Development and evaluation of an adaptive working memory training intervention

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Dissertation

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Deficits in working memory (WM) functions represent one of the main causes of limited participation in daily life and impaired recovery after brain injury. Based on promising research in clinically healthy individuals, which suggest that repetitive training may improve WM performance and other related cognitive functions, this thesis aimed at exploring the potential and limits of WM training in clinical populations. Existing research on WM training and relevant neuropsychological outcomes were examined with a special focus on individuals with acquired brain injury by means of a meta-analysis (study I). The findings indicated relevant impact of WM training on both behavioral performance and disease-related symptom reduction. To determine the primary outcome variable for the evaluation studies, the Corsi Block-Tapping Task was reviewed (study II). Due to the lack of an appropriate theory-based intervention tailored for the needs of individuals with low WM capacity, the program 'WOME' was developed (study III). Three randomized, double-blind, placebo-controlled trials were carried out to evaluate the efficacy of the new intervention and to provide valuable recommendations for its application in clinical practice (study IV, V and VI). Significant improvements in the trained tasks, moderate to large transfer effects in overall WM performance, and related benefits in daily life were demonstrated. The effects were short-termed with very limited evidence supporting transfer to other cognitive functions. In accordance with the results of the meta-analysis (study I), the number of sessions was identified as an important modulator of efficacy by comparing different training intensities and training tasks. The specific content, in contrast, seemed to be less relevant. Mediation analyses revealed that inter-individual differences influence the successful application of the intervention, in particular initial WM capacity. Implications for clinical application and WM training research are discussed.

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1. Introduction

Imagine that you are reading an interesting article in the newspaper when suddenly a phone ring interrupts. Following a short conversation, you may begin to do other things. Later, you find the unfolded newspaper lying on the table and you realize that you completely forgot to finish reading. So, to accomplish your initial plan (read the complete article), a specific goal has to be kept temporarily in mind (return to the table) while handling interfering activities or preparing multiple steps for further action (have a conversation). This process is ascribed to the working memory (WM) system. One can imagine WM as the brain's 'Post-it note' — we use it not only to remember important information, but also to work with it. In recent years, the desire to improve such an essential cognitive system emerged and gave rise to the idea of WM training. The current thesis aimed at contributing to better understand the mechanisms of WM training and to provide new insights regarding potential benefits in cognitive rehabilitation. The findings may also help to bridge the gap between science and clinical practice.

In the following, **chapter one** will present the theoretical framework of the thesis. This includes sections on the psychological concept of WM, its functional relevance and current state of literature regarding WM training. The research questions are summarized and the rational for the experimental work is derived. **Chapter two** will present the experimental work. In study I and II, existing literature on WM training and relevant outcome measures was reanalyzed. On this basis, a new WM training was developed. The development process of the intervention WOME (WOrking Memory; RehaCom®) and first feasibility trials are presented in study III. Study IV, V and VI represent randomized controlled trials evaluating the effectiveness and modulators of the novel

WM training program. **Chapter three** will close with a general discussion of the findings including implications for clinical practice and the research community.

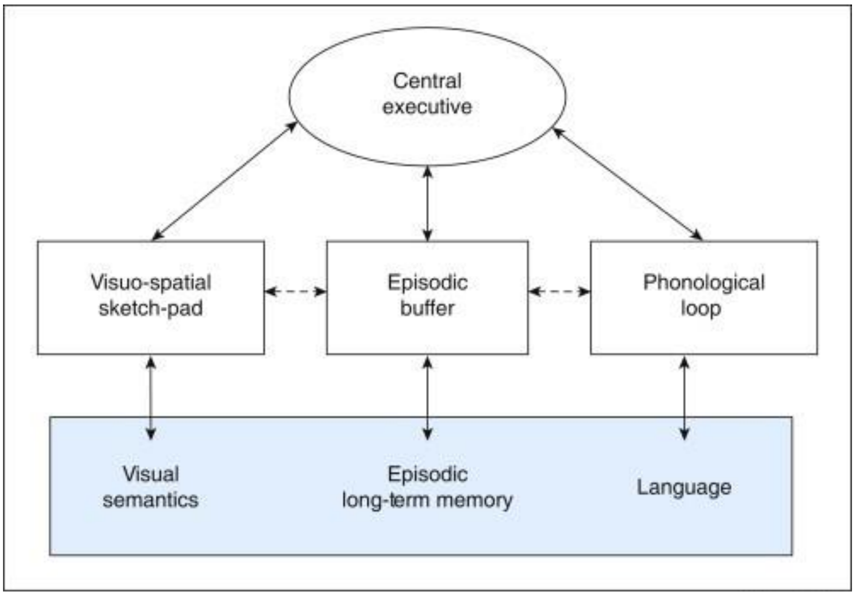
1.1. Definition of the working memory system

Although the essence of WM is easily comprehensible, it is difficult to agree on a consensus of its definition due to the conceptual overlap with long-term memory, attention and executive functions — "If you ask 100 cognitive psychologists what WM is, you will get 100 different answers" (Kimberg et al., 1997, p. 188). However, all theoretical models conform with the WM system consisting of a storage component, which maintains relevant information, and a manipulating component, which processes task-relevant content for various complex cognitions, e.g., making appropriate decisions (Miyake, 1999). While being separable from other cognitive systems, WM is neither unitary nor a closed system (Cowan, 2008; Engle et al., 1999). Its network spreads over wide areas of the brain and is engaged in continuous exchange with long-term memory: Information is retrieved to connect new content to personal experience and knowledge in order to make sense out of it; and meaningful information is integrated into long-term memory (Atkinson & Shiffrin, 1968).

The most established theoretical model and clearest conceptualization of WM is the multi-component model (Baddeley, 2000, 2003; Baddeley & Hitch, 1974). According to Baddeley's model, the system splits into various components: i) the *central executive* which acts as supervisory system that sets goals, controls and regulates attentional resources, and coordinates manipulates information held in WM; ii) two supportive systems which allow temporal storage of modality-related information (*phonological loop* for verbal content and *visuospatial sketch pad* for visual content); and iii) the *episodic buffer* which integrates the information of all domains and links the components to perception, long-term memory and goal-directed behavior. Figure 1 shows an illustration of the multi-component model. Alternative models of WM emphasize the role of the attentional focus and the blurred boundary between WM and long-term memory (Cowan, 1995; Kane & Engle, 2002). These explain limits in WM performance not by storage capacity per se, but rather by constraints in the size of the attentional focus (Cowan, 1995) and the ability to shield relevant information from distracting and interfering stimuli (Kane & Engle, 2002). A detailed overview of WM models is given by Miyake (1999).

Figure 1

The Multi-Component Model of the WM System



Note. Components of the WM system proposed by Baddeley (2000, 2003). Figure reprinted from Current Biology, 20 (4), Baddeley, A., Working memory, R136-R140, Copyright (2010), with permission from Elsevier.

For the following research questions, the theoretical framework was based primarily on the multi-component model because it enables to break down the complex WM system into distinct and comprehensible components, which can be examined, implemented, and evaluated. Individual differences, however, have been primarily explained by the ability to ignore distracting content and to quickly shift the attention back to relevant information (Adam et al., 2015; Fukuda & Vogel, 2011). That is why selective attention and inhibition processes, both included in the central executive of Baddeley's model, were highlighted in the development process of the intervention. The proposed model has been used in many studies in cognitive and clinical psychology and represents a solid basis for further research (Gruszka & Orzechowski, 2016).

1.2. Functional neuroanatomy of working memory

Although the components of the multi-component model are not thought to correlate with specific brain areas (Baddeley, 1986), neuroimaging techniques (e.g., functional magnetic resonance imaging, fMRI) identified several key regions underlying the WM system:

i) *Central executive processes* comprise complex attentional and cognitive control functions, which have been linked to neural activation of the dorsolateral prefrontal cortex, inferior frontal and parietal areas (Owen et al., 2005). However, the neuroanatomical organization of executive processes is still under debate. Evidence supports consistent activation of broad frontal and parietal regions with distinct activation patterns depending on content (verbal, visual, or visuospatial information) and sub function (maintenance or manipulation processes) of WM (Nee et al., 2013; Owen et al., 2005; Suchan, 2008; Vuontela & Carlson, 2011). Further, intensity of neural activity and hemispheric lateralization depend on various factors, e.g., task difficulty and temporal dynamics (Eriksson et al., 2015; Kim, 2019; Motes et al., 2011; Owen et al., 2005; Rottschy et al., 2012).

ii) *The two supportive systems* of WM for the temporal storage of information, i.e., the phonological loop and the visuospatial sketchpad, have been located in the respective sensory-specific association areas for the verbal and the visuospatial modality, respectively (Mishkin & Appenzeller, 1987; Petrides, 1994). Maintenance of verbal information is linked to left hemispheric activation in Brodmann's area 6, 40, and 44 (Awh et al., 1996; Baddeley, 2007; Smith et al., 1996). Maintenance of visuospatial information correlates with right hemispheric activation in Brodmann's area 6, 7 and 47 (Baddeley, 2007; Hamilton & Martin, 2007; Henson, 2001; Smith et al., 1996). Accordingly, lesions of the lateral temporal lobe lead to deficits in verbal WM performance while visuospatial WM remains unaffected (Bormann et al., 2015), whereas lesions of the parietal cortex result in the opposite pattern (Pisella et al., 2004).

iii) *The episodic buffer* seems to be represented by bilateral activations in prefrontal and parietal areas (Gruber & Cramon, 2003; Prabhakaran et al., 2000; Zhang et al., 2004). The hippocampus, the key region of long-term memory storage (Cave & Squire, 1992), has been found to engage in WM processing as well (Berlingeri et al., 2008; Buckner et al., 2000; Davachi & Wagner, 2002; Mitchell et al., 2000; Petersson et al., 2006). It has been proposed that the left anterior hippocampus plays an important role during encoding of information (Rudner & Rönnberg, 2008).

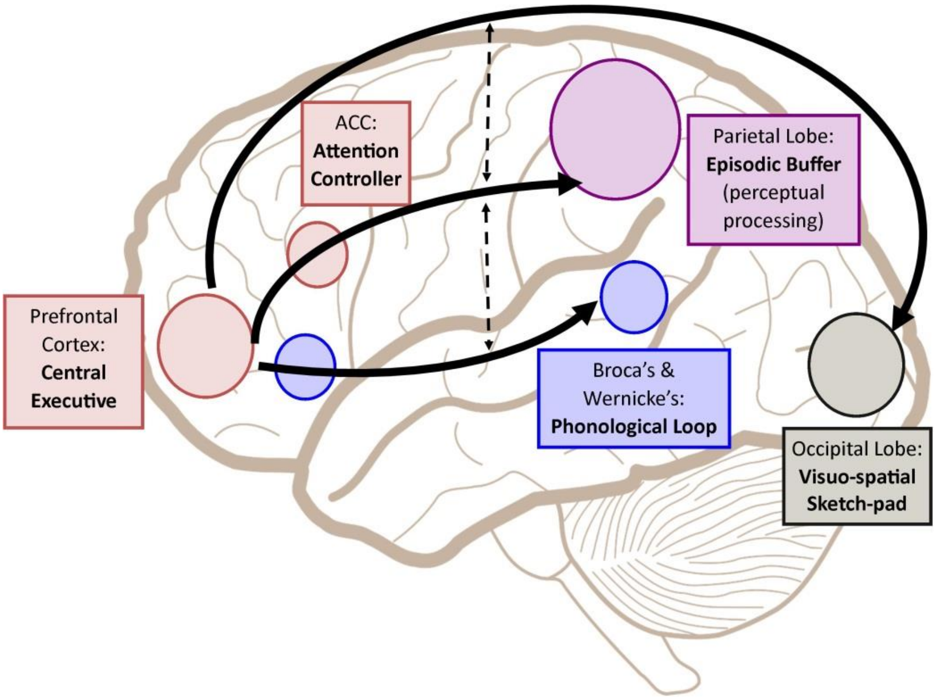
Despite the functional attribution of distinctive components, the WM system is not located in independent single areas but it is rather a large interacting network. According to the concept of WM being not only a system for short-term storage and manipulation of information but also a system that enables goal-directed behavior in a specific context, a large number of brain regions and their dynamic interconnections have been identified (for a review, see Eriksson et al., 2015). Relevant regions comprise the prefrontal, parietal, temporal cortex as well as regions in the basal ganglia, thalamus and cerebellum (Macher et al., 2014; Nee et al., 2013; O'Reilly & Frank, 2006; Vuontela & Carlson, 2011; Wager & Smith, 2003). They overlap with the dorsal attention network, which is engaged during goal-directed attentional processing (Corbetta & Shulman, 2002); the salience network, which is involved in the detection and evaluation of stimuli (Seeley et al., 2007); the fronto-striatal circuits, which support cognitive control and reinforcement learning (Frank et al., 2001); and the cerebro-cerebellar loop, which contributes to phonological rehearsal and maintenance (Chen & Desmond, 2005). The specific activation patterns differ depending on many variables, including the type of information to be remembered, the functional and temporal sub processes involved, the difficulty of the task and the specific goal which has to be achieved (Eriksson et al., 2015). See Figure 2 for an illustration of the neural WM network.

1.3. Functional relevance of working memory

The capacity of the WM system is highly stable over time and appears to be a personality trait (Kane & Engle, 2002). It develops during childhood and adolescence, showing linear increase until the late teens, relative stability between 20 and 50 years, and continuous decline thereafter (Nyberg et al., 2014; Ullman et al., 2014). Due to the bottleneck for information processing, individual WM capacity determines many 'higher order' cognitive functions, for example reasoning

Figure 2

The Neural WM Network



Note. Schematic illustration of the location and interaction of the WM components proposed by Baddeley (2000, 2003) in the brain. The central executive controls and allocates attentional resources of the supportive systems of WM and the episodic buffer. ACC = Anterior cingulate cortex. Figure reprinted from Frontiers in Psychology, 9, Chai et al., Working Memory From the Psychological and Neurosciences Perspectives: A Review, 401, Copyright (2018), with permission from Frontiers Media SA.

and intelligence (Unsworth et al., 2015), problem solving (Miyake, 1999), communication (Daneman & Carpenter, 1980), and reading abilities (Daneman & Merikle, 1996). Moreover, WM performance predicts acquisition of new skills and overall academic success (Alloway & Alloway, 2010; Pickering, 2006). Impairment of WM is not only observed during normal aging but in a range of neurological and psychiatric disorders, including attention deficit hyperactivity disorder (Martinussen et al., 2005), schizophrenia (Goldman-Rakic, 1994), dementia (Collette, 1999), and multiple sclerosis (Chiaravalloti & Deluca, 2008). Acquired brain injuries are caused by medical conditions after birth which lead to damage of the brain, i.e., stroke, traumatic brain injury, cerebral hemorrhage, meningitis and brain tumors (Sturm, 2009). Individuals may experience not only damage of sensory, physical or language functions but also serious cognitive impairments (Prigatano, 1999). Cognitive deficits represent a common problem in patients with an otherwise good neurological recovery, affecting quality of life, recovery from injury, and resumption of work (Baumann et al., 2014; Fried et al., 2016; Lundqvist et al., 2010; Robertson & Murre, 1999). Patients with WM deficits often report that they are forgetful and easily distracted, lose their concentration, have difficulties to understand complex written text passages, and struggle to switch between tasks or execute them simultaneously (Hinkeldey & Corrigan, 1990). Following acute treatment, multidisciplinary long-term care is required to rebuild the level of functioning and participation (Doering & Exner, 2011; Turner-Stokes et al., 2015). The objective of neurological rehabilitation is to help regain the patient’s autonomy, social integration and life satisfaction, which considerably depends on being able to return to work (Knecht et al., 2011). Cognitive resources are ranked among the top three factors indicating the patient’s subjective readiness for it (Vestling et al., 2003). Neuropsychological rehabilitation is the individual process that combines specific training to remediate cognitive functions as well as learning and adapting strategies to cope with the changed living conditions (Wilson, 2005). Due to the immensely adverse effects on the quality of life, functional improvement of WM processes appears to be highly relevant.

1.4. Training of working memory functions

As already indicated, WM capacity is regarded as relatively constant and, for a long while, it was thought that it may not be enhanced or remediated after injury or disease (Oberauer et al., 2000). For this reason, the therapeutic approach was based on compensation, providing strategies on how to use intact functions efficiently and promote strengths to balance out weaknesses (Moore Sohlberg et al., 2000). Treatment included teaching techniques for enhanced encoding, maintenance and retrieval of information to enhance performance in specific tasks, e.g., rehearsal which is repeating content over and over again (Klingberg, 2010). Such trainings have been shown to improve specific abilities, e.g., memorization of names or phone numbers, and better subjective memory performance (Morrison & Chein, 2011). In addition to increased performance in the trained tasks, it is highly desirable that training leads to generalization, i.e., transfer effects on unpracticed tasks or even everyday life functioning. Otherwise, the learned strategies would be applicable only in very specific circumstances and may not help when the context differs from the training paradigm.

At the beginning of the 21st century, cognitive neuroscience confirmed neural plasticity, i.e., the modifiability of brain structure and function according to internal and external demands, across the life span (Mora et al., 2007). As a consequence, researchers began to target the capacity and processing efficiency of the WM system by applying implicit or 'core' trainings (Cicerone, 2002; Klingberg et al., 2002; for reviews see Bastian & Oberauer, 2014; Morrison & Chein, 2011). Generally, they consist of demanding WM tasks that are presented repetitively to stimulate general mechanisms of WM processing. Following this rationale, numerous studies have applied such an implicit training approach without the supply of strategies to prevent task- or paradigm-specific improvements. Cognitive changes were investigated by comparing the performance in neuropsychological tests before and after training phase. Indeed, results suggested that WM capacity can be enhanced by certain interventions (for reviews, see Bastian & Oberauer, 2014; Klingberg, 2010; Morrison & Chein, 2011). Training-related changes were found in healthy individuals (children, younger, and older adults) and in individuals who suffer from low WM capacity (e.g., children with attention deficit hyperactivity disorder, low birth weight or learning disabilities).

Research suggests that WM training increases performance in various neuropsychological measures of WM, related cognitive functions, and in outcomes that indicate more successful coping with daily life (Bastian & Oberauer, 2014; Klingberg, 2010; Morrison & Chein, 2011). Studies yielded two types of transfer effects after WM training: 1) *near transfer effects,* describing improvements in tasks which are similar to the trained ones (e.g., WM tasks of another modality), and 2) *far transfer effects,* describing improvements in tasks of other cognitive domains (e.g., reasoning) (Morrison & Chein, 2011). Moreover, imaging studies uncovered neural correlates of WM training in multiple areas in the brain, showing changes in activation patterns, adaption of anatomical and functional connectivity, and improved efficiency of neurotransmitters (for a review, see Buschkuehl et al., 2012). Longitudinal studies investigating functional plasticity over time have proposed an inverted u-shape of neural activity when practicing a WM task repetitively, showing increase of activity within the first training sessions and decrease of activity in later stages of training (Hempel et al., 2004; Kühn et al., 2013). Increases in neural activity have been associated with the incorporation of new resources or the development of a new strategy while decreases in neural activity have been interpreted as more efficient processing of information within the WM network, e.g., due to a higher automaticity or a lower number of neurons involved while producing stable or even improved behavioral task performance (Buschkuehl et al., 2012; Hempel et al., 2004). A meta-analysis revealed significant changes (primarily decreases) of functional activity after WM training in prefrontal regions, in the striatum and in the posterior parietal cortex (Salmi et al., 2018). Fueled by the idea that WM training may lead to substantial improvements in overall cognition, a true hype of brain training emerged (Makin, 2016). Appealed by both commercial and scientific interests, literature on WM training increased dramatically in the late 2000s.

Despite the abundant research, yet little is known about clinical applications and potential benefit of WM training following impairment. While research suggests that recovery of damaged neural networks may be possible (Gauggel, 2003) and WM training in healthy individuals have yielded promising findings (for a review, see Klingberg, 2010) only three randomized controlled trials have been carried out in patients with brain lesions when the current research project started (Lundqvist et al., 2010; Vogt et al., 2009; Westerberg et al., 2007). The first study that investigated WM training in a clinical population was published in 2007 (Westerberg et al., 2007). 18 subjects with stroke were randomized into two conditions: Nine subjects exercised WM training daily over a period of five weeks and nine subjects received pre-/post assessments only. Following WM training, significant improvements in untrained verbal and visual WM tasks as well as attentional functions were observed. In addition, subjective appraisal of symptoms in everyday cognitive functioning had decreased. No far transfer effects on executive functions, intelligence and declarative memory were found. Caveats about methodological issues notwithstanding, the results of the study provided initial evidence for clinically relevant effects of WM training. The findings were later replicated in a sample of 21 subjects, confirming improved WM performance and positive subjective evaluation of the treatment (Lundqvist et al., 2010). Another study with 45 patients that suffered from multiple sclerosis substantiated the effectiveness of WM training (Vogt et al., 2009). Following 12 hours of WM training, both highly intensive and distributed exercises led to improved performances in WM, mental speed and decreased symptoms of fatigue in comparison to a passive control group. Taken together, 'core' training of the WM system seems to be a promising intervention to improve WM performance as well as related cognitive functions, and that it could have an impact on health and wellbeing.

Interestingly, no appropriate WM tasks have been developed specifically for individuals with brain lesions. Studies have either used simplified versions of the n-back task (Cicerone, 2002; Serino et al., 2007) or software packages that comprised diverse WM tasks (e.g., Vallat et al., 2005; Vogt et al., 2009; Westerberg et al., 2007). It is still under debate whether n-back tasks, which demand the continuous updating of information, represent an adequate assessment of WM capacity (Jarrold & Towse, 2006), however, researchers agree that a high number of *n* is required (Braver et al., 1997). Due to the impairment of WM functions, this is not achievable in clinical populations. On the other hand, the application of multiple WM tasks leads to difficulties because the training mechanisms are not well understood. They do not enable to target specific components of the WM system or to regulate task difficulty appropriately. Another critical aspect regarding the application of standard WM training in clinical populations is that most programs adapt difficulty by increasing or decreasing the number of items. However, patients may need a much more fine-tuned adjustment: Clinical experience shows that memorizing four items may be non-challenging, whereas five items may overstrain the individuals. So, other paradigms and further task characteristics needed to be identified to provide an appropriate treatment for clinical populations.

1.5. Objectives of the current thesis

The potential to enhance WM as well as related cognitive functions in individuals with acquired brain lesions to achieve functionally relevant improvements in everyday life calls for the implementation of WM training in neurocognitive rehabilitation. Based on the current state of the literature as summarized above, it is evident that (i) there is a lack of theory-based WM training programs and no intervention available that is specifically tailored to the patients' needs, and (ii) existing WM trainings have not been evaluated sufficiently to determine their effectiveness in patients and to provide recommendations for clinical application. Therefore, the aim of this thesis was to develop a theoretically based intervention for individuals with low WM capacity, focusing on patients with acquired brain lesions, and to evaluate it considering its justifiability in clinical treatment. Hereby, the thesis contributes significantly to translational science, i.e., to help bridge the gap between research and clinical practice.

INTRODUCTION

The research questions to be addressed and the derived experimental work may be summarized as follows:

(1) Is training WM functions beneficial from a clinical point of view? More precisely, does WM training lead to functionally relevant improvements for patients with acquired brain lesions?

Study I examines the literature systematically by means of a meta-analysis, addressing transfer effects of WM training on WM functions and related cognitive functions with regard to short-term and long-term effects. Due to controversial findings in individual trials, the study aimed to gather a better understanding on the potential and limits of WM training. A moderator analysis was performed to examine potential influencing factors of training efficacy, i.e., training duration. By this means, it was determined under which conditions the application of WM training may be justifiable in clinical populations.

Hypotheses: Based on previous reviews, it was hypothesized that patients with acquired brain lesions practicing 'core' WM training tasks a) would score significantly higher (i.e., accuracy, total score) in tests of WM performance at post-test after training than patients who receive alternative cognitive or physical interventions, and b) would show significantly lower scores in questionnaires and structured clinical observations measuring disorder symptoms in daily life (e.g., forgetfulness) after WM training compared to before. Further, the following moderating variables of the efficacy of WM training were investigated exploratively: training-related characteristics (i.e., training duration, type of intervention, improvement in the trained task, adaptivity of individual performance and task difficulty), subject group (i.e., age and cognitive abilities), and study design (i.e., type of control group).

(2) According to the previous meta-analysis (study I), one of the outcomes frequently used to assess WM functions is the Corsi Block-Tapping Task (Corsi, 1972). To determine whether the test represents a valid outcome measure for the following evaluation studies, it was analyzed in detail.

Study II investigates the gold standard of neuropsychological assessment for short-term and WM performance with respect to its underlying cognitive processes. The review aimed to elucidate the complexity of demands involved in the task in order to explain its role as an indicator of WM training success.

Explorative hypothesis: The Corsi Block-Tapping Task provides task characteristics that contribute to sensitivity of training-related changes in performance after 'core' WM training. Thus, it is a valid outcome test of WM training interventions.

(3) Based on the insights of study I and II, how should WM training tasks be designed and evaluated in patients with acquired brain injuries?

Study III presents the development process of the WM training intervention WOME (WOrking MEmory). Starting with the rational and framework conditions, the composition of the program and the applied tasks are described. Two pilot studies explored the feasibility of WOME WM training in N = 7 healthy adults and in N = 6 individuals with acquired brain lesions by examining the subject's rating of the enjoyment of the training tasks, by analyzing the performances in the trained tasks, and by investigating the applicability of the outcome parameters (i.e., understanding of the instructions, time and effort to execute the tasks, changes in performance from pretest to post-test). One main goal of the pilot studies was to apply training parameters such that a smooth, but increasing level of difficulty could be achieved. Based on the analyses of the performances in the trained tasks, revisions of the software and changes in the outcome assessment were enabled.

Explorative hypothesis: The new intervention is feasible in individuals with low WM capacity, i.e., healthy older adults and patients with acquired brain lesions, and they comply with the planned study design. Feasibility is indicated by compliance of the subjects (i.e., positive feedback regarding the training tasks, no drop out subjects during the exercise training period) and first indicators of effectivity (i.e., significant increases in the achieved level in the trained tasks, higher total scores in untrained WM tests after the intervention compared to before).

(4) The newly developed WM training intervention is first evaluated in individuals with healthy brain networks, but gradually low WM capacity due to normal aging, to determine its effectiveness by the means of a randomized controlled trial. The specific research questions were the following: Does WOME induce reliable and stable transfer effects on overall WM functioning? Is it possible to identify specific WM components which are affected by the intervention? Are potential increases in WM performance accompanied by changes in other cognitive functions, which partially rely on the WM system, and do individuals experience related improvements in their daily life? Is there an indication that behavioral changes are accompanied by changes in neural brain networks?

Study IV evaluates the efficacy of WOME WM training in a randomized, double-blind, and placebo-controlled trial in a sample of N = 60 clinically healthy older adults. The WOME intervention was compared to a non-adaptive control version and to a passive control group. Training took place over four weeks, resulting in 12 sessions overall. Transfer effects targeting WM as well as related cognitive functions and impact on everyday life were assessed both pre-/post-training and at three months follow-up. Analyses were carried out for subjects' raw scores considering individual neuropsychological tests and comprehensive cognitive functions, i.e., composite scores of multiple tests. Of particular interest was whether the theory-based program represents an appropriate, specific, and efficient intervention for training the WM system. To get a comprehensive picture of the impact of WOME WM training, an investigation of changes in neural brain networks following training was carried out in N = 58 individuals. These data were analyzed by Hudl (2019). As data acquisition was part of this study, the findings will be briefly presented.

Hypotheses: The theoretical framework of the program predicted a) significantly increased performance in the trained WM tasks (i.e., the achieved level) and b) transfer effects on untrained WM functions (i.e., significantly larger total scores in the post-test compared to the pretest) in individuals who receive the WOME intervention but not in individuals who receive a non-adaptive control version or no intervention. Potential benefits following the WOME intervention were expected c) to be sustained over three months, and therefore, performance in WM tasks should be significantly better at a follow-up test compared to baseline. Because of limited far transfer effects observed in the meta-analysis for elderly populations (study I), d) substantial improvements in other cognitive functions (i.e., executive functioning, logical reasoning, long-term memory, and attention) and generalization to everyday life requirements (i.e., subjective memory questionnaires) were not expected; but the conditions were investigated regarding the respective variables to determine whether differential treatment effects would be observed.

(5) Is WOME WM training feasible and effective concerning the primary target group? Precisely, are the near transfer effects on untrained WM tasks, which were found in the healthy sample of study IV, replicable in patients with brain lesions? Is there an indication of symptom reduction or other functional relevance in everyday life?

Study V investigates the efficacy of WOME WM training in a sample of N = 39 patients with brain lesions (n = 28 stroke and n = 11 traumatic brain injury). To determine its applicability, the design was similar to study IV (applying only the active but not the passive control group), featuring a randomized, double-blind controlled trial, and an extensive neuropsychological assessment before treatment, after treatment, and at three months follow-up. A special focus was on the impact of WM training on everyday life functioning. Training related factors as well as injury related variables are discussed.

Hypotheses: Based on the results of study I and study IV, we predicted substantial improvements in WM related outcome measures after four weeks of WOME WM training compared to a non-adaptive control version when applied in individuals with brain lesions. Significant improvements (i.e., higher achieved level, accuracy, or total score) should be observed in a) trained and untrained WM tasks, as well as b) facilitated handling of daily life demands (i.e., lower scores in WM related questionnaires, higher percentage of positive self-reports after WM training). The benefits following the WM training intervention were expected c) to be robust and long-lasting, meaning they are still present at a follow-up test after three months (i.e., significantly better performance in WM tasks and questionnaires at follow-up compared to baseline assessment). According to the results of study IV, d) far transfer on other cognitive functions than WM (i.e., executive functioning, logical reasoning, long-term memory, and attention) was not expected; nevertheless, these cognitive variables were examined to identify potential differences between the training conditions.

(6) Given that in clinical practice functional training is often only one aspect of rehabilitation, it was examined to what extent cognitive training in addition to the extensive standard care is effective in neurorehabilitation. Further, we investigated the influence of two relevant factors for the success of WM training, namely the impact of task specificity and training intensity.

Study VI focuses on the modulators of WM training efficacy examining a sample of N = 20 patients with heterogeneous brain lesions. To identify the dose-response relationship, neuropsychological assessments of WM and related cognitive functions took place before training, after 10 training sessions, and after 20 training sessions. To evaluate specificity, WOME WM training was compared to an unspecific training intervention of attentional functions. Treatment was carried out in addition to standard therapy in an interdisciplinary day-clinic to value the clinical relevance of complementary cognitive training in neurorehabilitation.

Hypotheses: Computer-based cognitive training applied in addition to the standard rehabilitation a) leads to near transfer effects, i.e., significant improvements (i.e., higher achieved level, accuracy, or total score) in untrained WM tests. Because of the modulating effect of training duration identified in study I and because of the brittle evidence of WM efficacy after 12 training sessions observed in study V, intensity was considered as an essential predictor of WM training efficacy. That is why we hypothesized that b) 20 sessions of WOME WM training when compared to 10 sessions would lead to larger effects in trained and untrained WM tasks (i.e., higher level achieved in the intervention, significant increases in accuracy and total scores in WM tests). The theoretical basis of the WM training program was expected to yield specific effects on the WM system, thus it was predicted that the intervention would c) significantly improve performance on untrained WM tests but not on attention tests, and d) produce superior transfer effects than a training program of attentional functions. Further, the experiment should replicate the findings of study I and V and show that e) WM training leads to relevant improvements in daily life as indicated by self-reports of the patients.

2. Experimental work

The present thesis is based on the experimental work presented in the following studies. They are referred to by roman numerals. Four papers have been published in international peer-reviewed journals (study I, II, IV and VI). The publications are:

Study I **Weicker, J.**, Villringer, A., & Thöne-Otto, A. (2016). Can impaired working memory functioning be improved by training? A meta-analysis with a special focus on brain injured patients. *Neuropsychology, 30*(2), 190-212. https://doi.org/10.1037/neu0000227

Study II **Weicker, J.**, Hudl, N., & Thöne-Otto, A. (2017). „Was misst eigentlich die Blockspanne?" - Der Gold-Standard im Fokus. *Zeitschrift für Neuropsychologie, 28*(1), 45-54. https://doi.org/10.1024/1016-264X/a000194

Study III **Weicker, J.**, Hudl, N., & Thöne-Otto, A. (2017). WOME working memory training — A new intervention for individuals with low WM capacity. Unpublished manuscript.

Study IV **Weicker, J.**, Hudl, N., Frisch, S., Lepsien, J., Mueller, K., Villringer, A., & Thöne-Otto, A. (2018). WOME: Theory-Based Working Memory Training A Placebo-Controlled, Double-Blind Evaluation in Older Adults. *Frontiers of Aging Neuroscience, 10,* 247. https://doi.org/10.3389/fnagi.2018.00247

Study V **Weicker, J.**, Hudl, N., Frisch, S., Obrig, H., Villringer, A., & Thöne-Otto, A. (2019). Effects of working memory training in patients with acquired brain injury: a double-blind randomized controlled trial. Unpublished manuscript.

Study VI **Weicker, J.**, Hudl, N.; Hildebrandt, H.; Obrig, H.; Schwarzer, M.; Villringer, A.; & Thöne-Otto, A. (2020). The effect of high vs. low intensity neuropsychological treatment on working memory in patients with acquired brain injury. *Brain Injury, 34*(8), 1051-1060. https://doi.org/10.1080/02699052.2020.1773536

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2.1. Study I: Can impaired working memory functioning be improved by training? A meta-analysis with a special focus on brain injured patients.

Nachweis über Anteile der Co-Autoren, Juliane Weicker
Development and evaluation of an adaptive working memory training intervention

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Nachweis über Anteile der Co-Autoren:

<u>*Titel:*</u> **Can impaired working memory functioning be improved by training? A meta-analysis with a special focus on brain injured patients.**

<u>*Journal:*</u> Neuropsychology, 30(2), 190-212.

<u>*Autoren:*</u> Juliane Weicker, Arno Villringer, Angelika Thöne-Otto

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<u>Anteil Juliane Weicker (Erstautorin):</u>

- Konzeption und detaillierte Gestaltung der Datenanalyse
- Literaturrecherche, Methodenauswahl und ggf. Datenanforderung
- Erfassung und Synthese der Daten mittels RevMan Software
- Analyse und Interpretation der Daten
- Schreiben des ersten Entwurfs des Manuskripts
- Schreiben und Einreichen der Publikation

<u>Anteil Arno Villringer (Autor 2):</u>

- Diskussion und Interpretation der Ergebnisse
- Schreiben der Publikation

<u>Anteil Angelika Thöne-Otto (Senior-Autorin):</u>

- Projektidee und Konzeption der Metaanalyse
- Diskussion und Interpretation der Ergebnisse
- Schreiben der Publikation

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Can Impaired Working Memory Functioning Be Improved By Training? A Meta-Analysis With a Special Focus on Brain Injured Patients

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Objective: Deficits in working memory (WM) are commonly observed after brain injuries and cause severe impairments in patients' everyday life. It is still under debate if training can enhance or rehabilitate WM in case of malfunction. The current meta-analysis investigates this issue from a clinical point of view. It addresses under which conditions and for which target group WM training may be justifiable. ***Method:*** Relevant WM training studies were identified by searching electronic literature databases with a comprehensive search term. In total, 103 studies, which added up to 112 independent group comparisons (N = 6,113 participants), were included in the analysis. ***Results:*** Overall, WM training caused a moderate and long-lasting improvement in untrained WM tasks. Moreover, improvement of WM functioning led to sustainable better evaluation of everyday life functioning, however, effect sizes were small. Concerning transfer effects on other cognitive domains, long-lasting improvements with small effect sizes were observed in cognitive control and reasoning/intelligence. In contrast, small immediate, but no long-term effects were found for attention and long-term memory. Studies with brain injured patients demonstrated long-lasting improvements in WM functions with moderate to large effect sizes. A main moderator variable of intervention efficacy is the number of training sessions applied. ***Conclusion:*** WM training produces long-lasting beneficial effects which are strongly pronounced in patients with acquired brain injuries. This finding supports the application of WM training in clinical settings. To determine optimal training conditions, future studies must systematically investigate the characteristics of interventions as they are at present inevitably confounded.

Keywords: working memory training, rehabilitation, meta-analysis, brain injury, cognitive plasticity

Supplemental materials: http://dx.doi.org/10.1037/neu0000227.supp

Working memory (WM) deficits often occur after brain damage (Cicerone et al., 2011) and are of high functional relevance in patients' everyday life. Patients with WM deficits report loss of concentration, distractibility, and forgetfulness; they have difficulties following longer conversations, understanding complex written text passages, and they struggle to do things simultaneously (Hinkeldey & Corrigan, 1990; Mateer, Sohlberg, & Crinean, 1987). Clearly, such impairments affect the daily routine and resumption of work (Crawford, Wenden, & Wade, 1996). WM is the cognitive system that keeps information in a temporarily accessible state while preprocessing them for higher order cognitive processes such as language comprehension (Daneman & Merikle, 1996), problem solving (Shah & Miyake, 1999), and intelligence (Kyllonen & Christal, 1990). In addition to predictions in laboratory settings, WM capacity plays a key role in real life success as it has been shown for acquisition of new skills (Pickering, 2006; Shute, 1991), academic achievement (Alloway & Alloway, 2010), emotion regulation (Schmeichel, Volokhov, & Demaree, 2008), and executive functioning in everyday life (Kane et al., 2007). WM impairment has been reported in a range of neurological as well as psychiatric disorders, for example schizophrenia (Goldman-Rakic, 1994), the attention deficit hyperactivity disorder (ADHD; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005), multiple sclerosis (Chiaravalloti & DeLuca, 2008), traumatic brain injury (Vallat-Azouvi, C., Weber, T., Legrand, L., & Azouvi, P., 2007), and stroke (Vallat et al., 2005).

Surprisingly, rehabilitation of WM is quite a recent endeavor. Until the late 1990s, it was assumed that WM capacity was fixed in its size and could not be trained or remediated in case of

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malfunction (Oberauer, Süss, Schulze, Wilhelm, & Wittmann, 2000). Patients were mainly treated by providing compensation strategies on how to deal with their persistent WM deficits in combination with social support (Sohlberg et al., 2000). However, novel studies indicated that WM performance can be enhanced by training (for reviews, see Klingberg, 2010; Morrison & Chein, 2011; von Bastian & Oberauer, 2014). Although the ways of treating WM are heterogeneous, typically, interventions are based on computer-based exercises that are conducted in a repetitive way over several weeks. The basic principle of all tasks is to maintain a certain amount of information over a brief period of time, sometimes combined with a secondary task to stress executive processes of WM, such as selective attention or inhibition. Usually the treatment is carried out adaptively to avoid underchallenge and overstraining by adjusting the task difficulty to the subjects' performance. Behavioral improvements after treatment were observed in the domain of WM (Vogt et al., 2009), as well as in linked cognitive functions (Nouchi et al., 2012) and, importantly, they transferred to the subjective appraisal of everyday life functioning (Johansson & Tornmalm, 2012). Imaging studies indicated that such behavioral effects are accompanied by changes in brain activation and structure (Brehmer et al., 2011; Takeuchi et al., 2011), in structural connectivity (Takeuchi et al., 2010), and in the neurotransmitter system (McNab et al., 2009). Nevertheless, not all studies yield consistent results and, currently, there is an intensive discussion if and under which Conditions WM training produces valid transfer effects (for a review, see Morrison & Chein, 2011). Particularly, the potential gain in fluid intelligence following WM training (Jaeggi, Buschkuehl, Jonides, & Perrig, 2008) ignited a heated debate from both researchers in cognitive neuroscience and the general public. Opinions vary from the appealing promise of WM training to be a panacea (Klingberg, 2010) to major doubts of the justification of its purpose (Shipstead, Redick, & Engle, 2012). A recent meta-analytic review by Melby-Lervåg and Hulme (2013) evaluated 23 WM training studies. They concluded that only short-term improvements in WM, but no transfer effects on other cognitive domains were produced by the interventions. Considering developmental perspectives, they advise against the use of WM training. Generally, critics emphasize methodological shortcomings of many studies, the lack of theory-based approaches, as well as the failure of a profound explanation as to why and how WM training should lead to beneficial effects at all. Although von Bastian and Oberauer (2013b) recently proposed a possible mode of action, the underlying neuronal mechanisms are largely unknown (for a review, see Buschkuhl, Jaeggi, & Jonides, 2012).

Since the last major review, numerous important studies have been published. Therefore, it is timely to update and expand the findings on WM training research as the question whether WM training improves WM capacity is still both controversial and important. Furthermore, the current meta-analysis investigates for which target group it may be justifiable. In contrast to previous reviews, we focus on the clinical point of view to answer two essential questions: First, is WM training capable of causing long-lasting WM improvements especially in patients with WM deficits? Second, is enhanced laboratory performance linked to the amelioration of everyday life so that training effects are of functional relevance for those patients and their families? For a better understanding and to improve the conditions of a successful treatment, various characteristics of WM training, for example, type and duration of the intervention, were examined. The findings of this meta-analysis provide crucial insights into future therapy of patients with persistent WM deficits.

Method

The meta-analysis was conducted according to the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analysis; Moher, Liberati, Tetzlaff, Altman, & the PRISMA Group, 2009) and the recommendations of the Cochrane Collaboration (Higgins & Green, 2008).

Literature Search

Relevant WM training studies were identified by two independent raters (J.W. & L.S.) searching the electronic literature databases PubMed and OvidSP (PsycINFO/PSYNDEX/Medline) from beginning to January 2015. Any discrepancies between raters were clarified by discussion. A wide search term was used to detect all trials that include the concept of WM in association with some kind of training (["working memory" or "fluid intelligence" or "workspace" or "executive function*" or"'working attention" or "updating" or "central executive"] and ["training" or "enhanc*" or "boost*" or "improv*" or "expand*" or "practic*" or "increas*" or "chang*" or "remediat*" or "rehabilitat*" or "gain*"]). Additionally, a manual search was performed by scanning reference lists and requesting researchers in the field. Studies meeting the following criteria were included: (a) English language, (b) published in a peer-reviewed journal, and (c) original trial of an intervention designed to improve WM functioning. Studies were excluded if they (a) analyzed only the trained task rather than reporting transfer effects on at least one neuropsychological outcome measure, (b) performed only one training session instead of a repeated intervention program, (c) lacked a control group (except for patient studies because of the small number of available studies), (d) represented case studies with $N < 5$ subjects, and (e) provided insufficient data for effect size calculations. According to our investigation, three study reports shared the same subjects (Dahlin, 2011 and Klingberg et al., 2005; Egeland, Aarlien, & Saunes, 2013 and Hovik, Saunes, Aarlien, & Egeland, 2013; Olesen, Westerberg, & Klingberg, 2004 and Westerberg et al., 2007b). To avoid doubling of included data sets, those studies were combined by integrating the respective outcome measures of each study into one trial. Figure 1 illustrates the processing of studies from initial identification to final inclusion in the meta-analysis.

Meta-Analytic Procedure

Meta-analyses were conducted using RevMan 5.1 software (The Cochrane Collaboration, 2011); additional statistical analyses were done with PASW Statistics 18 (SPSS Inc., 2009). Effect sizes were computed using Hedges' adjusted *g*, which is very similar to Cohens' *d*, but corrects for small sample bias (Hedges & Olkin, 1985). According to Cohen (1988), effect sizes can generally be classified as small ($g \geq 0.2$), moderate ($g \geq 0.5$) or large ($g \geq 0.8$). Hedges' adjusted *g* is calculated by dividing the difference between the experimental and control group mean values by the pooled *SD*. Usually, the *SD* of the change itself is unknown, and

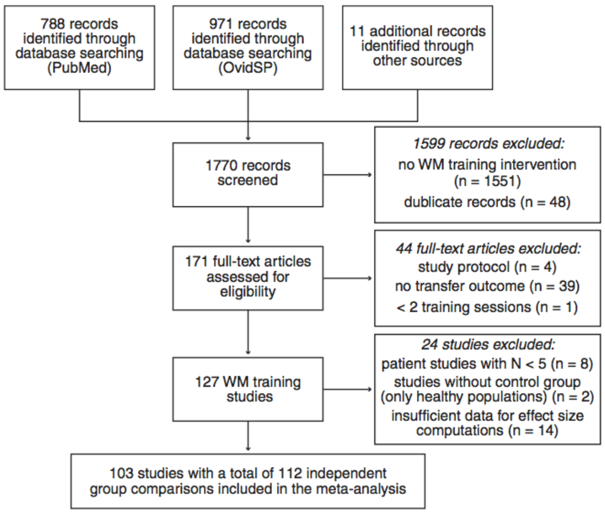

Figure 1. Flow of studies in the selection process of the meta-analysis. WM = working memory.

thus it remains unclear whether the changes were rather consistent or variable. That is why comparisons of the final measurements (posttreatment and follow-up assessment, respectively) were preferred over comparisons of gain scores (pre- to post-follow–up test changes). To ensure similar baseline levels before intervention, all variables were checked for significant pretest differences with unpaired *t* tests. Whenever significant differences emerged, the variables were excluded from the analyses. When studies reported comparisons of multiple groups, they were combined to a single training and a single control group by averaging data. In case of examinations with noninvasive brain stimulation only sham groups were included in the analysis to avoid overestimation of training effects. As patient studies were also allowed to be one-armed, the effect sizes were determined by the standardized mean difference of the pre- and post-follow–up assessment values. To prevent overestimation of the true intervention effect, effect sizes from within-group comparisons were only approved for analyses if they did not differ significantly from the averaged effect size of the studies that did include a control group; meaning significantly smaller as well as larger effect sizes could be excluded (see Morris & DeShon, 2002).

Effect sizes were determined for the trained task as well as for *near* transfer effects to WM and *far* transfer effects to other cognitive domains and everyday life functioning. Near transfer was examined by investigating frequently used neuropsychological tests of WM (namely digit span and span board tasks (e.g., Wechsler Memory Scale-Revised; Wechsler, 1987), Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977), and n-back task (Kirchner, 1958) and WM functioning in general. More precisely, general WM functioning was examined by computation of a mean score of all available WM tests per study ("overall WM") and also component-wise by selecting only simple or complex span measures for averaging. Simple span tasks stress primarily the storage component of WM by presenting a set of items which has to be remembered after a brief delay (e.g., digit span task). In contrast, complex span tasks interrupt the maintenance period by adding a secondary task for involving executive components of WM (e.g., reading span task; for further explanation see Unsworth, Redick, Heitz, Broadway, & Engle, 2009).

Far transfer was assessed by analyzing the following cognitive domains: (a) reasoning and intelligence (investigated by the well-established Ravens Progressive Matrices [RAVEN; Raven, 1990]), (b) cognitive control and executive functioning (specifically analyzed by the Stroop-task; Stroop, 1935), (c) attention and processing speed, and (d) long-term memory. In addition, the appraisal of everyday life functioning and disorder symptoms was explored. At first, effect sizes were computed for each neuropsychological test. If necessary, signs were flipped so that positive effect sizes always represented improved performance. If multiple variables were given for one test (e.g., reaction time [RT] and correct responses of the Stroop), either the most representative measure was chosen to define the effect size or the average of the effect sizes determined the final effect size for the test. The latter was used if variables were rated similarly important. Next, the tests were classified in the above-mentioned categories of cognitive domains. If a study reported multiple outcomes for the same domain, the mean of their effect sizes was used. Whenever possible, effect sizes were calculated from the means and variance statistics reported in the article. If the information was not available, the authors were contacted and requested to provide the required data, which was most often successful. Otherwise, missing measures were estimated by data depicted in figures or inferred from similar trials of the same research group. To ensure that all effect size computations produced comparable results, the following procedure was used: Estimated and inferred effect sizes for each particular outcome were only included in the analyses if they did not differ significantly from the averaged effect size calculated from originally provided data. In total, five studies required partial effect size estimations whereupon four of them were integrated in the analyses of the specific outcome (Nouchi et al., 2012; combined trial of Olesen et al., 2004 and Westerberg et al., 2007b; Schneiders et al., 2012; and Witt, 2011) and one had to be excluded (Chein & Morrison, 2010). If effect sizes could not be calculated for one outcome, the study was nevertheless included in the analyses if sufficient information was available for other outcome measures.

To help clarify the overview of studies, they were classified according to the trained subject group, namely either as healthy subjects (children, young, and elderly adults) or patients (children and adolescents with WM deficits, patients with acquired brain injuries, and otherwise diagnosed patients). Overall effect sizes and 95% confidence intervals (CIs) were calculated using a random-effects model that weighted individual effect sizes according to the inverse of their intrastudy variance. The random-effects model was chosen over the fixed-effects model because it assumes a distribution of true intervention effects, thus it provides a more realistic approach given large heterogeneity of treatments and study designs (see Borenstein, Hedges, Higgins, & Rothstein, 2010). To establish whether overall effect sizes were statistically significant, *Z* tests were applied. Forest plots were generated to illustrate the distribution of effect sizes. Additionally, a sensitivity analysis was carried out to estimate the influence of single effect sizes on the overall effect. By removing consecutively studies with the lowest and highest effect sizes from the analysis, the range of the adjusted overall effect size is shown. The variation of effect sizes between studies was assessed by the χ^2-test of homogeneity (Hedges & Pigott, 2001) and I^2 that estimates the proportion of total variability explained by heterogeneity (Higgins & Thompson, 2002). The presence of publication bias was examined both visually with the inspection of funnel plots (Egger & Smith, 1995) and analytically with Egger's Test (Egger, Smith, Schneider, & Minder, 1997). Funnel plots depict effect sizes against sample sizes and should be symmetrical in the absence of publication bias; similarly the *p* value of the intercept from standardized effect sizes (effect size divided by *SE*) regressed on precision (inverse of *SE*s) should be nonsignificant. In the case of significant heterogeneity or publication bias the analyses were repeated in consideration of outliers.

Finally, a moderator analysis was conducted to identify variables that influenced the efficacy of WM training (see Rosenthal & DiMatteo, 2001). The following variables were inspected as potential factors: study design, adaptivity, improvement in the trained task, training duration, type of intervention, and subject group. The main outcome of the moderator analysis was overall WM function immediately after the end of the training, so all factors were analyzed with respect to this outcome. Nevertheless, for some moderators it seemed important to display possible dependencies (e.g., the amount of training) or investigate additional outcomes (e.g., long-term effects of WM functioning), so the analyses were extended whenever it seemed appropriate. Concretely, the number of training sessions and training hours were included in the analysis of the trained task and type of intervention. The moderators training duration, type of intervention and subject group were examined with regard to long-term effects on WM functioning. A detailed analysis of WM outcome measures as well as far transfer on several cognitive domains was provided in the analysis of the intervention programs. Furthermore, we highlighted differential training effects depending on the subject group with a special focus on brain injured patients considering immediate and long-term changes of all cognitive domains and everyday-life functioning. To ensure unbiased results, all moderator analyses were conducted in consideration of previous reported outliers with extreme effect sizes. Additionally, visual scatter plot inspections clarified whether single studies distorted results and when indicated, they were removed. Furthermore, studies with excessive overall training length (≥100 sessions) and inadequate training time (≥60 min per session) were excluded for the analysis of training duration.

Results

In the Results section, first the study characteristics will be presented. Second, the analyses for all subjects regarding the trained task as well as immediate near and far transfer effects will be shown. Third, long-term effects of WM training will be examined. As far as enough data are available, detailed results for brain injured patients are provided. Finally, specific effects of WM training for different subject groups and moderator variables will be calculated. Here we will especially comment on training effects for patients with acquired brain injuries.

Study Characteristics

In total, 103 studies, which added up to 112 independent group comparisons, were included in the meta-analysis. Study characteristics including participants, study design, sample size, type of intervention, and control condition, as well as information about training program, follow-up assessment, and outcome measures are presented in Tables 1 and 2 (see Supplemental Materials 1).

Overall, $N = 6{,}113$ participants were included (WM training groups $n = 3{,}203$, controls $n = 2{,}910$); 905 healthy children, 2,113 healthy young adults, 978 healthy elderly people, 1,585 children and adolescents with WM deficits, 224 patients with stroke or traumatic brain injuries (hereinafter referred to as acquired brain injuries), and 308 patients otherwise diagnosed. Regarding study design, 74 studies conducted randomized controlled trials, 30 integrated control groups with a matching procedure or a quasi-experimental design, and 8 patient studies carried out within-group comparisons with no control group (originally six of them were not one-armed but control group data were not reported separately or the study compared multiple types of WM training). On average, WM training was conducted over 5 weeks ($SD = 4$, range = 1–27) with a mean duration of 21 sessions ($SD = 14$, range = 3–100) and 12 hr ($SD = 13$, range = 1–100). Forty-two studies performed a follow-up measurement after a mean period of 5 months ($SD = 4$, range = 1–18). As can be seen in Tables 1 and 2 (see Supplemental Materials 1), the studies show large heterogeneity concerning target group, training program, study design, and outcome measures. Most studies were carried out with healthy subjects; studies with patients suffering from acquired brain injuries are still scarce and lack methodological quality. Thus, only five of the eight studies targeting this subsample were conducted as controlled randomized trials and sample sizes were rather small. The patients had a mean age of 36 years ($SD = 11$) and they were in a chronic state of illness (mean time postinjury = 5 years, $SD = 4$).

Immediate Effects of WM Training

Improvement in the trained task. Eighty-seven of the 112 independent group comparisons analyzed the data of the trained task. All studies except one reported improvements, significance, however, was confirmed for only 79 studies. The mean improvement in the trained task, compared by the performance in the first and final training session, was large ($g = 1.80$ [1.58, 2.01][1], $p < .001$). The χ^2-test of homogeneity was significant ($\chi^2 = 406.93$, $p < .001$, $I^2 = 79\%$), suggesting large variations of the underlying effect size between the different training interventions. The sensitivity analysis showed that after removing outliers one by one, the effect size ranged from $g = 1.72$ [1.53, 1.90], $p < .001$ to $g = 1.82$ [1.61, 2.04], $p < .001$. Four studies with brain injured patients reported data for the analysis of the trained task. They revealed a large effect size, too ($g = 2.07$ [1.61, 2.52], $p < .001$). See Figure 2 for the illustration of the training effects as forest plots and Figure A of Supplemental Materials 2 for the corresponding funnel plot.

Near transfer effects on WM functions. Near transfer effects of WM training on WM functions were analyzed both generally (overall WM, simple, and complex WM tasks) and regarding specific neuropsychological WM tests (digit span, span board, PASAT, and n-back task). Here, we present only the domain general effect of WM training (see Figure 3 for the illustration of the training effects as forest plots and Figure B of Supplemental Materials 2 for the corresponding funnel plot). An overview of all near transfer effects including the detailed inspection of specific tests is provided in Table 3 of Supplemental Materials 1.

Overall WM. Near transfer effects of WM training on WM functions were analyzed by 97 independent group comparisons

[1] Terms in square brackets report 95% confidence intervals.

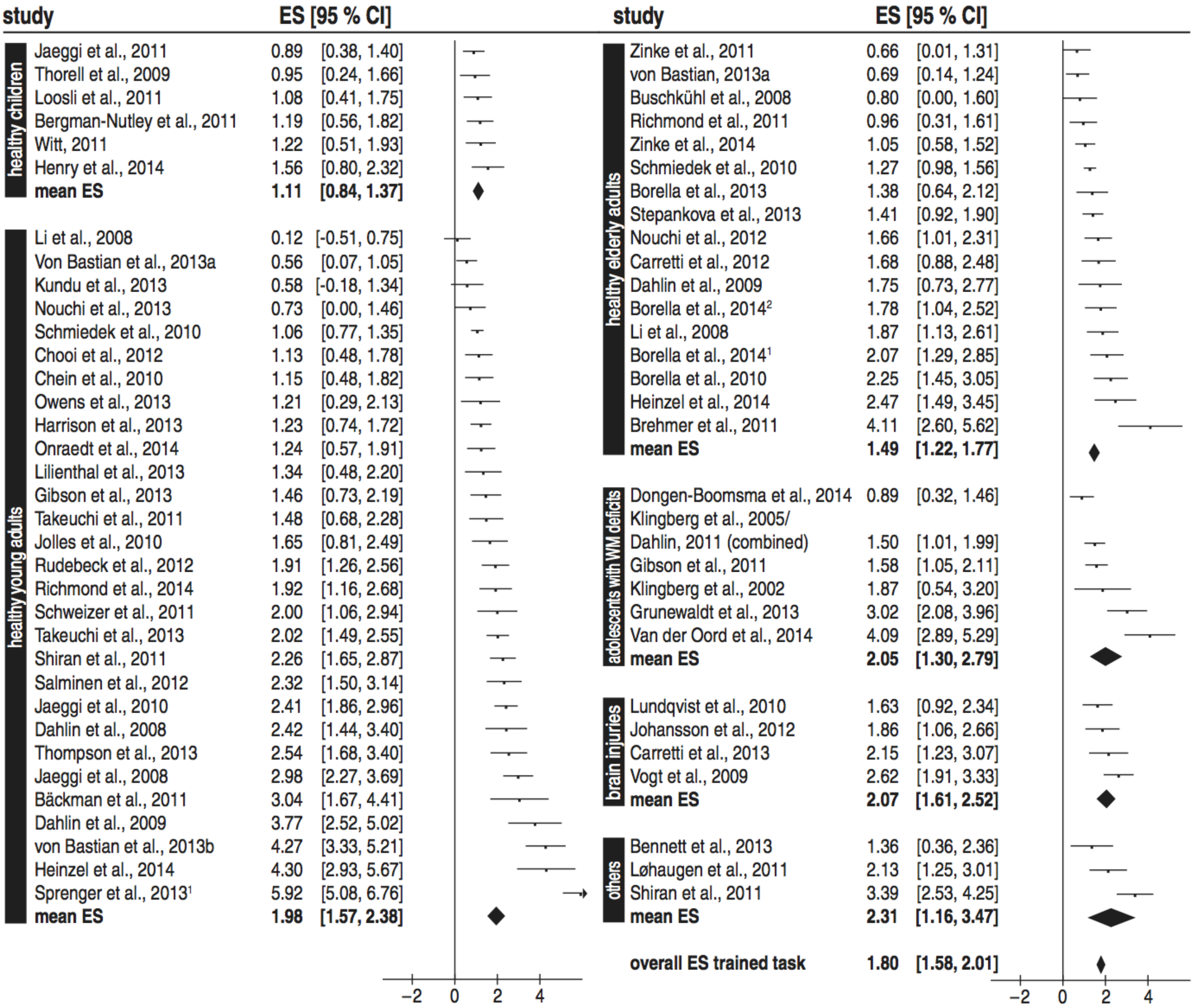

Figure 2. Forest plot for the improvement in the trained working memory (WM) intervention task. For each study, individual effect sizes (ES) and 95% confidence intervals (CIs) are depicted as rectangles and horizontal lines (the arrow indicates a CI exceeding 6). Mean effect sizes are illustrated by diamonds (width represents 95% CIs). All effect sizes represent Hedges' adjusted *g*. In studies with multiple independent group comparisons, first and second trials are labeled as [1] and [2], respectively.

(N = 4,487, n WM training group = 2,426, n controls = 2,061). Overall, WM training caused a significant effect in untrained WM tasks with a moderate effect size of g = 0.44 [0.35, 0.53], $p < .001$. The sensitivity analysis showed that after removing outliers one by one, the overall effect size ranged from g = 0.41 [0.34, 0.49], $p < .001$ to g = 0.45 [0.36, 0.54], $p < .001$. The χ^2-test of homogeneity was significant (χ^2 = 193.70, $p < .001$, I^2 = 50%) and, thus, indicated large variations of the underlying training effect between the studies. Heterogeneity could be reduced (χ^2 = *ns*) by removing seven outliers with extreme effect sizes from the analysis. The adjusted mean effect size was slightly smaller (g = 0.37 [0.31, 0.43], $p < .001$) and varied between g = 0.36 [0.30, 0.42], $p < .001$ and g = 0.38 [0.32, 0.44], $p < .001$ when another sensitivity analysis was undertaken without the outliers. In consideration of the outliers the inspection of the funnel plot indicated no publication bias and Egger's Test was not significant. Seven studies examined the efficacy of WM training specifically in patients with acquired brain injuries (N = 206, n WM training group = 126, n controls = 80). Despite the small sample, the mean effect size for near transfer on overall WM was moderate with g = 0.59 [0.33, 0.86], $p < .001$ and ranged from g = 0.48 [0.19, 0.77], $p < .01$ to g = 0.66 [0.37, 0.96], $p < .001$ according to the sensitivity analysis.

Simple WM. Near transfer effects on WM measured by simple span tasks were examined by 89 independent group comparisons (N = 4,114, n WM training group = 2,256, n controls =

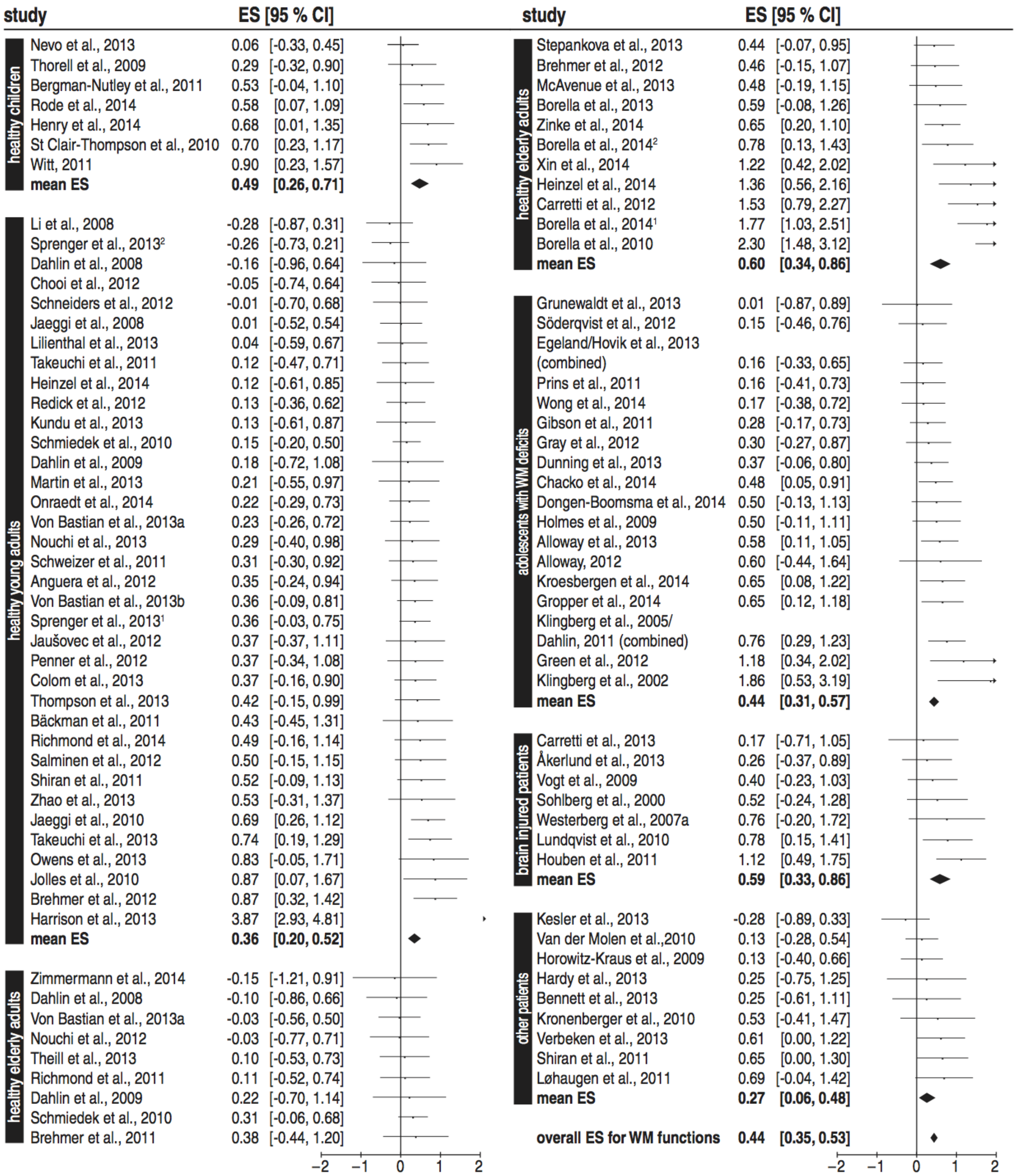

Figure 3. Forest plot for immediate near transfer effects on working memory (WM) functions. For each study, individual effect sizes (ES) and 95% confidence intervals (CIs) are depicted as rectangles and horizontal lines (arrows indicate CIs exceeding 2). Mean effect sizes are illustrated by diamonds (width represents 95% CIs). All effect sizes represent Hedges' adjusted *g*. In studies with multiple independent group comparisons, first and second trials are labeled as [1] and [2], respectively.

1,858). The resulting mean effect size was moderate with $g = 0.45$ [0.34, 0.55], $p < .001$. Because of significant heterogeneity ($\chi^2 = 214.37$, $p < .001$, $I^2 = 59\%$) and a possible publication bias (Egger's Test $p < .01$) the analysis was repeated with exclusion of five outliers. The adjusted mean effect size was slightly smaller with $g = 0.36$ [0.28, 0.44], $p < .001$. Still, heterogeneity between studies persisted that suggests large variation between the different interventions ($\chi^2 = 110.08$, $p < .05$, $I^2 = 25\%$), but there was no further indication of publication bias. Focused on brain injured patients, the available data from seven studies ($N = 206$, n WM training group = 126, n controls = 80) revealed a moderate effect size, too ($g = 0.59$ [0.32, 0.85], $p < .001$).

Complex WM. Forty independent group comparisons assessed the transfer effect on complex span WM tasks ($N = 2,409$, n WM training group = 1,279, n controls = 1,130). The mean effect size was moderate ($g = 0.40$ [0.25, 0.54], $p < .001$). As the χ^2-test of homogeneity was significant ($\chi^2 = 108.78$, $p < .001$, $I^2 = 64\%$) a repeated analysis was conducted after exclusion of four outliers. Heterogeneity was reduced, but still significant ($\chi^2 = 62.97$, $p < .05$, $I^2 = 44\%$). The adjusted mean effect size was small $g = 0.33$ [0.21, 0.44], $p < .001$. No indication of publication bias was found. Only two studies applied complex span tasks in brain injured patients ($N = 41$, n WM training group = 31, n controls = 10), they suggested a moderate effect size of $g = 0.63$ [0.12, 1.14], $p < .05$.

In summary, WM training caused a significant, moderate near transfer effect on WM. Outcome measures that used simple span tasks showed similar effect sizes as complex span task measures. Intervention studies that targeted specifically patients with acquired brain injuries demonstrated a significant moderate transfer effect on WM, too.

Far Transfer Effects on Other Cognitive Domains and Everyday Life Functioning

Far transfer was assessed by analyzing the following general cognitive domains: (a) reasoning and intelligence, (b) cognitive control and executive functioning, (c) attention and processing speed, and (d) long-term memory as well as (e) the effect of WM training on the appraisal of everyday life functioning and disorder symptoms (for forest plots see Figures 4 and 5, corresponding funnel plots can be found in Supplemental Materials 2: Figures C1–5). Because of insufficient data ($N < 5$ studies per domain), specific analyses for brain injured patients can only be provided for transfer on everyday life functioning. However, some subgroup differences regarding far transfer effects will be discussed in the context of the moderator analysis. A detailed report of far transfer effects after WM training including specific test analyses can be seen in Table 4 (see Supplemental Materials 1).

Generally, small but significant transfer effects were found on other cognitive domains. The effect of WM training on (a) *reasoning and intelligence* was analyzed by 56 independent group comparisons ($N = 3,273$, n WM training group = 1,719, n controls = 1,554). WM training caused a significant small effect of $g = 0.24$ [0.15, 0.34], $p < .001$. The χ^2-test of homogeneity showed significant differences ($\chi^2 = 85.90$, $p < .01$, $I^2 = 36\%$) and both, the inspection of the funnel plot and Egger's test ($p < .05$) indicated the presence of a publication bias. Therefore, outliers were removed from the dataset. The adjusted mean effect for the domain of reasoning and intelligence was similar ($g = 0.23$ [0.14, 0.32], $p < .001$). Note that heterogeneity could not be reduced ($\chi^2 = 79.05$, $p < .05$, $I^2 = 33\%$), showing that some interventions produced large transfer effects, whereas others didn't influence the performance on intelligence outcomes. Furthermore, the inspection of the funnel plot suggested an overestimation of the effect because of publication bias, albeit Egger's Test was no longer significant ($p = .12$). The effect of WM training on (b) *cognitive control and executive functioning* was analyzed by 55 independent group comparisons ($N = 3,093$, n WM training group = 1,535, n controls = 1,558). WM training caused a significant small effect of $g = 0.20$ [0.10, 0.29], $p < .001$. Because of significant heterogeneity ($\chi^2 = 89.72$, $p < .01$, $I^2 = 40\%$) the analyses were repeated without outliers. Heterogeneity was reduced to zero without affecting the mean effect size ($g = 0.20$ [0.13, 0.27], $p < .001$.). There was no indication of a publication bias. The WM training effect on (c) *attention and processing speed* was analyzed by 43 independent group comparisons ($N = 2,024$, n WM training group = 1,080, n controls = 944). WM training caused a significant small effect ($g = 0.20$ [0.08, 0.32], $p < .01$). Again, significant heterogeneity ($\chi^2 = 66.39$, $p < .05$, $I^2 = 37\%$) could be reduced to almost zero by the exclusion of outliers, yet the analysis yielded a similar mean effect size ($g = 0.18$ [0.09, 0.27], $p < .001$). No publication bias was found. The effect of WM training on (d) *long-term memory* was analyzed by 26 independent group comparisons ($N = 1,168$, n WM training group = 678, n controls = 490). Again, WM training caused a significant small effect of $g = 0.18$ [0.02, 0.33], $p < .05$. Neither heterogeneity ($\chi^2 = 37.63$, $p = ns$, $I^2 = 34\%$) nor the presence of a publication bias was found.

