

Working Memory Deficits can be Overcome: Impacts of Training and Medication on Working Memory in Children with ADHD

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SUMMARY

This study evaluated the impact of two interventions—a training program and stimulant medication—on working memory (WM) function in children with attention deficit hyperactivity disorder (ADHD). Twenty-five children aged between 8 and 11 years participated in training that taxed WM skills to the limit for a minimum of 20 days, and completed other assessments of WM and IQ before and after training, and with and without prescribed drug treatment. While medication significantly improved visuo-spatial memory performance, training led to substantial gains in all components of WM across untrained tasks. Training gains associated with the central executive persisted over a 6-month period. IQ scores were unaffected by either intervention. These findings indicate that the WM impairments in children with ADHD can be differentially ameliorated by training and by stimulant medication. Copyright © 2009 John Wiley & Sons, Ltd.

INTRODUCTION

Working memory (WM), the cognitive system responsible for the temporary storage and manipulation of information, is crucial for maintaining focused behaviour in practical situations (Kane, Brown, McVay Silvia, Myin-Germeys, & Kwapil, 2007). Deficits in WM are typical among individuals with attention deficit hyperactivity disorder (ADHD) (Barkley, 1997; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005). The purpose of the present study was to investigate the extent to which the WM deficits associated with ADHD can be ameliorated by two different forms of treatment: psychostimulant medication and WM training. ADHD is a diagnostic category applied to individuals with high levels of problem behaviours that are inattentive or hyperactive/impulsive in nature, or a combination of both. It is strongly associated with deficits in executive functions, an umbrella term for the systems involved in the high-level control of cognitive processes required for

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goal-directed behaviour, associated with the frontal lobes. ADHD is characterized by marked impairments in inhibitory behaviour (Barkley, 1997; Nigg, 2001; Willcutt, Pennington, Olson, Chhabildas, & Hulslander, 2005) and WM (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Martinussen & Tannock, 2006), particularly for visuo-spatial material (Barnett, Maruff, Vance, Luk, Costin, Wood et al., 2001; Martinussen et al., 2005).

The primary treatment option for reducing the behavioural symptoms of ADHD is psychostimulant medication in the form of methylphenidate or amphetamine compounds, and this has been found to enhance visuo-spatial WM (Bedard, Jain, Hogg-Johnson, & Tannock, 2007). A non-pharmacological behavioural intervention has recently been developed that is also associated with improvements both in the problem behaviours that are the hallmark of ADHD and in WM. This computerized training program involves participants completing 20–25 daily sessions involving a series of tasks requiring the storage and manipulation of sequences of verbal and/or visuo-spatial information (Cogmed, 2006). Difficulty level is calibrated on a trial-by-trial basis to match memory span, so that individuals continuously work close to their personal limits. The program also includes motivational features such as displays comparing current performance against personal best scores and a reward game at the end of each session.

The program has been found to boost WM substantially in children with ADHD, who are not medicated for the disorder (Klingberg et al., 2005), in children with poor WM (Holmes, Gathercole, & Dunning, 2009), and in adult neuropsychological patients following strokes (Westerberg et al., 2007). In the Klingberg et al. randomized-controlled trial study of children with ADHD in which the standard program was compared with a control non-adaptive version that required participants to work at levels substantially below memory span, adaptive training led to specific gains in visuo-spatial short-term memory (STM) and also to reductions in parent ratings of inattentive behaviours. Significant treatment effects were also seen in secondary outcome tasks measuring verbal STM, response inhibition, and complex reasoning. The same pattern of selective enhancement for the adaptive training program over the non-adaptive version was reported by Holmes et al. (2009) in their study of children with poor WM. Neuroimaging studies indicate that training has a significant impact on neural activity in the middle frontal gyrus and superior and parietal cortices, areas of the brain associated with WM (Olesen, Westerberg, & Klingberg, 2004; Westerberg & Klingberg, 2007; McNab, Varrone, Farde, Jucaite, Bystritsky, & Klingberg, 2009).

