CHAPTER 5

The differential effects of atomoxetine on executive functioning and lexical processing in Attention-Deficit Hyperactivity Disorder and Reading Disorder.

ABSTRACT

Background: The effects of a promising pharmacological treatment for Attention-Deficit Hyperactivity Disorder (ADHD), atomoxetine, were studied on executive functions in both ADHD and reading disorder (RD) since earlier research demonstrated an overlap in executive functioning deficits in both disorders. In addition, the effects of atomoxetine were explored on lexical processing. **Method**: Sixteen children with ADHD, 20 children with ADHD+RD, 21 children with RD and 26 normal controls were enrolled in a randomized placebo-controlled cross-over study. Children were measured on visuospatial working memory, inhibition and lexical processing on the day of randomization and following two 28-day medication periods. **Results:** Children with ADHD+RD showed improved visuospatial working memory performance and, to a lesser extent, improved inhibition following atomoxetine treatment compared to placebo. No differential effects of atomoxetine were found for lexical processing in comparison to placebo. In addition, no effects of atomoxetine were demonstrated in the ADHD and RD groups. **Conclusions**: Atomoxetine improved visuospatial working memory and to a lesser degree inhibition in children with ADHD+RD, which suggest differential developmental pathways for comorbid ADHD+RD as compared to ADHD and RD alone. **Keywords:** atomoxetine, ADHD, RD, inhibition, visuospatial working memory

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INTRODUCTION

Deficits in executive functioning, especially inhibition and visuospatial working memory, are hypothesised to be at the heart of Attention-Deficit/Hyperactivity Disorder (ADHD) (Willcutt, Doyle, Nigg, Faraone & Pennington, 2005). However, deficits in inhibitory control and in visuospatial working memory have been demonstrated in children with RD (Martinussen & Tannock, 2006; Närhi & Ahonen, 1995; Purvis & Tannock, 2000). The common executive functioning deficits in ADHD and RD suggest that an effective treatment in ADHD may also be effective in children with both ADHD and RD and children with RD.

Stimulants are widely used in the pharmacological treatment of ADHD. Since stimulants affect the striatum, they show abuse and addictive potential (Volkow, 2006). An effective alternative pharmacological treatment to methylphenidate is the noradrenaline reuptake inhibitor atomoxetine, which shows no risk of abuse because its site of action is presumed to be in the prefrontal cortex and it does not increase dopamine in the nucleus accumbens (Bymaster et al., 2002). Although the effects of atomoxetine on ADHD symptoms have been promising and extensively tested, the effects of atomoxetine on executive functioning are less studied than those for methylphenidate (Aron, Dowson, Sahakian, Robbins, 2003; Bedard, Martinussen, Ickowicz & Tannock, 2004; Kratochvil et al., 2006).

To our knowlegde, no studies have been reported that have investigated the effects of atomoxetine on executive functioning in children with ADHD. Only in adults with ADHD, there is some evidence for beneficial effects of atomoxetine on inhibition (Chamberlain et al., 2006; 2007; Faraone et al., 2005; Spencer et al., 1998). One aspect of inhibition, interference control, as assessed by the Stroop Colour Word task, has been shown to improve after ten weeks of atomoxetine treatment in comparison to placebo (Spencer et al., 2005). Faraone et al., (2005) found weak evidence for an interference effect of atomoxetine in comparison to placebo in subjects who scored relatively poorly at baseline.

Improved inhibition in adults as assessed by Stop Signal Reaction Time (SSRT) has been reported by Chamberlain et al., (2006; 2007). In both studies, SSRT improved (became faster) following a single dose of atomoxetine (60 mg) in healthy male volunteers as well as in adults with ADHD compared to placebo. Atomoxetine, however, showed no beneficial effects on visuospatial working memory (Chamberlain et al., 2007). This was surprising, since a substantial body of research suggests that noradrenaline manipulations in both animals and humans may affect component processes of working memory (Arnsten & Li, 2005; Coull, Middleton, Robbins & Sahakian, 1995). The hypothesised role of noradrenaline has emphasised the maintenance of information in visuospatial working memory as measured by a delayed response task (Arnsten & Li, 2005). Chamberlain et al. (2007) used the CANTAB Spatial Working Memory task which requires manipulation of information in working memory and strategy implementation which possibly explains the absence of effects of atomoxetine on visuospatial working memory.

In the present study, we focused on the beneficial effects of atomoxetine on the maintenance function of visuospatial working memory and inhibition in children with ADHD. Visuospatial working memory was measured by the Corsi Block Tapping test, a measure that taps on maintenance of information (Schellig, 1997). Inhibition was assessed by SSRT (Oosterlaan, Logan & Sergeant, 1998). To establish whether atomoxetine has effects on ADHD symptomatology, a 28 day treatment period of atomoxetine was chosen.

