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Neuropsychological Effects of Risperidone in Children with Pervasive Developmental Disorders: A Blinded Discontinuation Study

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ABSTRACT

Objective: **Little is known about the neuropsychological effects of risperidone in children with pervasive developmental disorders.**

Method: **Twenty-four children (aged 5–17 years) with pervasive developmental disorders and co-morbid disruptive behavior who responded favorably to open-label treatment with risperidone as part of a previously described controlled discontinuation study completed two different computerized attention tasks at baseline, weeks 4, 8, and 24 of open-label treatment, and, at 8 weeks after random assignment to either placebo or risperidone. The primary efficacy measures were response latencies to visually presented stimuli requiring two different types of attention-controlled processing, i.e., focused and divided attention.**

Results: **About half of the clinical responders did not produce valid performance measures. These could be shown to be of younger mental age and less adaptive as measured by the Vineland Behavior Scales. For the valid task performers divided attention (serial search in working memory) was shown to regress in the placebo group (n = 7), while in the risperidone group (n = 7) there was further improvement. No such group difference was found for focused attention.**

Conclusions: **The study suggests a beneficial effect of risperidone after several months of treatment, enhancing divided attention in children with pervasive developmental disorders.**

INTRODUCTION

In children and adolescents, the antipsychotic agent risperidone is increasingly being prescribed to ameliorate disturbed behavior in a variety of clinical conditions (Patel et al. 2005). Risperidone has a now well-established efficacy on severe tantrums, aggression, and self-injurious behavior in children with pervasive developmental disorders (PDDs) and also leads to improvements in the repetitive and stereotyped symptom domain (RUPP 2002; McDougle et al. 2005; RUPP 2005). As a worrying side effect, however, the use of risperidone may be associated with sedation (Aman et al. 2005). This could lead to cognitive dys-

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functions that may well interfere with performance at school with consequently unwanted stagnations in social, emotional, and cognitive development. On the other hand, sedative effects of risperidone frequently appear to be limited to the first weeks of treatment, while, moreover, risperidone may even have the potential to improve cognitive functioning. For example, in schizophrenia, atypical antipsychotic medications have been reported to have beneficial effects on a variety of cognition domains, including executive functions, vigilance, serial verbal learning, and complex visuo-motor skills (Keefe et al. 1999; Harvey et al. 2003). Interestingly, attention-related executive dysfunctions, among which is impaired working memory, have been proposed to underlie the core deficits of autism (Althaus et al. 1996; Benetto et al. 1996; Pierce et al. 1997; Althaus et al. 1999; Landa and Goldberg 2005).

In children, there is a lack of studies to address the neuropsychological effects of the atypical antipsychotics. In the case of the most widely used atypical agent risperidone, we know of only two studies in children with subaverage IQs who were treated for disruptive behavior disorders. In these studies of the Risperidone Disruptive Behavior Study Group, the degree of sedation was mild and not associated with cognitive deterioration (Turgay et al. 2002; Findling et al. 2004). In fact, there were similar improvements in tests for verbal learning, attention, and memory as reported for adult patients with schizophrenia. However, further evaluation of the neuropsychological effects of risperidone in the pediatric population is warranted. The primary aim of the present study was to examine the short- and long-term impact of risperidone on cognitive functioning in children and adolescents with pervasive developmental disorders in a previously described placebo-controlled discontinuation design. We expected that cognitive performance of clinical responders to risperidone would benefit from medication, and hypothesized that (after 6 months of open-label treatment) those patients who continued on risperidone would be significantly less likely to experience worsening of performance in a computerized cognitive task compared to those randomized to placebo.

METHODS AND MATERIALS

Subjects

Recruitment, clinical measures, and characteristics of study participants have been described in detail previously (Troost et al. 2005). Study participants were recruited from referred patients of the Groningen and Utrecht University Child and Adolescent Psychiatry Centers, and could be either inpatients or outpatients. All of the children had to meet *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition, text revision (DSM-IV-TR) criteria for a pervasive developmental disorder (American Psychiatric Association 2000). These diagnoses were made by use of the Autism Diagnostic Interview—Revised (Lord et al. 1994) complemented with a clinical judgment. Moreover, patients were required to demonstrate significant co-morbid tantrums, aggression, or self-injurious behavior. The aim and procedure of the study were fully explained to the subjects and their parents before the parent's written consent was requested. If the subject was 12 year old or older, then the written informed consent of the parents was obtained along with that of the patient. Twenty four subjects (age range 5–17 years) who were all clinical responders to open-label treatment with risperidone were randomly assigned after 24 weeks of treatment to either gradual tapering to placebo or the continued use of risperidone.

