

Serveur Académique Lausannois SERVAL serval.unil.ch

Author Manuscript

Faculty of Biology and Medicine Publication

This paper has been peer-reviewed but does not include the final publisher proof-corrections or journal pagination.

Published in final edited form as:

Title: Cognitive Working Memory Training (CWMT) in adolescents suffering from Attention-Deficit/Hyperactivity Disorder (ADHD): A controlled trial taking into account concomitant medication effects.

Authors: Ackermann S, Halfon O, Fornari E, Urben S, Bader M

Journal: Psychiatry research

Year: 2018 Nov

Issue: 269

Pages: 79-85

DOI: 10.1016/j.psychres.2018.07.036

In the absence of a copyright statement, users should assume that standard copyright protection applies, unless the article contains an explicit statement to the contrary. In case of doubt, contact the journal publisher to verify the copyright status of an article.

Accepted Manuscript

Cognitive working memory training (CWMT) in adolescents suffering from Attention-Deficit/Hyperactivity Disorder (ADHD): A controlled trial taking into account concomitant medication effects.

Sandie Ackermann , Olivier Halfon , Eleonora Fornari ,
Sébastien Urben , Michel Bader

PII: S0165-1781(18)30459-1
DOI: [10.1016/j.psychres.2018.07.036](https://doi.org/10.1016/j.psychres.2018.07.036)
Reference: PSY 11585



To appear in: *Psychiatry Research*

Received date: 12 March 2018
Revised date: 26 June 2018
Accepted date: 26 July 2018

Please cite this article as: Sandie Ackermann , Olivier Halfon , Eleonora Fornari , Sébastien Urben , Michel Bader , Cognitive working memory training (CWMT) in adolescents suffering from Attention-Deficit/Hyperactivity Disorder (ADHD): A controlled trial taking into account concomitant medication effects., *Psychiatry Research* (2018), doi: [10.1016/j.psychres.2018.07.036](https://doi.org/10.1016/j.psychres.2018.07.036)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Highlights

- CWMT allows obtaining working memory abilities similar to “control” adolescents.
- CWMT and medication allow the enhancement of executive aspects of WM.
- No transfer of these improvements to other cognitive abilities were observed.
- CWMT reduces hyperactivity / impulsivity symptoms at 2-month follow-up.
- The findings support multimodal interventions as effective in helping adolescents with ADHD.

Cognitive working memory training (CWMT) in adolescents suffering from Attention-Deficit/Hyperactivity Disorder (ADHD): A controlled trial taking into account concomitant medication effects.

Sandie Ackermann^a, Olivier Halfon^a, Eleonora Fornari^b, Sébastien Urben^{1a}, Michel Bader^{1a*}.

^a University Service of Child and Adolescent Psychiatry, University Hospital of Lausanne, Switzerland

^b Biomedical Imaging Center (CIBM), Department of Radiology, University Hospital of Lausanne, Switzerland

¹ Both authors contributed equally as senior authors

* **Corresponding author:** Michel Bader, Research Unit, University Service of Child and Adolescent Psychiatry, Av. Echallens 9, CH-1004 Lausanne; E-mail: Michel.Bader@chuv.ch

Abstract

Although, cognitive working memory training (CWMT) has been reported to enhance working memory functioning in youths with attention-deficit/ hyperactivity disorder (ADHD), few studies take into account the concomitant effects of medication. Sixty adolescents aged from 11 to 15 years were randomly assigned to CWMT treatment, whereas medication was either continued or not introduced (no randomization performed). Results revealed beneficial effects of CWMT on the different components of working memory (WM), namely the phonological loop, the visuospatial sketchpad and the central executive. In particular, CWMT allowed participants to obtain a level of performance similar to the typically-developing adolescents for the phonological loop (i.e., forward digit span) as well as for the visuospatial sketchpad (i.e., board span). For the central executive (i.e., backward digit span) the concomitant effects of CWMT and medication allows participants to obtain the performance level of the typically-developing adolescents. Although, no transfers were observed with respect to other cognitive functions, in medicated patients with ADHD, CWMT reduced hyperactivity / impulsivity symptoms at 2-month follow-up. The present study gives evidence of the efficacy of CWMT to enhance WM performance, as well as, to reduce symptoms. The overall results highlight the usefulness of multimodal interventions.

Keywords: Cognitive deficits; multi-modal intervention; cognitive training; stimulants.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a highly prevalent disorder, affecting about 5% of children, with no evidence of an increase over the three last decades (Polanczyk et al., 2014). It is a persistent neurobiological disorder caused by a complex interplay between genetic and environmental risk factors affecting brain networks, leading to emotional and behavioral disturbances, functional impairments, as well as academic failures (e.g., Barkley et al., 2006; Biederman et al., 2017; Francx et al., 2016; van Lieshout et al., 2016).

1.1. Working memory dysfunction

About 30% of ADHD children present working memory (WM) dysfunctions (Lambek et al., 2011; Nigg et al., 2005). WM is a central cognitive function allowing the encoding, storing and manipulating of information for a short period of time (Miyake and Shah, 1999). Baddeley's model (Baddeley & Hitch, 1974) decomposed WM in three subsystems: the central executive (i.e., attentional supervisory system), the phonological loop (i.e., process verbal information) and the visuospatial sketchpad (i.e., process visuospatial information). WM has been proposed as one exemplar process with substantial theoretical and empirical basis in the ADHD theories and literature not only to better understand ADHD but also to alleviate ADHD symptoms. For instance, individual differences in WM improvement, and in particular regarding the visuospatial component, during late childhood (from 7 to 13 years of age) predict ADHD symptoms changes (Karalunas et al., 2017). Moreover, WM dysfunctions in ADHD might have adverse functional consequences for learning and everyday life activities that might lead to academic failures (Rappoport et al., 2008; Rogers et al., 2011). However, WM dysfunctions may be targeted by specific interventions (Arnsten et al., 2010; Biederman et al., 2008; Swanson et al., 2011)

1.2. Cognitive working memory training

Cognitive Working Memory Training (CWMT) has been observed to be efficient in improving WM capacities in youths with ADHD (Beck et al., 2010; Klingberg et al., 2002; Rapport et al., 2013), with changes persisting to two months (Gropper et al., 2014) and even over 6 months (Klingberg et al., 2005). Two recent meta-analyses (Cortese et al., 2015; Melby-Lervåg & Hulme, 2013) observes that cognitive training (including CWMT) produces moderately sized gains on WM mainly when outcome measures are very similar to the trained task, but had very limited effects specifically on core ADHD symptoms according to assessments based on blinded measures. This suggests a dissociation between neuropsychological functioning and symptoms.