No other study has yet tested the effects of medication in a comorbid ADHD+RD or an only RD group. We tested the effects of atomoxetine in children with comorbid ADHD+RD and children with only RD. Improvements in visuospatial working memory and inhibition possibly lead to improvements in reading as assessed by a lexical decision task, since working memory and inhibition are related to reading (Gijsel, Van Bon & Bosman, 2004; Savage, Lavers & Pillay, 2007). Thus, the present study assessed the effects of atomoxetine on lexical processing. The outcome of the effects of atomoxetine in ADHD and RD, may give indications of the validity of the hypothesised common aetiology of ADHD and RD. For example, if atomoxetine is equally effective in children with ADHD and RD, this may suggest a common aetiology (Willcutt et al., 2005). However, when atomoxetine treatment is differentially effective in children with ADHD only, RD only or ADHD and comorbid RD, this could indicate that comorbid ADHD+RD is a different disorder than ADHD or RD alone (Purvis & Tannock, 2000).

The first goal of the current double-blind placebo controlled cross-over study was to investigate the effects of atomoxetine in children with ADHD, ADHD+RD or RD on visuospatial working memory and inhibition. A second goal was to study the effects of atomoxetine on reading in children with ADHD, ADHD+RD, RD. In order to obtain more homogeneous groups, only children with the combined subtype of ADHD were enrolled. Participants with comorbid disorders other than RD and ODD were excluded.

METHOD

Participants

Children in the ADHD and ADHD+RD groups were recruited via six paediatric outpatient clinics in The Netherlands and one paediatric outpatient clinic in Belgium. Children in the RD group were recruited via advertisements, since these children are not regularly seen by paediatricians. A total of 16 children with ADHD, 21 children with RD, and 20 children with ADHD+RD completed the study. Figure 5.1 displays eligible patients and reasons for dropout. In addition, 26 normal controls participated, who were recruited in regular primary schools. The sample consisted of 102 children aged 8 to 12 years. Any child who dropped out during the study was not entered in the analyses. Written informed consent was obtained from the parents and from the child if aged 12 years. The study was approved by the national research ethics committee in The Netherlands and the local research ethics committee of the participating sites.

Study procedure

The study consisted of two periods: Period I was the washout period for children that were already on medication in the screening phase, in which informed consent was obtained and potential eligibility determined. Eleven children in the ADHD group and 4 children in the ADHD+RD group received methylphenidate prior to this study. Period 1 had a duration of 1-62 days. In Period II, the children with ADHD, ADHD+RD and RD were randomly assigned to the two treatment orders; placebo-atomoxetine or atomoxetine-placebo. Each treatment (placebo or atomoxetine) lasted 28 days and was interspersed by a wash-out period of 14 days. The (neuro)psychological measures were administered on the day of randomisation and immediately after the 28 day periods. Normal controls performed the neuropsychological tests twice with an interval of 28 days.

Medication

Placebo and atomoxetine were dispensed in a double-blind fashion in identical appearing tablets, which contained 15, 25, 40, 50, 60 or 80 mg atomoxetine or lactose for the placebo pills. The dose was based on the child's weight and was initiated at approximately 0.6 mg/kg/day for the first 7 days. The dose for the next 21 days was 1.2 mg/kg/day (mean dose=1.11 mg/kg/day (SD=0.12 mg/kg/day) range=0.85-1.33 mg/kg/day). Atomoxetine and placebo were administered once daily in the morning or twice daily, when children were unable to tolerate a single dose. At each 28 day period, children returned their unused pills to assess compliance, which was determined as missing more than two consecutive days of full doses medication or failing to take at least 80% of prescribed medication. One patient with ADHD+RD in the placebo period and one patient with RD in the atomoxetine period were noncompliant. One patient in the ADHD only group was noncompliant in both 28-day periods. Normal controls did not receive medication.

Screening measures

All participants were screened for the presence of ADHD combined subtype (ADHD-C) with the Disruptive Behaviour Disorder Rating Scale (DBD) (Oosterlaan, Scheres, Antrop, Roeyers & Sergeant, 2000; Pelham, Gnagy, Greenslade & Milich, 1992). The parent version of the Diagnostic Interview Schedule for Children (PDISC-IV) was administered (Ferdinand, Van der Ende & Mesman, 1998; Shaffer, Fisher, Lucas, Dulcan & Schwab-Stone, 2000). The PDISC-IV is based on the Diagnostic and Statistical Manual of mental disorders, fourth edition, (DSM-IV) and the International Classification of Diseases (ICD -10). A diagnosis of ADHD-C was made if (a) parent and teacher scores on both the Inattention and Hyperactivity/Impulsivity scales on the DBD fell at least in the subclinical range (≥ 90th percentile) and (b) criteria for ADHD-C on the PDISC-IV were met.