Neuropsychological tasks

Two different computerized choice-reaction tasks from the de Sonneville Visual Attention Task Battery (De Sonneville 1993) were employed at baseline (prestudy), during open-label treatment with risperidone (weeks 4, 8, and 24), and after randomization to either placebo or continued use of risperidone (week 32 or last visit in case of early termination because of significant worsening on clinical

and parent-based measures as previously described).

The first task was a focused attention task designed to measure the degree of distractibility by irrelevant information. In this task, there are three conditions, each consisting of a number of stimulus presentations (trials) the children are required to respond to by pressing one of the two mouse buttons, representing a "yes" response or a "no" response, respectively. "Yes" responses are to be given with the index finger of the dominant hand and "no" responses with the index finger of the other hand. All stimuli are presented on a 17-inch personal computer screen. The stimuli are four pieces of fruit located at the corners of a virtual diamond. Children must press the "yes" button whenever a previously presented target (e.g., a cherry) occurs at one of the vertical positions of the diamond. These positions are told to be the only ones that should be paid attention to (relevant positions). The children are required to press the "no" button in case the target fruit is absent as well as whenever the target occurs at one of the (horizontal) positions they actually are required to ignore (irrelevant positions); these trials are called irrelevant target trials. There are 28 relevant target trials, 14 irrelevant target trials (so-called foils), and 14 nontarget trials. The three types of trials are presented in a random sequence.

If there is any distraction by the target occurring at one of the irrelevant positions, reaction times (RTs) for correctly rejecting irrelevant targets will be slower than reaction times to relevant targets. Distraction, moreover, may lead to incorrectly pressing the "yes" response key, this being denoted as a false alarm to an irrelevant target.

Dependent measures of this task are condition-dependent error rates as measures of accuracy, including the percentage of relevant targets missed (PM), the percentage of false alarms to relevant nontargets (PFNT), and the percentage of false alarms to irrelevant targets (PFIT) as well as mean RTs for the correct responses to the relevant targets (hits: RTRT), the relevant nontargets (RTRNT), and the irrelevant targets (RTIT).

The second task was a divided attention, or memory search task designed to measure serial search processes that are carried out in working memory (Schneider and Shiffrin 1977; Shiffrin and Schneider 1977). The task consists of two blocks containing 40 trials each. During the first block, *one* stimulus (i.e., a particular animal) has to be kept in mind (target). This has to be compared with subsequently displayed sets of four stimuli (again animals). These "display sets" may or may not contain the target. A "yes" response (to be given again with the index finger of the dominant hand) is required whenever the target makes part of the display set, otherwise a "no" response must be given (with the index finger of the nondominant hand). Fifty percent of the trials contain the target, the other 50% do not. Target and nontarget trials are randomly distributed. During the second task block, two stimuli (animals) have to be kept in mind. Whenever *one* of the memorized stimuli appears in the successively displayed sets of four animals, a "yes" response is required, otherwise again a "no" response must be given. In this block again, half of the trials (n = 20) contain the target.

The important manipulations are the number of stimuli to be kept in mind (memory load) and target appearance. In general, the correct rejection times of nontarget trials will be longer than the reaction times of responses to target trials (hits). This is because in the latter condition memory search is terminated as soon as the target has been detected, whereas it is exhaustive when the target is absent and all comparisons with the stimulus/stimuli of the memory set must be made. Moreover, RTs will be longer in response to trials where two animals have to be kept in mind (high load condition) as compared to those where only one animal must be memorized. This implies that RTs will be longest in the high memory load nontarget condition.

Accuracy measures are the percentages of targets missed in the low-load (PM1) and high-load (PM2) condition as well as the percentages of false alarms to nontarget trials in both load conditions (PF1 and PF2). Measures of processing speed are mean RTs of the cor-

rect responses to targets (hits) in both load conditions (RTHL1 and RTHL2) and mean RTs of the correct rejections of nontargets (RTCRL1 and RTCRL2). The divided attention task was always administered after the focused attention task.

Data analysis

Analyses were carried out for only those children that had valid task measures. These were defined as having percentages of errors smaller than 50% in any of the task conditions, given that higher error rates might reflect random pressing of the response buttons leading to noninterpretable effects of the task manipulations. Children with valid measures were compared to those with nonvalid measures on a comprehensive set of baseline characteristics (Independent-samples *t*-test and Pearson Chi-square test). Statistical testing of assessment-dependent changes and/or group differences was confined to RTs, as error rates appeared to be low and far from normally distributed. For the accuracy measures therefore, only the (condition dependent) medians are presented. For the RT analyses, effect sizes (partial eta squared: η^2) were provided in addition to *p* values because they may be more informative when power is low due to small sample sizes. In all tests, *p* values <0.05 were used to indicate statistical significance.