1.3. Concomitant medication effects

Moreover, stimulants (e.g., methylphenidate), referring to mainstream treatment of ADHD, improve WM functioning (e.g., Bedard et al., 2007; Mehta et al., 2004). Nevertheless, a few studies took into account the medication effects while studying the effects of CWMT. For instance, Holmes et al. (2010) assess sequentially, in an open-label design study, the effect of CWMT as well as medication on 25 children with ADHD aged 8-11 years. Although medication enhance visuospatial aspects of WM, CWMT has been observed to enhance all WM components, with gains to central executive aspects lasting up to 6 months. Likewise, Mawjee et al. (2015) randomized (stratified by medication and sex) ninety-seven students with ADHD aged from 18-35 either to standard-length CWMT, shortened-length CWMT or control group (i.e., waitlist). Both forms of CWMT have improved WM performances with the improvements remaining persistent at a 3-month follow-up visit. Others studies including participants taking a medication during CWMT did not investigate the possibility of a

specific concomitant effects of medication compared to cognitive training effects (e.g., Beck et al., 2010; Egeland et al., 2013; Green et al., 2012; Gropper et al., 2014; Hovik et al., 2013; van der Donk et al., 2015).

1.4. Benefit transfer to other cognitive functions and symptoms

If WM components have been improved with training and as such have been demonstrated as being plastic (Holmes et al., 2009; Jaeggi et al., 2008; Klingberg, 2010; Olesen et al., 2004), the question of transfer of the beneficial effects of CWMT to other cognitive functions (e.g., reasoning ability, attention and episodic memory) is less clear (Alloway et al., 2013; Schweizer et al., 2011; Shipstead et al., 2012; Thompson et al., 2013) as the existing evidences of transfer effects in children with ADHD are inconclusive (e.g., Rapport et al., 2013). For instance, a study has found large transfer effects of WM training on complex reasoning and inhibition abilities (Klingberg et al., 2005), while other studies have failed to find such transfer effects (Dongen-Boomsma et al., 2014; Egeland et al., 2013; Gray et al., 2012; Holmes et al., 2009; van der Donk et al., 2015). Finally, two recent meta-analyses (Cortese et al., 2015; Rapport et al., 2013) reported no transfer effects of cognitive trainings on other cognitive functions or academic performances. With regards to the question of transfer on the ADHD symptoms, as reported above, a meta-analysis (Cortese et al., 2015) described very limited alleviation of ADHD symptoms.

1.5. The current study

Taking into account all above mentioned studies, WM might be improved, but the concomitant effects of medication have not been well accounted for. Additionally, the questions of transfer of the benefits related to CWMT, when taking into account the concomitant medication effects, to other cognitive functions as well as to symptoms remain

poorly understood. Therefore, the current study aimed to (1) investigate the effects of 5-week CWMT on WM abilities while taking into account the medication effects; (2) assess the possible transfer of benefits to inhibition abilities (an executive function reported as deficient in individuals with ADHD), as well as on ADHD symptoms at a 2-month follow-up. The outcome were chosen to be able to compare the results of the current trial to previous studies.

2. Method

2.1. Participants and procedure

A total of 73 adolescents, aged from 11 to 15 years, 13 girls and 60 boys, that is representative of the sex ratio observed in ADHD literature (Barkley, 2015), participated in the study. ADHD participants were recruited from pediatrician and child psychiatrists informed on the study. Control participants were recruited from various sources, from local pediatricians, from private school, through flyer and an announcement posted by the web site of the University Hospital of Lausanne. All participants received a financial compensation for their participation in this study (150 CHF). The study and procedure were approved by the Ethics Committee of Vaud state.

Adolescents were first screened through a short phone interview with one of the parents. Diagnostic status of ADHD was established with the Diagnostic and Statistical Manual of Mental Disorders (APA, 2000) and comorbidities were evaluated using the Mini Neuropsychiatric Interview during the first visit (Sheehan, 2004) by a trained child psychiatrist with the presence of one parent or both parents. The ADHD symptoms were investigated using DSM-IV criteria as well by Conners's questionnaire (CPRS-R; Conners et al., 1998). This clinical interview investigated treatments for ADHD and comorbidities as well as medication effects and dosage. Participants showing signs of psychotic disorder

($n=1$), strong depression and low Intellectual Quotient (measured by the Wechsler Intelligence Scale for Children, $IQ < 70$, $n=0$) were excluded from the study. Participants with low suicidal risks ($n=5$), mood dysregulation ($n=11$), anxiety disorders ($n=6$) or obsessive-compulsive disorders ($n=1$) were not excluded, because of the frequent comorbidities of these mild diseases with ADHD (Barkley, 2014). Some participants with ADHD as comorbid learning disabilities (LD, $n=19$) or developmental coordination disorder (DCD, $n=5$) are in the sample which is consistent with the literature (e.g., Sexton et al., 2011). No participants present autism spectrum disorders. Moreover, participants without ADHD did not present LD or DCD.

The final sample consisted of 60 adolescents, 13 girls and 47 boys, divided into 4 groups: (1) a control group composed of participants without ADHD, but following CWMT, (2) a group of participants with ADHD following CWMT and taking medication (CWMT+ / M+), (3) a group of adolescents with ADHD, without CWMT but taking medication (CWMT- / M+), and (4) a group of adolescents with ADHD, following CWMT, but without medication (CWMT+ / M-). The Table 1 describes the socio-demographic and clinical data of the four groups. No significant differences regarding age, gender, diagnostic type and ADHD symptoms were observed between the groups at baseline. CWMT was randomized but the medication was not randomly assigned, the patients receiving medication continued their routine treatment. The patients in the CWMT+ / M- were not medicated for their ADHD symptoms, because their parents refused the prescription of stimulants to their children. The control group allows us to assess if the performances after the intervention arrive at the level of typically-developing children (Lambek et al., 2011). No significant difference in compliance to the program was found across groups (training time per day). Figure 1 reports

a CONSORT-like diagram.

