

### The effects of multimodal training on working memory in younger and older adults

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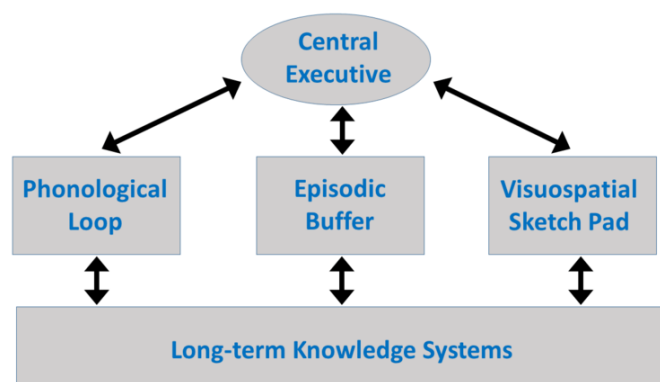
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#### What it is Working Memory?

Working Memory (WM) has been defined as an active memory system that is responsible for the temporary storage and simultaneous manipulation of information (Baddeley, 1992). Over the last decade, a considerable corpus of research has been conducted to examine how WM capacity can be efficiently maintained and improved throughout adulthood (Morrison & Chein, 2011; von Bastian et al., 2012). A potential reason for this widespread interest is that WM has often been linked to everyday functions, such as goal-directed behaviour, decision-making, emotional regulation, cognitive flexibility and general intellectual capacity (Del Missier et al., 2013; Engle, 2002; Mansouri et al., 2015; Xiu et al., 2018; Ye et al., 2019).

WM relies on various structural and functional brain connections compared to other cognitive processes, mainly involving the prefrontal, cingulate, and parietal cortices (Lenartowicz et al, 2005; Mackey & Curtis, 2017). Currently, the most accepted model for explaining WM is the multicomponent working memory model (Baddeley & Hitch, 1974; Baddeley, 2000) which defines WM as a network involving a set of different sub-systems (auditory & visual), each with its own capacity and characteristics processing different types of information. The original model proposed a control system (i.e. central executive) that is responsible for monitoring and coordinating two distinct short-term memory systems, one for verbal information (the phonological loop) and one for visuospatial information (the visuospatial sketchpad). An updated version of this model proposed by Baddeley (2000) added a fourth component, the "episodic buffer", which is a temporary store capable of integrating information from the other components of WM and potentially connecting information to long term memory (see Figure 1).

Fig 1. The working memory model proposed by Baddeley (2000).



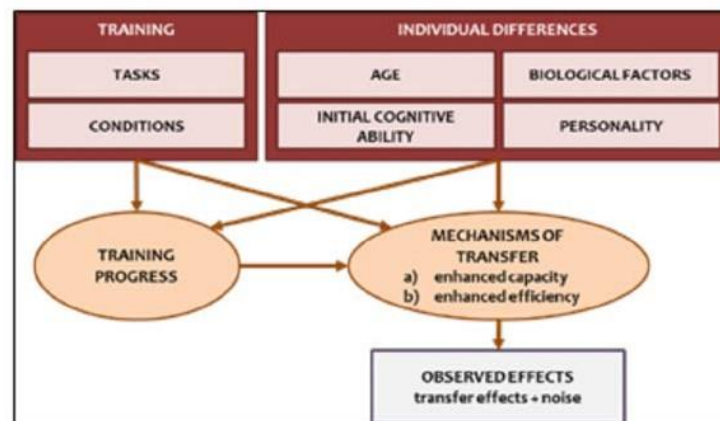
## The role of Working Memory training

The importance of WM training stems from evidence showing that WM may predict performance in a variety of cognitive abilities such as reasoning (Oberauer et al., 2008), reading comprehension (Goff et al., 2005), problem-solving (Swanson & Fung, 2017) and mathematical ability (Allen et al., 2020).

In addition, WM training programmes may have a crucial role in slowing down age-related cognitive decline. In particular, evidence showed a decline with age in both verbal and spatial WM tasks (Bo et al., 2008; Cargin et al., 2007), as well as alterations in other WM-related functions such as cognitive control, monitoring and inhibitory processes (Henderson et al., 2020; McDaniel et al., 2008; West & Alain, 2000). Also, a large number of studies have shown that the difference between younger and older people's performance is more accentuated with the increase in WM demands (e.g. updating information, inhibiting of task-irrelevant stimuli, shifting mental sets; Dorbath et al., 2011; Freitas et al., 2007; Oberauer, 2001; von Bastian et al., 2013; Yi & Friedman, 2015). These findings converge with functional magnetic resonance imaging (fMRI) studies showing bilateral activation of WM-related prefrontal areas in older adults, which may compensate for cognitive decline and to maintain performance in WM tasks at higher levels of complexity (Reuter-Lorenz et al., 2005), suggesting that WM is especially sensitive to age-related changes.