The purpose of the present study was to provide a detailed investigation of the impacts of behavioural and pharmacological interventions on the separate subcomponents of WM in children with ADHD. To date, both interventions have been associated with boosts in visuo-spatial memory. However, WM is a multi-component system served by a number of distinct neural circuits. According to the influential model advanced by Baddeley & Hitch (1974) and extended by Baddeley, (2000), WM consists of a central executive responsible for the control of attention, two storage buffers specialized for the storage and manipulation of verbal and visuo-spatial information, and an episodic buffer responsible for integrating multi-modal representations. These components are served by relatively distinct neural circuitry (e.g. Curtis & D'Esposito, 2003) and a primary aim of the study was to provide a comprehensive assessment of the impact of training and medication on these components. The Automated Working Memory Assessment (AWMA, Alloway, 2007; Alloway, Gathercole, & Pickering, 2006) provides multiple measures both of verbal and visuo-spatial storage, and of verbal and visuo-spatial WM; the latter tests involve both processing and storage, and depend both on the central executive and the relevant short-term store. The comprehensive theoretical analysis of WM provided by this tool enabled us

to compare, and potentially to distinguish, the impact of behavioural and drug treatments for ADHD on WM.

METHOD

Participants

Twenty-five children (21 boys, 4 girls), who were aged 8–11 years (mean 9 years, 9 months, SD 11 months) were recruited through pediatric psychiatrists and community pediatricians in the North-East of England. Study inclusion criteria were: (i) a DSM-IV diagnosis of combined-type ADHD for 6 months or longer, (ii) prescription of psychostimulant medication for ADHD (immediate release methylphenidate $n = 12$; dexamfetamine $n = 3$, extended release methylphenidate $n = 10$).

Ethical approval was obtained through the local National Health Service ethics board (Hartlepool & North Tees Local Research Ethics Committee) and through Durham and York University's Ethics Committees. Consent was obtained from parents/guardians and children, with appropriate opportunities for withdrawal.

Procedure

Each child completed four sets of assessments during individual testing sessions in a quiet area of the school. Medication was withdrawn at least 24 hours prior to the assessment at time 1. At time 2 (mean 5 months, SD 3.16, min. 1 month, max. 12 months later) and at all subsequent assessment points, children were receiving their regular medication. The Cogmed Working Memory Training (Cogmed, 2006) program commenced within 1 week of time 2. Each child completed 20–25 training sessions across an average period of 23.72 school days (min. 20, max. 25, SD 1.79). Upon completion of training at time 3, post-training assessments were completed. Children were re-tested on one test of each aspect of memory 6 months after training (time 4). All tests were administered in a fixed order, with regular breaks to reduce the effects of fatigue.

Time 1: Cognitive assessment off medication

All 12 subtests of the AWMA (Alloway, 2007) were administered, providing three tests each of verbal STM (Digit Recall, Word Recall and Nonword Recall), visuo-spatial STM (Dot Matrix, Block Recall and Mazes Memory), verbal WM (Backward Digit Recall, Listening Recall and Counting Recall), and visuo-spatial WM (Mr X, Spatial Span and Odd-One-Out). Standard scores were calculated for each test, plus a composite score for each of verbal STM, visuo-spatial STM, verbal WM and visuo-spatial WM based on the relevant three tests. All twelve subtests of the AWMA were administered as the data were collected as part of larger study. Test-retest reliabilities for these tasks are: Dot Matrix, .85; Mazes Memory, .86; Block Recall, .90; Odd-One-Out, .88; Mr. X, .84; Spatial Recall, .79; Digit Recall, .89; Word Recall, .88; Nonword Recall, .69; Listening Recall, .88; Counting Recall, .83; Backward Digit Recall, .86. The children also completed the Wechsler Abbreviated Scales of Intelligence (WASI, Wechsler, 1999), yielding measures of verbal IQ (based on vocabulary and similarities tests) and performance IQ (based on block design and matrix reasoning tests).