Regarding medication (M), across the 18 ADHD participants in the CWMT groups, all took methylphenidate (immediate or long-acting release). Medication did not vary across CWMT groups. Participants on medication were included only when they were well-adjusted to their medication. Medication status and dose remained the same throughout the training period (followed by the medical referee of the study), as prescribed by a community physician. Children were not medicated during the first visit. At the second visit, participants taking drug were medicated the day of the assessment to apprehend medication effects as well as their functioning after the study in “real” life condition.

This study was part of a larger study investigating also neural plasticity with functional Magnetic Resonance Imaging paradigm. Adolescents’ ADHD symptoms severity as rated by the parents and the adolescents themselves were collected through the Conners’ questionnaire, which was sent by postal mail with a response envelope. After receiving the completed questionnaires, the dates of the two visits were fixed by phone. For the first visit, adolescents were invited to answer to a clinical interview and to complete a neuropsychological assessment with a trained psychologist. Between the first and the second visit, the CWMT groups were asked to complete the CWMT at home. In the second visit, participants were invited to complete the same neuropsychological assessment than for the first visit. Two months after the study, we asked parents and adolescents to rate the ADHD symptoms by fulfilling the Conners’ questionnaire (CPRS-R; Conners et al., 1998) .

2.2. Cognitive Working Memory Training (CWMT)

Participants underwent the school-aged version of cognitive training developed by Cognitive Medical Systems AB (Stockholm, Sweden). The CWMT program, based on the

brain plasticity theory, targets individuals having poor WM abilities and attention deficits (Klingberg et al., 2005; Klingberg et al., 2002). The CWMT program was provided on a CD and used by the child on a personal computer at home. It included 15 exercises of verbal and visuospatial aspects of WM of increasing difficulty. Each child had to train 25 days (a minimum of 20 days was required to be included in the study), and perform 90 WM trials on each day of training. The difficulty level was automatically adjusted on a trial-by-trial basis to match the WM span of the child on each exercise (Olesen et al., 2004). Total time of training depended on the reached level of difficulty. Throughout the training, a trained psychologist coached the participants by weekly phone contacts with the adolescent ensuring quality of the training, encouraging adherence, enhancing motivation, providing feedback to help engagement during exercises.

2.3. Measures

2.3.1. Working Memory

The three components of WM, with regards to Baddeley's model (Baddeley & Hitch, 1974) were assessed, namely the central executive, the phonological loop (verbal component) and the visuospatial sketchpad (visuospatial component). The digit span subtest from the Wechsler Intelligence Scale for Children (WISC-IV; Wechsler, 2003) were used to index the phonological loop (i.e., forward digit span) and the executive central (i.e., backward digit span). The adolescents is asked to repeat numbers gradually enhancing (from 2 to 9) in the same order (forward) and in reverse order (backward). The Corsi Block-tapping test (Milner, 1971) was used to measure visuospatial sketchpad component of WM. The participant must repeat the sequence of cubes shown (arranged on a board), which gradually increases from two to nine cubes. The maximum span was used to index these abilities.

2.3.2. Inhibition abilities

The Stroop Color and Word Test (Golden & Freshwater, 1978; Stroop, 1992) measures a participant's ability to respond selectively to one dimension of a multidimensional stimulus (i.e., inhibition of non-relevant information). Each of the three conditions of the Stroop test contains five columns of 10 stimuli. First, the participant must name the colours, and, second, he must just read the word on the sheet representing colours. The third condition called "interference" contains the words *red*, *blue*, and *green* printed in a different colour, and the participant is asked to name the colour of the ink of each stimulus. In all cases the participant has been asked to read aloud as quickly as possible. The score is the number of items processed in the interference condition.

The subtest Go/no-go of the Test of Attentional Performance (Zimmermann & Fimm, 1995) is a computerized test measuring response inhibition abilities. We administered the Go/No-go – we used the form "5 stimuli including 2 targets": five rectangular shapes with different content and texture are displayed on the screen in a pseudo-random order. Two of these figures were defined as targets to which the subject had to react as quickly as possible by pressing the touch-response, and inhibiting the response in relation to the appearance of the other three figures. Mean reaction times and errors were the measures used in this study to index response inhibition from this task.

2.3.3. ADHD symptoms

The Conners' Parents Rating Scale (CPRS-R; Conners et al., 1998) was used to assess the severity of ADHD symptoms. Each question is rated from 0 (not at all) to 4 (very much). Two main scores are computed namely, the inattentive score and the impulsivity/hyperactivity

score. Internal consistency of the scores were acceptable (Cronbach's $\alpha > 0.78$). Notice that the adolescents and their parents were not blind towards CWMT and medication.

2.4. Data analysis

We used an "as-treated" analytic plan since the participants did not have their post-intervention assessments, it make little sense to keep the last observation carried forward (LOCF) as it refers to baseline assessment. Distributions of the data fit a Gaussian-like distribution which allowed the use of parametric tests. Analyses of variance (ANOVA) were computed on the post-test (T2) scores, with the four groups as between subject factor, and pre-test (T1) scores as covariate (ANCOVA). Post hoc tests were computed using a Sidak correction to assess specific group differences.

3. Results

Table 2 reports the descriptive of the main measures.

3.1. WM outcomes

The ANCOVA revealed a main effect of groups on the forward digit span ($F(3, 59) = 2.86$, $p < 0.05$, $\eta^2 p = 0.135$), the backward digit span ($F(3, 59) = 6.80$, $p \leq 0.001$, $\eta^2 p = 0.271$) and the board span ($F(3, 59) = 4.07$, $p \leq 0.01$, $\eta^2 p = 0.182$). Post hoc tests revealed, for the forward digit span, that the control group has marginally higher performances than the CWMT-/M+ group ($p = 0.054$). For the backward digit span, post hoc tests revealed that the CWMT+/M+ group as higher performances than the CWMT-/M+ group ($p = 0.041$). The control group has better performances than the CWMT-/M+ group ($p \leq 0.001$) and the CWMT+/M- group ($p = 0.017$). For the board span, post hoc tests revealed that the CWMT-/M+ group as lower performances than the CWMT+/M+ ($p = 0.023$) and the control group ($p = 0.017$). The figure 2 illustrates these results.