All children were thoroughly screened for the presence of RD using two technical word reading tests, namely, the One Minute Test (OMT) (Brus & Voeten, 1973) and the Pseudo-word Reading Test (PRT) (Van den Bos, Iutje Spelberg, Scheepsma & De Vries, 1999), and one text reading test: the Text Reading Test (TRT) (Visser, Van Laarhoven & Ter Beek, 1998). A diagnosis of RD was made, if children had at least 15 months delay on at least two of the three reading tests. Normal controls, who met the criteria for ADHD-C or any other subtype of ADHD or RD, were excluded.

Exclusion criteria for all groups

Children were excluded, if they met criteria for obsessive compulsive disorder, tic disorder (including Gilles de la Tourette syndrome), depression or conduct disorder as assessed by the PDISC-IV. In addition, children were excluded if they obtained a raw score of 40 or higher on the Children Depression Rating Scale indicating major depression (CDRS) (Poznanski & Mokros, 1996). Further exclusion criteria were a prior or current diagnosis of pervasive developmental disorder, anxiety disorder, post-traumatic stress disorder and neurological disorders, such as epilepsy as assessed by clinicians.

Children with severe arithmetic deficits were excluded as defined by a delay greater than 20 school months on the Speeded Arithmetic Test (SAT) (De Vos, 1992), and a score below the 3rd percentile on the Cognitive Subscales for Arithmetic (CSA) (De Clerq, Desoete & Roeyers, 2002).

Children were excluded if their estimated IQ was below 80, using four subtests of the Wechsler Intelligence Scale for Children 3rd edition (WISC-III, Wechsler, 1992): Picture Arrangement, Arithmetic, Block Design and Vocabulary (Sattler, 1992).

Measures

ADHD symptomatology. The *ADHD-Rating Scale-IV* (ADHD-RS-IV) (DuPaul, Power, Anastopoulos & Reid, 1998) was used to measure changes in ADHD symptoms in the ADHD and ADHD+RD groups during the two 28 day treatment periods as rated by the investigator with the parent as rating source. The ADHD-RS-IV consists of 18-items, with one item for each of the 18 symptoms of ADHD as listed in the DSM-IV. Each item is scored on a 0 to 3 scale, which indicates the frequency of ADHD symptoms in the child over the past week. Higher scores indicate more severe symptoms.

Neuropsychological measures

Visuospatial working memory. The Corsi Block Tapping task was administered to examine visuospatial working memory (Schellig, 1997). Nine blocks were displayed on a computer touch screen. A small cursor on the screen tapped a sequence of blocks, starting with a two-block sequence which could be increased to nine blocks. After a tone, the child had to re-tap the demonstrated sequence by touching the screen. The test stopped, when the child failed

to complete two trials of a block sequence. For each block sequence there were two trials, which could be extended with one trial, when the first or second trial was incorrect. The dependent variable was the total number of correct trials, Number Correct Sequences.

Inhibition. The Stop task was administered to measure response inhibition (Lijffijt, Kenemans, Verbaten & Van Engeland, 2005; Oosterlaan et al., 1998). In the first block of the task children had to indicate the position of a cartoon airplane on a computer screen by pressing one of two spatially compatible response buttons. In the next five blocks, a cross was imposed on the cartoon airplane in 25% of the trials, which indicated that the child had to inhibit his response. Using a tracking procedure, a 50% chance of response inhibition was established by decreasing or increasing the delay between the onset of the cartoon airplane and the cross depending on performance of the child (Logan & Cowan, 1984). SSRT can be determined by subtracting the mean delay time between the onset of the cartoon airplane and the cross from the mean reaction time (MRT) on cartoon airplanes. Latency and accuracy of the response execution process were also registered by MRT and number of errors (omission and commission errors), respectively (Band, Van der Molen & Logan, 2003).

Lexical processing. A lexical decision task was administered to measure lexical processing (Meyer & Schvaneveldt, 1971). Participants had to discriminate valid words from pseudowords, which were presented individually on a computer screen. The practice block of 25 words was followed by 5 blocks of each 25 valid words and 25 pseudowords presented pseudo-randomised.