Time 2: Pre-training assessment, on medication

Prior to commencing training, two assessment sessions were completed on average 1 day apart. In the first session, eight WM tasks from the AWMA (Alloway, 2007) were completed: two tests each of verbal STM (Digit Recall, Word Recall), visuo-spatial STM (Dot Matrix, Block Recall), verbal WM (Backward Digit Recall, Counting Recall) and visuo-spatial WM (Mr X, Spatial Span). Composite scores for each area of WM were obtained by averaging standard scores on relevant pair of tests. In the second session participants completed the WASI (Wechsler, 1999).

Cogmed Working Memory Training: Training was completed in school, supported by a training aide who was typically a paid classroom assistant. Children completed 20–25 training sessions over a period of between 6 and 10 weeks. In each session they completed 115 trials split across eight different tasks. These were selected from a bank of 10 tasks. Children trained on the same 8 tasks for the first 5 days of the training period. On the sixth day, and on every fifth day thereafter, one of the tasks was replaced by a different task from the bank of 10. Each training task involved the temporary storage and manipulation of sequential visuo-spatial or verbal information, or both (e.g. recalling either series of locations such as illuminated lamps on the screen, or lists of digits or letters, either in the order in which they were presented or in the reverse order). Task difficulty was matched to the child's current memory span on a trial-by-trial basis for each task. Motivational features included a display of the child's best scores, the accumulation of 'energy' based on performance levels that was spent on a racing game completed after training each day, and positive verbal and visual feedback for correct trials. The racing game was included as a reward and did not tax WM. Further details about the training program can be found at: www.cogmed.com

Time 3: Post-training

Eight tests from the AWMA (Alloway, 2007) were completed at this point. Four tests (Digit Recall, Dot Matrix, Backward Digit Recall and Mr X) had been administered at time 2 and the remaining four had not (Nonword Recall, Mazes Memory, Listening Recall and Odd-One-Out). Composite scores were calculated by averaging standard scores on the relevant pairs of tests for each aspect of WM. The children also completed the WASI (Wechsler, 1999). Different WM tests were used pre- and post-training to control for re-test effects: this design allowed a comparison between tests that had been repeated before and after training and tests that had not been repeated.

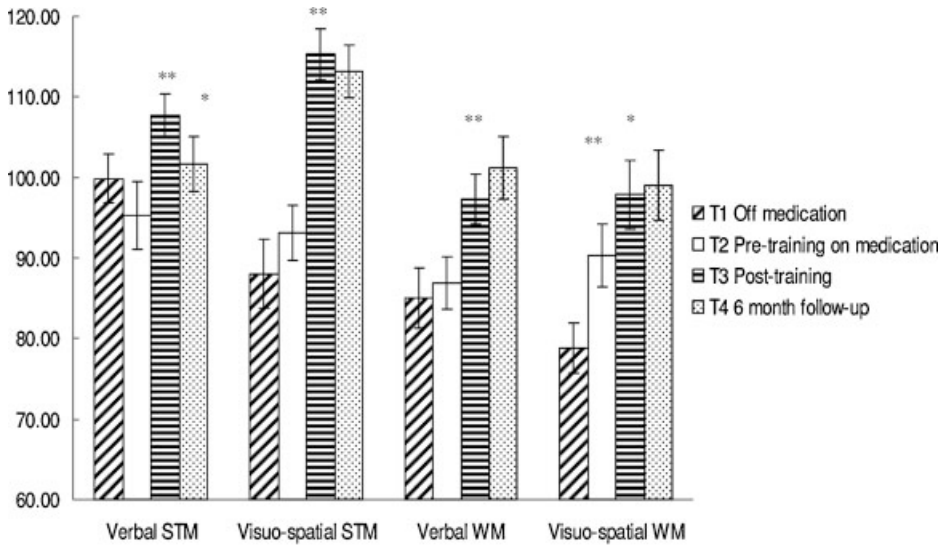
Time 4: 6-month follow-up

Four assessments from the AWMA (Alloway, 2007), consisting of one measure of each aspect of memory administered at both times 2 and 3 (Digit Recall, Dot Matrix, Backward Digit Recall and Mr X), were given to the children 6 months after training. It was only possible to administer four subtests due to time constraints working in the schools before the summer vacation.