3.2. Transfer to inhibition abilities and ADHD symptoms

No differences between groups were observed regarding the Stroop or the Go / no-go scores. The ANOVA conducted only on the participants with ADHD (three groups: CWMT+/M+; CWMT+/M-; CWMT-/M+) revealed no effect of treatment on inattention scores and the hyperactivity/impulsivity scores of the CPRS-R rated by the adolescents. A differential treatment effect was observed on the hyperactivity/impulsivity scores rated by the parents ($F(3, 38) = 4.34, p < 0.05, \eta^2 p = 0.203$). Post hoc tests using a Sidak correction revealed that the CWMT+/M+ group reported having diminished ADHD symptoms relative to the the CWMT-/M+ ($p = 0.024$) at 2-month follow-up. No group differences were observed on the inattention score rated by the parents.

4. Discussion

Primarily, the current study aimed to assess the WM functioning after participation in a CWMT program while taking into account the medication effects. As a second objective, we assess the possible transfer of benefits to inhibition abilities or to ADHD symptoms (at 2-month follow-up). Results revealed specific improvement related to CWMT as well as concomitant effects with medication. Moreover, although, no transfer of benefits was observed towards inhibition abilities, hyperactivity/impulsivity symptoms rated by parents decrease with the help of CWMT in medicated adolescents. More specifically, results suggested that the concomitant effects of medication and CWMT enabled participants with ADHD to show the same central executive abilities (i.e., backward digit span) than typically-developing adolescents benefitting from CWMT. Additionally, the phonological loop (forward digit span) and the visuospatial sketchpad (span board) aspects of WM seemed to be the mostly improved by CWMT.

4.1. Concomittant effects on central executive processes

We observed a concomittant effect of medication and CWMT on central executive abilities of WM. In the same line, previous studies already reported beneficial effect of stimulant medications on WM (e.g., Bedard et al., 2004; Mehta et al., 2004). The present study could indicate convergent effects of CWMT and medication on the central executive part of WM. We might hypothesize that the medication could potentiate the effects of CWMT by increasing attentional capacities and thus provides the most from CWMT. Being less distracted, adolescents might be more able to focus on CWMT training and thus benefit the most from CWMT. By increasing the amount of extracellular dopamine and norepinephrine, which are deficient in youths with ADHD and which is related to the executive control abilities (Nieoullon, 2002), psychostimulants medication (such as methylphenidate) may also help to potentialize the benefit of CWMT on WM central executive components.

4.2. Phonological loop and visuospatial sketchpad

Results on specific effects on phonological loop and visuospatial sketchpad are in line with previous findings (Gray et al., 2012; Gropper et al., 2014). Beneficial effects of CWMT training on auditory verbal and visuospatial WM performance in adolescents with ADHD or learning disabilities were observed. Other studies on children with ADHD also reported similar results (Beck et al., 2010; Klingberg et al., 2005; Klingberg et al., 2002). The present results showed that phonological loop as well as visuospatial sketchpad components of WM improvement appeared more closely related to CWMT than to medication. These results are sustained by the fact that CWMT exercices focused mainly on phonological loop and visuospatial sketchpad training.

4.3. Transfer of benefit to inhibition abilities

Results indicated no transfer of benefits related to CWMT or medication on inhibition abilities. The absence of transfer effects were consistent with recent meta-analyses examining transfer toward a wide range of cognitive abilities (Rapport et al., 2013; Sonuga-Barke et al., 2014, Cortese et al., 2015). We might hypothesize that the limited transfer effects generated by CWMT may come from the type of CWMT used in the study. A drill-and-practice strategy (which is the case of CWMT) may fail to generalize specific benefits to other cognitive functions. The participants seemed not to be able to generalize the improvement of WM towards other cognitive skills. Perhaps, cognitive training targeting multiple neuropsychological functions (Cortese et al., 2015) and focusing on metacognitive skills development approach (e.g., Franck et al., 2013) might help to enhance transfer of benefits to other cognitive functions. In this line, a study on the role of coaching in children with neuropsychiatric disorders (Roording-Ragetlie et al., 2017) showed that a less intensive version of CWMT with active coaching have benefits on other cognitive functions. Additionally, it might be also possible that the transfer effects of the CWMT training are delayed in time and might be observable only at follow up (Gray et al., 2012). Future researches should put more effort investigating why, how, and for whom CWMT is more effective (van der Donk et al., 2015).

4.4. Benefits on ADHD symptoms

Results indicated a beneficial effect of CWMT in participants taking medication. In participants taking medication a stronger reduction of the hyperactivity/impulsivity symptoms rated by parents two months after the study was observed for patients participating in the CWMT. A possible explanation for these results is the intense attentional effort triggered by the CWMT, which might be transferred to home environment, and therefore to parental report

(Gray et al., 2012) which seems to last at least two months after the study. However, parent's assessment is subjective and can be biased by their own representations about the impact of CWMT and the effects of stimulants.

4.5. Clinical implications

The design of this study corresponds to the clinical practice combining medication and other interventions. Moreover, results of the present study seem to support the idea that multimodal therapeutic approaches are more effective in enhancing cognitive abilities and reducing ADHD symptoms, which is in line with previous studies (Jensen et al., 2001). Thus, the combination between clinical and pharmacological interventions should be for now considered as first-line treatment for ADHD (e.g., Chacko, 2013). Nevertheless, future studies should investigate mechanisms underlying cognitive and symptoms enhancement (van der Donk et al., 2015) in order to design cost and time-effective multimodal treatments. There continues to be a great need to identify more effective and adjunctive interventions for ADHD (Rutledge et al., 2012). The degree of involvement of the coach and the quality of the relationships between professionals, parents and participants in CWMT is another aspect of the motivation and the involvements of the participants. Likewise, future researches should assess more specifically, the individual differences such as age, biological factors, neuropsychological profiles and broader ranges of functional outcomes (Cortese et al., 2015; Jaeggi et al., 2011; Jolles et al., 2012; von Bastian & Oberauer, 2014) as well as the role of coaching (Roording-Ragetlie et al., 2017) leading to the maximum benefits from CWMT.