The most common way to improve WM is through targeted computerised training (Melby-Lervåg & Hulme, 2013; Shinaver et al., 2014). Typically, WM training is adaptive so that task difficulty is adjusted to individual performance, or includes tasks or stimuli presented in different modalities (verbal, visuospatial or both modalities) commonly associated with feedback on accuracy (Adam & Vogel, 2018; Brehmer et al., 2012;). Furthermore, WM training could differ for aspects such as duration and intensity, the presence of a control active group rather than a passive group (Borella et al., 2013; Penner et al., 2012), as well as individual differences (see Figure 2; von Bastian & Oberauer, 2013).

Figure 2: Factors that could influence the effects of WM training and mechanisms of transfer (Adapted from



von Bastian & Oberauer, 2013)

WM training may typically comprise domain-specific techniques (e.g. method of loci, which trains to visualise spatial environments to improve information recall) or dual-task modalities (e.g. N-Back Task, which involves simultaneous completion of two tasks while relying on the same component of WM; Borella et al., 2010; Li et al., 2021). In particular, WM strategy-based training (e.g. organise individual pieces of information into chunks or inhibit irrelevant information) may benefit performance across different tasks (Chan et al., 2019; Robert et al., 2009, Thalman et al., 2019). Given WM's central role in everyday situations, some training programmes target different mechanisms of WM and/or related cognitive abilities. A good example of this approach is Cogmed (Roche & Johnson, 2014) in which participants are trained using multiple computerised verbal and visuospatial memory span tasks. Similarly, the COGITO study (Schmiedek et al., 2010) trained participants with WM tasks as

well as tasks involving episodic memory and perceptual speed.

Despite evidence showing transfer effects of WM training in both trained (e.g. transfer effect from verbal to visuospatial WM tasks) and untrained WM tasks (e.g. transfer effect from WM to short term memory), studies about the transfer effects on other untrained cognitive tasks (i.e. far transfer or generalisation of training effects to other cognitive abilities such as fluid intelligence or sustained attention) are limited (Borella et al., 2010; Brehmer et al., 2012; Richmond et al., 2011; Shipstead et al., 2012; Teixeira- Santos et al., 2019; Zinke et al., 2014). Moreover, research has examined the transfer and maintenance effects of WM training in older populations. For instance, a recent metanalysis (Soveri et al., 2017) showed a moderate effect of task-specific transfer to the untrained N-Back Tasks. Borella et al. (2010) showed the transfer effects of a verbal WM training programme on measures of visuospatial WM, short-term memory, inhibition, processing speed, and fluid intelligence in adults aged 65–75 years.

### **Multimodal working memory training: Evidence from physical activity, neurostimulation and neurofeedback intervention**

It is therefore not surprising that researchers have sought out alternative approaches to existing WM training to improve results.

In this context, multi-modal interventions have been proposed, becoming a new and promising approach for maintaining brain functions and enhancing neuroplasticity (Kane et al., 2017; Ward et al., 2017). Multimodal training refers to the use of multiple modalities or delivery methods to promote skill learning across various cognitive domains, including executive functions, WM, and problem-solving (Ward et al., 2017).

Multimodal interventions have been shown to be potentially effective in preventing age-related cognitive decline by eliciting changes in psychophysical function and quality of life (Baker et al., 2007; Kane et al., 2017; Morat et al., 2021). In accordance with this, a report from the Cambridge Institute of Public Health (2015) highlighted the need for using multimodal intervention to delay cognitive decline and dementia onset. However, the outcomes of multimodal cognitive training have rarely been examined directly, and so far, only a few studies have compared the effects of different multi-modal training in different age groups.

The main focus of this review is to evaluate the durability and effects of multimodal training and whether such interventions may impact near or far transfer measures in younger (people aged 18–55 years) and older adults (people aged 65 and over). In particular, we will focus on the empirical evidence regarding the effects of WM training paired with the following interventions: physical exercise, non-invasive brain stimulation (tDCS) and neurofeedback.

