvement of these abilities. Interestingly, in two studies, WM training led to the improvement of these abilities, not in the test soon after the training, but in follow-up tests, indicating the existence of a "delayed transfer". Perhaps, the effect might result from a second hand effect of the training.

4.6 Creativity

Creativity and (capacity of) WM have a unique relationship. One of the most robust findings about the association between creativity and WMC is that persons with schizotypal personality disorders, or schizotypy, are characterized by facilitated creativity and impaired WMC /37,48,71/. Furthermore, while impairment of WM systems has been associated with numerous psychiatric or neurological diseases (or disorders) as described above, facilitated creativity has been associated with numerous psychiatric or neurological disorders in its own way. For example, creativity is associated with the symptoms of ADHD /45,121/ and panic disorder, together with anxiety disorder, is more often observed among creative individuals than normal subjects /68/. Many people who are creative have the trait of high anxiety /21/. Affective disorders and alcoholism are more prevalent in people with creative jobs /85/. Additionally, a possible relationship between creativity and Tourette's syndrome has been indicated /93/.

A recent study of ours /105/ has shown that intensive adaptive training of WM using mental calculation reduces creativity as measured by a divergent thinking test. The finding may be comparable to that of the study reporting that Ritalin (methylphenidate) administration significantly decreased the symptoms of ADHD and also creativity /102/.

4.7 Cognitive functions that have not been shown to be affected by WM training

Processing speed is an individual cognitive ability measured by how fast individuals execute cognitive tasks, particularly elementary cognitive tasks. Studies of WM training have rather failed to show training related improvements in processing speed. WM training using basic-type WM tasks did not lead to improvements in processing speed as measured by both simple and choice reaction time tasks in children with ADHD /61/ and in young adults /61/. WM training using mental calculation did not lead to improvements in processing speed measured by the digit symbol test/105/. WM using updating tasks also failed to improve the performance of processing speed tasks /31/. WM training-related improvement in processing speed was measured by the face-symbol test in patients with multiple sclerosis /111/. However, in this study of patients with multiple sclerosis, WM training-related improvement of fatigue was observed. Because fatigue has been identified as an important contributor to cognitive performance in patients with multiple sclerosis /22/, training-related processing speed improvement in patients with multiple sclerosis may be mediated by the training-related improvement in fatigue. Alternatively, the finding that processing speed is primarily impaired in patients with multiple sclerosis /33/ may underlie WM training-related improvement in the processing speed of patients with multiple sclerosis.

The effects of WM training on memory other than WM have been investigated in a few studies, but the effects are not clear. WM training using basic-type WM tasks on the performance of declarative memory tests in which subjects had to recall as many words as they were able to memorize 30 minutes earlier, had no effect on stroke patients /119/. The effects of training, including basic-type and complex WM tasks, as well as reaction time tasks, on visual and verbal free recall tasks (declarative memory tasks) in which subjects have to recall as much information as they are able to memorize 20 or 30 minutes earlier, was not clear in healthy elderly adults /18/. There was an effect for WM training using a visual complex WM task on story recall tests /109/ in adolescents with lower IQ. In a recent study /110/, the effect was evident 10 weeks after training but not soon after training. In this test, subjects had to recall stories read to them aloud both soon after the story was finished and a second time 20 minutes after that. The first time subjects used immediate recall which is a kind of WM task, and the second time, subjects used delayed recall which is a declarative memory task. The total score of two tasks was analyzed in this study so WM training's effect on the delayed recall task was not clear.

5. EFFECTS OF WM TRAINING IN A GROUP WITH IMPAIRED COGNITIVE FUNCTIONS

As described below, the effects of WM training on a group with impaired or declined cognitive functions have been investigated in several studies of subjects with lower cognitive abilities, stroke patients, patients with ADHD and patients with multiple sclerosis, all of who are characterized with impaired WM, as described in introduction. As a whole, WM training seems to improve related cognitive functions in these groups and, in the case of clinical subjects, WM training seems to improve subject's clinical symptoms outside of the laboratory. Improvement of WM in these groups is not only important because WM itself is important, but also because the rehabilitation of other cognitive functions depends on WMC and the ability to focus one's attention /70,90/.