Evaluation of (e) *the quality of everyday life* was mainly assessed in patient studies ($n = 5$ studies targeted healthy subjects). Mostly, subjective appraisals from participants or significant others (e.g., parents, teachers, and partner) were taken through questionnaires (e.g., Cognitive Failures Questionnaire [CFQ]) or ratings (e.g., Behavior Rating Inventory of Executive Function [BRIEF]). Objective measurements (e.g., head movements and unintended behaviors in children with ADHD) were rare. In total, 32 independent group comparisons ($N = 1,439$, n WM training group = 797, n controls = 642) yielded a significant, but very small effect of WM training ($g = 0.17$ [0.05, 0.28], $p < .01$). There was no heterogeneity ($\chi^2 = 34.87$, $p = ns$, $I^2 = 11\%$) but the inspection of the funnel plot as well as Egger's Test ($p < .001$) revealed a publication bias. The repeated analysis without outliers confirmed the very small effect size ($g = 0.14$ [0.03, 0.25], $p < .05$). Still publication bias persisted (funnel plot, Egger's Test $p < .001$), suggesting that the effect of WM training on everyday life functioning is yet overestimated. Six out of the eight studies with brain injured patients assessed everyday life functioning ($N = 185$, n WM training group = 116, n controls = 69). The resulting mean effect size was also small with $g = 0.29$ [−0.01, 0.59], but the effect did not reach significance ($p = .06$).

In summary, WM training showed significant small far transfer effects on all presented cognitive domains. With respect to the evaluation of everyday life functioning and reduction of disorder symptoms, a significant small transfer effect was found, too. However, the indication of a publication bias suggests that the true effect is yet overestimated in the current literature. Focusing on patients with acquired brain injuries,

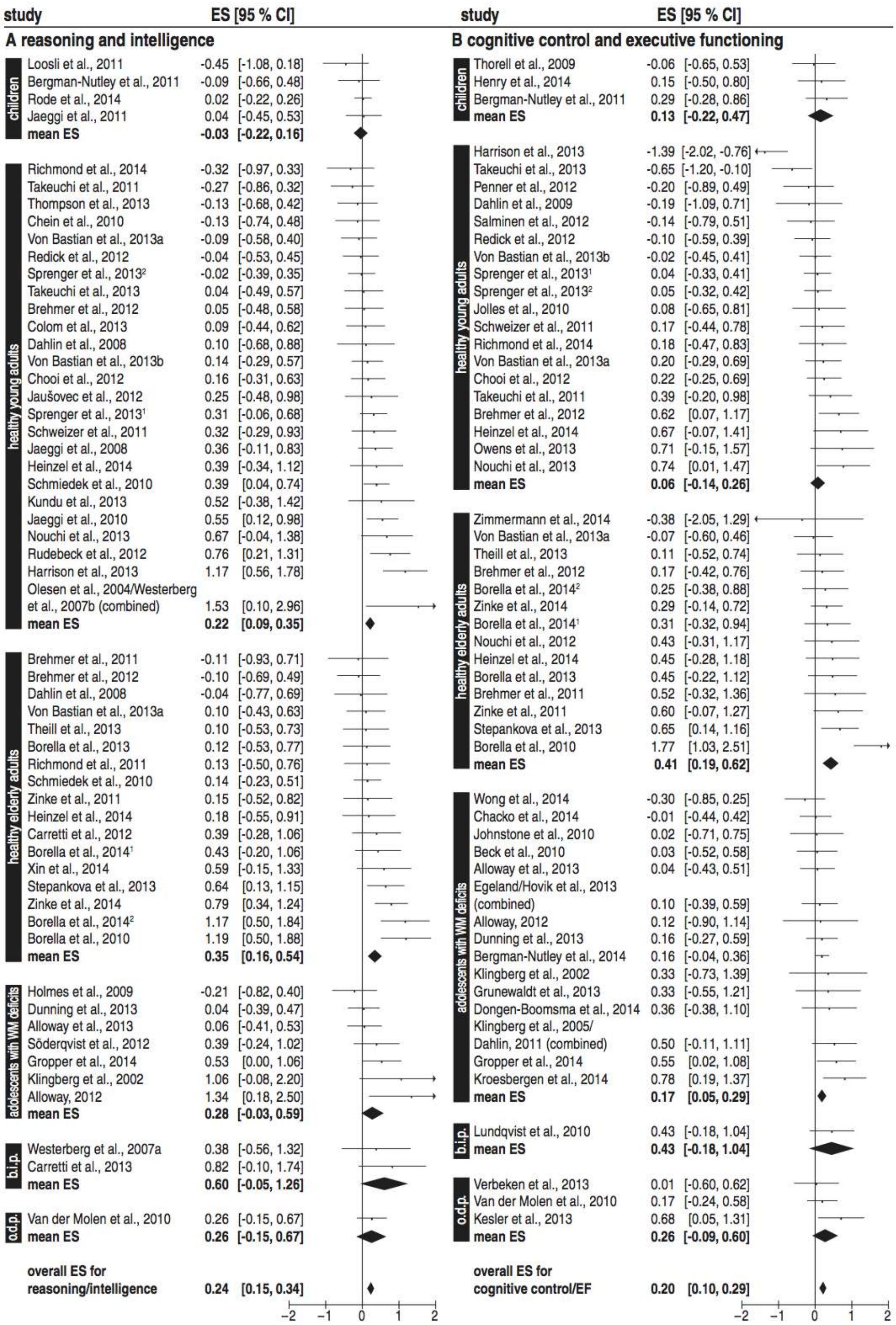

Figure 4. Forest plot for immediate far transfer effects on A reasoning/intelligence and B cognitive control/executive functioning. For each study, individual effect sizes (ES) and 95% confidence intervals (CI) are depicted as rectangles and horizontal lines (arrows indicate CIs exceeding 2). Mean effect sizes are illustrated by diamonds (width represents 95% CIs). All effect sizes represent Hedges' adjusted *g*. In studies with multiple independent group comparisons, first and second trials are labeled as [1] and [2], respectively. Subgroup abbreviations: b.i.p. = brain injured patients; children = healthy children; o.d.p. = otherwise diagnosed patients.

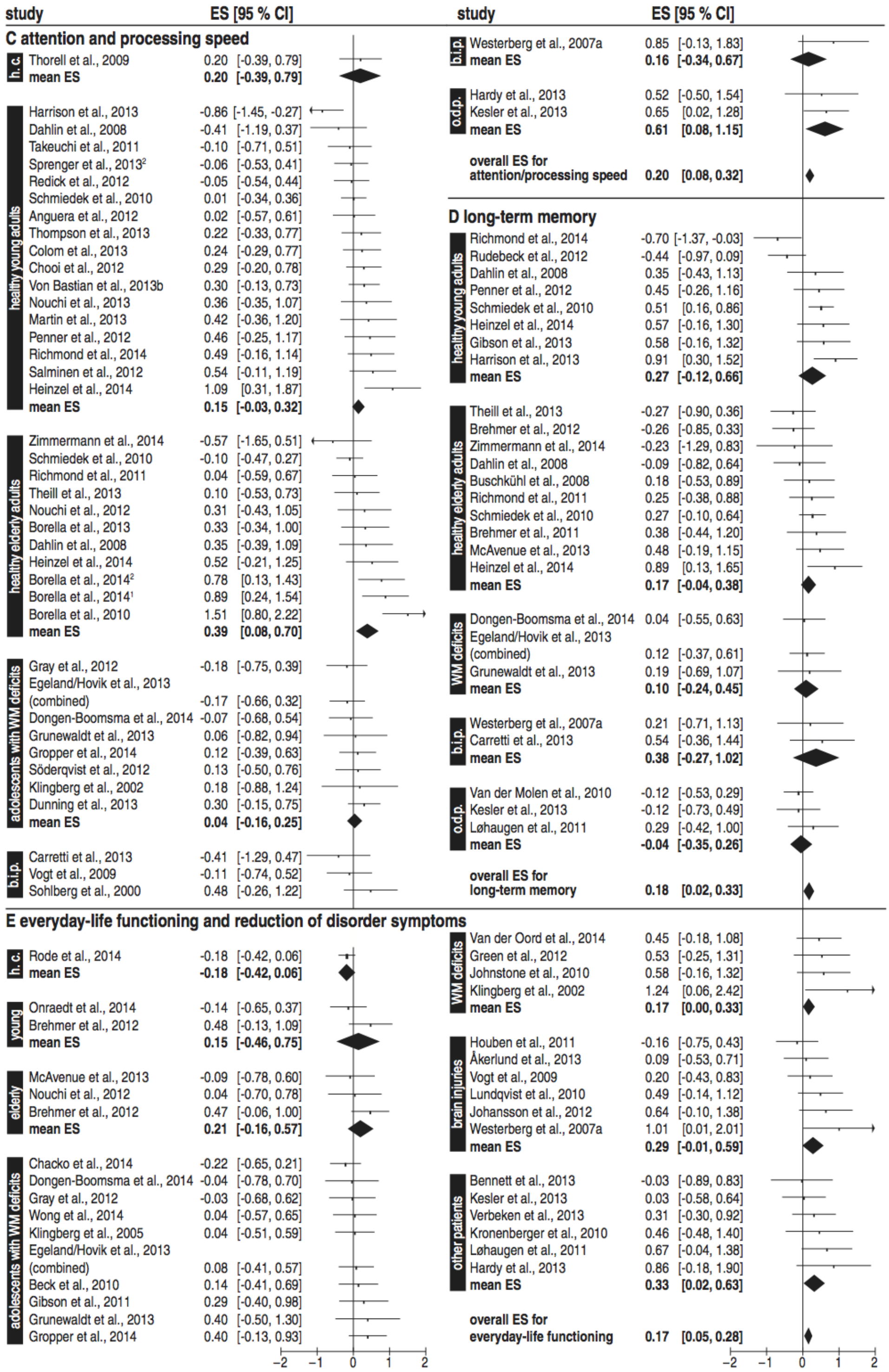

Figure 5. Forest plot for immediate far transfer effects on C attention/processing speed, D long-term memory and E everyday life functioning and reduction of disorder symptoms. For each study, individual effect sizes (ES) and 95% confidence intervals (CI) are depicted as rectangles and horizontal lines (arrows indicate CIs exceeding 2). Mean effect sizes are illustrated by diamonds (width represents 95% CIs). All effect sizes represent Hedges' adjusted *g*. In studies with multiple independent group comparisons, first and second trials are labeled as [1] and [2], respectively. Subgroup abbreviations: b.i.p./brain injuries = brain injured patients; elderly = healthy elderly adults; h.c. = healthy children; o.d.p. = otherwise diagnosed patients; WM deficits = children and adolescents with working memory deficits; young = healthy young adults.

WM trainings showed a small effect on the reduction of disorder symptoms that, certainly because of power issues did not reach significance.

Long-Term Effects of WM Training

Follow-up effects of WM training on near transfer tasks were analyzed for (a) *general WM functions* (overall WM, WM measured by simple or complex span tasks) and specifically for the digit span and span board tasks (for the analyses of the PASAT and the n-back tasks there were not enough data available). Far transfer effects were analyzed for other cognitive domains, that is, (b) *reasoning/intelligence*, (c) *cognitive control/executive functioning*, (d) *attention and processing speed,* (e) *long-term memory*, and for (f) *everyday life functioning/disorder symptoms*. For the specific analysis of the RAVEN and Stroop-test, the amount of available data was too small. Here, only the domain general effects of WM training are presented. For detailed data regarding WM measured with either simple or complex span tasks as well as concrete WM tests see the overview in Table 5 of Supplemental Materials 1. An overview of long-term effects after WM training is depicted in Figure 6. See Supplemental Materials 2 (Figure D 1–6) for the illustration of the corresponding funnel plots.

Near transfer effect on WM. The long-term effect of WM training on (a) *overall WM function* was analyzed by 32 independent group comparisons (N = 1,310, n WM training group = 728, n controls = 582). The WM training effect was maintained with a moderate effect size of g = 0.54 [0.40, 0.69], $p < .001$ with a range of g = 0.51 [0.38, 0.64], $p < .001$ to g = 0.57 [0.43, 0.71], $p < .001$ according to the sensitivity analysis. The χ^2-test of homogeneity was significant ($\chi^2 = 50.61$, $p < .05$, $I^2 = 39\%$) but heterogeneity could be reduced ($\chi^2 = ns$) by removing one outlier with an extremely high effect size off the analysis. The adjusted mean effect size remained moderate with g = 0.51 [0.38, 0.64], $p < .001$ and varied between g = 0.48 [0.36, 0.61], $p < .001$ and g = 0.53 [0.40, 0.66], $p < .001$ when another sensitivity analysis was undertaken. The inspection of the funnel plot and Egger's Test indicated no publication bias. Only three studies examined the long-term effect of WM training in brain injured patients (N = 106, n WM training = 60, n controls = 46). Despite the small sample size, the stability of the WM training effect on overall WM was confirmed with a moderate to large effect size (g = 0.73 [0.20, 1.25], $p < .001$).

Far transfer effect on other cognitive domains. The long-term effect of WM training on (b) *reasoning and intelligence* was analyzed by 19 independent group comparisons (N = 899, n WM training group = 472, n controls = 427). The significant small effect that was found immediately after the end of the training was maintained over the follow-up period (g = 0.20 [0.07, 0.34], $p <$ .01). There was no indication of heterogeneity or publication bias. The sustainability of the WM training effect on (c) *cognitive control and executive functioning* was examined by 18 independent group comparisons (N = 892, n WM training group = 464, n controls = 428). Here, the significant small effect was preserved, too (g = 0.21 [0.06, 0.36], $p < .01$). The intervention effects were homogeneous ($\chi^2 = 21.70$, ns, $I^2 = 22\%$) but the visual inspection of the funnel plot revealed a possible publication bias (Egger's Test p = .08). A repeated analysis without outliers showed a similar effect (g = 0.20 [0.06, 0.34], $p < .01$) but still publication bias was present, in both, the funnel plot and in Egger's Test ($p <$ .05). Consequently, the long-term transfer effect on the domain of cognitive control and executive functioning is presumably overrated. The long-term effect of WM training on (d) *attention and processing speed* was analyzed by 13 independent group comparisons (N = 506, n WM training group = 286, n controls = 220). The mean effect size was small but significant with g = 0.22 [0.02, 0.42], $p < .05$. There was no heterogeneity ($\chi^2 = 14.12$, ns, I^2 = 15%) and Egger's Test for publication bias was not significant but the visual inspection of the funnel plot revealed a slight overestimation of the effect. Therefore, another analysis without outliers was undertaken. The adjusted mean effect size was no longer significant (g = 0.15 [−0.04, 0.33], p = .13). Regarding the preservation of the WM training effect on (e) *long-term memory*, only eight independent group comparisons could be integrated in the analysis (N = 299, n WM training group = 160, n controls = 139). The small effect that was found immediately after the end of the training did not persist at follow-up period (g = −0.02 [−0.24, 0.20], p = .87). Heterogeneity was zero and no publication bias was present.

Far transfer effect on everyday life functioning. The long-term effect of WM training on (e) *appraisal of everyday life functioning and disorder symptoms* was examined by 17 independent group comparisons (N = 644, n WM training group = 343, n controls = 301). The small effect which was found directly after the end of the training period could be maintained (g = 0.17 [0.02, 0.32], $p < .05$). Heterogeneity was zero, indicating a common underlying effect size of the studies. The inspection of the funnel plot and Egger's Test showed no signs of publication bias. Only three studies provided data on long-term effects of everyday life functioning in patients with acquired brain injuries (N = 103, n WM training group = 58, n controls = 45). Currently, they provide no evidence for sustained improvements of disorder symptoms in brain injured patients (g = 0.06 [−0.30, 0.43], p = .72).

In summary, the meta-analysis showed that WM training interventions produced sustained effects on general WM functioning. These effects were moderate regarding simple, complex and overall WM functions and varied from small (digit span tasks) to relatively large effects (span board tasks) when specific WM tests were considered. Concerning far transfer, some small immediate effects were maintained over the follow-up period, whereas others did not persist. The analyses suggested that performance in reasoning and intelligence outcomes was steadily improved by WM training. The same holds true for cognitive control and executive functioning, although the presence of a publication bias indicated a slight overestimation of the true effect. No stability was found for effects on attention/processing speed and long-term memory. With respect to everyday life functioning, the small intervention effects were successfully maintained over the follow-up period. Unfortunately, empirical evidence for long-term effects in patients with acquired brain injuries is still scarce. Currently, there is no evidence for persisting improvements of their specific disorder symptoms.

Moderators of WM Training Efficacy

A moderator analysis was carried out to identify variables that influence the efficacy of WM training. The following factors were

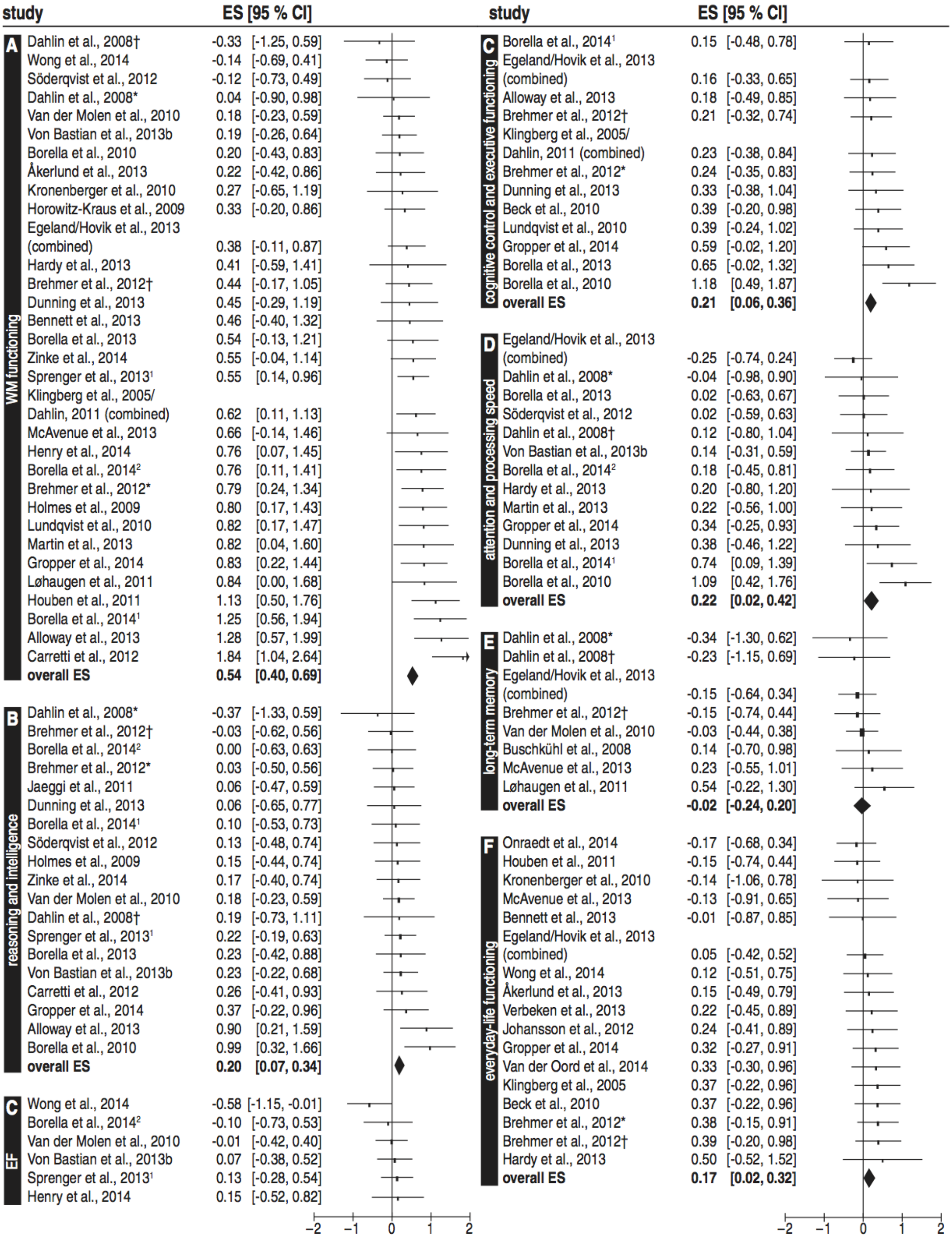

Figure 6. Forest plots for long-term effects of working memory (WM) training. For each study, individual effect sizes (ES) and 95% confidence intervals (CIs) are depicted as rectangles and horizontal lines (the arrow indicates a CI exceeding 2). Mean effect sizes are illustrated by diamonds (width represents 95% CIs). All effect sizes represent Hedges' adjusted *g*. In studies with multiple independent group comparisons, first and second trials are labeled as [1] and [2], respectively, and the trials with healthy young adults are marked with an asterisk (*), whereas the trials with healthy elderly adults are labeled with a dagger (†).

analyzed: study design, adaptivity, improvement in the trained task, training duration, type of WM training intervention, and subject group.

Study design. To determine whether the study design influences the effect size of WM training outcomes, the type of control group was examined. Accordingly, the studies were classified as passive (only pre- and postmeasurement), nonspecific active (any treatment not demanding the WM system, e.g., RT training or discussion rounds) and nonadaptive active (same intervention as the WM training but on a fixed low level with no adaption of difficulty). The inclusion of passive or active control groups did not lead to significant differences regarding the overall WM training effect (passive control groups: $g = 0.37$ [0.27, 0.46], $p < .001$; active control groups: $g = 0.37$ [0.28, 0.47], $p < .001$; $\chi^2 = 0.01$, *ns*). Thus, in general, the choice of passive or active control groups did not influence the resulting intervention outcome. A closer examination of the active control groups, however, revealed significant difference between the use of nonspecific and nonadaptive designs; with nonadaptive fixed low WM trainings showing superior effect sizes than alternative types of interventions (nonspecific active control groups: $g = 0.24$ [0.12, 0.37], $p < .001$; nonadaptive active control groups: $g = 0.52$ [0.37, 0.66], $p < .001$; $\chi^2 = 7.54$, $p < .01$).

Adaptivity. One widely discussed factor of training efficacy is the adaptivity of the training program. The issue whether interventions with continuous adjustment of task difficulty according to subject's performance are superior to other training schedules was approached in several steps. First, the effect of WM training was computed when adaptive training was compared with correspondent fixed low-level practice (i.e., control training, which consisted of the same tasks as the WM training but were fixed at low levels with no or low WM demands). A significant effect with moderate effect size emerged ($g = 0.54$ [0.40, 0.68], $p < .001$). Second, adaptive WM training was compared with nonadaptive interventions that did increase difficulty, but in a predefined scheme. Analyses showed that adaptive WM training produced similar effect sizes to nonadaptive WM training with respect to passive control groups (adaptive WM training: $g = 0.37$ [0.28, 0.46], $p < .001$, nonadaptive WM training: $g = 0.32$ [−0.03, 0.68], $p = .07$[2]; χ^2 -test for subgroup differences: $\chi^2 = 0.05$, *ns*). Hence, it seems essential to increase task difficulty to challenge the subject's WM system continuously. In adaptive programs it is certain that this increase always matches the individual performance level; thus, they represent the ideal implementation of WM training. Nonetheless, other designs may achieve the same objective.

Improvement in the trained task. The issue was addressed whether the slope of performance during training may predict the transfer effect of the training on WM. Therefore, the effect size of the trained task (performance in the first vs. last training session) was correlated with the effect size of transfer on overall WM. As no significant correlation emerged ($r = .17$, *ns*), overall training success seems to be irrelevant for the generation of transfer effects. Furthermore, the improvement in the trained task was independent of training duration (number of training sessions: $r = -.21$, *ns*; number of training hours: $r = .01$, *ns*).

Training duration. Next, the relationship between training duration and WM training efficacy was investigated. Correlation analyses showed a significant positive relation between the number of training sessions and the transfer effect on overall WM, $r = .24$, $p < .05$, likewise the number of sessions proved to be a predictor for training efficacy ($R^2 = .057$, $F = 4.85$, $p < .05$). In contrast, no significant correlation was found between the number of training hours and the transfer effect on overall WM ($r = .06$, *ns*). To further investigate the connection between training duration and efficacy, each study was categorized as short or long WM training, defined by median split for training sessions and hours separately. WM trainings with more than 20 training sessions produced significant larger effect sizes than WM trainings with less than 20 training sessions ($g = 0.47$ [0.38, 0.55], $p < .01$ and $g = 0.29$ [0.20, 0.38], $p < .01$, respectively; $t(74) = 2.94$, $p < .01$). Again, no significant differences were found between WM trainings with many and few training hours (≥10 and <10 hr, respectively; $t(74) = -0.02$, *ns*). To further examine the evidently crucial factor training sessions, in a next step; all studies were divided into four subgroups according to quartile split. The comparison of the resulting mean effect sizes of overall WM were significant for each training length, but increased with the number of training sessions (less than 15 sessions: $g = 0.25$ [0.10, 0.40], $p < .01$, 15–20 sessions: $g = 0.35$ [0.10, 0.61], $p < .05$, 20–25 sessions: $g = 0.35$ [0.26, 0.45], $p < .001$, more than 25 sessions: $g = 0.49$ [0.38, 0.60], $p < .001$; $F(3) = 2.78$, $p < .05$). Post hoc tests revealed a significant difference between the group that trained less than 15 sessions and more than 25 sessions ($p < .01$), a nearly significant effect was found for interventions with 20–25 sessions and more than 25 sessions ($p = .06$).

Did training duration predict not only the strength but also the maintenance of transfer effects? Indeed, at follow-up a strong positive relationship between the number of training sessions and the long-term improvement of overall WM was established, $r = .50$, $p < .01$. Training duration was found to be a strong predictor and explained more than 25% of variance of the WM performance ($R^2 = .252$, $F = 7.42$, $p < .05$). The comparison of studies with ≥20 and <20 training sessions revealed a nearly significant effect, $t(22) = 2.03$, $p = .05$; note that only five studies remained in the category of few training sessions. Likewise, the comparison of the groups according to quartile split was only by trend significant ($F(2) = 2.71$, $p = .09$; no studies with less than 15 training sessions assessed long-term transfer on WM functions). However, a detailed analysis of the remaining studies revealed a significant preservation of the training effect only for interventions that trained 20 sessions or more (15–20 sessions: $g = 0.16$ [−0.56, 0.88], *ns*; 20–25 sessions: $g = 0.35$ [0.03, 0.66], $p < .05$; ≥ 25 sessions: $g = 0.61$ [0.40, 0.83], $p < .001$). Post hoc tests revealed a significant difference between intervention effects of studies that conducted 15–20 sessions and studies with more than 25 sessions ($p < .05$). Still, the amount of training hours had no influence on WM functioning ($r = -.04$, *ns*; no difference between the effect sizes of studies with ≥10 and <10 training hours: $t(22) = -0.27$, *ns*).

Another approach to examine the influence of training duration was to look at studies that were specifically designed to investigate the dose effect of training efficacy. First, the isolated effect of low and high dose trainings (8–12 and 17–32 training sessions, respectively) in comparison with passive control groups was analyzed.

[2] The effect of nonadaptive WM training did not reach significance because of small power ($N = 5$ studies).

High dose trainings showed a significant transfer on overall WM functioning immediately after the training ($g = 0.38$ [0.09, 0.66], $p < .01$), whereas low dose trainings failed to produce such an effect ($g = 0.02$ [−0.29, 0.33], *ns*). Next, both interventions were compared directly with each other to evaluate the possible advantage of the high dose group over the low dose group. Again, a small to moderate effect size emerged with $g = 0.34$ [0.01, 0.67], $p = .05$, which only approached significance because of power reasons (only $n = 4$ studies included in this meta-analysis reported the required data). Unfortunately, these studies analyzed no follow-up effects.

In summary, the results indicate that more training sessions result in a greater WM effect, whereas the amount of time spent on training does not seem to be predictive. The implementation of at least 20 training sessions ought to be a guideline for the achievement of substantial effects on WM functioning.

Type of intervention. One key factor for training success is certainly the character of the training task. To be able to compare the existing programs despite their large heterogeneity, each intervention was categorized according to the structure and demands of the applied WM tasks. Concretely, we compared trainings that were based on simple span tasks and trainings that did include complex span tasks ($n = 76$ and $n = 36$, respectively).

Regarding the near transfer effect on overall WM, the training types did not differ in their efficacy (simple span task trainings: $g = 0.37$ [0.29, 0.45], $p < .001$, complex span task training: $g = 0.34$ [0.23, 0.46], $p < .001$; $\chi^2 = 0.18$, *ns*). The same result was found for the preservation of the WM effect after the follow-up period (simple span task trainings: $g = 0.51$ [0.37, 0.65], $p < .001$, complex span task training: $g = 0.52$ [0.24, 0.80], $p < .001$; $\chi^2 = 0.00$, *ns*). Note that simple span task trainings were applied in all subject groups and diverse settings, whereas complex span task trainings were almost exclusively done with healthy subjects in rather experimental conditions. Consequently, the latter involved fewer training sessions (means [*SD*s] = 21.4 [7.0] and 17.1 [9.1] for simple and complex span task trainings, respectively; $t(88) = 2.54$, $p < .05$). To disentangle the influence of training tasks, subject group and training duration, the analyses were repeated only with healthy subjects. Here, both types of interventions were carried out with the same number of sessions, $t(55) = 1.04$, *ns*, still showing equal effect sizes regarding immediate ($\chi^2 = 0.05$, *ns*) and long-term ($\chi^2 = 0.25$, *ns*) transfer on overall WM.

Next, it was examined whether simple span and complex span training showed differential effects on WM measured either by simple or complex span tests. One would assume that each training type produces higher effects on the corresponding transfer tests. Of interest to the authors, both training types showed similar transfer on simple span measures (simple span task trainings: $g = 0.38$ [0.29, 046], $p < .001$; complex span task trainings: $g = 0.39$ [0.26, 0.51], $p < .001$; $\chi^2 = 0.03$, *ns*) as well as transfer effects on complex span measures (simple span task trainings: $g = 0.33$ [0.15, 0.52], $p < .001$; complex span task trainings: $g = 0.37$ [0.20, 0.54], $p < .001$; $\chi^2 = 0.08$, *ns*).

The examination of far transfer effects revealed no significant differences between the two treatments either, although trainings with complex span tasks failed to produce a significant transfer on long-term memory ($g = 0.14$ [−0.16, 0.43], *ns*). The transfer on everyday life functioning was primarily assessed in studies that used simple span task trainings; only one study with complex span treatment considered this domain. Simple span task trainings were able to generate significant transfer ($g = 0.19$ [0.08, 0.31], $p < .01$), whereas the single intervention with complex span tasks did not ($g = -0.18$ [−0.42, 0.06], *ns*; $\chi^2 = 7.72$, $p < .01$). For a differentiated analysis of far transfer effects at follow-up data were insufficient.

An alternative approach is to examine specific training types that were used frequently. Cogmed (Cogmed, 2006) is a commercially available WM training program on the basis of simple span tasks that is currently most often applied in WM training studies ($n = 30$). It showed a moderate effect on overall WM immediately after the training period as well as at follow-up test (immediate transfer: $g = 0.47$ [0.34, 0.59], $p < .001$; long-term transfer: $g = 0.52$ [0.35, 0.70], $p < .001$). Furthermore, Cogmed produced transfer on both, simple and complex span WM measures (simple spans: $g = 0.44$ [0.32, 0.56], $p < .001$; complex spans: $g = 0.60$ [0.36, 0.83], $p < .001$). Regarding far transfer effects, Cogmed was able to produce small but significant effects on cognitive control and everyday life functioning ($g = 0.22$ [0.10, 0.34], $p < .001$ and $g = 0.24$ [0.10, 0.39], $p < .01$, respectively). Another type of WM training that was frequently applied was an intervention that required a continuous updating process of the to-be-remembered stimuli (e.g., n-back tasks; $n = 33$). Updating trainings yielded a significant immediate transfer effect on overall WM ($g = 0.31$ [0.19, 0.42], $p < .001$). Long-term effects were only assessed in four studies; they confirmed a similar effect size that was not significant because of power issues ($g = 0.34$ [−0.18, 0.87], *ns*). With respect to different WM tests, updating trainings showed only transfer on WM measured with simple span tasks ($g = 0.26$ [0.05, 0.48], $p < .05$; no transfer on complex WM: $g = 0.12$ [−0.04, 0.28], *ns*). Far transfer effects were only expressed in the domain of reasoning and intelligence ($g = 0.27$ [0.14, 0.39], $p < .001$). In direct comparison, Cogmed showed by trend a stronger immediate transfer on overall WM and a significantly higher effect size on WM measured by complex span tests than updating trainings ($\chi^2 = 3.39$, $p = .07$ and $\chi^2 = 3.39$, $p < .001$, respectively). No other subgroup differences were found.

Taken together, simple and complex span task trainings did not differ in their efficacy regarding transfer effects on all cognitive domains. However, only interventions with simple span tasks provided evidence for improved everyday life functioning; currently this domain is insufficiently assessed by complex span task trainings. With regard to the most frequently used training types, Cogmed produced stable improvements of WM as well as cognitive control and everyday life functioning, whereas updating trainings demonstrated rather immediate transfer effects on WM and reasoning/intelligence.

Subject group. A crucial question is whether various subject groups benefit differently from WM training. Here, it is of special interest if patients with acquired brain injuries showed similar efficacy compared with the other treatment groups regarding overall WM and everyday life functioning.

With respect to immediate near transfer effects on overall WM function, all subject groups improved their performance significantly (healthy children: $g = 0.49$ [0.26, 0.71], $p < .001$; healthy young adults: $g = 0.29$ [0.19, 0.39], $p < .001$; healthy elderly: $g = 0.40$ [0.22, 0.58], $p < .001$; patients with acquired brain injuries: $g = 0.59$ [0.33, 0.86], $p < .001$; children and adolescents with WM deficits: $g = 0.43$ [0.30, 0.56], $p < .001$; patients otherwise diagnosed: $g = 0.27$ [0.06, 0.48], $p < .05$). In comparison with healthy subjects, patients with acquired brain injuries demonstrated a higher effect size by trend ($\chi^2 = 3.11$, $p = .08$), which turned significant when compared with healthy young adults only ($\chi^2 = 4.46$, $p < .05$). In contrast, all patient groups benefited from WM training to the same degree ($\chi^2 = 3.52$, *ns*).

When immediate transfer on the domain of reasoning and intelligence was considered, the χ^2-test for subgroup differences indicated subtle differences ($\chi^2 = 9.83$, $p = .08$). Detailed single group analyses revealed that exclusively healthy adults produced significant transfer effects (healthy young adults: $g = 0.21$ [0.08, 0.34], $p < .01$; healthy elderly: $g = 0.35$ [0.16, 0.54], $p < .001$). Notwithstanding, patients with acquired brain injuries yielded with $g = 0.60$ [−0.05, 1.26], *ns*, the highest effect size; however, significance could not be confirmed as only two studies assessed this outcome. No subgroup differences were found with respect to immediate far transfer on cognitive control, attention processes or long-term memory ($\chi^2 \leq 4.72$, *ns*). In terms of transfer effects on everyday life functioning, no subgroup differences emerged either. A closer look at the separate group levels showed that brain injured patients exhibited a larger effect size than healthy subjects; however, neither the *Z* tests for the overall effect size of the single groups nor the χ^2-test for subgroup differences was significant (brain injured patients: $g = 0.29$ [−0.01, 0.59], *ns*; healthy subjects: $g = 0.05$ [−0.21, 0.31], *ns*; $\chi^2 = 1.42$, *ns*).

Did the subject groups differ in their ability to maintain the acquired WM training effects? Generally, all groups showed sustained improved WM functioning at follow-up test (healthy children: $g = 0.76$ [0.07, 1.45], $p < .05$; healthy young adults: $g = 0.49$ [0.22, 0.75], $p < .001$; healthy elderly: $g = 0.54$ [0.26, 0.82], $p < .001$; patients with acquired brain injuries: $g = 0.73$ [0.20, 1.25], $p < .01$; children and adolescents with WM deficits: $g = 0.49$ [0.17, 0.81], $p < .01$; patients otherwise diagnosed: $g = 0.33$ [0.07, 0.59], $p < .05$). As can be seen, brain injured patients demonstrated a large effect size; however, the χ^2-test for subgroup differences showed no superiority of the effect over the other treatment groups ($\chi^2 = 2.89$, *ns*). Note that only three studies were available for the analysis of sustained WM improvement in brain injured patients. With respect to far transfer at follow-up, no subgroup differences emerged ($\chi^2 \leq 2.32$, *ns*). Regarding the preservation of effects on everyday life functioning, data was scarce ($n \leq 6$ studies per treatment group) and no subgroup differences were found ($\chi^2 = 0.75$, *ns*). The only group that preserved a maintained significant effect at the follow-up test represented children and adolescents with WM deficits ($g = 0.24$ [0.01, 0.48], $p < .05$).

In summary, WM trainings improved significantly and persistently overall WM functioning in healthy subjects as well as in patients. Patients with acquires brain injuries demonstrated large effect sizes, immediately after the end of the training, as well as after the follow-up period. Generally, long-term data on other cognitive domains and everyday-life functioning is still scarce. No subgroup differences were found for sustained changes regarding far transfer effects. Unfortunately, no sustained improvements in everyday-life functioning can be confirmed for brain injured patients. To date, only children and adolescents with WM deficits show reduced disorder symptoms.

Discussion

The aim of this meta-analysis was to examine existing WM training studies with respect to near and far transfer effects as well as to identify moderator variables that influence the efficacy of WM training. We were especially interested in whether or not WM training is able to improve the capabilities of patients with acquired brain injuries. In total, 103 studies, which added up to 112 independent group comparisons and an overall number of $N = 6{,}113$ subjects, were analyzed. Brain injured patients were analyzed in 8 studies, examining $n = 224$ patients.

Transfer Effects Caused by WM Training

As expected, the performance on the training task itself increased dramatically during training, which was represented by a very large effect size. A more relevant point, however, is that WM training caused a significant immediate near transfer effect on untrained WM tasks with a moderate effect size. This moderate effect on overall WM was long-lasting and maintained over the follow-up period. Considering the type of applied WM measures, both, tests that assessed simple and complex WM functions yielded significant results. Apparently, WM training impacts maintenance and manipulation processes as well as central executive processes of WM. With regard to specific neuropsychological WM tests, robust effects of WM training were shown for the PASAT and digit span as well as span board task, whereas only a very small effect was found in the n-back task. Substantial changes in WM were accompanied by an increased quality of life and reduced disorder symptoms of patients with WM deficits. The significant small effect was successfully maintained over the follow-up period. Concerning far transfer, WM trainings caused significant small effects on all the cognitive domains examined. Long-lasting improvements could be shown for reasoning and intelligence, as well as for cognitive control and executive functioning. No stability was confirmed concerning long-term memory and attention or processing speed.

Regarding immediate near and far transfer effects, the main findings of our study are consistent with previous meta-analyses of WM and executive functioning trainings (Karbach & Verhaeghen, 2014; Melby-Lervåg & Hulme, 2013). In agreement with our results, the authors found a moderate transfer effect of WM training on WM functions, as well as small to moderate transfer effects on other cognitive domains. Karbach and Verhaeghen concluded that “WM training [. . .] is highly effective” and “might be a useful tool for cognitive intervention” (p. 2035). In contrast, Melby-Lervåg and Hulme (2013) argued that WM trainings are not suitable rehabilitation programs for WM functioning or other cognitive skills because, in contrast to our results, they found only limited evidence for sustained effects in WM and no maintenance in any other cognitive function. The discrepant conclusion drawn from their and the present meta-analysis surely lies in the different number of studies included, as they examined, at most, six studies per outcome (mainly because the studies were not published at that time). Thus, some effects were possibly obscured because of insufficient power to yield significant results (e.g., the effect sizes for verbal WM are similar, but only in the present analysis they did reach statistical significance).

Influencing Factors of WM Efficacy

To determine optimal training conditions, a moderator analysis was performed. A main research question was whether various *subject groups* benefit differentially from WM interventions. Our analysis showed that all subject groups were able to improve their WM functions, not only immediately, but long-lasting over the follow-up period. A closer look at the effect sizes revealed that brain injured patients produced the highest effect sizes among the inspected groups (note that the difference was only by trend significant because of the small number of studies available). Thus, those subjects who suffered from deficits in WM gained the most. This finding contrasts with the so-called Matthew effect that is known from education (Bakermans-Kranenburg, van Ijzendoorn, & Bradley, 2005). It describes the phenomenon that individuals with already high cognitive abilities tend to profit even more from interventions than individuals with low abilities. In clinical settings, however, people with initially low performances experience large room for improvement. This knowledge highlights the relevance of specific WM interventions in rehabilitation. For patients with acquired brain injuries, the recovery of WM function itself is the main focus; beneficial transfer effects to other cognitive domains rank secondary. This crucial fact tends to be neglected when the implications of WM training are discussed (see, e.g., Conway & Getz, 2010; Moody, 2009).

Another crucial factor is the *type of the WM training*. Because of the large heterogeneity of applied programs, the interventions were compared on a general level according to their structure and demands. No differences were found regarding near and far transfer effects by comparing WM training based on simple span tasks and WM training based on complex span tasks. Of interest to the authors, the training types did not even show differentiated effects on the corresponding WM tests. Therefore, although complex span tasks are usually seen as more appropriate measures of WM (because of their correlation with a wide range of higher order cognitive abilities; see, e.g., Daneman & Carpenter, 1980; Kane, Hambrick, & Conway, 2005; Unsworth et al., 2009), as training tasks they are not able to produce superior effects. Just recently, Gibson et al. (2012, 2013) compared simple and complex span approaches directly with respect to transfer on primary (short-term) and secondary (long-term) memory tests, and obtained similar results. Considering the two most frequently applied specific types of training, Cogmed and updating training, both showed an immediate transfer on WM functions with small to moderate effect sizes. Because of power reasons, the stability of this effect was confirmed for Cogmed only. Additionally, both trainings demonstrated transfer on WM functions measured with simple span tasks, but only Cogmed was able to exhibit transfer on complex span tasks. Regarding far transfer effects, Cogmed caused small effects on cognitive control and everyday life functioning, whereas updating training mainly improved reasoning skills. Generally, a confound between complexity of training tasks, training setting and subject groups has to be taken into account. Complex span trainings were almost restricted to healthy subjects with application in an experimental context because of the demands of the tasks, which may be difficult to execute especially by patients. In contrast, training based on simple span tasks was carried out with various subject groups and included also rehabilitation purposes. In our experience, there are some task characteristics that may be especially important for patients with WM impairment. While most programs modulate difficulty by increasing or decreasing the number of items to-be-remembered, for patients a much more fine-tuned adjustment of difficulty may be necessary to adapt exactly to their performance level. Memorizing three items can be too easy, but doing the same task with four items might be too hard. Here, other task characteristics like selective attention and inhibition processes should be addressed via parallel tasks or distractors. Another parameter for increasing task difficulty could be manipulation of the presentation time of the stimuli. An attempt to address these issues was lately realized in the clinical rehabilitation software RehaCom, which is currently under evaluation (Weicker, Hudl, Marichal, & Thöne-Otto, 2014).

Performance slope in the training intervention itself had no influence on the effect of WM training. Thus, it seems to be the continuous challenge of WM tasks on an adequate level, rather than the progression within the training program, which indicates the efficacy of the training. This fits to the result of the inspection of *adaptivity* aspects in WM intervention programs. They show that it is essential to increase task difficulty to challenge the subject's WM system continuously; nonetheless, adaptivity to individual task performance does not seem to be mandatory if it is possible to realize other designs that achieve the same objective (e.g., fixed predefined variation of difficulty; note that Karbach and Verhaeghen (2014) found similar results in their meta-analysis). Unfortunately, to our knowledge, so far no studies have assessed the influence of the slope of the training curve itself. It is unclear whether subjects who plateau at a certain level benefit equally from WM training compared with subjects whose performance continues to increase over the whole training. Especially with respect to low performing patients, it is important to clarify this issue. If an asymptotic curve progression (that we experience frequently in patients with WM deficits) accompanies a larger training effect, it would support once more the application of WM training in the rehabilitation context.

Another aspect analyzed in the moderator analysis was the influence of the *training duration*. Indeed, there is a positive dose-response relationship, indicating that a longer period of training increases the WM training effect. It is, however, the number of training sessions, rather than the hours spent in training, which predicts efficacy. This finding is in line with Karbach and Verhaeghen (2014) who observed that total training time does not predict outcome performance. Misleadingly, they interpreted their result as if training duration was no moderator of training efficacy. Our analysis showed clearly that only interventions that included more than 20 training sessions were able to produce long lasting effects on WM functioning. The impact of training duration was also illustrated in five studies that compared low and high dose interventions directly (Alloway, Bibile, & Lau, 2013); Bergman-Nutley et al., 2014; Chooi et al., 2012; Jaeggi et al., 2008 and Stepankova et al., 2014). When the effect sizes for immediate transfer on overall WM functioning were averaged, a significant effect was found for high dose training in comparison with passive control groups ($g = 0.38$ [0.09, 0.66], $p < .01$) but not for low dose training ($g = 0.02$ [−0.29, 0.33], *ns*). Furthermore, Jaeggi et al.'s study (Jaeggi et al., 2008) indicated that WM training efficacy is not a threshold phenomenon. Aside from the total number of training sessions, it is still an open question whether high intensity or distributed training leads to larger training effects. To our knowledge, only two WM training studies directly compared the effect of different training schedules. In each case, Vogt et al. (2009) and Penner et al. (2012) conducted 16 sessions of WM training, either intensive (four times per week for 4 weeks) or distributed (two times per week for 8 weeks). Vogt et al. (2009) found both versions to be effective compared with a passive control group, solely in one test (span board task backward) the distributed training group outperformed the high intensity training group. In contrast, Penner et al. (2012) reported a clear advantage of the distributed training group that showed significant effects compared to a passive control group in five outcomes, while no significant effect was demonstrated for the intensive training group. It can be assumed that motivation, vigilance, and memory consolidation may play an important role in an optimal training dosage, but, up to now, such variables have not been examined systematically. From learning theory it is known that distributed treatment is more effective than massed treatment (e.g., Goverover, Arango-Lasprilla, Hillary, Chiaravalloti, & Deluca, 2009), in speech and language therapy for aphasia, it is essential to repeat exercises multiple times and many hours per week (Bhogal, Teasell, Speechley, & Albert, 2003; Cherney, Patterson, Raymer, Frymark, & Schooling, 2008). In summary, at present it is still not possible to clearly recommend a specific WM training time schedule with an optimal cost-benefit ratio. However, based on current literature the suggestion seems justified to conduct future WM training studies with an overall minimum number of 20 sessions, realized multiple times per week over a longer period.

Despite the intense effort to analyze various moderator variables of the WM training effect, still more research is needed to disentangle the impact of particular variables. We discovered that brain injured patients tend to benefit more from WM training than healthy subjects. Certainly, it must be considered that interventions within rehabilitation settings use different training tasks, namely primarily simple spans, and usually last longer than complex span trainings that are conducted with healthy subjects in an experimental environment. Therefore, the variables subject group, training type, and duration are inevitably confounded. Similarly, the use of outcome measures is not equally distributed; healthy subjects are tested for cognitive transfer variables while patient studies usually imply information on changes in their everyday life situation. Moreover, some tasks are not at all feasible with patients because of their high demands; on the other hand digit or block span paradigms may provide ceiling effects in healthy subjects. Consequently, a systematic examination of the complex relations of these variables is needed to understand the training benefit of various subject groups on an unbiased level. Furthermore, additional factors that may influence training efficacy need to be investigated. Apart from age and cognitive abilities, other individual differences like genetic predispositions, personality, and motivation may contribute to a better understanding of the mechanisms of WM training. Regarding biological factors, first studies showed that the neurotransmitter dopamine (Bellander et al., 2011; Brehmer et al., 2009) and the brain-derived neurotrophic factor (Colzato, van Muijden, Band, & Hommel, 2011) seem to play important parts in training success. As examples of the influence of personality traits, currently neuroticism and conscientiousness are discussed, to date with inconsistent results (Studer-Luethi, Jaeggi, Buschkuhl, & Perrig, 2012; Thompson et al., 2013). A deeper understanding of presented variables in relation to WM training will lead to a profound knowledge about what kind of intervention with which conditions best suits which individual to be able to produce the best outcome effects.

Challenging Issues in WM Training Research

There is still a lack of methodological quality in the present WM training literature regarding study designs; patient studies include small sample sizes and often lack a control group. These shortcomings are observed generally in neuropsychological intervention studies and have been reported in multiple reviews (Chung, Pollock, Campbell, Durward, & Hagen, 2013; Rosti-Otajärvi & Hämäläinen, 2014). To fulfill the requirements of evidence-based medicine, methodological aspects became more important in clinical studies; thus, there is hope of an increasing number of high-quality studies in the future. Nonetheless, there are numerous studies with healthy subjects using matched-group or quasi-experimental designs without randomization, presumably because the first prevents unexpected group differences and the latter is easier to conduct. However, randomization represents the most valid study design and should be realized whenever possible. Another problem is the preference of passive control groups although it is well known that they entail problems of validity (see Oken et al., 2008). Of interest to the authors, our analysis revealed no difference between the effect sizes of study designs with active versus passive control groups (note that Karbach & Verhaeghen, 2014, found a similar result). Therefore, we recommend including active control groups since they prevent misinterpretation of expectancy and placebo effects, and are more reliable in proving the specificity of the training effects.

Current WM training researchers have to face various other theoretical and methodological issues. The most dramatic concern is whether WM training can indeed enhance general WM functions: First, multiple outcomes should be assessed to represent such complex constructs as WM or cognitive control to draw justifiable conclusions. Second, in most cases simple span tasks were administered to evaluate WM efficacy. In contrast to complex span tasks, they are a less reliable measure of complex cognition and their possibility to illustrate WM capacity is seen controversial (see Shipstead et al., 2012). Third, it cannot be excluded that other factors, independent of the improvement of general WM functions, have led to enhanced performance in untrained tasks. One such candidate is task-specificity. Frequently, interventions are based on the principle to remember a range of items from a brief period and reproduce them in their serial order afterward, which is the same procedure as in most transfer tasks. Similar modalities of training and transfer tasks might also play a role (for a discussion, see Engle, 2002). Finally, the mechanism of transfer is yet not well understood. When increased WM capacity should lead to improved functioning in another domain, they should share at least some underlying processes, otherwise the justification why change of one function should influence another is scarce. However, a lot of WM training studies examined transfer on tasks that do not correlate with individual WM capacity or they found far transfer effects in the absence of WM enhancement (e.g., Nouchi et al., 2012; see also Shipstead et al., 2012). Buschkuhl and colleagues who reviewed studies that used imaging techniques to explore the neuronal basis of WM trainings concluded: "There is currently no clear pattern of results that would single out a specific neural mechanism underlying training and transfer that would fit within one single framework" and that "the results suggest a dynamic pattern of functional and structural plasticity underlying experience and learning" (Buschkuhl et al., 2012, p. 176–177). Recently, von Bastian and Oberauer (2013b) proposed a model that tries to explain the diverse, sometimes contradictory findings in the WM training literature. According to the authors, training-induced transfer may be mediated by two general mechanisms: enhanced capacity or enhanced efficiency of the WM system. Enhanced capacity could result from a persistent cognitive demand that leads to an extension of the present limits enabling more items to be held in WM than before. Enhanced efficiency, in contrast, could boost the performance by improved strategies, chunk learning, or a higher level of automating. Whereas larger WM capacity is likely to produce broad transfer effects in multiple WM measures and other cognitive domains, higher efficiency may impact solely task- or process similar measures. To disentangle both mechanisms and determine which one may be primarily responsible for observed training gains will be an important issue for future research.

Limitations of the Present Meta-Analysis

An important consideration of the validity of all meta-analyses is the potential presence of publication bias. The publication of negative results is still a problem of science in general (Kicinski, 2013). This means, in the context of the present analysis, that the effect of WM training could be overestimated based on the available studies included. To detect possible publication bias we applied visual inspection of the funnel plot and Egger's Test (see Method section). Hints for overestimated effects were found in reasoning and intelligence outcomes, as well as in the appraisal of changes in everyday life after WM training; however, no indication of publication bias was detected in the same domains at follow-up testing. In contrast, a slight overestimation of the effect is assumed in the long-term assessment of cognitive control and executive functioning. The presence of possible publication bias should be kept in mind when interpreting the results of this meta-analysis. Furthermore, detection tests for publication biases underlie some restrictions themselves because of their basis on funnel plot asymmetry (e.g., validity of publication bias, low power; for details see, e.g., Lau, Ioannidis, Terrin, Schmid, & Olkin, 2006).

Furthermore, some methodological decisions in the meta-analytic process could have affected its validity, such as selection criteria. For the purpose of an adequate representation of the existing literature, all studies that applied a control group were accepted (regardless of randomized, matched, or quasi-experimental designs). Additionally, patient studies were also included if they applied within-group comparisons because of the small number of patient studies with adequate control groups, especially concerning brain injuries subjects. Nonetheless, to prevent inadvertent overestimation of effects, effect sizes from within-group comparisons were only approved for analyses if they did not differ significantly from the averaged effect size of studies with control group designs. Accordingly, the χ^2-test for subgroup differences revealed that the size of the WM training effect did not differ between the study designs ($\chi^2 = 2.20$, *ns*) and all groups independently showed a significant overall effect on WM functions. This finding suggests that the meta-analysis was not biased by the partial inclusion of nonrandomized studies. Regardless of this, future research is needed to replicate and to expand on the present findings based on updated data. Second, the calculation of the effect sizes in the current meta-analysis was based on comparisons of the final measurements, not on gain scores, because of several methodological issues (see Method section). Of interest to the authors, in their meta-analysis, Karbach and Verhaeghen (2014) computed gain scores as well as net effects and found similar results for both methods, which, in turn, were comparable with our results. The last methodological issue relates to the clustering of the cognitive domains. As psychological constructs are very heterogeneous and no consistent agreement regulates how they should be integrated, first, an expert team of clinical neuropsychologists predefined the categories of interest. Second, the specific neuropsychological tests were arranged into these domains. It should be taken into account that the definition of other domains and a different allocation of tests could lead to other results. An example in the present analysis is the PASAT, which was taken as a measure of WM. As the successful completion of the task requires a combination of various cognitive functions, it could be seen as a measure of sustained attention or arithmetic capabilities, too. If we had used the PASAT to depict attention, the transfer effect of WM training on attention would have probably yielded larger effect sizes.

Conclusions

The presented meta-analysis suggests that WM training is effective. WM training does improve various aspects of WM functioning permanently and provides sustainable transfer effects to other cognitive domains, such as reasoning and intelligence, as well as cognitive control and executive functioning. Most important, the enhanced function of the system is reflected in the better performance of everyday life tasks and reduces disease-related symptoms in patients suffering from WM deficits. Patients with acquired brain injuries benefited strongly from the intervention that was shown by an increased WM performance immediately and at follow-up after several months. Thus, a fairly circumscribed specific intervention has an impact of functional and clinical relevance. Training WM may not be a panacea for the treatment of various cognitive functions as it was expected at first, but it is an adequate and specific instrument that can be used to rehabilitate people with WM deficits.

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2.2. Study II: „Was misst eigentlich die Blockspanne?“ — Der Gold-Standard im Fokus.

Nachweis über Anteile der Co-Autoren, Juliane Weicker
Development and evaluation of an adaptive working memory training intervention

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Nachweis über Anteile der Co-Autoren:

<u>*Titel:*</u> **„Was misst eigentlich die Blockspanne?“ — Der Gold-Standard im Fokus.**

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<u>*Autoren:*</u> Juliane Weicker, Nicole Hudl, Angelika Thöne-Otto

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- Konzeption und detaillierte Gestaltung des Reviews
- Literaturrecherche
- Interpretation der Befunde
- Schreiben des ersten Entwurfs des Manuskripts
- Schreiben und Einreichen der Publikation

<u>Anteil Nicole Hudl (Autor 2):</u>

- Diskussion und Interpretation der Befunde
- Schreiben der Publikation

<u>Anteil Angelika Thöne-Otto (Senior-Autorin):</u>

- Projektidee
- Diskussion und Interpretation der Befunde
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Übersichtsarbeit

„Was misst eigentlich die Blockspanne?“ – Der Goldstandard im Fokus

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Zusammenfassung: Die Blockspanne ist eines der verbreitetsten Testverfahren in der klinischen Neuropsychologie, auch bekannt als Corsi-/Block-Tapping-Test. Das Verfahren gilt als Goldstandard zur Messung des räumlichen Kurzzeit- und Arbeitsgedächtnisses (Baddeley, 2003). Trotz der häufigen Anwendung im klinischen Alltag fand die Erforschung zugrunde liegender kognitiver Prozesse erstaunlich wenig Beachtung. Dieser Übersichtsartikel vermittelt den aktuellen Forschungsstand durch Beschreibung der wichtigsten Studien, die anhand von Befragungen, Blickbewegungen oder Parallelaufgaben untersuchten, was die Blockspannenaufgabe tatsächlich misst. Dabei wird deutlich, dass nicht nur nonverbale räumliche Aspekte erfasst werden, sondern, insbesondere unter hohen Anforderungen, zusätzlich verbale und exekutive Ressourcen rekrutiert werden. Es wird diskutiert, inwieweit Zahlen- und Blockspannen als Analoga gelten können und ob die Darbietung der Blockspanne rückwärts im Vergleich zur Vorwärtsvariante einen diagnostischen Mehrwert bietet.

Schlüsselwörter: Blockspanne, Corsi, räumliches Arbeitsgedächtnis, Zahlenspanne, Review

Underlying cognitive processes of the Corsi Block-Tapping Task

Abstract: The Corsi Block-Tapping Task represents the gold standard of neuropsychological assessment of visuospatial short-term and working memory. Despite its frequent application in clinical practice, very little is known about the underlying cognitive processes involved. The present review describes the historical development of the task, its heterogeneity as well as moderators that affect performance. We present existing research on the basis of studies using interviews, eye-tracking, or dual-task paradigms and investigate what the Block-Tapping Task actually measures. The results support the assumption that not only visuo-spatial memory is being assessed, but also verbal and executive components, especially in light of higher demands. We discuss whether the spatial span can be regarded as analogous to the digit span and provide information on differential processes with respect to forward and backward performance.

Keywords: Corsi, Block-Tapping Task, visuospatial working memory, digit span, review

Historische Entwicklung

Die Entwicklung der Blockspanne geht zurück auf Philip Michael Corsi, der 1972 seine Dissertation zum Thema „Human memory and the medial temporal region of the brain” unter Supervision von Brenda Milner schrieb. Milner gilt mit ihren Arbeiten zur Erforschung von Konsolidierungsprozessen von Gedächtnisinhalten als eine der Begründerinnen der klinischen Neuropsychologie. Besonders einflussreich waren ihre Studien mit dem Patienten Henry Gustav Molaison, in der Literatur bekannt als H. M. (Milner, 1965, 1971; Milner, Corkin & Teuber, 1968; Scoville & Milner, 1957). Dieser litt nach bilateraler temporaler Lobektomie, bei dem große Teile beider Hippokampi entfernt wurden, an einer schweren anterograden Amnesie und war somit unfähig, neues Wissen zu erwerben. Um die funktionelle Organisation des Gehirns und die Auswirkungen von chirurgischen Läsionen auf die kognitive Leistungsfähigkeit besser zu verstehen, führte Corsi Studien mit Epilepsiepatienten nach Resektion des medialen Temporallappens durch (Corsi, 1972). Er untersuchte u.a. 39 Patienten mit linksseitigen und 39 Patienten mit rechtsseitigen Schädigungen anhand jeweils zwei verbaler und zwei nonverbaler Lern- und Gedächtnistests. Die Blockspannenaufgabe führte er hierbei als nonverbale visuell-räumliche Alternative zur bereits etablierten verbalen Zahlenspanne ein (Hebb, 1961). Die ursprüngliche Aufgabe der Patienten bestand darin, von neun fixierten Blöcken auf einem Brett exakt die Reihenfolge anzutippen, die ein Versuchsleiter unmittelbar zuvor zeigte (s. Abb. 1). Ermittelt wurde zum einen die Merkspanne, also die maximale Anzahl korrekt erinnerter Items, und zum anderen das implizite Lernverhalten bei wiederkehrenden Durchgängen mit identischen Reihenfolgen.

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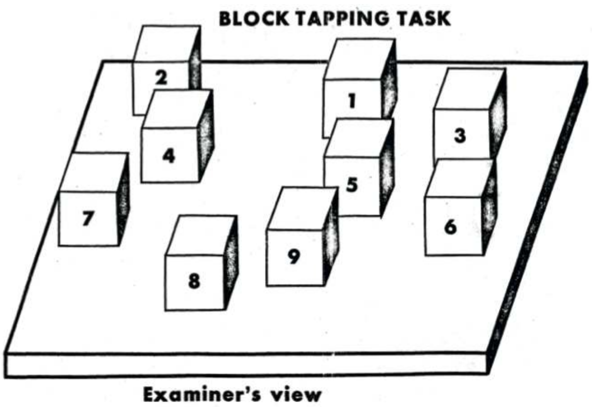

Abbildung 1. Die originale Blockspanne nach Corsi (Nachdruck aus der Dissertation von Corsi, 1972)

Während sich die unmittelbaren Merkspannen zwischen den Patientengruppen nicht unterschieden, zeigten Patienten mit Läsionen des rechten Temporallappens deutliche Einbußen beim Erlernen wiederkehrender Sequenzen. Umgekehrt hatten Patienten nach Entfernung des linken Temporallappens Schwierigkeiten, verbale Informationen längerfristig aufzunehmen. Das Ausmaß dieser modalitätsspezifischen Auswirkungen war zudem abhängig von der Läsionsgröße: Je umfangreicher die Läsionen im Temporallappen waren, desto auffälliger zeigten sich die jeweiligen kognitiven Einbußen. Corsis Studienergebnisse trugen maßgeblich dazu bei, die Lateralisierung des Gehirns sowie die zentrale Rolle des Hippokampus in der Konsolidierung von Gedächtnisinhalten zu erforschen (vgl. Squire & Knowloton, 2000). Zudem legte er mit der Einführung der Blockspanne den Grundstein für eines der verbreitetsten Testverfahren in der klinischen Neuropsychologie, heute auch bekannt als *Corsi-* oder *Block-Tapping-Test*. Die Blockspanne hat im Laufe der Jahrzehnte eine vielfache Bestätigung ihrer Validität erfahren und gilt als Goldstandard zur Messung des räumlichen Kurzzeit- und Arbeitsgedächtnisses (Baddeley, 2003). Als ein System der kurzfristigen Speicherung und Bereitstellung von Informationen zur weiteren Verarbeitung (Baddeley, 2003; Cowan, 1995) stellt das Arbeitsgedächtnis eine Schlüsselrolle zur Funktionsfähigkeit vieler höherer Funktionen dar, darunter Sprachverständnis (Daneman & Merikle, 1996), Problemlösen (Shah & Miyake, 1999) und Intelligenzleistungen (Kyllonen & Christal, 1990). Arbeitsgedächtnisdefizite, wie sie häufig nach Hirnerkrankungen auftreten, haben tiefgreifende Konsequenzen für die Funktionsfähigkeit im Alltag (Cicerone et al., 2011). Im klinischen Kontext wurde die Blockspanne zur Diagnostik von einer Reihe neurologischer Patienten mit sehr unterschiedlichen Ätiologien verwendet, darunter Epilepsie (Wisniewski, Wendling, Manning & Steinhoff, 2012), Schädel-Hirn-Trauma (Ruff, Evans & Marshall, 1986; Woods, Wyma, Herron & Yund, 2016), Schlaganfall (Kessels, van Zandvoort, Postma, Kappelle & de Haan, 2000; Kessels, de Haan, Kappelle & Postma, 2002; Nys, van Zandvoort, van der Worp, Kappelle & de Haan, 2006; van Asselen et al., 2006), psychiatrischen Störungen (Salamé, Danion, Peretti & Cuervo, 1998), Parkinson (Kemps, Szmalec, Vandierendonck & Crevits, 2005; Stoffers, Berendse, Deijen & Wolters, 2003), Korsakow-Syndrom (Haxby, Lundgren & Morley, 1983) und Demenz (Carlesimo, Fadda, Lorusso & Caltagirone, 1994; Millet et al., 2009; Pasquier, Grymonprez, Lebert & Van der Linden, 2001). Durch die formlose Veröffentlichung des Verfahrens im Rahmen der Dissertation wurde kein standardisiertes Vorgehen definiert, weshalb sich eine breite Variabilität der Aufgabe etablierte. Die verschiedenen Testvarianten unterscheiden sich vorrangig hinsichtlich Layout (Größe des Blockspannenbretts sowie Farbe, Anzahl, Größe und Anordnung der Blöcke), Durchführung (Zeigeprozedur und -geschwindigkeit, Anzahl der Trials, Länge und Reihenfolge der Sequenzen, Start- und Abbruchkriterium) und Auswertung (für ein ausführliches Review siehe Berch, Krikorian & Huha, 1998). Die gängigen Blockspannenaufgaben in Deutschland sind Bestandteil von Testbatterien basierend auf den Arbeiten von Wechsler (WMS-R, Wechsler, 1987; WMS-III, Wechsler, 1997b). Trotz der vielfachen Anwendung im klinischen Kontext fand die Erforschung zugrunde liegender kognitiver Prozesse erstaunlich wenig Beachtung, ebenso wurde kaum hinterfragt, welchen Einfluss die Heterogenität der Aufgabe auf die Interpretation der Leistungsfähigkeit haben könnte. Woods und Kollegen verglichen kürzlich publizierte Studienergebnisse zur Anwendung der Blockspanne und fanden erhebliche Differenzen in den ermittelten Maximalspannen sowie den geschätzten tatsächlichen Spannen (Woods, Wyma, Herron & William, 2015). Diese Heterogenität in der Methodik erschwert nicht nur die Interpretation und den Vergleich von Studienergebnissen, sondern auch das Verständnis zugrunde liegender kognitiver Prozesse.

Moderatoren der Aufgabenschwierigkeit

Die Schwierigkeit einer Aufgabe kann trotz gleicher Itemanzahl deutlich variieren, da die erzielte Leistung von den Eigenschaften der Aufgabe, ihrer Darbietungsform und interindividuellen Merkmalen abhängig ist. Die wichtigsten Moderatoren der Aufgabenschwierigkeit werden im Folgenden kurz vorgestellt.

Eigenschaften der Aufgabe. Die Präsentation einzelner Items nacheinander forciert eine sequenzielle Verarbeitung der Stimuli. Damit unterscheidet sich die Blockspannenaufgabe maßgeblich von anderen räumlichen Gedächtnisverfahren, die auf einem Abruf simultan dargebotener Informationen basieren (bspw. der Visual-Pattern-Test; Della Sala, Gray, Baddeley & Wilson, 1997). Untersuchungen mit bildgebenden Verfahren sowie klinische Läsionsstudien konnten diese unterschiedlichen Verarbeitungsprozesse für simultan-räumliche und sequenziell-räumliche Informationen (mit zusätzlichen Anforderungen an das Merken einer Reihenfolge) nachweisen (Smith & Jonides, 1995, 1998; Smith et al., 1995). Eine Untersuchung mit variierter Darbietung der Blockspannenaufgabe zeigte, dass eine längere Präsentationsdauer der Items sowie eine größere Zeitspanne zur Vorbereitung des Abrufs die Performanz erhöht (Fischer, 2001). Interessanterweise beeinflussen aber auch die absolute Pfadlänge, also die physische Entfernung der zu merkenden Blöcke, sowie das Kreuzen der imaginären Verbindungen zwischen den Items und deren Winkel die Aufgabenschwierigkeit (Busch, Farrell, Lisdahl-Medina & Krikorian, 2005; Orsini, Simonetta & Marmorato, 2004; Parmentier, Andrés, Elford & Jones, 2006; Parmentier, Elford & Mayberry, 2005; Parmentier & Andrés, 2006; Smirni, Villardita & Zappala, 1983; für eine beispielhafte Illustration siehe Abb. 2). Diese Ergebnisse deuten darauf hin, dass die präsentierten Sequenzen weniger als seriell-geordnete Positionen, sondern eher als Verbindungen oder Pfad gemerkt werden. Die zeitliche Anordnung von Informationen ist somit ein wichtiger strukturgebender Bestandteil des Kurzzeitgedächtnisses, komplexere Eigenschaften wie Vertrautheit, Ähnlichkeit und Distanz werden durch die Aufgabe jedoch ebenso aktiviert. Eine systematische Untersuchung der einzelnen Komponenten mit einem experimentellen Design gestaltete sich bislang schwierig (Woods et al., 2015). Woods und Kollegen fanden beispielsweise nur einen geringen Einfluss von Pfadlänge und -kreuzungen, da diese jeweils komplex mit der durch die Verbindungen erzeugten Gesamtgestalt interagierten: So konnte ein Pfad zwar sehr lang sein, aber eine besser zu merkende Form bilden, sodass die Länge des Pfades nur noch eine untergeordnete Rolle spielte. Das Bilden solcher Gruppierungen oder Gestalten ist bei sequenzieller Präsentation der Items schwieriger als bei simultaner Darbietung. Dennoch konnten Untersuchungen anhand der Blockspannenaufgabe zeigen, dass strukturierte Pfade mit symmetrischen oder wiederholten Teilstücken sowie Items mit größerer räumlichen Nähe zu einer deutlich erhöhten Performanz führen (De Lillo, 2004; Kemps, 2001). Die Abbildung der räumlichen Komponente durch die Zuordnung von einzelnen Positionen im Raum wird somit von zusätzlichen nichträumlichen Merkmalen beeinflusst. Ob die Items in steigendem Schwierigkeitsgrad dargeboten werden oder einem anderen Schema folgen (z.B. mit schwerstem Item beginnend), erzeugt jeweils einen erleichternden und einen erschwerenden Effekt: Einerseits tritt im Verlauf ein Übungseffekt ein, die Probanden entwickeln beispielsweise erfolgreiche Strategien. Mit steigender Darbietungsdauer kommt es aber auch zu Interferenzen aufgrund des ähnlichen Aufgabenmaterials. Bislang gibt es keine Belege für eine unterschiedliche Performanz aufgrund der dargebotenen Itemreihenfolge (Cornoldi & Mammarella, 2008; Fischer, 2001).