RESULTS

Medication

Mean WM component scores on and off medication (at times 1 and 2) are shown in Figure 1; descriptive statistics for individual tests are provided in Table 1. Medication



* $p < .05$, ** $p < .01$

Figure 1. Impact of training and medication on working memory component scores. * $p < .05$, ** $p < .01$. NB. Asterisk above a bar denotes a significant change in score from the previous testing point

significantly improved composite scores for visuo-spatial WM, $F(1, 24) = 11.73$, $MSE = 111.38$, $p < .01$, $\eta_p^2 = .35$, but no other aspect of WM; verbal STM, $F(1, 24) = 1.05$, $MSE = 69.13$, $p = .32$, $\eta_p^2 = .05$; visuo-spatial STM, $F(1, 24) = 1.51$, $MSE = 147.14$, $p = .23$, $\eta_p^2 = .07$; verbal WM, $F(1, 24) = .73$, $MSE = 122.59$, $p = .40$, $\eta_p^2 = .03$. There was a significant effect of medication on both visuo-spatial WM tasks, Mr X, $F(1, 24) = 7.13$, $MSE = 115.03$, $p = .01$, $\eta_p^2 = .25$; Spatial Span, $F(1, 24) = 7.51$, $MSE = 132.27$, $p = .01$, $\eta_p^2 = .26$ and on one visuo-spatial STM task; Block Recall, $F(1, 24) = 4.75$, $MSE = 191.47$, $p = .04$, $\eta_p^2 = .18$. Medication did not have a significant effect on either verbal IQ, $F(1, 24) = .50$, $MSE = 117.59$, $p = .49$, $\eta_p^2 = .02$, or performance IQ, $F(1, 24) = .61$, $MSE = 43.37$, $p = .45$, $\eta_p^2 = .03$.

Working memory training

Cogmed Working Memory Training (comparing times 3 and 2) led to significant gains in all four memory component scores: verbal STM, $F(1, 24) = 8.64$, $MSE = 162.58$, $p = .01$, $\eta_p^2 = .27$; visuo-spatial STM, $F(1, 24) = 47.00$, $MSE = 130.13$, $p < .01$, $\eta_p^2 = .66$; verbal WM, $F(1, 24) = 9.66$, $MSE = 113.88$, $p = .01$, $\eta_p^2 = .29$; visuo-spatial WM, $F(1, 24) = 4.27$, $MSE = 170.82$, $p = .05$, $\eta_p^2 = .15$. A significant interaction between training and the different aspects of WM, $F(3, 72) = 5.65$, $MSE = 97.53$, $p < .01$, $\eta_p^2 = .20$, reflected significantly greater gains in visuo-spatial STM than in verbal STM, $t(24) = 3.51$, $p < .01$, $d = .63$; verbal WM, $t(24) = 3.78$, $p < .01$, $d = .80$ and visuo-spatial WM, $t(24) = 3.40$, $p < .01$, $d = .78$. Overall, the effect sizes show that training led to greater gains in WM than medication alone (training η_p^2 range from .15 to .66, medication alone η_p^2 ranges from .03 to .07 for all aspects of WM except visuo-spatial WM, where $\eta_p^2 = .35$).