4.6. Limitations

Results of this study should be considered in the light of several limitations. First, the design did not compare CWMT with an active comparison group, so that those receiving

CWMT and those without CWMT training differ in expectation of change/improvement as well as in terms of clinical attention they receive. Moreover, the study did not randomized participants to medication or placebo using double-blind methods. It is possible that parents who are ambivalent about stimulants would have been more collaborating with this study and would evaluate more positively the changes of their siblings or have different expectations which might have potentially biased the results (Mawjee et al., 2017). A teacher assessment of symptoms is lacking (at the request of the regional Ethics Committee). This would have added an additional independent assessment of outcomes on symptoms.

4.7. Conclusions

In this study, we observed that CWMT is an appropriate therapeutic strategy to improve WM capacity. The combination of interventions (CWMT and medication) showed positive effects on WM functioning, evidence which supports the multimodal interventions model. Future studies should be conducted to assess the effect of metacognitive strategies and transferring newly-learned strategies to other environmental situations (classroom, homework and social demands).

Conflict of interest: MB received honoraries from Pearsons for two talks and a grant from the “Fondation Novartis pour la Recherche en Sciences Médico-biologique”, for conducting the study. No financial support from Cogmed company was received, and MB remains independent for analyzing, interpreting and reporting the data.

Acknowledgment: The authors wish to express their gratitude to Sarah Leopizzi, Lisa Fernandez, and Magali Tinguely in helping collecting the data. Furthermore, our thanks go also to the participants and their families for their time and investment in the study. This study was support by FNRS Subside 3200B0-118373.

References

- Alloway, T. P., Bibile, V., & Lau, G., 2013. Computerized working memory training: Can it lead to gains in cognitive skills in students? *Computers in Human Behavior*, 29, 632-638.
- APA, 2000. *DSM-IV-TR: Diagnostic and statistical manual of mental disorders, text revision*. Washington, DC: American Psychiatric Association, 75.
- Arnsten, A. F. T., Paspalas, C. D., Gamo, N. J., Yang, Y., & Wang, M., 2010. Dynamic Network Connectivity: A new form of neuroplasticity. *Trends in Cognitive Sciences*, 14, 365-375.
- Baddeley, A. D., & Hitch, G., 1974. Working memory. *Psychology of learning and motivation*, 8, 47-89.
- Barkley, R. A., 2014. *Attention-deficit hyperactivity disorder: A handbook for diagnosis and treatment*: Guilford Publications.
- Barkley, R. A., 2015. Emotional dysregulation is a core component of ADHD. *Attention-deficit hyperactivity disorder: a handbook for diagnosis and treatment* 81-115.
- Barkley, R. A., Fischer, M., Smallish, L., & Fletcher, K., 2006. Young adult outcome of hyperactive children: adaptive functioning in major life activities. *Journal of the American Academy of Child & Adolescent Psychiatry*, 45, 192-202.
- Beck, S. J., Hanson, C. A., Puffenberger, S. S., Benninger, K. L., & Benninger, W. B., 2010. A controlled trial of working memory training for children and adolescents with ADHD. *Journal of Clinical Child & Adolescent Psychology*, 39, 825-836.

- Bedard, A. C., Jain, U., Hogg-Johnson, S., & Tannock, R., 2007. Effects of methylphenidate on working memory components: influence of measurement. *J Child Psychol Psyc*, 48, 872-880.
- Bedard, A. C., Martinussen, R., Ickowicz, A., & Tannock, R., 2004. Methylphenidate improves visual-spatial memory in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*, 43, 260-268.
- Biederman, J., Hammerness, P., Sadeh, B., Peremen, Z., Amit, A., Or-Ly, H., et al., 2017. Diagnostic utility of brain activity flow patterns analysis in attention deficit hyperactivity disorder. *Psychol. Medicine* 1-12.
- Biederman, J., Petty, C. R., Fried, R., Black, S., Faneuil, A., Doyle, A., et al., 2008. Discordance Between Psychometric Testing and Questionnaire-Based Definitions of Executive Function: Deficits in Individuals With ADHD. *J. Attent. Dis.*, 12, 92-102.
- Chacko, A., Feirsen, N., Bedard, A. C., Marks, D., Uderman, J. Z., & Chimiklis, A. , 2013. Cogmed working memory training for youth with ADHD: A closer examination of efficacy utilizing evidencebased criteria. *J. Clin. Child Adol. Psy.*, 42, 1-15.
- Conners, C. K., Sitarenios, G., Parker, J. D., & Epstein, J. N., 1998. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. *J. Abnorm. Child Psy.* , 26, 257-268.
- Cortese, S., Ferrin, M., Brandeis, D., Buitelaar, J., Daley, D., Dittmann, R. W., et al., 2015. Cognitive training for attention-deficit/hyperactivity disorder: meta-analysis of clinical and neuropsychological outcomes from randomized controlled trials. *J Am Acad Child Adolesc Psychiatry*, 54, 164-174.