Darbietungsform. Neben der Standardpräsentation der Items auf einem Blockspannenbrett werden zunehmend computerbasierte Verfahren eingesetzt. Die Leistung in herkömmlichen Tests übersteigt dabei oft Merkspannen, die durch Computerverfahren erhoben werden (Claessen, van der Ham, & van Zandvoort, 2015). Des Weiteren zeigen sich vereinzelt Interaktionen mit der geforderten Abrufreihenfolge: Während bei Standardpräsentation der Items ein Vorteil der Blockspanne vorwärts gegenüber rückwärts gefunden wurde, verschwand dieser bei compu-

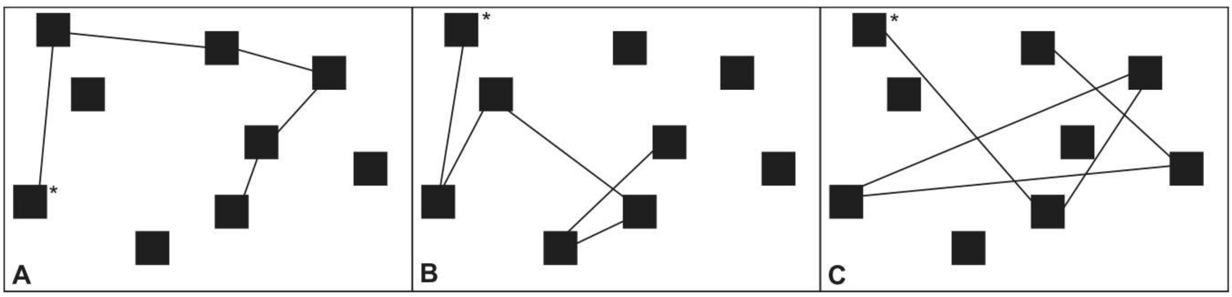

Abbildung 2. Beispielhafte Illustration für unterschiedliche Eigenschaften von Pfaden

Die Grafik verdeutlicht unterschiedliche Schwierigkeitsgrade der Blockspannenaufgabe bei gleicher Anordnung der Blöcke und gleicher Anzahl zu merkender Items. Die Markierung kennzeichnet jeweils den Beginn des Pfades. Pfad A ist am leichtesten zu lösen: die Blöcke liegen dicht beieinander, die Winkel sind groß und es gibt keine Kreuzungen. Pfad B ist aufgrund der spitzeren Winkel und einem gekreuztem Weg etwas schwieriger. Pfad C stellt mit weit auseinanderliegenden Blöcken und fünf Kreuzungen die höchste Schwierigkeitsstufe dar.*

terisierter Darbietung (Claessen et al., 2015; aber siehe Brunetti, Del Gatto & Delugo, 2014). Als Erklärungsansatz wurde die Aktivierung von Spiegelneuronen, wie sie aus der Motorikforschung bekannt sind, herangezogen (Iacoboni, 2009): Bereits während wir Handlungen beobachten, werden Neurone in unserem eigenen Motorikareal aktiviert und damit die Ausführung bereits voraktiviert („Priming"). Die identische Reihenfolge von beobachteter und eigener Handlung, wie es beim Bearbeiten der Blockspanne vorwärts der Fall ist, führt nach dieser Theorie zu einer leichten Reduktion der Beanspruchung des Gedächtnisses und somit zu einer besseren finalen Leistung. Bei umgekehrter Reihenfolge greifen diese Erleichterungseffekte nicht und erzeugen womöglich sogar Interferenzen, sodass die Leistung in der Blockspanne rückwärts eine höhere Anstrengung benötigt. Unter computerisierter Darbietung verschwindet die motorische Komponente, sodass hier keine Erleichterungseffekte auftreten und beide Spannen vergleichbar schwierig sind. Eine besondere Darbietungsform der Blockspannenaufgabe stellten Piccardi und Kollegen mit einem lebensgroßen, begehbaren Corsi-Test vor. Das Ablaufen der zu merkenden auf den Boden gezeichneten Felder führte zu einem schnelleren Lernen und einer größeren Merkspanne im Vergleich zur Standardversion (Piccardi et al., 2008). Die Autoren sehen ihr Verfahren weniger als einen Test zum Lernen räumlich getrennter Items, sondern im Sinne der Pfadtheorie eher zum Erlernen eines Weges im Raum.

Interindividuelle Merkmale. Die Leistung in der Blockspannenaufgabe nimmt, analog zur Kapazität des Arbeitsgedächtnisses, linear mit steigendem Lebensalter ab und zwar tendenziell stärker als bei der Zahlenspanne (Glisky, 2007; Wilde, Strauss & Tulsky, 2004; Woods et al., 2015). Unter Betrachtung allgemeiner Arbeitsgedächtnisleistungen zeigt sich ein deutlicherer Effekt des Alterns auf exekutive als auf reine Speicherprozesse (Payer et al., 2006) und tendenziell mehr auf die visuelle im Vergleich zur räumlichen Komponente (Beigneux, Plaie & Isingrini, 2007). Geschlechtsspezifische Unterschiede treten eher selten und vermutlich nur innerhalb eines bestimmten Lebensabschnitts auf (Pagulayan, Bush, Medina, Bartok & Krikorian, 2006). Ein Einfluss des Bildungsniveaus wird dagegen von den meisten Studien belegt (Fournet et al., 2012; Kessels, van den Berg, Ruis & Brands, 2008; Monaco, Costa, Caltagirone & Carlesimo, 2013; aber siehe Woods et al., 2015). Interindividuelle kognitive Fähigkeiten, auch unabhängig von Kurzzeit- und Arbeitsgedächtnisleistungen, spielen hingegen eine bedeutsame Rolle. So korreliert beispielsweise die Informationsverarbeitungsgeschwindigkeit positiv mit der Leistung in Arbeitsgedächtnisaufgaben (für ein aktuelles Review siehe Hurlstone, Hitch & Baddeley, 2014).

Strategien der Aufgabenbearbeitung

Eine Methode, um herauszufinden, wie die Blockspannenaufgabe tatsächlich gelöst wird, ist die direkte Befragung von Teilnehmern. Ridgeway legte dazu $N = 20$ gesunden Erwachsenen computerisierte Aufgaben vor, die in Spannenlänge und räumlicher Anordnung variierten (Ridgeway, 2006). Nach jedem Trial wurden die Teilnehmer befragt, welche der folgenden Strategien sie zur Aufgabenlösung angewandt hatten: 1) Rehearsal während des Enkodierens (sukzessive innerliche Wiederholung des Pfades), 2) Zählen während des Enkodierens („1, 2, 3, ..."), 3) Strategisches Zusammenfassen einzelner Pfadabschnitte während des Enkodierens (z. B. „Dreieck plus Linie"), 4) Visualisierung der Verbindungen zwischen den Items als ganzheitliche Form (z. B. Gestalt eines Dreiecks), oder 5) Rehearsal zwischen Enkodierung und Abruf (jegliche Verbalisierung oder Visualisierung der Lösung). Die Ergebnisse zeigten, dass die Probanden keine konstante Strategie verfolgten, sondern diese häufig wechselten. Welche Strategie letztendlich zum Einsatz kam, war abhängig von verschiedenen Faktoren wie Pfadlänge, Gestalt, usw. So nahm die Häufigkeit, einen Pfad zu visualisieren, mit dessen Länge ab, das strategische Zusammenfassen einzelner Pfadabschnitte nahm hingegen mit größerer Itemanzahl zu. Insgesamt zeigten Probanden, die Items zu einzelnen Abschnitten oder Formen zusammenfassten, eine bessere Leistung als Probanden, die dies nicht taten. Eine erfolgreiche Aufgabenbearbeitung stellt demnach nicht nur hohe Anforderungen an Gedächtnisprozesse, sondern auch an eine flexible und in Abhängigkeit von den Anforderungen günstige Strategiewahl. Des Weiteren fiel auf, dass die Hälfte der Probanden die Items zählte und Merkprozesse verbalisierte. Dieses Verhalten wurde unabhängig vom Schwierigkeitsgrad beobachtet.

Patt und Kollegen (2014) näherten sich der Herangehensweise bei der Blockspanne ebenfalls durch eine direkte Befragung der Probanden, zogen aber die Beobachtung natürlicher Blickbewegungen mittels Eye-Tracking als Informationsquelle hinzu. Ähnlich wie bei Ridgeway (2006) gab der Großteil der 25 befragten gesunden Erwachsenen an, aus den Items Formen gebildet zu haben. Verbalisiert und gezählt hatte hier nur ein Viertel der Probanden. Die Analyse der Blickbewegungen zeigte, dass beim Enkodieren und Behalten eine diffuse Strategie gewählt wurde, bei der die Probanden tendenziell zentral in die Bildschirmmitte blickten. Die Items wurden also nicht einzeln seriell enkodiert, sondern möglichst als Ganzes erfasst. Dazu war anscheinend kein offensichtlicher Blickwechsel notwendig, sondern es fand eine verdeckte Aufmerksamkeitsverschiebung statt, da nur 40 % der Items direkt angeschaut wurden. Beim Abruf wurden hingegen die Items seriell lokalisiert und zu 80 % direkt betrachtet, ähnlich einem Anklicken mit der Maus oder dem Tippen eines Fingers.

Aus den vorgestellten Untersuchungen lässt sich schlussfolgern, dass höhere Kognitionen mit stimulusspezifischen Eigenschaften interagieren. Die Leistung in der Blockspannenaufgabe hängt demnach nicht allein vom visuellen Kurzzeitgedächtnis ab, sondern auch von der Fähigkeit zur verdeckten Aufmerksamkeitsverschiebung, der Integration von Items durch strategisches Zusammenfassen einzelner Pfadabschnitte oder Gestalten, der flexiblen Anwendung von Strategien und Strategiewechseln sowie der Rekrutierung unterstützender exekutiver und verbaler Ressourcen bei der Aufgabenbearbeitung.

Der Einfluss von Parallelaufgaben

Um den Einfluss der verschiedenen vorgestellten kognitiven Komponenten systematisch zu untersuchen, ließen Vandierendonck und Kollegen Probanden jeweils verschiedene Parallelaufgaben während der computerbasierten Darbietung der Blockspannenaufgabe durchführen (Vandierendonck, Kemps, Fastame & Szmalec, 2004). Jede Parallelaufgabe beanspruchte eine Komponente des Arbeitsgedächtnisses: a) Matrix-Tapping die räumliche Komponente (kontinuierliches Drücken der vier Ecken des Nummernblocks auf einer Tastatur gegen den Uhrzeigersinn), b) artikulatorische Unterdrückung die verbale Komponente (kontinuierliches Aussprechen des Wortes „das"), und c) Generierung von zufälligen Intervallen die exekutive Komponente (Drücken der Taste „0" in jeweils unterschiedlichen Intervallen). Als Kontrollbedingung für die motorische Ausführung der Parallelaufgaben wurde zusätzlich eine Parallelaufgabe durchgeführt, bei der fixe Zeitintervalle generiert werden sollen (Drücken der Taste „0" jeweils ein Mal pro Sekunde). Die Ergebnisse zeigten, dass Matrix-Tapping die Leistungen in der Blockspanne vorwärts und rückwärts beeinträchtigte, während die artikulatorische Unterdrückung nur einen Einfluss auf die Version rückwärts und zwar ausschließlich auf längere Sequenzen hatte. Das Generieren zufälliger Intervalle führte immer zu reduzierten Leistungen, am stärksten war der Effekt jedoch auch hier bei längeren Sequenzen. Die Kontrollaufgabe hatte wie erwartet keinen Einfluss auf die Leistung. Die Autoren schlussfolgerten aus ihren Untersuchungen, dass das Merken der Pfade in der Blockspannenaufgabe hauptsächlich durch das räumliche System kodiert wird, bei höheren Anforderungen jedoch zusätzlich exekutive und verbale Bestandteile rekrutiert werden.

Um die Anforderungen der beteiligten kognitiven Prozesse zu differenzieren, führten Higo und Kollegen systematische Untersuchungen mit verschiedenen Parallelaufgaben durch (Higo, Minamoto, Ikeda & Osaka, 2014). Sie analysierten jedoch nicht nur die Gesamtleistung, sondern berücksichtigten auch die Art der produzierten Fehler, da das Erinnern der Items sowohl eine korrekte serielle Reihenfolge als auch deren räumliche Position erfordert und beide Faktoren somit miteinander konfundiert sind (Berch et al., 1998). Wie bei Vandierendonck und Kollegen (2004) wurden folgende Parallelbedingungen gewählt: a) Matrix-Tapping zur Beanspruchung der räumlichen Komponente, b) serielle artikulatorische Unterdrückung zur Beanspruchung der verbalen Komponente, und c) keine Zweitaufgabe. Im Einklang mit den Vorbefunden beeinträchtigte Matrix-Tapping sowohl die Gesamtleistung als auch die Produktion von Positions- und Reihenfolge-Fehlern. Artikulatorische Unterdrückung beeinflusste ausschließlich die Leistung der Blockspannenaufgabe rückwärts im höchsten Schwierigkeitsgrad, was nicht anhand der Gesamtperformanz, sondern anhand vermehrt falscher Reihenfolgen der sieben zu merkenden Items ersichtlich wurde. Um zu untersuchen, ob der verbale Anteil auf Strategien zur räumlichen Kodierung der Items („oben links, unten rechts, ...") zurückgeht, wurde in einem zweiten Experiment ausschließlich die Blockspanne im höchsten Schwierigkeitsgrad erneut untersucht. Neu war, dass die Anordnung der Blöcke diesmal von Trial zu Trial variiert wurde. Eine verbale Kodierung der Positionen sollte damit erschwert werden und artikulatorische Unterdrückung somit keinen Einfluss mehr haben. Die Auswertung der Ergebnisse zeigte entgegen der Hypothese unter beiden Parallelaufgaben Leistungseinbußen, diesmal sogar sowohl bei der Blockspanne vorwärts als auch rückwärts. Ursache der reduzierten Performanz war auch hier eine erhöhte Anzahl von Reihenfolge-Fehlern. Die unerwarteten Ergebnisse werden mit einem insgesamt erhöhten Schwierigkeitsgrad sowie einer verstärkten sequenziellen Repräsentation durch das kontinuierlich veränderte Design erklärt (vgl. Ridgeway, 2006, die ebenfalls eine unterstützende serielle verbale Kodierung beobachtete). Zusammenfassend legten auch die Untersuchungen mit Parallelaufgaben nahe, dass die Bearbeitung der Blockspannenaufgabe maßgeblich auf einer räumlichen Verarbeitung basiert, bei hohen Anforderungen (große Itemzahl, Reproduktion in umgekehrter Reihenfolge) jedoch zusätzlich exekutive und auch verbale Ressourcen rekrutiert werden (vgl. Vecchi & Richardson, 2001).

Blockspanne als Analogon zur Zahlenspanne?

Historisch wurde die Blockspanne als nonverbales Äquivalent zur Zahlenspanne eingeführt (Corsi, 1972). Tatsächlich finden Studien zwischen Zahlen- und Blockspannen überwiegend moderate Korrelationen (Orsini, 1994; Tulsky & Price, 2003; Wilde & Strauss, 2002; aber siehe Kessels et al., 2008). Die Zahlenspanne vorwärts erfordert das Speichern verbaler Informationen und der Abruf rückwärts wird meist ausgeführt, indem die Informationen in der originalen Sequenz aufrechterhalten und dann Zahl für Zahl in umgekehrter Reihenfolge wiedergegeben werden, was eine hohe exekutive Kontrolle erfordert (Thomas, Milner & Haberlandt, 2003). Zwischen beiden Bedingungen besteht ein gut dokumentierter Unterschied, Speicherfunktion und exekutive Kontrolle sind im verbalen Arbeitsgedächtnis somit voneinander getrennte Funktionen (Gardener, 1981; Kessels et al., 2008; Wilde & Strauss, 2002). Hinsichtlich der Blockspanne wird gemeinhin postuliert, dass die Blockspanne vorwärts visuell-räumliche Kurzzeitgedächtnisleistungen misst, während die Blockspanne rückwärts zusätzlich exekutive Anforderungen stellt (Hester, Kinsella & Ong, 2004). Unter der Annahme, dass bei der Umkehrung der Reihenfolge eine aktive Manipulation erfolgt und diese das Arbeitsgedächtnis beansprucht, sollte die Ausführung der Blockspannenaufgabe rückwärts anstrengender und schwieriger sein (Baddeley, 1986; Lichtenberger, Kaufman & Lai, 2002). Eine Vielzahl an Studien fand jedoch keinen Unterschied in der Gesamtperformanz zwischen der Blockspanne vorwärts und rückwärts (Berch et al., 1998; Higo et al., 2014; Kessels et al., 2008; Mammarella & Carnoldi, 2005; Wilde & Strauss, 2002; aber siehe Helmstaedter, Kemper & Elger, 1996). Zudem ist eine schlechte Performanz in der Blockspanne rückwärts meist auch mit niedrigerem Abschneiden in der Blockspanne vorwärts assoziiert (Kessels et al., 2008; Wilde et al., 2004). Bei der Durchführung der Blockspannen sind die Blöcke immer optisch präsent, die Sequenzierung der Items in vorwärts oder rückwärts spielt im komplexen räumlichen System vermutlich eher eine untergeordnete Rolle (De Lillo, 2004; Kemps, 2001; Patt et al., 2014; Ridgeway, 2006). Dafür spricht auch, dass Positionsmarker (Primacy- und Recency-Effekte) wesentlich schwächer ausgeprägt sind als bei Zahlenspannen (Woods et al., 2015). Eine Untersuchung der Faktorenstruktur von Block- und Zahlenspannen des WAIS-III (Wechsler Adult Intelligence Scale; Wechsler, 1997a) brachte ein Modell hervor, das zwischen verbalen und räumlichen Aspekten trennte, aber keinen weiteren dissoziierenden Faktor innerhalb der Blockspannen hatte (Kessels et al., 2008). Die Architektur des visuell-räumlichen Arbeitsgedächtnisses unterscheidet sich somit grundlegend von der verbalen Modalität. Hier können gespeicherte Informationen zugleich verarbeitet werden, Speicherfunktion und Exekutivfunktion sind in diesem System kaum zu trennende Komponenten und können sowohl Anforderungen der Blockspannenaufgabe vorwärts als auch rückwärts erfüllen (Cornoldi & Mammarella, 2008). Unterstützung für dieses Modell liefern zahlreiche bildgebende Untersuchungen und Läsionsstudien mit Patienten, die zeigen, dass Blockspanne vorwärts und rückwärts ähnliche neuronale Aktivitäten hervorrufen (für einen aktuellen Überblick der neuronalen Korrelate von Arbeitsgedächtnisprozessen siehe D'Esposito & Postle, 2015, und Eriksson, Vogel, Lansner, Bergström & Nyberg, 2015). Die Blockspanne stellt somit kein nonverbales Äquivalent zur Zahlenspanne dar.

Blockspanne vorwärts vs. rückwärts

Eine häufige klinische Beobachtung ist, dass die Performanz in der Blockspanne rückwärts ähnlich oder sogar höher ist als vorwärts. Empirisch wurde diese Einschätzung durch die Analyse intraindividueller Leistungen bestätigt (Kessels et al., 2008; Wilde & Strauss, 2002; Wilde et al., 2004). Der Prozentsatz von Probanden, die mehr Items rückwärts als vorwärts korrekt generierten, lag bei etwa einem Drittel – ein Phänomen, das bei der Zahlenspanne äußerst selten auftritt (Wilde et al., 2004). Wilde und Kollegen (2004) untersuchten anhand der Daten aus dem WAIS-III/WMS-III-Manual, ob größere Diskrepanzen zwischen einzelnen Subtests bei klinischen Stichproben auftraten. Auch hier fand sich eine weite Übereinstimmung der Leistungsfähigkeit: Schnitt eine Gruppe in einem Maß schlecht ab, so tat sie das auch bei der entsprechend umgekehrten Reihenfolge. So unterschieden sich lediglich 15% der untersuchten Patienten hinsichtlich Zahlenspanne vorwärts und rückwärts (Ätiologie: Schizophrenie, Huntington, Schädel-Hirn-Trauma). Bei der Blockspanne gab es 10% auffällige Unterschiede (Ätiologie: Alzheimer Krankheit, Lobektomie des linken Temporallappens). Einige Wissenschaftler schlussfolgerten aus der Zusammenschau der Befunde, dass die Blockspanne vorwärts ein gutes Verfahren zur Erhebung des visuell-räumlichen Kurzzeitgedächtnisses sei, die Blockspanne rückwärts darüber hinaus keinen Mehrwert an Informationen liefere (Claessen et al., 2015; Kessels et al., 2008; Wilde & Strauss, 2002; Wilde et al., 2004). Zudem befanden Wilde und Kollegen (2004), dass die Blockspanne rückwärts daher kein klinisch sensitives Maß für die Identifizierung von Arbeitsgedächtnisdefiziten darstelle.

Die bereits vorgestellten Studien mit Parallelaufgaben legen indes nahe, dass sich die geforderten Funktionen je Variante durchaus unterscheiden. So wurde die Leistung in der Blockspanne vorwärts nicht durch artikulatorische Unterdrückung beeinträchtigt, die Rückwärtsvariante durchaus (Higo et al., 2014; Vandierendonck et al., 2004). Bei Higo und Kollegen (2014) fanden sich u.a. Sequenzierungsfehler, was die Autoren annehmen ließ, dass die serielle Verarbeitung der Items der kritische Faktor sei, der die beiden Bedingungen voneinander unterscheidet. Vandierendonck und Kollegen (2004) stellten zudem fest, dass die Probanden initial längere Merkspannen vorwärts als rückwärts hatten, dieser Unterschied mit der Übung jedoch immer geringer wurde. Gezielte Trainingsstudien legen ebenfalls unterschiedliche Funktionsmechanismen nahe. So zeigte sich nach einem metakognitiven Strategietraining die Leistung in der Blockspanne rückwärts signifikant verbessert, die Blockspanne vorwärts jedoch nicht (Caviola, Mammarella, Cornoldi & Lugangelli, 2009). Eine Metaanalyse zur Wirksamkeit von Arbeitsgedächtnistrainings identifizierte die Blockspanne rückwärts von allen erhobenen Arbeitsgedächtnismaßen als am sensitivsten für Veränderungsprozesse (Weicker, Villringer & Thöne-Otto, 2016).

Cornoldi und Mammarella näherten sich dem Phänomen Blockspanne, indem sie Personen mit geringen räumlichen Fähigkeiten multimodal untersuchten. Zunächst untersuchten sie Kinder mit visuell-räumlichen Störungen sowie gesunde Kontrollen (Mammarella & Cornoldi, 2005). Die Stichproben unterschieden sich nicht in ihren Leistungen bei den Zahlenspannen und der Blockspanne vorwärts, die beeinträchtigten Kinder zeigten jedoch einen Leistungseinbruch in der Blockspanne rückwärts. Da die Zahlenspanne rückwärts, die hohe Anforderungen an exekutive Funktionen stellt, gut bewältigt wurde, musste der Leistungseinbruch also auf andere Defizite zurückzuführen sein. In einer Folgestudie wurden von einer Originalstichprobe von über 400 jungen Erwachsenen jeweils n =20 Personen mit sehr starken und sehr schwachen Leistungen in einer mentalen Rotationsaufgabe ausgewählt (Cornoldi & Mammarella, 2008). Erstaunlicherweise zeigten sich auch im Vergleich dieser Extremgruppen isolierte Schwierigkeiten bei der Blockspanne rückwärts, die anderen Spannenmaße unterschieden sich nicht zwischen den Gruppen. Die Ergebnisse der beiden Studien erklärten die Annahme, dass die Reihenfolge in der Reproduktion durchaus unterschiedliche kognitive Prozesse anspricht. Die Autoren gehen davon aus, dass die Blockspanne rückwärts spezifische räumliche Fähigkeiten verlangt sowie mehr simultane und weniger sequenzielle Anforderungen zur Aufgabenbearbeitung erfordert. Diese These steht der von Higo und Kollegen vorgeschlagenen konträr gegenüber. Vermutlich interagieren interindividuelle Merkmale mit dem Aufgabenmaterial. Eine Erklärung wäre, dass unterstützende verbale Ressourcen und Strategien bei der Blockspannenaufgabe vorwärts erfolgreich eingesetzt wurden, diese aber in der Variante rückwärts nicht mehr griffen. Auch eine domänenspezifisch reduzierte exekutive Kontrolle ist denkbar (vgl. Cornoldi & Mammarella, 2008). Kürzlich veröffentlichte Analysen des Antwortverhaltens legen nahe, dass die Formulierung der Lösung bei der Blockspannenaufgabe vorwärts bereits während der Enkodierung stattfindet, die Blockspanne rückwärts jedoch erst nach Ende der Präsentation aller Items generiert wird (Brunetti et al., 2014). Hierbei wurden verzögerte Reaktionszeiten als Zeichen einer stärkeren Beanspruchung der zentralen Exekutive interpretiert.

Zusammenfassend sind sich Blockspanne vorwärts und rückwärts in der Beanspruchung kognitiver Prozesse ähnlicher und differenzieren weniger zwischen Speicher- und Verarbeitungsprozessen als beispielsweise Zahlenspannen. Dies bedeutet jedoch nicht, dass die Bedingungen funktionell gleichzusetzen sind. Auch wenn sich Empfehlungen auf Basis der aktuellen Forschungslage diesbezüglich noch unzureichend gestalten, ist sowohl der Einsatz der Blockspanne vorwärts als auch rückwärts gerechtfertigt und Patientenstudien geben Hinweise auf einen sinnvollen diagnostischen Mehrwert (vgl. Cornoldi & Mammarella, 2008; Mammarella et al., 2006).

Zusammenfassung und klinische Implikationen

Die vorliegende Arbeit widmete sich den zugrunde liegenden kognitiven Prozessen der Blockspannenaufgabe. Trotz der häufigen Verwendung in der klinischen Praxis gibt es bislang erstaunlich wenige Studien, die das Verfahren gezielt untersuchten. Die Literaturanalyse zeigte, dass eine große Heterogenität besteht, die sowohl die Interpretation als auch Vergleichbarkeit von Studienergebnissen erschwert. Sofern eine standardisierte Durchführung verfügbar ist, sollten sich Anwender unbedingt an die Vorgaben halten, da selbst kleine Veränderungen (beispielsweise in der versehentlichen Auswahl falscher Blöcke oder Verzögerungen in der Präsentationsrate) Einfluss auf den Schwierigkeitsgrad haben. Eine maßgebliche Aufgabe für die Forschung der nächsten Jahre wird ein besseres Verständnis der Interaktion von stimulusspezifischen Eigenschaften mit höheren kognitiven Funktionen sein. Die dargelegten Studien zeigten, dass eine erfolgreiche Bearbeitung nicht nur von einem guten visuell-räumlichen Kurzzeitgedächtnis abhängig ist, sondern auch von der Fähigkeit zur verdeckten Aufmerksamkeitsverschiebung, dem strategischen Zusammenfassen einzelner Pfadabschnitte und dem Bilden von Gestalten sowie der flexiblen Auswahl und Anwendung profitabler Strategien. Unter Hinzunahme von Parallelaufgaben wurde deutlich, dass die Blockspanne kein rein nonverbales Verfahren ist, da insbesondere bei höheren Schwierigkeitsgraden unterstützende verbale und exekutive Ressourcen zur Aufgabenbearbeitung hinzugezogen wurden. Klar wurde auch, dass die Blockspanne aufgrund ihrer unterschiedlichen Architektur nicht als paralleles Testverfahren zur Zahlenspanne gelten kann. Das Wissen um die Komplexität des Verfahrens wird im klinischen Alltag dazu beitragen, individuelle Defizite und Ressourcen besser zu erkennen und therapeutische Ziele entsprechend anzupassen. Wahrscheinlich ist es gerade die Vielschichtigkeit der erforderlichen kognitiven Ressourcen bei höherer Itemschwierigkeit, die die Blockspanne rückwärts zu einem sensitiven Indikator für den Trainingserfolg von Arbeitsgedächtnistrainings macht (vgl. Weicker et al., 2016).

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2.3. Study III: WOME working memory training — A new intervention for individuals with low WM capacity.

Nachweis über Anteile der Co-Autoren, Juliane Weicker
Development and evaluation of an adaptive working memory training intervention

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Nachweis über Anteile der Co-Autoren:

Titel: **WOME working memory training — A new intervention for individuals with low WM capacity.**

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- Unterstützung bei der Programmierung der Operation Span Task
- Entwicklung des Aufgabenkonzeptes und Unterstützung bei der Programmierung der Blockspannenaufgabe für die Durchführung bei funktionaler Magnetresonanztomografie (MRT)
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WOME working memory training —

A new intervention for individuals with low WM capacity

Unpublished manuscript

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Abstract

Abundant studies have been published that showed promising results of working memory (WM) training in healthy individuals. Individuals with low WM capacity may benefit even more from an intervention. Since existing programs are not suitable for the application in patients, e.g., with acquired brain injury, a new WM training program was developed. In this manuscript, we present the rational and framework of the intervention along with a description of the composition of the program and the corresponding training tasks. Two pilot studies were carried out to evaluate the feasibility of the intervention in N = 7 healthy older adults and N = 6 individuals with brain lesions, respectively. The training phase consisted of daily sessions over three weeks, each lasting 45 min, resulting in 15 sessions overall. Before and after the training phase, neuropsychological tests targeting WM and related cognitive functions were carried out. Additionally, the subjects were questioned regarding strategies used during training and the subjective evaluation of the training effects in daily life. Feasibility was confirmed in both subject groups. Moreover, the analyses showed first trends of effectiveness in measures of WM and executive functions. Based on the results, the composition of the program and the specific implementation of the training tasks were improved.

Keywords:

Cognitive intervention, acquired brain injury, working memory training, WOME, neuropsychology

Rational and framework of the development

To date, no appropriate interventions are available for training WM functions in patients with acquired brain lesions. Existing programs lack (i) a theoretical foundation allowing targeting specific components of the WM system, (ii) a level structure which adapts difficulty in very fine-tuned steps, and (iii) contents of tasks that are tailored to adults with low WM capacity. The new WM training program was developed in consideration of the framework conditions proposed by Perrig et al. (2009), which comprise

1) the presentation of throughout demanding and effortful WM tasks, which minimize the generation of task-specific strategies to promote task-general mechanisms;
2) a paradigm that exercises various components of WM, including not only storage but also executive control processes;
3) adaptive regulation of the level of difficulty (i.e., continuous adjustment of task demands to the individual performance level), ideally implemented using a computer-based format to support motivation and to even out inter-individual differences in WM capacity;
4) the supply of sufficient stimuli material for high training intensity.

In addition, the issues of impairments following brain injuries require specific considerations. Comorbid deficits, e.g., in basic attentional functions or language skills, may limit the ability to understand and comply with the tasks. Consequently, instructions and exercises should be designed as simple and familiar as possible. The level of difficulty must not be too demanding to ensure compliance, so adaptivity has to be very fine-tuned to balance demands and abilities. Sufficient motivation is essential, especially since WM tasks are very demanding and they have to be exercised for many training sessions repetitively. Generally, functional training in patients represents a carefully guided progress with a lot of positive feedback and reinforcement.

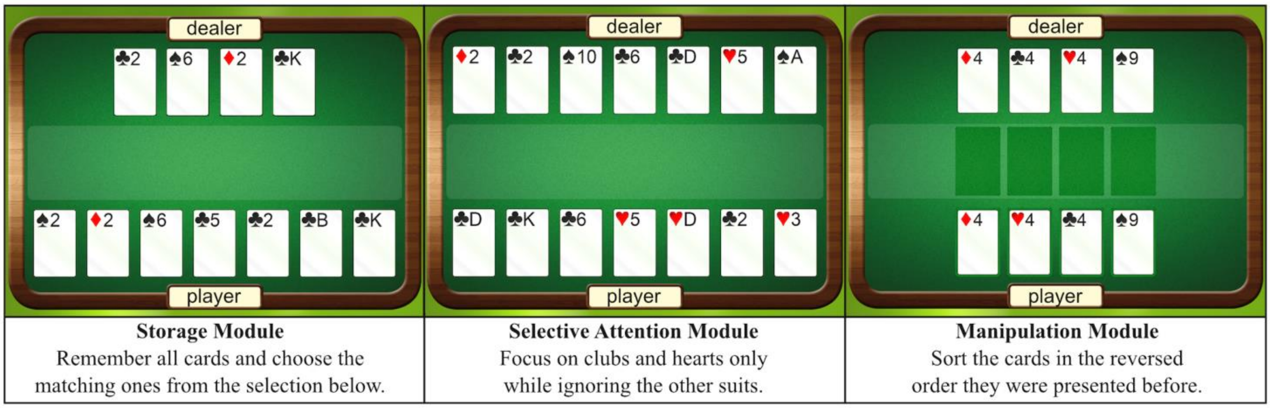
The new WM training program was developed considering the presented criteria. The paradigm incorporated the following principles: (i) a theoretical foundation on the multi-component model of Baddeley (2003) emphasizing executive control processes, (ii) a clear structure that enables training specific WM components, (iii) a fine-tuned composition with many modifiable parameters, and (iv) stimuli material with reference to everyday life that is enjoyable for adults. A computer based format was chosen to secure continuous and automated adaptivity based on performance accuracy. Stimuli were common playing cards, optionally French or German card sheets, as well as colors only (this version was developed for individuals with few experience with card games or difficulties in the verbalization of the values, e.g., people with aphasic disorders). In principal, cards are presented by a virtual dealer. They have to be remembered, sorted in the right order, or chosen according to specific criteria depending on the respective training module (for an illustration, see Figure 3). Instructions are given via multiple modalities, i.e., they are read out and presented on the screen. The intervention was implemented in cooperation with the Hasomed GmbH, one of the leading companies for rehabilitation software in Germany. The novel WM training program WOME (WOrking MEmory) has been integrated in the internationally available cognitive enhancement software RehaCom®.

Description of the training program

The composition of the training program was derived from the multi-component model, yielding three hierarchically ordered modules that specifically exercise different components of WM: (1) storage systems (maintenance of information), (2) selective attention (focusing on some information while inhibiting others), and (3) central executive processes (active manipulation of the information kept in WM). Each module is represented by a different type of task: remembering all the cards presented (1), remembering only certain cards and ignore others depending on the suit announced previous to each task (2), sorting the cards in the same or reversed order (3). Cards are presented one by one and they are turned around after a brief period of time. Relevant cards have to be chosen from a set on the player's side and put on the middle of the gaming table. Following each reaction, the individuals receive detailed feedback on their performance. Errors are pointed out and the possibility to correct the response is given. The level of difficulty achieved and the progress within a level is visible to the participant.

Figure 3

Training Modules and Tasks of WOME



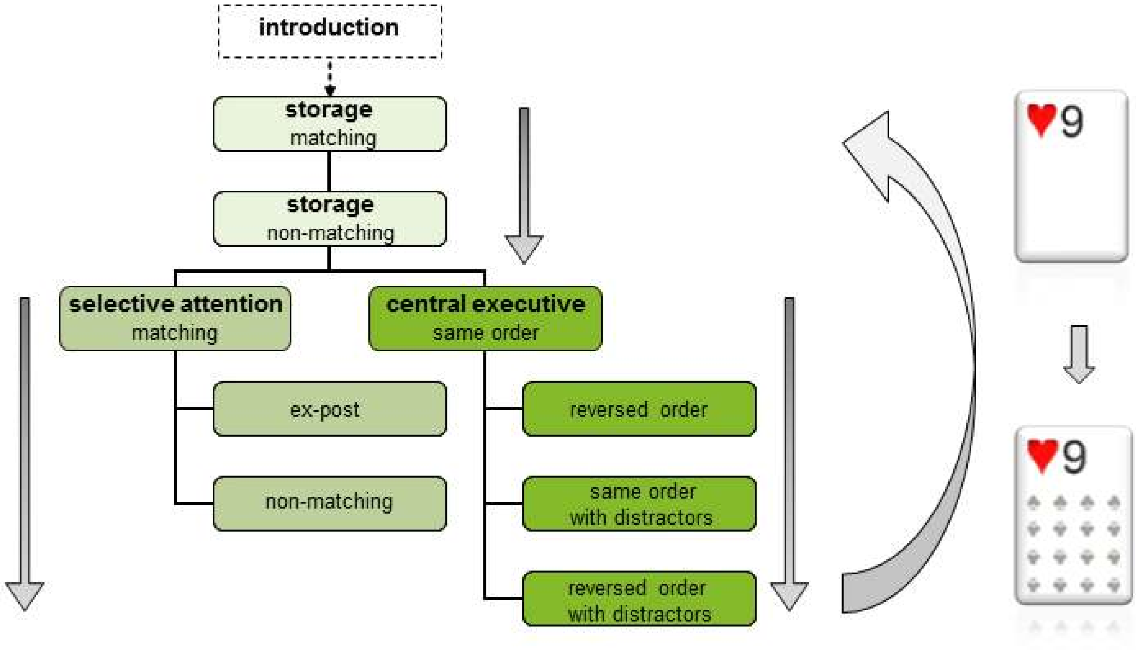
Note. The graphic presents the three training modules and their respective task instructions. Here, the cards to be remembered on the dealer's side are shown overtly for the purpose of the explanation. Figure adapted from Frontiers in Aging Neuroscience, 10, Weicker et al., WOME: Theory-based working memory training — A placebo-controlled, double-blind evaluation in older adults, 247, Copyright (2018), with permission from Frontiers Media SA.

Overall, there are 62 levels of difficulty. Subjects begin with a brief introduction of the task. Next, they exercise the storage component of WM. After reaching the highest level of difficulty, they continue to train the module of both, selective attention and central executive processes successively in each session. Within a module, difficulty is increased slowly by enhancing the number of distracting stimuli, i.e., irrelevant cards in the set on the player's side. Once all levels are accomplished, the intervention starts over but this time with distractors displayed on the card's surface to promote interference effects (e.g., diamonds on a hearts suit). Figure 4 presents the composition and procedure of the WOME intervention in detail.

In addition to the fine-tuned level structure provided by the composition of the program, difficulty can be varied by a wide range of parameters that can be switched on or off individually. By this means, specific components of WM, visual or auditory modality, and interference processes may be emphasized. A screenshot of the parameter menu is provided in Figure 5.

Figure 4

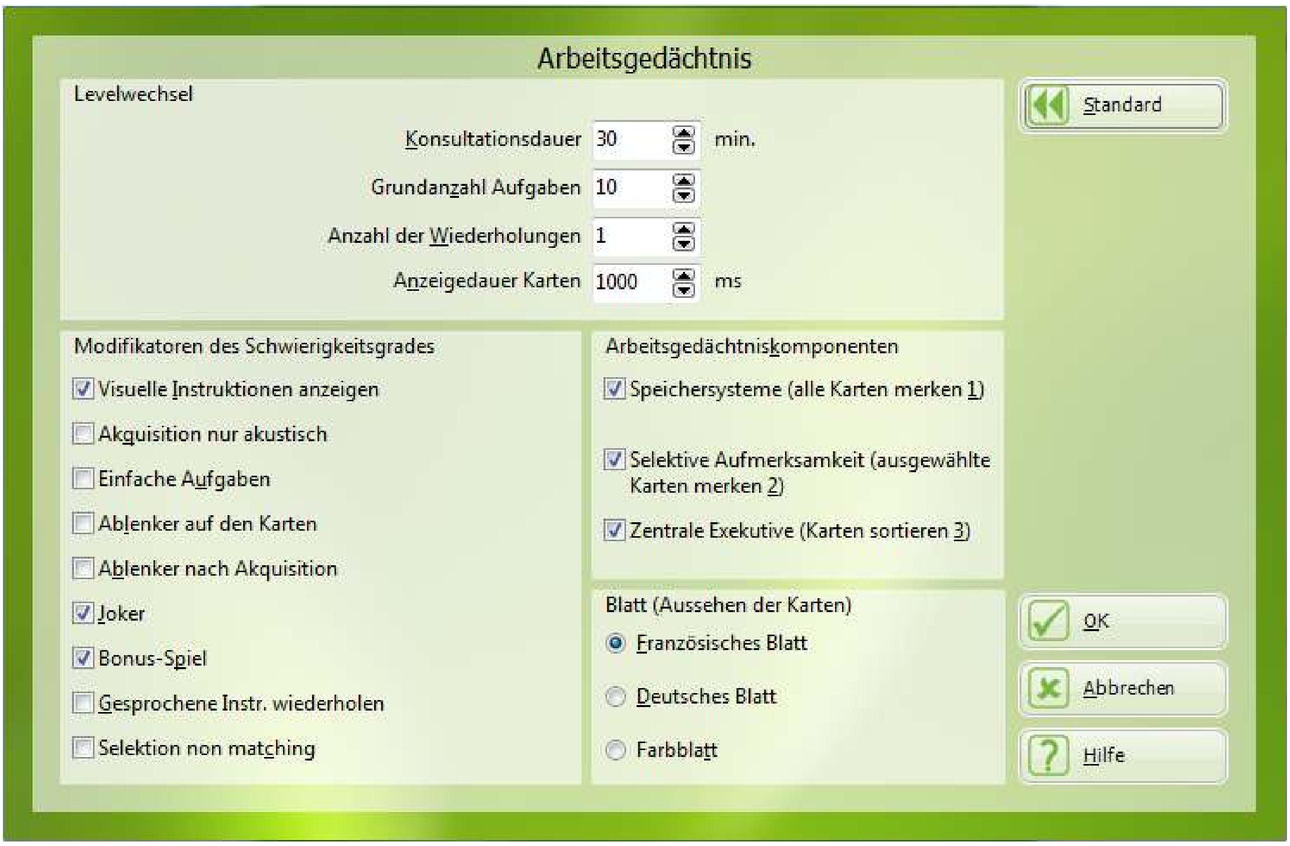
Composition and Procedure of the WOME Intervention



Note. The flowchart shows the hierarchical order of the WM components trained in the WOME intervention. The specific instructions of the presented modules are the following: to remember all the cards presented by the dealer (storage matching); to remember the cards presented by the dealer and select the ones that were not shown before (storage non-matching); to remember a specific suit announced before the presentation of the stimuli (selective attention matching); to select cards of a specific suit named after the presentation of the stimuli (selective attention ex-post); to remember the cards presented by the dealer and select cards of a specific suit, which were not shown before (selective attention non-matching); to sort the cards in the same order they were presented before (central same order), to sort the cards in the reversed order they were presented before (central executive reversed order), to sort the cards in the same/reversed order while distractors are presented between encoding and response (animated animals that 'walk' over the gaming table; central executive same/reversed order with distractors). On the right, an example of distractors displayed on the card's surface is shown.

Figure 5

Parameter Menu of WOME



Note. A wide range of parameters may be defined individually. Here, the default settings are displayed in German. In the upper area, basic settings are available (training duration, number of tasks per level, number of repetitions in case of errors, presentation time of the stimuli). In the left area, moderators of difficulty and elements promoting motivation are presented (here, written instructions and the presence of wild cards and a bonus game are activated). In the upper right section, training specific WM components (storage systems, selective attention, and central executive processes) can be selected and deselected. The card sheet (French, German, or colors only) can be selected in the bottom right. For a detailed description of all the parameters, see the manual of WOME in the supplemental material in the appendix.

Control intervention

With respect to the planned evaluation studies, a comparable control intervention to WOME was designed. It was implemented as a low-level WM training, i.e., the framing conditions and stimuli were identical to WOME, but the level of difficulty was fixed and did not adapt to the subjects' performance. The level structure was rebuilt to minimize the involvement of the WM system. Specifically, the modules were simplified (e.g., no backward orders) and required remembering at most three cards. A wide range of levels was obtained by introducing distracting cards on the player's side. Additionally, the number of correct responses, which was needed to achieve the next level, was increased. Participants were motivated by instructing them to react as fast and correct as possible and by giving feedback on their performance and the level achieved.

Feasibility studies

Feasibility of WOME WM training was assessed in two pilot studies focusing on individuals with low WM capacity (i.e., healthy older adults and individuals with acquired brain injury). Aims of the studies were to validate the composition of the tasks and the level structure, to evaluate acceptance of the stimuli, to investigate compliance with the planned training schedule, to examine the applicability of the outcome parameters, and to explore the potential effectivity of the intervention.

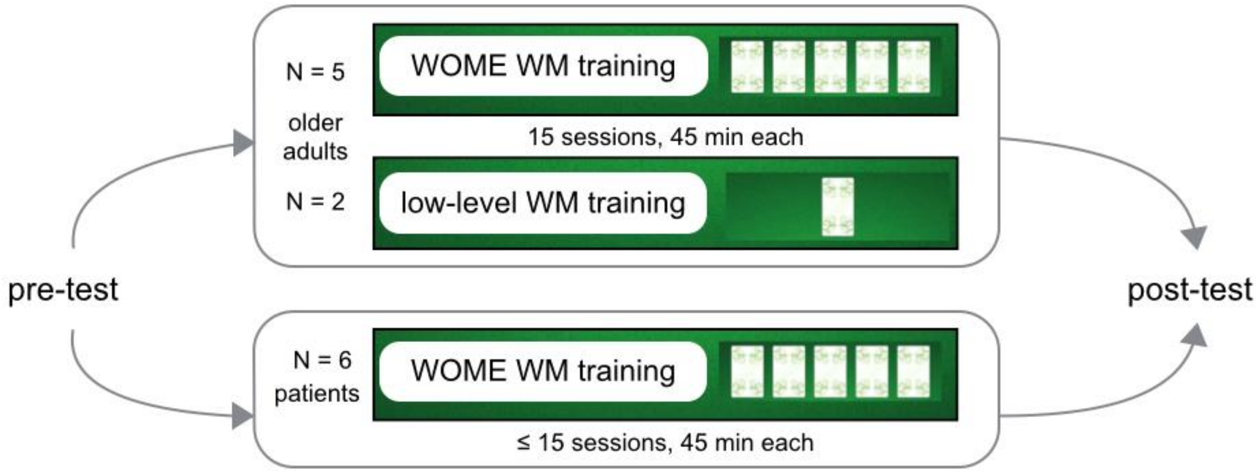
Procedure. The first pilot study was carried out in N = 7 healthy older adults (3 male, 4 female) with a mean age of 64.43 years (SD = 4.32, range 60-72 years). They were recruited via the subject database of the Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany. Inclusion criteria were age between 60 and 80 years, fluent German Language, and written informed consent. Exclusion criteria were history of neurological disease, psychiatric disorders, and severe cognitive deficits. Presence of acute depression was screened with the Becks Depression Inventory (Hautzinger et al., 1995) during initial contact.

All subjects were randomized to the WOME WM training condition (*n* = 5) or the low-level WM training condition (*n* = 2). Both groups practiced their respective training daily Mondays to Fridays 45 min each session over three weeks, resulting in 15 sessions overall. Before and after the intervention, a test battery of neuropsychological tests and a questionnaire targeting strategies used and subjective appraisal of the training effects in daily life was completed. Table 1 presents the cognitive functions and the respective outcome measures assessed: WM functions, attention, executive functions, and long-term memory. The pre-/post assessments and the training sessions were carried out in separate quiet rooms in the Max Planck Institute.

The second pilot study was carried out in N = 6 individuals (1 male, 5 female) with brain lesions with a mean age of 43.17 years (SD = 10.36, range 32-61 years). The mean time since brain injury was 14 month (SD = 10.46, range 5-33 months). Neurological etiologies were heterogeneous (*n* = 2 with hypoxia, *n* = 1 with stroke, traumatic brain injury, cerebral hemorrhage, and frontotemporal lobar degeneration, respectively). The patients were recruited by personal contact in the Clinic for Cognitive Neurology, University Hospital of Leipzig, Germany. Inclusion criteria were age between 18 and 80 years, history of acquired brain lesion with a time since injury not less than three months, fluent German Language, and written informed consent. Exclusion criteria were severe acute psychiatric disease and insufficient cognitive abilities to complete the training tasks. Procedure and outcome assessment were similar to pilot study one, except that all subjects underwent WOME WM training. The patients participated in addition to their standard therapy in a multidisciplinary rehabilitation setting. Depending on their individual time schedule, they carried out up to 15 training sessions (mean = 10.5, SD = 3.30, range = 5-15 sessions). The design of the feasibility studies is depicted in Figure 6.

Figure 6

Design of the Feasibility Studies of WOME



Note. The graph illustrates the design of the feasibility studies featuring two subject groups: healthy older adults (upper section) and individuals with acquired brain injuries (lower section). All subjects underwent neuropsychological assessments before and after the intervention. Training took place over three weeks Mondays to Fridays, 45 min per session, accumulating in 15 sessions at maximum (patients were allowed to conduct fewer sessions). While all patients underwent WOME WM training, healthy older adults were randomized to receive either WOME WM training or low-level WM training, which is similar to WOME but with a fixed level of difficulty.

Table 1

Neuropsychological Outcomes of the Feasibility Studies

WM functions	executive functions	attention	long-term memory
Digit span (forwards)	LPS-3	TMT A/B	VLMT
Digit span (backwards)	Stroop task		
Span board (forwards)	6 elements task		
Span board (backwards)	TAP task switching		
PASAT			
TAP n-back			
Reading span task			
Operation span task			

Note. Digit span and Span board task forwards/backwards (Härting et al., 2004), PASAT = Paced Auditory Serial Addition Test (Gronwall, 1977), TAP = Test of Attentional Performance (Zimmermann & Fimm, 2007), Reading span task (Daneman & Carpenter, 1980), Operation span task (Turner & Engle, 1989; Unsworth et al., 2005), LPS-3 = Subtest 3 of the German intelligence battery 'Leistungsprüfsystem' (Horn, 1983), Stroop task (Stroop, 1935), 6 elements task (B. A. Wilson et al., 1996), TMT A/B = Trail Making Test A and B (Reitan, 1958), VLMT = German version of the Auditory Verbal Learning Test (Helmstaedter et al., 2001).

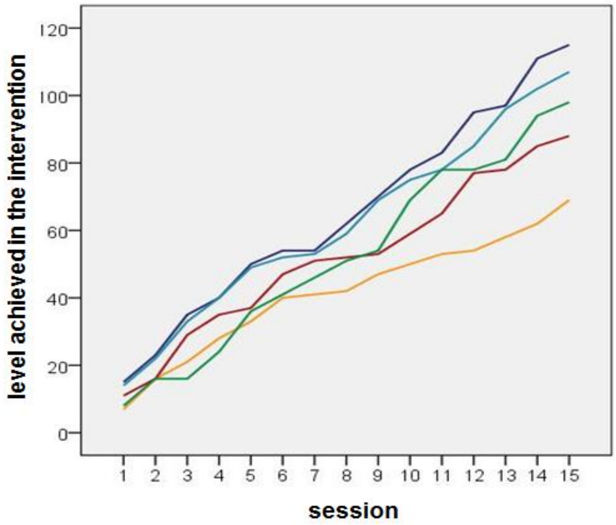
Results. Feasibility of WOME WM training and the low-level WM training condition were confirmed in both pilot studies. All subjects completed the planned schedules, reported high commitment and gave positive feedback regarding the training tasks of both conditions. On a 5pt Likert scale (ranging from 1 = 'not at all' to 5 = 'very much'), training was rated as enjoyable (mean (SD) of pilot study one and two is 4.22 (0.66) and 4.44 (0.49), respectively) and subjects reported high motivation (mean (SD) of pilot study one and two is 4.18 (0.32) and 4.60 (0.55), respectively). WOME WM training was perceived as demanding but not overwhelming (mean (SD) of pilot study one and two is 3.01 (1.0) and 3.80 (0.40), respectively), indicating successful adaptivity of the level of difficulty. The performances in the trained task are shown in Figure 7.

Following WOME WM training, a positive effect on daily life performance was reported by the subjects (e.g., „keep several steps of a recipe in mind when cooking“, „better concentration in discussions“, „improved memory for digits and numbers“, and „higher self-confidence in my own abilities“). However, a nonparametric analysis of medians and distributions of the performances in the outcome measures did not yield significant differences between baseline and post-test. Descriptive pre-post comparisons indicated improved performances in two tests of WM (PASAT, Operation span task) and two tests of executive functions, which require cognitive control (Stroop task, TAP task switching). No changes were observed in other outcome measures.

Despite continuous improvements in the trained tasks, an in-depth analysis of the performances showed weaknesses of the composition of the intervention. First, overall difficulty was too easy because many subjects reached the highest level of difficulty within ten training sessions. Second, in contrast to the expected linear increase of difficulty, data showed wild fluctuations of the error rate between modules and levels (see Figure 8). In addition, some modules appeared to be less challenging than expected by theory (e.g., the module of selective attention showed higher accuracy rates than the storage module) and modifying parameters failed to produce interference (e.g., visual distractions on the cards' surface). Third, the questionnaire, which investigated the subject's strategies during in the training tasks, revealed smart strategies to avoid cognitive effort (e.g., in the central executive module, which requires to sort cards in the reversed order, they inserted the cards from right to left without mental manipulation of the stimuli).

Figure 7

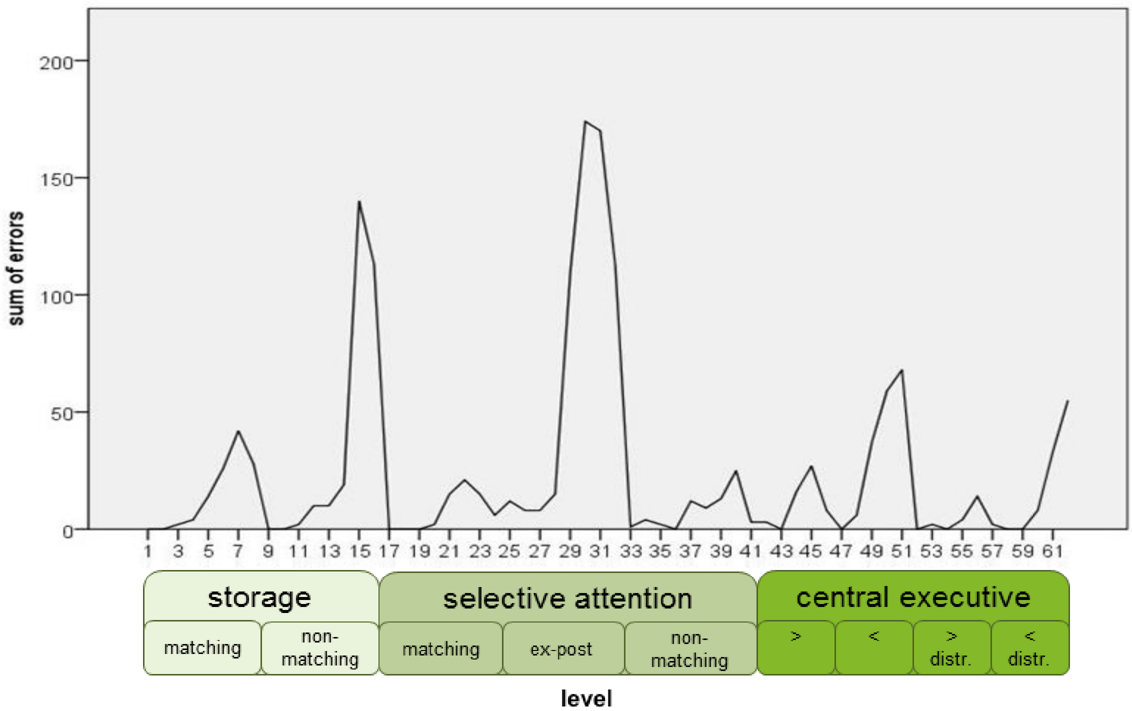
Performance in the Trained Tasks



Note. The progress of the individual performances in the trained tasks of N = 5 healthy elderly adults is presented. The intervention consisted of 62 levels without distractors and 62 levels with distractors which add up to a total of 124 levels available. All subjects showed continuous improvement without indication of a ceiling effect.

Figure 8

Analysis of the Level Structure



Note. The graph shows the sum of errors in N = 5 healthy elderly adults in the trained WM task from level 1 to 62 as an indicator of difficulty. Below the x-axis, the training modules, which correspond to a specific level, are displayed. Abbreviations: central executive processes with same order (>), central executive processes with reversed order (<), distractors (distr.).

Table 2

Changes of Neuropsychological Outcomes following the Feasibility Studies

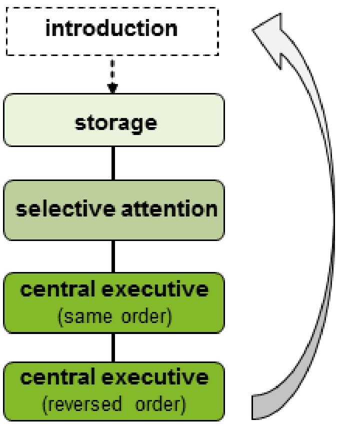
Feasibility studies	Evaluation studies	Rationale for the changes
Reading span task	Symbol Span	replaced due to low cost-benefit ratio
	Spatial Addition	added to examine spatial WM performance
6 elements task		removed due to low cost-benefit ratio
	TAP Go-NoGo	added to examine inhibition processes
	TAP Alertness	added to include a non-target outcome
	CFQ/FEAG	added to examine everyday life performance

Note. TAP = Test of Attentional Performance (Zimmermann & Fimm, 2007), Symbol Span and Spatial Addition are WM tests of the Wechsler Memory Scale IV (Petermann & Lepach, 2012), CFQ = Canadian Failure Questionnaire (Broadbent et al., 1982), FEAG = Inventory of Memory Experiences (Herrmann & Neisser, 1978).

Implications. Based on the findings and cost-benefit ratio of the applied outcome measures, the neuropsychological test battery was adapted for the following evaluation studies. Table 2 defines the specific changes and their rationales. The analysis of the performance of the trained tasks and the subject's statements in the questionnaires led to a structural revision of the software. Overall difficulty was increased by raising the number of stimuli and distractors displayed. At the same time, the lower levels were maintained so that the intervention would be applicable in both, low- and high performing individuals. Additionally, revisions in usability secured that the subjects performed the tasks without cheating. Most importantly, the whole composition of the intervention was adapted. The objective was to generate a fine-tuned, linear increase of difficulty by rearranging modules, levels and parameters. Instead of exercising only one component of WM and add other WM processes only when all tasks of a specific type are accomplished, multiple stages have to be passed determined by the number of items to-be-remembered. Figure 9 illustrates the procedure that is the following: Individuals begin with exercising to maintain a certain amount of information (e.g., three playing cards; storage systems module). Next, the same amount of information has to be focused selectively and shielded from further irrelevant information (selective attention module). Subsequently, it needs to be actively manipulated, i.e., reproduced in the same or reversed order (central executive module). Not until the participant is able to accomplish all degrees of difficulty, the number of items is increased and the procedure restarts with the storage systems module (e.g., now with four playing cards). Overall, there are 69 levels of difficulty with a maximum of eight cards to-be-remembered. The final structure of WOME is presented in Table 3.

Figure 9

Revised Procedure of the WOME Intervention



Note. The flowchart depicts the hierarchical structure of the trained WM components. After successful completion of all modules, the sequence restarts with an increased degree of difficulty.

Table 3

Composition of the WOME Intervention

level	module/WM component	number of cards to be remembered	number of cards presented by the dealer	number of distracting cards
1	introduction (overt presentation of cards)	2	2	2
2		3	3	2
3	storage systems	2	2	2
4		2	2	3
5		3	3	2
6		3	3	3
7	selective attention (easy)	3	5	3
8		3	5	4
9		3	6	4
10	selective attention	3	5	2
11		3	5	3
12		3	6	3
13		3	6	4
14		3	6	5
15	central executive processes (manipulation forwards)	3	0	0
16		4	0	0
17	central executive processes (manipulation backwards)	3	0	0
18	storage systems	4	4	1
19		4	4	2
20		4	4	3
21		4	4	4
22		4	4	5
23	selective attention	4	7	3
24		4	7	4
25		4	7	5
26	central executive processes (manipulation forwards)	5	0	0
27	central executive processes (manipulation backwards)	4	0	0
28	storage systems	5	5	1
29		5	5	2
30		5	5	3
31		5	5	4
32		5	5	5
33		5	5	6
34	selective attention	5	8	3
35		5	8	4
36		5	8	5
37		5	8	6
38	central executive processes (manipulation forwards)	6	0	0
39	central executive processes (manipulation backwards)	5	0	0

Table 3 (continued)

level	module/WM component	number of cards to be remembered	number of cards presented by the dealer	number of distracting cards
40	storage systems	6	6	3
41		6	6	4
42		6	6	5
43		6	6	6
44	selective attention	6	9	3
45		6	9	4
46		6	9	5
47		6	9	6
48	central executive processes (manipulation forwards)	7	0	0
49	central executive processes (manipulation backwards)	6	0	0
50	storage systems	7	7	3
51		7	7	4
52		7	7	5
53		7	7	6
54	selective attention	7	9	3
55		7	9	4
56		7	9	5
57		7	9	6
58	central executive processes (manipulation forwards)	8	0	0
59	central executive processes (manipulation backwards)	7	0	0
60	storage systems	8	8	3
61		8	8	4
62		8	8	5
63		8	8	6
64	selective attention	8	9	3
65		8	9	4
66		8	9	5
67		8	9	6
68	central executive processes (manipulation forwards)	9	0	0
69	central executive processes (manipulation backwards)	8	0	0

Note. The table presents the final structure of the WOME intervention. The easy version of the selective attention module consists of memorizing one specific suit instead of two. The item number in the manipulation forwards condition is always presented with n + 1 because this task produced the lowest error rate of all submodules.

Further developments

The intervention is constantly updated. The changes were implemented following the evaluation studies, based on the findings, subject’s reports and new insights from research. For example, the distractors presented between encoding and response (animals 'walking' over the gaming table) were changed to decision making tasks, which stress both verbal and executive aspects to promote interference effects (e.g., 'What can you buy from a butcher - meat or cheese?'). To promote compliance and motivation based on the self-determination theory (Ryan & Deci, 2000), several structural elements of gamification have been derived, i.e., the integration of game-design elements or mechanics (Deterding et al., 2011). They not only lead to variety in the tasks but promote larger autonomy, competence and relatedness of the individuals. For example, correctly in a row responded tasks result in wild cards, which may be used later as a joker. Additionally, a bonus game was implemented that enables to select cards and collect points in competition with the dealer. A league system was implemented, which correlates with the level structure. Good performances lead to win trophies and to advance in championships, and the gaming table becomes more neat (see Figure 10).

Figure 10

Structural Elements of Gamification Implemented in WOME

Note. The screenshots show the user interface of the same training module (storage systems) in different degrees of difficulty. On the left, level 5 is presented, which correlates to a game table available in the village league. On the right, level 43 and the world championships are illustrated. In addition to the noble appearance, trophies and wild cards are displayed.

Conclusions

Despite the potential of WM training observed in healthy and clinical populations, no appropriate intervention tailored to the needs of patients with acquired brain lesions has been available. Therefore, WOME WM training was developed, considering theory-based as well as patient-specific requirements. Two pilot studies in individuals with low WM capacity confirmed the feasibility of the program and yielded first indications of efficacy. Based on performance analyses and interviews with the subjects substantial revisions were made for both, the software and the planned study design for the subsequent evaluation studies.

2.4. Study IV: WOME: Theory-based working memory training — A placebo-controlled, double-blind evaluation in older adults.

Nachweis über Anteile der Co-Autoren, Juliane Weicker
Development and evaluation of an adaptive working memory training intervention

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- Erhebung, Auswertung und Interpretation der Daten
- Schreiben des ersten Entwurfs des Manuskripts
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WOME: Theory-Based Working Memory Training — A Placebo-Controlled, Double-Blind Evaluation in Older Adults

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Background: Scientifically evaluated cognitive intervention programs are essential to meet the demands of our increasingly aging society. Currently, one of the "hottest" topics in the field is the improvement of working memory function and its potential impact on overall cognition. The present study evaluated the efficacy of *WOME* (WOrking MEmory), a theory-based working memory training program, in a double-blind, placebo-controlled, and randomized controlled trial (www.drks.de, DRKS00013162).

Methods: N = 60 healthy older adults were allocated to (1) the *WOME* intervention, (2) an active low-level intervention, or (3) a passive control group. Overall, the intervention groups practiced twelve sessions of 45 min within 4 weeks of their respective training. Transfer effects were measured via an extensive battery of neuropsychological tests and questionnaires both pre-/post-training and at a 3-month follow-up.

Results: *WOME* led to a significant improvement in working memory function, demonstrated on a non-trained near transfer task and on two different composite scores with moderate to large effect sizes. In addition, we found some indication of relevant impact on everyday life. The effects were short-term rather than stable, being substantially diminished at follow-up with only little evidence suggesting long-term maintenance. No transfer effects on other cognitive functions were observed.

Conclusion: *WOME* is an appropriate and efficient intervention specifically targeting the working memory system in healthy older adults.

Trial Registration: German Clinical Trials Register (DRKS), Identifier: DRKS00013162.

Keywords: working memory training, cognitive training, plasticity, aging, neuropsychology, rehabilitation, cognitive decline, mild cognitive impairment

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INTRODUCTION

In an increasingly aging population, we would benefit from reliable research data concerning appropriate prevention and intervention treatments. Longer lifespans and aging baby boomers will lead to a dramatic rise of about one billion adults aged 65 years and older by 2030 worldwide. In addition to obvious physiological changes, aging is accompanied by declines in a range of cognitive functions including processing speed, attention, memory, reasoning, mental flexibility, and working memory (Glisky, 2007). Healthy older adults have to deal with these reductions in their mental capacity (experienced, for example, in subjective memory complaints), and it is coherent that the need for maintenance or extension of cognitive function is increasing (Fernandez, 2011). Scientifically evaluated cognitive intervention programs are therefore essential to meet the demands of our aging society.

One of the current "hot" topics in the field is the improvement of working memory (WM) function and its potential impact on overall cognition. WM, the memory system that holds contents in a temporarily accessible state, is a key predictor for successfully managing life's demands successfully, for example, academic achievement (Gathercole et al., 2003), professional success (Higgins et al., 2007), acquisition of new skills (Pickering, 2006), and emotion regulation (Schmeichel et al., 2008). Fueled by cognitive neuroscience that discovered the plasticity of the human brain (i.e., the malleability of neuronal structure, function, and cognitive abilities), the idea emerged that by practicing WM tasks, substantial improvements could be induced in the overall WM system (Klingberg et al., 2002). In contrast to strategy based approaches, core training programs promote domain-general mechanisms which are the requirements for transfer to other tasks than the trained ones (Morrison and Chein, 2011). Given the important role of the WM capacity for many higher order cognitive functions (Baddeley, 2003), an expansion of this capacity was hypothesized to improve not only WM performance but also broader abilities, such as reasoning or intelligence (Jaeggi et al., 2008a). Indeed, multiple meta-analyses showed that intensive WM training led to significant and long-lasting improvements in overall WM functioning, and there was some indication that it transfers to associated cognitive functions (Karbach and Verhaeghen, 2014; Lampit et al., 2014; Weicker et al., 2016). Although the underlying neuronal mechanism of such transfer effects remain largely unknown, behavioral changes are found to be accompanied by transformations in brain activation, brain structure, and connectivity (for a review, see Buschkühl et al., 2012). Despite such promising findings, many studies support the assumption that age serves as a negative predictor for training benefits, especially with regard to changes beyond the WM system, which limits the potential of WM training in older adults (Brehmer et al., 2012) and some meta-analyses question the efficacy of WM training in comparison to practicing daily routines (Dougherty et al., 2016; Melby-Lervag et al., 2016). One of the main reasons for missing guidelines and recommendations arises from methodological limitations of cognitive training research (Shipstead et al., 2012; Dougherty et al., 2016). Given the nature of individually adapted treatments, which usually cannot be fully concealed from the participants, implementations of randomized, double-blind, and placebo-controlled designs are hardly feasible. While observations show cumulative implementations of randomized controlled trials over the past few years, no-contact control groups are widely used that do not account for expectancy effects (e.g., belief about performance improvements), social aspects (e.g., personal contact with laboratory assistants or other participants), or motivation (e.g., taking part in a research study; Shipstead et al., 2012). The operationalization of treatment effects is another issue, because it is necessary to demonstrate not only task-specific enhancements, but also an improvement of more general processes underlying the construct of WM function (e.g., higher capacity or cognitive control). However, many studies apply very similar tasks to evaluate WM training efficacy, and there has been doubt that the claimed transfer was valid (Melby-Lervag and Hulme, 2013). An elegant way to assess the psychological construct rather than task-specific relationships between training and transfer tasks is the analysis of multiple tests via composite scores or latent variables, which is rarely realized in WM research (Schmiedek et al., 2010; von Bastian et al., 2013; Stepankova et al., 2014; Lawlor-Savage and Goghari, 2016). Due to the complexity of intervention designs as well as the huge amount of time and effort to conduct such studies, sample sizes are usually small [e.g., the median in older adults is approximately $N = 36$ and have a high risk of producing unreliable results (Lampit et al., 2014; Weicker et al., 2016)].

The computer software industry has launched several cognitive training programs within a short time (e.g., Brain Age®, Lumosity®, NeuroNation®) despite the controversial conceptualization of these evaluation studies. Brain training appeals to both consumers and health economics. So-called "serious games," easily and cheaply available on the Internet, promise a true panacea despite missing evidence (Rabipour and Raz, 2012; Federal Trade Commission, 2016). It remains rather unclear as to which task characteristics provoke transfer effects and impact the WM system successfully (Morrison and Chein, 2011). In the absence of knowledge about specific task characteristics, most of the available training programs represent a compilation of various WM tasks. The diversity of exercises increases the chance of tapping one task, or a certain combination of tasks, that successfully improves WM capacity and reduces strategy-based performance gains. Nevertheless, this "kitchen sink" approach neither reveals information about necessary components that influence the WM system nor does it refer to assumptions regarding its theoretical structure. Furthermore, many tasks that are used to train WM in young adults, for example, dual n-back tasks, are known to be inadequate or inefficient for older adults (Jaeggi et al., 2008b; Lawlor-Savage and Goghari, 2016).