Table 1. Effects of training and medication on working memory and IQ test scores

Task	T1 off medication		T2 Pre-training		T3 Post-training		T4 6month follow-up		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Verbal STM:	Digit recall	98.64 ¹	14.09	93.68 ^{1,13}	14.38	108.68 ^{**13,25}	14.69	101.67 ^{*25}	14.65
	Word recall	97.27 ²	15.04	100.48 ^{2,14}	19.63				
	Nonword recall	103.14	16.48			106.68 ¹⁴	19.61	113.11 ²⁶	13.95
Visuo-spatial STM:	Dot matrix	90.14 ³	17.45	93.04 ^{3,15}	19.77	120.96 ^{**15,26}	18.86		
	Block recall	85 ⁴	18.76	93.32 ^{*4,16}	19.51				
	Mazes memory	93.55	20.3			109.64 ^{**16}	19.82		
Verbal WM:	Backward digit recall	89.27 ⁵	12.31	95.04 ^{5,17}	15.87	102.60 ^{*17,27}	18.25	101.22 ²⁷	16.62
	Counting recall	84.45 ⁶	20.38	80.8 ^{6,18}	15.07				
	Listening recall	89.63	18.29			92.00 ^{*18}	16.7		
Visuo-spatial WM:	Mr X	81.23 ⁷	15.57	90.28 ^{*7,19}	19.12	102.16 ^{**19,28}	24.3	98.94 ²⁸	18.46
	Spatial span	79.55 ⁸	16.19	90.24 ^{*8,20}	21.62				
	Odd one out	86	18.17			93.64 ^{**20}	22.79		
Verbal IQ:	Similarities	49.91 ⁹	10.22	48.72 ^{9,21}	10.27	52.08 ²¹	12.12		
	Vocabulary	39.95 ¹⁰	12.36	39.64 ^{10,22}	11.19	36.56 ²²	14.35		
Performance IQ:	Block design	49.14 ¹¹	9.42	48.44 ^{11,23}	12.74	51.20 ²³	8.09		
	Matrix reasoning	39.55 ¹²	10.02	41.88 ^{12,24}	12.86	43.32 ²⁴	9.64		

* $p < .05$; ** $p < .01$.

¹⁻¹² pairs of tasks administered both off medication and on medication; ¹³⁻²⁴ pairs of tasks administered pre- and post-training; ²⁵⁻²⁸ pairs of tasks administered post-training and at 6 month follow-up.

Significant training gains were found on all four tests administered both before and after training: $p < .05$ in each case, $d_s = .34$ – 1.18 . Comparison of pre- and post-training scores in the non-repeated tests identified significant training gains across task pairs in two of the four aspects of WM (verbal WM: Counting Recall to Listening Recall, $F(1, 24) = 7.70$, $MSE = 203.54$, $p = .01$, $\eta_p^2 = .24$; visuo-spatial STM: Block Recall to Mazes Memory, $F(1, 24) = .13.69$, $MSE = 243.20$, $p < .01$, $\eta_p^2 = .36$).

Importantly, training gains in three of the four aspects of WM remained significant 6 months after training (comparing times 4 and 2): visuo-spatial STM, $F(1, 17) = 26.84$, $MSE = 128.22$, $p < .01$, $\eta_p^2 = .61$; verbal WM, $F(1, 17) = 25.58$, $MSE = 68.14$, $p < .01$, $\eta_p^2 = .60$; visuo-spatial WM, $F(1, 17) = 9.16$, $MSE = 98.82$, $p = .01$, $\eta_p^2 = .35$. A comparison of post-training scores (time 3) with follow-up scores (time 4) showed there was no significant decrease in visuo-spatial STM, verbal WM or visuo-spatial WM scores (all $p_s > .05$, $d_s = .13$ – $.61$) 6 months after training (comparing times 3 and 4), although there was a significant decline in verbal STM scores, $t(17) = 2.43$, $p < .05$, $d = .47$.

Training did not significantly influence either WASI verbal IQ, $F(1, 24) = .00$, $MSE = 87.56$, $p = .99$, $\eta_p^2 = .00$, or performance IQ scores, $F(1, 24) = .80$, $MSE = 62.17$, $p = .38$, $\eta_p^2 = .03$, nor did it influence performance on the individual WASI subtests (see Table 1).

DISCUSSION

This study compared the extent to which elements of the multi-component WM model (Baddeley & Hitch, 1974; Baddeley, 1986) can be modified by two therapeutic interventions for ADHD: an intensive WM training program and psychostimulant medication. Significant but distinctive patterns of gains in WM were found for both interventions. By far the most dramatic gains in WM function were observed with WM training. Significant and substantial improvements were found in all assessed aspects of WM, in each case taking the group from a level below average to one within the average range of scores for children of their age. Gains in measures of verbal and visuo-spatial WM associated with the central executive component of WM (Alloway et al., 2006) and in visuo-spatial STM were maintained 6 months after training.