5.1 Groups with lower cognitive abilities

Van der Molen et al. /110/ investigated the effects of WM training in adolescents with mild to borderline intellectual disabilities. The authors showed that training WM 6 minutes per day, 3 times per week over a 5 week period, which resulted in less than 2 hours of total training time, was associated with the improvement of visuo-spatial and verbal WM tasks, a story recall test, and scholastic abilities compared with non-intervention. The training used one complex WM training task which required the maintenance of information and concurrent task execution. Scholastic abilities were measured by tests in which subjects were required to do arithmetic operations or read words aloud as quickly as possible. The training did not lead to the improvement of reasoning nor response inhibition performance. Interestingly, in this study, the non-adaptive WM training, which has been used as an ineffective control training, was also associated with similar improvements compared with not performing an intervention. This is in contrast to other studies that showed larger training related improvement in adaptive WM training when compared with non-adaptive WM training. Reasons for this could include the characteristic of subjects or even a relatively lower WM burden during training may be effective for subjects with lower intellectual abilities. Other factors, such as the complex WM task used in this study, could also explain the contrast.

Holmes et al. /47/ investigated the effects of WM training on children with poor WM (children who scored at or below the 15th percentile on verbal WM tasks). They showed that, in a study using 10 basic-type WM training tasks and a racing game without a WM burden as the reward, performing adaptive training of WM 35 minutes per day, for at least 20 days over a 5-7 week period, resulting in 11 hours of total training time, was associated with improved performance of non-trained WM tests, when compared with non-adaptive training of WM, immediately after training. Furthermore, adaptive WM training was associated with improved performance of mathematical reasoning 6 months after training had been completed, but not with improved performance of a basic reading test, verbal IQ, or performance IQ.

5.2 ADHD

Klingberg et al. /60,61/ investigated the effects of WM training in children with ADHD. Training in the earlier study /61/ lasted 25 minutes per day, for about 24 training days over a 5-6 week period, making for a total of 10 hours of training. It included not only 3 basic types of WM training tasks, but also a choice-reaction time task with a component of the go/no-go task (inhibition). The second study's training lasted 40 minutes per day, for about 27 training days over a 5 week period which resulted in 17 hours of total training time. The training consisted of only 6 basic types of WM training tasks. These two studies showed that training was associated with improved performance on non-trained WM tests /61/, a Stroop test, and a reasoning test (Raven's progressive matrices). Furthermore, the first study showed that training was associated with the reduction of head movement while performing the continuous performance task, suggesting an improvement in the symptoms of hyperactivity. Although, this first study's training task included a non-WM choice-reaction task with an inhibition component, Thorell et al. /107/ reported that this kind of training on inhibition tasks does not lead to any improvement on non-trained tasks. Thus, the first study's effect on non-trained tasks may be entirely due to WM training.

5.3 Stroke

In a clinical study, Westerberg et al. /119/ investigated the effects of WM training in adult (mean age = 54 y.o.) patients with stroke. They showed that, using 7 basic-type WM training tasks, training WM 40 minutes per day, for 23 training days over a 5 week period, for a total training time of 15 hours, was associated with improved performance of non-trained WM tests and attention tests (PASAT version A /43/, RUFF 2&7 /92/, as well as the improvement of cognitive functioning in daily life. However, in this study, WM training was not associated with improved performance on a reasoning test (Raven's matrices test) (possibly due to a ceiling effect), the Stroop test, nor a declarative memory test (word list learning).

5.4 Multiple sclerosis

In a clinical study, Vogt et al. /111/ investigated the effects of WM training in adult (mean age = 44 y.o.) patients with multiple sclerosis. They used the 2 types of training protocols; the first was performed 45 minutes per day, 4 times per week over a 4 week period and the second was performed 8 times per week over an 8 week period. The total amount of training time in both studies was 12 hours. They showed that training WM with 2 basic-type (visual and verbal) WM tasks, 1 complex verbal WM task, 1 updating task) was associated with improved performance of non-trained WM tests, processing speed tests, and an attention test. The training was also associated with an improvement in fatigue symptoms. No training effects were found on the quality of life or depression. Since fatigue has been identified as an important contributor to cognitive performance in patients with multiple sclerosis /22/, training-related cognitive improvement in patients with multiple sclerosis may be mediated by a training-related improvement in fatigue. The effects of the difference in training protocol were not clear in this study.