The lack of a theory-based training program with specific, age-appropriate training tasks led the authors to develop an intervention that focuses on individuals with low WM abilities. The new WM training, called *WOME* (WOrking MEmory), is part of the cognitive rehabilitation software RehaCom®. The intervention fulfills the criteria for successful WM training postulated by Buschkühl (2007). The main principles of the program are (a) its theoretically derived structure, implemented in hierarchically ordered modules that enable targeted training of specific WM components and examine the efficacy of specific training tasks, (b) fine-tuned automatic adaptivity for preventing under challenging or over demanding task difficulty by not only adjusting the number of items to be remembered, but enable modifications of many additional task features, and (c) the implementation of everyday life stimuli to facilitate transfer effects and preserve high motivation by using age-appropriate content. The theoretical considerations were derived from Baddeley's multi-component model of the WM system but also include insights from neurophysiological findings that emphasize the relevance of selective attention and inhibition processes in WM (Baddeley, 2003; Miyake and Shah, 2007).

The present study was designed to evaluate feasibility and efficacy of the *WOME* intervention with a solid methodological design to explore the essence of WM functioning and cognitive plasticity. Specifically, we aimed to answer the following questions: does the intervention reveal reliable effects on either the WM system or related cognitive functions? If so, do they remain stable over a long period? Are performance changes reflected in broader psychological constructs, so that factors that were affected by the intervention (e.g., specific WM components) could be identified? Are the potential cognitive improvements functionally relevant in the participants' everyday lives? We conducted a double-blind, placebo-controlled, randomized controlled trial implementing three conditions: (1) a high-level WM training group (HT) that received the *WOME* intervention at a high level with increasing difficulty, (2) a low-level WM training group (LT) that received the same intervention, but on a low level with stable difficulty, and (3) a no-contact control group (CG). Before and after the intervention, as well as at a 3-month follow-up, we applied an extensive battery of neuropsychological tests and questionnaires to target different components of WM and related cognitive functions that require WM, as well as impact on everyday life outside a laboratory setting. Based on the presented literature, our hypothesis was that the HT would show more improvement in post-treatment performances relative to both LT and CG, in measures of WM, but only limited transfer to other cognitive domains and everyday life functions. We expected that potential benefits be preserved over the follow-up period.

MATERIALS AND METHODS

Participants

Sixty older adults (28 male, 32 female) were selected for participation in the study according to the following inclusion criteria: (a) aged between 60 and 79 years, (b) fluent in German, (c) clinically healthy, and (d) willingness and ability to take part in an intensive training program. Exclusion criteria were (a) history of neurological and/or psychiatric disease, (b) severe cognitive deficits, (c) alcohol or drug abuse, and (d) participation in other cognitive enhancement programs. Subjects were recruited via the Institute's database and by means of flyers distributed in the local community. The mean age of participants was 67.7 years (*SD* = 4.3, range 60–77). **Table 1** lists detailed sample characteristics for each condition. All participants gave written informed consent in accordance with the Declaration of Helsinki and were financially rewarded for participation. The study was conducted according to the CONSORT statement, approved by the ethics committee of the University of Leipzig (033-12-23012012) and registered at the German Clinical Trials Register (DRKS00013162).

Procedure

Participants were screened for inclusion criteria via telephone and during initial personal contact. The baseline assessment consisted of various neuropsychological tests that were administered in a predefined order, balancing cognitive demands as well as computer and paper–pencil exercises. The subjects were then randomized into one of three conditions: (a) high-level WM training group (HT; *WOME* intervention), (b) low-level WM training group (LT; active control group), or (c) passive control group (CG; no contact). Participants were randomized with equal probability and stratified by sex by using the online software Research Randomizer (Urbaniak and Plous, 2013). Group allocation was concealed in envelopes and not revealed until the end of the pretest. The final groups did not differ significantly with respect to gender distribution, age, education, medication, subjective mood, functioning in everyday life, and initial WM performance (see **Table 1**).

Overall, both training groups practiced twelve sessions of 45 min of their respective training, taking part in supervised training sessions three times a week within 4 weeks. Following the training phase, a questionnaire was provided to evaluate the training, task strategies, and subjective training effects in everyday life. All participants undertook individual neuropsychological assessments at three time points: at baseline 1 week before the training phase, post-treatment within 1 week after the end of the training, and at a 3-month follow-up after training completion. If possible, parallel versions of standardized tests were used to minimize practice effects. The neuropsychological assessments lasted approximately two and a half hours.

To ensure a double-blind procedure of all participants in the training groups, the supervision of training sessions and the execution of neuropsychological assessments was carried out by different staff and in different locations: the testing took place at the Max Planck Institute for Human Cognitive and Brain Sciences Leipzig, whereas the training sessions were conducted nearby at the Clinic of Cognitive Neurology, University of Leipzig. The subjects in the training groups were told that multiple programs were evaluated in their efficacy to enhance cognitive performance.

Of the 64 subjects that were eligible, 60 were willing to take part in the study and completed the neuropsychological baseline assessment. All training participants completed their schedules successfully and everyone returned for the post-test. In the follow-up assessment six subjects were absent: two subjects missed it due to a long period of illness, one moved away, one had a car accident and suffered severe traumatic brain injury, and two passed away. **Figure 1** presents the study design including the flow of participants from baseline to the follow-up assessment.

Outcome Measures

Effectiveness of cognitive training was investigated on the basis of five sets of measures: (1) WM functioning was analyzed using multiple standardized neuropsychological tests to target different components of WM. (2) Other cognitive functions that partially rely on WM and could be influenced by changes in the

TABLE 1 | Sample characteristics.

Sample characteristics	HT (high-level WM training; *n* = 20)	LT (low-level WM training; *n* = 20)	CG (passive control group; *n* = 20)	Difference
Male/female	10/10	9/11	9/11	χ^2 = 0.13, n.s.
Age (mean, *SD*)	67.8 (3.9)	67.7 (3.1)	67.5 (5.7)	*F* = 0.34, n.s.
Education level (*n*)				χ^2 = 7.07, n.s.
<9 years	1	3	2	
10–12 years	5	11	6	
>12 years	14	6	12	
Subjective everyday life functioning rated on a 3-point Likert scale (*n*)				χ^2 = 2.85, n.s.
No complaints	15	17	16	
Complaints not impairing everyday life	5	3	3	
Impairments in everyday life	0	0	1	
Mood (Beck Depression Inventory: mean, *SD*)	4.5 (3.2)	4.7 (2.8)	3.7 (2.9)	*F* = 0.666, n.s.
WM performance (Span Board backward: mean, *SD*)	6.5 (1.1)	7.6 (1.7)	7.2 (1.6)	*F* = 2.796, n.s.

WM, working memory; HT, high-level WM training group; LT, low-level WM training group; CG, control group.

WM system were examined. (3) To evaluate the specificity of the training, a non-target measure (reaction time) was included. (4) Questionnaires were utilized to survey the consequences of WM training in everyday life. (5) To ensure that changes were not based on unintended factors, questionnaires for various control measures, for example, depressive mood, were added. For an overview of the applied neuropsychological test battery, see **Table 2**.

WM Functioning

Digit Spans and Span Board tasks

Verbal and visuo-spatial WM spans were selected from the German Wechsler Memory Scale revised (WMS-R; Härting et al., 2004). In the Digit Span task, a series of digits were presented that the participant had to repeat immediately, forward or in reversed order. In the Span Board task, the examiner tapped on blocks that were placed irregularly on a board and the participant had to repeat the sequence forward or backward. Span lengths increased successively until the participant failed both trials of a given length. Dependent variables were the number of correct trials. A recent meta-analysis (Weicker et al., 2016) showed that the Span Board task backward is the most sensitive variable to assess changes in WM, therefore it was chosen as a criterion task.

Spatial Addition

The Spatial Addition is a subtest from the Wechsler Memory Scale IV (WMS-IV) that assesses visual-spatial WM (Petermann and Lepach, 2012). The examiner sequentially presented two grids filled with blue and red circles. Participants had to remember the positions of the circles and replace them with different colored circles according to a set of rules. Task difficulty increased successively, and one point was given for each correct trial. The task was stopped after producing three failed patterns. The dependent variable was the number of correct trials.

Symbol Span

The Symbol Span is a subtest from the WMS-IV measuring visual short-term memory. The examiner briefly displayed abstract symbols on a page that the participant had to recognize from a larger array of symbols and consider the correct order. Two points were awarded for each correct trial, one point was given if the elements but not the order matched. Task difficulty increased until five trials were answered incorrectly. The dependent variable was the total number of points.

N-back task

The subtest WM of the computerized Test for Attentional Performance (TAP) was used to measure updating and central executive processes of WM (Zimmermann and Fimm, 2007). Double-digits were presented one at a time, and participants had to press a button as soon as the current number matched a number that was presented two items prior. The dependent variable was the number of errors.

The Paced Auditory Serial Addition task (PASAT)

The Paced Auditory Serial Addition task (PASAT) measures continuous updating of information held in WM (Gronwall, 1977). The participant is instructed to listen to sequentially presented digits and add the current one to the preceding digit. Each correct calculation was rewarded with a point. The test was done twice, one trial with an inter-stimulus interval (ISI) of 3 s, and another one with an ISI of 2 s. The dependent variables were the number of correct answers.

Operation Span task

The Operation Span task stresses the process component of WM by introducing a secondary task (Turner and Engle, 1989; Unsworth et al., 2005). A simple mathematical equation was presented on a computer screen, and participants had to decide whether it was right or wrong (e.g., "$2 \times 5 - 1 = 8$"). Immediately after this, a letter was presented which had to be

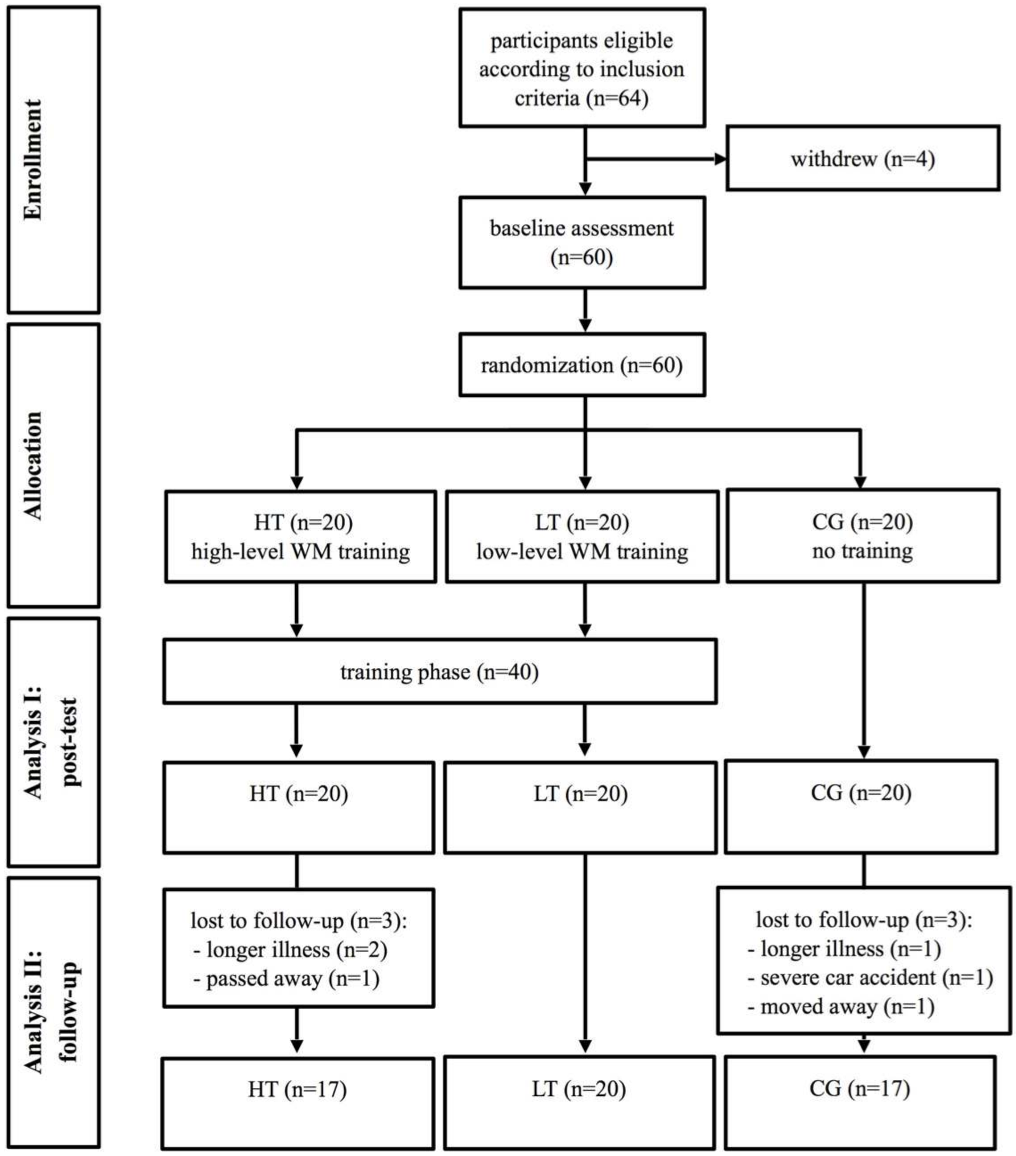

FIGURE 1 | Flow chart of the study design. WM, working memory; HT, high-level WM training group; LT, low-level WM training group; CG, control group.

remembered. Subsequently, the next equation was shown. The number of sequences increased successively from two to seven. The dependent variable was the number of correctly recalled letter sequences. To ensure that attention was paid to both tasks, only trails with ≥75% correct answers in the mathematical tasks were included in the analyses.

Cognitive Functions That Require WM

Executive functioning

Stroop task. The Stroop task is a measure of conflict resolution that requires inhibition of an over-learned response (Stroop, 1935). Participants were first asked to read aloud a list of color words (BLUE, GREEN, RED, and YELLOW) as fast as possible. After this, they were instructed to label the color in which the words are printed, hence experiencing interference of word and color name (e.g., RED written in blue). The dependent variable was the time needed for color naming.

Go-NoGo task. The Go-NoGo Task from the TAP measures response inhibition. On a screen, the symbols × and + were presented alternately in random order. Participants had to press a button immediately when an × appeared, but suppress their reaction when a + was shown. The outcome variable was the total number of errors.

TABLE 2 | Applied neuropsychological test battery.

WM functioning	Cognitive functions that require WM	Everyday life functions	Non-target outcome
Digit Span (forward)	Stroop	CFQ	TAP Alertness (reaction time)
Digit Span (backward)		FEAG	
Span Board (forward)	TAP Go-NoGo	Own questionnaire	
Span Board (backward)	TMT A/B		
Spatial Addition	TAP Mental Flexibility		
Symbol Span	LPS-3		
TAP n-back			
PASAT (ISI 3/2 s)	VLMT		
Operation Span			

WM, working memory; TAP, Test for Attentional Performance; PASAT, Paced Auditory Serial Addition task; TMT, Trail Making Test; LPS-3, Subtest 3 of the German intelligence battery "Leistungsprüfsystem"; VLMT, German version of the Auditory Verbal Learning Test; CFQ, Canadian Failure Questionnaire; FEAG, Inventory of Memory Experiences.

Trail Making Test. The Trail Making Test (TMT) is an instrument for visuomotor processing speed and cognitive flexibility, which consists of two parts (Reitan, 1958). Part A required the participants to connect numbered circles in ascending order. In part B, numbers and letters were presented; both had to be linked alternately in ascending (numbers) and alphabetic (letters) order. The dependent variable was the ratio of time needed for both parts (TMT A − TMT B/TMT A).

TAP mental flexibility. The ability to switch quickly between different concepts was examined using the subtest Mental Flexibility from the TAP. A letter and number were presented simultaneously on random sides of a screen. Participants were required to press a button alternately on the side where the letter appeared, then on the side where the number appeared. The outcome variable was the total number of errors.

Logical reasoning

Subtest three of the German intelligence battery "Leistungsprüfsystem" (LPS-3) was used to examine logical reasoning (Horn, 1983). On a sheet of paper a series of abstract symbols were shown. Each row was constructed according to a certain rule that had to be identified. Participants had 5 min to cancel the symbols that didn't fit to the respective rule. The outcome variable was the number of correct items.

Long-term memory

The German version of the Rey Auditory Verbal Learning Test (AVLT) is a word list recall test (Rey, 1941; Helmstaedter et al., 2001). A fixed sequence of 15 nouns was vocally presented five times, and participants had to repeat all remembered items after each trial. The dependent variable was the sum of correct words in this learning phase.

Non-target Outcome

TAP Alertness

Reaction time was measured using the subtest Alertness of the TAP. The task required participants to tap a button as fast as possible every time a cross appeared on a screen. The task differentiated between tonic alertness, which is the ability to generally maintain a high level of responsiveness, and phasic alertness, which is the immediate allocation of resources after the presentation of an audio warning to process an expected stimulus. The dependent variable was the mean reaction time of tonic and phasic alertness.

Everyday Life Functioning

Self-rating questionnaires

Currently, no German questionnaires are available that assess WM-related difficulties in everyday life. Hence, questionnaires were selected that largely overlap with WM demands. We used the German version of the Canadian Failure Questionnaire (CFQ), which is a self-rating scale for the assessment of cognitive failures in everyday life (Broadbent et al., 1982; Klumb, 1995); and the German version of the Inventory of Memory Experiences (FEAG) that considers memory impairments (Holzapfel, 1990). In both questionnaires, participants had to rank statements concerning everyday life memory performance on a 5-point Likert scale. The final scores were the sum of all items. Additionally, we asked the participants whether they felt any changes in everyday life performance as a result of the training. If participants answered yes, they were requested to list activities or situations where they had experienced improvements in daily life.

Control Measures

Depressive mood was screened with the Beck Depression Inventory (BDI; Hautzinger et al., 1995), which is based on 21 multiple choice self-reports of the severity of depressive symptoms. The sum of selected items represented the outcome variable, with scores lower than 18 indicating no acute clinical depression. After the training was completed, participants gave detailed feedback on the intervention with respect to enjoyment, motivation, subjective demands, applied strategies, previous experiences, etc.

Intervention

The training sessions were held in a quiet room in small groups, each with a maximum of five persons and each person working at an individual computer. *WOME* consists of three hierarchically ordered modules that are designed to exercise the main components of WM on the basis of a card game: storage systems (maintenance of information), selective attention (memorizing selective parts of information and inhibiting others), and central executive/manipulation processes (active operating with the content retained in WM). For an illustration and detailed explanation of each task, see **Figure 2**. The computer-based format enabled automated and continuous adjustment of difficulty depending on the individual's performance by modifying a range of fine-tuned parameters: presence and number of distracting stimuli (irrelevant cards on the player's side), appearance of visual distractors (irritating illustrations on the cards surface), occurrence of distractors between encoding and response (animated animals that "walk" over the gaming table following the presentation of cards), and many more. The control training was constructed as low-level WM training. Concretely, framing conditions and stimuli were identical to the intervention, but the level of difficulty essentially stayed the same to minimize the involvement of the WM system. Motivation was kept high enhancing the level number, giving continuous feedback, and by instructing participants to react as fast as possible while avoiding slips.

Statistical Analyses

Quantitative analyses were conducted for subjects' raw scores in neuropsychological tests and standardized questionnaires to evaluate the effectiveness of the intervention. All raw data are provided in the **Supplementary Files**. Baseline performances of HT, LT, and CG were inspected with separate one-way analyses of variances (ANOVA). Changes over time were analyzed with a repeated measurements ANOVA model with the between-subjects factor condition (HT, LT, and CG) and within-subjects factors time point of assessment (performance at baseline, post training, and follow-up): (1) training-related improvements were inspected by comparing baseline and immediate post-training performance, (2) stability of improvements was examined by including baseline, post-test and follow-up measurements in the analyses. To investigate the impact of the intervention on comprehensive cognitive functions, performance was evaluated with respect to composite scores of multiple tests. Raw scores were converted in standardized z-scores to make the separate scoring systems comparable. Immediate transfer effects were calculated by subtracting the standardized z-scores of the pretest from the post-test. Long-term transfer effects were determined by subtracting the standardized z-scores of the pretest from follow-up test.

Composite scores were formed based (a) on pre-defined clusters with respect to common psychological constructs, and (b) on statistically derived data-based clusters. Psychological constructs referred to WM functioning (considering all WM tests or exclusively span tests), cognitive functions that require WM (in general as well as executive functions, logical reasoning, and long-term memory), and everyday life functioning (standardized questionnaires). Data-based clusters of WM tests were obtained using principal component analysis with oblique rotation (direct oblimin, missing values replaced with means). The Kaiser–Meyer–Olkin measure confirmed the sampling adequacy for the analysis, KMO = 0.73. The initial analysis revealed three components with eigenvalues over Kaiser's criterion of 1 that in combination explained 61% of the variance. The first component was composed of the Span Board tasks, both versions of the PASAT, and the n-back task; the second component included the Digit Span task forward and the Operation Span task; and the third component consisted of the Symbol Span, Spatial Addition, and Digit Span task backward.

Analyses were carried out with the Statistical Package for Social Sciences SPSS, version 22 (IBM Corp, 2013). The overall significance level was set to $p < 0.05$ (two-tailed). For all ANOVAs concerning intervention effects, we applied false discovery rate (FDR, $q = 0.20$) to correct for multiple comparisons in consideration of the large test battery. FDR has been shown to be an adequate method to preserve power when sample size is limited (Benjamini and Hochberg, 1995). Interactions were decomposed conducting *post hoc t* tests with Bonferroni's correction for multiple comparisons. An effect size estimate for describing the proportion of variability represented by independent factors is given by partial eta-squared (η_p^2), with $\eta_p^2 \geq 0.01$ indicating a small effect, $\eta_p^2 \geq 0.06$ a moderate effect, and $\eta_p^2 \geq 0.14$ a large effect; effect sizes for differences between two conditions and dependent variables are specified by Cohens's d, with $d \geq 0.2$ indicating a small effect, $d \geq 0.5$ a moderate effect, and $d \geq 0.8$ a large effect (Cohen, 1988).

RESULTS

Training Benefits

Improvement in the Training Task

Figure 3A illustrates the improvements of HT and LT in the trained task. HT showed continuous progression of the mean level of difficulty from the first to last training session, $t(19) = 16.32$, $p < 0.001$, $d = 1.29$. Although individual task performance varied between subjects, nobody showed signs of a ceiling effect after twelve sessions of training [e.g., mean improvement from 11th to 12th training session: $t(19) = 6.94$, $p < 0.001$, $d = 0.20$]. Progress in the trained task was limited per definition in LT. Training success in HT was predictable by performance at the initial session [$\beta = 0.54$, $t(19) = 2.75$, $p = 0.013$], as well as by WM functioning at baseline [e.g., Digit Span backward: $\beta = 0.63$, $t(19) = 3.44$, $p = 0.003$, spatial addition: $\beta = .68$, $t(19) = 3.94$, $p = 0.001$], arguing for the validity of the training. Moreover, the correlations between the initial performance in the trained task and WM outcome measures support the hypothesis that they tap overlapping processes and should improve following the intervention.

Feedback

Both training conditions received comparable positive feedback. Training was rated as enjoyable (HT: $M = 4.05$, $SD = 0.61$, LT: $M = 4.30$, $SD = 0.47$; difference according to Median Test $p = 0.715$) and both groups were equally motivated ($M = 4.10$, $SD = 0.45$, and $M = 4.15$, $SD = 0.49$, respectively; $p = 1.00$). Nevertheless, training difficulty was judged differently, with the adaptive WM training program evaluated as more demanding than the low-level control training program (HT: $M = 3.35$,

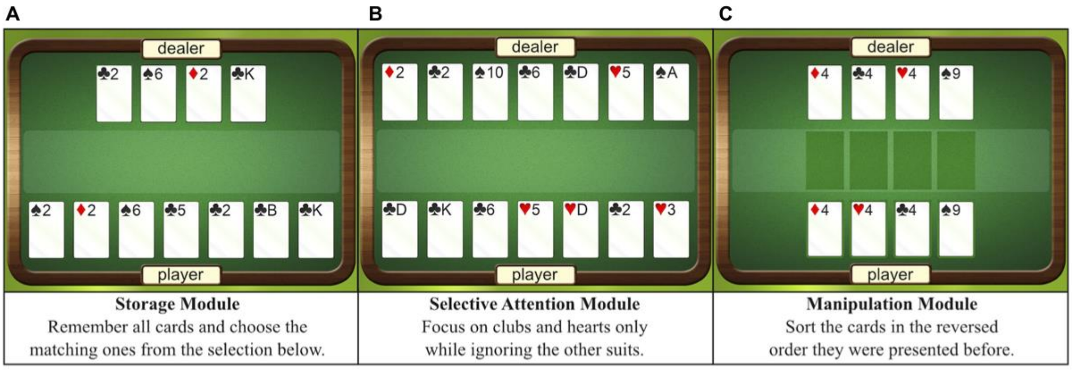

FIGURE 2 | Graphical interface of the intervention. **(A–C)** Show the various modules with their respective instructions that were trained in the intervention group. During the actual training, the dealer shows several cards, which are turned over after 1 s. Here, the cards are illustrated overtly for the purpose of explanation.

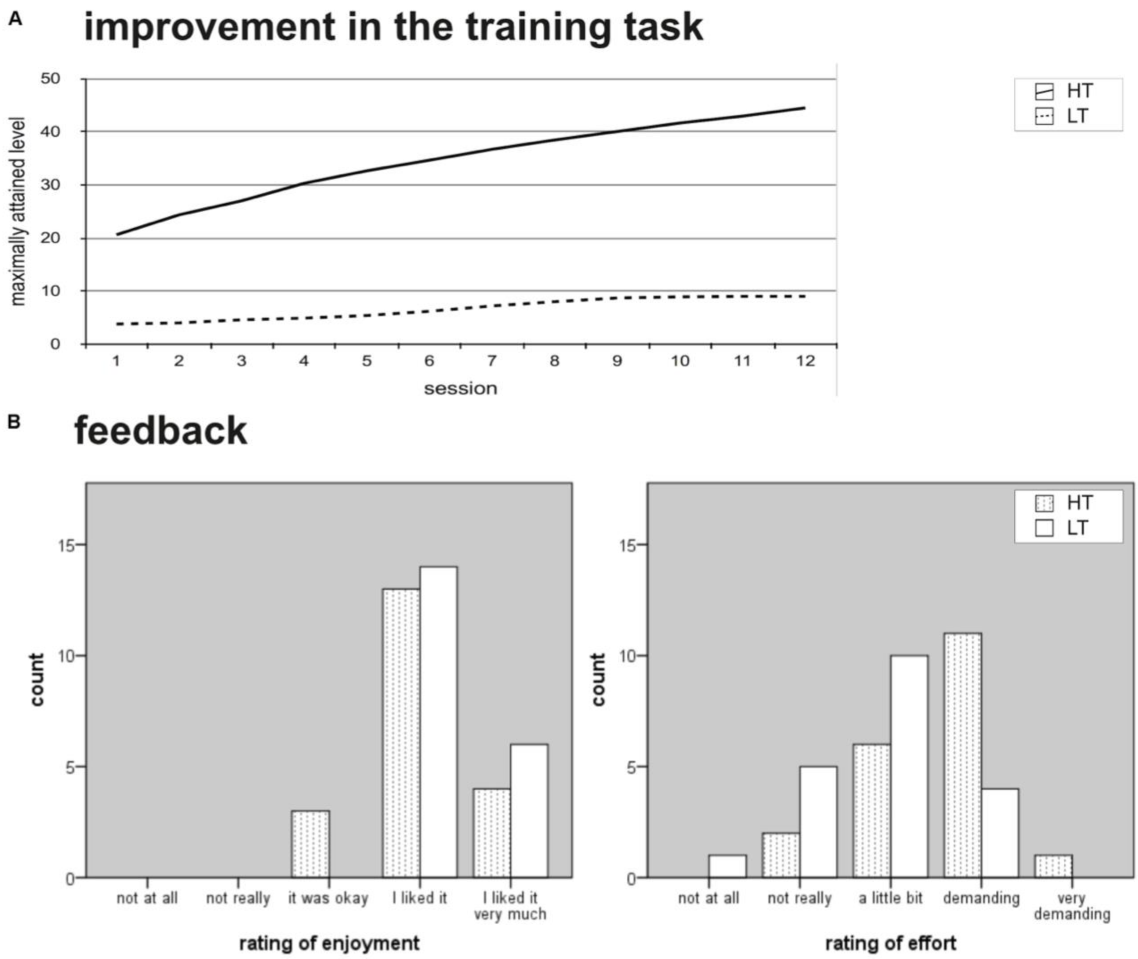

FIGURE 3 | Training benefits. WM, working memeory; HT, high-level WM training group; LT, low-level WM training group. **(A)** Illustrates the performance in the trained tasks for each of the 12 training sessions. The lines show the mean level for each session per group. Note that the level structure of the low-level training program was designed to be limited in progression. **(B)** Illustrates the feedback given from HT and LT regarding enjoyment and subjective effort.

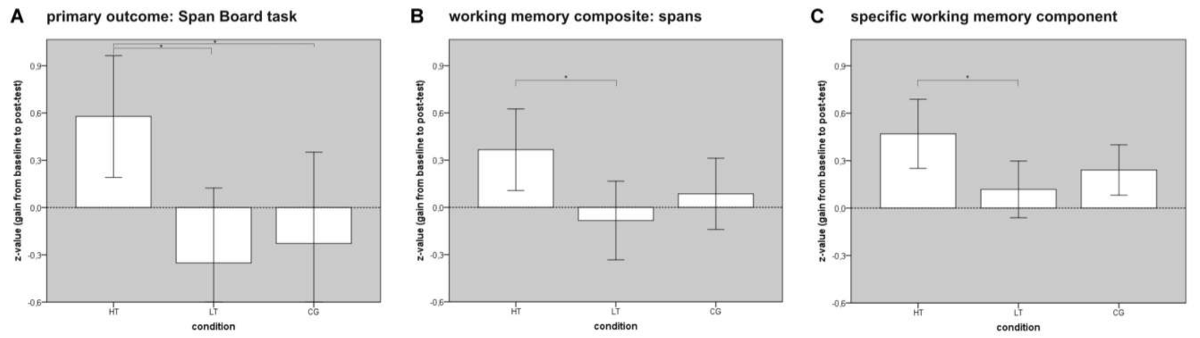

FIGURE 4 | Effect of *WOME* WM training. WM, working memory; HT, high-level WM training group; LT, low-level WM training group; CG, control group. The bars show significant gains from baseline to post-test in WM function in the intervention group. Error bars represent ± 2 standard errors. Significant group differences are marked with an asterisk. **(A)** Illustrates the improvement in the primary outcome variable (Span Board task backward), **(B)** shows the improvement in a WM composite score (Digit Spans and Span Board tasks), **(C)** illustrates the improvement in the first WM component of the multiple component analysis (composed of Span Board, PASAT, and n-back tasks).

SD = 0.76, LT: *M* = 2.85, *SD* = 0.81; $p = 0.024$). The groups did not differ with regard to prior experience with card games (HT: *M* = 1.61, *SD* = 0.92, LT: *M* = 2.25, *SD* = 0.40; $p = 0.718$) or computers (HT: *M* = 4.61, *SD* = 0.98, LT: *M* = 3.80, *SD* = 1.47; $p = 0.957$). Altogether, the manipulation check indicated that the blinding procedure was successful: The WM training as well as the control training was accepted and diligently completed, with the only difference being the perceived difficulty of the applied tasks (see **Figure 3B**).

Immediate Transfer Effects

No significant performance differences between the conditions were found at pretest assessment [except for the Span Board task forward, $F(2,57) = 4.17$, $p = 0.02$, $\eta_p^2 = 0.13$, where LT outperformed HT: $t(38) = 2.78$, $p = 0.008$, $d = 0.88$].

After training, near transfer effects on untrained WM tasks were found on several levels:

(1) Considering single test results of the primary outcome variable, there was a significant improvement in the Span Board task backward [significant time × condition interaction: $F(2,57) = 4.38$, $p = 0.017$, $\eta_p^2 = 0.13$; no significant main effect of time: $F(1,57) = 1.84$, $p = 0.180$, $\eta_p^2 = 0.03$; no significant main effect of condition: $F(2,57) = 0.54$, $p = 0.536$, $\eta_p^2 = 0.02$; see **Figure 4A**]. *Post hoc t*-tests with a Bonferroni adjusted alpha level of 0.017 per test (0.05/3) revealed a significant improvement from baseline to post-test for HT, $t(19) = 4.06$, $p = 0.001$, $d = 0.88$, whereas the other groups did not show any changes [LT: $t(19) = 0.71$, $p = 0.489$, $d = 0.16$, CG: $t(19) = 0.12$, $p = 0.909$, $d = 0.18$]. With respect to the other WM tests, no significant time × condition interactions were found.

(2) Regarding composite scores based on neuropsychological constructs, a significant intervention effect was shown on a composite score of different WM spans [$F(2,57) = 3.42$, $p = 0.040$, $\eta_p^2 = 0.11$; see **Figure 4B**]. *Post hoc t*-tests with a Bonferroni adjusted alpha level of 0.017 per test (0.05/3) showed a significantly higher gain for HT compared to LT [$t(38) = 2.50$, $p = 0.017$, $d = 0.79$], but not compared to CG [$t(38) = 1.63$, $p = 0.112$, $d = 0.52$]. No difference between LT and CG was found [$t(38) = 1.01$, $p = 0.321$, $d = 0.32$]. No significant interaction was found when all applied WM tests were combined into a general WM functioning score [$F(2,57) = 2.38$, $p = 0.102$, $\eta_p^2 = 0.08$]; however, a closer inspection of the subgroups revealed a significantly larger gain for HT compared to LT [$t(38) = 2.06$, $p = 0.046$, $d = 0.65$], which was not the case for other direct comparisons [HT vs. CG: $t(38) = 0.83$, $p = 0.415$, $d = 0.26$; difference between LT and CG: $t(38) = 1.46$, $p = 0.153$, $d = 0.46$].

(3) The first WM component of the multiple component analysis (composed of Span Board, PASAT, and n-back tasks) was significantly influenced by the intervention [$F(2,57) = 3.62$, $p = 0.033$, $\eta_p^2 = 0.11$; see **Figure 4C**]. Pairwise comparisons showed a significant advantage of HT over LT with a moderate to large effect size [$t(38) = 2.49$, $p = 0.017$, $d = 0.79$], but not over CG [$t(38) = 1.69$, $p = 0.100$, $d = 0.53$], according to Bonferroni's adjusted alpha level of 0.017 per test (0.05/3). LT and CG showed similar gains [$t(38) = 1.03$, $p = 0.312$, $d = 0.33$]. The other WM components were not affected by the intervention [second component: $F(2,56) = 0.31$, $p = 0.736$, $\eta_p^2 = 0.01$; third component: $F(2,57) = 0.62$, $p = 0.540$, $\eta_p^2 = 0.02$].

In contrast to the significant effects on near transfer measures of WM, no far transfer on cognitive functions that require WM was found [$F(2,55) = 0.21$, $p = 0.812$, $\eta_p^2 = 0.01$].

Individual evaluation of everyday life functioning indicated substantial changes in favor of HT [$\chi^2(1, N = 40) = 12.79$, $p < 0.001$; illustrated in **Figure 5**]. In particular, subjects reported improved memorization of shopping lists, names, telephone numbers, and vocabularies in foreign language acquisition, as well as enhanced attention and navigation while driving. These effects, however, were not found on standardized questionnaires of everyday life performance [$F(2,49) = 0.28$, $p = 0.759$, $\eta_p^2 = 0.01$].

No changes were found in the non-target outcome [mean reaction time, $F(2,56) = 0.46$, $p = 0.635$, $\eta_p^2 = 0.01$], demonstrating the specificity of the WM training.

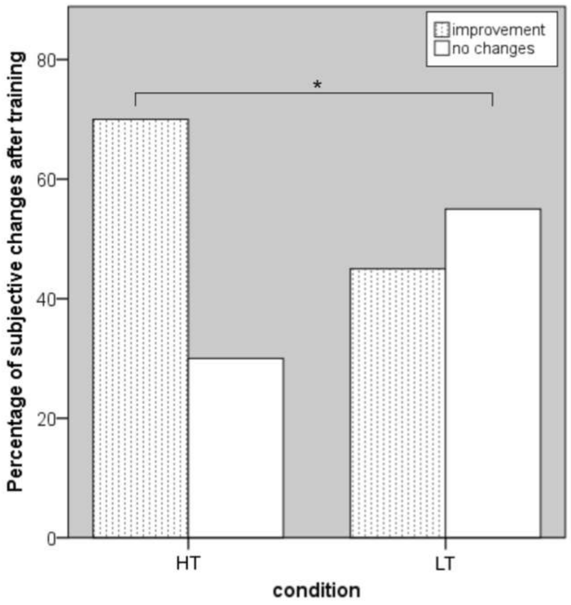

FIGURE 5 | Subjective evaluation of improvements in everyday life functions. WM, working memory; HT, high-level WM training group; WM, working memory; LT, low-level WM training group. HT significantly outperformed LT by reporting more positive changes in daily life performance (significant effect marked with an asterisk). Note that both training groups were blind with respect to their condition.

Long-Term Maintenance of Transfer Effects

The near transfer effects on untrained WM tasks that were seen immediately after the end of training were not maintained over a 3-month follow-up period. A trend for stability was seen in the Span Board task backward [$F(4,102) = 2.44$, $p = 0.052$, $\eta_p^2 = 0.09$] but vanished for the training gain regarding the combined score of all WM span tests [$F(4,102) = 1.72$, $p = 0.152$, $\eta_p^2 = 0.06$] and the initially affected WM component [$F(4,102) = 1.52$, $p = 0.202$, $\eta_p^2 = 0.06$]. For detailed information regarding means and standard deviations of all neuropsychological outcomes, see supporting information (**Supplementary Table S1**).

DISCUSSION

There is an intensive need for effective and scientifically evaluated cognitive intervention programs in order to meet the demands of our increasingly aging society. The present study evaluated the feasibility and effectiveness of *WOME*, a new theory-based WM training program, by implementing a randomized, placebo-controlled, and double-blind trial in healthy older adults, featuring: (1) a high-level WM training group (HT) that received the new intervention, (2) a low-level WM training group (LT) that represented an active control condition, and (3) a passive control group (CG). The results of our study suggest that WM training can indeed enhance specific cognitive functioning, that is, WM, in an older population. Improvement in WM function was demonstrated on enhanced performance in non-trained near transfer tasks with moderate to large effect sizes, shown on a single test level (span board task backward), and in two different composite scores (data-driven cluster of WM tests, and theoretically motivated construct of WM functioning, i.e., span measures). What may be highly relevant is that subjects reported a positive impact on everyday life (e.g., better able to memorize telephone numbers, shopping lists, and improved concentration). We showed that the intervention effects were specific for the WM system and that there was no transfer to other cognitive functions. Furthermore, the effects were short-term rather than stable, being substantially diminished by the 3-month follow-up with only little evidence suggesting long-term maintenance of WM training.

The result that WM training produces enhanced functioning of the WM system, observed in performance gains in tasks more or less similar to the trained ones, is in line with recent meta-analyses (Karbach and Verhaeghen, 2014; Melby-Lervag et al., 2016; Weicker et al., 2016; Soveri et al., 2017), thus strengthening the evidence that training WM has the potential to improve WM function, even in older subjects. Although the majority of subjects declared that they used some kind of strategy, the observed transfer to untrained WM tasks suggests that domain-general mechanisms in terms of a core training program were promoted by *WOME* (Morrison and Chein, 2011). The mechanism of such transfer effects is still unknown. Several studies have proposed that shared cognitive processes (e.g., updating) and neuronal substrates enable transfer from trained to untrained tasks (Dahlin et al., 2008; Salminen et al., 2012; Harrison et al., 2013; Beatty et al., 2015; Waris et al., 2015). In our data, the idea that WM training and outcome measures tap overlapping processes was supported by correlations between the initial performance in the trained task and various WM outcome measures. Other hypotheses state that increased attention control is responsible for performance changes, which is supported by studies that showed enhanced WM performance after training of selective attention (Shin et al., 2015; Greenwood and Parasuraman, 2016; Schmicker et al., 2016), and that WM is not enhanced by capacity but by efficiency training (von Bastian and Oberauer, 2014). To date, it is assumed that WM training does induce some kind of change in the underlying cognitive system, but we do not yet understand exactly what these are.

Despite several single studies indicating widespread transfer to other cognitive functions in older populations (Borella et al., 2010, 2013; Brehmer et al., 2012), our findings agree with more rigorous meta-analyses accounting for methodological issues that transfer effects which go beyond WM are non-existent or very small at older ages (Redick et al., 2015; Schwaighofer et al., 2015; Melby-Lervag et al., 2016; Soveri et al., 2017). The absence of far transfer effects in the present study could be rooted in the high specificity of the stimuli and the limited diverseness of the training tasks which may have reduced overlapping processes of WM and, for example, executive functions. Training alternately various components of WM may also have induced adverse effects. Possibly, efficient training of selective attention processes was interrupted by including sessions of (unnecessary) storage or manipulation training (cf. Greenwood and Parasuraman, 2016; Schmicker et al., 2016). Only a few studies explored clinical or everyday relevance in older populations with promising, yet mixed results (Brehmer et al., 2012; McAvinue et al., 2013; Cantarella et al., 2017). Our study fits in as we have found a perceived positive impact on everyday life in HT compared to LT, but there were no differences in standardized questionnaires on memory and attention performance. A possible explanation is that questionnaires on cognitive functioning are conceptualized to identify trait rather than state measures (Bridger et al., 2013) and may therefore be less sensitive for changes within a short period of time, whereas self-reports have been shown to reveal rapid alterations (Mulligan et al., 2017).

In contrast to previous studies (Dahlin et al., 2008; Li et al., 2008; Borella et al., 2010; Richmond et al., 2011), the intervention delivered only limited evidence for sustained training effects (but see Buschkühl et al., 2008, for similar results). This raises the question of whether there are special features of interventions that are able to produce long-term effects. One crucial predictor already identified for long-lasting efficacy is the amount of training (Karbach and Verhaeghen, 2014; Weicker et al., 2016). More than 20 sessions seem to be necessary in order to induce long-term effects (Thöne-Otto, 2017). Bearing this in mind, our intervention of 12 sessions may have been too short. An indication for this hypothesis is provided in the analysis of course of performance on the trained task, showing no asymptotic course or ceiling effect of the individual's performance, a typical trajectory found by the end of a learning task (Ritter and Schooler, 2001).

Other moderators that are discussed to influence training efficacy include motivation (Jaeggi et al., 2014; Au et al., 2015), self-perceived stress (Leung et al., 2016), initial cognitive capacities (Basak and Zelinski, 2013; Holmes and Gathercole, 2014; Titz and Karbach, 2014; Weicker et al., 2016; Borella et al., 2017), and personality measures (Studer-Luethi et al., 2012; Alesi et al., 2015; Minear et al., 2016). To account for such differences, we did not only include a passive control group, but also an active condition to check for various placebo effects. By setting comparable time schedules, training conditions, and a double-blind procedure, we ensured that both training groups received the same amount of care from the staff and were equally involved in the study. Despite that LT performed an intervention with low-level difficulty overall, the level description numbers increased in a comparable way to HT, providing feedback and perseverative motivation for the individuals. The procedure was successful because both groups responded similarly in rating the motivation and enjoyment of their intervention; it was exclusively the perceived effort and demand on the WM system that separated the conditions. The descriptive analysis of the data of CG showed that different experiences can lead to result patterns that are difficult to understand and hinder comparisons between conditions. Therefore, we agree with leading researchers in the field who urged future studies to always provide comparable placebo-controlled conditions (Shipstead et al., 2012; Dougherty et al., 2016; Melby-Lervag et al., 2016; Weicker et al., 2016).

Redick et al. (2015) recommended seven methodological criteria for the evaluation of WM trainings to produce valid and reliable results: (1) use of an active control group, (2) sufficient sample size, (3) use of objective measures and double-blind study design, (4) evidence for positive transfer results to WM, (5) transfer results follow a sensible pattern, (6) follow-up transfer assessment, and (7) multiple measures of each construct. Although we accurately implemented each element, there are several limitations regarding the interpretation of the results. The first and most obvious issue refers to the relatively small sample size compared to large-scale evaluations. The achieved power computed *post hoc* for our study was 0.74 at the post-test and 0.66 and follow-up measurement given an estimated effect size of $g = 0.60$ for immediate near transfer and $g = 0.54$ for long-term maintenance in healthy older adults (Weicker et al., 2016). Hence, there was a chance of around 70% of observing a near transfer effect after WM training. The realization of intervention designs with larger sample sizes is difficult to conduct in a local setting, and, consequently, implies either home-based training or a multi-center application—which we explicitly avoided by focusing on the control of side effects provoked by various surrounding conditions (Lampit et al., 2014). Beyond traditional significance testing and power analyses, the observed effect sizes were moderate to large, which confirms the assumption that a meaningful improvement was achieved after WM training. The observed moderate effect size regarding our criterion task in the follow-up test revealed indication that efficacy of WM training might last longer than proposed by null-hypotheses testing. Another limitation refers to the critical analysis of the descriptive data; transfer results should follow a sensible pattern that consists of similar results of all conditions at pretest and a greater improvement of the intervention group compared to the control group at post-test. The requested pattern is observed in most outcomes, but our criterion task fails to demonstrate this (there was an improvement in HT, while both LT and CG showed stable or slightly decreased performances). Hence, in addition to the conclusion that WM training resulted in improved WM function, measured by the span board task backward, critical alternatives refer to sampling errors or regression toward the mean (Moreau et al., 2016). By demonstrating the effect not only in a single test, but also on latent factors, we expect the observed interaction effects to be justified as improvements in WM function (Ackerman et al., 2005).

CONCLUSION

The *WOME* is a new, specific and theory-based WM training program that efficiently improves WM function, and there is some indication that it has a relevant effect on everyday life. To date, there is little evidence that benefits are long lasting, so continuous or intermittent training sessions are highly recommended. By finding no evidence of transfer effects to other cognitive domains, we join rather skeptical researchers in the field in assuming that WM training represents a specific intervention targeting WM function, and that it is neither a panacea for various cognitive functions nor a key for slowing down cognitive decline in general. It is, however, quite conceivable that continuous training contributes to a deceleration of cognitive decline with respect to WM. Numerous studies have shown that the brain remains modifiable across one's lifespan and that even old-old adults are able to benefit from an enriched environment with the potential to improve cognitive performance (Kramer and Willis, 2002; Greenwood, 2007; Mora et al., 2007). If interventions manage to stabilize WM performance over several years, we should pursue this approach to allow people to live as high functioning individuals for as long as possible. The challenge of future research is to detect mechanisms that provide the best transfer effects on cognitive functions and, more importantly, on everyday life by methodologically solid designs that account for a manageable feasibility/cost–benefit ratio. Much work is still needed regarding variability in older populations and individual differences (genetic predispositions, lifestyle, physical and mental activity) to discover moderators of resilience in aging and understand their impact on the plasticity of cognitive functions.

DATA AVAILABILITY

All datasets collected and analyzed for this study are included in the manuscript and the **Supplementary Files**.

AUTHOR CONTRIBUTIONS

JW, SF, JL, KM, AV, and AT-O substantially contributed to conception and design of the study. JW and NH organized and performed the experiments, collected the data, and performed the statistical analyses. JW wrote the first draft of the manuscript. All authors discussed the results and contributed to manuscript revision.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2018.00247/full#supplementary-material

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

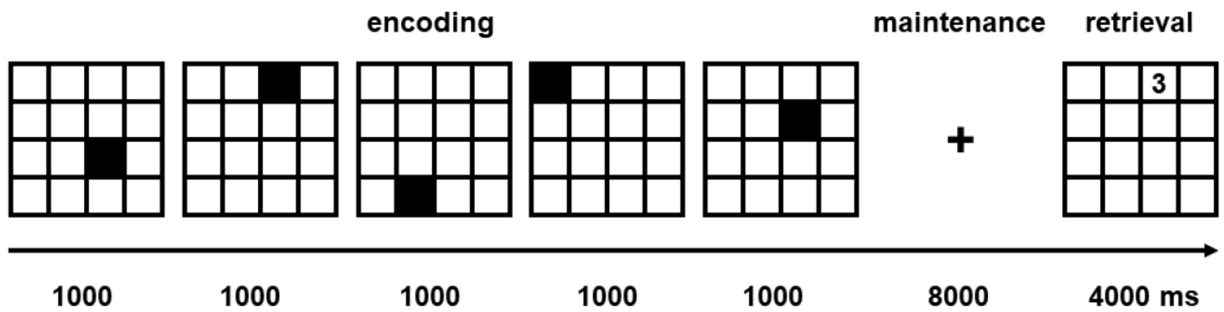
Neural effects of WOME working memory training

The neural changes following training with the WOME intervention are beyond the focus of this thesis. However, to present a comprehensive picture, the results of an analysis using fMRI, which was carried out in the context of study IV, will be briefly summarized. The aim of the investigation was to identify whether and how brain areas of the WM network may be affected by training. The author of this thesis was responsible for designing the experiment, the development and programming of the in-scanner task, and the supervision and execution of all time points of assessments. The preprocessing, statistical analyses and interpretation of the imaging data was done by Nicole Hudl (for details, see Hudl, 2019).

N = 58 healthy older adults (aged 60 to 77 years, *M* = 67.78, *SD* = 4.3) were randomized to three conditions: WOME WM training, low-level WM training and no training. Training groups practiced the respective intervention over four weeks (12 sessions). Prior and after the intervention as well as three months follow-up, fMRI scans were carried out in addition to the neuropsychological assessments described in study IV. During scanning, a visuospatial WM task was presented, which required to remember a sequence of five items and to decide whether or not a probe stimulus matched the previous pattern. The in-scanner task was adapted from Brehmer et al. (2011). A detailed description is provided in Figure 11.

Figure 11

Visuospatial WM task Presented During fMRI Scanning



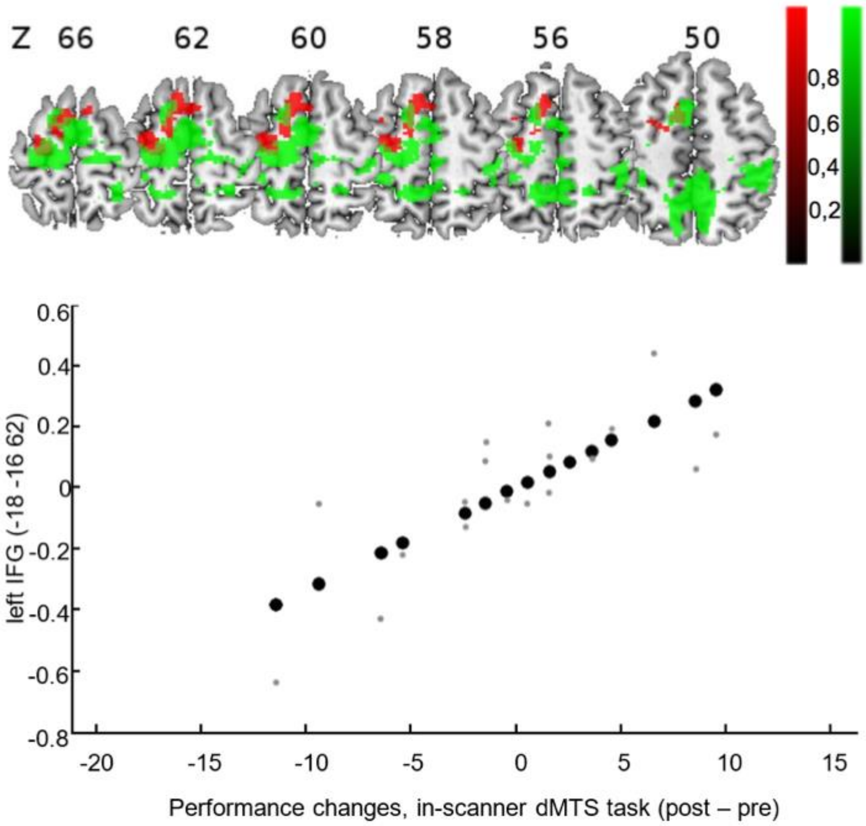
Note. One trial of the presented delayed matching to sample (dMTS) task during fMRI is shown. Subjects had to remember the location of five black boxes in a 4-by-4 grid, each presented for one second (encoding phase). Next, a fixation cross was shown for eight seconds (maintenance phase). After this delay, the subjects had to decide whether a probe stimulus did or did not match the location and sequence presented before (retrieval phase). In total, subjects completed 50 trials.

Pre- to post-training analyses showed no significant interaction when the WOME WM training group was compared to the low-level WM training, neither regarding behavioral performance in the visuospatial WM task nor regarding neural activity. However, an indication for training efficacy was found when WOME WM training was compared to the passive control group, showing significant activation differences in the bilateral frontal lobe and the right middle frontal gyrus. Moreover, a positive correlation of the changes in behavioral performance and neural activation in the in-scanner task was detected. Specifically, performance gains following WOME WM training were accompanied by increases in neural activation in the left middle frontal gyrus and in the left precentral gyrus during the encoding phase of the visuospatial WM task. A more in depth analysis revealed that this brain-behavior-correlation was mediated by individual WM capacity, i.e., subjects with high WM performance at baseline measurement showed an increase in functional activity and performance gains in the in-scanner task while subjects with low initial WM performance did not demonstrate relevant changes. Figure 12 illustrates the neural effects of the WOME intervention.

Together, the findings suggest that WOME WM training leads to changes in neural activity in fronto-parietal areas of the WM network, though the analyses only yielded significant differences between the intervention group and the passive control group. Activation patterns showed primarily increases of neural activity, which have been related to the redistribution of resources or the development of a new strategy (Hempel et al., 2004). As prolonged training phases amplify neural changes, it can be assumed that the effects observed after 12 sessions reflect only the beginning of neural reallocations, which might be more pronounced in the course of the intervention, if more training sessions were applied. According to the brain-behavior-correlation detected, individuals with high initial WM capacity seem to benefit most from the intervention.

Figure 12

Neural Effects of WOME WM Training



Note. The graph presents the results of a multiple regression analysis showing a positive brain-behavior correlation of performance in an in-scanner delayed matching to sample (dMTS) task and brain activity in N = 58 healthy older adults. The lower section illustrates that activity increases in the left inferior frontal gyrus (IFG) correlate with performance gains from pre to post-training. The upper section shows further brain areas with positive brain-behavior correlations (all subjects in red, high performers of WOME in green), indicating that the high performing individuals promote the effects found. Figure adapted from Hudl, N., Neural correlates of working memory training — fMRI analyses in healthy older adults, Copyright (2019), with permission of the author.

2.5. Study V: Effects of working memory training in patients with acquired brain injury: a double-blind randomized controlled trial.

Nachweis über Anteile der Co-Autoren, Juliane Weicker
Development and evaluation of an adaptive working memory training intervention

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Nachweis über Anteile der Co-Autoren:

Titel: **Effects of working memory training in patients with acquired brain injury: a double-blind randomized controlled trial.**

Journal: unpublished manuscript

Autoren: Juliane Weicker, Nicole Hudl, Stefan Frisch, Hellmuth Obrig, Arno Villringer, Angelika Thöne-Otto

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Anteil Juliane Weicker (Erstautorin):

- Konzeption und detaillierte Gestaltung des Experiments
- Erhebung, Auswertung und Interpretation der Daten
- Schreiben des Manuskripts

Anteil Nicole Hudl (Autor 2):

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Effects of working memory training in patients with acquired brain injury:

A double-blind randomized controlled trial

Unpublished manuscript

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Abstract

The novel computer-based working memory training 'WOME' is the first one that is specifically tailored to the needs of patients with acquired brain injury. In a double-blind randomized controlled trial, we evaluated its feasibility and effectiveness regarding working memory, related cognitive functions and its impact on daily life in a sample of 39 participants (*n* = 28 stroke, *n* = 11 TBI). They were randomized to a) the WOME intervention (*n* = 20) or b) a non-adaptive control version (*n* = 19). Neuropsychological assessments were carried out at baseline, after four weeks of training, and three months follow-up. The intervention was well received and its validity was confirmed. After 12 training sessions of WOME, participants showed significantly enhanced performance in the trained tasks and improved self-reported coping with everyday life situations. Both treatments led to increased performance in multiple untrained WM tasks as well as long-term memory and logical reasoning, but evidence of specific effects of WOME were brittle. The observed changes post-treatment were not stable three months follow-up. Compared to a previous evaluation of the effectiveness of WOME in healthy subjects, the effects in patients were small. We discuss several factors including training duration and chronicity of the brain injury.

Keywords:

cognitive rehabilitation, brain injury, plasticity, working memory training, WOME, neuropsychology

Introduction

'Brain training' is one of the most exciting scientific developments in the 21st century, appealing to both health industry and consumers. The major advance within the last 15 years was to target 'core' functions, namely the capacity or processing efficiency of the working memory (WM) system (Bastian & Oberauer, 2014). It is the cognitive structure that holds information temporarily available for further goal directed behavior, which is the basis of many complex cognitive functions, such as problem solving and intelligence (Miyake, 1999). Studies in healthy individuals suggest that repetitive training increases WM performance not only in trained but untrained tasks, and show transfer effects in many cognitive functions relying on WM (e.g., executive functions and reasoning; Morrison & Chein, 2011). Such transfer may be supported by the partial cortical co-localisation of the respective neuronal networks in prefrontal and parietal cortices (Klingberg, 2010). Moreover, neuroimaging research suggests behavioral changes to correlate with altered brain activation, structural connectivity and neurotransmitter distribution (Buschkuehl et al., 2012). There is some evidence that improvements in WM performance may generalize and impact on the quality of life (Cantarella et al., 2017; Johansson & Tornmalm, 2012; Spencer-Smith & Klingberg, 2015).

Despite the abundant literature on WM training effects in healthy subjects, little is known about the impact of residual cognitive abilities required for successful WM training. Especially after diffuse lesions (e.g., after traumatic brain injury, TBI), learning and transfer abilities may be expected to be lesser when compared to unaffected individuals due to reduced plasticity of the brain (Prigatano, 1999). In contrast, the findings of a meta-analysis on the effectiveness of WM training suggest that training-related benefits may be even greater in brain-lesioned when compared to healthy individuals (Weicker et al., 2016). But aside from studies examining children with low WM capacity, e.g., due to learning disability or attention-deficit disorder (Bergman Nutley & Söderqvist, 2017), research has widely neglected individuals who are in need of innovative approaches to enhance their impaired WM performance. To date, only ten randomized controlled trials targeted patients with acquired brain lesions (Akerlund et al., 2013; Björkdahl et al., 2013; Carretti et al., 2013; Johansson & Tornmalm, 2012; Lundqvist et al., 2010; Moore Sohlberg et al., 2000; Phillips et al., 2016; Richter et al., 2015; Vogt et al., 2009; Westerberg et al., 2007). Most of them used exercises from the software package Cogmed®, which comprises various visuospatial and verbal WM span tasks, applied 25 sessions within five weeks. The first published study focused on a small sample of stroke patients (Westerberg et al., 2007). Compared to a passive control group, training led to improved performance in untrained WM and attention tasks as well as reduced subjective memory complaints. The results were replicated in larger samples (Akerlund et al., 2013; Björkdahl et al., 2013; Lundqvist et al., 2010; Phillips et al., 2016). Overall, the findings suggest improvements in untrained WM tasks, which are rather similar to the training material, and no or only small transfer effects on other cognitive functions. The changes observed immediately after WM training were long-lasting, being stable three to six months follow-up. Most importantly, the patients reported an enhanced activity level, decreased fatigue, depression, and memory symptoms following the interventions. Qualitative analyses on the impact on daily life activities revealed three dimensions of change: (1) self-awareness, (i.e., better acknowledgement of own WM dysfunction and coping strategies), (2) meaningful improvements in everyday life (e.g., "Now I dare go for a walk, I think I can find my way back"), and (3) less specific effects including the motivation to meet people with similar problems and training related consequences ranging from "I'm less tired and more alert" to "I get very tired and I need to sleep the whole day after a training day" (Johansson & Tornmalm, 2012). Taken together, evidence calls for a broader and structured implementation of WM training in neurocognitive rehabilitation.

The issue which tasks should be applied during WM training remains unsettled. Many WM training tasks established in healthy young adults are too challenging for patients with acquired brain lesions, e.g., the dual n-back paradigm, which demands remembering two independent sequences of visual and auditory information simultaneously while the stimuli are continuously updated (Jaeggi et al., 2008; Weicker et al., 2016). Because interventions tailored to clinical populations are missing, either simplified versions of established paradigms (Cicerone, 2002; Serino et al., 2007) or compilations of various WM tasks like Cogmed® have been applied (e.g., Vallat et al., 2005; Vogt et al., 2009; Westerberg et al., 2007). The first may not represent an adequate measure of WM, for example due to the low number of 'n' in n-back tasks, which is required to stress WM function (Braver et al., 1997). The latter is questionable because the training content is neither derived from theoretical models nor can the mechanisms of training and transfer effects be investigated in detail. Without distinct modules or predefined task requirements, it is not possible to allow for training of particular WM components, which may be selectively impaired in individuals (Wilde et al., 2004). Additionally, existing programs typically provide short-term memory tasks without the involvement of more complex processes such as updating of information, task switching and inhibitory control (Bastian & Oberauer, 2014). Another issue is the necessity of adaptive training. Though it has been shown that healthy subjects benefit from unpredictable levels of difficulty and variations in demands (Bastian & Eschen, 2016), compliance is a key requirement in rehabilitation. WM tasks are cognitively effortful per se for individuals with WM deficits, so careful adjustment of performance accuracy and difficulty may be mandatory to grant success in clinical populations. Usually, adaptivity is implemented automatically in computer-based approaches by varying the number of items to be recalled. Clinical experience, however, shows that neurologic patients need a more very fine-tuned adjustment because WM capacity may be very limited (e.g., three items may be handled easily while four items lead to persistent failure). This aspect has been not addressed in previous approaches.

The present study

Existing evidence, as summarized above, calls for treatment protocols specifically tailored to the needs and capacities of patients with acquired brain lesion. Therefore, WOME (WOrking MEmory) was developed, which is a WM training program designed especially for this target group. It has been implemented in the rehabilitation software RehaCom®. The intervention offers a theoretically derived composition of tasks that are rooted in Baddeley's multi-component model of WM (Baddeley, 2003). Various modules allow for targeted therapy of specific sub processes of the WM system. The computer based paradigm enables continuous and auto-adaptive adjustment of the level of difficulty. In addition to the number of items, various task features are modifiable to provide challenging but not over demanding tasks according to the individual's performance. Feasibility and efficacy of the intervention were investigated in a sample of healthy elderly adults previously (Weicker et al., 2018). Following 12 sessions of WM training, significant improvements in trained and untrained WM tasks were found. Moreover, the subjects reported relevant effects in their daily life, e.g., better memory for shopping lists and improved overall concentration. However, no transfer effects on other cognitive domains were observed and evidence for stability at three months follow-up was brittle. Taken together, the findings suggest that WOME is an efficient training program to temporarily enhance WM performance with a relevant impact on daily life in elderly populations.

Here we evaluate the efficacy of WOME WM training in individuals with acquired brain lesions. The double-blind randomized controlled trial addresses (i) the validity and specificity of the WM training program in a clinical population, (ii) its applicability to enhance WM performance with respect to short-term and long-term benefits, (iii) the potential to improve cognitive functions that partially rely on WM capacity and may benefit from increased performance (e.g., executive control processes), and (iv) the functional relevance of transfer effects with respect to coping with daily life demands. Based on our previous results in healthy elderly adults, we predict high validity and specificity of the intervention regarding its suitability to target WM functions. Post-test performances of the WM training group are expected to show significant improvements in WM tests, which are accompanied by positive changes in daily life. Improvements are hypothesized to be long-lasting, and still present at follow-up assessment after three months. Transfer effects on other cognitive functions that may benefit from enhanced WM performance are not predicted because they were rarely observed in previous studies that investigated clinical populations.

Method

<u>Participants</u>

Thirty-nine patients with acquired brain lesions (24 male, 15 female) were collected from former outpatients of the Clinic of Cognitive Neurology, University of Leipzig, Germany, and of two other local cognitive rehabilitation centers. Inclusion criteria were a) stroke or TBI > three months post onset, b) deficits in WM function (defined by percentile value < 16 in at least one out of the following tests: Span Board task forwards/backwards or Digit Span task forwards/backwards (Härting et al., 2004), or clinically diagnosed by a qualified psychologist), c) sufficient cognitive abilities to attend the training and testing sessions, and d) aged between 16 and 69 years. Exclusion criteria were a) acute psychiatric diagnosis, b) alcohol and drug abuse, and c) participation in other cognitive training programs. The final sample consisted of 28 patients with stroke and 11 patients with TBI. Time post-onset was 39 month (SD = 61.7, range 3-300). Mean age was 50 years (SD = 12.7, range 21-69). Stroke- and TBI- patients did not differ in sex, education, time post-onset, depressive mood, and initial WM performance; but as expected by epidemiology the stroke group was older and received more medications than the TBI group (for more details please refer to Table 4). All patients gave written informed consent in accordance with the Declaration of Helsinki. They were financially rewarded for participation. Ethical approval for the trial was obtained from the ethics committee of the University of Leipzig, Germany.

Table 4

Sample Characteristics

	overall (*N* = 39)	WOME WM training group (*n* = 20)	active control training group (*n* = 19)	difference
etiology (stroke/TBI)	28/11	13/7	15/4	$\chi^2 = 0.94$, $p = 0.333$
gender (male/female)	24/15	13/7	11/8	$\chi^2 = 0.21$, $p = 0.648$
age *M (SD)*	50.2 (12.7)	52.6 (7.8)	47.7 (16.1)	$T = 0.84$, $p = 0.406$
education level (*n*)				$\chi^2 = 0.74$, $p = 0.693$
≤ 9 years	4	2	2	
10-12 years	25	13	12	
≥ 12 years	10	5	5	
premorbid intelligence				
LPS-3 (*M, SD*)	22.1 (5.8)	21.1 (5.6)	23.1 (5.9)	$T = 1.12$, $p = 0.272$
subjective everyday life functioning rated on a 3-point Likert scale (*n*)				$\chi^2 = 0.15$, $p = 0.93$
no complaints	17	8	9	
complaints not impairing everyday life	10	6	4	
impairments in everyday life	11	5	6	
month since brain injury *MD (SD, range)*	39 (61.7, 3-300)	44 (68.3, 15-300)	23 (49.8, 3-144)	$U = 81.00$, $p = 0.033$
medication (yes/no)	31/8	14/6	17/2	$\chi^2 = 2.27$, $p = 0.132$
mood (BDI: *M, SD*)	9.6 (5.7)	10.7 (5.8)	8.5 (5.6)	$T = 1.16$, $p = 0.253$
WM performance (Span Board backward: *M, SD*)	7.7 (1.9)	7.7 (2.0)	7.7 (1.9)	$T = 0.54$, $p = 0.957$
use of additional treatments (yes/no)	17/22	10/10	7/12	$\chi^2 = 0.68$, $p = 0.408$

Note. BDI = Beck's Depression Inventory (Hautzinger et al., 1995), TBI = traumatic brain injury. Sample size is N = 34 for month since brain injury and N = 38 for subjective performance in everyday life due to missing data.

Procedure

The design was similar to our previous study that investigated the effectiveness of WOME in healthy older adults (Weicker et al., 2018). A double-blind randomized controlled trial was performed with neuropsychological assessments at three time points: at baseline one week prior to the training phase, post-treatment, and at three month follow-up. Outcome measures comprised (1) tests of WM functions, (2) tests of other cognitive functions closely linked to the WM system, (3) questionnaires that target coping with daily life experiences, (4) questionnaires to provide insight in intervention-related behavior (e.g., strategies), and (5) questionnaires that control for unintended factors (such as depressive symptoms). Table 5 specifies the neuropsychological test battery applied. Following baseline assessment, participants were allocated to a) the WOME intervention (n = 20) or b) a non-adaptive control version of the intervention with very low WM demands (n = 19). Randomization was realized with the online software Research Randomizer (Urbaniak & Plous, 2013), which accounted for equal probability of the number of subjects and their respective etiology (stroke or TBI). The final groups did not differ significantly regarding all sample characteristics except for months since injury (the WOME intervention group had longer intervals). Training sessions took place three times a week for four weeks, 45 min each, summing up to a total of 12 sessions. If appointments were missed the participants were allowed to extend the training phase up to one week. Additionally, all patients were free to complete up to a total of 15 sessions.

Of the 39 participants recruited at baseline, all completed the training phase successfully. One patient missed post-measurement due to illness, but returned for the follow-up assessment. Another patient missed follow-up testing due to time constraints. A flowchart of the study design and number of participants is provided in Figure 13. For a detailed explanation of the procedure, concerning a detailed description of the outcome measures, training sessions, the allocation and blinding procedure, please see our previous study (Weicker et al., 2018).