Focused attention task

Open label phase: For those children from whom valid measures were obtained for all assessments, a repeated measures analysis of variance (GLM, RM, SPSSPC) was applied, including the within-subject variable "assessment" with four levels (weeks 0, 4, 8, and 24) and the within-subject variable "task" with three levels, i.e., the three task conditions. Contrasts were analyzed while comparing the RTs of irrelevant targets (RTIT) with both the RTs of relevant targets (RTIT vs. RTRT) and the RTs of relevant nontargets (RTIT vs. RTRNT), these contrasts being labeled "relevance 1 " and "relevance 2," respectively. A general medication effect on task performance would manifest itself as a main effect "assessment," whereas a more selective effect on distractibility would be reflected by the interaction "assessment by relevance."

Discontinuation phase: A repeated measures design was used to compare the treatment groups including mental age as a covariate. This design consisted of the between-subjects variable "medication" (placebo vs. risperidone) and the two within-subject variables "assessment" (week 24 vs. last visit) and "relevance," respectively. Again, two types of relevance were defined as being the contrasts of, respectively, RTIT vs. RTRT, and RTIT vs. RTRNT. A medication effect would appear as a difference between the groups in processing times at the last visit as compared to week 24 (interaction "group by assessment"). If the effect would hold for especially their responses to irrelevant stimuli, a three-way interaction "medication by assessment by relevance" should emerge.

Divided attention task

Open-label phase: For this task too, statistical analyses were conducted on only the data of subjects with valid repeated measures for all four assessments. A repeated measurement analysis of variance was applied with the following three within-subject variables: (1) "assessment" with the four levels of weeks 0, 4, 8, and 24, (2) "load" with the two levels of 1 vs. 2 animals to be kept in mind, and (3) "target" with the two levels of target presence vs. absence in the display set. A main effect of "assessment" could be indicative of a general medication effect, whereas any interaction with the variable "load" would reflect a more selective effect of medication on serial search processes.

Discontinuation phase: A repeated measures design was used with the between-subjects variable "medication" and the three within subject variables "assessment," "load," and "target." Mental age was entered as a covariate into the design. The "group by assessment" interactions would indicate medication effects, which, if appearing in combination with the variable "load," would point to serial search processes being susceptible to the compound.

RESULTS

For the focused attention task, valid cognitive measures were obtained for 15, 15, 15, 16, and 12 out of 24 children at baseline, weeks 4, 8, 24, and week 8 after random assignment to either placebo or risperidone, respectively. For the divided-attention task, valid measures were obtained for 14, 14, 18, 16, and 14 children, respectively. The valid and nonvalid children significantly differed at all time points for both focused attention and divided attention in age, mental age, and the three subscales of the Vineland Adaptive Behavior Scales (Table 1; numbers only shown for divided attention at week 24).

Open label phase

Focused attention: Of the different types of errors, the greatest percentage (7.1%) was found for the false alarms in response to irrelevant stimuli (PFI). For the reaction times, the greatest response latencies were found for the con-

TABLE 1. BASELINE CHARACTERISTICS OF 24 CHILDREN ENTERING THE DISCONTINUATION PHASE

	Divided attention task				
	Valid (n = *14)*			*Non valid* (n = *10)*	*p*[b]
Characteristic	*Risperidone* (n = *7)*	*Placebo* (n = *7)*	p[a]	*Risperidone* (n = *5) and placebo* (n = *5)*	
Age, mean (SD)	11.3 (3.2)	9.0 (1.2)	0.116	7.5 (1.4)	0.004[c]
Mental age	9.45 (2.9)	8.42 (2.2)	0.431	6.4 (0.4)	0.002[c]
Male/female, n (%)	6/1 (86/14)	6/1 (86/14)	1.00	10/0 (100/0)	0.212
DSM-IV TR diagnosis of PDD, *n* (%)			0.580		0.314
Autistic disorder	1 (14)	1 (14)		4 (25)	
Asperger's disorder	—	1 (14)		1 (10)	
PDD not otherwise specified	6 (86)	5 (71)		5 (50)	
Score on Vineland Adaptive Behavior Scales, mean (SD)					
Communication	104.3 (16.6)	109.3 (11.3)	0.524	82.2 (24.9)	0.014[c]
Socialization	88.9 (12.6)	83.9 (15.5)	0.522	59.5 (18.4)	0.001[c]
Daily Living	119.9 (13.9)	121.7 (13.2)	0.801	95.3 (24.0)	0.009[c]
Concomitant medication status, *n* (%)			0.513		0.180
None	5	6		—	
Stimulant	1	2		—	
Stimulant and anticonvulsant	1	—		—	
Weight, kg, mean (SD)	47.4 (16.7)	37.7 (10.7)	0.221	35.5 (7.0)	0.127
Daily doses, mg, mean (SD)	1.7 (.64)	1.6 (.38)	0.804	2.0 (.71)	0.237
Score on Aberrant Behavior Checklist, mean (SD)					
Irritability	11.3 (10.7)	10.6 (8.3)	0.891	13.2 (.187)	0.455
Social Withdrawal	5.0 (7.1)	6.7 (6.0)	0.656	5.8 (6.0)	0.983
Stereotypy	2.0 (2.6)	4.9 (5.0)	0.213	3.6 (3.8)	0.917
Hyperactivity	13.4 (10.9)	13.0 (10.8)	0.942	20.6 (8.9)	0.076
Inappropiate Speech	2.1 (1.6)	1.6 (1.3)	0.470	3.9 (3.4)	0.101
Clinical Global Impressions, *n* (%)			0.534		
Minimally Improved	2 (29)	1 (14)		5 (50)	0.336
Much Improved	3 (43)	3 (43)		3 (33)	0.336
Very Much Improved	2 (29)	3 (43)		2 (20)	0.336