The dependent variable was d´, measuring the accuracy by which subjects correctly discriminated valid words from pseudowords, independent of response bias (Macmillan & Creelman, 1991). The hit rate and the false positive rate of each child were normalised by a probit function because responses were binomial. In addition to d´, MRT of correctly discriminated valid words and pseudowords were noted. MRT for valid words reflects the latency of lexical decision, since valid words are hypothesised to be stored in the mental orthographical lexicon (Manis, Seidenberg, Doi, McBride-Chang & Petersen, 1996). MRT for pseudowords indicates the latency of the decoding process, since pseudowords are not stored in the mental lexicon. Pseudowords must be decoded, letter by letter or by letter cluster, to determine what is written (Manis et al., 1996).

Data analysis

Seven data points for the visuospatial working memory task, the Corsi Block tapping task, were randomly missing due to technical errors and were replaced by regression analysis (Tabachnick & Fidell, 2007). The lexical decision task was not administered to one child, because this child had not received sufficient reading instruction to complete this task. Results did not change after removing non-compliant children, thus these children were retained in the analyses for power reasons. To reduce the influence of extreme values, such values were replaced by the next most extreme value in the distribution plus one unit (Tabachnick & Fidell, 2007).

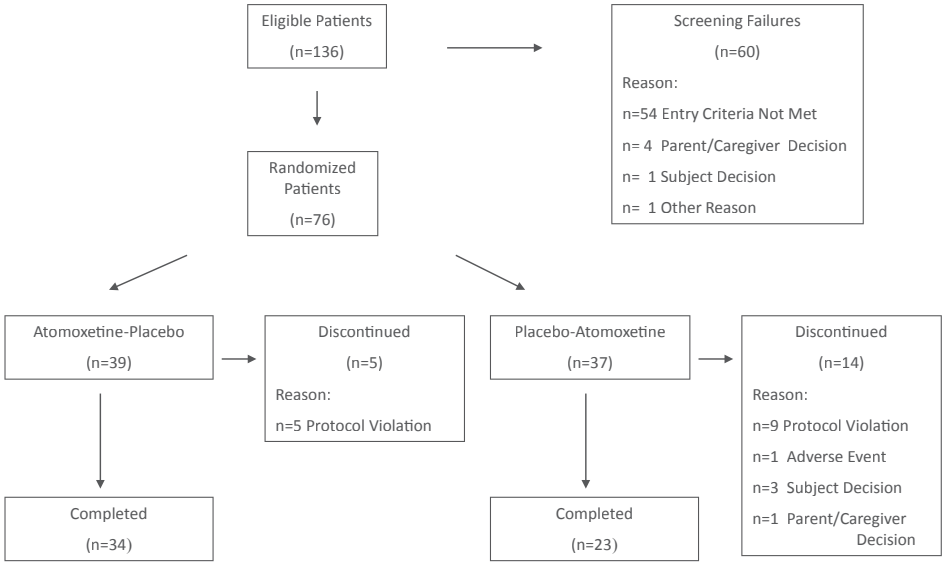

Figure 5.1 Patient flow diagram for the children that received treatment.

The data were analysed for the groups, who received treatment (ADHD, ADHD+RD and RD). To test for order effects of treatment, the dependent measures were subjected to ANOVAs with treatment as within subject factor (baseline, placebo and atomoxetine) and as between subject factors, treatment order (placebo-atomoxetine or atomoxetine-placebo) and group. When treatment order was not significant, the dependent variables were subjected to an ANOVA with treatment as a within subject factor and group as a between subject factor. When an overall significant treatment effect and/or a treatment by group interaction was found, repeated contrasts were performed to compare placebo with atomoxetine. When the placebo-atomoxetine repeated contrast led to a significant group by treatment interaction, paired sample t-tests tests were performed per group to study the origins of the interaction. For these paired sample t-tests, the study wide alpha level was adjusted for multiple comparisons. Since the baseline-placebo comparison was not the objective of this study, results of this comparison were left out of the results text. The interested reader is referred to Table 5.1. Group effects were tested with Tukey post-hoc tests.

If a significant treatment order effect occurred (treatment by treatment order interaction, or a treatment by treatment order by group interaction), only data for the first 28 day medication period were analysed. An ANOVA was conducted with visit (baseline and visit after the first 28 day medication period) as within subject factor and treatment (placebo or atomoxetine) and group as between subject factors. Order effects were limited to MRT valid words in the lexical decision task. The two orders (atomoxetine-placebo or placebo-

atomoxetine) did not lead to differences with respect to baseline ADHD severity, reading, age, IQ, inhibition, visuospatial working memory and lexical processing.

When the placebo-atomoxetine comparison was significant, the treatment groups were compared to normal controls to test whether normalisation occurred. Scores for the medication groups on placebo and atomoxetine were compared to the scores of the second visit of normal controls to account for possible retest effects with univariate ANOVAs. Tukey post-hoc tests were used to further test the group differences. Alpha was set at $p < .05$ for all comparisons except the paired sample t-tests.