- Dongen-Boomsma, M., Vollebregt, M. A., Buitelaar, J. K., & Slaats-Willems, D., 2014. Working memory training in young children with ADHD: a randomized placebo-controlled trial. *J. Child Psy. Psych.*, 55, 886-896.
- Egeland, J., Aarlien, A. K., & Saunes, B.-K., 2013. Few effects of far transfer of working memory training in ADHD: a randomized controlled trial. *PloS one*, 8, e75660.
- Franck, N., Duboc, C., Sundby, C., Amado, I., Wykes, T., Demily, C., et al., 2013. Specific vs general cognitive remediation for executive functioning in schizophrenia: a multicenter randomized trial. *Schizophr Res*, 147, 68-74.
- Francx, W., Llera, A., Mennes, M., Zwiers, M. P., Faraone, S. V., Oosterlaan, J., et al., 2016. Integrated analysis of gray and white matter alterations in attention-deficit/hyperactivity disorder. *NeuroImage: Clinical*, 11, 357-367.
- Golden, C. J., & Freshwater, S. M., 1978. Stroop color and word test. *age*, 15, 90.
- Gray, S., Chaban, P., Martinussen, R., Goldberg, R., Gotlieb, H., Kronitz, R., et al., 2012. Effects of a computerized working memory training program on working memory, attention, and academics in adolescents with severe LD and comorbid ADHD: a randomized controlled trial. *J. Child Psy. Psych.*, 53, 1277-1284.
- Green, C. T., Long, D. L., Green, D., Iosif, A. M., Dixon, J. F., Miller, M. R., et al., 2012. Will working memory training generalize to improve off-task behavior in children with attention-deficit/hyperactivity disorder? *Neurotherapeutics*, 9, 639-648.
- Gropper, R. J., Gotlieb, H., Kronitz, R., & Tannock, R., 2014. Working memory training in college students with ADHD or LD. *J Atten Disord*, 18, 331-345.

- Holmes, J., Gathercole, S. E., & Dunning, D. L., 2009. Adaptive training leads to sustained enhancement of poor working memory in children. *Developmental science*, 12, F9-F15.
- Holmes, J., Gathercole, S. E., Place, M., Dunning, D. L., Hilton, K. A., & Elliott, J. G., 2010. Working memory deficits can be overcome: Impacts of training and medication on working memory in children with ADHD. *Applied Cognitive Psychology*, 24, 827-836.
- Hovik, K. T., Saunes, B. K., Aarlien, A. K., & Egeland, J., 2013. RCT of working memory training in ADHD: long-term near-transfer effects. *PLoS One*, 8, e80561.
- Jaeggi, S. M., Buschkuhl, M., Jonides, J., & Perrig, W. J., 2008. Improving fluid intelligence with training on working memory. *Proceedings of the National Academy of Sciences*, 105, 6829-6833.
- Jaeggi, S. M., Buschkuhl, M., Jonides, J., & Shah, P., 2011. Short-and long-term benefits of cognitive training. *Proceedings of the National Academy of Sciences*, 108, 10081-10086.
- Jensen, P. S., Hinshaw, S. P., Swanson, J. M., Greenhill, L. L., Conners, C. K., Arnold, L. E., et al., 2001. Findings from the NIMH Multimodal Treatment Study of ADHD (MTA): implications and applications for primary care providers. *Journal of Developmental & Behavioral Pediatrics*, 22, 60-73.
- Jolles, D. D., van Buchem, M. A., Rombouts, S. A., & Crone, E. A., 2012. Practice effects in the developing brain: A pilot study. *Dev. Cog. Neuroscience*, 2, S180-S191.
- Karalunas, S. L., Gustafsson, H. C., Dieckmann, N. F., Tipsord, J., Mitchell, S. H., & Nigg, J. T., 2017. Heterogeneity in development of aspects of working memory predicts

- longitudinal attention deficit hyperactivity disorder symptom change. *J Abnorm Psychol*, 126, 774-792.
- Klingberg, T., 2010. Training and plasticity of working memory. *Trends Cog. Sci.*, 14, 317-324.
- Klingberg, T., Fernell, E., Olesen, P. J., Johnson, M., Gustafsson, P., Dahlström, K., et al., 2005. Computerized training of working memory in children with ADHD—a randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry*, 44, 177-186.
- Klingberg, T., Forssberg, H., & Westerberg, H., 2002. Training of working memory in children with ADHD. *J. Clin. Exp. Neuropsych.*, 24, 781-791.
- Lambek, R., Tannock, R., Dalsgaard, S., Trillingsgaard, A., Damm, D., & Thomsen, P. H., 2011. Executive dysfunction in school-age children with ADHD. *J Atten Disord*, 15, 646-655.
- Mawjee, K., Woltering, S., Lai, N., Gotlieb, H., Kronitz, R., & Tannock, R., 2017. Working Memory Training in ADHD: Controlling for Engagement, Motivation, and Expectancy of Improvement (Pilot Study). *J Atten Disord*, 21, 956-968.
- Mawjee, K., Woltering, S., & Tannock, R., 2015. Working Memory Training in Post-Secondary Students with ADHD: A Randomized Controlled Study. *PLoS One*, 10, e0137173.
- Mehta, M. A., Goodyer, I. M., & Sahakian, B. J., 2004. Methylphenidate improves working memory and set-shifting in AD/HD: relationships to baseline memory capacity. *J. Child Psy. Psych.*, 45, 293-305.
- Melby-Lervåg, M., & Hulme, C., 2013. Is working memory training effective? A meta-analytic review. *Dev. Psy.*, 49, 270.

- Milner, B., 1971. Interhemispheric differences in the localization of psychological processes in man. *Br. Med. Bull.*
- Nieoullon, A., 2002. Dopamine and the regulation of cognition and attention. *Progr. Neurol.*, 67, 53-83.
- Nigg, J. T., Willcutt, E. G., Doyle, A. E., & Sonuga-Barke, E. J., 2005. Causal heterogeneity in attention-deficit/hyperactivity disorder: do we need neuropsychologically impaired subtypes? *Biol Psychiatry*, 57, 1224-1230.
- Olesen, P. J., Westerberg, H., & Klingberg, T., 2004. Increased prefrontal and parietal activity after training of working memory. *Nature neuroscience*, 7, 75-79.
- Polanczyk, G. V., Willcutt, E., Salum, G. A., Kieling, C., & Rohde, L. A., 2014. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. *Int. J. Epidemiol.*, 43, 434-442.
- Rapport, M. D., Alderson, R. M., Kofler, M. J., Sarver, D. E., Bolden, J., & Sims, V., 2008. Working memory deficits in boys with attention-deficit/hyperactivity disorder (ADHD): the contribution of central executive and subsystem processes. *J. Abnorm. Child Psy.*, 36, 825-837.
- Rapport, M. D., Orban, S. A., Kofler, M. J., & Friedman, L. M., 2013. Do programs designed to train working memory, other executive functions, and attention benefit children with ADHD? A meta-analytic review of cognitive, academic, and behavioral outcomes. *Clin. Psy. Rev.*, 33, 1237-1252.
- Rogers, M., Hwang, H., Toplak, M., Weiss, M., & Tannock, R., 2011. Inattention, working memory, and academic achievement in adolescents referred for attention deficit/hyperactivity disorder (ADHD). *Child Neuropsych.*, 17, 444-458.