Table 5

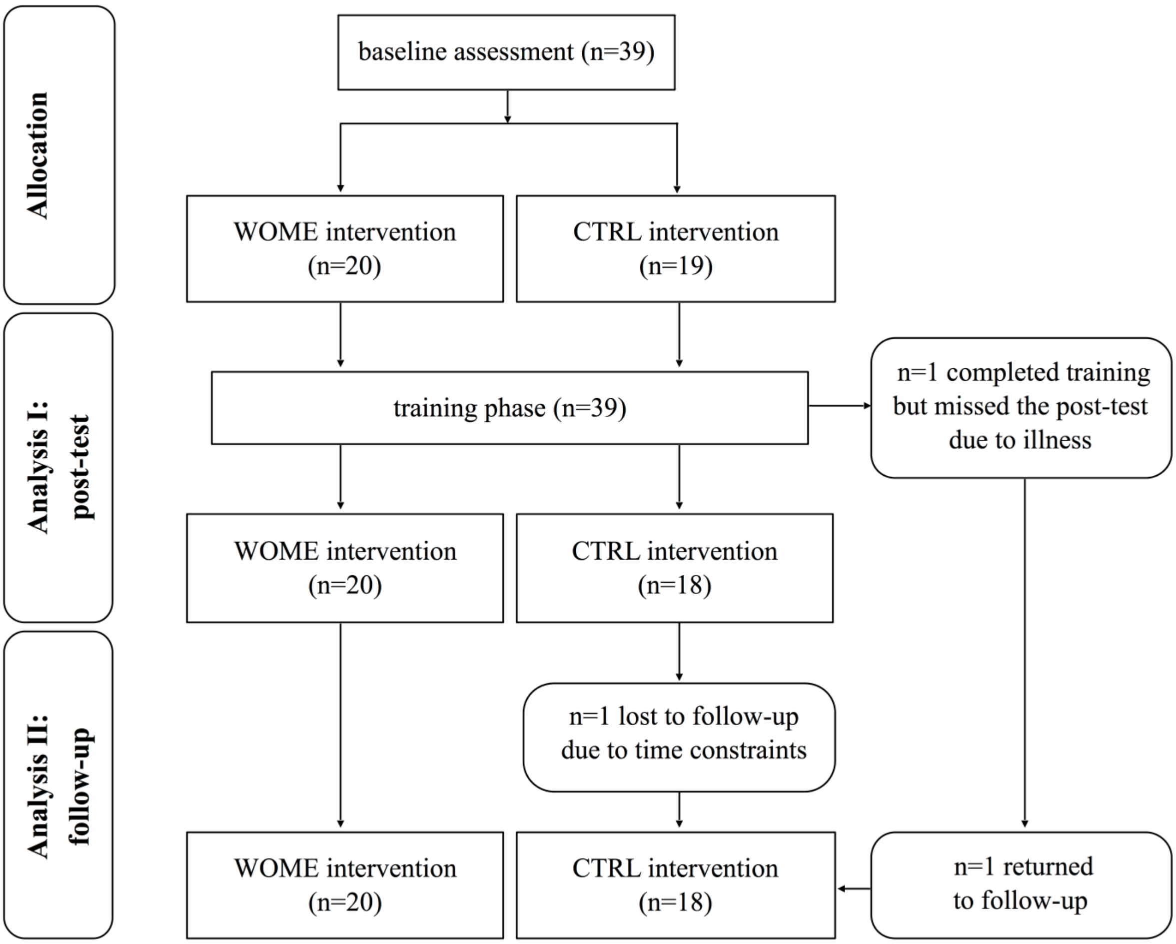
Neuropsychological Test Battery Applied

WM functioning	cognitive functions requiring WM	questionnaires	non-target outcome
Digit Span (forwards)	*executive functioning*	*daily life functions*	TAP Alertness (reaction time)
Digit Span (backwards)	Stroop	CFQ	
Span Board (forwards)	TAP Go-Nogo	FEAG	
Span Board (backwards)	TMT A/B	own questionnaire	
Spatial Addition	TAP Mental Flexibility		
Symbol Span	*logical reasoning*	*strategies*	
TAP n-back	LPS-3	own questionnaire	
PASAT	*long-term memory*	*unintended factors*	
	VLMT	BDI	

Note: BDI = Beck Depression Inventory (Hautzinger et al., 1995), CFQ = Canadian Failure Questionnaire (Broadbent et al., 1982), FEAG = Inventory of Memory Experiences (Herrmann & Neisser, 1978), LPS-3 = Subtest 3 of the German intelligence battery 'Leistungsprüfsystem' (Horn, 1983), PASAT = Paced Auditory Serial Addition Test (Gronwall, 1977), TAP = Test for Attentional Performance (Zimmermann & Fimm, 2007), TMT A/B = Trail Making Test A and B (Reitan, 1958), VLMT = German version of the Auditory Verbal Learning Test (Helmstaedter et al., 2001).

Figure 13

Flowchart of the Study Design



Note. The graph shows the flow of participants from baseline to follow-up measurement.

Intervention

The intervention (WOME) is a computer-based WM training program developed specifically for patients with acquired brain lesions. It features (i) a theory-based modular structure that targets particular components of the WM system (storage systems, selective attention, and central executive processes), (ii) fine-tuned and automatic adjustment of the difficulty level, and (iii) motivating stimuli with reference to everyday life. In principle, a dealer presents playing cards on a gambling table, which are turned around after a brief period of time. The specific instructions depend on the trained WM component: In the storage systems module, all the cards presented have to be remembered; in the selective attention module, only cards of certain suits have to be chosen; and in the central executive module, the cards have to be sorted either in the same or in the reverse order. Overall, WOME comprises 69 levels of difficulty.

The non-adaptive control version of the intervention (CTRL) used the same stimuli and types of tasks, but difficulty was fixed at a very low level with minor demands on the WM system. The level structure was revised, so that the maximum number of cards to be remembered was three, and the modules were simplified (e.g., no backward manipulation). The final range of 59 levels was obtained by adding distracting cards. Additionally, the number of responses was increased, so that more time was spent within the same difficulty level. Participants were motivated to work conscientiously by providing continuous feedback on speed and accuracy.

<u>Statistical analyses</u>

Intervention feedback and prior experiences were measured on 5 point Likert scales (ranging from 1 = 'not at all' to 5 = 'very much'). Nominal data were analyzed with Fisher’s exact test, non-parametric data with the Wilcoxon-Rank test for dependent variables and Mann-Whitney U-test for independent samples. Improvements in the trained tasks were investigated by comparing the maximally attained level from session to session within groups with dependent samples *t* tests and between groups with independent samples *t* tests. For this purpose, the level structure of the non-adaptive control version was converted into the structure of the WOME intervention considering item length and number of distractors, which were limited per definition. To investigate the effectiveness of the treatment, the participant’s raw scores in neuropsychological tests and standardized questionnaires were analyzed. Baseline performance of the groups was inspected with independent samples *t* tests. Training-related changes were analyzed by analyses of variances (ANOVA) with the between-subjects factor intervention (WOME, CTRL) and the within-subjects factor time point of assessment (baseline, post-treatment, follow-up). To control for differences between conditions, the number of sessions and months elapsed since brain injury were included as covariates. Within-group changes from baseline to post-test were analyzed separately with dependent *t* tests for paired samples by considering a Bonferroni adjusted alpha level. The Statistical Package for Social Sciences SPSS, version 22 (IBM Corp., 2013) was used for all analyses. The significance level was set to $\alpha = 0.05$ (two tailed). Effect size estimates are given by partial eta-squared (η_p^2) for ANOVAs (small effect: $\eta_p^2 \geq 0.01$, moderate effect: $\eta_p^2 \geq 0.06$, and large effect: $\eta_p^2 \geq 0.14$ a large effect) and by Cohens's *d* for *t* test differences (small effect: $d \geq 0.2$, moderate effect: $d \geq 0.5$, and large effect: $d \geq 0.8$; Cohen, 1988).

Results

Feedback

Both interventions were rated as enjoyable (WOME: $M = 4.20$, $SD = 0.62$, CTRL: $M = 3.89$, $SD = 0.74$) and 38 out of the 39 participants described themselves as motivated (WOME: $M = 4.20$, $SD = 0.41$, CTRL: $M = 4.16$, $SD = 0.50$; differences between conditions n.s., $p = 0.224$ and $p = 0.879$, respectively). Confirming the design, the WOME intervention was perceived as more demanding than the non-adaptive control version (WOME: $M = 3.75$, $SD = 0.64$, CTRL: $M = 2.74$, $SD = 1.05$; $p = 0.003$). Prior experience with card games and computers was mostly given, but there were also patients who had no experience at all (computers WOME: $M = 4.10$, $SD = 1.48$, CTRL: $M = 3.84$, $SD = 1.46$; card games: WOME: $M = 2.06$, $SD = 1.35$, CTRL: $M = 2.11$, $SD = 1.23$; differences between conditions n.s., $p = 0.647$ and $p = 0.815$, respectively).

Reported task strategies used in the WOME intervention were chunking ($n = 18$), remembering selective items only ($n = 16$), rehearsal ($n = 14$), and pure visual imprinting ($n = 7$). Rarely, other strategies were applied, such as associations or making use of fingers ($n \leq 2$, respectively).

Improvement in the trained task

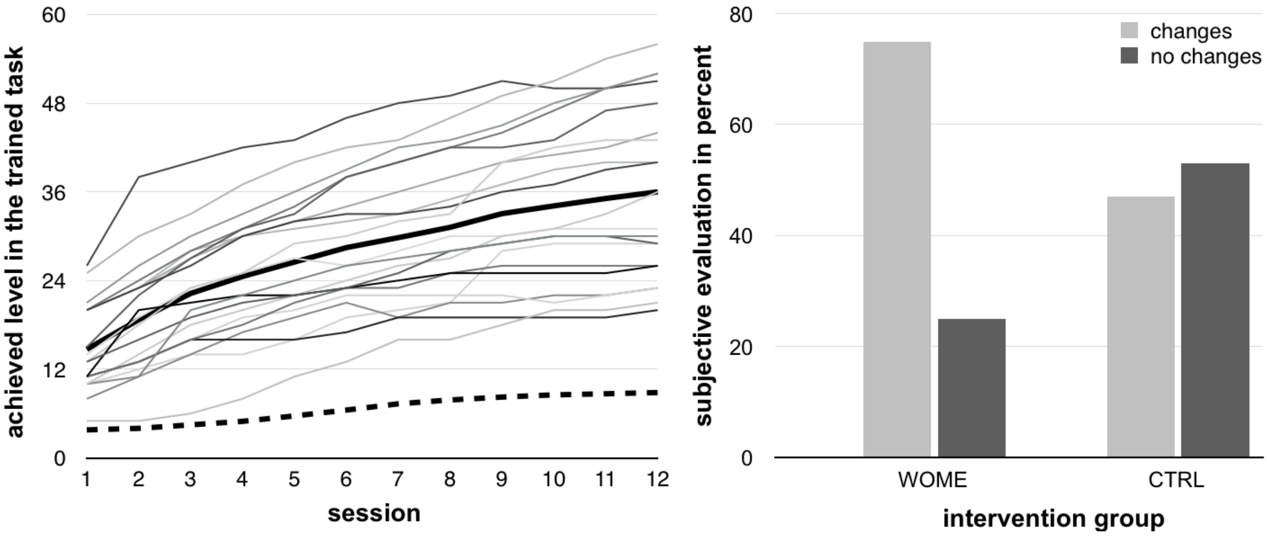
All participants completed at least 12 training sessions. The mean number of sessions was 12.87 (*SD* = 1.24) and corresponded to 9.18 hours (*SD* = 0.88). Note that participants were free to perform additional sessions, thus groups differed in the amount of training (sessions WOME: M = 13.25, SD = 1.41; CTRL: M = 12.47, SD = 0.91; $t(37) = 2.04$, $p = 0.049$, $d = 0.65$).

Figure 14 depicts the course of performance in the trained tasks. While the improvement of the maximally attained level was limited per definition in the non-adaptive control version, the WOME intervention showed continuous improvements from session to session with no indication of plateau-performance or ceiling effects (first vs. last session: $t(19) = 13.21$, $p = 0.000$, $d = 1.57$; 11th vs. 12th session: $t(19) = 4.16$, $p = 0.001$, $d = 0.07$). On average, participants increased their ability to remember suits and values of playing cards from three to five items.

The progression in the trained task was predictable by the participant's performance in WM tests at baseline assessment (e.g., digit span backwards: $\beta = 0.49$, $t(19) = 2.39$, $p = 0.028$, spatial addition: $\beta = 0.67$, $t(19) = 3.78$, $p = 0.001$, symbol span: $\beta = 0.52$, $t(19) = 2.59$, $p = 0.019$) and at the initial training session ($\beta = 0.86$, $t(19) = 7.09$, $p < 0.001$). The correlations suggest that the WOME intervention targets similar WM processes to established outcome measures, which indicates high validity.

Figure 14

Performance and Subjective Evaluation of the Intervention



Note. The graph on the left displays the progress in the trained task for each of the 12 training sessions of the WOME intervention group (solid black line) and of the CTRL intervention group (dotted black line). The composition of the CTRL intervention was designed to be limited in progression. For the WOME intervention group, individual performances are shown (thin grey lines). The graph on the right illustrates the subjective evaluation of the effectiveness of the interventions. Reported changes in daily life are illustrated in bright grey, the lack of changes are illustrated in dark grey.

Transfer effects

At baseline assessment, no significant differences were observed between the intervention groups. Both groups achieved improvements in multiple untrained WM tasks after training (significant main effects of time: Span Board Task forwards $F(1,30) = 4.89$, $p = 0.035$, $\eta_p^2 = 0.14$; Span Board Task backwards $F(1,30) = 7.62$, $p = 0.010$, $\eta_p^2 = 0.20$; n-back task $F(1,29) = 9.22$, $p = 0.005$, $\eta_p^2 = 0.24$), but no significant interactions were found. Hence, both interventions yielded similar effects.

Separate group analyses of changes from baseline to post-treatment with a Bonferroni adjusted alpha level of 0.006 per test (0.05/9) indicated selective improvements only following the WOME intervention with small to moderate effect sizes (Paced Auditory Serial Addition Test: $t(17) = -3.43$, $p = 0.003$, $d = 0.40$, and Symbol Span: $t(19) = -3.47$, $p = 0.003$, $d = 0.62$). The observed improvements were partially stable three months follow-up (n-back task $F(2,56) = 6.20$, $p = 0.004$, $\eta_p^2 = 0.18$). No significant effects were found regarding other cognitive functions.

The subjective evaluation of the double-blind treatment favored WM training: 75 % of the participants who underwent the WOME intervention reported improved coping with everyday life situations compared to only 47 % of the participants who received the non-adaptive control intervention ($\chi2$ (1, N = 37) = 16.48, $p < 0.001$). In particular, they cited facilitated dealing with letters and numbers (e.g., telephone numbers, names, shopping lists) and an enhanced overall alertness. However, standardized questionnaires on cognitive performance in everyday life showed no significant changes.

Discussion

The novel WM training 'WOME' was developed to meet the special requirements for patients with acquired brain lesions. In a double-blind randomized controlled trial, we evaluated feasibility and effectiveness with respect to WM and related cognitive functions as well as its impact on daily life. Participants underwent either 12 sessions of WOME or of a non-adaptive control version with very low WM demands.

The study confirmed the applicability of WOME in clinical populations. The intervention was well received, which was reflected in positive feedback ('enjoyable and motivating'), high commitment (no drop-outs during the training phase) and motivation (e.g., voluntary extra sessions). Participants improved their performance in the trained tasks continuously and no indication of plateau- or ceiling effects were observed. Significant correlations of baseline raw scores in WM measures and success in WOME suggest high validity of the intervention. Self-reports indicated functionally relevant improvements in everyday life. Participants declared facilitated dealing with WM demands (e.g., memorizing telephone numbers, names, shopping lists) and enhanced alertness. The double-blind study design allows for ascribing this impact on daily life to WOME.

In contrast, standardized neuropsychological tests and questionnaires did not substantiate the findings. Both, the WOME intervention and the non-adaptive control version with very low WM demands led to transfer effects in various untrained WM tasks. No significant interactions between time point of assessment and treatment condition were found; hence, superior effects of WOME could not be shown. There were some selected improvements in favor of the WOME intervention when the pre to post-treatment changes were examined separately for each intervention group, but overall, evidence of specific effects were brittle. The observed changes were only partially stable three months follow-up. No transfer effects in other cognitive functions were observed.

<u>Limited transfer effects</u>

Compared to our previous trial (study IV), which investigated the effectiveness of WOME in healthy elderly adults using the same study design (Weicker et al., 2018), the effects of the current trial are small. While healthy subjects showed substantial benefits not only in the trained tasks and in self-reports but also in standardized neuropsychological WM tests, similar effects were not detectable in patients. We identified the following factors as possible explanations for the low efficacy of the WOME intervention in the present study:

1) Duration of the intervention may be critical since several studies suggest that clinical populations need more intensive training than their uncompromised peers (Hildebrandt et al., 2006; Weicker et al., 2016). Generally, training intensity has been shown to be one of the most important modulators of WM training efficacy (Thöne-Otto, 2017; Weicker et al., 2016). Of the existing studies in clinical populations, only one has applied less than 15 training sessions and was able to

discover transfer effects (Carretti et al., 2013). Hence, it is possible that the training duration was not sufficient in the current trial.

2) Another issue refers to the chronicity of the acquired brain lesions and the patients' potential to benefit from functional training. Due to randomization, the WOME intervention group had a significantly larger time since brain injury compared to the non-adaptive control training group — almost twice as much. The absence of reliable benefits could be explained by the different plasticity of the brain and the potential to adapt neuropsychological changes (Hu et al., 2010). In addition to the group differences, the patient's status in the current trial has to be classified as very chronic with a time since injury onset of approximately 3,3 years. An application of WOME in an earlier phase of rehabilitation would possibly yield larger effects (Hellgren et al., 2015).

3) The third possible reason for the small differences observed between the training conditions refers to choice of the control group. First, it is possible that active control groups, who engage in a similarly demanding task, bear the danger of underestimating the true effect (Bastian & Oberauer, 2014). Second, our purpose was to design the non-adaptive control intervention such that working memory processes were supposed to be reduced to a minimum. This intention may have been incomplete. Potentially, remembering three playing cards — affording six items to be held in WM, namely values and suits — is already a challenging task for individuals with WM deficits and therefore may have been a way of training. Furthermore, WM and attention are closely related concepts per se and by the means of the central executive component, the WM system can distribute attentional resources and guide the focus of attention (Baddeley, 2003). This 'controlled attention' shows the interconnection of WM, attention and executive functions (Cowan, 1999; Engle, 2002). Moreover, it has been proposed that altered WM performance may be actually *based* on higher attentional control (Greenwood & Parasuraman, 2016). In this vein, filter exercises, e.g., selective attention of relevant stimuli while inhibiting irrelevant information, have been shown to initiate changes in WM efficiency more than consolidation training (Schmicker et al., 2016; Shin et al., 2015). Such filter processes were explicitly required in the control treatment. Similar cognitive

processes promoted by both training programs, despite of different levels of difficulty, may have prevented to detect greater efficacy of WOME compared to the non-adaptive control intervention based on statistical analyses.

Modularity in cognitive rehabilitation

WOME was developed as a specific, theory-based WM training program with a modularized structure that allows targeting selectively impaired WM components in patients with brain injury. Despite the absence of specific effects in the current trial, the approach remains plausible and should be pursued in clinical rehabilitation research. Several case studies have demonstrated selective improvements in impaired sub processes of WM that were the focus of the treatment. For example, intensive verbal WM training was applied in a patient with isolated deficits in central executive component and phonological loop of the WM system after left hemisphere stroke (Vallat et al., 2005). The intervention led to enhanced verbal WM capacity and coping with related daily life demands and the individual was able to resume his work. Another study focused on two patients with severe traumatic brain injury, who suffered from isolated deficits in the central executive component of WM (Vallat-Azouvi et al., 2009). Specific cognitive training caused enhanced performance only in outcomes measures that targeted the central executive but not in other WM domains. Modularity in cognitive rehabilitation was demonstrated in a single case study in a patient with chronic stroke who experienced impairments in WM functions (Vallat-Azouvi et al., 2014). After multiple baseline assessments, specific therapy targeted consecutively different sub processes of the WM system. Indeed, each training phase induced domain-specific gains (i.e., verbal aspects improved after training the phonological loop, visuo-spatial performance improved after training the visuo-spatial sketchpad, and executive control processes improved after training the central executive). Taken together, despite the low specificity found in the current trial, there is evidence that cognitive therapy should be tailored to the individual deficits. Due to its theory-based approach and the adjustment to the particular needs of patients with brain injuries, it is reasonable that the WOME intervention may represent a suitable device for the rehabilitation of WM deficits.

Limitations

A major limitation of the current trial refers to the lack of a passive control group to account for test-retest effects. To evaluate efficacy and specificity effects, we focused on the comparison of an intervention previously shown to be effective to control version. Active control groups have been recommended because only they can account for factors that may moderate performance such as motivation, expectancy, and social interaction (Oken et al., 2008). Due to absent interactions of treatment and time point of assessment, however, it remains open whether the non-adaptive version may have produced similar effects as the more demanding original intervention or whether the observed improvements are rather based on the repeated measurements.

Conclusion

The current trial confirmed validity and applicability of the computer-based WM training program WOME in patients with acquired brain injury. Findings suggest that impairments in WM can be ameliorated by repetitive training and that specific cognitive therapy improves coping with related daily life demands. To produce reliable benefits, however, 12 training sessions may not be sufficient and longer treatments are recommended. Future research must address the commonalities and differences between the healthy and the lesioned network with regard to plasticity. Moreover size and site of the lesion can be expected to play a crucial role.

2.6. Study VI: The effect of high vs. low intensity neuropsychological treatment on working memory in patients with acquired brain injury.

Nachweis über Anteile der Co-Autoren, Juliane Weicker
Development and evaluation of an adaptive working memory training intervention

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Nachweis über Anteile der Co-Autoren:

Titel: **The effect of high vs. low intensity neuropsychological treatment on working memory in patients with acquired brain injury.**

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Autoren: Juliane Weicker, Nicole Hudl, Helmut Hildebrandt, Hellmuth Obrig, Magdalena Schwarzer, Arno Villringer, Angelika Thöne-Otto

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Anteil Juliane Weicker (Erstautorin):

- Projektidee
- Konzeption und detaillierte Gestaltung des Experiments
- Unterstützung bei der Datenerhebung
- Datenanalyse und Interpretation der Ergebnisse
- Schreiben des ersten Entwurfs des Manuskripts
- Schreiben und Einreichen der Publikation

Anteil Nicole Hudl, Hellmuth Obrig & Arno Villringer (Autor 2,4,6):

- Diskussion und Interpretation der Ergebnisse
- Schreiben der Publikation

Anteil Helmut Hildebrandt (Autor 3):

- Diskussion des experimentellen Designs
- Unterstützung bei der statistischen Datenanalyse
- Diskussion und Interpretation der Ergebnisse
- Schreiben der Publikation

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- Supervision der Patientenrekrutierung und Trainingsdurchführung
- Diskussion und Interpretation der Ergebnisse
- Schreiben der Publikation

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The effect of high vs. low intensity neuropsychological treatment on working memory in patients with acquired brain injury

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ABSTRACT

Aim: To evaluate the combined effect of compensation therapy and functional training on working memory (WM) in patients with acquired injury and chronic cognitive deficits by investigating the dose-response relationship and specificity of transfer effects.
Research design: Double-blind randomized controlled trial.
Methods: All patients underwent 4 weeks of compensation therapy in a day-care setting. In addition, they received either 20 sessions of computer-based WM training (n = 11) or attention training (n = 9). Transfer effects on cognition and their functional relevance in daily life were assessed before treatment, after 2 weeks (10 additional training sessions), and after 4 weeks (20 additional training sessions) of therapy.
Results: The combined treatment led to significant improvements in WM performance, verbal memory, and self-reported changes in daily life. The amount of training was identified to modulate efficacy: Significant improvements showed only in the later training phase. We observed no differences between the two training schemes (WM vs. attentional training).
Conclusions: Even in the chronic phase after brain lesion WM performance can be enhanced by the combination of compensation therapy and computerized cognitive training when applied intensely; both a more general attention and a specific WM training regimen are effective.

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Cognitive rehabilitation; brain injury; plasticity; working memory training; dose-response relationship

Introduction

Persistent cognitive deficits are a major cause of impairment of activities of daily life. This even applies in patients with otherwise good neurological recovery after acquired brain injury (1). Working memory (WM) deficits may play a crucial role; since they entail 'higher order' cognitive dysfunctions, affect communication skills and intellectual performance (2–4) and interfere with the acquisition of new skills, academic achievement, recovery from injury, and resumption of work (5–8). Patients with low WM capacity report that they cannot follow long conversations, struggle with attending to simultaneous tasks, are easily distracted, and forget to continue a task when interrupted. Thus, the WM system can be considered a bottleneck of information processing, which in turn is critical for goal-directed behavior (9,10). While the literature on WM training in healthy participants is abundant (11), studies in clinical populations are surprisingly rare. For decades deficits in WM performance were treated by compensation therapy, providing internal or external strategies on how to use intact functions efficiently and promote strategies to compensate for weaknesses (12). We are aware of only ten randomized controlled trials investigating functional WM training in patients with acquired brain injury. Largely studies report clinically relevant, long-lasting changes in WM functions after training (12–21), leading to symptom reduction (e.g. fatigue or subjective memory failures) and enhanced daily activities (15–17,19–22). Moreover WM training has been demonstrated to elicit specific adaptive plasticity in the neuronal network affording WM functioning (23–25). Due to greater prediction of functional outcomes in earlier stages of rehabilitation (26), cognitive training is expected to be less effective when applied in the chronic phase (> 3 month) after brain lesion (27,28). A meta-analysis of WM training studies and a large, multicenter, randomized controlled trial in aphasia therapy has provided strong evidence that intensity is an important modulator of training success, suggesting that even patients with chronic cognitive deficits may benefit from treatment if it is administered with sufficient training duration (11,29).

In a double-blind, randomized controlled design the current trial addresses: (i) The combined effect of WM training and compensation therapy in brain injured patients with chronic cognitive deficits; (ii) The time course of the dose-response relationship, i.e. how treatment intensity modulates transfer effects on untrained WM tasks, related cognitive functions, and functional relevance to everyday life; (iii) The specificity of the WM training content in comparison to a less specific training of attentional functions. Targeted are individuals with acquired non-progressive brain injury (after stroke, traumatic brain injury or encephalitis) who undergo rehabilitation in an intensive interdisciplinary day-clinic setting due to chronic neuropsychological deficits that impair their potential to resume work.

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Supplemental data for this article can be accessed on the publisher's website.

The hypotheses targeted by the current study are: 1.) Treatment in general leads to better performance in trained tasks, and generalizes to WM functions and daily life requirements (18,19,30). 2.) Specific and larger effects on WM when compared to unspecific cognitive training are expected, since the WM training intervention is grounded on theories of WM. 3.) Conversely, substantial transfer to other cognitive functions is not predicted, since evidence for 'far' transfer in the elderly and patients is brittle (11). 4.) More intensive therapy should elicit larger benefits indicating a dose-effect; specifically 4 weeks of compensation training and 20 sessions of functional WM training when compared to 2 weeks of compensation training and 10 sessions of WM training.

Methods

Procedure

The study was conducted as a double-blind, randomized controlled trial. All subjects gave written informed consent. The study was approved by the ethics committee of the University of Leipzig, Germany, and registered at the German Clinical Trials Register (DRKS00016403). Four weeks of compensation therapy were provided in a multidisciplinary rehabilitation setting. In addition, computerized functional training was carried out daily on weekdays for four weeks, 30 min each, resulting in 20 sessions overall.

To explore dose-response effects, neuropsychological assessments were performed before treatment (T1), after 2 weeks including 10 cognitive training sessions (T2), and after 4 weeks including 20 cognitive training sessions (T3). The assessments were carried out by trained psychology students. When available, parallel versions of standardized tests were administered and counterbalanced across measurements to minimize practice effects. After the last training session, all participants completed a questionnaire supplying feedback regarding the training tasks, strategies, and subjective effects in everyday life.

After baseline assessment patients were randomized to a) WM training, or b) attention training to investigate the specificity of training content. Randomization was realized with Microsoft Excel by the generation of a random number list according to which the patients were allocated to either condition (the lower half of numbers corresponded to WM training, the upper half of numbers corresponded to attention training) with equal probability and stratified by sex. The groups did not differ regarding epidemiology or the amount of standard therapy supplied. Blinding of examiners was ensured by allocating different staff for testing and training. Subjects were blind to the training condition in that they were told that concurrent cognitive enhancement programs were examined.

Participants

A sample of 30 patients was selected from the Clinic of Cognitive Neurology, University of Leipzig, Germany. Participants fulfilled the following inclusion criteria: a) acquired brain injury ≥ three months post onset, b) sufficient language skills for participation in the intervention and outcome tests, and c) informed consent to take part in the study. Exclusion criteria were a) history of severe psychiatric disorders, b) alcohol or drug abuse, and c) severe cognitive deficits interfering with completion of the tasks. Eight subjects withdrew from the study prior to the start of the intervention, one subject declined participation after two training sessions because of time constraints, and another completed the training phase but was excluded from the final analyses due to profound difficulties with test and task material. An overview of the flow of participants from recruitment to study completion is provided in Figure 1. A comparison of the demographic and cognitive profile of the participants included in the final analyses vs. the participants that dropped out after group allocation is provided in Table 1; note that no significant differences were present.

Given an estimated effect size of $d = 0.79$ in the WM composite based on a previous study of the same WM training in elderly adults (30), the required total sample size is N = 42 to achieve a sufficient statistical power to detect differences between groups after the intervention (34). The WM composites of the previous and the present study are specified in Table 2. Due to organizational constraints, data collection was limited to six months and had to stop after this time period. This is why the final sample comprised only 20 patients (WM training, $n = 11$; attention training, $n = 9$). Mean age was 48.6 years (SD = 12.8, range 27–75) and mean time since acquired brain injury was 16 month (SD = 85.3, range varied between five months and 29 years). Patients suffered from stroke ($n = 11$), inflammatory diseases of the central nerve system ($n = 5$), traumatic brain injury ($n = 2$), or chronic non-progressive low-grade Glioma ($n = 2$). Sample characteristics are detailed in Table 3.

Outcome measures

The following outcome measures were assessed: (i) WM functions; (ii) other cognitive functions: attention, executive functions, verbal learning; (iii) everyday life performance (standardized questionnaires and self-reported changes in cognitive performance); and (iv) control measures (factors that could bias the intervention outcomes, e.g. premorbid intelligence). All neuropsychological outcome measures that target transfer effects were applied at T1 and T3. At T2 only a subgroup of WM- and attention-tests were assessed because of the small retest interval and the additional effort for the patients. An overview of all outcomes and the time of assessment is provided in Table 4. Detailed explanation of each task and the respective outcome parameters are provided in the supplemental material (S2).

Intervention

Procedure

The compensation therapy comprised the regular individualized daycare-clinic program of the Clinic of Cognitive Neurology, University of Leipzig, including neuropsychological, occupational, visual, speech, and physical therapy approximately four to five hours between 9 a.m. and 3 p.m. daily on weekdays. The total hours of received regular therapy during the course of the intervention were $M = 112.5$ ($SD = 23.2$), including $M = 36.1$ hours ($SD = 8.0$) of neuropsychological

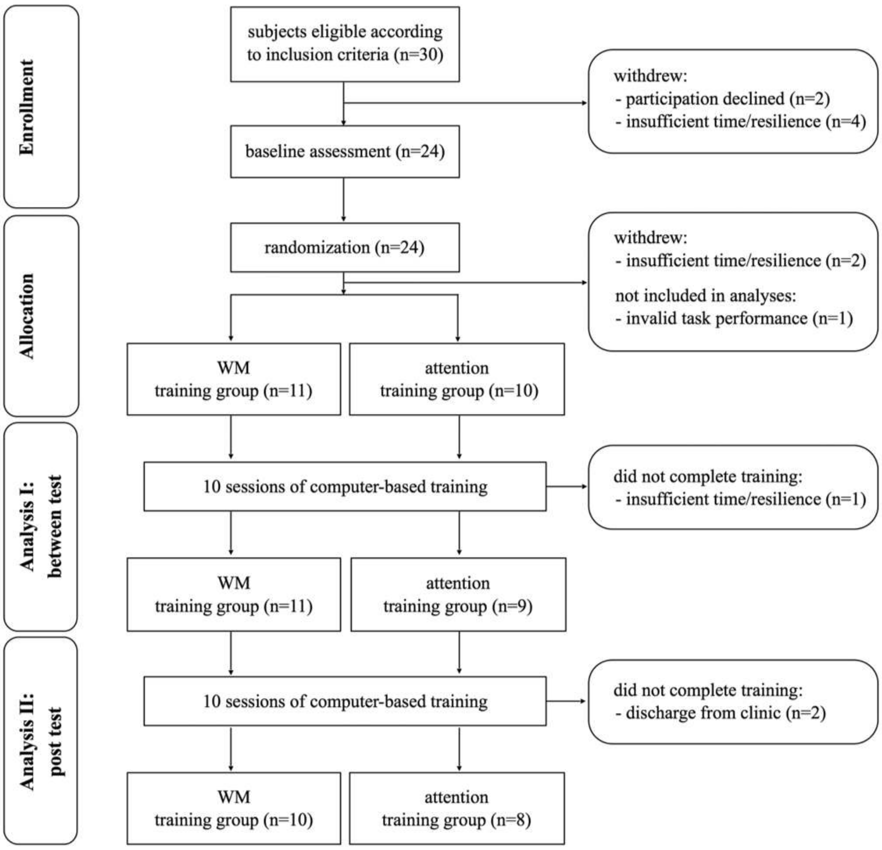

Figure 1. Flow chart of the study design.

Table 1. Demographic and cognitive profile of included vs. drop-out participants.

	participants included in the data analyses	drop-out participants	difference
age *M (SD)*	48.9 (12.9)	51.6 (15.0)	*T* = 0.44, *p* = .663
premorbid intelligence			
LPS-3 (*M, SD*)	21.3 (7.1)	19.2 (6.1)	*T* = 0.65, *p* = .523
WST (*M, SD*)	28.0 (4.0)	27.0 (5.0)	*T* = 0.50, *p* = .626
mood (BDI-II: *M, SD*)	12.2 (6.8)	13.6 (8.3)	*T* = 0.39, *p* = .698
months since brain injury *MD (SD, range)*	16.0 (46.7, 5–192)	12.0 (149.2, 10–348)	*T* = 0.70, *p* = .508

Note: Depicted are all drop-out participants after group allocation (n = 6). Reasons for drop out were insufficient time/resilience (n = 3), invalid test and task performance (n = 1), and early discharge from clinic (n = 2). BDI-II = Beck Depression Inventory II (31), LPS-3 = Subtest 3 of the German intelligence battery 'Leistungsprüfsystem' (32), WST = German verbal comprehension test (33).

treatment. The additional functional training sessions were carried out computer-based in smalls groups of maximally four persons. Participants practiced either in the morning before their regular treatments (between 8 a.m. and 11 a.m.) or in the afternoon after the end of the standard therapy (between 2 p.m. and 4 p.m.). No significant differences were found between the amount of standard compensation therapy regarding the two conditions (see Table 3). To reduce interference of fatigue effects and disruption of consolidation processes, resting periods of at least 20 minutes before and after

Table 2. Composition of working memory composites.

Weicker et al. (2018)	present study
Digit Span (forwards/backwards)	Digit Span (forwards/backwards)
Span Board (forwards/backwards)	Span Board (forwards/backwards)
PASAT	Letter-Number Sequencing
Spatial Addition	Digit-Symbol Coding
Symbol Span	
TAP n-back	

Note: The following tests were included in the composite score calculated by Weicker et al. (2018): Digit Span (forwards/backwards), Span Board (forwards/backwards), PASAT (Paced Auditory Serial Addition task (35)), Spatial Addition and Symbol Span (subtests from the Wechsler Memory Scale IV (36)), and TAP n-back (TAP = Test for Attentional Performance (37)). The present study used similar tests (Digit Span and Span Board tasks) but also other outcome measures (Letter-Number Sequencing, Digit-Symbol Coding) to assess working memory functions, because some tasks applied by Weicker et al. (2018) appeared too difficult or time-consuming for the current sample.

the training sessions were advised. To ensure high quality of the intervention, a trained supervisor was available for questions and provided feedback at the end of each session.

WM training

The applied WM training program *WOME* (WOrking MEmory; RehaCom®, Hasomed GmbH) was specifically tailored to the needs of patients with acquired brain injury. Its feasibility and efficacy were confirmed recently (18,19,30). The intervention (i) has a structure theoretically rooted in Baddeley's multicomponent model of WM and neurophysiological evidence on

Table 3. Sample characteristics.

	overall (n = 20)	working memory training group (n = 11)	attention training group (n = 9)	difference
sex (male/female)	10/10	5/6	5/4	$\chi 2$ = 2.02, p = .653
age *M (SD)*	48.5 (12.8)	48.4 (15.0)	48.8 (10.5)	T = 0.07, p = .945
education level (*n*)				$\chi 2$ = 3.39, p = .183
≤ 9 years	2	1	1	
10–12 years	11	8	3	
≥ 12 years	7	2	5	
premorbid intelligence				
LPS-3 (*M, SD*)	21.1 (6.8)	21.4 (8.4)	20.8 (4.6)	T = 0.19, p = .854
WST (*M, SD*)	27.9 (4.3)	26.4 (4.4)	29.7 (3.7)	T = 1.79, p = .09
months since brain injury *MD (SD, range)*	16.0 (85.2, 5–348)	14.5 (106.0, 5–348)	17.0 (59.5, 5–192)	T = 0.45, p = .656
medication (yes/no)	16/4	10/1	6/3	$\chi 2$ = 1.82, p = .178
mood (BDI-II: *M, SD*)	12.0 (7.0)	12.9 (8.4)	10.9 (5.01)	T = 0.63, p = .534
total hours of received therapy (*M, SD*)	112.5 (23.2)	107.0 (9.9)	119.2 (32.56)	T = 1.19, p = .251
total hours of received neuropsychological therapy (*M, SD*)	36.1 (8.0)	34.0 (8.7)	38.6 (6.58)	T = 1.29, p = .212

Note: BDI-II = Beck Depression Inventory II (31), LPS-3 = Subtest 3 of the German intelligence battery 'Leistungsprüfsystem' (32), WST = German verbal comprehension test (33). Sample size is n = 19 for month since brain injury due to missing data.

selective attention and inhibitory control (9,44), (ii) offers hierarchically ordered modules for distinct WM components, (iii) includes a fine-tuned automatic adaption of difficulty based on modifications of specific task features, and (iv) comprises a motivational training environment close to everyday life requirements by means of a common card game. A wide range of parameters can adjust task difficulty exactly to the individual's performance, e.g. item length, presence and number of distracting stimuli.

Attention training

One out of five modules from RehaCom® was applied each day: (i) alertness (fast reaction on targets presented on the screen), (ii) attention and concentration (comparison and identification of similar stimuli from a selection of samples), (iii) reaction behavior (fast and accurate reaction depending on various targets), (iv) exercises for attention (everyday life tasks that focus on concentration, e.g. identifying grammatical and orthographic errors in a letter), and (v) visuomotor coordination (requires tracing of moving objects with a computer mouse).

Statistical analyses

Training benefits in WM were analyzed with respect to improvements (highest level attained per session) in the trained task by dependent *t* tests for paired samples, feedback regarding the two interventions was inspected with Mann-Whitney U-test for independent samples. The dose-response relationship was investigated by repeated measurements analyses of variances (ANOVA) model with the between-subjects factor condition (WM training, attention training) and the within-subjects factor time point of assessment (T1, baseline; T2, assessment after 2 weeks of compensation therapy and 10 sessions of functional training; T3, post-assessment after 4 weeks of compensation therapy and 20 sessions of functional training). To investigate the time course in more detail, separate ANOVA models focusing only on T1 vs. T2, as well as on T2 vs. T3 were conducted. The specificity of the WM training content compared to attention training was inspected with a repeated measurements ANOVA model including T1 and T3 when all relevant outcomes were assessed. No covariates were included in the models. Transfer effects were examined based on composite scores of comprehensive cognitive functions: WM functions, other cognitive functions (attention, executive functions, verbal learning), and everyday life performance (for the detailed outcome measures, see Table 4). To compare the separate scoring systems, composite scores were calculated by averaging the standardized z-scores of each outcome, based on performance at T1. Transfer effects after 2 weeks were calculated by subtracting the standardized z-scores of T1 from T2; transfer effects after 4 weeks were determined by subtracting the standardized z-scores of T1 from T3.

All analyses were carried out with the Statistical Package for Social Sciences SPSS, version 22 (45). The 'last observation carried forward method' was applied in case of missing data. An overall significance level of $p < .05$ (two tailed) was used. Interactions were resolved by post-hoc *t* tests with Bonferroni's correction for multiple comparisons. Effect size estimates of ANOVAs are given by partial eta-squared ($\eta_p 2$), with $\eta_p 2 \geq 0.01$ indicating a small effect, $\eta_p 2 \geq 0.06$ a moderate effect, and $\eta_p 2 \geq 0.14$ a large effect; effect sizes for *t* test differences are indicated by Cohen's *d*, with $d \geq 0.2$ indicating a small effect, $d \geq 0.5$ a moderate effect, and $d \geq 0.8$ a large effect (46).

Results

Benefits of functional training

Improvement in the WM training task

The WM training group completed M = 19.78 training sessions (SD = 0.67), with a mean duration of M = 32.40 minutes per session (SD = 2.69). Overall, they practiced a total of M = 10.66 training hours (SD = 0.75). Participants exhibited constant progression of the mean level of difficulty, resulting in a significant improvement in the training task (first vs. last session: $t(10) = 6.84$, $p < .001$, $d = 2.56$; 1st vs. 10th session: $t(10) = -5.94$, $p < .001$, $d = 1.84$; 10th vs. 20th sessions: $t(7) = -3.92$, $p = .006$, $d = 1.77$). Means and individual courses revealed no indications of a plateau or ceiling effect (see Figure 2 for an illustration). Better WM

Table 4. Neuropsychological outcomes and time points of assessment.

T1: baseline assessment (before training)	T2: between assessment (after 10 training sessions)	T3: post assessment (after 20 training sessions)
working memory functions (Digit Span (forwards/ backwards), Span Board (forwards/backwards), Digit-Symbol Coding, Letter-Number Sequencing)	*working memory functions* (Digit Span (forwards/ backwards), Span Board (forwards/backwards), Digit-Symbol Coding	*working memory functions* (Digit Span (forwards/ backwards), Span Board (forwards/backwards), Digit-Symbol Coding, Letter-Number Sequencing)
attention (TAP Alertness, TAP Divided Attention)	*attention* (TAP Alertness, TAP Divided Attention)	*attention* (TAP Alertness, TAP Divided Attention)
executive functions (Stroop task)		*executive functions* (Stroop task)
verbal learning (CVLT)		*verbal learning* (CVLT)
everyday life performance (CFQ, FEDA)		*everyday life performance* (CFQ, FEDA)
control measures (general questionnaire, premorbid intelligence: WST, LPS-3; mood: BDI-II)		*control measures* (questionnaire on the interventions: feedback, applied strategies)

Note: After 10 training sessions (T2), only a subgroup of outcomes that measure working memory function and attention were assessed because of the small retest interval and the additional effort for the patients. BDI-II = Beck Depression Inventory II (31), CFQ = Canadian Failure Questionnaire (38,39), CVLT = California Verbal Learning Test (40), Digit-Symbol Coding and Letter-Number Sequencing = Subtests from the German intelligence battery WIE (41), FEDA = German questionnaire on subjective attention deficits (42), LPS-3 = Subtest 3 of the German intelligence battery 'Leistungsprüfsystem' (32), Stroop task (43), TAP = Test for Attentional Performance (37), WST = German verbal comprehension test (33).

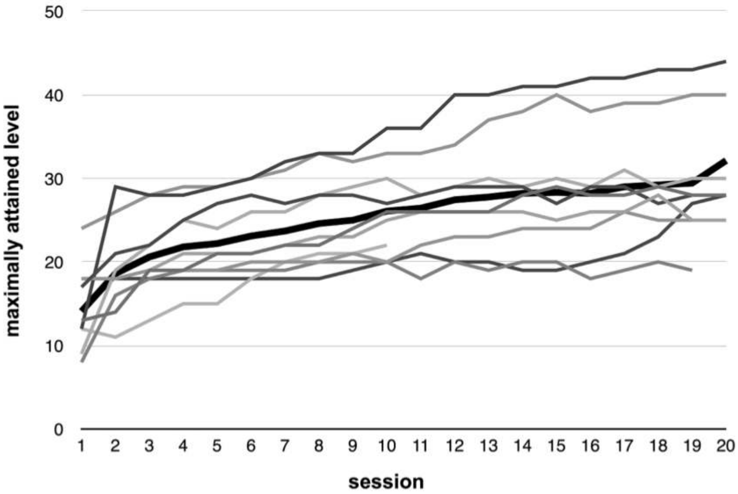

Figure 2. Performance in the trained working memory task. *Note*: The graph illustrates the performance of the working memory training group during the course of the 20 training sessions. The thin lines show the progression for each individual, the thick line represents the mean level. Depicted is the maximally attained level per session.

performance in the baseline assessment predicted larger improvements in the performance of the training task (e.g. Span Board task backwards: $\beta = 2.28$, $t(7) = 2.90$, $p = .03$). Due to the varying tasks applied in the attention training, group progression could not be formally analyzed; descriptively patients also showed improved performance.

Feedback

Both training interventions received positive feedback and were rated as comparably enjoyable (WM training group: $M = 4.20$, $SD = 0.42$, attention training group: $M = 4.13$, $SD = 0.64$). There were no differences in subjective effort and usual computer usage between the conditions ($p = .965$ and $p = .315$, respectively). Preferred strategies for solving the WM tasks were rehearsal ($n = 8$), chunking methods ($n = 5$), and memorization of selected items ($n = 5$). Five out of nine patients reported that they changed their task approach in the course of the intervention.

Dose-response effect

WM functions

Means and standard deviations of all neuropsychological outcomes are provided in Table S1. Significant improvements in WM functions were found in both groups (significant main effect of time in the WM composite: $F(2, 36) = 8.13$, $p = .001$, $\eta_p 2 = .31$; no time x condition interaction: $F(2, 36) = 0.19$, $p = .831$, $\eta_p 2 = 0.01$). Significant changes in WM performance were only found in the later training phase after 4 weeks of compensation therapy and 20 session of functional training ($F(1, 18) = 5.96$, $p = .025$,

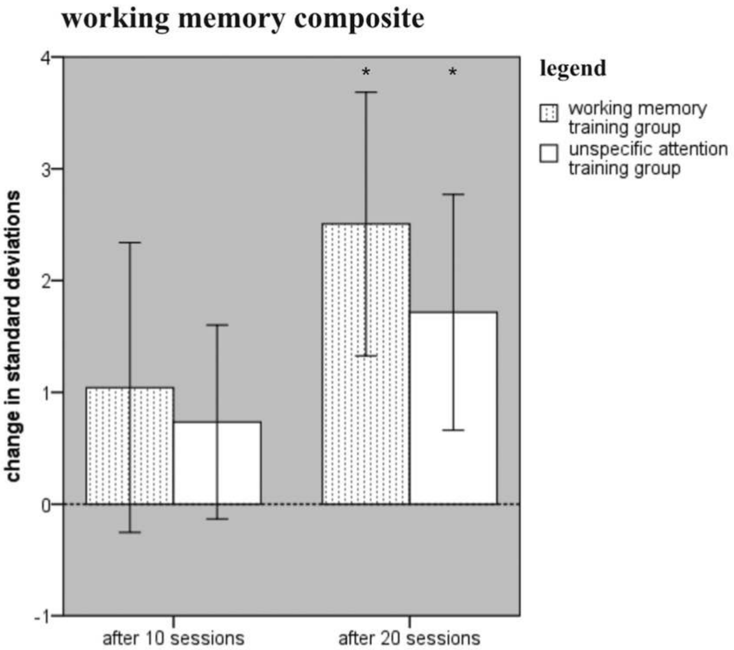

Figure 3. Dose-response effect. *Note*: The bars show significant gains from baseline to posttest in the working memory composite after 20 sessions of functional training. Error bars represent ± 1 standard error.

η_p2 = .25) but not in the early training phase after 2 weeks of compensation therapy and 10 sessions of functional training ($F(1, 18) = 2.25$, $p = .151$, $\eta_p2 = .11$); for an illustration see Figure 3.

Other cognitive functions

Neither a significant time x condition interaction nor a main effect of time point of assessment were found for the composite score of attention ($F(2, 36) = 0.36, p = .701, \eta_p2 = 0.02$, and $F(2, 36) = 0.93, p = .404, \eta_p2 = 0.05$, respectively).

Specificity of WM training

WM functions

No evidence for the specificity of WM training was found regarding superior improvements in WM functions compared to attention training (significant main effect for time point of assessment from T1 to T3, $F(1, 18) = 20.73$, $p = .000$, $\eta_p2 = .54$; no significant time x condition interaction, $F(1, 18) = 0.02$, $p = .882$, $\eta_p2 = 0.00$).

Other cognitive functions

A main effect for time point of assessment was found in the verbal learning composite indicating improvements in both training groups, $F(1, 18) = 11.93, p = .003, \eta_p2 = 0.40$. No other significant main effects were found ($F(1, 18) = 0.92, p = .351, \eta_p2 = 0.05$ for the attention composite, or $F(1, 18) = 3.92, p = .063, \eta_p2 = 0.18$ for executive functions) and no significant time x condition interactions were observed with respect to either composite scores of attention, $F(1, 18) = 0.00, p = .954, \eta_p2 = 0.00$, verbal learning, $F(1, 18) = 0.03$, $p = .869$, $\eta_p2 = 0.00$, or executive functions, $F(1, 18) = 0.28, p = .604, \eta_p2 = 0.02$.

Functional relevance to everyday life

Individual evaluation suggested functionally relevant improvements in everyday life functions after the interventions: 88% of the patients in the WM training group and 75% of the patients that underwent the attention training program reported that the interventions would have led to improvements in their daily routines. The everyday life situations, which were mentioned, are depicted in detail in Figure 4. Standardized questionnaires did not reflect these changes (daily life composite: $F(1, 18) = 0.00$, $p = .958$, $\eta_p2 = 0.00$).

Discussion

Rehabilitation of WM deficits is highly relevant for patients with acquired brain injury; however, as yet adequate intervention schemes and recommendations for the use in clinical practice are largely missing. We evaluated efficacy and modulators of combined compensation therapy and functional WM training addressing the dose-response relationship and the specificity of the cognitive training content.

Dose-response effects

We identified training intensity as an important moderator of efficacy: We were able to show that 4 weeks of standard compensation training and 20 sessions of additional computerized functional training (either WM or attention) led to significant improvement of WM functions, while no such effect was evident after 2 weeks of compensation training and 10 sessions of additional functional training. These results substantiate the justifiability of prolonged therapy or repeated periods of treatment in later stages of rehabilitation, given that our sample was in

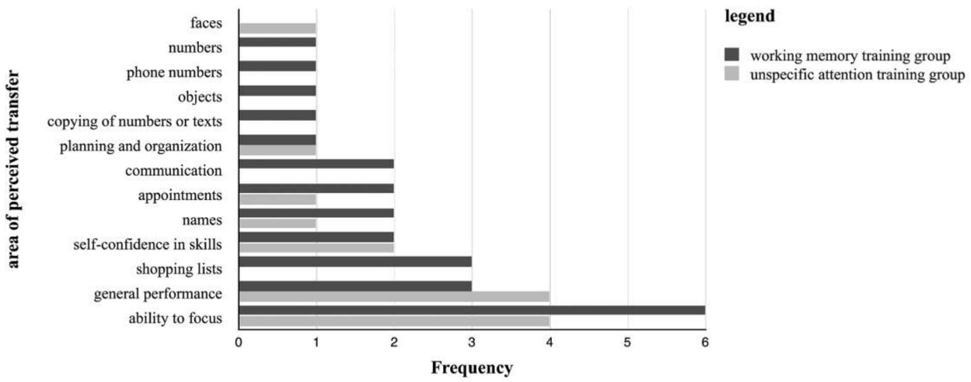

Figure 4. Functional relevance to every-day life performance. *Note*: The bars present subjective improvements in every-day life functions following treatment, mostly the ability to remember certain things but also changes related to attentional functions. Multiple statements were possible.

a chronic state (about 16 month post-onset). The majority of the patients reported relevant improvements in their daily routines, stating, for example, enhanced ability to focus, to remember shopping lists and to keep their appointments. In addition, both interventions yielded relevant transfer effects on verbal learning. No further transfer effects to other cognitive functions were seen in standardized tests (i.e. attention, executive functions). Although WM plays a crucial role in a number of cognitive domains, it is remarkable that in clinical populations, improvements of WM functions barely seem to induce transfer effects to other cognitive functions (12,14,15,18,20,21,47). We suggest that the effects may be either too small to be quantified or alternatively lesion size and location may limit such transfer. Alternatively, cognitive training may not have increased the capacity of the WM system in terms of a 'core' training intervention (48), but rather improved its efficiency in terms of learning a strategy (49,50). The new skills may have been broad enough to be applicable to similar tasks of WM and verbal memory, but they did not promote further transfer effects on other cognitive outcomes.

Specificity effects

We did not find improvements in overall WM functions when WM training was compared to the control intervention targeting attentional functions, while it has been observed in several studies before (18,19,30). We identified several explanations for the low specificity of the training content: a) insufficient statistical power to detect differences between the treatment conditions, b) large overlap of similar treatments provided by the standard compensation therapy in both conditions, or c) it may be attentional control rather than WM efficiency that results in transfer effects (51–53) – a process, which was explicitly required in the attention training program.

Of note, the training intervention of attentional functions did not result in an improved performance in untrained tests of attention. On the one hand, the effectivity of cognitive rehabilitation targeting attention has shown to be limited per se (54–56). On the other hand, our paradigm exercised diverse subdomains of attention with low intensity, while effective training should be intensive and adjusted to individual deficits (57). Without intending to do so, the results suggest that with this training approach, we improved attentional control and flexibility rather than primary attentional processes.

Clinical implications

The clinically pivotal question who benefits the most from cognitive training has not yet been addressed systematically in clinical contexts. Here we contribute some first evidence to the discussion. Post-hoc analyses of the data of the WM training group revealed that success in the trained task was partially predicted by higher performance in baseline measures of WM functions. Instead, there was neither a significant correlation of initial WM function and transfer effects on untrained WM tasks, nor a relation with age or time since injury onset. This so-called Matthew effect has been shown in other studies (58,59) and suggests that compute-based functional training should be offered to individuals with relatively mild deficits who face complex cognitive demands in their daily or professional life.

Limitations

Interpretations of the presented data are restricted by several issues that may have influenced the findings. First and foremost, sample sizes were small and power was low to detect differences between the treatment conditions. The trial, did, however, provide sufficient power to indicate that the observed positive effects of both training groups do not reflect mere time effects (34). Second, we included subjects with heterogeneous etiologies. Despite resulting in higher variance, we focused on clinical symptoms rather than homogeneous etiology, increasing chances to recruit eligible patients and to promote generalization of training effects. The recruiting of eligible participants is a common problem because they often struggle with fatigue, which limits their ability to engage in clinical intervention studies. Because of the difficulty to recruit large samples, we did not include an additional passive control group. Developing our paradigm we followed the recommendation for the implementation of an active control group, which is supported by leading researchers in the field of cognitive training (60). The lack of significant differences between the intervention groups makes the interpretation of the data difficult, i.e. the specific impact of the compensation therapy and the functional therapy remain open. We interpret the significant effect of time as an indicator of the effect of training intensity. Despite the absence of a no-treatment control group, it is unlikely that we observed a 'mere' time effect. The fact that we found changes of performances only at the third assessment, plus high reliabilities of the applied tests (see supplemental information S2) indicate that the changes we detected reflect not only test-retest effects.

Another caveat to be considered is that effects might partially stem from spontaneous recovery. Improvement of cognitive functions is understood to occur mainly within the first 3 months after stroke, the major cause of injury of the current sample (61,62), hence spontaneous recovery is unlikely based on the mean time since injury onset of about 1,5 years. Likewise aging might alter performance independent of the intervention. Since the interval between the assessments was only few weeks, we regard this effect, which moreover should counteract improvement, of negligible relevance. Last but not least, the short time separating the compensation therapy and the functional cognitive training may have led to difficulties in attention or interference effects in learning.

Conclusions

The presented study suggests that the combination of computer-based cognitive training and compensation therapy is effective in patients with acquired brain injury even after several years. It led to significant improvements in WM functions, verbal memory and self-reported functional benefits in daily life. Essentially, efficacy was dependent on training intensity, suggesting a dose-effect of neurocognitive rehabilitation. To achieve relevant transfer effects it seems imperative to provide a minimum of 20 training sessions. No evidence was found for the superiority of WM training compared to an attention training program, suggesting that various training content of attention and/or WM processes may lead to improvements in WM performance. Given the limited power of the study to detect differences between the treatment groups, it is for future studies to further investigate the dynamics of training intensity in relation to the applied tasks.

Declaration of interest

The authors declare that there is no conflict of interest. Hasomed GmbH, the company that distributes the cognitive training software 'RehaCom' evaluated in the present study, provided the interventions free of charge for the purposes of this research. From 03/2017 to 02/2019 as well as since 03/2020, Juliane Weicker is employed at Hasomed GmbH in the context of a new research project. The company was not involved in protocol designing, data analyses or interpretation of the results. The company did not read or approve the manuscript before submission.

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3. General discussion

This thesis aimed to bridge the gap between research and clinical practice with respect to neurocognitive rehabilitation of WM deficits. While literature on WM training studies in healthy populations is abundant and indicates beneficial effects in cognitive performance as well as in daily life, the empirical basis for clinical populations is rather limited. Given the importance of WM performance for many more complex cognitive functions and activities of daily life, it seemed imperative to explore the potential of WM training in people with low WM capacity. Therefore, existing training paradigms and evaluation studies were investigated with a special focus on patients with WM impairments (study I and II). Based on the insights of the meta-analysis and the literature review, the WM training program 'WOME' (WOrking MEmory) was developed, a theory-based intervention tailored to the needs of clinical populations (study III). One objective of the thesis was the thoroughly evaluation of the new intervention with double-blind, placebo-controlled, and randomized controlled trials to determine its potential and its limits to provide valuable recommendations for the use in clinical practice (study IV, V and VI). The main findings of the experimental work are summarized in the following section.

3.1. Summary of the empirical findings

Based on a meta-analysis integrating 103 individual WM training studies of various subjects groups (healthy children, younger and older adults, and clinical populations), **study I** (Weicker et al., 2016) showed that existing training programs are able to produce long-lasting improvements in trained and untrained WM tasks. These changes were reflected in improved coping with everyday life demands and disease-related symptom reduction in clinical populations. Small but reliable far transfer effects on other cognitive functions were found regarding cognitive control and logical reasoning, in contrast, the performance of attentional and long-term memory functions was boosted for a short period. The number of training sessions was identified as a main moderator of training efficacy, while the total amount of training hours, adaptivity of task difficulty and the applied training content seemed less relevant. Larger effect sizes in clinical populations indicated that patients who suffered from WM deficits may benefit to a greater extent than healthy subjects. Taken together, the results of the meta-analysis confirmed our hypotheses and supported the application of WM training in neurocognitive rehabilitation.

A typical outcome used to measure performance changes in WM functions is the Corsi Block-Tapping Task (Corsi, 1972). By reviewing studies which investigated the characteristics of this task, **study II** (Weicker et al., 2017) revealed that it is the complexity of task demands — involving visuospatial, executive and verbal components — that explains its sensitivity to changes after WM training. Consequently, the Corsi Block-Tapping Task was chosen as the primary outcome variable for the following evaluation studies.

Due to the lack of appropriate WM training interventions for patients with acquired brain lesions, **study III** comprised the development of the theory-based WM training WOME. Two pilot studies confirmed the feasibility of the program in individuals with low WM capacity. Moreover, pre-post comparisons of WM performance indicated cognitive improvements after intensive training. Based on the findings, the structure and implementation of the training tasks were revised and some aspects of the study design, e.g., outcome measures, were adjusted for the evaluation studies.

To determine the efficacy of the novel WM training program, **study** IV (Weicker et al., 2018) targeted 60 clinically healthy older adults — individuals having low WM capacity due to developmental changes but undamaged neural brain networks. After 12 sessions of WOME WM training, improved performance in the trained tasks and overall WM functioning were observed. Moreover, the subjects reported WM related improvements in their everyday life experiences (e.g., improved memorization of shopping lists, names, telephone numbers, and vocabularies in foreign language acquisition). However, the effects were short-term and diminished at follow-up after three month. No far transfer effects on other cognitive functions were found. The transfer effects found correspond to our hypotheses, but we expected long-term stability of the intervention effects.

Overall, the study demonstrated that WOME is an appropriate intervention for individuals with low WM capacity, which induces moderate to large transfer effects on WM functions and has an impact on everyday life. An fMRI analysis of the neural effects of WOME WM training indicated a redistribution of resources in fronto-parietal areas, which overlap with the WM network. Further, the findings suggested that training success may be mediated by inter-individual differences, i.e., initial WM capacity. We found confirmation of the so-called Matthew effect (MT 25:29 “whoever has will be given more” (Bakermans-Kranenburg et al., 2005; Rode et al., 2014)), describing that individuals with higher pre-training performance show larger improvements during and after training.

Study V addressed the applicability of WOME in the primary target group — 39 patients with acquired brain lesions who suffered from impairments in WM functioning. The intervention was well received and validity of the treatment was high. Using the similar design as the previous trial, WM training led to significant improvements in the performance of the trained tasks and self-reported cognitive changes in daily life. However, neuropsychological assessments failed to demonstrate reliable transfer effects on WM or other cognitive functions. Compared to the findings of study I and IV, the achieved effects were small. Our hypotheses were confirmed with respect to significant improvements in the trained tasks and facilitated handling of daily life demands reported in questionnaires. Further, as predicted no far transfer effects on other cognitive functions than WM were observed. In contrast, the hypotheses that significant changes would be observed in untrained WM tasks and that potential effects would be long-lasting over three months had to be rejected.

Based on study I that identified the number of training sessions as a modulator of training efficacy and indications of study IV and V that clinical populations may need longer training periods to gain substantial benefits, **study VI** (Weicker et al., 2020) targeted the dose-response relationship of WM training. Additionally, the influence of specificity of the training content was examined by comparing WOME to unspecific attention training tasks. To implement realistic conditions of use, the trial took place in a day care rehabilitation setting in 20 patients with heterogeneous brain lesions. While the specificity of training content seemed less important, the amount of training again represented an essential predictor of efficacy: No transfer effects were detectable after 10 sessions, but 20 sessions led to significant improvements in untrained WM tasks and verbal memory performance. Moreover, patients reported relevant impact in their daily life. Thus, the findings of study I and V were replicated and confirmed our hypothesis that subjective improvements would be observed in self-reports following WM training. Further, the results confirmed the predicted dose-response hypothesis and supported a certain specificity of the intervention (improved WM performance without influencing the attention system). In contrast, unexpected transfer effects were found on verbal memory and the WOME intervention did not lead to superior effects than a training program of attentional functions, so overall the hypothesis of the WOME intervention being specific for the WM system had to be rejected. Nevertheless, the findings support the effectiveness of WM training, even when applied in addition to highly intensive neurorehabilitation.

Taken together, the experimental work demonstrated beneficial effects of WM training in general and the novel program WOME in particular, showing the potential to improve WM performance and to have a clinically relevant impact on individuals with low WM capacity. The intervention was well-received and commitment was high. The findings suggest rather short-term than long-term benefits and the specificity of the applied training content may play a negligible role. Far transfer on other cognitive functions was limited. In order to yield substantial benefits in clinical populations, it seems imperative to provide a minimum of 20 training sessions.

3.2. Implications for clinical practice

First and foremost, WM training is effective. WOME reliably improves WM performance, perceived cognitive abilities and disease-related symptoms. By this means, a relatively circumscribed computer-based intervention contributes to participation in personal and professional life. The experimental work has shown that individuals of various age, education, etiologies, time passed since brain injury and rehabilitation settings may benefit from training.

3.2.1. Benefits and limits of working memory training

The observation of study I, IV, V and VI regarding moderate near transfer effects on tasks, which are more or less similar to those that are trained, is consistent with other meta-analyses targeting training of WM and executive functions (Au et al., 2015; Karbach & Verhaeghen, 2014; Melby-Lervåg et al., 2016; Melby-Lervåg & Hulme, 2013; Soveri et al., 2017). Study I and VI indicated small but significant far transfer effects on related cognitive functions (cognitive control, logical reasoning, and verbal memory), in contrast, study IV and V did not. Though some individual studies (Carretti et al., 2013; Lundqvist et al., 2010; Westerberg et al., 2007) and meta-analyses (Au et al., 2015; Karbach & Verhaeghen, 2014; Spencer-Smith & Klingberg, 2015) demonstrated transfer effects that go beyond WM functions, recent analyses that account for methodological issues argue that they are either very small or nonexistent (Dougherty et al., 2016; Melby-Lervåg et al., 2016; Redick et al., 2015; Schwaighofer et al., 2015; Soveri et al., 2017). Study I, IV, V and VI suggest that the improvements in WM performance lead to better coping with everyday life situations and to a relevant reduction of disease-related symptoms.

In agreement with the results, many authors claim that WM training may serve as an adjunctive therapy in clinical populations. Positive effects with significance in daily life have been reported in many other clinical populations, among them individuals with attention deficit hyperactivity disorder (for a meta-analysis, see Spencer-Smith & Klingberg, 2015), human immunodeficiency virus (Chang et al., 2017), substance abuse (Bickel et al., 2014; Houben et al., 2011), and low birth weight (Grunewaldt et al., 2016; Løhaugen et al., 2011). A prospective study in patients with stroke and traumatic brain injury suggested that WM training induces a redistribution of brain activity patterns, substantiating plasticity of the brain (Yun et al., 2016). However, there are also studies that did not show clinically relevant effects and some authors claim that the observed effect sizes are generally too small to be clinically relevant (Melby-Lervåg et al., 2016). Having said that, effect sizes of about 0.3 are similar to standard pharmacological or educational treatments and should be considered as useful (Spencer-Smith & Klingberg, 2015).

From the perspective that 'real-world' effects may be small, it seems plausible that the cost-benefit ratio of WM trainings keeps being questioned (e.g., Melby-Lervåg et al., 2016; Redick et al., 2015). Indeed, most commercial programs are time-consuming and possibly cost a lot of money — which both may be spent otherwise by individuals affected by WM deficits, their carers, involved schools or other institutions. This is of special concern in the pedagogical and developmental context when WM training may be favored over specific education (e.g., arithmetical training), occupational therapy or pharmaceutical treatment (Redick et al., 2015; Rode et al., 2014). The findings of the experimental work substantiate the argumentation that the learning of a specific skill should be preferred over general cognitive (WM) training if the acquisition of a desired behavior is focused. Functional therapy is, however, an efficient tool if the main emphasis is on common WM deficits impairing participation in various personal or professional life situations. Taken together, training WM functions is not a panacea, but it represents a specific intervention that improves the performance of the WM system with a relevant impact on the daily life.

3.2.2. The importance of training dose and its practical implementation

The findings of the thesis show that it is imperative to provide sufficient training to achieve functionally relevant effects: 1) data of study I showed a positive dose-response relationship for the number of training sessions and the resulting effect sizes of the interventions, 2) the comparison of the findings from study IV and V suggests that individuals with WM impairments may need more intensive training than healthy subjects, and 3) study VI showed significant improvements after 20, but not after 10 sessions of training. The influence of training intensity has been observed in several studies comparing low and high dose training schemes directly (Alloway et al., 2013; Bergman-Nutley & Klingberg, 2014; Chooi & Thompson, 2012; Jaeggi et al., 2008; Stepankova et al., 2014). In addition, it has been suggested that training success is not a threshold phenomenon; that is the more training, the better its effect (Jaeggi et al., 2008; Rogers et al., 2018). The majority of existing WM training studies in patients with brain injury have carried out interventions that comprised more than 20 sessions (M = 20.5, SD = 7.77 according to Online Resource 1 of study I). Only one study that targeted a clinical population has implemented a short-term intervention completed within one week and found some positive effects (Carretti et al., 2013).

Recommendations for training time schedules with respect to an optimal cost-benefit ratio are still missing. Study I suggests that the total amount of time spent in training as well as the duration of an individual training session (e.g., if it lasts 30 minutes or 45 minutes) seems to be less relevant. This is in line with the findings of a meta-analysis of WM and executive functioning trainings that reported no correlation of training hours and effect sizes (Karbach & Verhaeghen, 2014). Confirming the findings of study V and VI, numerous studies in patients with brain lesion have shown benefits after daily practice (Johansson & Tornmalm, 2012; Lundqvist et al., 2010; Westerberg et al., 2007). Research on learning and memory, however, suggest that time intervals are needed for consolidation, potentially explaining distributed sessions to be more effective (Goverover et al., 2009). Additionally, three or more training sessions per week might produce cognitive fatigue effects or decrease motivation (Lampit et al., 2014). Indeed, a meta-analysis of cognitive remediation after stroke observed higher effect sizes for treatments applied three times per week compared to treatments applied daily (Rogers et al., 2018). Penner and colleagues observed an advantage of a WM training program applied twice a week over eight weeks compared to the same intervention applied four times a week for four weeks in healthy adults (Penner et al., 2012). The effect was less pronounced when the same study design was conducted in patients with multiple sclerosis (Vogt et al., 2009). Taken together, there is not enough evidence to recommend a specific training time schedule yet, but current data justifies aiming at a minimum of 20 training sessions, applied three times per week. Though the findings of study I suggest that high training intensity promotes maintenance of achieved effects, there is no reliable data basis available for WOME because a follow-up assessment was not included in the design of study VI.

Hence, recurring training sessions as in physical exercise or learning processes in general are highly recommended to maximize long-term effects (Cepeda et al., 2008; Haskell et al., 2007).

The demand for high training intensity claimed by the research community poses a particular challenge in the context of clinical rehabilitation. In an early phase of rehabilitation basic attentional functions will have to be trained rather than WM, which is more challenging. In addition, the schedule for computer-based cognitive interventions in the clinic depends on organizational rather than clinical matters. The realization of highly intensive WM training schedules may conflict with competing interests or overall period of rehabilitation. Therefore, the continuation of functional training after discharge from clinical setting in form of home-based tasks is of high relevance and should be pursued in health care systems. If implemented accurately, home-based WM training has high potential, which was shown in a sample of patients with multiple sclerosis (Pedullà et al., 2016). That is why a new research project is currently implementing an online platform for both patients and therapists to provide cognitive rehabilitation suited for the individual's needs at home (Weicker et al., in press). By this means, the continuation of training but also the realization of intermittent training sessions may be facilitated.