Table 5.1 Results of the baseline-placebo comparison

	Treatment		Treatment by Group Interaction		Follow-up Paired t-test[a]
Measure	*F*(1,54)	η_p^2	*F*(2,54)	η_p^2	
Stop Signal Paradigm					
SSRT	1.0	.01	2.7	.09	-
MRT	17.1**	.2	.2	.008	-
Errors	9.5**	.1	.1	.004	-
Corsi Block Tapping Test					
Number of Correct Sequences	13.6**	.2	3.2*	.1	ADHD, RD
Lexical Processing[b]					
d'	2.8	.04	1.0	.04	-
MRT Pseudowords	1.8	.03	.7	.02	-

Note. ADHD=Attention Deficit Hyperactivity Disorder, MRT=Mean Reaction Time, SSRT=Stop Signal Reaction Time, RT=Reaction Time, RD=Reading Disorder.

[a]Follow-up paired t-tests tested for the effects of placebo as compared to baseline within each of the groups. Indicated groups showed significant effects in the baseline-placebo comparison, $p<.05$.

[b]One child was missing.

* significant at $p<.05$. ** significant at $p<.01$.

RESULTS

Group characteristics and results for the neuropsychological measures are provided in Table 5.2.

ADHD symptomatology

A significant treatment effect was found on ADHD symptoms as assessed by the ADHD-RS, $F(2,68)=10.26$, $p<.001$, $\eta_p^2=.23$. A repeated contrast revealed that ADHD symptoms diminished, after taking atomoxetine compared to placebo, $F(1,34)=6.91$, $p<.013$, $\eta_p^2=.16$. Treatment effects for atomoxetine were comparable for children with ADHD and ADHD+RD, since no significant group by treatment interaction occurred in the placebo-atomoxetine comparison. No significant effect of group was found which indicated that there was no significant difference in ADHD symptoms between the ADHD+RD and ADHD only groups.

Neuropsychological measures

Visuospatial working memory. Treatment significantly improved visuospatial working memory, $F(2,108)=20.52$, $p<.001$, $\eta_p^2=.27$. A repeated contrast showed that a larger Number Correct Sequences was completed with atomoxetine compared to placebo, $F(1, 54)=8.21$, $p=.006$, $\eta_p^2=.13$. Groups differed in visuospatial working memory, $F(2,54)=4.18$, $p=.02$, $\eta_p^2=.13$. Tukey post-hoc tests revealed that the ADHD group had a lower Number Correct Sequences than either the RD or ADHD+RD groups, $p=.02$ and $p=.05$, respectively. No significant differences occurred between the ADHD+RD and RD groups, $p>.10$.

A significant treatment by group interaction was observed for visuospatial working memory, $F(4,108)=2.56$, $p=.042$, $\eta_p^2=.08$. A repeated contrast indicated differential group effects after taking atomoxetine compared to placebo, $F(2,54)=5.35$, $p=.008$, $\eta_p^2=.16$. Figure 5.2 shows that only children with ADHD+RD had a larger Number Correct Sequences following atomoxetine compared to placebo, which was confirmed by a significant paired sample t-test, $p<.01$. Paired sample t-tests for the other two groups were not significant, all $ps>.10$.

Visuospatial working memory was poorer in children with ADHD compared to both the ADHD+RD and RD groups. Atomoxetine improved visuospatial working memory only in the ADHD+RD group.

Table 5.2 Group characteristics and neuropsychological performance per group and condition