6. EFFECTS OF WM TRAINING IN HEALTHY ELDERLY ADULTS

The effects of WM training in healthy elderly adults have been investigated in a few studies and the results may indicate a relatively limited extent of plasticity in them. Buschkuehl et al. /18/ investigated the effects of training with a basic-type visual WM task and complex WM tasks using animal pictures as stimuli, as well as reaction time tasks in healthy elderly adults. Training protocol lasted 45 minutes per day, for 23 training days over a period of 12 weeks, for a total training time of 17 hours. The training led to the improved performance of non-trained basic-type visual WM, but the training did not lead to an improvement of non-trained basic-type verbal WM (note: verbal WM tasks were not included in the training tasks) or visual and verbal free recall tasks (declarative memory tasks). However, in the Dahlin et al. /31/ study, training that used 5 updating tasks in a training protocol lasting 45 minutes per day, performed 3 times per week over 5 weeks, for a total training time of 11 hours in elderly healthy adults did not lead to improved performance of either the non-trained updating task (N-back task) or any other tasks. The same training used with young healthy adults led to improved performance of the N-back task (However, see also the study by Li et al. /66/ that showed the similar effects of non-adaptive WM training on both young and elderly healthy adults.) Together with previous studies that showed elderly adults are limited in the capacity of plasticity /124/, studies now seem to suggest that WM training in elderly adults may not be able to cause the same amount or the same range of cognitive improvement as it can in young adults, at least under certain conditions.

7. EFFECTS OF WM TRAINING ON NEURAL SYSTEMS

Several studies have examined the effect of intensive adaptive training on various aspects of neural systems including functional activity, cortical dopamine density, and brain structures, as described below. These studies have demonstrated that the intensive adaptive training of WM impacts multiple aspects of the neural systems in the fronto-parietal network, which play a key role in WM /7,58/. The front-parietal network is engaged in a wide range of externally-directed attention-demanding tasks /20,27/. Thus, the altered neural mechanisms in the fronto-parietal network may underlie the improvement of, not only WM, but also a wide range of improvement in cognitive functions, as described above.

7.1 Functional activity

In a functional magnetic resonance imaging study, Olesen et al. /78/ showed that, using young adult samples and training WM with 3 basic-type WM training tasks 40 minutes per day, for 18 days over a period of 5 weeks, resulting in 12 hours of total training time, was associated with an increase in functional activity during a WM task in the lateral frontal and parietal regions, together with other regions. However, Dahlin et al. /30/ showed that training which used 5 updating tasks over 5 weeks for 45 minutes each session, 3 times per week, resulting in 11 hours as a whole, was associated with decreases of brain activity in both frontal and parietal regions in one updating task. The training was associated with increases in activity in frontal and parietal regions in another updating task, along with brain activity changes in other regions. Whether the activity of frontal and parietal regions after WM training increased or decreased may depend on the task during which brain activity was measured or the training tasks and other factors.

7.2 Cortical dopamine D1 receptor density

In a PET study, McNab et al. /72/ showed that using young adult male samples and training WM with 10 basic types of WM training tasks 30-45 minutes per training session, for 24 sessions over 5 weeks, resulting in 14 hours total training time, was associated with changes in dopamine D1 receptor density in the right prefrontal and bilateral parietal regions.

7.3 White matter structural integrity

Using diffusion tensor imaging, our previous study /104/ showed that in young adult samples, training WM using 1 basic-type WM training task, 1 complex N-back (update) task, and 1 dual N-back (update) task for 2 months (1 session was 25 minutes, frequency of training depended on subjects), was associated with increases in white matter structural integrity in the white matter regions adjacent to the intra parietal sulcus and the anterior part of the body of the corpus callosum, which connects the bilateral DLPFCs /10/.

7.4 Gray matter structure

Using voxel-based morphometry, our recent study /105/ showed that using young adult samples and training WM using mental calculation 4 hours per day, 5 times over a 1 week period, for a total of 20 hours training, was associated with a reduction in the regional gray matter volume of the bilateral DLPFCs, the bilateral parietal cortices, and the left superior temporal gyrus.

8. GENETIC STUDY

The practice effects of WM training are shown to be affected by genotype in a recent study /14/. In this study, 29 young adults (mean age 26) received WM training on 7 basic-type WM training tasks which they performed 25 minutes per session, for about 23 sessions over a 4 week period (a total training time of 9 hours). An increase in the performance of trained visuospatial WM tasks is substantially related to genotype in the dopamine transporter (DAT1) gene. The genotype (DAT1 10-repeat allele) that showed larger practice effects of WM tasks is associated with a higher striatal DA level. The finding is interesting considering the association between dopamine and neural plasticity level /101/. Further research on genetic studies may give us new insights into the underlying physiological mechanism of WM training and how the training effects can be enhanced.