### **Physical activity and WM**

Several studies have reported positive effects of combined physical activity (i.e. aerobic or cardiovascular training) and cognitive stimulation in younger (Elkana et al., 2020; Mekari et al., 2015) and older adults (Tait et al., 2017; Theill et al., 2013; Zhang et al., 2018). These findings suggest that the combined training may benefit both cognition and mood, in younger adults. In particular, exercise affects cognitive functions (executive and non-executive) when the physical workload increases. In older adults, results showed that combining physical and cognitive interventions yielded significant improvements in cognitive-motor tasks and life satisfaction when compared to unimodal training.

Systematic reviews and meta-analyses have shown that the synergistic effect of exercise and cognitive training interventions were associated with enhanced physical abilities (e.g. balance, endurance, postural control, etc.), psychological wellbeing and cognitive performance, particularly on attentional control, executive functions and WM (Eggenberger et al., 2016; Lauenroth et al., 2016). This might be owing to the fact that physical activity increases blood supply and synaptic plasticity in frontal and parietal areas, allowing greater recruitment of these areas and their metabolic resources whenever a task with higher cognitive demands is performed (Hashimoto et al., 2018; Hsu et al., 2017; Thomas et al., 2012).

In support of these findings, a study by Colcombe et al. (2004) demonstrated that aerobic exercise (six months, three times weekly) and cognitive training (task-related attention and executive control) increased activation in the frontal, parietal and cingulate cortices, brain areas involved in attentional control and WM. Therefore, the combination of the two interventions potentially increases these

effects rather than each one alone, both in younger and older adults, as also confirmed by several studies (Barnes et al., 2003; Desjardins-Crépeau et al., 2016; Elkana et al., 2020; Sofi et al., 2011).

When embarking on this multimodal approach, several factors such as length, frequency, intensity, duration of the cognitive training, and individual differences (i.e. education, cognitive baseline performance) ought to be considered (Lauenroth et al., 2016), as they may predict long-term effects, particularly in WM performance (Kalbe et al., 2018). Additionally, it is important to consider whether physical and cognitive training sessions are implemented sequentially (Legault et al., 2011) or simultaneously (Theill et al., 2013). Based on evidence from simultaneous cognitive training and physical exercise, significant benefits for older adults typically appear after a minimum of 12-weeks or 16.5h of training, with a frequency between 1 and 3 times per week (Tait et al., 2007). For example, Falbo et al. (2016) investigated the effects of 12 weeks of physical training (10 minutes warm-up made of walking at different speeds followed by 30 minutes of coordination training and 20 minutes of stretching) and cognitive dual-task training on executive function and gait performance in older adults. For the experimental group, the physical training was associated with concomitant cognitive tasks specifically engaging three core executive functions: inhibition, WM and shifting. Both types of training improved gait performance, but only the physical-cognitive intervention contributed to improving the inhibitory efficiency.

A systematic review (Laureonth et al., 2016) revealed that the effect of combined physical and cognitive training (WM + other cognitive domains) concerned mostly cognitive improvement in trained cognitive functions rather than a generalisation to daily-living skills or long-term effects on cognition. For example, studies involving simultaneous WM training with physical exercise for older adults have demonstrated a cognitive improvement in executive functions and similar trained tasks (e.g. paired associated task; Takeuchi et al., 2020; Theill et al., 2013). A study by Desjardins-Crépeau et al. (2016) showed the transfer effects of a 12-weeks dual-task training (a mixed aerobic and resistance training + visual discrimination tasks) on the speed of processing, inhibition and task-switching abilities in older adults. In another study, a simultaneous verbal WM (30 minutes) and cardiovascular training (30 minutes) were found effective in improving cognitive performance in the trained working memory task as well as in the executive control task, paired-associates task, and motor-cognitive dual-task in old adults (tot. duration = 20 sessions, 10 weeks), whereas the single cognitive training only increased performance in the trained working memory task and executive control task (Theill et al., 2013).

However, it remains to be determined whether WM training and physical exercise may improve untrained cognitive abilities.

### **Transcranial direct current stimulation combined with WM training**

Another promising intervention combined with WM training that has gained increasing traction in recent years is transcranial direct current stimulation (tDCS). tDCS is a non-invasive brain stimulation method to facilitate (anodal stimulation) or inhibit (cathodal stimulation) neural activity, via electrodes applied on the scalp (Nitsche et al., 2008; Thair et al., 2017).