	ADHD n=16 (♂=14)		ADHD+RD n=20 (♂=15)		RD n=21 (♂=8)		NC n=26 ♂=16		Pairwise Comparisons using Tukey*
Variable	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	
Age	8.8	1.3	9.8	1.2	9.9	1.0	9.3	0.9	A<R
IQ	99.3	14.0	94.5	8.2	100.0	7.2	107.3	9.4	A+R<NC
Mean Dose per kg/day	1.11	.12	1.14	.11	1.06	.13	-	-	ns
ADHD-RS									
Baseline	37.8	9.0	39.0	9.1	-	-	-	-	ns
Placebo	35.1	12.3	36.9	11.1	-	-	-	-	
Atomoxetine	32.2	13.4	26.4	13.7	-	-	-	-	
Stop Signal Task									
SSRT									
Baseline	285.3	67.2	284.1	72.2	284.9	64.1	245.7	56.2	ns
Placebo	279.4	52.1	296.5	85.2	254.2	66.0	249.2[1]	57.7[1]	
Atomoxetine	294.2	83.1	263.0	43.8	261.8	77.8	-	-	
MRT									
Baseline	549.6	64.8	564.3	81.1	613.1	117.2	501.3	63.0	R<NC
Placebo	503.9	90.6	533.5	89.9	570.8	89.0	448.0[1]	72.1[1]	
Atomoxetine	481.2	68.6	540.3	76.3	572.3	91.8			
Errors									
Baseline	9.7	8.5	13.0	11.5	8.0	7.3	4.2	4.0	A+R<NC
Placebo	7.3	5.7	9.8	7.8	4.4	3.6	6.0[1]	7.0[1]	
Atomoxetine	7.5	5.0	9.8	7.5	5.6	6.6	-	-	
Corsi Block Tapping Test									
Number Correct Sequences									
Baseline	7.8	2.8	10.0	2.5	10.1	2.0	10.8	1.8	A<A+R,R,NC
Placebo	10.0	2.3	10.2	2.5	11.1	2.5	12.0[1]	2.2[1]	
Atomoxetine	9.7	2.2	12.0	2.5	11.7	1.6	-	-	
Lexical Decision Task									
d´									
Baseline	2.5	0.5	1.9	0.7	2.2	1.0	3.0	0.6	A+R,R<NC
Placebo	2.5	0.6	1.8	0.6	1.9	0.8	3.0[1]	0.7[1]	
Atomoxetine	2.4	0.9	2.0	0.7	2.0	0.6	-	-	
MRT Valid Words									
Baseline	1246.5	408.8	1251.8	415.9	1317.6	430.3	939.6	209.5	A+R,R>NC
Placebo	1238.2	408.6	1298.0	407.9	1209.1	420.1	858.0[1]	211.4[1]	
Atomoxetine	1096.9	281.5	1277.0	501.6	1180.0	401.6	-	-	
MRT Pseudowords									
Baseline	1410.0	437.8	1470.9	524.0	1572.0	467.6	1033.9	225.6	A, A+R,R<NC
Placebo	1364.0	396.5	1469.0	495.6	1461.3	467.9	916.8[1]	237.5[1]	
Atomoxetine	1247.7	371.4	1498.4	569.7	1415.4	537.3	-	-	

Note. A=Attention Deficit Hyperactivity Deficit, ADHD-RS=Attention Deficit Hyperactivity Disorder - Rating Scale, MRT=Mean Reaction Time, NC=Normal Controls, R=Reading Disorder, SSRT= Stop Signal Reaction Time.
[1]Scores for the second visit of the normal control group.
* $p<.05$

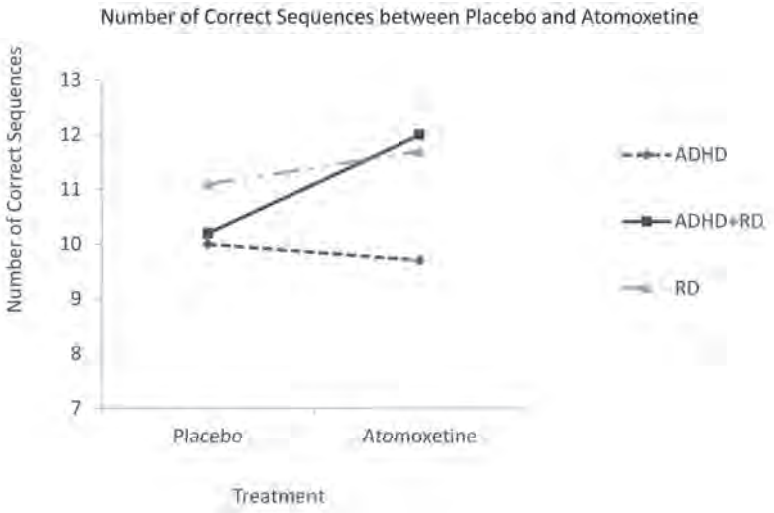

Figure 5.2 Number Correct Sequences per group and treatment. Number Correct Sequences improved only in the ADHD+RD group after taking atomoxetine in comparison to placebo.

Inhibition. Inhibitory control (SSRT) was not affected by treatment nor were there significant group differences in inhibitory control. A significant treatment by group interaction was observed, $F(4,108)=2.48$, $p=.048$, $\eta_p^2=.08$. The contrast comparing atomoxetine to placebo marginally interacted with group, $F(2,54)=2.66$, $p=.07$, $\eta_p^2=.09$. Figure 5.3 shows that only children with ADHD+RD had faster SSRTs following atomoxetine compared to placebo, which was supported by a nearly significant paired sample t-test, $p=.07$. The paired sample t-test comparing SSRTs of the ADHD+RD and RD groups on placebo and atomoxetine were not significant, $p>.10$.