- Roording-Ragetlie, S., Klip, H., Buitelaar, J., & Slaats-Willemse, D., 2017. Working memory training in children with neuropsychiatric disorders and mild to borderline intellectual functioning, the role of coaching; a double-blind randomized controlled trial. *BMC Psychiatry*, 17, 114.
- Rutledge, K. J., van den Bos, W., McClure, S. M., & Schweitzer, J. B., 2012. Training cognition in ADHD: current findings, borrowed concepts, and future directions. *Neurotherapeutics*, 9, 542-558.
- Schweizer, S., Hampshire, A., & Dalgleish, T., 2011. Extending brain-training to the affective domain: increasing cognitive and affective executive control through emotional working memory training. *PLoS One*, 6, e24372.
- Sexton, C. C., Gelhorn, H., Bell, J., & Classi, P., 2011. The cooccurrence of reading disorder and ADHD: Epidemiology, treatment, psychosocial impact, and economic burden. *J. Learn. Dis.* , 45, 538-564.
- Sheehan, D., 2004. Mini International Neuropsychiatric Interview (MINI) Tampa, Florida, FL, USA.
- Shipstead, Z., Hicks, K. L., & Engle, R. W., 2012. Cogmed working memory training: Does the evidence support the claims? *J. App. Res. Mem. Cog.*, 1, 185-193.
- Stroop, J. R., 1992. Studies of interference in serial verbal reactions. *J. Exp. Psy: Gen.* , 121, 15.
- Swanson, J., Baler, R. D., & Volkow, N. D., 2011. Understanding the Effects of Stimulant Medications on Cognition in Individuals with Attention-Deficit Hyperactivity Disorder: A Decade of Progress. *Neuropsychopharmacol.*, 36, 207-226.

- Thompson, T. W., Waskom, M. L., Garel, K.-L. A., Cardenas-Iniguez, C., Reynolds, G. O., Winter, R., et al., 2013. Failure of working memory training to enhance cognition or intelligence. *PloS one*, 8, e63614.
- van der Donk, M., Hiemstra-Beernink, A.-C., Tjeenk-Kalff, A., Van Der Leij, A., & Lindauer, R., 2015. Cognitive training for children with ADHD: a randomized controlled trial of cogmed working memory training and 'paying attention in class'. *Frontiers Psy.*, 6.
- van Lieshout, M., Luman, M., Twisk, J. W., van Ewijk, H., Groenman, A. P., Thissen, A. J., et al., 2016. A 6-year follow-up of a large European cohort of children with attention-deficit/hyperactivity disorder-combined subtype: outcomes in late adolescence and young adulthood. *Europ. Child and Adol. Psych.*, 25, 1007-1017.
- von Bastian, C. C., & Oberauer, K., 2014. Effects and mechanisms of working memory training: a review. *Psychological research*, 78, 803-820.
- Wechsler, D., 2003. Wechsler intelligence scale for children-WISC-IV: Psychological Corporation.
- Zimmermann, P., & Fimm, B., 1995. Test for attentional performance (TAP). *PsyTest*, Herzogenrath76-77.

Table 1.

Sociodemographic data

	Controls	ADHD		
	CWMT+ (n=19)	CWMT+ / M+ (n=18)	CWMT- / M+ (n=10)	CWMT+ / M- (n=13)
Male/Female	14/5	14/4	9/1	10/3
Age (years) ^b	13.6 (1.7)	13.8 (0.9)	13.3 (1.0)	13.4 (1.2)
Diagnosis ^a				
Mixed type	0	8	4	11
Inattentive predominant type	0	10	6	2
Conners, ADHD parent	7.6 (5.4)	10.2 (4.6)	14.3 (6.2)	13.6 (5.5)
Methylphenidate Dose Mg/Day ^b	-	31.2 (13.7)	35.0 (12.8)	-
Duration of CWMT (days) ^b	23.4 (3.0)	25.1 (1.3)	0	22.8 (4.2)
Effective time CWMT / day	38.8 (6.5)	37.0 (8.5)	0	37.2 (9.2)

Note. ^aData expressed in n, ^bData expressed in Mean (SD)