In recent years, there has been great interest in improving or stabilising WM, by pairing non-invasive brain stimulation with WM training, often using the N-Back paradigm (Jones, 2015; Nissim et al., 2019). Findings indicate that the effect of tDCS plus WM training on WM capacity may depend on the polarity and site of stimulation (Ke et al., 2019). For instance, anodal tDCS (1mA, 10 minutes) and WM task (3-back letter working memory task; 5 minutes; Mull & Seyal, 2001) applied to the left dorsolateral prefrontal cortex (DLPFC), has been reported to enhance WM accuracy in healthy adults (Fregni et al., 2005). However, the same task when performed with anodal stimulation over the primary motor cortex or cathodal stimulation over the left DLPFC did not improve WM accuracy.

In addition, other parameters, such as the location of electrodes, task difficulty, length of stimulation or individual differences (e.g. baseline ability, gender, motivation level or genetic factors) were found to be important factors on affecting the efficacy of neurostimulation on WM capacity (Gill et al., 2015; Gözenman & Berryhill, 2016; Katz et al., 2017; Talsma et al., 2017). Interestingly, it was found that higher education or WM capacity was associated with better WM performance after tDCS stimulation (Berryhill & Jones, 2012; Berryhill, 2017).

Despite the variability in single-session protocols (Nilsson et al., 2015; Imburgio & Orr, 2018), multiple tDCS-WM training protocols seem to generate more consistent WM benefits in healthy adults. For

example, four days of WM training paired with frontoparietal tDCS (anodal, 1.5 mA, 15 min) improved WM performance significantly more than training alone (Jones et al., 2020). Another experiment (Dong et al., 2020) explored the effect of N-Back training and active or sham tDCS (30 minutes every day for 10 days) using the analysis of event-related potentials (ERPs). This study showed that the amplitude of ERPs increased in the frontoparietal and occipital regions 1-day post-training and alterations were further enhanced 20 days post-training only in the active group, indicating that tDCS-linked WM training can provide accumulative positive effects in those brain areas related to WM after repeated sessions.

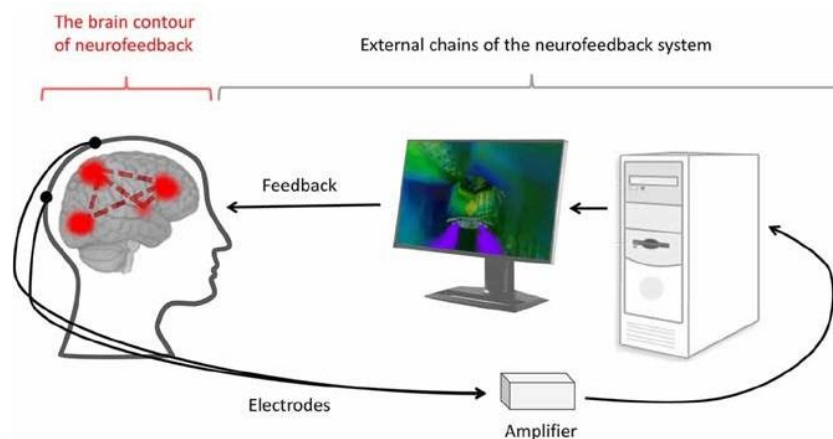
The improvements of tDCS paired WM training were found to be transferred to untrained WM or untrained executive functions (e.g. processing speed, cognitive flexibility, etc.) in young adults (Au et al., 2016; Ke et al., 2019; Richmond et al., 2014; Ruf et al., 2017; Trumbo et al., 2016) and older adults (Jones et al., 2015; Stephens & Berryhill, 2016).

Studies indicated that after 4–7 sessions of tDCS (1 - 2 mA) + WM training, in young adults, maintenance of effects have been observed both after the training and in the follow-up session up to 9–12 months, as compared to the sham conditions (Au et al., 2016; Katz et al., 2017; Ruf et al., 2017). Although limited, also studies in older adults showed maintained significant improvement in trained WM (e.g. recall) and other untrained tasks (e.g. Digit Span Task, Stroop Task, spatial 2-Back Task) at 1-month follow-up after providing 5–10 sessions of WM training paired with mA tDCS when compared to sham condition (Jones et al., 2015; Stephens & Berryhill, 2016).

### Neurofeedback and WM training

A recent approach to multimodal intervention was developed by combining neuro- feedback with WM training. Neurofeedback is a technique of neuromodulation where a computer interface is used to teach self-control of brain functions to subjects by providing feedback about brain functions, with a video display or sound (Marzabani et al., 2016; see Figure 3). During the task, electrical activity from the brain is measured via sensors placed on the scalp using electroencephalography (EEG). Typically, brain activity can be represented by five brain waves based on their frequency that is related to different states of the brain activity such as wakefulness or different sleep stages (Roohi-Azizi et al., 2017).