3.2.3. The influence of inter-individual differences on training efficacy

The experimental work of study I, V and VI has revealed that evidence for functionally relevant transfer effects is neither robust nor consistent in clinical populations. A possible explanation is that transfer may be affected by other confounding variables, which may conceal the true individual training outcome. Inter-individual differences represent a source of large variance compared to the relatively small effects obtained by cognitive training (Hertzog et al., 2008). Hence, from the clinical perspective, one of the most relevant questions is: Who will benefit from WM training — and who might not? If several factors predicted the likelihood of a positive outcome, the decision whether a specific patient should be included in WM training or receive an alternative treatment would be facilitated. The contribution of the experimental work to the following variables and their potential impact are presented in this section: a) preserved cognitive resources, b) the slope of performance during training, c) age, and d) chronicity of an acquired brain lesion.

a) Preserved cognitive resources

Perhaps the most urging question is whether individuals with deficient cognitive abilities benefit most from WM training or whether it rather boosts the performance of individuals who are already high functional. The answer implies the justification of treatments with computer-based WM training, which may or may not be applied, during cognitive rehabilitation. Study I demonstrated higher effect sizes of patients with brain lesions compared to healthy subjects. The finding suggests that people with low WM performance — thus, those individuals who suffer from their WM deficits — experience large room for improvement and benefit the most of an intervention. This pattern has been observed in patients with acquired brain injury (e.g., Johansson & Tornmalm, 2012) and in healthy older adults (e.g., Zinke et al., 2012). A case report in individuals with Down syndrome revealed beneficial effects particularly in deficient cognitive domains (Costa et al., 2015). Of note, young subjects tend to perform close to ceiling in trained tasks and transfer measures, limiting performance increases and lowering the observed effect sizes (Price et al., 2014; Schmicker et al., 2016; Soveri et al., 2017). Because of the reduction of deficits and performance differences following treatment, it is referred to as compensation account.

In contrast, post-hoc analyses of the patient's data in study V and VI revealed that higher performance in baseline measures of WM functions correlated with larger training gains. The results indicate that individuals with higher initial WM performance benefit more from treatment than individuals with lower initial WM performance. The brain-behavior-correlation reported in study IV substantiates the findings and suggests that this effect holds true for the reallocation of neural activity patterns as well. In agreement with the results of the thesis, research in healthy subjects indicated that individuals with higher initial cognitive abilities improved more in trained WM tasks (and partially in transfer measures) than individuals with lower initial cognitive abilities (Bürki et al., 2014; Guye et al., 2017; Lövdén et al., 2012; Rode et al., 2014). Similar observations were reported in children with WM deficits, who benefited more when they had better initial intellectual and arithmetic abilities (Holmes et al., 2015; Swanson et al., 2015). Further, near transfer effects have been shown to be moderated by age and crystallized intelligence (Hering et al., 2017). These findings suggest that it is not only initial WM capacity but global cognitive functioning per se that determines success of cognitive training. Due to the magnification of existing differences between individuals, this is called Matthew effect or scissor effect (Bakermans-Kranenburg et al., 2005; Rode et al., 2014).

Studies IV, V and VI have confirmed that WM training is perceived as very demanding and tiring and requires a high level of sustained attention. Seeing that WM tasks stress more basic sub processes, it seems plausible that the application of WM training requires at least some preserved cognitive resources. To date it remains open whether there is (i) a minimum threshold for preserved cognitive functions, (ii) a linear relation between initial WM performance and training gains, or (iii) an optimal level of WM performance, enabling individuals to benefit most from training. It has been suggested that traditional therapeutic approaches like strategic training promote magnification effects, whereas process-based training like WM training support compensation effects (Lövdén et al., 2012; Titz & Karbach, 2014). Specific conditions under which the rate of learning may be influenced in low performers highlight the potential to reduce cognitive inequalities, e.g., by applying noninvasive brain stimulation (Katz et al., 2017; Looi et al., 2016).

b) The slope of performance during training

While the focus of interest has been on training efficacy rather than on progression during training, the experimental work in study I, IV, V and VI provided evidence that improvement during training does not correlate with transfer effects after training. It seems to be the continuous challenge of the training tasks rather than success within these tasks which influences effectiveness. No further data is available in clinical populations. In healthy subjects, a few mixed findings are reported with no clear conclusion overall (Bürki et al., 2014; Jaeggi et al., 2011; Richmond et al., 2014; Rode et al., 2014; Wiemers et al., 2019). By addressing the learning rate across training sessions, a link between the slope of the training curve and transfer effects was discovered, suggesting larger transfer effects after steeper learning rates (Bürki et al., 2014). If this applies to clinical populations, it would provide another explanation of inconsistent transfer effects: individuals with low WM capacity usually show flat and asymptotic curve progressions. Note, however, that study V and VI provide evidence that even low performing individuals improved their performance in the trained tasks, even at the end of the training phases.

c) Age

While study IV, V and VI as well as other studies in clinical populations did not find a significant correlation of age and improvement in WM functions (e.g., Johansson & Tornmalm, 2012), in healthy subjects it has been shown repeatedly that younger adults tend to benefit more from WM training than older adults, regarding both improvements in trained tasks (Bürki et al., 2014; Heinzel et al., 2014) and transfer effects (Brehmer et al., 2012; Dahlin et al., 2008), as well as regarding neural plasticity and changes in brain activation patterns (Brehmer et al., 2011; Dahlin et al., 2008; Hudl, 2019). Recent studies suggest a very complex relationship of initial cognitive abilities, improvement in the trained tasks and age (Bürki et al., 2014; Rhodes & Katz, 2017; Zinke et al., 2012). For example, these analyses revealed that age contributes less to training gains than initial WM performance. Age is of cause not independent of preserved cognitive functions as they decline with both, healthy aging and brain damage. Given a sufficient basic level of cognition, however, this might one reason why age is a negligible variable in clinical populations.

d) Chronification of an acquired brain lesion

In the post-acute phase after brain injury, the treatment of physical impairments and basic resilience as well as attentional functions receive priority (Bendz, 2000). Due to greater plasticity of the brain and more positive prediction of functional outcomes in earlier stages of rehabilitation (Hu et al., 2010), cognitive training in general and WM training in specific may have higher potential when applied promptly (Rogers et al., 2018). Differences in effectiveness of WM training depending on time passed since injury have been confirmed previously: Patients that experienced brain injury within the last 18 months expressed 77 % of clinically relevant improvements in a WM index compared to 39 % of patients whose events occurred more than 18 months ago (Hellgren et al., 2015). Once in the chronic phase of disease, no relation between the months since injury and training efficacy emerged (Johansson & Tornmalm, 2012). In line with this finding, study V and VI, which investigated individuals with chronic impairments years after incidence, did not observe a correlation between the time post-injury and training gains. The fact that we found only small effects of training, as discussed above, may however be due to the fact that we mainly included patients in the very chronic state (i.e., on average 39 and 16 months after injury, respectively). This assumption is supported by larger effects of two studies, which used WOME WM training in combination with exercises in semantic structuring (Richter et al., 2015, 2018), in brain injured patients who were treated approximately one to two months after brain injury. Despite its potential, clinical experience shows that the application of complex training tasks (such as WM training) are judged as too difficult in early stages after brain injury. There is no evidence that the application of WM training or other complex cognitive functions would lead to null effects or harm cognitive recovery after stroke, yet it seems reasonable to supply basic attention training first, followed by more complex cognitive functions including WM (Sturm et al., 1997; van de Ven et al., 2016). Considering the potential of early treatment and the finding that higher abilities predict larger training outcomes, WM training may be applied independently of the time since brain injury if sufficient cognitive functions are preserved.

3.3. Implications for working memory training research

A challenging issue in WM training research is to better understand the mechanism of transfer effects. A model has been proposed, which provides two mechanisms to explain enhanced performance in untrained WM tests after training: improved capacity and improved efficiency of the WM system (Bastian & Oberauer, 2014). Enhanced capacity emerges if there is a discrepancy of (environmental) demands and (individual) resources, that leads to an adaption of the system to fulfill the external requirements, e.g., more items that can be maintained in WM (Lövdén et al., 2010). This plasticity of the cognitive system will only occur if the system is able to cope with the demands; if they are too high, individuals may avoid excessive demand and develop task-specific strategies. In the course of training, automation of processes used in the trained task may alter performance. In either case, performance may improve due to better efficiency of the WM system but capacity does not change. Therefore, transfer will only occur for those tasks, which allow the application of the new strategies established during training, while generalization and far transfer effects only occur if WM capacity is improved (Bastian & Oberauer, 2014). If training does not increase WM capacity but WM efficiency, this model provides a possible explanation of the diverse and inconsistent observations of transfer effects in the literature, especially with respect to far transfer effects (Melby-Lervåg et al., 2016). In general, far transfer effects have been viewed critically by the research community. Skepticism towards the improvement of other cognitive functions than WM is based on (i) possible overestimation of effects due to small sample bias, (ii) diminished effects if only treated control groups are being investigated, (iii) enhanced sub processes which are basically similar to the trained tasks, (iv) result patterns which are difficult to interpret (e.g., improvements in other cognitions without considerable changes in WM performance), and (v) the practical relevance of very small effect sizes (Melby-Lervåg et al., 2016; Minear et al., 2016; Soveri et al., 2017).

The present experimental work of study IV, V and VI support the assumption that WM training promoted efficiency of the WM system rather than capacity. Although WOME did not convey strategies, the majority of subjects reported that they developed some kind of strategy during the course of the intervention. Some were rather general (e.g., rehearsal), others were specific coping behavior (e.g., calculating the sum of values from the playing cards). These strategies helped to accomplish the training tasks but may have prevented from larger transfer effects on WM measures or generalization to other cognitive abilities. By demonstrating improvements not only in a single WM measure but in composite scores of multiple WM tests and latent variables (study IV), it can be assumed that WOME did induce domain-general effects in terms of a core training program (Ackerman et al., 2005; Morrison & Chein, 2011). Additionally, participants reported relevant impact on their everyday life independently of the training context (study IV, V and VI). However, with exception of a small transfer effect observed in verbal memory in study VI, the lack of far transfer effects to other cognitive functions argues in favor of enhanced efficiency following WM training. This argumentation is substantiated by the fMRI analysis reported in study IV, which found increases of activation in the WM network following training, which has been interpreted as the recruiting of new resources to improve information processing — e.g., by the means of a new strategy.

Considering the question *what* aspect of the WM system is actually trained, literature suggests that similar underlying cognitive processes (e.g., updating) and shared neural networks allow transfer from training tasks to untrained transfer measures (Beatty et al., 2015; Buschkuehl et al., 2012; Dahlin et al., 2008; Harrison et al., 2013; Salminen et al., 2012; Waris et al., 2015). Hence, both training tasks and outcome measures should share at least some commonalities. In line with this assumption, study IV, V and VI provided significant correlations between the initial performance level in WOME and baseline measures of WM performance. Some researches go even further, proposing that WM training is nothing less than learning a new skill (Fellman et al., 2020). The argumentation is based on comparisons of various training and test paradigms that suggest that *all* transfer effects may be based on some kind of similarity with respect to stimuli or information processing (Holmes et al., 2019; Lindeløv et al., 2016). To elaborate on this point, differences of healthy subjects and clinical populations to show reliable transfer effects may be explained by the lesser ability of patients to learn these new skills (Fellman et al., 2020; Lindeløv et al., 2016). However, several studies observed patterns of transfer that do not fit within the basic assumption of shared underlying processes. For example, far transfer effects were observed without related improvements in WM outcomes (e.g., Nouchi et al., 2012).

An alternative mechanisms proposed is that improvements in WM outcomes are not based on enhanced WM processes but on increased attentional control (Greenwood & Parasuraman, 2016). Supporting this hypothesis, several studies have shown that training selective attention and distraction suppression resulted in improved WM performance (Schmicker et al., 2016; Shin et al., 2015). Study VI supports the argumentation by observing that both WM training and training of attentional functions enhanced performance in untrained WM measures. In conclusion, the basis of transfer is not yet fully explained, but our studies contributed to enlighten the issue providing evidence for (i) underlying commonalities of trained tasks and transfer measures, (ii) improved efficiency of the WM system rather than greater capacity, and (iii) an indication that increased attentional control may play a role in improved WM performance as well.

Another issue refers to the design of WM training studies. Study I showed that the majority of the published studies suffered from methodological limitations; among them the conceptual design of the control conditions. Most studies compared the intervention to a no-treatment control group. This is critical because they do not account for the impact of expectations, beliefs, social aspects, and motivation. Interestingly, a post-hoc comparison of trials that used active control groups and trials that used passive control groups revealed no significant differences in the effect sizes. This indicates that the choice of the control group is negligible from a statistical point of view — a common concern of researchers — but it is essential from a conceptual point of view to ensure methodological quality. Over the past few years awareness of this issue increased and leading researchers in the field of cognitive training even called journals to stop publishing studies with only no-treated control groups (Melby-Lervåg et al., 2016).

The recommendation for an implementation of active control groups was followed during the conceptual design of the evaluation studies. So in study IV, both an active and a passive control group were investigated. While the active control group provided data that was plausible and clear to interpret, the passive control group showed an inconsistent and ambiguous behavior, which was difficult to understand (e.g., significant improvements in some outcome measures with no comparable pattern in the other conditions so that test-retest effects seemed unlikely). This observation substantiated the need for active control conditions. Hence, in study V and VI, which focused on patients with acquired brain injury — a limited subject group per definition — only active control groups were scheduled. In contrast to pharmacological studies, where a placebo condition is easy to apply, in neuropsychological training it is tricky to define an active treatment condition that does not include the critical variable (WM). The difficulty in interpreting the results of the active control condition were obvious in study VI, where the differences found between the treatment groups were negligible (i.e., disentangling the effect of 'mere' time and dose-response relationship). Due to the lack of a passive control group, conclusions had to be drawn with caution and they were left open to question.

In conclusion, while active control groups are essential to promote the quality of cognitive training research, their implementation entail also confounding variables, which may be difficult to interpret. As a consequence, one may recommend a passive as well as an active control group, which however is difficult and time-consuming given that suitable patients are always difficult to recruit. Therefore, the researcher is tempted to accept the negative aspects of no-treated conditions; in addition, they make the organization of a trial easier, especially in clinical settings. Here, publishers are responsible to ensure methodological quality of the journal’s trials and that striving for it does not backfire on the author.

3.4. Critical comments and directions for future research

The presented studies face several methodological issues that may restrict the generalization of the findings. In study I, a meta-analysis of published WM training studies was conducted. Inspection of the literature revealed that WM research in general, and studies targeting clinical population in specific, lack adequate study designs. A common problem observed in translational research is that relatively small sample sizes are being investigated and passive control groups are used (Kühberger et al., 2014). This affects not only statistical power and validity of the interpretations of the individual studies but also contribute to publication bias in meta-analyses and inflate effect sizes in the body of scientific results (Earp, 2018; Melby-Lervåg et al., 2016; Spencer-Smith & Klingberg, 2015). Though it can be observed that during the last years, the quality of WM research has increased (e.g., higher prevalence of randomized controlled trials and implementation of active control groups), methodological issues continue to present important shortcomings in clinical studies (Rogers et al., 2018).

For this reason, the evaluation of WOME was approached striving for high demands of methodological quality following the criteria postulated for valid and reliable evaluations of WM training interventions: double-blind study design with an active control condition and sufficient sample size, multiple objective outcome measures per cognitive function, rigorous investigation of transfer effects considering sensible patterns, and assessment of long-term maintenance (Redick et al., 2015). All evaluation studies featured randomized controlled trials with double-blind, active control groups and transfer effects were assessed comprehensively by multiple neuropsychological outcomes. Additionally, assessments three months follow-up were included in study IV and V to investigate the stability of training effects. Despite the rigorous designs or may be because of it, the studies lacked to fully comply with sufficient sample size. To investigate the probability to detect transfer effects despite the relatively small sample sizes, the achieved power was computed post hoc for the evaluation studies. Given an alpha value of 0.05 and an estimated effect size of g = 0.60 according to study I, the achieved power for study IV was 0.74. The effect size of the WOME intervention yielded by study IV (d = 0.79) was then used to compute the achieved power for study V and VI, which was 0.78 and 0.52, respectively. Hence, the evaluation studies had a chance of about 50 to 80 % to identify transfer effects on WM functions. So, while the sample sizes of study IV and V may be considered as acceptable, study VI was clearly underpowered. One reason for the difficulty to recruit sufficient subjects was the decision to conduct the training sessions in a local setting to control for possible side effects (e.g., no distractions during the treatment, continuous and comparable feedback). Refraining from multi-center or home-based training entailed a huge organizational effort and access to a limited sample. Moreover, each training session was costly and time-consuming for staff and subjects (e.g., the time to get to the institution, various staff to ensure the double-blind procedure). Whereas the data collection in study IV and V was extended up to one year, the data collection in study VI was limited to six months due to organizational reasons. Within these time constraints it was not possible to include more subjects that were eligible according to the inclusion criteria and both willing and able to cope with the tight schedule in addition to their usual treatment in the rehabilitation setting.

Another limitation of the experimental work is that the long-term effect of the treatment with WOME remains unclear. Based on literature of cognitive remediation, it is reasonable to assume long-term benefits in patients with brain lesions (Rogers et al., 2018). Study I demonstrated that, in general, WM training programs yield benefits which may be maintained over several months. However, study IV and V did not observe significant transfer effects at 3-month follow-up assessments, most likely because of the insufficient number of training sessions (cf. study I; Karbach & Verhaeghen, 2014). Moderate effect sizes, though not significant, indicated at least some evidence of stability in elderly adults. Due to organizational reasons, a follow-up measurement was not included in study VI, hence, evidence could not be provided for long-lasting transfer effects in clinical populations.

Although the experimental work confirmed WOME as a valid intervention targeting the WM system, study VI did also indicate that the specificity of the treatment may not be as high as expected. No superior efficacy was observed when it was compared to an unspecific training of attentional functions. In addition to the explanation that the lack of significant differences between the treatments is based on insufficient statistical power or the large overlap of standard therapy applied due to the rehabilitation setting, another possibility is that specific therapy actually may not be as important as assumed. Attention and WM may be such basic cognitive processes that highly specific interventions are either not required or both, training of WM and attention, are equally effective (cf. Schmicker et al., 2016; Shin et al., 2015). Alternatively, it has been argued that the importance of training specificity may increase during the course of an intervention, suggesting that first more general processes are promoted (e.g., information processing, selective attention) and only later more specific processes (e.g., executive aspects of the WM system) are engaged (Jaeggi et al., 2011; Salmi et al., 2018). Furthermore, a recent meta-analysis of cognitive remediation following stroke (Rogers et al., 2018) found no difference in effectiveness of cognitive training (i.e., repetitive tasks to improve specific abilities) and cognitive rehabilitation (i.e., strategies and skills), suggesting that various approaches and types of interventions may lead to the same functional outcome.

When the idea of process-based cognitive training was introduced, the major focus of WM training research was to determine its effectivity: Evaluation studies yielded significant gains in trained tasks, improvements similar but untrained WM tasks, transfer effects on other cognitive domains, exciting ones such as intelligence, and a relevant impact on everyday life (Jaeggi et al., 2008; Klingberg et al., 2005; Westerberg et al., 2007). Following the initial euphoria, reviews and meta-analyses have been more skeptical, pointing out methodological and conceptual shortcomings (Melby-Lervåg et al., 2016; Melby-Lervåg & Hulme, 2013; Shipstead et al., 2012; Weicker et al., 2016). In recent years, the research focus shifted from exploring *whether* WM training works to investigate for *whom* and *under what conditions* it may be most effective (Meiran et al., 2019; Wiemers et al., 2019). Study I emphasized that WM training interventions were remarkably heterogeneous regarding the applied training tasks, participants, and outcome measures, an aspect that is certainly responsible for inconsistent findings and vague conclusions. Further, the meta-analysis showed that existing interventions for clinical populations mostly comprised a compilation of various exercises. Despite referred to as WM training, many programs actually consisted of short-term memory tasks and neglect central executive processes. These so-called 'kitchen sink' programs do not yield information about components or task features that are critical for efficacy. They have proven to be effective, which is of cause the most important issue for the potential application in clinical practice. However, in order to understand *what* is trained due to *which* changes in underlying brain structures and networks, it is essential to develop training tasks that are theory-based and accordingly, guided by hypotheses. Only by naming a clear theoretical framework, aspects that are primarily accountable for transfer effects in clinical populations will be identified. Hence, unspecific WM training interventions may be effective but they neither support the understanding of relevant characteristic nor lead to an efficient application.

In this vein, this thesis contributed to the research community by providing a modularized training program that enables further inspection of relevant attributes. WOME offers a clearly organized structure that targets differential WM functions. Study IV already indicated that specific components are being influenced by training (i.e., on the one hand the theoretically motivated construct of span measures and on the other hand a data-driven cluster, which reflects most likely enhanced updating performance). By investigating the impact of single or combined components, future studies will identify which task features lead to which transfer effects and determine whether the efficiency of the applied training content may follow a particular timeline. Continued research on potential modulators of training efficacy including inter-individual variables, such as motivation (Au et al., 2015; Jaeggi et al., 2014) and individual beliefs (Alesi et al., 2015), is required along with cost-benefit analyses to optimize and individualize cognitive therapy following brain injury.

3.5. Conclusion

Impairment in WM performance affects quality of life and recovery following brain injury. The experimental work presented in this thesis substantiates and extends previous findings regarding the benefit of training WM functions from a clinical point of view. Specifically, a novel WM training was developed that is tailored to the particular needs of individuals with low WM capacity. Three consecutive randomized controlled trials highlighted that the new intervention WOME does not only improve the performance in the trained WM tasks, but it leads to improvement in overall WM functioning with moderate to large effect sizes. Moreover, participants reported functional benefits in their daily life. These were also present when the treatment was applied in addition to highly individualized therapy in a clinical rehabilitation setting. In contrast, only limited evidence was found for far transfer effects on other cognitive functions. Together, these findings support the application of WM training in individuals with acquired brain injury as it represents an effective resource to reduce the impact of functional deficits in their daily life.

The theory-based development of WOME and its modularized structure will enable future studies to further explore the underlying mechanisms of WM training and to determine relevant task features promoting transfer effects. For the application in clinical rehabilitation, however, targeting specific components seems less relevant than the combined effect of intervention tasks, inter-individual differences and external factors that 'makes WM training work'. Crucially, it was shown that training efficacy is strongly determined by training dose, i.e., the number of training sessions. To achieve functionally relevant effects, it is imperative to provide at least 20 training sessions applied about three times per week. Further, results suggest that the application of the intervention is not suitable for everyone. Patients with mild deficits seem to benefit more from WM training than patients with severe impairments in cognitive abilities. To translate the findings of this thesis into clinical practice, therapists should offer the intervention to individuals with low but sufficient WM capacity and strong motivation, independently of their age and time since injury. The presented work highlighted the potential and the limits of WM training, and by this means contributed to a deeper and more complete understanding of its use in neuropsychological rehabilitation.

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5. Summary

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Development and evaluation of an adaptive working memory training intervention

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Dissertation

Working memory (WM) is an essential component of cognitive processing, which determines many complex functions, for example, to communicate with each other, to make appropriate decisions, and to learn new skills (Alloway & Alloway, 2010; Miyake, 1999). The WM system consists of a storage component, which keeps relevant information in an active state, and a manipulating component, which processes and integrates information (Miyake, 1999; Baddeley, 2007). In doing so, WM acts as the brain's 'Post-it note': it keeps a specific goal temporarily present while preparing multiple steps for further action. Impairments in WM are observed during normal aging and after damage of the brain, e.g., stroke or traumatic brain injury (Nyberg et al., 2014; Hinkeldey & Corrigan, 1990). Individuals with WM deficits may experience forgetfulness, distractibility, difficulty to understand complex written text passages and incapability to execute tasks simultaneously (Hinkeldey & Corrigan, 1990). Treatment of WM impairments after acquired brain injury plays an important role in recovery, resumption of work and participation in daily life (Baumann et al., 2014; Lundqvist et al., 2010). While research in healthy individuals indicated that WM performance may be improved by repetitive training (Bastian & Oberauer, 2014; Morrison & Chein, 2011), so far little was known about benefits in cognitive rehabilitation. First intervention studies in the late 2000s yielded promising findings, indicating a positive impact on cognition, health and wellbeing (Lundqvist et al., 2010; Vogt et al., 2009; Westerberg et al., 2007). However, evidence was limited and there was no appropriate intervention specifically tailored to the patients' needs. The present thesis tackled these issues and explored the potential and limits of WM training in clinical populations. The aim of the experimental work was to develop a theoretically grounded intervention for individuals with low WM capacity, to determine its effectiveness in clinical treatment, and to identify modulators that may influence its efficacy.

SUMMARY OF DISSERTATION

Experimental Work

Study I and II focused on the analyses of existing research on WM training and neuropsychological outcome measures by means of a meta-analysis and a literature review. On this basis, study III describes the development process of the novel intervention WOME (WOrking MEmory). Study IV, V and VI represent double-blind, placebo-controlled, and randomized trials to evaluate its efficacy and application in clinical practice.

Study I (Weicker et al., 2016, publication 1) is a meta-analysis of N = 103 WM training trials with a pretest-posttest design, targeting various subject groups and focusing on patients with acquired brain injuries. The results suggested that repetitive training sessions lead to significant, long-lasting improvements in trained and untrained WM tasks with moderate to large effect sizes, and small transfer effects on other cognitive functions (i.e., cognitive control and logical reasoning). Increased WM performance correlated with disease-related symptom reduction and coping with daily life demands (e.g., self-reports of subjects regarding memory failures). By investigating variables, which may influence training efficacy, the number of sessions but not the amount of training hours was identified as a main moderator of the effect size. In contrast, adaptivity of the degree of difficulty or the specific training tasks had no significant effect on the outcome variables. A comparison of healthy subjects and clinical populations showed larger effect sizes in patients, arguing for the application of WM training in neurocognitive rehabilitation.

Study II (Weicker et al., 2017, publication 2) took a closer look at the Corsi Block-Tapping Task (Corsi, 1972), one of the outcome measures most frequently used to assess performance changes in WM functions. The review summarizes the historical development of the test, describes its characteristics and modulators of difficulty, and presents studies that investigated the underlying cognitive processes of the task. The analysis revealed that the sensitivity to training-related changes derives from the complexity of task demands, which include visuo-spatial, verbal, and executive components of WM. Due to its indication of WM training success, this outcome was selected as primary outcome variable for the evaluation studies.

Study III comprises the development process of the new intervention WOME. Rooted in Baddeley's multicomponent model of WM (Baddeley, 2003) and taking the framework conditions of WM trainings proposed by Perrig et al. (2009) into account, important task characteristics are presented that respond to the special needs of patients with WM deficits. Two consecutive pilot studies in N = 7 healthy adults (mean age = 64.4 years) and in N = 6 individuals with acquired brain injury (mean age = 43.2 years, heterogeneous etiologies) confirmed the feasibility of the program as well as compliance with the training schedule and the outcome measures. Based on analyses of performance in the trained tasks, the composition of the intervention was revised.

Study IV (Weicker et al., 2018, publication 3) evaluated the efficacy of the novel intervention in healthy older adults. N = 60 individuals (mean age = 67.7 years) were randomized to a) the WOME intervention (n = 20), b) a non-adaptive control version of the intervention with very low WM demands (n = 20), or c) a passive control group (n = 20). An extensive battery of neuropsychological tests and questionnaires were assessed at three time points: at baseline before training, immediately after the training phase, and at a three months follow-up. Additionally, functional magnetic resonance imaging (fMRI) scans were carried out to examine the brain activity pattern changes following WM training. These data are reported elsewhere (Hudl, 2019). Twelve sessions of WM training led to significant improvements in the trained tasks and overall WM function with moderate to large effect sizes, which was shown by increased performances in an untrained WM task (Corsi Block-Tapping Task, the primary outcome variable) and in two different composite scores of WM tests. Additionally, the subjects reported WM related improvements in their everyday life, e.g., better memory for shopping lists and names. However, no transfer effects on other cognitive functions were observed. Evidence for the stability of the effects at three months follow-up was small. An analysis of inter-individual differences revealed that individuals with higher initial WM capacity showed larger improvements during and after training, confirming the so-called Matthew effect (MT 25:29 "whoever has will be given more" (Bakermans-Kranenburg et al., 2005; Rode et al., 2014)). Overall, the findings suggested that WOME is an efficient training program to enhance WM functions and to have a relevant impact on daily life.

Study V evaluated the efficacy of WOME in the primary target group. N = 39 patients with stroke or traumatic brain injury (mean age = 50.2 years) received either a) the WOME intervention (n = 20), or b) the non-adaptive control version of the intervention (n = 19) over four weeks. The neuropsychological assessments and the training phase were similar to the previous trial. Subjects who underwent WM training showed significant improvements in the trained tasks and experienced more changes in daily life compared to the control group. In contrast to study IV, no transfer effects on untrained WM tests were observed at post-test. Taken together, the study confirmed the validity of the intervention and produced first evidence of its efficacy in patients with acquired brain injury, but due to the absence of transfer effects, the proof of effectiveness was still pending for the primary target group.

Study VI (Weicker et al., 2020, publication 4) targeted the dose-response relationship of WM training and the specificity of the training program, i.e., whether changes occur only in WM functions after WM training, and whether the effects differ from training attentional functions. N = 20 patients with heterogeneous brain lesions (mean age = 48.6 years) were randomized to a) the WOME intervention (n = 11), or b) training of attentional functions (n = 9). To investigate the dose-response effect, neuropsychological assessments took place prior to the training phase, after two weeks (10 sessions), and after four weeks (20 sessions). Indeed, the amount of training modulated efficacy: 20 sessions of training led to significant improvements in untrained WM tasks and in a related cognitive function (verbal memory), whereas no transfer effects were evident after 10 training sessions. Similar to the previous trials, subjects stated that they experienced positive changes in their everyday life following training. No significant differences were found between the training conditions, hence, specific task characteristics during training seem less important. Of note, the trial was carried out in addition to highly intensive neurorehabilitation in a day care rehabilitation setting. Thus, the study demonstrated not only the effectiveness of WM training in patients with brain lesions; moreover, it supported the positive effect of additional WM training even in chronic stages after brain injury.

SUMMARY OF DISSERTATION

Conclusions

This experimental work created a solid basis of a theoretically grounded and effective WM training program specifically tailored to the needs of individuals with low WM capacity. The evaluation studies confirmed beneficial effects on trained and untrained WM tasks with moderate effect sizes, demonstrating the potential to improve overall WM functions. The observed effects are consistent with recent meta-analyses targeting training of WM and executive functions in other populations (Karbach & Verhaeghen, 2014; Melby-Lervåg et al., 2016; Soveri et al., 2017). Reports of the subjects suggest that the WOME intervention may have a positive impact on daily life, facilitating to deal with WM demands (e.g., to remember names and faces). Efficacy was shown for individuals of various age, etiologies, and time periods since brain injury. Thus, a relatively circumscribed computer-based intervention like WOME may serve as adjuvant therapy for cognition and social as well as vocational participation.

In agreement with our findings, positive effects of WM training on disease-related symptoms were observed in other clinical conditions as well, for example, in attention deficit hyperactivity disorder (Spencer-Smith & Klingberg, 2015) and substance abuse (Bickel et al., 2014; Houben et al., 2011). Benefits of WM training, however, are largely limited to WM functions. While study I and VI observed significant small transfer effects on related cognitive functions (cognitive control, logical reasoning, and verbal memory), study IV and V did not find changes that go beyond WM. These controversial findings are discussed in ongoing debates within the research community, because authors of some individual studies (Carretti et al., 2013; Lundqvist et al., 2010; Westerberg et al., 2007) and meta-analyses (Au et al., 2015; Karbach & Verhaeghen, 2014; Spencer-Smith & Klingberg, 2015) argue in favor of „far“ transfer effects on related cognitive functions. In contrast, reanalyses that account for methodological issues ascertain that far transfer effects are negligible (Dougherty et al., 2016; Melby-Lervåg et al., 2016; Redick et al., 2015; Schwaighofer et al., 2015; Soveri et al., 2017).

This experimental work contributes to the question which aspect of the WM system is actually trained by confirming that underlying commonalities of trained tasks and transfer measures play an important role (Buschkuehl et al., 2012; Lindeløv et al., 2016) and that it may be efficiency of the WM system and not capacity that is improved by training (Bastian & Oberauer, 2014). Taken together, WM training is an efficient functional treatment of WM deficits, leading to improved coping with related issues in daily life situations.

One of the main objectives of the thesis was to contribute significantly to translational science, that is, to bridge the gap between research and practical application. Study I, IV, V and VI indicated that the number of training sessions determine training efficacy. Further, the effects of WM training were found to be rather short-termed and demand intermittent training sessions to maintain the effects achieved. Both claims are a particular challenge for the practical application of WM training in the context of clinical rehabilitation. Due to the limited possibilities during an inpatient stay, depending on organizational rather than clinical matters, extended training time implies the continuation of functional training with home-based tasks. A first attempt to provide an online platform for both patients and therapists is currently under evaluation (Weicker, 2020).

The findings of study I, IV, V and VI facilitate the decision whether a specific patient should receive WM training or an alternative treatment. Among the inter-individual variables which were analyzed, preserved cognitive resources have the strongest predictive value of training gains. That is, the higher the WM performance at baseline, the better the benefit from the intervention. Another variable of interest is the time passed since brain injury. Even if training seems to be more effective in earlier stages of rehabilitation (Hellgren et al., 2015), the trials confirmed a positive effect in the chronic phase of disease (i.e., after approximately 1.5 years). Moreover, once individuals reached a chronic state, no correlation between the months since injury and training efficacy was detectable. To summarize, WM training should be offered to patients with low but sufficient WM capacity, independently of their age, etiology and time since injury. While the modularized structure of the novel intervention WOME will enable future research to explore the underlying mechanisms of WM training, it is the combined effect of task characteristics, inter-individual differences and factors of the training scheme that 'makes WM training work' in clinical rehabilitation.

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6. Zusammenfassung

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Entwicklung und Evaluation eines adaptiven Arbeitsgedächtnistrainings

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Dissertation

Das Arbeitsgedächtnis (AG) ist ein grundlegender Bestandteil der menschlichen Informationsverarbeitung und beteiligt an vielen 'höheren' kognitiven Funktionen, z.B. Kommunikation, Intelligenz und Lernen (Alloway & Alloway, 2010; Miyake, 1999). Es besteht aus einer Speicherkomponente, die relevante Informationen aufrechterhält, und einer Manipulationskomponente, die Inhalte verarbeitet und zueinander in Beziehung setzt (Miyake, 1999; Baddeley, 2007). Das AG entspricht dem Schreiben eines Notizzettels: man hält ein Ziel und dafür relevante Informationen fest, während man sich um andere Dinge kümmert oder weitere Handlungsschritte vorbereiten kann. Einschränkungen in der AG-Leistung lassen sich einerseits bei normalen Alterungsprozessen beobachten, andererseits können diese auch nach Schädigungen des Gehirns, z.B. einem Schlaganfall, auftreten (Nyberg et al., 2014; Hinkeldey & Corrigan, 1990). Betroffene berichten von vermehrter Vergesslichkeit und Schwierigkeiten, mehrere Aufgaben gleichzeitig zu erledigen (Hinkeldey & Corrigan, 1990). Die Behandlung von AG-Defiziten spielt eine wichtige Rolle beim Erfolg von Therapien, beruflicher Reintegration und Teilhabe am alltäglichen Leben (Baumann et al., 2014; Lundqvist et al., 2010). Während Studien mit gesunden Erwachsenen darauf hinweisen, dass wiederholtes Training zu verbesserter AG-Leistung führt (Bastian & Oberauer, 2014; Morrison & Chein, 2011), lagen am Beginn dieses Promotionsprojektes zum Einsatz in der klinischen Neurorehabilitation kaum Erkenntnisse vor. Erste Interventionsstudien fanden vielversprechende Effekte (Lundqvist et al., 2010; Vogt et al., 2009; Westerberg et al., 2007), die Datengrundlage war jedoch gering und kein geeignetes Behandlungsprogramm verfügbar. Die vorliegende Dissertation diente daher der Erforschung des Potentials und der Grenzen von AG-Trainings bei Patienten mit erworbenen Hirnschädigungen.

Ziel war es, ein theoretisch fundiertes und speziell für Individuen mit geringer AG-Kapazität konzipiertes Programm zu entwickeln und dieses hinsichtlich seiner Wirksamkeit zu evaluieren.

Experimentelle Arbeiten

Studie I und II konzentrieren sich auf die Analyse bisheriger Forschungsarbeiten zu AG-Trainings und geeigneten neuropsychologischen Verfahren mittels einer Metaanalyse und eines Literatur-Reviews. Auf dieser Grundlage wurde das neue AG-Training WOME (WOrking MEmory) konzipiert, dessen Entwicklungsprozess in Studie III beschrieben ist. Studie IV, V und VI stellen doppelblinde, placebo-kontrollierte und randomisierte Evaluationsstudien dar, die die Wirksamkeit und praktische Anwendung von WOME im klinischen Kontext untersuchten.

Studie I (Weicker et al., 2016, Publikation 1) ist eine Metaanalyse von N = 103 AG-Trainingsstudien mit einem Vorher-Nachher-Test Design bei verschiedenen Personengruppen mit Fokus auf Personen mit erworbenen Hirnschädigungen. Die Ergebnisse zeigen, dass wiederholtes Training zu signifikanten, langfristigen Verbesserungen in trainierten und nicht trainierten AG-Aufgaben mit mittlerer bis großer Effektstärke führen. Darüber hinaus fanden sich kleine Transfereffekte auf weitere kognitive Funktionen (kognitive Kontrolle und logisches Schlussfolgern). Die Steigerung der AG-Leistungen führte bei Betroffenen zu einer Verringerung der wahrgenommenen Einschränkungen im Alltag. Als Variable, die einen entscheidenden Einfluss auf die Wirksamkeit von AG-Trainings hat, wurde die Anzahl der absolvierten Trainingseinheiten identifiziert. Keine Relevanz schienen dagegen die Gesamtzahl der Trainingsstunden und die konkreten Trainingsaufgaben zu haben. Ein Vergleich von Gesunden und Patienten zeigte höhere Effektstärken in klinischen Populationen, sodass der Einsatz von AG-Trainings in der klinischen Neurorehabilitation sinnvoll scheint.

Studie II (Weicker et al., 2017, Publikation 2) untersuchte die Corsi-Blockspanne (Corsi, 1972) als eines der am häufigsten verwendeten Verfahren, um Veränderungen in AG-Leistungen abzubilden. Das Literatur-Review stellt die historische Entwicklung des Tests dar, beschreibt seine

Eigenschaften und Moderatoren der Aufgabenschwierigkeit, und präsentiert Studien, die an der Aufgabe beteiligte kognitive Prozesse identifizierten. Die Analyse deckte auf, dass der Test eine Vielzahl komplexer Anforderungen stellt, darunter an visuell-räumliche, verbale und exekutive Aspekte. Aufgrund der hohen Sensitivität für trainingsinduzierte Veränderungen wurde das Verfahren als primäre Outcome-Variable für die Evaluationsstudien (Studie IV, V, VI) gewählt.

Studie III beschreibt den Entwicklungsprozess der neuen Intervention WOME. Auf Basis von Baddeleys Multi-Komponentenmodell (Baddeley, 2003) und geltenden Empfehlungen zur Umsetzung von AG-Trainings (Perrig et al., 2009) wurden Aufgaben für die Bedürfnisse von Patienten mit AG-Defiziten konzipiert. Zwei Pilotstudien mit N = 7 älteren Erwachsenen (Mittelwert = 64.4 Jahre) und mit N = 6 Personen mit erworbenen Hirnschädigungen heterogener Ätiologien (Mittelwert = 43.2 Jahre) bestätigten Machbarkeit und Umsetzung von Trainingsprogramm, Zeitplan und neuropsychologischen Outcome-Maßen. Auf Basis der Leistungen und Beobachtungen wurden die Struktur des Trainings und Aspekte des Studiendesigns überarbeitet.

Studie IV (Weicker et al., 2018, Publikation 3) evaluierte die Wirksamkeit der neuen Intervention an gesunden, älteren Erwachsenen. N = 60 Probanden (Mittelwert = 67.7 Jahre) wurden randomisiert folgenden Bedingungen zugewiesen: a) dem neuen AG-Training (WOME; *n* = 20), b) einer nicht-adaptiven Kontrollversion mit geringen Anforderungen an das AG (*n* = 20), oder c) einer passiven Kontrollgruppe (*n* = 20). Vor und nach der Trainingsphase, sowie nach einem Intervall von drei Monaten, wurden umfassende neuropsychologische Tests und Fragebogen erhoben. Darüber hinaus wurde die neuronale Plastizität nach dem Training mittels funktioneller Magnetresonanztomografie (fMRT) zu den drei Testzeitpunkten erhoben. Diese Ergebnisse werden an anderer Stelle berichtet (Hudl, 2019). Zwölf Trainingseinheiten mit WOME führten zu signifikanten, aber eher kurzfristigen Steigerungen in den trainierten Aufgaben und der generellen AG-Leistung mit moderaten bis großen Effektstärken. Dies konnte durch Leistungssteigerungen in untrainierten AG-Tests (Corsi Blockspanne, die primäre Outcome-Variable; verschiedene Composite Scores) gezeigt werden. Darüber hinaus berichtete die Interventionsgruppe von positiven Auswirkungen im Alltag, z.B. dem besseren Merken von Namen und Gesichtern.

Transfereffekte auf weitere kognitive Funktionen wurden nicht beobachtet. Eine Analyse der interindividuellen Unterschiede deckte auf, dass Personen mit höherer AG-Kapazität während und nach dem Training größere Leistungssteigerungen zeigten als Personen mit geringerer AG-Kapazität. Insgesamt wiesen die Ergebnisse der Studie darauf hin, dass WOME ein wirksames Trainingsprogramm zur Verbesserung der AG-Funktionen ist und positive Auswirkungen auf den Alltag erzeugen kann.

Studie V evaluierte die Wirksamkeit von WOME in der primären Zielgruppe. N = 39 Patienten (Mittelwert = 50.2 Jahre) mit Schlaganfall oder Schädel-Hirn-Trauma erhielten über vier Wochen entweder a) das AG-Training (n = 20), oder b) die nicht-adaptive Kontrollversion (n = 19). Untersuchungszeitpunkte und Trainingsphase entsprachen der vorausgegangenen Studie. Das AG-Training führte zu signifikanten Leistungssteigerungen in den trainierten Aufgaben und die Teilnehmer von WOME berichteten von signifikant mehr positiven Veränderungen in ihrem Alltag im Vergleich zur Kontrollgruppe. Im Unterschied zu Studie IV wurden jedoch keine Transfereffekte auf nicht trainierte Tests beobachtet. Die Studie bestätigte die Validität der Intervention und erbrachte erste Hinweise zur Wirksamkeit in der klinischen Anwendung. Aufgrund der fehlenden Transfereffekte stand der Wirksamkeitsnachweis zu diesem Zeitpunkt für die primäre Zielgruppe jedoch noch aus.

Studie VI (Weicker et al., 2020, Publikation 4) untersuchte den Einfluss von Trainingsdauer und Aufgabenspezifität, d.h. ob Veränderungen ausschließlich im AG auftreten und ob die Wirkung von der eines Aufmerksamkeitstrainings abgrenzbar ist. N = 20 Patienten mit heterogenen Hirnläsionen (Mittelwert = 48.6 Jahre), die sich in einer intensiven neurologischen Rehabilitation in einem tagesklinischen Setting befanden, wurden randomisiert zum zusätzlichen Training von a) AG (n = 11), oder b) Aufmerksamkeit (n = 9) zugewiesen. Um den Einfluss der Trainingsdauer zu untersuchen, wurde vor Trainingsbeginn, nach zwei Wochen und nach vier Wochen eine neuropsychologische Untersuchung durchgeführt. Die Trainingshäufigkeit war der entscheidende Faktor für die Wirksamkeit von WOME: 20 Trainingseinheiten führten zu signifikanten Transfereffekten, nachweisbar in nicht trainierten AG-Tests und im verbalen Gedächtnis, nach 10

Trainingseinheiten konnten jedoch noch keine Veränderungen festgestellt werden. Zwischen den Untersuchungsbedingungen konnten keine signifikanten Unterschiede entdeckt werden, die Überlegenheit von WOME im Vergleich zu einem Aufmerksamkeitstraining ist somit nicht belegt. Wie in den vorausgegangenen Evaluationsstudien IV und V gaben die Probanden an, positive Auswirkungen im Alltag zu spüren. Die Ergebnisse erbringen demnach den Wirksamkeitsnachweis von AG-Trainings für Personen mit erworbenen Hirnschädigungen. Zudem weisen die Daten darauf hin, dass eine zusätzliche Intervention sinnvoll ist, auch wenn Betroffene bereits andere kognitive Behandlungen erhalten und wenn sie im chronischen Stadium der Erkrankung sind.

Schlussfolgerungen

Die experimentellen Arbeiten bildeten eine solide Grundlage für ein theoretisch fundiertes und effektives AG-Training, das den Bedürfnissen von Personen mit AG-Defiziten gerecht wird. Die Evaluationsstudien wiesen positive Effekte auf trainierte und untrainierte AG-Aufgaben mit moderater bis großer Effektstärke nach und zeigten damit das Potential der Intervention, die generelle AG-Leistung zu steigern. Die beobachteten Effekte sind vergleichbar mit Metaanalysen zur Wirksamkeit des Trainings von AG und Exekutivfunktionen in anderen Personengruppen (Karbach & Verhaeghen, 2014; Melby-Lervåg et al., 2016; Soveri et al., 2017). Aussagen der Trainingsteilnehmer deuteten darauf hin, dass die Intervention den Umgang mit Situationen erleichtert, die im Alltag hohe Anforderungen an das AG stellen. Die Wirksamkeit des Trainings wurde für verschiedene Altersgruppen und Hirnschädigungen gezeigt, sodass WOME als Therapieoption zur Verbesserung von kognitiver Leistung und Teilhabe sinnvoll erscheint.

Übereinstimmend mit unseren Befunden wurden auch in anderen klinischen Stichproben positive Effekte berichtet, z.B. bei Personen mit Aufmerksamkeitsdefizitsyndrom (Spencer-Smith & Klingberg, 2015) und Substanzmissbrauch (Bickel et al., 2014; Houben et al., 2011). Die Effekte von AG-Trainings sind dabei weitgehend auf die AG-Leistung beschränkt. Während Studie I und VI kleine Transfereffekte auf andere kognitive Funktionen fanden (kognitive Kontrolle, logisches

Denken und verbales Gedächtnis), konnten Studie IV und V keine Effekte über das AG-System hinaus nachweisen. Diese Befunde spiegeln den aktuell geführten wissenschaftlichen Diskurs wieder, in dem Autoren einiger Experimente (Carretti et al., 2013; Lundqvist et al., 2010; Westerberg et al., 2007) und Metaanalysen (Au et al., 2015; Karbach & Verhaeghen, 2014; Spencer-Smith & Klingberg, 2015) 'ferne' Transfereffekte finden und daher den Einsatz von AG-Trainings auch für andere Bereiche befürworten, während kritische methodische Analysen nahelegen, dass solche Effekte kaum existieren (Dougherty et al., 2016; Melby-Lervåg et al., 2016; Redick et al., 2015; Schwaighofer et al., 2015; Soveri et al., 2017).

Hinsichtlich der Frage, was genau im AG-System eigentlich trainiert wird, liefern die experimentellen Arbeiten Hinweise darauf, dass es zugrundeliegende strukturelle Ähnlichkeiten von trainierter Aufgabe und Transfermaßen geben muss (Buschkuehl et al., 2012; Lindeløv et al., 2016). Dies spricht dafür, dass eher die Effizienz und nicht die Kapazität des Systems gesteigert wird (Bastian & Oberauer, 2014). Zusammenfassend bieten AG-Trainings eine effiziente, funktionelle Therapie von AG-Defiziten, die sich positiv auf den Alltag der Betroffenen auswirken.

Ein Ziel dieser Dissertation war zur translationalen Forschung beizutragen und damit Erkenntnisse aus der Grundlagenforschung in die klinische Anwendung zu übertragen. Studie I, IV, V und VI zeigten, dass die Anzahl der Trainingseinheiten maßgeblich für die Wirksamkeit von AG-Trainings ist. Die Effekte waren eher kurzfristiger Natur und erfordern somit Wiederholungssitzungen. Beides stellt Herausforderungen in der klinischen Praxis dar, da während eines stationären Aufenthaltes häufig auch organisatorische und monetäre Überlegungen die Anwendung von kognitiven Trainings bestimmen. Eine Möglichkeit, den Anforderungen an Häufigkeit und Kontinuität von AG-Trainings nachzukommen, bieten Online-Trainings im häuslichen Kontext, deren Anwendbarkeit aktuell erprobt wird (Weicker, 2020). Die Daten von Studie I, IV, V und VI tragen zu der Entscheidung bei, welcher Patient ein AG-Training und welcher eher eine alternative Behandlung erhalten sollte. Von den betrachteten Variablen stellte sich die kognitive Reservekapazität bzw. erhaltene Leistungsfähigkeit als stärkster Prädiktor für den Trainingserfolg heraus, d.h. je besser die Ausgangsleistung ist, desto mehr profitiert ein Patient. In der frühen Phase der Rehabilitation scheinen Interventionen effizienter zu sein (Hellgren et al., 2015), die vorliegenden Studien zeigten jedoch, dass auch in der chronischen Phase nach ca. 1,5 Jahren positive Effekte zu erzielen sind. Zusammenfassend ist zu empfehlen, das neue AG-Training WOME Patienten mit relativ gut erhaltener Kognition anzubieten, unabhängig von Alter, Ätiologie und Dauer seit der Hirnschädigung. Der modularisierte Aufbau des Programms wird zukünftigen Studien ermöglichen, zugrundeliegende Mechanismen von AG-Trainings zu untersuchen. Für die klinische Neurorehabilitation ist es hingegen weniger die spezifische Struktur der Intervention, sondern eine Kombination von geeigneten Aufgaben, interindividuellen Eigenschaften und einer ausreichenden Trainingsdauer, die eine erfolgreiche Anwendung von AG-Trainings nach einer erworbenen Hirnschädigung vorhersagen.

Referenzen siehe Summary

Appendices

APPENDICES

List of abbreviations

d	Cohen's d (effect size)
fMRI	functional magnetic resonance imaging
g	Hedge's g (effect size)
M	mean
n	sample size
SD	standard deviation
WM	working memory
WOME	working memory intervention (program implemented by HASOMED, RehaCom®)

APPENDICES

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Supplemental material

Study I Supplemental Materials 1 (Table 1-5)

For: Weicker, J., Villringer, A., & Thöne-Otto, A. (2016). Can impaired working memory functioning be improved by training? A meta-analysis with a special focus on brain injured patients. *Neuropsychology, 30*(2), 190-212. https://doi.org/10.1037/neu0000227

Table 1 Study characteristics

participants	study	study design	N (n WM training, n control group)	control group	type of WM intervention	adaptivity	mean number of sessions	hours	training schedule	FU (month)
children and adolescents with WM deficits	Klingberg et al. (2002)	RCT	14 (7, 7)	active°	simple span WM tasks (Cogmed)	yes	25	10,5	5 weeks 5x weekly 25 min	no
	Klingberg et al. (2005)	RCT	50 (26, 24)	active	simple span WM tasks (Cogmed)	yes	26	17,5	5 weeks 5x weekly 40 min	yes (3)
	Klingberg et al. (2005)/ Dahlin (2011) combined	quasi-exp.	93 (68, 25)	active°	simple span WM tasks (Cogmed)	yes	25	15,6	5 weeks 5x weekly 35 min	yes (3-7)
	Holmes et al. (2009)	quasi-exp.	42 (22, 20)	active°	simple span WM tasks (Cogmed)	yes	20	11,5	in 4-7 weeks 20 x 35 min	yes (6)
	Beck et al. (2010)	RCT	51 (27, 24)	passive	simple span WM tasks (Cogmed)	yes	25	14,6	in 5-6 weeks 25 x 35 min	yes (4)
	Johnstone et al. (2010)	RCT	29 (15, 14)	active°	simple span WM tasks	yes	22	7,3	5 weeks 5x weekly 20 min	no
	Gibson et al. (2011)	within-group'	38	none	simple span WM tasks (Cogmed)	yes	25	14,5	5 weeks 5x weekly 25 min	no
	Prins et al. (2011)	within-group'	41	none	simple span WM tasks	yes	3	1,3	3 weeks 1x weekly 25 min	no
	Alloway (2012)	RCT	15 (8, 7)	active	simple/compl. span WM tasks	yes	25	12,5	8 weeks 3x weekly 30 min	no
	Gray et al. (2012)	RCT	52 (32, 20)	active	simple span WM tasks (Cogmed)	yes	22,5	16,9	5 weeks 4-5x weekly 45 min	no
	Green et al. (2012)	RCT	26 (12, 14)	active°	simple span WM tasks (Cogmed)	yes	24,3	14,2	in 3-4 weeks 25 x 35 min	no
	Söderqvist et al. (2012)	RCT	41 (22, 19)	active°	simple span WM tasks (Cogmed)	yes	24,5	8,2	5 weeks 5x weekly 20 min	yes (12)
	Alloway et al. (2013)	RCT	94 (23, 71)	active° & passive	simple/compl. span WM tasks	yes	28	14	8 weeks 4x weekly 30 min	yes (8)
	Dunning et al. (2013)	quasi-exp.	94 (34, 60)	active° & passive	simple span WM tasks (Cogmed)	yes	22,5	14,1	5 weeks 5x weekly 30-45 min	yes (3)
	Egeland/ Hovik et al. (2013) combined	RCT	67 (33, 34)	passive	simple span WM tasks (Cogmed)	yes	25	15,6	5 weeks 5x weekly 30-45 min	yes (8)
	Grunewaldt et al. (2013)	RCT	20 (9, 11)	passive	simple span WM tasks (Cogmed)	yes	25	5,2	5 weeks 5x weekly 10-15 min	no
	Bergman-Nutley et al. (2014)	quasi-exp.	480 (176, 304)	passive	simple span WM tasks (Cogmed)	yes	25	14,5	5 weeks 5x weekly 35 min	no
	Chacko et al. (2014)	RCT	85 (44, 41)	active°	simple span WM tasks (Cogmed)	yes	25	16,7	5 weeks 5x weekly 30-45 min	no
	Gropper et al. (2014)	RCT	62 (39, 23)	passive	simple span WM tasks (Cogmed)	yes	25	18,8	5 weeks 5x weekly 45 min	yes (2)
	Kroesbergen et al. (2014)	RCT	51 (30, 21)	passive	simple/compl. span WM tasks	yes	8	4	4 weeks 2x weekly 30 min	no

Table 1 continued

participants	study	study design	N (n WM training, n control group)	control group	type of WM intervention	adaptivity	mean number of sessions	mean number of hours	training schedule	FU (month)
children and adolescents with WM deficits	Van der Oord et al. (2014)	RCT	40 (18, 22)	passive	simple span WM tasks	yes	25	16,7	5 weeks 5x weekly 40 min	yes (2)
	Van Dongen-Boomsma et al. (2014)	RCT	47 (26, 21)	active°	simple span WM tasks (Cogmed)	yes	25	6,25	5 weeks 5x weekly 15 min	no
	Wong et al. (2014)	quasi-exp.	53 (27, 26)	passive	simple span WM tasks	yes	25	15,4	5 weeks 5x weekly 37 min	yes (1)
healthy children	Thorell et al. (2009)	quasi-exp.	47 (17, 30)	active & passive	simple span WM tasks (Cogmed)	yes	25	6	5 weeks 5x weekly 15 min	no
	St Clair-Thompson et al. (2010)	quasi-exp.	254 (117, 137)	passive	simple span WM tasks	yes	14	7	6-7 weeks 2x weekly 30 min	no
	Bergman Nutley et al. (2011)	RCT	49 (24, 25)	active°	simple span WM tasks (Cogmed)	yes	25	6,3	5-7 weeks 5x weekly 15 min	no
	Loosli et al. (2011)	quasi-exp.	40 (20, 20)	passive	complex span WM tasks	yes	10	2	2 weeks 5x weekly 12 min	no
	Witt (2011)	matched-group	38 (19, 19)	passive	simple/compl. span WM tasks	no	30	7,5	6 weeks 5x weekly 15 min	no
	Jaeggi et al. (2012)	matched-group	62 (32, 30)	active	simple span WM tasks (Updating)	yes	19	4,8	5-6 weeks 5x weekly 15 min	yes (3)
	Nevo et al. (2013)	quasi-exp.	97 (50, 47)	active & passive	simple span WM tasks	yes	12	4,8	4 weeks 3x weekly 24 min	no
	Henry et al. (2014)	RCT	36 (18, 18)	active°	complex span WM tasks	yes	18	3	6 weeks 3x weekly 10 min	yes (6)
	Rode et al. (2014)	quasi-exp.	282 (156, 126)	passive	complex span WM task	yes	17	7,1	4 weeks 5x weekly 20-30 min	no
healthy young adults	Olesen et al. (2004)/ Westerberg et al. (2007b) combined	quasi-exp.	25 (14, 11)	passive	simple span WM tasks (Cogmed)	yes	21	14	5 weeks 4-6x weekly 40 min	no
	Dahlin et al. (2008)	RCT	26 (15, 11)	passive	complex span WM tasks (Updating)	yes	15	11,3	5 weeks 3x weekly 45 min	yes (18)
	Jeaggi et al. (2008)	matched-group	69 (34, 35)	passive	simple span WM tasks (Updating)	yes	13,7	5,7	1-4 weeks 5x weekly 25 min	no
	Li et al. (2008)	quasi-exp.	46 (19, 27)	passive	simple span WM tasks (Updating)	no	45	11	6-7 weeks 7x weekly 15 min	yes (3)
	Dahlin et al. (2009)	RCT	22 (15, 7)	passive	complex span WM tasks (Updating)	yes	15	11,3	5 weeks 3x weekly 45 min	no
	Chein et al. (2010)	RCT	42 (20, 22)	passive	complex span WM tasks	yes	20	12,5	4 weeks 5x weekly 40 min	no
	Jaeggi et al. (2010)	matched-group	89 (46, 43)	passive	simple span WM tasks (Updating)	yes	20	6,2	4 weeks 5x weekly 20 min	no
	Jolles et al. (2010)	RCT	29 (15, 14)	passive	simple span WM tasks	no	16	6,7	6 weeks 4x weekly 25 min	no

Table 1 continued

participants	study	study design	N (n WM training, n control group)	control group	type of WM intervention	adaptivity	mean number of sessions	mean number of hours	training schedule	FU (month)
healthy young adults	Schmiedek et al. (2010)	RCT	145 (101, 44)	passive	simple span WM tasks (Updating)	no	100	100	in 27 weeks 101 x 60 min	no
	Bäckman et al. (2011)	RCT	20 (10, 10)	passive	complex span WM tasks (Updating)	yes	15	11,3	5 weeks 3x weekly 45 min	no
	Schweizer et al. (2011)	RCT	45 (29, 16)	active	complex span WM tasks (Updating)	yes	18,5	7,7	4 weeks 5x weekly 25 min	no
	Shiran et al. (2011)	matched-group	50 (35, 15)	active	simple span WM tasks	yes	24	6	6 weeks 4x weekly 15 min	no
	Takeuchi et al. (2011)	RCT	52 (16, 36)	active° & passive	simple span WM tasks	yes	5	20	in 1 week 5 x 240 min	no
	Anguera et al. (2012)	RCT	44 (22, 22)	active	simple span WM tasks (Updating)	yes	21	8,8	5 weeks 4-5x weekly 25 min	no
	Brehmer et al. (2012)	RCT	55 (29, 26)	active°	simple span WM tasks (Cogmed)	yes	23	10	5 weeks 5x weekly 25 min	yes (3)
	Chooi et al. (2012)	quasi-exp.	93 (22, 71)	active & passive	simple span WM tasks (Updating)	yes	8/20	4/10	2/5 weeks 4x weekly 30 min	no
	Jaušovec et al. (2012)	matched-group	29 (14, 15)	active	simple/compl. span WM tasks	yes	36	30	12 weeks 3x weekly 40 min	no
	Penner et al. (2012)	matched-group	36 (24, 12)	passive	simple span WM tasks	yes	16	12	4/8 weeks 4/2x weekly 45 min	no
	Rudebeck et al. (2012)	RCT	55 (28, 27)	passive	simple span WM tasks (Updating)	yes	20	6,7	4 weeks 5x weekly 20 min	no
	Salminen et al. (2012)	RCT	38 (20, 18)	passive	complex span WM tasks (Updating)	yes	14	4,7	3 weeks 5x weekly 20 min	no
	Schneiders et al. (2012)	matched-group	32 (16, 16)	passive	simple span WM tasks (Updating)	yes	8	6,7	in 2 weeks 8 x 50 min	no
	Colom et al. (2013)	matched-group	56 (28, 28)	passive	simple span WM tasks (Updating)	yes	24	12	12 weeks 2x weekly 30 min	no
	Gibson et al. (2013)	quasi-exp.	31 (19, 12)	passive	simple/compl. span WM tasks (modified Cogmed)	yes	25	12,5	5 weeks 5x weekly 30 min	no
	Harrison et al. (2013)	RCT	55 (38, 17)	active	simple/compl. span WM tasks	yes	20	15	in 4 weeks 20 x 45 min	no
	Kundu et al. (2013)	RCT	29 (14, 15)	active	simple span WM tasks (Updating)	yes	24	16	5 weeks 5x weekly 40 min	no
	Lilienthal et al. (2013)	RCT	52 (13, 39)	active & passive	complex span WM tasks (Updating)	yes	8	4	in 2 weeks 8 x 30 min	no
	Martin et al. (2013)	RCT	31 (21, 10)	passive	complex span WM tasks (Updating)	yes	10	4,2	2 weeks 5x weekly 25 min	yes (1)
	Nouchi et al. (2013)	RCT	32 (16, 16)	active	simple span WM tasks	yes	25	6,3	4 weeks 5x weekly 15 min	no
	Owens et al. (2013)	RCT	22 (11, 11)	active°	simple span WM tasks (Updating)	yes	8	4	2 weeks 4x weekly 30 min	no

Table 1 continued

participants	study	study design	N (n WM training, n control group)	control group	type of WM intervention	adaptivity	mean number of sessions	mean number of hours	training schedule	FU (month)
healthy young adults	Redick et al. (2013)	matched-group	73 (24, 49)	active & passive	complex span WM tasks (Updating)	yes	20	11,7	in 7 weeks 20 x 35 min	no
	Sprenger et al. (2013) Trial 1	RCT	115 (59, 55)	passive	simple span WM tasks	yes	20	20	3-6 weeks 3-7x weekly 60 min	yes (3)
	Sprenger et al. (2013) Trial 2	RCT	138 (101, 37)	active	simple span WM tasks	yes	32	14	4-5 weeks 5x weekly 25 min	no
	Takeuchi et al. (2013)	RCT	61 (41, 20)	passive	simple span WM tasks (Updating)	yes	26	17,3	4 weeks 7x weekly 20-60 min	no
	Thompson et al. (2013)	matched-group	58 (20, 38)	active & passive	simple span WM tasks (Updating)	yes	20	13,3	4 weeks 5x weekly 40 min	no
	von Bastian et al. (2013a)	RCT	66 (34, 32)	active	simple/compl. span WM tasks	yes	20	10	4 weeks 5x weekly 30 min	no
	von Bastian et al. (2013b)	RCT	90 (60, 30)	active	simple/compl. span WM tasks	yes	20	11,7	4 weeks 5x weekly 30-40 min	yes (6)
	Zhao et al. (2013)	RCT	23 (12, 11)	passive	simple span WM tasks (Updating)	yes	20	10	3 weeks 7x weekly 30 min	no
	Heinzel et al. (2014)	RCT	30 (15, 15)	passive	simple span WM tasks (Updating)	yes	12	9	4 weeks 3x weekly 45 min	no
	Onraedt et al. (2014)	RCT	72 (21, 51)	passive	simple span WM tasks (Updating)	yes	6	2,5	1 week 6x weekly 25 min	yes (0,5)
	Richmond et al. (2014)	RCT	38 (20, 18)	passive	complex span WM tasks	yes	10	5	2 weeks 5x weekly 30 min	no
healthy elderly adults	Buschkühl et al. (2008)	RCT	32 (13, 19)	active	complex span WM tasks	yes	24	18	12 weeks 2x weekly 45 min	yes (12)
	Dahlin et al. (2008)	RCT	29 (13, 16)	passive	complex span WM tasks (Updating)	yes	15	11	5 weeks 3x weekly 45 min	yes (18)
	Li et al. (2008)	quasi-exp.	41 (21, 20)	passive	simple span WM tasks (Updating)	no	45	11	7 weeks 7x weekly 15 min	yes (3)
	Dahlin et al. (2009)	RCT	19 (11, 8)	passive	complex span WM tasks (Updating)	yes	15	11	5 weeks 3x weekly 45 min	no
	Borella et al. (2010)	RCT	40 (20, 20)	active	complex span WM tasks	yes	3	1,8	1 week 3x weekly 35 min	yes (8)
	Schmiedek et al. (2010)	RCT	142 (103, 39)	passive	simple span WM tasks (Updating)	no	100	100	in 27 weeks 101 x 60 min	no
	Brehmer et al. (2011)	RCT	23 (12, 11)	active°	simple span WM tasks	yes	25	10,4	5 weeks 5x weekly 25 min	no
	Richmond et al. (2011)	RCT	40 (21, 19)	active	complex span WM tasks	yes	20	10	4 weeks 5x weekly 30 min	no
	Zinke et al. (2011)	matched-group	36 (20, 16)	passive	simple span WM tasks	yes	10	4,5	2 weeks 5x weekly 30 min	no
	Brehmer et al. (2012)	RCT	45 (26, 19)	active°	simple span WM tasks (Cogmed)	yes	24,5	10,6	5 weeks 5x weekly 25 min	yes (3)

Table 1 continued

participants	study	study design	N (n WM training, n control group)	control group	type of WM intervention	adaptivity	mean number of sessions	mean number of hours	training schedule	FU (month)
healthy elderly adults	Carretti et al. (2012)	RCT	36 (17, 19)	active	complex span WM tasks	yes	3	3	in 1 week 3 x 60 min	yes (6)
	Nouchi et al. (2012)	RCT	28 (14, 14)	active	simple span WM tasks	no info	20	5	4 weeks 5x weekly 15 min	no
	Borella et al. (2013)	RCT	36 (18, 18)	active	complex span WM task	yes	3	3	in 1 week 3 x 60 min	yes (8)
	McAvenue et al. (2013)	RCT	36 (19, 17)	active°	simple span WM tasks (Updating)	yes	25	14,8	5 weeks 5x weekly 30 min	yes (3&6)
	Stepankova et al. (2013)	RCT	65 (40, 25)	passive	simple span WM tasks (Updating)	yes	14,5	6	5 weeks 2/4x weekly 25 min	no
	Theill et al.(2013)	quasi-exp.	40 (23, 17)	passive	simple/compl. span WM tasks	yes	20	10	10 weeks 2x weekly 30 min	no
	von Bastian et al. (2013a)	RCT	57 (27, 30)	active	simple/compl. span WM tasks	yes	20	10	4 weeks 5x weekly 30 min	no
	Borella et al. (2014) Trial 1	RCT	40 (20, 20)	active	complex span WM task	yes	3	3	in 1 week 3 x 60 min	yes (8)
	Borella et al. (2014) Trial 2	RCT	40 (20, 20)	active	complex span WM task	yes	3	3	in 1 week 3 x 60 min	yes (8)
	Heinzel et al. (2014)	RCT	30 (15, 15)	passive	simple span WM tasks (Updating)	yes	12	9	4 weeks 3x weekly 45 min	no
	Xin et al. (2014)	matched-group	29 (15, 14)	active	simple span WM tasks (Updating)	yes	20	8,3	3 weeks 7x weekly 25 min	no
	Zimmermann et al. (2014)	RCT	14 (8, 6)	active	simple span WM tasks	no	12	24	6 weeks 2x weekly 120 min	no
	Zinke et al. (2014)	RCT	80 (40,40)	passive	simple span WM tasks	yes	9	4,5	3 weeks 3x weekly 30 min	yes (9)
patients with acquired brain injuries	Sohlberg et al. (2000)	within-group'	14	none	simple/compl. span WM tasks	no info	24	24	10 weeks 3x weekly 60 min	no
	Westerberg et al. (2007a)	RCT	18 (9, 9)	passive	simple span WM tasks (Cogmed)	yes	23	15	5 weeks 5x weekly 40 min	no
	Vogt et al. (2009)	RCT	45 (30, 15)	passive	simple span WM tasks	yes	16	12	4/8 weeks 4/2x weekly 45 min	no
	Lundqvist et al. (2010)	within-group'	21	none	simple span WM tasks (Cogmed)	yes	25	22	5 weeks 5x weekly 45-60 min	yes (5)
	Houben et al. (2011)	RCT	48 (20, 28)	active°	simple span WM tasks	yes	25	6	in 4 weeks 25 x 15 min	yes (1)
	Johansson et al. (2012)	within-group	18	none	simple span WM tasks (Cogmed)	yes	23	14,4	8 weeks 3x weekly 40 min	yes (6)
	Åkerlund et al. (2013)	RCT	40 (22, 18)	active	simple span WM tasks (Cogmed)	yes	25	15,6	5 weeks 5x weekly 30-45 min	yes (3)
	Carretti et al. (2013)	RCT	20 (10, 10)	active	complex span WM tasks	yes	3	1,8	1 week 3x weekly 35 min	no

Table 1 continued

participants	study	study design	N (n WM training, n control group)	control group	type of WM intervention	adaptivity	mean number of sessions	hours	training schedule	FU (month)
patients otherwise diagnosed	Horowitz-Kraus et al. (2009)	within-group'	27	none	simple span WM tasks	yes	24	7	6 weeks 4x weekly 20 min	yes (6)
	Van der Molen et al. (2010)	RCT	93 (41, 52)	active & active°	complex span WM tasks	yes	15	1,5	5 weeks 2-4x weekly 6 min	yes (2-3)
	Kronenberger et al. (2011)	within-group	9	none	simple span WM tasks (Cogmed)	yes	25	14,5	5 weeks 5x weekly 35 min	yes (1&6)
	Løhaugen et al. (2011)	within-group'	16	none	simple span WM tasks (Cogmed)	yes	25	14,5	5 weeks 5x weekly 35 min	yes (6)
	Shiran et al. (2011)	matched-group	41 (26, 15)	active	simple span WM tasks	yes	24	6	6 weeks 4x weekly 15 min	no
	Bennett et al. (2013)	RCT	21 (10, 11)	passive	simple span WM tasks (Cogmed)	yes	25	9,6	13 weeks 3x weekly 25 min	yes (4)
	Hardy et al. (2013)	RCT	17 (11, 6)	active°	simple span WM tasks (Cogmed)	yes	25	14,4	5-8 weeks 5x weekly 35 min	yes (3)
	Kesler et al. (2013)	RCT	41 (21, 20)	passive	simple span WM tasks	yes	48	20	12 weeks 4x weekly 25 min	no
	Verbeken et al. (2013)	RCT	43 (21, 22)	passive	simple span WM tasks	yes	25	16	6 weeks 4x weekly 40 min	yes (2&3)

Note. As the studies from Klingberg et al. (2005) and Dahlin (2011), Olesen et al. (2004) and Westerberg et al. (2007b), as well as Egeland et al. (2013) and Hovik et al. (2013) shared the same subjects, doubling of datasets was avoided by combining the respective outcome measures of each study into one trial. ADHD = attention deficit hyperactivity disorder; RCT = randomized controlled trial; quasi-exp. = quasi-experimental design; within-group = within-group design; within-group' = originally multiple WM training groups or waitlist groups were studied, but as no control group was examined the trial was treated like a within-group design in the present meta-analysis; N = number of participants included in the final analysis of the study; active° = active control group doing fixed low WM training; WM = working memory; FU = follow-up test.