Speed of processing was significantly influenced by treatment, $F(2,108)=16.74$, $p<.001$, $\eta_p^2=.23$. The effects of treatment were due to a significant baseline-placebo comparison, see Table 5.1. Groups differed in MRT, $F(2,54)=3.93$, $p=.02$, $\eta_p^2=.12$. Children with RD had slower MRTs than children with ADHD, $p=.02$. MRTs of children with ADHD+RD fell between the MRTs of the RD group and ADHD group, but did not significantly differ from these two groups, $p>.10$. No significant group by treatment interaction was observed.

Accuracy was affected by treatment, $F(2,108)=6.39$, $p=.002$, $\eta_p^2=.10$, which was due to a significant baseline-placebo comparison, see Table 5.1. The group effect escaped conventional levels of significance, $F(2,54)=3.05$, $p=.055$, $\eta_p^2=.10$. Tukey post-hoc tests showed that children with RD made fewer errors than children with ADHD+RD, $p=.006$. The ADHD group did not significantly differ from the RD and ADHD+RD groups, all p-values>.10. No significant group by treatment interaction was observed.

Some evidence for beneficial effects of atomoxetine on inhibition as assessed by SSRT was found in the ADHD+RD group, whereas atomoxetine did not impact the ADHD or RD groups in this test.

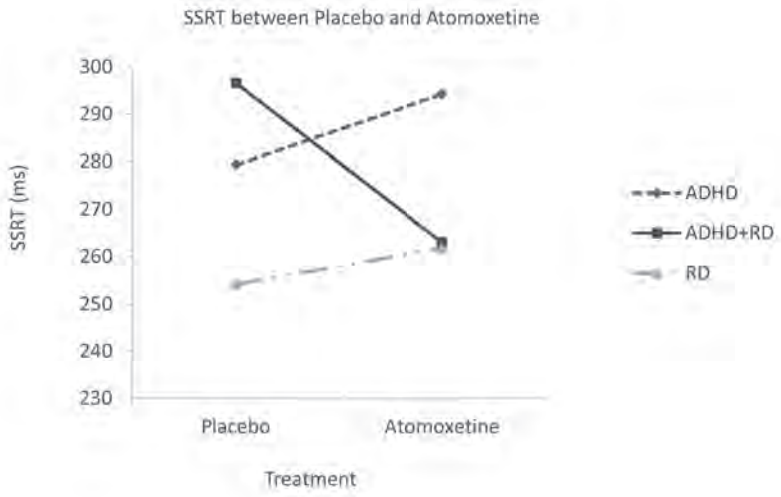

Figure 5.3 Mean SSRT per group and treatment. SSRT became faster only in children with ADHD+RD after taking atomoxetine in comparison to placebo.

Lexical processing. Lexical decision accuracy, as assessed by d', was not significantly influenced by treatment. The group effect was marginally significant, $F(2,53)=2.85$, $p=.066$, $\eta_p^2=.09$. Children with ADHD+RD had lower d' values than children with ADHD, although this group difference fell shy of significance, $p=.057$. No other significant group differences or group by treatment interactions were found.

MRT pseudowords showed a significant treatment effect, $F(2,106)=3.14$, $p=.04$, $\eta_p^2=.05$. However, no significant differences were found between either the baseline and placebo or placebo and atomoxetine comparisons. No significant group differences were observed for MRT pseudowords nor did a group by treatment interaction occur.

MRT valid words was affected by treatment order, $F(2,49)=4.18$, $p=.02$, $\eta_p^2=.14$ Therefore, only data for the baseline and the visit after the first 28 day medication period were analysed. No significant effects were observed for treatment or group.

To summarize, accuracy and speed of lexical processing were not influenced by atomoxetine.

Normalisation

In order to test whether performance normalised for variables that showed an effect of atomoxetine, performance on placebo and atomoxetine of the treatment groups were compared to the performance of normal controls on their second visit. On placebo, groups differed on visuospatial working memory (Number Correct Sequences), $F(3,79)=3.15$, $p=.02$, $\eta_p^2=.10$. Tukey post-hoc tests showed that both the ADHD and the ADHD+RD groups had poorer visuospatial working memory than normal controls, $p=.048$ and $p=.071$, respectively.

The RD group did not differ from other groups, all p-values, p>.10. There was a group effect following atomoxetine on visuospatial working memory, $F(3,79)=4.51$, p=.006, η_p^2=.14. Only the ADHD group remained different from normal controls (p=.007) when treated with atomoxetine, p-values for other groups, p>.10.

On placebo, groups marginally differed on SSRT, $F(3,79)=2.36$, p=.07, η_p^2=.08. Tukey post-hoc tests revealed that SSRTs of the ADHD+RD group were marginally slower compared to normal controls, p=.08, all other group differences were not significant, p>.10. After taking atomoxetine, no significant group differences were observed for SSRT, $F(3,79)=1.55$, p=.20, η_p^2=.05.