Table 2

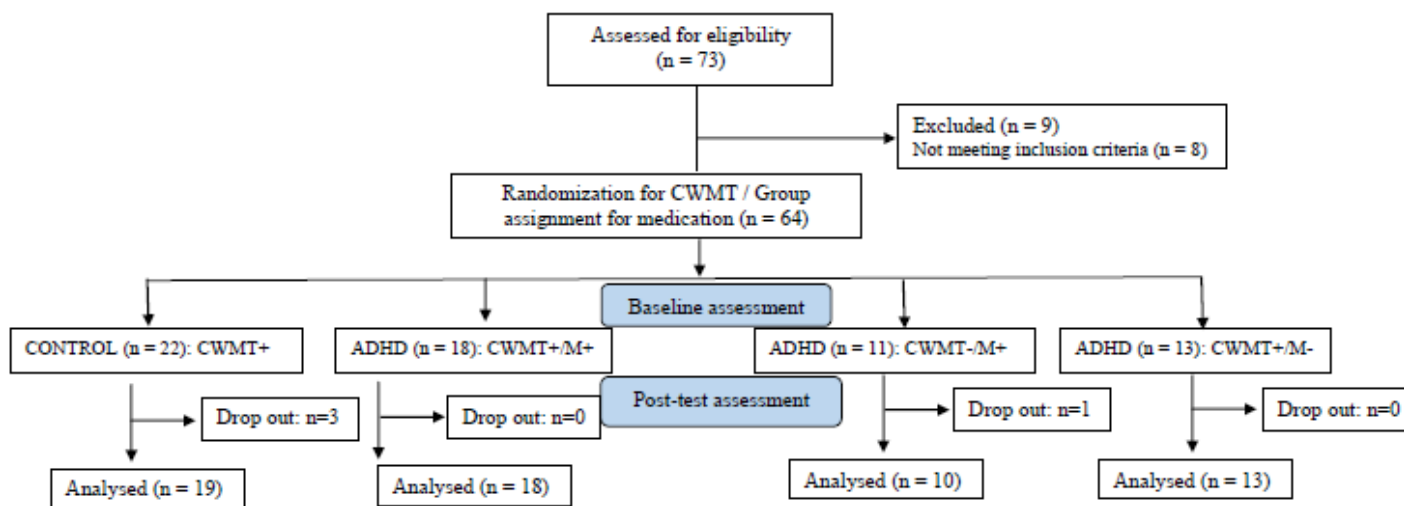
Descriptives of the cognitive tests

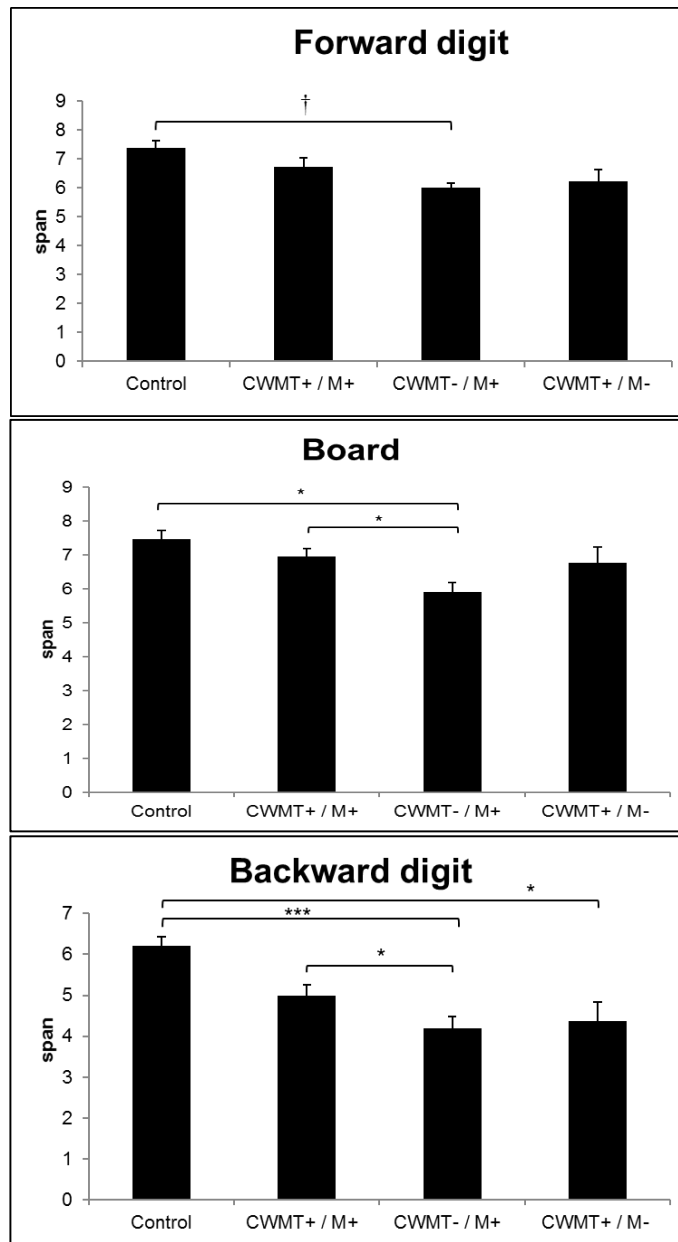
Test	Controls		ADHD					
	Pre	Post	CWMT+ / M+		CWMT- / M+		CWMT+ / M-	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Digit								
Forward span	6.6 (1.2)	7.4 (1.1)	5.8 (1.0)	6.7 (1.3)	6.1 (0.6)	6.0 (0.5)	5.7 (1.0)	6.2 (1.5)
Backward span	5.5 (1.3)	6.2 (1.2)	4.2 (1.0)	5.0 (1.1)	4.7 (1.1)	4.2 (0.8)	4.3 (1.3)	4.4 (1.4)
Spatial								
Forward span	6.3 (1.2)	7.5 (1.0)	5.5 (0.9)	6.9 (1.1)	5.6 (1.1)	5.9 (0.9)	5.9 (1.4)	6.8 (1.6)
Stroop								
Interference score	41.4 (9.7)	47.0 (10.0)	40.7 (27.7)	41.0 (6.8)	42.9 (14.1)	39.9 (3.8)	33.1 (8.5)	33.2 (10.0)
Go/ no-go								
RT [ms]	548.8 (58.4)	525.1 (57.3)	609.5 (85.4)	598.9 (52.9)	573.8 (60.9)	597.6 (95.2)	632.5 (59.1)	620.5 (55.8)
Errors	0.7 (0.7)	0.5 (0.6)	1.7 (3.2)	0.9 (.9)	3.0 (4.5)	0.8 (0.6)	1.8 (1.8)	0.9 (0.6)
ADHD symptoms ¹								
Inattentive	4.1 (4.8)	4.8 (5.8)	21.8 (5.6)	13.6 (5.2)	20.9 (4.6)	17.4 (6.7)	24.8 (5.6)	18.3 (4.9)
Impulsivity / hyperactivity	1.1 (1.5)	1.9 (2.2)	7.8 (4.8)	4.4 (3.6)	7.0 (3.8)	6.4 (3.2)	10.8 (4.7)	9.4 (4.5)

Note. Data expressed in Mean (SD); RT: Reaction Time; ADHD: Attention-Deficit/Hyperactivity Disorder; CWMT: Cognitive working memory training. ¹ Post refer to the 2-month follow-up.

Figure 1: Consort-like Diagram

See other file

**Figure 2.** Post treatment differences on primary outcomes



Note. Data expressed as mean (+standard errors). CWMT, Cognitive Working Memory Training ; M, Medication ; Control, adolescents without ADHD with CWMT; CWMT+/M+, adolescents with ADHD with CWMT and medication; CWMT-/M+, adolescents with ADHD without CWMT but with medication; CWMT+/M-, adolescents with ADHD and CWMT but without medication. † $p < 0.10$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.