The generality of the training gains across all aspects of WM assessed in this study is notable and poses a theoretical challenge, as the separate components of the system are widely conceived as having distinct neural and cognitive underpinnings (e.g. Curtis & D'Esposito, 2003). It is unlikely that the boost in scores is due to test practice, as previous studies have shown children who repeat the tests across the same period with no intervention between testing showed no such change (Holmes et al., 2009).

One possibility is that plasticity of the neural systems underlying each component enables their basic function to be enhanced by the intense training (Westerberg & Klingberg, 2007; McNab et al., 2009), contrary to evidence that WM is highly heritable (Kremen et al., 2007) and impervious to environmental experience (e.g. Engel, Dos Santos, & Gathercole, in press). Alternatively, training may not increase WM capacity *per se*. Instead, the intense and prolonged nature of the program may stimulate the development either of WM strategies that compensate for weaknesses in basic processes, or of the voluntary control of attention. Some support for this position was provided by post-training interviews, in which the children were asked to describe what had helped them to improve on the training activities. Of the 15 children who answered this question, four reported concentrating harder by closing their eyes or focusing more on the presented information,

and a further 10 children reported using a variety of other strategies that included rehearsing the information or tracing the patterns on the computer screen with their eyes. These reports suggest that training may indeed enhance attentional focus and stimulate a range of possibly idiosyncratic strategies.

A final possibility is that the WM training gains in this study are the consequence of features of the intervention program other than intensive and prolonged practice at difficulty levels corresponding to personal WM capacity limits. Children participating in the program benefited from near-daily one-to-one support from their training aide, received small rewards as well as constant encouragement during the training, and regularly engaged in a computer-based activity for 35 minute periods. It is not possible to rule out the possibility that the training gains obtained here are a product of these more general factors in the absence of comparison conditions that control for these elements of the intervention and that were beyond the scope of the present study. However, reassurance is provided by previous studies showing that comparable boosts to performance on untrained WM tasks are not found with a program employing the same task environment and reward structure but in which the difficulty level falls below the participants' memory span. This non-adaptive program failed to generate consistent WM gains in either children with ADHD (Klingberg et al., 2005) or in children with poor WM (Holmes et al., 2009). Neither does the adaptive feature of the program alone appear to be crucial: Thorell, Lindqvist, Bergman, Bohlin, & Klingberg (2008) found no improvements in WM scores with an adaptive training program that involved tasks requiring inhibitory control. It should also be noted that the training gains observed in the present study did not extend to all cognitive assessments: IQ, which included individual tests of fluid cognitive ability such as block design, was unaffected by training. Unless the WM assessments were differentially sensitive to the non-specific benefits of the program, these findings favour a direct impact of training on WM.

Psychostimulant medication prescribed for ADHD significantly enhanced WM performance, although its impacts were more specific than that of the training program. Consistent with previous findings (e.g. Bedard et al., 2007; Mehta, Goodyear, & Sahakian, 2004), medication was associated with significant improvements on tests of visuo-spatial WM, but not on either verbal STM or verbal WM. IQ scores were also unaffected. It has been speculated that this highly selective impact of medication may arise from its predominant influence on right hemisphere brain structures associated with visuo-spatial WM (see Bedard et al., 2007). Alternatively, visuo-spatial tasks may be more sensitive to the quality of attentional control than those involving verbal material, which gains obligatory access to WM (Baddeley, 1986).

The generalized WM gains following computer-based training may have important practical benefits for all children with poor WM, who are often unable to meet the heavy WM loads imposed by many learning activities within the predominantly verbal environment of the classroom, and who often fail to remember instructions and complete tasks that require verbal storage as well as demanding cognitive processing (Gathercole, Evans, Pratt, Jeffcock, & Stone, 2008). These failures to handle high WM loads are likely to contribute to the slow academic learning progress of children with poor WM (Gathercole & Alloway, 2008). An intervention such as the training program, leading to generalized improvements in WM, particularly for verbal material, holds the promise of reducing these problems across time and so of enhancing learning in the substantial minority of children with WM problems. In this way, the findings of this study offer important insights for applied psychology, WM theory and educational and clinical practice.

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