DISCUSSION

The first goal of this study was to examine the effects of atomoxetine on visuospatial working memory and inhibition in children with ADHD, ADHD+RD or RD. Visuospatial working memory improved after taking atomoxetine in children with ADHD+RD compared to placebo. Atomoxetine showed, compared to placebo, a marginally significant positive effect on inhibition in the ADHD+RD group. Both the ADHD and RD groups showed no improved neuropsychological functioning following atomoxetine. The second goal of this study was to determine possible effects of atomoxetine on lexical decision; no beneficial effects were found. Atomoxetine had the expected beneficial effects on ADHD symptomatology compared to placebo.

Atomoxetine affected executive functioning only in children with ADHD+RD, which suggests that ADHD and ADHD+RD are not only different subtypes of ADHD at a neuropsychological level (Purvis & Tannock, 2000), but possibly also at the neurochemical level (Halperin et al., 1997). Previous research suggests a difference in noradrenaline levels between children with ADHD and children with ADHD+RD. Children with ADHD+RD had higher plasma levels of the noradrenaline metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) than children with ADHD. MPHG appeared to be inversely associated with academic achievement and verbal processing but was not related to behaviour ratings or measures of attention and impulsivity (Halperin et al., 1997).

As expected, atomoxetine improved the maintenance function of visuospatial working memory. Although the exact mechanism is unclear, working memory may be mediated by modulation of the noradrenaline α_2.receptor and the dopamine D1 receptor in the prefrontal cortex (Arnsten & Li, 2005). Atomoxetine increases both noradrenaline and dopamine in the prefrontal cortex (Bymaster et al., 2005), which may possibly be related to the improved visuospatial working memory performance. Unclear is whether verbal and visuospatial working memory tap the prefrontal cortex to the same extent despite evidence that verbal working memory is oriented more left in the brain and visuospatial working memory is more

right oriented in the brain (Smith & Jonides, 1998). We did not include a measure of verbal working memory, hence it was not possible to conclude whether atomoxetine improves working memory in general or only visuospatial working memory.

Lexical processing appeared insensitive to atomoxetine. Previous research indicated that visuospatial working memory was associated with reading ability (Savage et al., 2007). However, the results of this study show no evidence of improvements in visuospatial working memory leading to equivalent benefit in reading as assessed by lexical processing.

The results should be interpreted in light of several limitations. Mean dose (1.11 kg/day) was relatively low compared to other studies with atomoxetine. Generally, other studies have used a higher mean end dose since these studies were longer in duration and titrated to 1.8 mg/kg, when 1.2 mg/kg was not effective after 4 weeks (Crommen & Dankaerts, 2005; Kratochvil, Vaughen, Daughton, Mayfield-Jorgensen & Burke, 2004). However, no relation was demonstrated between weight adjusted dose and our dependent variables. There was a relation between absolute dose and score on ADHD-RS (r=-.52, p=.001) and the speed measures (MRT, r=-.30, p=.01, MRT valid words, r=-.29, p=.02 and MRT pseudowords, r=-.27, p=.041). Children with higher absolute doses were heavier and thus generally older: However, a recent meta-analysis indicated no relation between age and efficacy of atomoxetine (Cheng, Chen, Ko & Ng, 2007). Future research with higher absolute dose in larger groups might reveal effects of atomoxetine in neuropsychological performance in children with ADHD and children with RD.

The results may be confounded by age and IQ, since the groups differed in age and IQ. We have chosen not to covary for age and IQ because age and IQ are related to the groups (Miller & Chapman, 2001). A lower IQ is consistently found in children with ADHD (Frazier, Demaree & Youngstrom, 2004). Thus, covarying for IQ may remove crucial variance. Differences in age are more or less inherent to the disorders. In order to diagnose RD, a child must have followed 2-3 years of reading education; in our sample, children with ADHD+RD and RD were older than children with ADHD. Thus, age was related to groups in a non-random fashion, which makes covarying for age inappropriate.

Unfortunately, disproportionately more children had atomoxetine than placebo in the first period, respectively n=34 and n=23. To test whether order influenced the results, we reran the analyses with treatment order as covariate, which did not alter the results. Thus, the findings on atomoxetine are not confounded by placebo or learning effects in the first period.

In summary, this is the first study to demonstrate beneficial effects of atomoxetine on visuospatial working memory and to a lesser extent on inhibition in children with ADHD+RD. Atomoxetine did not affect lexical processing and EF in children with ADHD and children with RD. The present findings suggest there may be separate developmental pathways for comorbid ADHD+RD and ADHD or RD alone.