Table 2 Outcome measures

participants	study	outcomes immediately after training								outcomes after the follow-up period						
		improved trained task	near transfer on WM		far transfer on other domains					near transfer on WM		far transfer on other domains				
			simple	complex	reasoning	EF	attention	memory	everyday	simple	complex	reasoning	EF	attention	memory	everyday
children and adolescents with WM deficits	Klingberg et al. (2002)	yes*	BSPt		RAVEN	S	CRT		HEAD							
	Klingberg et al. (2005)	no info							HEAD PR ~~TR~~							HEAD PR ~~TR~~
	Klingberg et al. (2005)/ Dahlin (2011) combined	yes*	BSPf BSPb DSPf DSPb		~~RAVEN~~	S				BSPf BSPb DSPf DSPb		~~RAVEN~~	S			
	Holmes et al. (2009)	no info	STMBv ~~STMBs~~ ~~WMBv~~ WMBs IT		WASI					STMBv STMBs WMBv WMBs IT		WASI				
	Beck et al. (2010)	no info				BRIEFp BRIEFt			PR TR				BRIEFp BRIEFt			PR TR
	Johnstone et al. (2010)	yes				GO			PR OR							
	Gibson et al. (2011)	yes*	IFRr IFRpr						PR TR							
	Prins et al. (2011)	no	BSPf													
	Alloway (2012)	no info		AWMA	WASI	WOND										
	Gray et al. (2012)	no info	DSPf DSPb SSP ~~SWM~~				D2		IOWACS SWAN WMRS							
	Green et al. (2012)	no info	WMI						RAST PR							
	Söderqvist et al. (2012)	no info	WR	OOO	BD RAVEN		NEPSYa		~~SDQ~~	WR	OOO	BD RAVEN		NEPSYa		~~SDQ~~
	Alloway et al. (2013)	no info		AWMAv AWMAvs	WASIv	WOND					AWMAv AWMAvs	WASIv WASInv	WOND			
	Egeland/ Hovik et al. (2013) combined	no info	DSP LNS/SC VSP			CAC MATHS	CPT PSC TMT4	BVRT WLL	ARS-IV BRIEFp SDQ	DSP LNS/SC VSP			CAC MATHS	CPT PSC TMT4	BVRT WLL	ARS-IV BRIEFp SDQ
	Dunning et al. (2013)	no info	AWMAv CLASSdr CLASSfi	AWMAvs CLASSsr	WASIv WASInv	WOND	CPT ~~VISC~~			AWMAv CLASSdr CLASSfi	AWMAvs CLASSsr	WASIv WASInv	WOND	CPT VISC		
	Grunewaldt et al. (2013)	yes*	BSPf BSPb DSPf DSPb			NEPSYef	NEPSYa	NEPSYm	~~ARS-IV~~ PAS							
	Bergman-Nutley et al. (2014)	yes*	~~CLASSfi~~	~~OOO~~		MATHS										

Table 2 continued

participants	study	outcomes immediately after training									outcomes after the follow-up period						
		improved trained task	near transfer on WM		far transfer on other domains						near transfer on WM		far transfer on other domains				
			simple	complex	reasoning	EF	attention	memory	everyday		simple	complex	reasoning	EF	attention	memory	everyday
children and adolescents with WM deficits	Chacko et al. (2014)	yes	DSP LIR SPR	DM		axCPT			DBDp DBDt WRAT4								
	Dongen-Boomsma et al. (2014)	yes*	DSPf DSPb LDT			S SHAPE	SADT	ST	ADHD-RS BRIEF CGAS								
	Gropper et al. (2014)	yes	PASAT SWM WMBs WMBv		WJa	MATHS	2&7		ADHD-RS CFQ		PASAT SWM WMBs WMBv		WJa	MATHS	2&7		ADHD-RS CFQ
	Kroesbergen et al. (2014)	no info	WR	OOO		MATHS											
	Van der Oord et al. (2014)	yes*							BRIEF DBDp DBDt								BRIEF DBDp DBDt
	Wong et al. (2014)	no info	BSP DSP			S			BRIEFp BRIEFt SWANp SWANt		BSP DSP			S			BRIEFp BRIEFt SWANp SWANt
healthy children	Thorell et al. (2009)	yes*	WSP			BD GO	~~CPT~~ ~~GO~~										
	St Clair-Thompson et al. (2010)	no info	DSPf BSPf IT	RSP													
	Bergman Nutley et al. (2011)	yes*	WSP	OOO	RAVEN LB	BD											
	Loosli et al. (2011)	yes*			TONI												
	Witt (2011)	yes*	VP														
	Jaeggi et al. (2012)	yes*			RAVEN TONI								RAVEN TONI				
	Nevo et al. (2013)	no info	BR ~~SER~~ WR	~~LIR~~ OOO													
	Henry et al. (2014)	yes*	BR CR DSPf WR			MATHS					BR CR DSPf WR			MATHS			
	Rode et al. (2014)	yes		AWMA	WIAT-M				WMRS								
healthy young adults	Olesen et al. (2004)/ Westerberg et al.(2007b) combined	yes*			RAVEN												
	Dahlin et al. (2008a)	yes*	NB			S											

Table 2 continued

participants	study	outcomes immediately after training								outcomes after the follow-up period						
		improved trained task	near transfer on WM		far transfer on other domains					near transfer on WM		far transfer on other domains				
			simple	complex	reasoning	EF	attention	memory	everyday	simple	complex	reasoning	EF	attention	memory	everyday
healthy young adults	Dahlin et al. (2008b)	yes*	DSPf DSPb NB	CPSP	RAVEN		DST COWAT	WLL WP		DSPf DSPb NB	CPSP	RAVEN		DST COWAT	WLL WP	
	Jeaggi et al. (2008)	yes*	DSPt	RSP	RAVEN BOMAT											
	Li et al. (2008)	yes*	NB	OSPAN ROSP						~~NB~~	~~OSPAN~~ ~~ROSP~~					
	Chein et al. (2010)	yes*			RAVEN RC	S										
	Jaeggi et al. (2010)	yes*	NB	OSPAN	RAVEN BOMAT											
	Jolles et al. (2010)	yes*	DSPf DSPb MCT			LGT WCST TOL										
	Schmiedek et al. (2010)	yes*	ASP NB SMU	ROSP RSP CSP	RAVEN BIS		BIS	WP BIS								
	Bäckman et al. (2011)	yes*	NB													
	Schweizer et al. (2011)	yes*	DSPt		RAVEN	S										
	Shiran et al. (2011)	yes*	SBT													
	Takeuchi et al. (2011)	yes*	LMR LESP		RAVEN SACT	S	TMT DSS									
	Anguera et al. (2012)	yes*	NB	OSPAN ~~CDR~~			DSS									
	Brehmer et al. (2012)	yes*	DSPf DSPb ~~BSPf~~ ~~BSPb~~ PASAT		RAVEN	S		~~RAVLT~~	CFQ	DSPf DSPb BSPf BSPb PASAT		RAVEN	S		~~RAVLT~~	CFQ
	Chooi et al. (2012)	yes*		OSPAN	CDR MHT ~~MROT~~ PF RAVEN VOC	WBE	CPST FAT IDP									
	Jaušovec et al. (2012)	no info	DSPt		RAVEN PFCB VAT											
	Penner et al. (2012)	yes*	DSPf DSPb BSPf BSPb PASAT NB			VFT	SDMT	SPR								

Table 2 continued

participants	study	outcomes immediately after training								outcomes after the follow-up period						
		improved trained task	near transfer on WM		far transfer on other domains					near transfer on WM		far transfer on other domains				
			simple	complex	reasoning	EF	attention	memory	everyday	simple	complex	reasoning	EF	attention	memory	everyday
healthy young adults	Rudebeck et al. (2012)	yes*			BOMAT			RMT								
	Salminen et al. (2012)	yes*	NB		~~RAVEN~~	DT TSW	ABT									
	Schneiders et al. (2012)	yes*	NB													
	Colom et al. (2013)	yes*		CPSP DM RSP	DAT-AR DAT-NR DAT-VR PMA-R PMA-V RAVEN		FLTn FLTv SIMON									
	Gibson et al. (2013)	yes*						WLL								
	Harrison et al. (2013)	yes*	~~ARSP~~ KTT ~~LESP~~ ~~SSP~~ ~~VISAT~~ ~~WSP~~	~~ROSP~~ RSP	RAVEN	CT ~~SWT~~	~~LS~~ NUS	WLL								
	Kundu et al. (2013)	yes*	DDT TEDT	OSPAN	RAVEN	S										
	Lilienthal et al. (2013)	yes*	BSPf CRS RSPT	FSW OSPAN												
	Martin et al. (2013)	yes*	DSPt LNS				COWAT SERIAL7 TMT			DSPt LNS				COWAT SERIAL7 TMT		
	Nouchi et al. (2013)	yes*	BSPf BSPb DSPf DSPb LNS LMR MATHS	OSPAN	RAVEN	S WCST	DCT DSS RT SYS									
	Owens et al. (2013)	yes*	CDTwm			CDTfe			~~BDI-II~~							
	Redick et al. (2013)	yes*	NB	SYMSP	ANL CFT INF LS NS PFCB RAVEN	ATCLS CT SWT	LEC NUC		SR							
	Sprenger et al. (2013) Trial 1	yes*		LISP OSPAN ROSP SYMSP	DL ILR	ANTIS S					LISP OSPAN ROSP SYMSP	DL ILR	ANTIS S			

Table 2 continued

participants	study	outcomes immediately after training									outcomes after the follow-up period						
		improved trained task	near transfer on WM		far transfer on other domains					near transfer on WM		far transfer on other domains				
			simple	complex	reasoning	EF	attention	memory	everyday	simple	complex	reasoning	EF	attention	memory	everyday
healthy young adults	Sprenger et al. (2013) Trial 2	yes*	NB SHB	RSP	RAVEN	TSW	ANT									
	Takeuchi et al. (2013)	yes*	BSP DSP MATHS		BOMAT RAVEN SACT SXT TB-IT	S										
	Thompson et al. (2013)	yes*		OSPAN RSP	RAVEN WAIS	DST WJpc WJvm										
	von Bastian et al. (2013a)	yes*	BIND NB	VCSP	BOMAT RAVEN	KI TSW										
	von Bastian et al. (2013b)	yes*	BIND	MUT SBPMT	BIS SYL	FLT S TSW	MT			BIND	MUT SBPMT	BIS SYL	FLT S TSW	MT		
	Zhao et al. (2013)	no info	NB													
	Heinzel et al. (2014)	yes*	DSPf DSPb		RAVEN LPS-3	VFT	DSS	WLL								
	Onraedt et al. (2014)	yes*	IST RSPT						BDI-II RRS							BDI-II RRS
	Richmond et al. (2014)	yes*		OSPAN SYMSP	RAVEN	ANTIS S	SART VT	WLL								
healthy elderly adults	Buschkühl et al. (2008)	yes*	~~DSPt~~ ~~BSPt~~					CGFT ~~WMS-R~~		~~DSPt~~ ~~BSPt~~					CGFT ~~WMS-R~~	
	Dahlin et al. (2008a)	yes*	NB													
	Dahlin et al. (2008b)	yes*	DSPf DSPb NB	CPSP	RAVEN		COWAT DST	WLL WP		DSPf DSPb NB	CPSP	RAVEN		COWAT DST	WLL WP	
	Li et al. (2008)	yes*	~~NB~~	~~OSPAN~~ ~~ROSP~~						~~NB~~	~~OSPAN~~ ~~ROSP~~					
	Borella et al. (2010)	yes*	DSPf DSPb	DM	~~CFT~~	S	~~PC~~			DSPf DSPb	DM	CFT	S	PC		
	Schmiedek et al. (2010)	yes*	~~ASP~~ NB SMU	CSP ROSP RSP	BIS RAVEN		BIS	BIS WP								
	Brehmer et al. (2011)	yes*	DSPf DSPb BSPf BSPb PASAT		RAVEN	S		RAVLT								
	Richmond et al. (2011)	yes*	DSPf DSPb	RSP	RAVEN		~~SR~~ TAP	CVLT								
	Zinke et al. (2011)	yes*			RAVEN	S										

Table 2 continued

participants	study	outcomes immediately after training								outcomes after the follow-up period						
		improved trained task	near transfer on WM		far transfer on other domains					near transfer on WM		far transfer on other domains				
			simple	complex	reasoning	EF	attention	memory	everyday	simple	complex	reasoning	EF	attention	memory	everyday
healthy elderly adults	Brehmer et al. (2012)	yes*	DSPf DSPb BSPf BSPb PASAT		RAVEN	S		RAVLT	CFQ	DSPf DSPb BSPf BSPb PASAT		RAVEN	S		RAVLT	CFQ
	Carretti et al. (2012)	yes*	WSP		CFT					WSP		CFT				
	Nouchi et al. (2012)	yes*	DSPf DSPb			FAB	DCT DSS SYS TMT		MMSE							
	Borella et al. (2013)	yes*	DSPf DSPb	DM	CFT	S	PC			DSPf DSPb	DM	CFT	S	PC		
	McAvenue et al. (2013)	no info	DSPf DSPb LNS					RAVLT RBMT	ARCES COPM MFS	DSPf DSPb LNS					RAVLT RBMT	ARCES COPM MFS
	Stepankova et al. (2013)	yes*	DSPt LNS		MR	BD										
	Theill et al. (2013)	yes*	CB7		RAVEN	IGD	CPT DSS	PA								
	von Bastian et al. (2013a)	yes*	BIND NB	VCSP	RAVEN	KI TSW										
	Borella et al. (2014) Trial 1	yes*	BSPf BSPb	CWMS	CFT	S	PC			BSPf BSPb	CWMS	CFT	S	PC		
	Borella et al. (2014) Trial 2	yes*	BSPf BSPb	CWMS	CFT	S	PC			BSPf BSPb	CWMS	CFT	S	PC		
	Heinzel et al. (2014)	yes*	DSPf DSPb		LPS-3 RAVEN	VFT	DSS	WLL								
	Xin et al. (2014)	no info	DSPf DSPb NUM		RAVEN											
	Zimmermann et al. (2014)	no info	DSPf WSP			HT VFT WCST	TMT	WLL								
	Zinke et al. (2014)	yes*	BSPf LESP		RAVEN	S TOH				BSPf LESP		RAVEN				
patients with acquired brain injuries	Sohlberg et al. (2000)	no info	PASAT				COWAT DIT TMT VT									
	Westerberg et al. (2007a)	yes	DSPt BSPt PASAT		RAVEN	S	2&7	WLL	CFQ							

Table 2 continued

participants	study	outcomes immediately after training								outcomes after the follow-up period						
		improved trained task	near transfer on WM		far transfer on other domains					near transfer on WM		far transfer on other domains				
			simple	complex	reasoning	EF	attention	memory	everyday	simple	complex	reasoning	EF	attention	memory	everyday
patients with acquired brain injuries	Vogt et al. (2009)	yes*	BSPf BSPb DSPf DSPb NB PASAT				FST SDMT		CES-D FAMS FSMC MFIS							
	Lundqvist et al. (2010)	yes*	BSPf BSPb ~~PASAT~~	LISP PICSP		S			COPM EQ-5D SR	BSPf BSPb PASAT	LISP PICT		S			
	Houben et al. (2011)	yes*	WMI						ALCI	WMI						ALCI
	Johansson et al. (2012)	yes*							CFQ COPM							CFQ
	Åkerlund et al. (2013)	no info	BSPf BSPb DSPf DSPb WAISwm						BNIS DEX	BSPf BSPb DSPf DSPb WAISwm						BNIS DEX
	Carretti et al. (2013)	yes*	DSPf DSPb	DM	CFT		PC	WLL								
patients otherwise diagnosed	Horowitz-Kraus et al. (2009)	no info	~~DSP~~ SBT	OPP						DSP SBT	OPP					
	Van der Molen et al. (2010)	yes	BSPf DSPf DSPb NWR SSP VP	LIR	RAVEN	S		STR		BSPf DSPf DSPb NWR SSP VP	LIR	RAVEN	S		STR	
	Kronenberger et al. (2011)	yes	BSPf BSPb DSPf DSPb						BRIEF	BSPf BSPb DSPf DSPb						BRIEF
	Løhaugen et al. (2011)	yes*	~~BSPf~~ ~~BSPb~~ DSPf DSPb LNS					WLL WMS-R	PR	BSPf BSPb DSPf DSPb LNS					WLL WMS-R	
	Shiran et al. (2011)	yes*	SBT													
	Bennett et al. (2013)	yes*	CR WR	DM OOO					BRIEF	CR WR	DM OOO					BRIEF
	Hardy et al. (2013)	no info	WRAMLv WRAMLs				FW NL		PR	WRAMLv WRAMLs				FW NL		PR
	Kesler et al. (2013)	no info	DSP			WCST VFT	SYS	HVLT	BRIEF CAD							
	Verbeken et al. (2013)	no info	BSPf BSPb			TST			BMI BRIEF							BMI

Note. As the studies from Klingberg et al. (2005) and Dahlin (2011), Olesen et al. (2004) and Westerberg et al. (2007b), as well as Egeland et al. (2013) and Hovik et al. (2013) shared the same subjects, doubling of datasets was avoided by combining the respective outcome measures of each study into one trial; ADHD = attention deficit hyperactivity disorder; yes* = statistically significant improvement in the trained task confirmed; no info = no information on improvement in the trained task provided; WM = working memory; simple = near transfer on WM measured with simple span WM tasks; complex = near transfer on WM measured with complex span WM tasks; reasoning = outcomes testing reasoning and intelligence; EF = outcomes testing cognitive control and executive functioning; attention = outcomes testing attention and processing speed; memory = outcomes testing long-term memory; everyday = outcomes testing everyday life functioning and disorder symptoms; ~~outcome~~ = outcome not included in the meta-analysis (e.g., due to significant pre-test differences); outcome = significant improvement in the outcome after WM training/follow-up period; outcome = no significant improvement in the outcome after WM training/follow-up period. *Abbreviations of outcome measures:* 2&7 = RUFF 2&7 Test; ABT = Attentional Blink Task; ADHD-RS = ADHD Rating Scale; ALCI = Alcohol Use Index; ANL = Analogies; ANT = Attention networks' task; ANTIS = Antisaccade; ARCES = Attention-related cognitive error scale; ARS-IV = ADHD Rating Scale; ARSP = Arrow Span; ASP = Animal Span; ATCLS = Air Traffic Control Laboratory Simulator; AWMA = Automated Working Memory Assessment (verbal/visuo-spatial); axCPT = A-X Continuous Performance Test; BD = Block Design; BDI-II = Becks Depression Inventory II; BIND = Binding task; BIS = Berliner Intelligenzstruktur-Test; BI = Body Mass Index; BNIS = Barrow Neurological Institute Screen for Higher Cerebral Functions; BOMAT = Bochumer Matrizentest; BRIEFp/t = Behavior Rating Inventory of Executive Function (parent's/teacher's version); BR =Block Recall; BSPb/f/t = Span Board Task (backwards/forwards/total); BVRT = Benton Visual Retention Test; CAC = Controlled Attention Composite; CAD = Clinical Assessment of Depression; CB7 = Counting Backwards in steps of seven; CDR = Card Rotation; CDT = Change Detection Task (-fe = filter efficiency score, -wm = working memory capacity score); CES-D = Center for Epidemiologie Studies Depression Scale; CFQ = Cognitive Failures Questionnaire; CFT = Culture Fair Test; CGAS = Children's Global Assessment Scale; CGFT = Computergestützter Gedächtnis-Funktionstest; CLASS = classroom skill activities (dr = detecting rhymes, fi = following instructions, sr = sentence counting and recall); COPM = Canadian Occupational Performance Measure; COWAT = Controlled Oral Word Association Test; CPSP = Computation Span; CPST = Colorado Perceptual Speed Test; CPT = Continuous Performance Task; CR = Counting Recall; CTS = Cued Recall Span; CRT = Choice Reaction Time Task; CSP = Counting Span; CT = Control Tower Task; CVLT = California Verbal Learning Test; DBDp/t = Disruptive Behavior Disorders Rating Scale (parent/teacher evaluation); DCT = Digit Cancellation Task; DDT = Delay Distraction Task; CWMS = Categorization Working Memory Span Task; D2 = D2 Test of Attention; DAT = Differential Aptitude Test (subtest reasoning: -AR = abstract, -NR = numerical, -VR = verbal); DEX = The Dysexecutive Questionnaire; DIT = Distractibility Task; DL = ETS - Deciphering Languages; DM = Dot Matrix Task; DSPb/f/t = Digit Span Task (backwards/forwards/total); DSS = Digit Symbol Subsitution Task; DST = Digit-Symbol Test; DT = Dual Task; EAP = Test for the Examination of Aphasia; ECVB = L'Echelle de communication verbale de Bordeaux; EQ-5D = EuroQol Questionnaire; FAB = Frontal Assessment Battery at bedside; FAT = Finding A's Test; FAMS = Functional Assessment of Multiple Sclerosis; FLT =Flanker Task (-N = numerical, -V = verbal); FSMC = Fatigue Scale for Motor and Cognitive Functions; FST = Faces Symbol Test; FSW = Focus Switching Task; FW = Finger Windows task; GO = Go/No-Go Task; HADS = The Hospital Anxiety and Depression Scale; HEAD = number of head movements; HT = Hayling Test; HVLT = Hopkins Verbal Learning Test; IDP = Identical Pictures; IFRr/pr = Immediate Free Recall (recency/pre-recency positions); IGD = Inventar zur Gedächtnisdiagnostik; ILR = ETS - Inference and Logical Reasoning; INF = Inferences; IOWACS = IOWA Conners Scale; IST = Internal Shift Task; IT = Instructions Task; KI = Kinship Integration task; KTT = Keep Track Task; LB = Leiter Battery; LDT = Knox Cubes LDT; LEC = Letter Comparison; LESP = Letter Span; LGT = Local Global Task; LIR = Listening Recall; LISP = Listening Span; LMR = Letter Mental Rotation; LNS = Letter-Number Sequencing; LNS/SC = Composite of LNS and Sentence Span task; LPS-3 = Leistungsprüfsystem Subtest 3; LS = Letter Sets; MATHS = Composite Mathematics Score; MCT = Mental Counters Task; MFIS = Modified Fatigue Impact Scale; MFS = Memory Failure Scale; MHT = Mill Hill Test; MMSE = Mini-Mental State Examination; MR = Matrix Reasoning; MROT = Mental Rotation; MT = Monitoring Task; MUT = Memory Updating Task; NB = N-Back Task; NEPSY = A Developmental Neuropsychological Assessment (subtests: -a = attention, -ef = executive functioning, m = memory); NL = Number Letter Task; NS = Number Series; NUC = Number Comparison; NUM = Numerical Updating task; NUS = Number Sets; NWR = Nonword Recall; OOO = Odd One Out; OPP = Opposites Test; OR = Significant Other's Rating of Symptoms; OSPAN = Operation Span Task; PA = Pair-Associates Learning; PAS = Preschool Anxiety Scale; PASAT = Paced Auditory Serial Addition Test; PC = Pattern Comparison; PF = Paper Folding; PICSP = Picture Span; PMA = Primary Mental Abilities Battery (-R = inductive reasoning, -V = Vocabulary); PR = Parent's Rating of Symptoms; PSC = Processing Speed Composite; RAST = Restricted Academic Setting Task; RAVEN = Raven's Progressive Matrices; RAVLT = Rey Auditory Verbal Learning Test; RBMT = Rivermead Behavioral Memory Test; RC = Reasoning Composite; PFCB = Paper Folding and Cutting Test-Battery; RMT = Recognition Memory Task; ROSP = Rotation Span; RRS = Ruminative Response Scale; RSP = Reading Span; RSPT = Running Span Task; RT = simple reaction time task; S = Stroop Task; SACT = S-A Creativity Test; SADT = Sustained Attention Dots Task; SART = Sustained Attention Response Task; SBPMT = Simultaneous Brown-Peterson and Memory Task; SBT = Sternberg Task; SDMT = Symbol Digit Modalities Test; SDQ = Strength and Difficulties Questionnaire; SER = Sentence Recall; SERIAL7 = Serial Seven's Test; SHAPE = Shape School; SHB = Shapebuilder task; SIMON = spatial Simon task; SMU = Spatial Memory Updating; SPMT = Serial Position Memory Task; SPR = Spatial Recall; SR = Self-Report; SRT = Selective Reminding Test; SSP = Spatial Span; ST = Sentences Task of WPPSI-RN; STMBs/v = Short Term Memory Battery (visuo-spatial/verbal); STR = Story Recall; SWAN = Strength and Weakness of ADHD-symptoms and Normal-behavior scale; SWM = CANTAB Spatial Working Memory; SWT = Syn-Win Task; SXT = Kyodai SX test; SYL = Syllogisms; SYMSP = Symmetry Span; SYS = Symbol Search; TAP = Tests of Attentional Performance; TB-IT = Tanaka B-type Intelligence Test; TEDT = Target-Epoch Distraction Task; TMT = Trail Making Test; TMT4 = D-KEFS Trail Making Test task 4: divided attention; TOH = Tower Of Hanoi; TOL = Tower Of London; TONI = Test of Nonverbal Intelligence; TR = Teacher's Rating of Symptoms; TST = The Stop Task; TSW = Task Switching; VAT = Verbal Analogies Test; VISAT = Visual-Arrays Task; VISC = Visual Scanning subtest of the D-KEFS; VCSP = Verbal Complex Span task; VFT = Verbal Fluency Test; VOC = Vocabulary Test; VSP = Visual Span of Leiter-International Performance Scale-Revised; VP = Visual Patterns Test; VT = Vigilance Task; WAIS = Wechsler Adult Intelligence Scale (-b = blocks; -s = similarities; -v = vocabulary; -wm = working memory); WASI = Wechsler Abbreviated Scales of Intelligence (verbal/nonverbal); WBE = Word Beginning and Ending Test; WCST = Wisconsin Card Sorting Test; WIAT-M = Wechsler Individual Achievement Test – II, Subtest mathematical reasoning; WJ = Woodcock Johnson-III-Test (-a = achievement, -pc = pair cancellation, -vm = visual matching); WLL = Word List Learning; WMBs/v = Working Memory Battery (visuo-spatial/verbal); WMI = Working Memory Index; WMRS = Working Memory Rating Scale; WMS-R = Wechsler Memory Scale-Revised; WOND = Wechsler Objective Numerical Dimensions; WP = Word Pairs; WR = Word Recall; WRAML = Wide Assessment of Memory and Learning (-v = verbal working memory, -s = symbolic working memory; WRAT4 = Wide Range Achievement Test 4 - Progress Monitoring Version; WSP = Word Span.

Table 3 Immediate near transfer effects on WM functions

a) uncorrected data

			sensitivity analysis		heterogeneity		
outcome measure	*k*	mean ES [95 % CI]	min. mean ES [95 % CI]	max. mean ES [95 % CI]	X^2	I^2	publication bias
overall WM	97	0.44 [0.35, 0.53]***	0.41 [0.34, 0.49]***	0.45 [0.36, 0.54]***	193.70***	50	overestimation of the effect
simple WM	89	0.45 [0.34, 0.55]***	0.41 [0.32, 0.50]***	0.46 [0.35, 0.56]***	214.37***	59	overestimation of the effect
complex WM	40	0.40 [0.25, 0.54]***	0.36 [0.23, 0.49]***	0.42 [0.28, 0.56]***	108.78***	64	no
digit span task forwards	29	0.37 [0.19, 0.55]***	0.29 [0.17, 0.41]***	0.39 [0.21, 0.58]***	62.90***	55	slight overestimation of the effect
digit span task backwards	26	0.51 [0.29, 0.74]***	0.44 [0.25, 0.63]***	0.55 [0.33, 0.77]***	69.10***	64	slight overestimation of the effect
span board task forwards	18	0.51 [0.31, 0.71]***	0.45 [0.28, 0.63]***	0.54 [0.34, 0.75]***	35.23**	52	no
span board task backwards	14	0.62 [0.33, 0.91]***	0.54 [0.28, 0.79]***	0.68 [0.38, 0.97]***	33.94**	62	no
n-back task	18	0.25 [0.06, 0.44]**	0.14 [0.00, 0.28]	0.28 [0.08, 0.47]**	29.71*	43	no
PASAT	8	0.47 [0.24, 0.70]***	0.45 [0.21, 0.70]***	0.49 [0.24, 0.74]***	0.87	0	no

b) data corrected for outliers

			sensitivity analysis		heterogeneity		
outcome measure	*k*	mean ES [95 % CI]	min. mean ES [95 % CI]	max. mean ES [95 % CI]	X^2	I^2	publication bias
overall WM	92	0.37 [0.31, 0.43]***	0.36 [0.30, 0.42]***	0.38 [0.32, 0.44]***	93.60	3	no
simple WM	84	0.36 [0.28, 0.44]***	0.34 [0.27, 0.41]***	0.37 [0.30, 0.44]***	110.08*	25	no
complex WM	36	0.33 [0.21, 0.44]***	0.30 [0.19, 0.41]***	0.35 [0.23, 0.46]***	62.97**	44	no
digit span task forwards	26	0.24 [0.12, 0.36]***	0.22 [0.11, 0.34]***	0.25 [0.13, 0.37]***	16.15	0	no
digit span task backwards	23	0.35 [0.20, 0.50]***	0.32 [0.17, 0.46]***	0.40 [0.25, 0.55]***	17.28	36	no
span board task forwards	17	0.45 [0.28, 0.63]***	0.40 [0.25, 0.54]***	0.49 [0.31, 0.66]***	24.38	34	no
span board task backwards	12	0.46 [0.26, 0.65]***	0.41 [0.21, 0.62]***	0.50 [0.30, 0.70]***	9.13	0	no
n-back task	17	0.14 [0.00, 0.28]	0.12 [-0.02, 0.27]	0.16 [0.01, 0.31]*	6.80	0	no
PASAT	8	0.47 [0.24, 0.70]***	0.45 [0.21, 0.70]***	0.49 [0.24, 0.74]***	0.87	0	no

Note. All effect sizes represent Hedges' adjusted *g*. Sensitivity analyses estimate the influence of possible outliers by excluding studies one by one and thereby adjusting the overall effect size. Heterogeneity is measured by the χ^2-test of homogeneity and I^2 which estimates the proportion of total variability explained by heterogeneity. The presence of publication bias was examined both visually with the inspection of funnel plots and analytically with Egger's Test. WM = working memory; PASAT = Paced Auditory Serial Addition Test; k = number of analyzed effect sizes; ES = effect size; 95 % CI = 95 % confidence interval; * significant at p < .05; ** significant at p < .01; *** significant at p < .001.

Table 4 Immediate far transfer effects to other cognitive domains and everyday life functioning

a) uncorrected data

			sensitivity analysis		heterogeneity		
outcome measure	*k*	mean ES [95 % CI]	min. mean ES [95 % CI]	max. mean ES [95 % CI]	X^2	I^2	publication bias
reasoning/intelligence	56	0.24 [0.15, 0.34]***	0.22 [0.13, 0.31]***	0.25 [0.16, 0.34]***	85.90**	36	overestimation of the effect
RAVEN	38	0.23 [0.13, 0.33]***	0.21 [0.11, 0.31]***	0.25 [0.15, 0.35]***	45.59	19	slight overestimation of the effect
cognitive control/EF	55	0.20 [0.10, 0.29]***	0.17 [0.08, 0.26]***	0.21 [0.11, 0.31]***	89.72**	40	no
Stroop	23	0.31 [0.14, 0.48]***	0.25 [0.11, 0.39]***	0.35 [0.20, 0.50]***	39.87**	45	no
attention/processing speed	43	0.20 [0.08, 0.32]**	0.16 [0.06, 0.27]**	0.22 [0.11, 0.33]***	66.39*	37	no
long-term memory	26	0.18 [0.02, 0.33]*	0.14 [0.00, 0.29]	0.21 [0.07, 0.35]**	37.63	34	no
everyday life functioning	32	0.17 [0.05, 0.28]**	0.14 [0.03, 0.25]*	0.21 [0.09, 0.33]***	34.87	11	overestimation of the effect

b) data corrected for outliers

			sensitivity analysis		heterogeneity		
outcome measure	*k*	mean ES [95 % CI]	min. mean ES [95 % CI]	max. mean ES [95 % CI]	X^2	I^2	publication bias
reasoning/intelligence	54	0.23 [0.14, 0.32]***	0.21 [0.12, 0.30]***	0.24 [0.15, 0.33]***	79.05*	33	slight overestimation of the effect
RAVEN	38	0.23 [0.13, 0.33]***	0.21 [0.11, 0.31]***	0.25 [0.15, 0.35]***	45.59	19	slight overestimation of the effect
cognitive control/EF	52	0.20 [0.13, 0.27]***	0.19 [0.12, 0.27]***	0.21 [0.13, 0.28]***	39.07	0	no
Stroop	21	0.30 [0.17, 0.43]***	0.28 [0.14, 0.41]***	0.33 [0.20, 0.46]***	13.43	0	no
attention/processing speed	41	0.18 [0.09, 0.27]***	0.16 [0.07, 0.26]***	0.20 [0.10, 0.29]***	40.73	2	no
long-term memory	26	0.18 [0.02, 0.33]*	0.14 [0.00, 0.29]	0.21 [0.07, 0.35]**	37.63	34	no
everyday life functioning	31	0.14 [0.03, 0.25]*	0.11 [0.01, 0.22]*	0.20 [0.08, 0.32]***	31.44	5	overestimation of the effect

Note. All effect sizes represent Hedges' adjusted *g*. Sensitivity analyses estimate the influence of possible outliers by excluding studies one by one and thereby adjusting the overall effect size. Heterogeneity is measured by the χ^2-test of homogeneity and I^2 which estimates the proportion of total variability explained by heterogeneity. The presence of publication bias was examined both visually with the inspection of funnel plots and analytically with Egger's Test. RAVEN = Raven's Progressive Matrices; EF = Executive Functioning; k = number of analyzed effect sizes; ES = effect size; 95 % CI = 95 % confidence interval; * significant at $p < .05$; ** significant at $p < .01$; *** significant at $p < .001$.

Table 5 Long-term effects of WM training

a) uncorrected data

			sensitivity analysis		heterogeneity		
outcome measure	*k*	mean ES [95 % CI]	min. mean ES [95 % CI]	max. mean ES [95 % CI]	X^2	I^2	publication bias
overall WM	32	0.54 [0.40, 0.69]***	0.51 [0.38, 0.64]***	0.57 [0.43, 0.71]***	50.61*	39	no
simple WM	29	0.48 [0.34, 0.62]***	0.44 [0.32, 0.57]***	0.51 [0.37, 0.65]***	41.34	32	no
complex WM	15	0.55 [0.21, 0.89]**	0.39 [0.15, 0.63]**	0.60 [0.25, 0.95]***	60.67***	77	no
digit span task forwards	13	0.31 [0.12, 0.51]**	0.27 [0.09, 0.45]**	0.35 [0.17, 0.53]***	14.28	16	no
digit span task backwards	12	0.26 [0.04, 0.49]*	0.22 [-0.02, 0.45]	0.31 [0.07, 0.56]*	15.75	30	no
span board task forwards	10	0.67 [0.36, 0.98]***	0.56 [0.31, 0.81]***	0.76 [0.46, 1.05]***	22.38**	60	no
span board task backwards	9	0.73 [0.47, 0.99]***	0.65 [0.40, 0.90]***	0.81 [0.58, 1.04]***	11.35	30	no
reasoning/ intelligence	19	0.20 [0.07, 0.34]**	0.17 [0.04, 0.31]*	0.22 [0.08, 0.35]**	13.13	0	no
cognitive control/ EF	18	0.21 [0.06, 0.36]**	0.16 [0.02, 0.29]*	0.24 [0.10, 0.38]***	21.70	22	slight overestimation of the effect
attention/processing speed	13	0.22 [0.02, 0.42]*	0.15 [-0.04, 0.33]	0.29 [0.09, 0.48]**	14.12	15	slight overestimation of the effect
long-term memory	8	-0.02 [-0.24, 0.20]	-0.07 [-0.31, 0.16]	0.02 [-0.24, 0.27]	3.68	0	no
everyday life functioning	17	0.17 [0.02, 0.32]*	0.15 [-0.01, 0.31]	0.20 [0.04, 0.36]*	7.29	0	no

b) data corrected for outliers

			sensitivity analysis		heterogeneity		
outcome measure	*k*	mean ES [95 % CI]	min. mean ES [95 % CI]	max. mean ES [95 % CI]	X^2	I^2	publication bias
overall WM	31	0.51 [0.38, 0.64]***	0.48 [0.36, 0.61]***	0.53 [0.40, 0.66]***	40.06	25	no
simple WM	28	0.44 [0.32, 0.57]***	0.41 [0.29, 0.53]***	0.47 [0.35, 0.59]***	29.88	10	no
complex WM	14	0.39 [0.15, 0.63]**	0.32 [0.11, 0.53]**	0.43 [0.17, 0.69]**	27.98**	54	no
digit span task forwards	11	0.30 [0.12, 0.49]**	0.28 [0.09, 0.47]**	0.33 [0.14, 0.52]***	4.10	0	no
digit span task backwards	12	0.26 [0.04, 0.49]*	0.22 [-0.02, 0.45]	0.31 [0.07, 0.56]*	15.75	30	no
span board task forwards	10	0.67 [0.36, 0.98]***	0.56 [0.31, 0.81]***	0.76 [0.46, 1.05]***	22.38**	60	no
span board task backwards	9	0.73 [0.47, 0.99]***	0.65 [0.40, 0.90]***	0.81 [0.58, 1.04]***	11.35	30	no
reasoning/ intelligence	16	0.15 [0.01, 0.29]*	0.14 [0.00, 0.28]	0.16 [0.02, 0.31]*	1.94	0	no
cognitive control/ EF	16	0.20 [0.06, 0.34]**	0.18 [0.04, 0.32]*	0.23 [0.08, 0.38]**	6.63	0	slight overestimation of the effect
attention/processing speed	12	0.15 [-0.04, 0.33]	0.09 [-0.10, 0.29]	0.21 [0.01, 0.42]*	6.98	0	no
long-term memory	8	-0.02 [-0.24, 0.20]	-0.07 [-0.31, 0.16]	0.02 [-0.24, 0.27]	3.68	0	no
everyday life functioning	17	0.17 [0.02, 0.32]*	0.15 [-0.01, 0.31]	0.20 [0.04, 0.36]*	7.29	0	no

Note. All effect sizes represent Hedges' adjusted *g*. Sensitivity analyses estimate the influence of possible outliers by excluding studies one by one and thereby adjusting the overall effect size. Heterogeneity is measured by the χ^2-test of homogeneity and I^2 which estimates the proportion of total variability explained by heterogeneity. The presence of publication bias was examined both visually with the inspection of funnel plots and analytically with Egger's Test. WM = working memory; EF = Executive Functioning; k = number of analyzed effect sizes; ES = effect size; 95 % CI = 95 % confidence interval; * significant at p < .05; ** significant at p < .01; *** significant at p < .001.

Study I Supplemental Materials 2 (Figures A-D)

For: Weicker, J., Villringer, A., & Thöne-Otto, A. (2016). Can impaired working memory functioning be improved by training? A meta-analysis with a special focus on brain injured patients. Neuropsychology, 30(2), 190-212. https://doi.org/10.1037/neu0000227

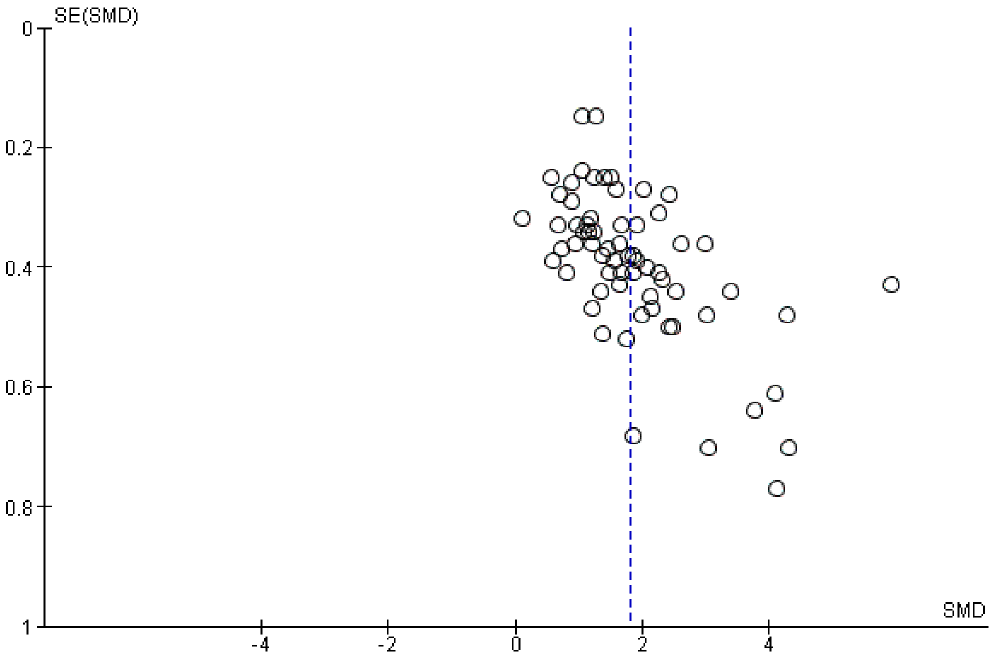

Figure A Funnel plot for the improvement in the trained WM intervention task. Funnel plots depict effect sizes against sample sizes. The circles represent single effect sizes and the dashed line displays the corresponding mean effect size. As funnel plots should be symmetrical in the absence of publication bias, here, an overestimation of the effect is indicated.

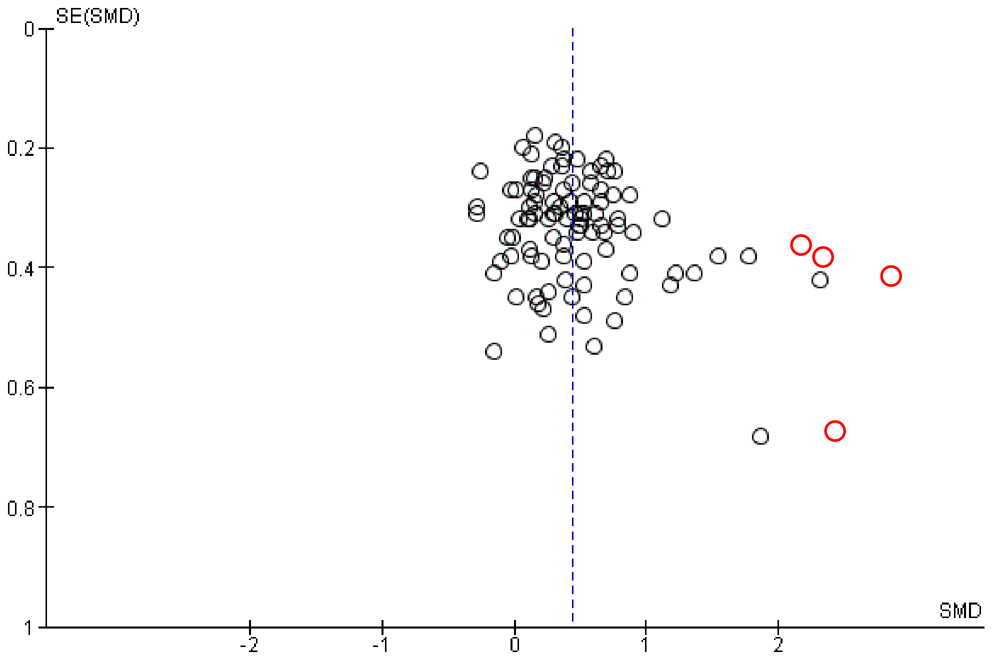

Figure B Funnel plot for immediate near transfer effects on WM functions. Funnel plots depict effect sizes against sample sizes. The circles represent single effect sizes and the dashed line displays the corresponding mean effect size. Red circles depict outliers that were removed from the dataset when a second analysis was performed. As funnel plots should be symmetrical in the absence of publication bias, an overestimation of the effect is indicated in the uncorrected dataset, but not in the corrected dataset without outliers.

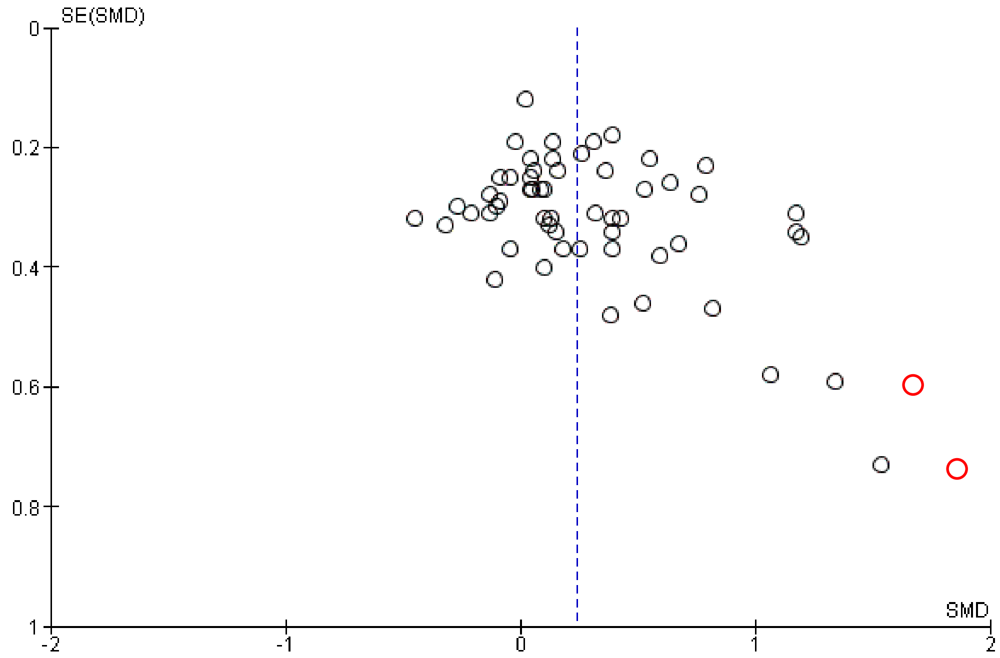

Figure C-1 Funnel plot for immediate near transfer effects on reasoning and intelligence. Funnel plots depict effect sizes against sample sizes. The circles represent single effect sizes and the dashed line displays the corresponding mean effect size. Red circles depict outliers that were removed from the dataset when a second analysis was performed. As funnel plots should be symmetrical in the absence of publication bias, an overestimation of the effect is indicated in both, the uncorrected and corrected dataset without outliers.

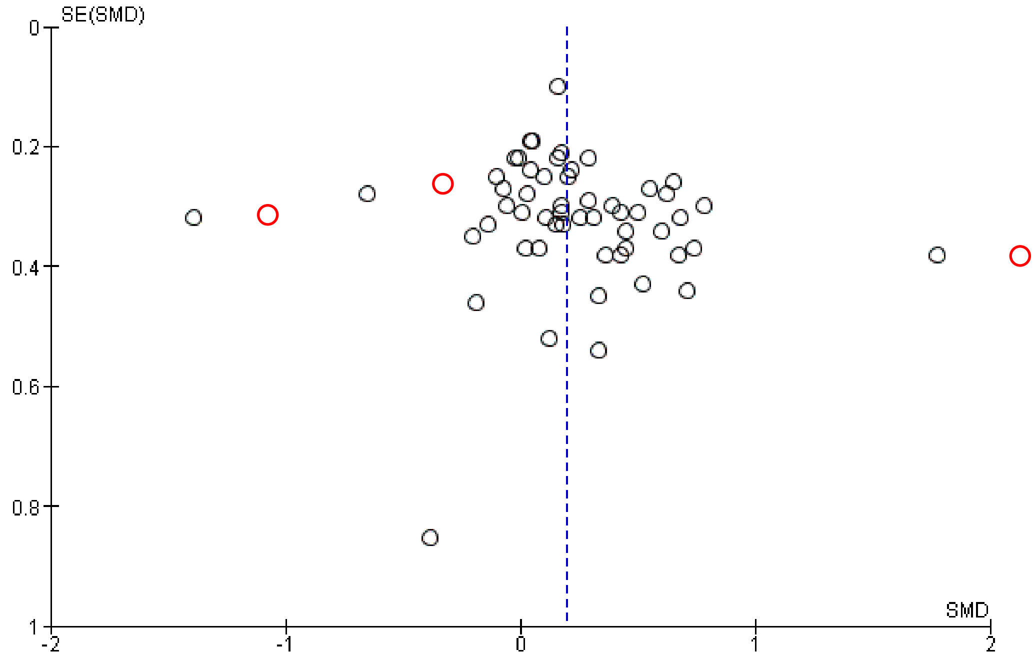

Figure C-2 Funnel plot for immediate near transfer effects on cognitive control and executive functioning. Funnel plots depict effect sizes against sample sizes. The circles represent single effect sizes and the dashed line displays the corresponding mean effect size. Red circles depict outliers that were removed from the dataset when a second analysis was performed. As the funnel plot is symmetrical in the uncorrected as well as in the corrected dataset, no publication bias is indicated.

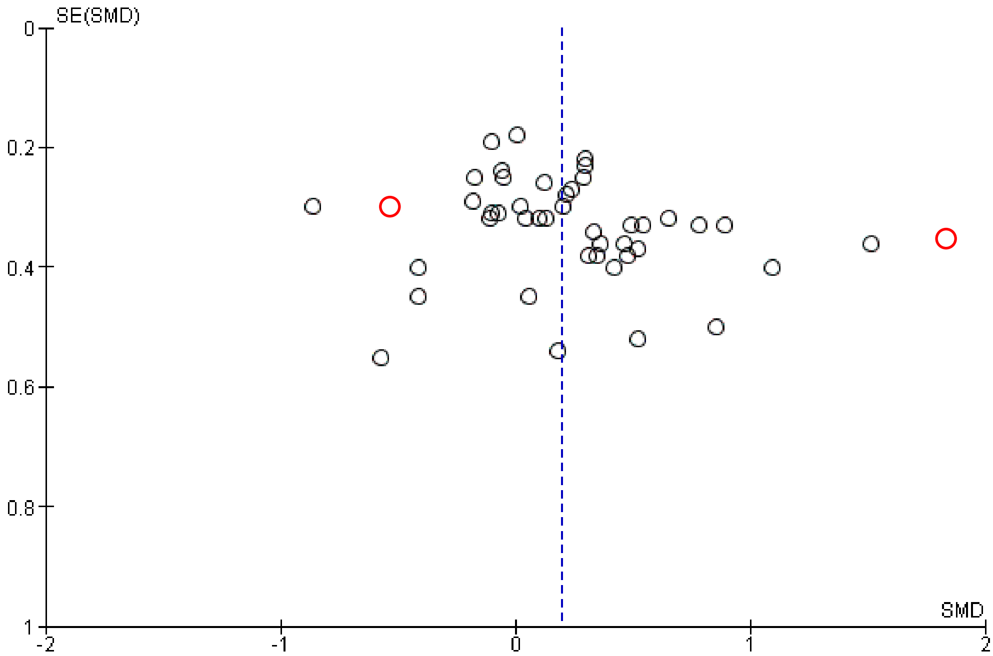

Figure C-3 Funnel plot for immediate near transfer effects on attention and processing speed. Funnel plots depict effect sizes against sample sizes. The circles represent single effect sizes and the dashed line displays the corresponding mean effect size. Red circles depict outliers that were removed from the dataset when a second analysis was performed. As the funnel plot is symmetrical in the uncorrected as well as in the corrected dataset, no publication bias is indicated.

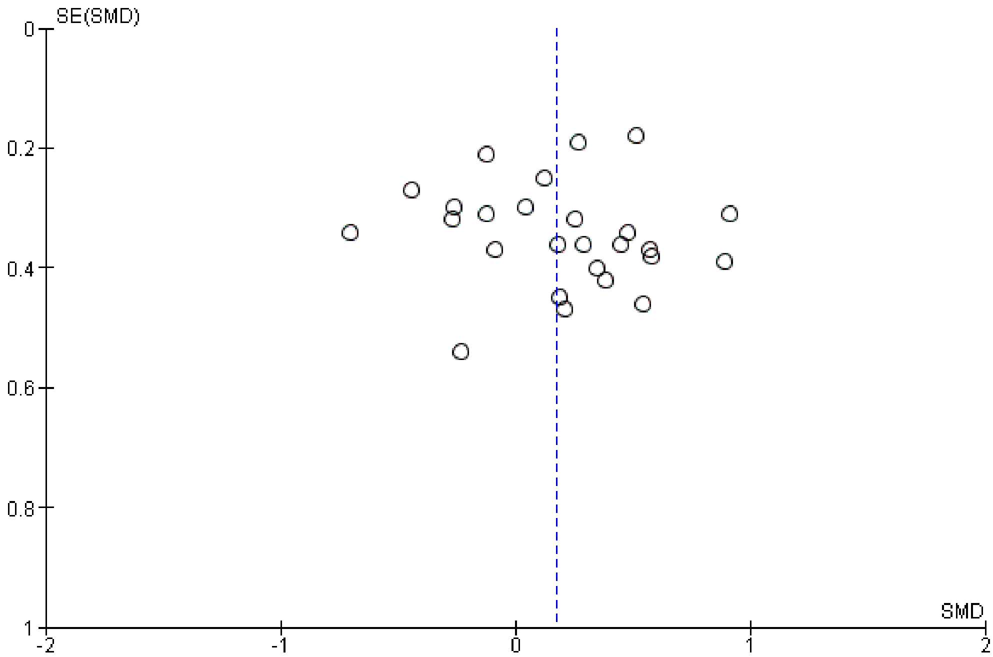

Figure C-4 Funnel plot for immediate near transfer effects on long-term memory. Funnel plots depict effect sizes against sample sizes. The circles represent single effect sizes and the dashed line displays the corresponding mean effect size. As the funnel plot is symmetrical, no publication bias is indicated.

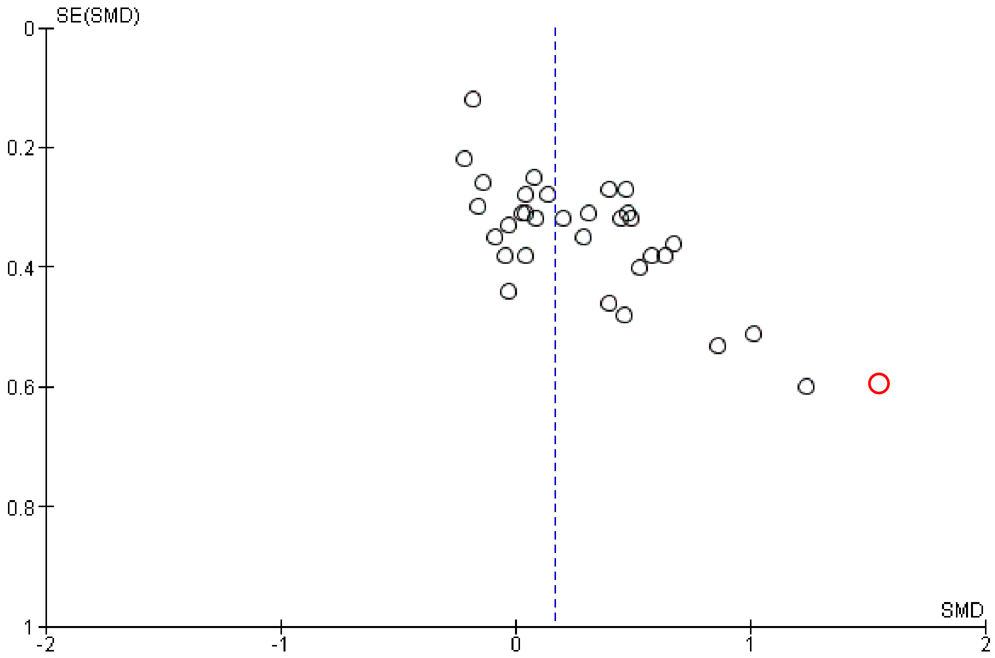

Figure C-5 Funnel plot for immediate near transfer effects on everyday-life functioning and disorder symptoms. Funnel plots depict effect sizes against sample sizes. The circles represent single effect sizes and the dashed line displays the corresponding mean effect size. The red circle depicts an outlier that was removed from the dataset when a second analysis was performed. As funnel plots should be symmetrical in the absence of publication bias, an overestimation of the effect is indicated in both, the uncorrected and corrected dataset without the outlier.

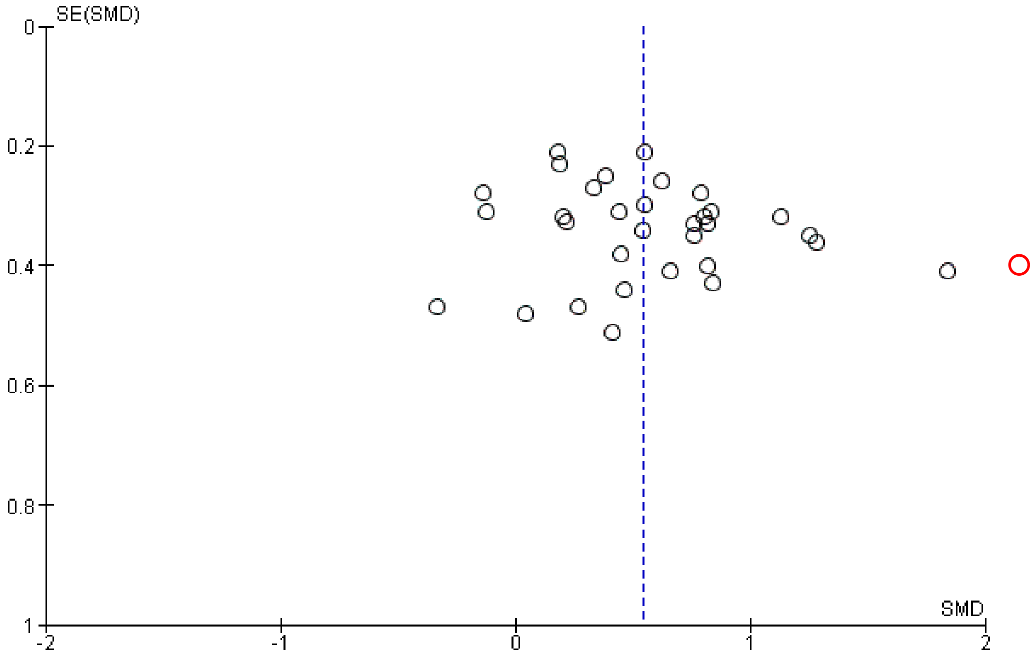

Figure D-1 Funnel plot for long-term effects of WM training on overall WM functioning. Funnel plots depict effect sizes against sample sizes. The circles represent single effect sizes and the dashed line displays the corresponding mean effect size. The red circle depicts an outlier that was removed from the dataset when a second analysis was performed. As the funnel plot is symmetrical in the uncorrected as well as in the corrected dataset, no publication bias is indicated.

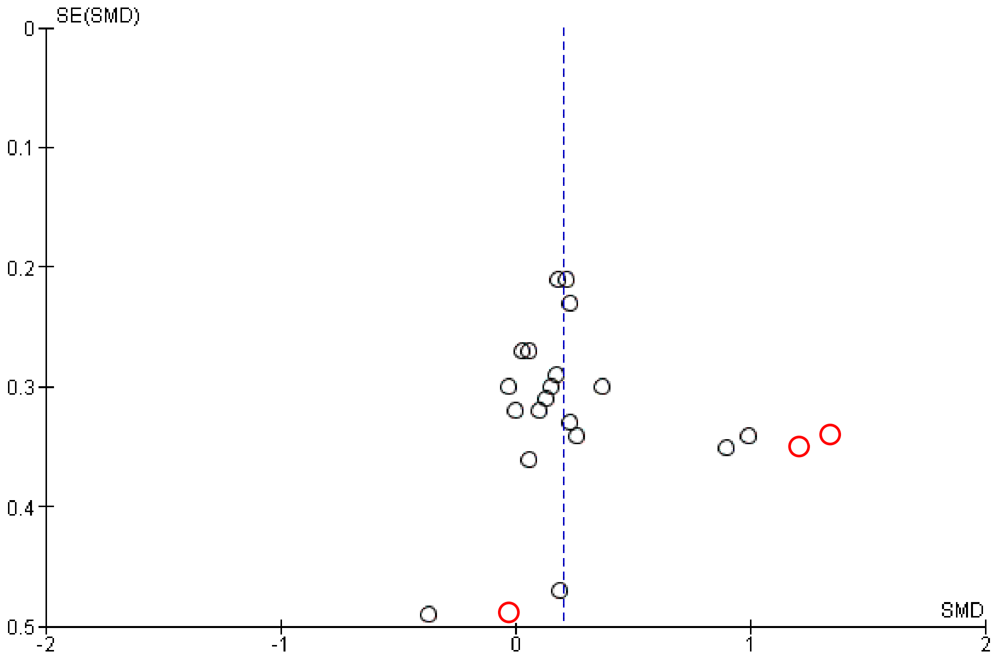

Figure D-2 Funnel plot for long-term effects of WM training on reasoning and intelligence. Funnel plots depict effect sizes against sample sizes. The circles represent single effect sizes and the dashed line displays the corresponding mean effect size. Red circles depict outliers that were removed from the dataset when a second analysis was performed. As the funnel plot is symmetrical in the uncorrected as well as in the corrected dataset, no publication bias is indicated.

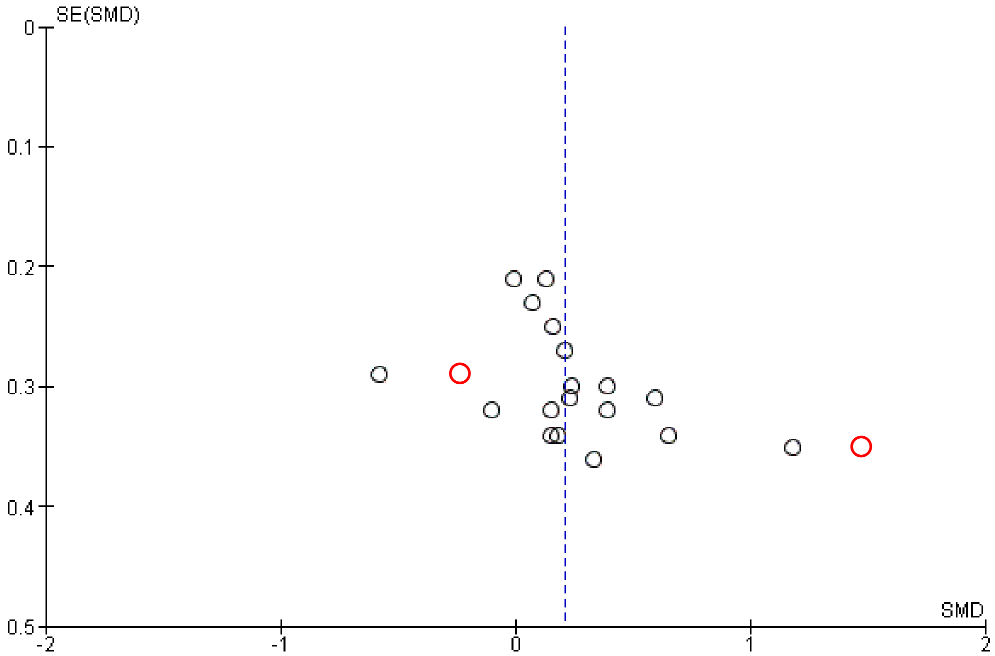

Figure D-3 Funnel plot for long-term effects of WM training on cognitive control and executive functioning. Funnel plots depict effect sizes against sample sizes. The circles represent single effect sizes and the dashed line displays the corresponding mean effect size. Red circles depict outliers that were removed from the dataset when a second analysis was performed. As funnel plots should be symmetrical in the absence of publication bias, a slight overestimation of the effect is indicated in both, the uncorrected and corrected dataset without outliers.

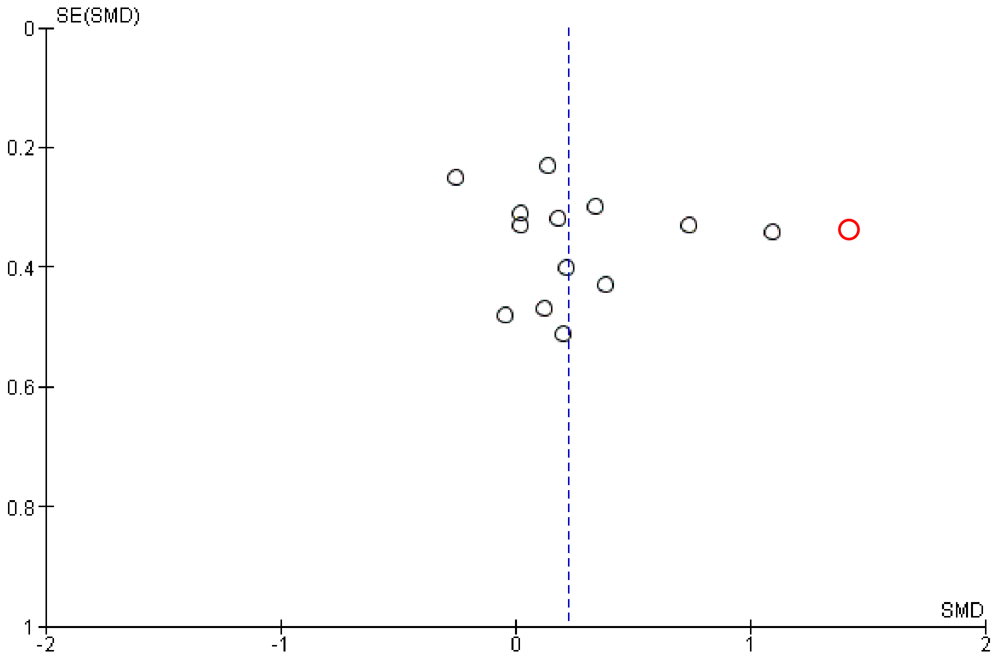

Figure D-4 Funnel plot for long-term effects of WM training on attention and processing speed. Funnel plots depict effect sizes against sample sizes. The circles represent single effect sizes and the dashed line displays the corresponding mean effect size. The red circle depicts an outlier that was removed from the dataset when a second analysis was performed. As the funnel plot is symmetrical in the uncorrected as well as in the corrected dataset, no publication bias is indicated.

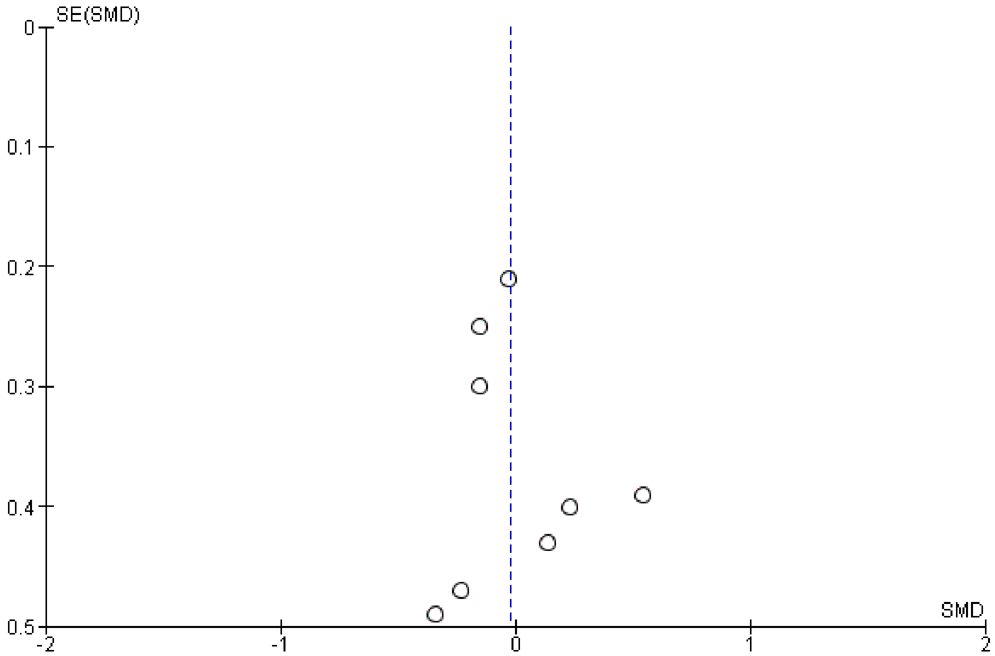

Figure D-5 Funnel plot for long-term effects of WM training on long-term memory. Funnel plots depict effect sizes against sample sizes. The circles represent single effect sizes and the dashed line displays the corresponding mean effect size. As the funnel plot is symmetrical, no publication bias is indicated.