9. ANOTHER METHODOLOGICAL ISSUE

Another important methodological issue that is not described in the section above is how to design the control group that does not receive the experimental intervention, but still receives the cognitive tests or imaging measures. This is important because (a) if participants perform the cognitive tests twice, without any intervention, participants may improve on the tests probably mainly because of the practice effects and (b) the expectancy effects of subjects (as observed in the placebo effect), at least in some cases, may affect their improvement in tests performance. The recommendation in previous reviews /17,59/ is the inclusion of the "active" control group which receives believable alternative intervention and controls for the expectancy of effects, contact with experimenters, use of a computer and so on. However, how to design the control group is a difficult issue. In some previous studies, the active control group received non-adaptive WM training in which the difficulty of the tasks did not change from the initial low level /60,61/. It is reported that when subjects perform WM tasks that do not adapt the difficulty level, WMC is typically not increased /63,84/. However, a recent study in which WM training's effects on subjects with a low IQ were investigated, not only adaptive WM training, but also non-adaptive WM training led to an improvement of performance on the cognitive tests, although the differences between the effects of non-adaptive WM training and adaptive WM training were not clear. The cause of this phenomenon may remain unknown, but the methodological characteristics, including subjects' individual characteristics, might be one factor. Whether or not non-adaptive WM training is ineffective in a study should be considered carefully. In some studies, computer games without WM demand have been used /107/. However, since it is well known that certain computer games affect cognitive functions and neural systems /41,44/, that point should be considered carefully when computer games are used in a control group. In some studies, when the active control group and the non-intervention group ('passive' control group) are compared, no effects of active control intervention on cognitive functions are observed. This suggests that the expectancy effects are only observed or not negligible under certain methodological characteristics /66/).

In imaging studies of intensive adaptive training of WM, usually, or often, to show the effect of WM training, the associations between training related variables and changes in imaging measures among the intensive adaptive WM training groups were investigated without any control groups /72,78,104/. However, when training-related (training other than WM training) regional gray matter changes have been investigated, studies have rather consistently failed to identify the linear relationship between gray matter change and intervention-related variables /13,34,35,53/. These results may suggest the inappropriateness of these correlation methods when we investigate certain imaging measures. In other imaging studies of intensive adaptive WM training, the no-intervention control group (or passive control group) was used /30/. Because interventions that have not been shown to cause transfer effects can affect brain structures /e.g., 34/ when using the active control group in imaging studies, that point should be considered carefully.

It seems that, as a whole, how to design the control group or active control tasks should be decided based on the other methods of the study. Designing both the appropriate non-intervention control group and the "active" control group can universally work; however, it obviously increases the burden of the study and increases the study's statistical difficulty because of the increased statistical comparisons. Furthermore, because the expectancy of the testers affects the performance of subjects /54-56/, the testers should be blind to the information of the group that the subjects belong to.

10. UNINVESTIGATED ISSUES.

Many psychological, clinical, and neuroimaging WM training studies have been performed. However, considering the importance of WM and fluid intelligence, which are deeply associated with WM /26/ and which can be improved through at least certain kinds of WM training, numbers of interesting topics remain to be investigated in terms of numerous psychological, clinical, and neural aspects.

As for the subjects of the studies, for example, the deficits of WM systems are associated with numerous psychiatric and neurological developmental diseases, and with aging, as described in the Introduction. Improvements of both cognitive functions and symptoms in some of the diseases have already been reported as were introduced previously. Still, whether these kinds of improvements, including cognitive functions that are relatively distant from WM, such as theory of mind or affective states, are observed in other diseases remain to be investigated. Also, some studies have reported that fluid intelligence plays a key role in experts of certain fields such as chess (e.g., /38,49/ but also see /12/). Also fluid intelligence contributes, not only to academic performance /25/ but also to job performance /89/. Thus, other interesting research topics are whether WM training can enhance the abilities of experts in certain fields, improve academic and job performance, or help improve novice learning of certain skills.

As described previously, a genetic study has been performed in relation with WM training. Furthermore, a recent animal study using mice has shown intensive adaptive training of WM (using a radial maze) improves performance of several independent cognitive tasks in mice /67/. Further genetic and animal studies will help us understand the genetic and physiological basis of WM training and how the effects of WM training can be improved (such as pharmacologically). The differences in the effects of different WM training tasks (such as visual WM vs. verbal WM) as described above are another interesting topic, but because the difference between the two effects are small, it would probably be challenging to show the difference statistically. This largely remains an issue to be investigated.

11. CONCLUSION

The training of WM was associated with a wide range of cognitive improvements in non-clinical and clinical subjects, though, on certain points, the results are divided. In clinical studies, training of WM was associated with the improvement of clinical symptoms outside the laboratory. Neuro-imaging studies of WM training revealed the effect of WM training on the neural systems of the fronto-parietal network which play a key role in WM. Still, as described just above, there are a number of uninvestigated important issues, and we anticipate future studies will solve these.

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