Figure 3: The neurofeedback system. Source: Drobrushina et al., 2020



The effectiveness of neurofeedback on cognitive and affective outcomes can depend on many factors such as different protocols (e.g. alpha, beta), different EEG electrode placements in the brain areas, electrode montages (unipolar, bipolar), types of neurofeedback (i.e. frequency, power, etc.) and neurofeedback software (Marzabani et al., 2016).

A recent systematic review has provided promising evidence for neurofeedback in boosting cognition,

particularly executive functions and WM, in healthy adults, including older adults (Viviani & Vallesi, 2021). For example, a neurofeedback protocol using a 19-channels EEG (twice a week for 5 weeks; Campos da Paz et al., 2018) showed improved performance in a WM task (completed before and after neurofeedback) with activation in alpha and beta band frontal and temporal in a group of older adults, compared to a group that did not receive neurofeedback. In another study (Reis et al., 2016), an intense alpha and theta training (8-days training protocols, 30 minutes: 32-channel EEG + computerized tests) seemed to improve WM performance (particularly Digit Span and Matrix Rotation) and basal EEG in older adults. Similarly, significant results were also observed in a shorter alpha neurofeedback protocol (N. 4 training sessions) in adults aged over 65 (Lecomte & Juhel, 2011).

Recent research supports the concept that alpha-theta neurofeedback is an effective tool in boosting WM and executive functions also in young adults (Xiong et al., 2014; Viviani & Vallesi, 2021). In a study by Hosseini and colleagues (2016), participants simultaneously received 12 sessions of behavioural feedback regarding their performance on the WM task as well as their brain activity (increased oxygenated haemoglobin in the prefrontal cortex by means of Near-infrared spectroscopy (NIRS). Results showed significant improvements in executive functions performance (in N-Back Task and a switching task) and reduced post-training activity in the prefrontal regions. Of interest is another study that used neurofeedback of alpha activity + WM training (10 training sessions, twice a week; see for details Shahar & Meiran, 2015) to improve executive functions in a group of young soldiers (Gordon et al., 2020), whilst recording EEG. In this study, the combined training was more effective than single protocol (WM training or neurofeedback only) and it also showed a far transfer effect (mental rotation), which remained significant after one month.

### **So, what do these studies tell us about why and how to get benefits from multi-modal training?**

Multimodal interventions were developed in part as a response to the concern about the limited far transfer effects of unimodal interventions. Taken together, these results suggest that benefits in each multimodal intervention seem to be particularly evident when the effect is transferred from a trained task to a similar trained task. Despite the number of experimental studies in each multimodal intervention, the far transfer effects and the generalised effects on cognitive skills are still uncertain and need further investigation.

In both younger and older groups, the results showed similar trends indicating that participants benefited more from the multi-modal intervention than from the unimodal intervention (or sham condition), cross-sectionally. However, to strengthen these conclusions, the findings should be assessed in three dimensions: the magnitude of the improvements in the WM trained tasks or other types of cognition (or other types of memory); generalisability of transfer; durability of training effects. While the positive effects of multimodal training seem to be related to the recruitment of multiple skills that promote neural activity and changes in brain structure and function, future studies should identify the underlying neural and physiological mechanisms to evaluate the observed effects more accurately.

It is worth noting that multimodal interventions can differ significantly according to the type of trial and specific parameters. We assume that, for example, some factors such as individual differences (e.g. age, education, etc.) and training characteristics (i.e. mode of combination, tasks, frequency, session length, etc.) could influence the effect of each multimodal intervention on cognitive performance. Additionally, in the previous studies, there is heterogeneity in the measures used to train or evaluate WM and cognitive abilities, thus severely limiting their comparability. As a result, it is difficult to draw definitive conclusions about the effectiveness of each intervention, particularly when comparing studies between younger and older people. Researchers will need to explore the effects of multimodal interventions on WM and global cognitive function, as well as to address these limitations in future studies.

In summary, the findings reported here show that some multimodal interventions were found to have positive effects on executive functions and WM performance. In particular, tDCS and EEG-neurofeedback intervention were found to improve WM capacity by activating the prefrontal lobes. An important direction for future research will be to estimate the effect of these interventions in WM, executive functions and other cognitive abilities. Overall, the multi-modal approach might help identify key areas for future research to improve mental health and quality of life in both healthy and

clinical populations.

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