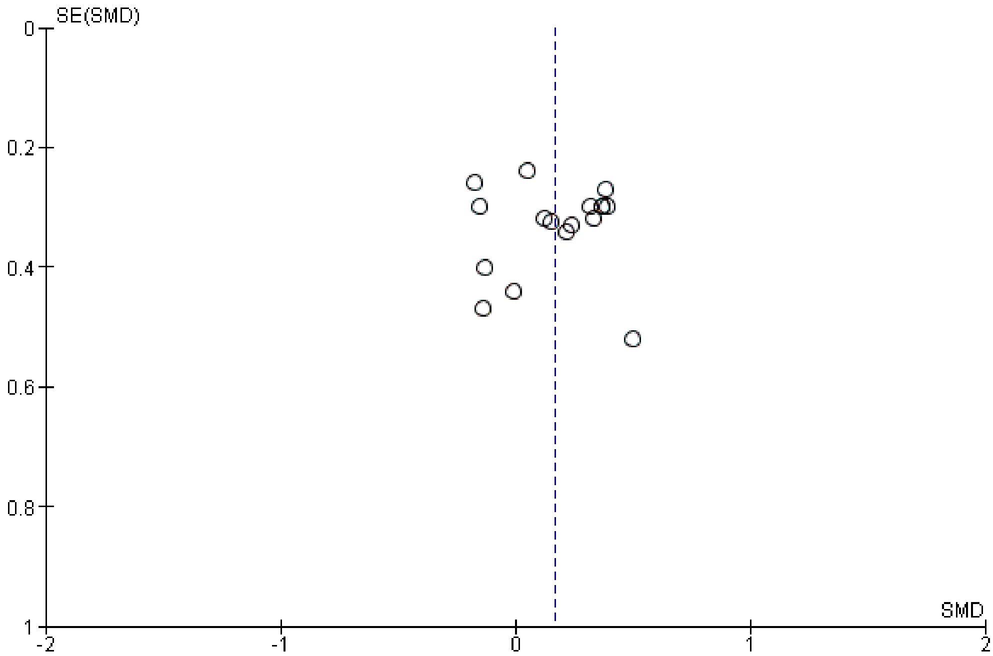

Figure D-6 Funnel plot for long-term effects of WM training on everyday-life functioning and disorder symptoms. Funnel plots depict effect sizes against sample sizes. The circles represent single effect sizes and the dashed line displays the corresponding mean effect size. As the funnel plot is symmetrical, no publication bias is indicated.

Study III Manual of WOME (RehaCom Arbeitsgedächtnistraining)

For: Weicker, J., Hudl, N., & Thöne-Otto, A. (2017). WOME working memory training — A new intervention for individuals with low WM capacity. Unpublished manuscript.

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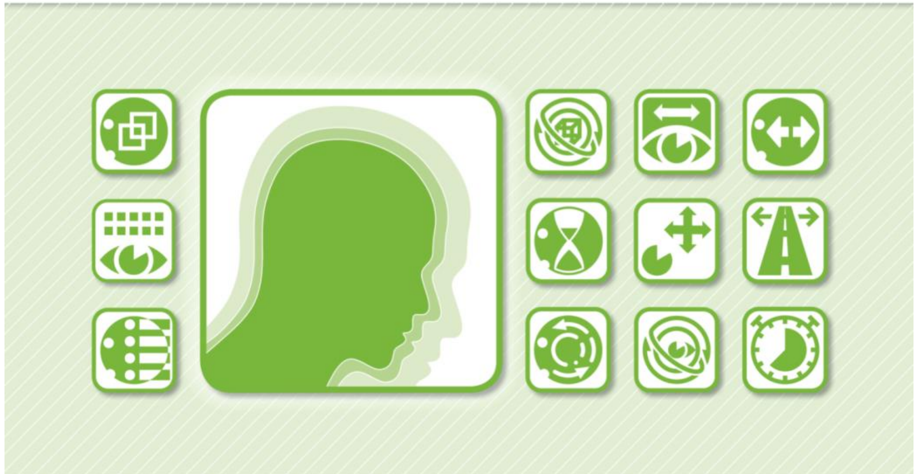

Arbeitsgedächtnis

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Inhaltsverzeichnis

1 Trainingsbeschreibung

1.1 Trainingsaufgaben

Entwicklung

Das Therapiemodul "Arbeitsgedächtnis" wurde in Zusammenarbeit mit Frau Dr. Dipl. Psych. Angelika Thöne-Otto (Tagesklinik für kognitive Neurologie, Universitätsklinikum Leipzig), Frau Dipl. Psych. Juliane Weicker (Tagesklinik für kognitive Neurologie, Universitätsklinikum Leipzig/Max-Planck-Institut für Kognitions- und Neurowissenschaften Leipzig) und Herrn Dr. Dipl. Psych. Stefan Frisch (Psychotraumatologisches Zentrum für Diagnostik und Therapie an der BG Unfallklinik Frankfurt am Main) entwickelt. Hintergründe zum Arbeitsgedächtnis sowie zur theoretischen Fundierung und wissenschaftlichen Evaluation des vorliegenden Programms finden Sie im Kapitel Grundlagen.

Material

Das Arbeitsgedächtnis wird alltagsnah und auf spielerische Weise mit Hilfe eines Kartenspiels trainiert. Verwendet wird ein vollständiges Kartenspiel (52 Karten) mit wahlweise französischem, deutschem oder Farbblatt. Ergänzt wird das Trainingsmaterial durch eine komplexe Schwierigkeitsstruktur, verschiedene Modifikatoren (s. Kapitel Trainingsparameter) und Grafiken zur Verstärkung des Leistungsfeedbacks. Zu Beginn des Trainings wird die Oberfläche des Trainingsprogramms vorgestellt und die Bedienung geübt, Arbeitsgedächtnisprozesse werden dabei noch nicht beansprucht. Das Aufgabenprinzip besteht darin, sich bestimmte Karten, die der „Mitspieler" (oberer Bildschirmrand) zeigt, zu merken, anschließend je nach Modul aus den eigenen Karten des „Spielers" (unterer Bildschirmrand) auszuwählen und per „Drag and Drop" oder Doppelklick „auf den Tisch" (Bildschirmmitte) zu legen.

Module

Das Training ist in drei verschiedene Module gegliedert (zu theoretischen Hintergründen s. Kapitel Trainingsziel). Jedes Modul wird durch einen konkreten Aufgabentyp repräsentiert: alle Karten merken (Speichersysteme), bestimmte Karten merken (Selektive Aufmerksamkeit) und Karten sortieren (Zentrale Exekutive):

- Im **Modul „Speichersysteme"** werden die Karten des „Mitspielers" nach einer kurzen Präsentationszeit wieder verdeckt. Der „Spieler" muss sich die gezeigten Karten einprägen, dieselben Karten aus den eigenen auswählen und „auf den Tisch" legen.
- Im **Modul „Selektive Aufmerksamkeit"** soll sich der Trainierende jeweils nur die Karten einer bzw. zweier Farben merken, die der Sprecher vor jeder Aufgabe neu ankündigt (z. B. „Merken Sie sich nur die Herzkarten"). Die Karten, die der genannten Farbe entsprechen und auf Mitspielerseite gezeigt wurden, soll der Trainierende in die Mitte legen.
- Das **Modul „Zentrale Exekutive"** ist analog zu neuropsychologischen Kurz- und Arbeitsgedächtnistests (z. B. Zahlen- und Blockspannen) in zwei Varianten geteilt. Beim Aufgabentyp „vorwärts sortieren" soll der Trainierende die Karten in der gleichen Reihenfolge „auf den Tisch" legen wie der „Mitspieler", bei „rückwärts sortieren" in der umgekehrten Reihenfolge. Dazu zieht er die Karten des „Spielers" nacheinander auf die markierten Bereiche in der Bildschirmmitte.

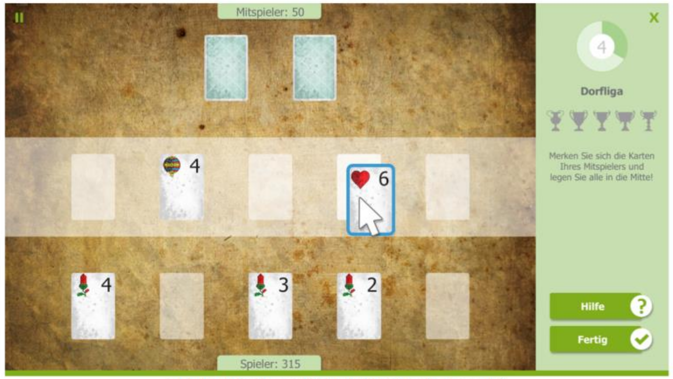

Abb1: Arbeitsgedächtnistraining im Level 4

Abb. 1 Aufgabe ist es, sich die oberen zwei Karten des „Mitspieler" zu merken, diese aus den Karten des „Spielers" auszuwählen und in die Bildschirmmitte zu legen.

Optional motivierende Elemente

Zusätzlich enthält das Modul Arbeitsgedächtnis zwei weitere Elemente zur Motivationssteigerung, die optional (siehe Trainingsparameter) auswählbar sind: Das Jokersystem und das Bonus-Spiel. Wenn jeweils der entsprechende Parameter aktiviert ist, steht das Bonus-Spiel ab Level 17 und das Jokersystem ab Level 18 zur Verfügung.

Das ***Jokersystem*** belohnt den Trainierenden für sehr gute Leistungen mit Jokerkarten, die im weiteren Spielverlauf gegen verschiedene Hilfsmittel eingetauscht werden können, die die Lösung einer Aufgabe erleichtern. Um einen Joker zu sammeln, muss eine bestimmte Anzahl an Aufgaben hintereinander fehlerfrei gelöst werden. In der Dorfliga sind das 10 Aufgaben. Mit jedem Ligaaufstieg verringert sich die Zahl um eine Aufgabe, sodass der Proband in der Kreisliga nach 9, in der Stadtliga nach 8 Aufgaben einen Joker erhält, bis hin zur Weltliga, wo bereits nach 5 fehlerfrei gelösten Aufgaben der Joker vergeben wird. Der Fortschritt beim Erarbeiten des Jokers wird durch eine sich füllende Jokerkarte visualisiert.

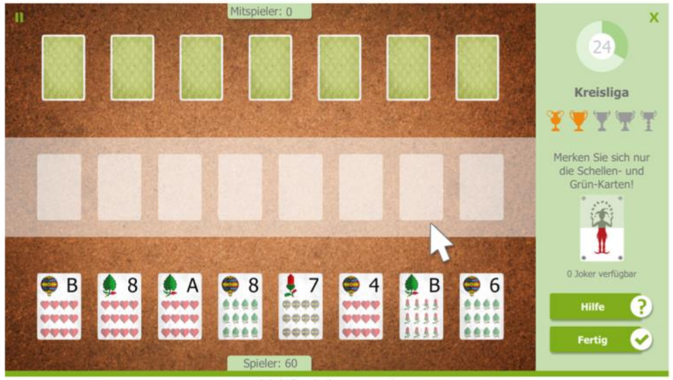

Abb2: Jokeranzeige

Abb. 2 Auf der rechten Seite ist im Metabereich die **Jokeranzeige** zu sehen. Der Teil der Jokerkarte, der farblich hervorgehoben ist, zeigt den Fortschritt beim Sammeln eines Jokers. Ist die Karte vollständig gefüllt, wird der Joker vergeben.

Gesammelte Joker werden im Metabereich in Form eines Stapels abgelegt und können per Drag&Drop ins Spielfeld gezogen und damit ausgespielt werden. Dabei gibt es folgende Einsatzmöglichkeiten:

- Ein Joker dient als Ersatz für eine beliebige Karte. Hat der „Spieler" eine Karte vergessen oder ist sich unsicher, kann er den Joker anstelle der Karte spielen. Die Aufgabe gilt in diesem Fall als richtig gelöst.
- Zieht der „Spieler" den Joker auf die verdeckten Mitspielerkarten, werden diese zeitgleich erneut umgedreht und für die eingestellte Anzeigedauer erneut präsentiert.
- Gelingt es dem „Spieler", mindestens fünf Joker zu sammeln, kann er ab der Landesliga über einen Button in der Ligaanzeige des Metabereichs in die nächsthöhere Liga aufsteigen. Das bedeutet, er spielt ab sofort mit höherwertigen Karten auf einem schöneren Spieltisch der nächsten Liga. Level und Schwierigkeit der Aufgaben bleiben unverändert. Analog kann, ebenfalls durch den Einsatz von fünf Jokern, der Abstieg in eine niedrigere Liga verhindert werden.

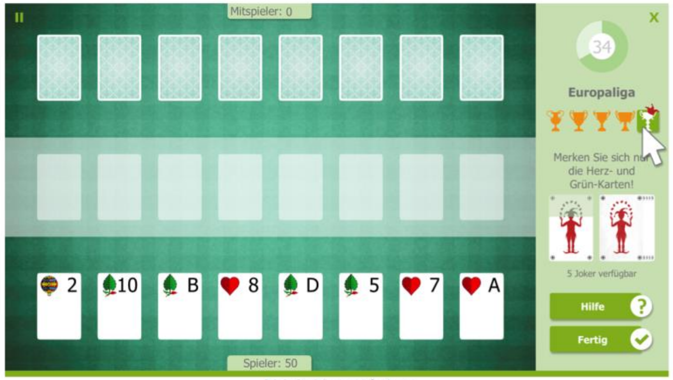

Abb3: Ligaaufstieg

Abb. 3 Nachdem fünf oder mehr Joker gesammelt wurden, können diese über den **Ligaaufstiegs-Button** (rechts oben) für den Aufstieg in die nächsthöhere Liga eingelöst werden.

Das **Bonus-Spiel** stellt eine weitere Spielebene dar, durch die der „Spieler" zusätzlich Punkte verdienen kann. Ist das Bonus-Spiel aktiviert, kann der „Spieler" nach jeder erfolgreich bearbeiteten Aufgabe eine der von ihm gelegten Karten auswählen und in die Bonus-Spielablage im Metabereich ziehen.

Jede auf diese Weise gesammelte Karte steht nach dem Wechsel ins Bonus-Spiel (über Klick auf den „Bonus-Spiel"-Button unten rechts) dort zur Verfügung. Im Gegenzug wählt für jede falsch bearbeitete Aufgabe der „Mitspieler" eine Karte aus und schiebt sie in seine Ablage. Im Bonus-Spielbildschirm können dann aus den zuvor gesammelten Karten Drillinge gebildet und gegen Punkte eingetauscht werden. Die Karten müssen dafür einzeln in die Mitte gezogen und anschließend der „Einlösen"-Button geklickt werden.

Die beim Einlösen erspielte Punktzahl hängt vom gespielten Drilling ab. So erhält der Spieler zum Beispiel für einen Drilling aus Karten mit fortlaufenden Werten und gleichem Symbol mehr Punkte als für fortlaufende Werte mit beliebigem Symbol. Der folgenden Tabelle ist die Bewertung für gespielte Karten zu entnehmen:

Kartenkombination	Beispiel	Punktzahl
3 beliebige Werte mit gleichem Symbol	6 2 9	5 Punkte
3 gleiche Werte mit beliebigem Symbol	3 3 3	10 Punkte
3 aufsteigende Werte mit beliebigem Symbol	6 7 8	20 Punkte
3 aufsteigende Werte mit gleichem Symbol	7 8 9	50 Punkte
3 identische Spielkarten	5 5 5	50 Punkte

Tabelle 1: Punktevergabe im Bonus-Spiel

Erreicht der „Mitspieler" eine Mindestanzahl an Karten, wird er automatisch damit beginnen, seinerseits im Bonus-Spiel Karten einzutauschen und dadurch Zusatzpunkte zu sammeln. Die Herausforderung für den Trainierenden ist es, durch gute Leistungen im Hauptspiel und geschickte Auswahl der Sammelkarten möglichst viele Punkte zu erspielen.

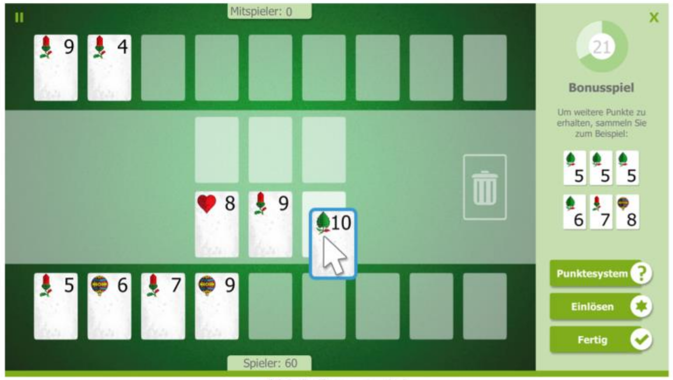

Abb4: Bonusspiel

Abb. 4 Nachdem die dritte Karte in die Mitte gezogen wurde, können die Karten über den **"Einlösen"-Button** (rechts unten) gegen Punkte eingetauscht werden.

1.2 Leistungsfeedback

Der Trainierende erhält auf vielfältige Weise Rückmeldung über seine Leistung:

Lösung der Aufgabe. Nach dem Lösen einer Aufgabe erhält der Trainierende ein ausführliches Feedback:

- Im Informationsbereich rechts neben dem Tisch wird die Bewertung schriftlich aufgeführt
- Ein Smiley zeigt eine grafische Bewertung der Lösung (es gibt Abstufungen für die Darstellung von „gut" und „schlecht", je nachdem ob eine Aufgabe bereits beim ersten Lösungsversuch gelang oder ob wiederholt Fehler gemacht wurden)
- Die Karten werden gekennzeichnet, um eine detaillierte Rückmeldung zu geben: grüner Haken (richtige Karte), rotes Kreuz (falsche Karte), gelber Haken (vergessene Karte)

Schwierigkeitsgrad. Der aktuelle Schwierigkeitsgrad wird auf dem Bildschirm oben rechts angezeigt. Das Kreisdiagramm zeigt den Fortschritt innerhalb eines Levels an. Erreicht die Füllung des Kreises 100 %, gelangt der Trainierende in das nächste Level und der Schwierigkeitsgrad des Trainings wird erhöht. Ist der Kreis leer und der Trainierende macht Fehler, wird er ein Level zurückgestuft und der Schwierigkeitsgrad des Trainings damit verringert.

Ligasystem und Pokale. Die Schwierigkeitsstruktur korreliert mit einem Ligensystem. Die aktuelle Liga sowie die Anzahl der gewonnenen Pokale sieht der Spieler auf der rechten Bildschirmseite.

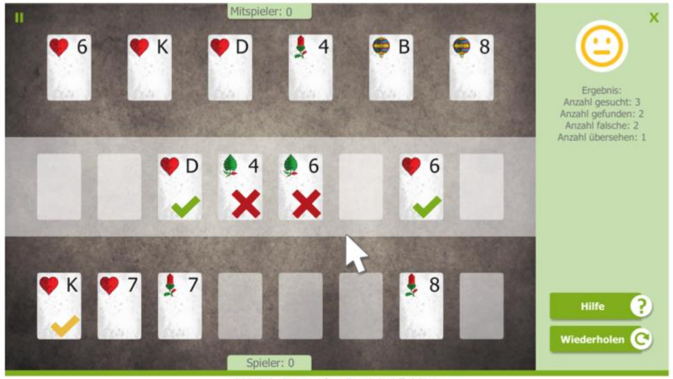

Abb5: Leistungsfeedback bei Fehlern

1.3 Schwierigkeitsstruktur

Autoadaptivität

Die Einstellung des Schwierigkeitsgrades erfolgt autoadaptiv, das heißt die Aufgabenschwierigkeit wird automatisch an die Leistung des Trainierenden angepasst: Am Anfang jedes Levels ist die Leistungsanzeige bereits mit einem Punkt gefüllt. Löst der Trainierende eine Aufgabe beim ersten Versuch, bekommt er einen weiteren Punkt gutgeschrieben. Gelingt die Lösung nicht beim ersten Versuch, erhält er in der Wiederholung keine Punkte usw. Wird die Aufgabe (trotz mehrfacher Wiederholung) nicht gelöst, wird ein Punkt abgezogen. Löst der Trainierende die geforderten Aufgaben pro Level, die laut der Trainingsparameter definiert wurden, gelangt er in den nächst höheren Schwierigkeitsgrad. Wenn der Trainierende durch Punkteabzug weniger als null Punkte hat, wird der Schwierigkeitsgrad verringert. Auf diese Weise stellen die Aufgaben stets eine angemessene Herausforderung dar, welche weder über- noch unterfordert. Um dieses individuelle Schwierigkeitsniveau möglichst rasch zu erreichen und die Trainingszeit effektiv zu nutzen, werden in der ersten Trainingseinheit jeweils nur zwei Aufgaben benötigt, um in höhere Level aufzusteigen. Werden wiederholt Fehler gemacht, signalisiert dies dem Programm, dass die Leistungsgrenze vorerst erreicht ist und es wird automatisch in den vom Therapeuten eingestellten Trainingsmodus gewechselt.

Schwierigkeitsgrade

Das Training verfügt insgesamt über 69 Level, deren Schwierigkeitsgrade durch die Variation zahlreicher Eigenschaften und Parameter feingradig und linear zunehmen. Die Schwierigkeitsstruktur korreliert mit einem Ligensystem. Dieses stellt die grafische Wertigkeit des Spieltisches und der Karten dar und dient zur Motivation (siehe Kapitel Grundlagen). Kritischer Parameter stellt jeweils die Anzahl zu merkender bzw. legender Karten dar.

Folgende Tabelle zeigt den Schwierigkeitsverlauf des Trainings:

Level	Aufgabe	Anzahl zu merkender/ legender Karten	Anzahl präsentierter Karten (auf Mitspielerseite)	Anzahl ablenkender Karten (auf Spielerseite)	grafische Wertigkeit (Liga)
1	Einführung	**2**	2	2	Dorfliga
2		**3**	3	2	Dorfliga
3	alle Karten merken	**2**	2	2	Dorfliga
4		**2**	2	3	Dorfliga
5		**3**	3	2	Dorfliga
6		**3**	3	3	Dorfliga
7	selektiv merken (1 Farbe)	**3**	5	3	Dorfliga
8		**3**	5	4	Dorfliga
9		**3**	6	4	Stadtliga
10	selektiv merken (2 Farben)	**3**	5	2	Stadtliga
11		**3**	5	3	Stadtliga
12		**3**	6	3	Stadtliga
13		**3**	6	4	Stadtliga
14		**3**	6	5	Stadtliga
15	sortieren (aufwärts)	**3**	0	0	Stadtliga
16		**4**	0	0	Stadtliga
17	sortieren (abwärts)	**3**	0	0	Kreisliga
18	alle Karten merken	**4**	4	1	Kreisliga
19		**4**	4	2	Kreisliga
20		**4**	4	3	Kreisliga
21		**4**	4	4	Kreisliga
22		**4**	4	5	Kreisliga
23	selektiv merken (2 Farben)	**4**	7	3	Kreisliga
24		**4**	7	4	Kreisliga
25		**4**	7	5	Landesliga
26	sortieren (aufwärts)	**5**	0	0	Landesliga

27	sortieren (abwärts)	4	0	0	Landesliga
28	alle Karten merken	5	5	1	Landesliga
29		5	5	2	Landesliga
30		5	5	3	Landesliga
31		5	5	4	Landesliga
32		5	5	5	Landesliga
33		5	5	6	Europaliga
34	selektiv merken (2 Farben)	5	8	3	Europaliga
35		5	8	4	Europaliga
36		5	8	5	Europaliga
37		5	8	6	Europaliga
38	sortieren (aufwärts)	6	0	0	Europaliga
39	sortieren (abwärts)	5	0	0	Europaliga
40	alle Karten merken	6	6	3	Europaliga
41		6	6	4	Europaliga
42		6	6	5	Europaliga
43		6	6	6	Weltliga
44	selektiv merken (2 Farben)	6	9	3	Weltliga
45		6	9	4	Weltliga
46		6	9	5	Weltliga
47		6	9	6	Weltliga
48	sortieren (aufwärts)	7	0	0	Weltliga
49	sortieren (abwärts)	6	0	0	Weltliga
50	alle Karten merken	7	7	3	Weltliga
51		7	7	4	Weltliga
52		7	7	5	Weltliga
53		7	7	6	Weltliga
54	selektiv merken (2 Farben)	7	9	3	Weltliga
55		7	9	4	Weltliga
56		7	9	5	Weltliga
57		7	9	6	Weltliga
58	sortieren (aufwärts)	8	0	0	Weltliga
59	sortieren (abwärts)	7	0	0	Weltliga
60	alle Karten merken	8	8	3	Weltliga
61		8	8	4	Weltliga
62		8	8	5	Weltliga
63		8	8	6	Weltliga
64	selektiv merken (2 Farben)	8	9	3	Weltliga
65		8	9	4	Weltliga
66		8	9	5	Weltliga

67		8	9	6	Weltliga
68	sortieren (aufwärts)	9	0	0	Weltliga
69	sortieren (abwärts)	8	0	0	Weltliga

Es kann festgelegt werden, ob alle Komponenten bearbeitet werden oder Level mit bestimmten Aufgabentypen übersprungen werden sollen. Die entsprechende Einstellung kann bei den Parametern unter "Arbeitsgedächtniskomponenten" vorgenommen werden (s. Kapitel Trainingsparameter).

Zur genauen Erläuterung der einzelnen Arbeitsgedächtniskomponenten und theoretischem Hintergrund der Module siehe Kapitel Trainingsziel, zur Erklärung der konkreten Aufgaben siehe Kapitel Trainingsaufgaben.

1.4 Trainingsparameter

In den Grundlagen RehaCom werden allgemeine Hinweise zu Trainingsparametern und ihrer Wirkung gegeben. Diese Hinweise sollten im Weiteren berücksichtigt werden.

Abb 6: Parameter-Menü

Allgemeine Einstellungen

Konsultationsdauer. Die Konsultationsdauer bestimmt die Länge der geplanten Trainingseinheit. Empfohlen wird eine Trainingsdauer von 30 Minuten. Bei Patienten mit Aufmerksamkeits- und Konzentrationsproblemen sollte die Konsultationsdauer gesenkt und eine Pause integriert werden.

Grundanzahl Aufgaben. Dieser Parameter gibt an, wie viele korrekte Aufgaben gelöst werden müssen, um in das nächste Level zu wechseln. Diese Einstellung hat Einfluss auf die Autoadaptivität des Trainings (s. Kapitel Schwierigkeitsstruktur): Je weniger Aufgaben eingestellt sind, umso schneller steigert sich bei korrekter Lösung der Schwierigkeitsgrad. Eine hohe Aufgabenzahl ermöglicht dagegen ein längeres Trainieren im gleichen Schwierigkeitsgrad. Als Standard werden 10 Aufgaben pro Level empfohlen.

Anzahl der Wiederholungen. Wird eine Aufgabe falsch gelöst, kann der Trainierende die Möglichkeit bekommen, dieselbe Aufgabe noch einmal zu bearbeiten. Die Einstellung zeigt die Anzahl der erlaubten Wiederholungen an. Je weniger Wiederholungen eingestellt werden, desto besser kann die Aufgabenschwierigkeit an das Leistungsniveau des Trainierenden angepasst werden. Eine höhere Anzahl an Wiederholungen stärkt dagegen durch die Möglichkeit zur Korrektur die Motivation und das Einüben von Strategien. Als Standard wird eine Wiederholung empfohlen.

Anzeigedauer Karten. Diese Einstellung regelt die Präsentationszeit je Karte, bevor diese wieder verdeckt wird. In der Regel sind dies 1000 ms. Für Probanden, die mehr Zeit benötigen (z. B. aufgrund von Wahrnehmungsstörungen oder um die Informationen besser verbalisieren/rehearseln zu können), kann die Präsentationszeit erhöht werden. Allerdings sollte dabei beachtet werden, dass sich dadurch auch die die Zeit bis zum Abruf und somit auch die Behaltensdauer verlängert.

Arbeitsgedächtniskomponenten

Als Standard wird der Durchlauf des gesamten Trainings empfohlen. Soll ausschließlich eine spezielle Arbeitsgedächtniskomponente trainiert werden, kann dies hier eingestellt werden. In Einzelfällen kann es auch hilfreich sein, einzelne Module des Trainings auszulassen (z. B. weil ein Patient die Aufgabe nicht versteht oder wiederholt nicht bewältigt). Durch Deaktivieren eines Häkchens wird das entsprechende Modul im Trainingsverlauf übersprungen. Die Beschreibung und Funktionalität der einzelnen Komponenten entnehmen Sie bitte dem Kapitel Trainingsziel.

Blatt (Aussehen der Karten)

Das Aussehen der Karten sollte für jeden Trainingsteilnehmer individuell nach Belieben, Gewohnheit und Leistungsniveau gewählt werden. Zur Verfügung stehen das französische (Pik, Karo, Herz, Kreuz) und das deutsche (Schellen, Grün, Herz, Eichel) Kartenspielblatt, sowie ein Farbblatt, welches die Karten anhand einfacher Farben (rot, gelb, grün und blau) kategorisiert. Das Farbblatt empfiehlt sich für Patienten, die überhaupt keine Erfahrung mit Kartenspielen haben und Schwierigkeiten beim Erlernen oder Verbalisieren der Farbnamen angeben. Auch für Kinder ist das Farbblatt am besten geeignet.

Modifikatoren des Schwierigkeitsgrades

Durch das Aktivieren von Modifikatoren können die normalen Trainingsaufgaben variiert werden. Je nach Modifikator wird die Schwierigkeit des Trainings beeinflusst und/oder eine spezifische Arbeitsgedächtniskomponente verstärkt trainiert (zum besseren Verständnis der beschriebenen Arbeitsgedächtnisfunktionen s. Kapitel Grundlagen und Trainingsziel).

Visuelle Instruktionen anzeigen. Standardmäßig werden während der Aufgabenbearbeitung die gesprochenen Instruktionen zusätzlich in einem Textfenster schriftlich angezeigt. Ein Deaktivieren des Häkchens führt zu einer erhöhten Schwierigkeit, da die Aufgabenstellung nur noch akustisch dargeboten wird und später nicht mehr nachzulesen ist.

Akquisition nur akustisch. Ist dieser Modifikator eingeschaltet, werden die Karten nicht visuell präsentiert, sondern nur auditiv dargeboten. Damit erfolgt die Speicherung relevanter Informationen ausschließlich über die phonologische Schleife, welche auf diese Weise gezielter trainiert wird. Durch die unimodale Darbietung wird die Schwierigkeit des Trainings zudem deutlich erhöht. Ein weiteres Anwendungsgebiet stellen zum Beispiel visuell stark eingeschränkte Patienten dar. Diese können das Arbeitsgedächtnistraining mit entsprechender therapeutischer Unterstützung somit trotzdem durchführen.

Einfache Aufgaben. Normalerweise werden auf der Seite des Mitspielers häufig Karten mit den gleichen Werten präsentiert, die sich nur in ihrer Farbe unterscheiden. Dies soll die Trainierenden auffordern, sich alle Informationen auf den Karten zu merken und nicht nur einzelne Werte. Durch Aktivieren des Parameters werden keine Karten mit gleichem Wert mehr dargeboten, die Aufgaben werden dadurch etwas leichter. Die Einstellung empfiehlt sich bei schwerer betroffenen Patienten oder wenn sich im Trainingsverlauf vermehrt Schwierigkeiten zeigen.

Ablenker auf den Karten. Bei Aktivierung des Parameters werden auf dem sonst weißem Kartenhintergrund Symbole anderer Kartenfarben eingeblendet. Diese erschweren das Enkodieren der zu merkenden Karten, fördern aktive Interferenzabwehrprozesse und trainieren die Fokussierung auf relevante Informationen. Der Schwierigkeitsgrad des Trainings wird somit leicht erhöht, ohne dass die Anzahl der zu merkenden Karten oder die Auswahlmöglichkeiten auf der

Spielerseite verändert werden.

Ablenker nach Akquisition. Bei Aktivierung des Häkchens wird nach der Präsentation der Karten des Mitspielers eine einfache Quizfrage mit zwei Antwortmöglichkeiten präsentiert. Dies erhöht zum einen die Zeit, in der relevante Informationen im Arbeitsgedächtnis gehalten werden müssen, und erzeugt zum anderen Interferenz, weil die neue Information (die Frage) mit den alten Informationen (den Karten) konkurriert. Der Trainierende muss durch aktive Inhibitionsprozesse verhindern, dass der Ablenker die relevanten Inhalte im Arbeitsgedächtnis verdrängt und sich mit Hilfe selektiver Aufmerksamkeit auf das Ziel der Aufgabe konzentrieren.

Joker. Löst der Trainierende mehrere Aufgaben hintereinander sofort korrekt, so erhält er einen Joker. Diesen kann er später zu seinem Vorteil einsetzen. Die Integration von Jokern fördert auf vielfältige Weise die Motivation des Spielers (siehe Kapitel Grundlagen) und wird damit grundsätzlich empfohlen. Schwerer betroffene Patienten sind von den Einsatzmöglichkeiten der Joker jedoch eventuell überfordert und werden von den eigentlichen Trainingsaufgaben zu stark abgelenkt. In diesem Fall sollte das Training ohne Joker durchgeführt werden.

Bonus-Spiel. Nach jeder korrekt gelösten Aufgabe kann sich der Spieler eine Karte aussuchen, die er zurücklegt, um damit Extrapunkte zu sammeln. Dieses läuft im Hintergrund und ermöglicht das Verdienen von zusätzlichen Punkten. Das Bonus-Spiel dient als motivationsförderndes Element insbesondere bei langen Trainingsphasen (siehe Kapitel Grundlagen). Für schwerer betroffene Patienten ist das Bonus-Spiel eventuell zu komplex (Erklärung, Funktion, Bedeutung) und sie verstehen es nicht oder sind davon zu sehr von den eigentlichen Trainingsaufgaben abgelenkt. In diesem Fall sollte das Bonus-Spiel deaktiviert werden.

Gesprochene Instr. wiederholen. Ist der Parameter aktiviert, werden die Instruktionen vor jeder Aufgabe angesagt.

Selektion non-matching. Ist dieser Parameter aktiviert, so soll der Trainierende aus seiner Auswahl genau die Karten in die Mitte legen, die vom Mitspieler *nicht* gezeigt wurden. Diese Aufgabe erfordert eine erhöhte kognitive Flexibilität und ist daher als schwerer einzuordnen als die Standardeinstellung. Da bei einer geringen Anzahl ablenkender Karten auf der Spielerseite dies jedoch nicht zutrifft, wird die eigentlich linear verlaufende Schwierigkeitsstruktur deutlich modifiziert. Der Parameter ist somit als Abwechslung schaffende Variation im Verlauf, jedoch nicht dauerhaft, einzusetzen.

Bei Neudefinition eines Trainings werden automatisch folgende **Standardwerte** festgelegt:

Levelwechsel

Konsultationsdauer	30 Minuten
Grundanzahl Aufgaben	10
Anzahl der Wiederholungen	1
Anzeigedauer Karten	1000 Millisekunden
Modifikatoren des Schwierigkeitsgrades	
Visuelle Instruktionen anzeigen	ein
Akquisition nur akustisch	aus
Einfache Aufgaben	aus
Ablenker auf den Karten	aus
Ablenker nach Akquisition	aus
Joker	ein
Bonus-Spiel	ein
Gesprochene Instr. wiederholen	aus
Selektion non matching	aus
Arbeitsgedächtniskomponenten	
Speichersysteme	ein
Selektive Aufmerksamkeit	ein
Zentrale Exekutive	ein
Blatt (Aussehen der Karten)	Französisches Blatt

Tab. 1: Standardparameter

1.5 Auswertung

Die vielfältigen Möglichkeiten der Datenanalyse werden in den Grundlagen RehaCom beschrieben.

Relevant für die Interpretation des Arbeitsgedächtnistrainings ist vor allem die Bearbeitungsqualität, Tempoaspekte spielen eine deutlich untergeordnete Rolle. Die Lösungsgüte ist einerseits anhand des erreichten Levels ersichtlich, da die Schwierigkeitsstruktur linear ansteigt, andererseits anhand der Anzahl der korrekt gelösten Aufgaben innerhalb einer Sitzung. Desweiteren können Sie bei der Interpretation der Leistung klinische Beobachtungen (z. B. Ermüdungserscheinungen, Anzahl der Pausen, Reizbarkeit) berücksichtigen.

Level	Schwierigkeitsgrad, in dem gearbeitet wurde, s. auch Kapitel Schwierigkeitsstruktur
Anz. Aufg.	Anzahl der bearbeiteten Aufgaben in diesem Schwierigkeitsgrad
Richtige	Anzahl richtig gelöster Aufgaben
Fehler	Anzahl der Gesamtfehler

Wiederh.	Anzahl Wiederholungen
Lösg.-zeit Q1	Lösungszeit Quartil 1 in ms
Lösg.-zeit Med	Median über alle Lösungszeiten in ms
Lösg.-zeit Q3	Lösungszeit Quartil 3 in ms
Richtige im ersten Versuch	Die Anzahl der Aufgaben die im ersten Versuch richtig gelöst wurden in %.
Train.-zeit Aufgabe	effektive Arbeitszeit des Trainierenden (ohne Titelbild und Pausen) in h:mm:ss
Pausen	Anzahl der Unterbrechungen durch den Patienten

2 Theoretisches Konzept

2.1 Grundlagen

Das Arbeitsgedächtnis ist ein kognitives System, welches Informationen kurzfristig speichert und zur weiteren Verarbeitung bereitstellt[1]. Damit gilt es als grundlegende Funktion der Informationsverarbeitung und stellt eine Schlüsselrolle für viele höhere Kognitionen wie Problemlösen, Sprachverständnis, Rechen- und Intelligenzleistungen dar[2]. Gute Arbeitsgedächtnisleistungen werden mit schulischem und beruflichem Erfolg, besserem Lern- und Fähigkeitserwerb, sowie gelungener Emotionsregulation in Verbindung gebracht[3].

Im klinischen Kontext sind Störungen der Arbeitsgedächtnisfunktionen bei vielen neurologischen (z. B. Schlaganfall, Schädel-Hirn-Traumata, Multiple Sklerose, Alzheimer Demenz) und psychiatrischen Erkrankungen (z. B. Schizophrenie, Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung) zu beobachten[4]. Betroffene erleben sich als schnell ablenkbar, vergesslich und wenig zielorientiert. Sie verlieren in Gesprächen häufig „den roten Faden“ und haben Schwierigkeiten beim Problemlösen und Erledigen von mehreren parallelen Aufgaben[5]. Arbeitsgedächtnisdefizite reduzieren die Lebensqualität und den Erfolg von beruflicher Wiedereingliederung[6].

Die Fähigkeit des Gehirns, sich an neue Bedingungen anzupassen und je nach aktuellen Anforderungen verändern zu können (neuronale Plastizität), ermöglicht es, durch ein intensives Training die Leistung des Arbeitsgedächtnisses zu steigern[7]. Studien konnten sowohl bei gesunden Kindern, jungen und älteren Erwachsenen, als auch bei Patienten mit unterschiedlichen Ätiologien (z. B. Kinder mit Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung, sowie Schlaganfall, Schädelhirntrauma und Multiple Sklerose) bedeutsame Verbesserungen belegen[8]. Diese betreffen nicht nur die trainierten Aufgaben, sondern auch ungeübte Arbeitsgedächtnisaufgaben, sodass eine Verbesserung der Kapazität oder Effizienz des Systems an sich anzunehmen ist[9]. Darüber hinaus wurde vereinzelt der Transfer auf angrenzende kognitive Funktionen, z. B. Problemlösen und Intelligenz, beobachtet[10]. Begleitend zu den Verhaltensänderungen wiesen Studien mit bildgebenden Verfahren Veränderungen auf neuronaler Ebene in der Hirnstruktur, -aktivität und den Neurotransmittersystemen nach[11].

Laut Baddeleys Multikomponentenmodell besteht das Arbeitsgedächtnis aus verschiedenen Speichersystemen (phonologische Schleife, visuell-räumlicher Notizblock und episodischer Puffer) und der zentralen Exekutive, welche diese Systeme überwacht und zu verteilende Ressourcen koordiniert[12]. Zusätzlich zu den von Baddeley beschriebenen Komponenten spielt die selektive Aufmerksamkeit eine wichtige Rolle, da sie notwendig ist, um relevante Informationen zu filtern und im Fokus zu halten[13]. Gleichermaßen ist es notwendig, gespeicherte Informationen von anderen, konkurrierenden Reizen abzuschirmen und ein übergeordnetes Ziel zu verfolgen. Daher ist Interferenzabwehr ebenfalls ein zentrales Konzept bei

Arbeitsgedächtnisprozessen[14].

Das RehaCom Trainingsmodul „Arbeitsgedächtnis" wurde auf Basis der vorgestellten Theorien konzipiert und fördert sowohl die Speicher- als auch die Manipulationskomponenten des Arbeitsgedächtnisses. Im Trainingsverlauf werden zunehmend selektive Aufmerksamkeits- und Inhibitionsprozesse involviert. Zusätzlich zu dem im Programm hinterlegten adaptiv steigenden Schwierigkeitsgrad, können anhand individuell veränderlicher Parameter sowohl die zu trainierenden Arbeitsgedächtniskomponenten (Speichersysteme, selektive Aufmerksamkeit, zentrale Exekutive) als auch der Schwerpunkt der Trainingsmodalität (visuell, auditiv) und der Grad der Interferenz (verschiedene zur Verfügung stehende Ablenker) beeinflusst werden. Im Zentrum steht ein "Kern-Funktionstraining" der Arbeitsgedächtnisleistung, dass sich an den von Perrig und Kollegen entwickelten Kriterien orientiert[15]. Im Unterschied zu anderen Trainingsformen soll explizit die Bildung von Strategien minimiert werden, um nicht aufgabenspezifisches Wissen zu generieren, sondern die Kapazität des Systems selbst zu erhöhen bzw. eine effizientere Verarbeitung anzuregen. Der Transfer auf andere, ungeübte Aufgaben und Alltagsleistungen soll auf diese Weise erleichtert werden.

Das Trainingsmodul wurde anhand von mehreren unabhängigen wissenschaftlichen Studien evaluiert[16]. Die Ergebnisse zeigen große Verbesserungen in der Trainingsaufgabe sowie Transfereffekte auf die generelle Arbeitsgedächtnisleistung. Vereinzelt traten auch Verbesserungen im verbalen und prospektiven Gedächtnis auf. Die Teilnehmer erlebten das Training überwiegend als freudvoll, motivierend und angemessen anstrengend. Im Vergleich zu Kontrollgruppen berichteten sie vermehrt von positiven Veränderungen im Alltag, beispielsweise von einer erhöhten Konzentration beim Autofahren oder dem Merken von Namen, Gesichtern und Einkaufslisten. Als wichtiger Faktor für den Trainingserfolg stellte sich die Trainingsdauer heraus. Da auf Basis der Studienlage davon auszugehen ist, dass spezifische Trainingseffekte erst im längeren Trainingsverlauf wirken, wird ein Trainingsumfang von ca. 20 Sitzungen à 30 min empfohlen (etwa 3x wöchentlich).

Um eine solch intensive Trainingsdauer erfolgreich realisieren zu können, ist eine sehr hohe Trainingsmotivation erforderlich. Unter Berücksichtigung der Selbstbestimmungstheorie[17] wurden motivationsfördernde Elemente zur Steigerung von Kompetenz, sozialer Eingebundenheit und Autonomie integriert (z. B. die Anpassung der Benutzeroberfläche mittels eines Belohnungssystems (Pokale, Ligen), vielfältig verwendbare Joker, Bonus-Spiel). Es handelt sich hierbei um strukturelle Elemente der "Gamification", der Einbettung von spieltypischen Elementen in einen anderen Kontext[18]. Dadurch erhöht sich nicht nur die Abwechslung im Training, sondern auch die Anzahl der Freiheitsgrade, die Wahlmöglichkeiten und die Selbstbestimmung des Probanden.

2.2 Trainingsziel

Ziel des Therapiemoduls "Arbeitsgedächtnis" ist die Verbesserung von Arbeitsgedächtniskapazität und -effizienz mittels eines spezifischen, intensiven Funktionstrainings. Basierend auf den aktuellen theoretischen Erkenntnissen der Arbeitsgedächtnisstruktur (siehe Kapitel Grundlagen) wurden hierarchisch gegliederte Module entwickelt, die jeweils verschiedene Komponenten durch einen konkreten Aufgabentyp trainieren. Im Folgenden werden Aufbau und Arbeitsgedächtnisfunktionen der Module beschrieben. Für eine konkrete Erläuterung der entsprechenden Aufgabentypen siehe Kapitel Trainingsaufgaben.

*Das **Modul „Speichersysteme"*** trainiert die von Baddeley (2003) beschriebenen Speicherkomponenten des Arbeitsgedächtnissystems. Ziel ist das Enkodieren und kurzfristige Halten von Informationen. Durch die parallele Darbietung von visuellen (Spielkarten) als auch auditiven (Vorlesen der Karten) Reizen werden sowohl der räumlich-visuelle Notizblock als auch die phonologische Schleife beansprucht. Durch das Aktivieren von Modifikatoren (s. Kapitel Trainingsparameter) kann auch ein Schwerpunkt auf eine Modalität gelegt werden (z. B. durch ausschließlich akustische Präsentation der Karten).

Das ***Modul „Selektive Aufmerksamkeit"*** trainiert ebenfalls die Speicherfunktion des Arbeitsgedächtnisses, jedoch wird zusätzlich der Aspekt der selektiven Aufmerksamkeit hinzugefügt (Fokussierung auf Karten einer bzw. zweier Farben). Hinzu kommen Inhibitionsprozesse, da sowohl bei der Enkodierung der Informationen (Präsentation der Karten des „Mitspielers") als auch beim Abruf (Auswahl der gemerkten Karten auf Seite des „Spielers") irrelevante Reize (Karten anderer Farben) unterdrückt werden müssen.

Das ***Modul „Zentrale Exekutive"*** erfordert die mentale Manipulation der Informationen, die aktuell in den Speichersystemen des Arbeitsgedächtnisses gehalten werden. Dieses Modul stellt den höchsten Schwierigkeitsgrad der Aufgaben dar. Besonders bei der Aufgabenstellung „rückwärts sortieren der Karten" wird dabei die Prozesskomponente des Arbeitsgedächtnisses beansprucht.

Das Trainingsprogramm ist so konstruiert, dass die Schwierigkeit im Verlauf kontinuierlich zunimmt (für den detaillierten Aufbau s. Kapitel Schwierigkeitsstruktur). Dafür durchläuft der Teilnehmer die o. g. Module mehrfach: Zunächst werden die Speichersysteme mit einer konstanten Anzahl an Informationen trainiert. Wenn sichergestellt ist, dass der Teilnehmer sich eine bestimmte Anzahl von Karten merken kann, folgen die Module „Selektive Aufmerksamkeit" und „Zentrale Exekutive" mit gleicher Informationsmenge unter Beanspruchung von selektiven, inhibitorischen und exekutiven Prozessen. Sind alle Module mit einer Kartenanzahl erfolgreich bearbeitet worden, beginnt der Proband das Speichern von zusätzlichen Informationen, d. h. eine Karte mehr, zu üben. Gelingt dies erfolgreich, kann er sich anschließend diese erhöhte Kartenanzahl selektiv merken, manipulieren usw. Auf diese Weise wird gewährleistet, dass der Teilnehmer die wichtigsten Komponenten des Arbeitsgedächtnisses sukzessive auf allen Schwierigkeitsebenen trainiert.

Innerhalb der Module erfolgt eine feine Abstufung des Schwierigkeitsgrades durch die schrittweise Erhöhung von zusätzlich dargebotenen irrelevanten Informationen (Karten auf der Seite des Spielers, die als Ablenker dienen). Zusätzlich gibt es die Möglichkeit, mit Hilfe der Aktivierung von spezifischen Modifikatoren, Schwerpunkte auf bestimmte Arbeitsgedächtnisprozesse zu setzen und/oder die Schwierigkeit differenzierter zu beeinflussen (z. B. Modalität der Enkodierung, Grad der Interferenz). Die Beschreibung der verfügbaren Modifikatoren finden Sie im Kapitel Trainingsparameter.

2.3 Zielgruppen

Das Arbeitsgedächtnistraining wurde speziell für Personen mit Arbeitsgedächtnisdefiziten entwickelt. Störungen der Arbeitsgedächtnisfunktionen treten bei vielen neurologischen (z. B. Schlaganfall, Schädel-Hirn-Traumata, Multiple Sklerose, Alzheimer Demenz) und psychiatrischen Erkrankungen (z. B. Schizophrenie, Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung) auf. Betroffene erleben sich als schnell ablenkbar, vergesslich und wenig zielorientiert. Sie verlieren in Gesprächen häufig „den roten Faden" und haben Schwierigkeiten beim Problemlösen und Erledigen von mehreren parallelen Aufgaben.

Durch eine fein gegliederte Schwierigkeitsstruktur, die Autoadaptivität des Programms, sowie die Möglichkeit der Variation von zahlreichen anspruchsverändernden Parametern, ist das Training individuell abstimmbar und damit sowohl für schwerer betroffene Patienten als auch für Personen mit wenigen Leistungseinbußen geeignet. Eine Anwendung bei Kindern (z. B. Kinder mit Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung) ist ebenfalls möglich, sobald Zahlen im einstelligen Raum beherrscht werden.

Da die Schwierigkeit bis zu einem sehr hohen Grad ansteigt, ist zudem das Training von gesunden jungen oder älteren Erwachsenen denkbar, die zwar eine durchschnittliche Arbeitsgedächtnisleistung aufweisen, diese aber steigern möchten. Es ist ebenso empfehlenswert für leistungsstarke Patienten mit einem hohen Anspruchsniveau, die von anderen RehaCom-Programmen nicht ausreichend gefordert werden.

Voraussetzung für das Training sind grundlegende Funktionen der Merkfähigkeit und selektiven Aufmerksamkeit. Können weniger als 3 Informationseinheiten behalten werden, sollte auf ein basaleres Training der Merkfähigkeit zurückgegriffen werden (z. B. figurales Gedächtnis, Wortgedächtnis). Patienten mit schweren Aufmerksamkeitsdefiziten üben zunächst mit entsprechenden Aufmerksamkeitstrainingsprogrammen (z. B. Aufmerksamkeit und Konzentration, Reaktionsfähigkeit). Bei Patienten mit Aphasien muss geprüft werden, ob die sprachlichen Leistungen ausreichend sind, um einfache Anweisungen zu verstehen und die Grundanforderungen zu bewältigen. Für Patienten mit visuellen Wahrnehmungsstörungen besteht die Möglichkeit zur rein auditiven Enkodierung der

Informationen (da die Auswahl der Lösungsmöglichkeiten jedoch auf visueller Basis erfolgt, ist in diesem Fall eine Unterstützung bei der Bedienung erforderlich).

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Study IV Supplemental Material (S1 Table)

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Table S1 Mean performance and standard deviations of the neuropsychological outcomes.

outcomes	WOME WM training group			active control group			passive control group		
	T1	T2	T3	T1	T2	T3	T1	T2	T3
WM functions									
Digit Span (forwards)	6.90 (1.52)	7.70 (1.72)	7.35 (1.66)	7.00 (1.08)	7.05 (1.73)	7.20 (1.44)	7.30 (1.53)	7.55 (1.73)	7.47 (2.15)
Digit Span (backwards)	6.75 (1.68)	6.65 (1.76)	7.06 (1.48)	5.85 (1.46)	5.95 (1.64)	6.20 (1.51)	6.25 (1.37)	6.55 (1.57)	7.06 (1.71)
Span Board (forwards)	7.20 (1.11)	7.45 (1.70)	7.76 (2.02)	8.30 (1.38)	7.95 (1.28)	8.75 (1.41)	7.95 (1.19)	7.95 (1.88)	8.88 (1.65)
Span Board (backwards)	6.55 (1.10)	7.70 (1.46)	7.12 (1.54)	7.65 (1.67)	7.40 (1.54)	7.70 (2.00)	7.20 (1.61)	7.15 (1.39)	8.00 (1.46)
Spatial Addition	10.25 (2.12)	11.75 (2.85)	11.88 (3.46)	10.90 (2.77)	12.00 (2.97)	12.45 (2.80)	11.05 (3.55)	11.80 (3.65)	12.59 (3.00)
Symbol Span	20.00 (5.18)	21.25 (4.63)	24.82 (6.91)	18.50 (5.32)	20.85 (4.52)	21.85 (4.56)	18.00 (4.85)	22.85 (5.33)	22.47 (5.90)
N-back	5.40 (9.37)	2.35 (2.93)	2.88 (5.41)	3.80 (4.63)	3.55 (5.33)	2.40 (2.33)	6.45 (9.45)	2.05 (3.40)	2.24 (3.93)
PASAT (ISI 3 sec)	41.45 (11.55)	46.95 (9.32)	48.18 (7.43)	42.20 (11.02)	47.30 (9.84)	45.65 (10.33)	44.40 (10.51)	49.35 (9.00)	50.00 (8.63)
PASAT (ISI 2 sec)	30.25 (9.81)	35.20 (8.68)	38.53 (6.86)	29.05 (7.35)	34.10 (8.78)	33.65 (9.34)	34.30 (10.86)	36.60 (11.08)	39.88 (9.24)
cognitive functions that require WM									
executive functioning									
Stroop	114.53 (29.67)	112.74 (26.97)	108.65 (27.01)	128.20 (23.83)	114.80 (13.36)	117.30 (18.80)	120.40 (31.31)	113.20 (24.97)	107.38 (22.69)
Go-NoGo	1.10 (2.15)	1.00 (1.49)	0.41 (0.62)	0.50 (1.19)	0.90 (1.25)	1.20 (2.33)	0.80 (0.70)	0.80 (1.28)	0.47 (0.72)
TMT	1.28 (0.68)	1.25 (0.73)	1.10 (0.56)	1.17 (0.58)	1.14 (0.72)	1.50 (0.75)	1.27 (0.85)	1.22 (0.75)	1.11 (0.51)
Mental Flexibility	2.65 (2.89)	1.30 (1.87)	0.71 (1.11)	2.45 (3.49)	1.40 (3.24)	2.00 (4.70)	2.30 (4.14)	2.30 (3.59)	1.24 (2.71)
logic reasoning									
LPS-3	23.40 (4.31)	25.10 (6.10)	26.41 (4.30)	22.05 (4.27)	23.85 (4.43)	24.50 (4.35)	23.30 (4.80)	24.70 (4.53)	26.18 (4.14)
long-term memory									
VLMT	49.05 (9.18)	50.60 (7.37)	54.47 (7.01)	51.35 (6.31)	51.70 (7.18)	54.75 (7.70)	51.60 (8.75)	52.55 (9.17)	53.29 (9.30)
non-target outcome									
reaction time	264.36 (49.24)	264.34 (47.10)	280.22 (55.93)	260.17 (30.37)	266.58 (43.41)	276.70 (68.06)	255.30 (44.84)	262.40 (54.94)	266.37 (72.64)
everyday life functions									
CFQ	17.25 (12.31)	17.83 (12.30)	16.35 (10.57)	20.53 (10.51)	20.82 (8.88)	21.20 (10.12)	22.45 (7.07)	19.39 (8.71)	17.56 (6.96)
FEAG	27.15 (14.47)	27.44 (16.28)	26.94 (13.94)	27.18 (12.70)	27.76 (11.76)	29.07 (14.46)	29.80 (8.80)	28.28 (10.79)	27.13 (9.62)

Note: All values represent raw scores and refer to correct items, except for N-back, Go-NoGo and Mental Flexibility (errors), Stroop (time in sec), TMT (ratio (A – B) / A), reaction time (time in msec) and everyday life questionnaires (sum of items). N = 60 for baseline (T1) and post assessment (T2), N = 54 at 3-month follow-up (T3; WM training group (WOME) n = 17, active control group (aCtrl) n = 20, passive control group (pCtrl) n = 17), except for Stroop (WOME T1/T2: n = 19; pCtrl T3: n = 16), TMT (pCtrl T1: n = 19), reaction time (aCtrl T1: n = 19), CFQ and FEAG (WOME T2: n = 18; aCtrl T1/T2: n = 17, T3: n = 15; pCtrl T2: n = 18, T3: n= 16).

Study VI Supplemental Material (S1 Table, S2 Outcome measures)

For: Weicker, J., Hudl, N.; Hildebrandt, H.; Obrig, H.; Schwarzer, M.; Villringer, A.; & Thöne-Otto, A. (2020). The effect of high vs. low intensity neuropsychological treatment on working memory in patients with acquired brain injury. *Brain Injury, 34*(8), 1051-1060. https://doi.org/10.1080/02699052.2020.1773536

S1 Table Means and standard deviations of the neuropsychological outcomes.

	outcomes	working memory training group			unspecific attention training group			overall		
		T1	T2	T3	T1	T2	T3	T1	T2	T3
working memory tasks	Digit Span (forwards)	7.64 (1.57)	7.91 (1.45)	7.45 (1.51)	7.00 (1.66)	7.33 (0.87)	7.33 (1.58)	7.35 (1.60)	7.65 (1.23)	7.40 (1.50)
	Digit Span (backwards)	5.82 (1.08)	5.64 (2.01)	7.00 (1.61)	5.89 (1.27)	6.22 (0.97)	6.33 (1.58)	5.85 (1.14)	5.90 (1.62)	6.70 (1.59)
	Span Board (forwards)	7.91 (2.07)	7.91 (2.17)	8.18 (2.32)	7.56 (1.74)	8.22 (1.56)	7.78 (0.83)	7.75 (1.89)	8.05 (1.88)	8.00 (1.78)
	Span Board (backwards)	7.27 (2.20)	7.64 (1.96)	8.36 (1.86)	6.67 (2.35)	7.00 (1.73)	8.44 (2.13)	7.00 (2.22)	7.35 (1.84)	8.40 (1.93)
	Digit-Symbol Coding	50.73 (12.89)	57.09 (16.96)	58.18 (17.94)	48.78 (16.36)	52.22 (17.73)	58.89 (19.87)	49.85 (14.18)	54.90 (17.03)	58.50 (18.32)
	Letter-Number Sequencing	9.82 (3.25)	-	11.36 (2.58)	9.56 (2.35)	-	9.22 (1.20)	9.70 (2.81)	-	10.40 (2.30)
comprehensive cognitive functions	working memory composite	0.42 (3.10)	1.04 (4.30)	2.51 (3.91)	-0.51 (3.47)	0.73 (2.61)	1.72 (3.16)	0.00 (3.22)	0.90 (3.55)	2.15 (3.52)
	attention composite	0.06 (2.45)	-0.55 (4.72)	-0.93 (5.62)	-0.08 (3.40)	0.52 (3.40)	-0.96 (5.16)	0.00 (2.83)	-0.07 (4.11)	-0.94 (5.27)
	executive functions	140.45 (41.87)	-	131.27 (23.33)	141.68 (42.14)	-	125.81 (31.95)	141.01 (40.88)	-	128.82 (26.91)
	verbal learning	45.45 (10.16)	-	51.45 (9.35)	45.22 (7.87)	-	50.67 (8.40)	45.35 (8.97)	-	51.10 (8.71)
	daily life composite	-0.08 (0.46)	-	-0.04 (1.46)	0.18 (0.61)	-	0.17 (1.86)	0.03 (0.53)	-	0.06 (1.61)

Note: All working memory values represent raw scores and refer to correct items. Composite scores are presented as standardized z-scores and refer to mean number of correct items (working memory composite); mean reaction time of TAP Alertness, and mean number of errors and omission of TAP Divided Attention (attention composite); and mean number of the sum of items in CFQ and FEDA (daily life composite). Executive functions and verbal learning refer to single measures, hence values represent raw scores (critical time in sec in the Stroop task, and number of correct items in five trials in the CVLT, respectively).

S2 Outcome measures Detailed explanation of each task applied.

1) Working memory functions

Digit Span and Span Board (forwards/backwards). Digit Span and Span Board measure verbal and visuospatial working memory functions. The German version of the Wechsler Memory Scale revised was administered (WMS-R; Härting et al., 2004). In the Digit Span task, a series of digits were read aloud that the participant had to repeat immediately, forwards or in reversed order. In the Span Board task, the examiner tapped on blocks that were placed irregularly on a board and the participant had to repeat the sequence forwards or backwards. Span lengths increased successively until the participant failed both trials of a given length. Dependent variables were the number of correct trials. Test-retest reliability of the Digit Span is $r = .83$ and of the Span Board $r = .60$ (Härting et al., 2000).

Digit-Symbol Coding. The Digit-Symbol Coding task measures working memory as well as attention and visuomotoric coordination. The German version of the Wechsler Adult Intelligence Scale was applied (WAIS-III, Wechsler, 1997; WIE, Aster et al., 2006). A series of digits, each paired with an abstract symbol, was presented to the participant who then must convert each number into the corresponding symbol. Dependent variable is number of correct entries. The average reliability is $r = .84$ (Aster et al., 2006).

Letter-Number Sequencing. The Letter-Number Sequencing task measures verbal working memory. The German version of the Wechsler Adult Intelligence Scale was administered (WAIS-III, Wechsler, 1997; WIE, Aster et al., 2006). Series of digits and letters are read out to the participants. They are asked to rearrange them in ascending (numerical/alphabetical) order – first, by digits, and second, by letters. The average reliability is $r = .85$ (Aster et al., 2006).

2) Attention

TAP Alertness. The Alertness subtest of the Test for Attentional Performance (TAP; Zimmermann & Fimm, 2014) measures processing speed. The task requires participants to tap a button as fast as possible every time a cross appeared on a screen. The task differentiates between tonic alertness, which is the ability to generally maintain a high level of responsiveness, and phasic alertness, which is the immediate allocation of resources after the presentation of an audio warning to process an expected stimulus. The dependent variable was the mean reaction time of tonic and phasic alertness. Test-retest reliability in patients with brain injury is $r = .86$ (Zoccolotti et al., 2002).

TAP Divided Attention. This subtest of the Test for Attentional Performance (TAP; Zimmermann & Fimm, 2014) measures divided attention. Participants worked on two tasks simultaneously: they had to detect a square of four crosses in a matrix of changing crosses and to monitor repetitions of presented audio signals. The dependent variable was the mean number of omissions and errors. Test-retest reliability in patients with brain injury is $r = .65$ for errrors and $r = .73$ for omissions (Zoccolotti et al., 2002).

3) Executive functions

Stroop task. The Stroop Task is a measure of conflict resolution that requires inhibition of an over-learned response (Stroop, 1935; adaption of Bäumler, 1985). Participants were first asked to read aloud a list of color words (BLUE, GREEN, RED, and YELLOW) as fast as possible. After this, they were instructed to label the color in which the words are printed, experiencing interference of word and color name (e.g., RED written in blue). The dependent variable was the time needed for color naming. The test-retest reliability is $r = 93$ (Bäumler, 1985).

4) Verbal learning

California Verbal Learning Test (CVLT). This test is a word list recall test assessing learning strategies and verbal memory processes (Niemann et al., 2008). A fixed sequence of 16 nouns was vocally presented five times and participants had to repeat all remembered items after each trial. The dependent variable was the sum of correct words in this learning phase. Two parallel versions were administered. The odd-even reliability is r = .96 (Niemann et al., 2008).

5) Daily life performance

Canadian Failure Questionnaire (CFQ). The German version of the Canadian Failure Questionnaire (Broadbent et al., 1982; Klumb, 1995) was used to indicate difficulties in everyday life related to working memory demands. This self-report questionnaire comprises 25 items with statements regarding cognitive failures in perception, memory and action due to interruptions in memory processes, which were ranked on a 5-point Likert scale. Dependent variable was the sum of all items. The questionnaire has an internal consistency of Cronbachs α = .78 and a test-retest reliability of r = .71 (Klumb, 1995; Bridger et al., 2013).

German questionnaire on subjective attention deficits (FEDA). The self-report questionnaire focuses on critical situations in daily life targeting distractibility, tiredness and drive (Zimmermann et al., 1991). Overall, 27 statements had to be ranked on a 5-point Likert scale. Dependent variable was the sum of all items. Data on validity and test-retest reliability are not available.

6) Control measures

German verbal comprehension test „Wortschatztest“ (WST). The test indicates premorbid intelligence in patients with brain injury based on their vocabulary (Schmidt & Metzler, 1992). The task is to recognize a real word out of five distractors. The internal consistency is α = .94 (Schmidt & Metzler, 1992).

Subtest 3 of the German intelligence battery Leistungsprüfsystem (LPS-3). The test is used to estimate premorbid intelligence based on logical reasoning (Kreuzpointner et al., 2013). A series of abstract symbols was shown. Each row of symbols was constructed according to a certain rule that had to be identified. Participants had five minutes to cancel the symbols that did not fit to the respective rule. The outcome variable was the number of correct items. The internal consistency ranges between $\alpha = .86$ and $\alpha = .94$ (Kreuzpointner et al., 2013).

Beck Depression Inventory (BDI-II). Depressive mood was screened with the self-report of the severity of depressive symptoms (Hautzinger et al., 2009). It consists of 21 items (concerning e.g., sadness, dissatisfaction, and social withdrawal). The sum of selected items represented the outcome variable, with scores lower than 13 indicating no clinically relevant symptoms. The internal consistency ranges between $\alpha = .89$ and $\alpha = .93$ (Hautzinger et al., 2009).

Curriculum vitae

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List of publications

Peer-reviewed publications

Weicker, J., Hudl, N., Hildebrandt, H., Obrig, H., Schwarzer, M., Villringer, A., & Thöne-Otto, A. (2020). The effect of high vs. low intensity neuropsychological treatment on working memory in patients with acquired brain injury. *Brain Injury, 34*(8), 1051-1060. https://doi.org/10.1080/02699052.2020.1773536

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Weicker, J. (2020). Evaluation of gamification elements in neuropsychological therapy. Talk presented at 4th Scientific Summer School of the Federation of the European Societies of Neuropsychology (FESN), Virtual Conference.

Weicker, J., & Knop, A. (2019). Pro und Contra: Kognitive Therapie via Hometraining? Talk presented at the 1st workshop conference of the Gesellschaft für Neuropsychologie (GNP), Fulda, Germany.

Weicker, J. (2019). Neuropsychologische Therapie von Gedächtnisfunktionen: Forschungseinblicke und praktische Empfehlungen. Talk presented at therapie Leipzig – Fachmesse mit Kongress für Therapie, Medizinische Rehabilitation und Prävention, Leipzig, Germany.

Weicker, J., Schwarzer, M., Hildebrandt, H., & Thöne-Otto, A. (2017). Arbeitsgedächtnis- versus Aufmerksamkeitstrainings bei Patienten mit erworbenen Hirnschädigungen – eine randomisierte, doppelblinde Studie. Talk presented at 32th Annual Meeting of Gesellschaft für Neuropsychologie (GNP), Konstanz, Germany.

Weicker, J., da Silva Ramos, S., & O'Neill, B. (2017). Making the most of technology in neuro-rehabilitation: Training and supporting cognitive functions. Talk presented at RehabWeek, London, UK.

Hudl, N., **Weicker, J.**, Lepsien, J., Müller, K., Villringer, A., & Thöne-Otto, A. (2016). Structural plasticity in healthy elderly after working memory training – a double-blind, randomized control group trial. Poster presented at 46th Annual Meeting of the Society of Neuroscience (SFN), San Diego, USA.

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Weicker, J., Hudl, N., & Thöne-Otto, A. (2016). Wirksamkeit von Arbeitsgedächtnistrainings mit RehaCom – Daten von 2 RCT. Talk presented at Joint Meeting of Gesellschaft für Neuropsychologie Österreich (GNPÖ), Schweizerische Vereinigung der Neuropsychologinnen und Neuropsychologen (SVNP-ASNP) & Gesellschaft für Neuropsychologie (GNP), Würzburg, Deutschland.

Hudl, N., **Weicker, J.**, & Thöne-Otto, A. (2016). Auswirkungen eines adaptiven Arbeitsgedächtnistrainings auf das fronto-parietale Arbeitsgedächtnisnetzwerk bei gesunden Älteren – eine randomisierte kontrollierte Studie. Talk presented at 6th Joint Meeting of Deutsche Gesellschaft für Neurorehabilitation (DGNR) and Deutsche Gesellschaft für Neurotraumatologie und Klinische Neurorehabilitation (DGNKN), Bad Godesberg, Germany.

Hudl, N., **Weicker, J.**, Villringer, A., & Thöne-Otto, A. (2015). Webbasierte neuropsychologische Diagnostik und funktionsorientiertes Training. Talk presented at 30th Annual Meeting of Gesellschaft für Neuropsychologie (GNP), Lübeck, Germany.

Hudl, N., **Weicker, J.**, Villringer, A., & Thöne-Otto, A. (2015). Multicenter studies in neuropsychology: Working memory training for brain damaged patients. Poster presented at MaxNetAging Conference, Leipzig, Germany.

Weicker, J., & Thöne-Otto, A. (2015). Mediengestützte neuropsychologische Therapie von Gedächtnisfunktionen. Talk presented at Annual Meeting of Deutsche Gesellschaft für Neurotraumatologie und Klinische Neurorehabilitation (DGNKN), Leipzig, Germany.

Weicker, J., Hudl, N., Marichal, E., & Thöne-Otto, A. (2014). Training of working memory in brain injured patients and healthy elderly subjects: Two randomized controlled trials. Talk presented at 29th Annual Meeting of Gesellschaft für Neuropsychologie (GNP), Oldenburg, Germany.

Weicker, J., & Thöne-Otto, A. (2013). Training of working memory – A meta-analysis. Talk presented at 55th Tagung experimentell arbeitender Psychologen (TeaP), Vienna, Austria.

Weicker, J., Hudl, N., Marichal, E., Müller, K., Lepsien, J., Trapp, S., Frisch, S., & Thöne-Otto, A. (2013). Training of working memory in healthy elderly subjects - A randomized controlled trial. Poster presented at 4th Joint Meeting of the European Societies of Neuropsycholgy (ESN) and the 28th Annual Meeting of Gesellschaft für Neuropsychologie (GNP), Berlin, Germany.

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Weicker, J. & Thöne-Otto, A. (2012). Training von Arbeitsgedächtnisfunktionen – Eine systematische Literaturanalyse. Talk presented at 56th Annual Meeting of Deutsche Gesellschaft für Neurotraumatologie und Klinische Neurorehabilitation (DGNKN), Köln, Germany.

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Leipzig, den 31.08.2020

Juliane Weicker