PDD = Pervasive developmental disorder; CGI = Clinical Global Impressions (Guy 1976); ABC=Aberrant Behavior Checklist (Aman 1985).

[a]*p* differences in baseline descriptions between valid and nonvalid groups.

[b]*p* differences in baseline descriptions between placebo and risperidone groups with valid Divided Attention Tasks (independent-samples *t*-test for continuous variables and Pearson Chi-square test for categorical variables, two-sided).

[c]Significant.

dition where irrelevant information had to be ignored (RTIT), whereas children responded much faster to relevant targets (RTRT). Response latencies for the rejection of relevant nontargets (RTRNT) were found to lie in between these two conditions. In all the three conditions, RTs became shorter with increasing time of assessment (Table 2).

Analyses of variance ($n = 11$) revealed significant assessment effects for the RTs of all three conditions, this being greatest for the rejection times of irrelevant targets showing a high effect size of $\eta^2 = 0.69$. There was a significant difference between RTs for correctly rejecting irrelevant targets (RTIT) and correctly responding to relevant targets (RTRT), having a high effect size of $\eta^2 = 0.59$ (Table 2, Relevance 1). The difference between response times for correctly rejecting irrelevant targets and correctly rejecting relevant nontargets (Relevance 2) did not appear to be statistically significant.

Finally, there was a significant two-way interaction between RT differences for relevant and irrelevant targets (Table 2, Relevance 1) and the time of assessment, indicating that the differences indeed became smaller with prolonged risperidone treatment. This interaction had an effect size of $\eta^2 = 0.46$. For the second type of the relevance manipulation (Table 2, Relevance 2), the assessment dependent decrease was not found to be statistically significant though the effect size was moderate ($\eta^2 = 0.13$).

Divided attention: With regard to accuracy, relatively more targets were missed (PM1/PM2) than false alarms to nontargets had been given (PF1/PF2). In general, error percentages were rather low, with the highest percentage referring to the targets missed in the high load condition (11%). No systematic decrease with increasing time of assessment could be observed.

With respect to processing speed, for each assessment, RTs increased from the low-load target (RTHL1) to the high-load nontarget (RTCRL2) condition. Moreover, RTs decreased from baseline to week 24 as well as from baseline to week 8; these decreases, however, were only small for the low-load conditions (RTHL1 and RTCRL1). Of note, the steepest decreases were found from baseline to the first assessment after baseline at week 4. From this timepoint on, RTs did not show any further remarkable changes (Table 2).

When testing task manipulation and assessment effects ($n = 11$), a significant assessment effect was found only for the high-load target condition (RTHL2), with a high-effect size of $\eta^2 = 0.71$. The decrease in RTs of the high-load nontarget condition did not reach statistical significance, although it showed a high-effect size too ($\eta^2 = 0.18$). Concerning the task manipulation effects, there were significant differences between the high-load and low-load as well as between the nontarget and target response times when pooled across the various assessments. Both "load" and "target" effects turned out to be statistically significant with high effect sizes of $\eta^2 = 0.78$ and $\eta^2 = 0.80$, respectively.

When finally turning to the question of whether the effects of the task manipulations became smaller with increasing time of assessment, a significant interaction was found between the "load" manipulation and "assessment," with a high-effect size ($\eta^2 = 0.65$) indicating that the impact on memory search processes indeed became lower. The three-way interaction "load by target by assessment" was not found to be significant, although it turned out to have a high effect size ($\eta^2 = 0.21$).

Discontinuation phase

Focused attention: Twelve out of 24 children had valid measures at both assessments. Of the 12 children with valid measures, there were no significant differences in the two treatment groups (i.e., risperidone vs. placebo) with respect to clinical, developmental, and demographic characteristics (Table 1; numbers only shown for the divided attention task).

There was no increase of RTs from week 24 to the last visit for the placebo group (Fig. 1). Whereas both types of the "relevance" manipulation showed significant effects, there were no interactions with the group ("medication") and assessment variable (Table 3A).

Divided attention: Of the 14 children with valid measures, there were no significant differences in the two treatment groups with respect to baseline characteristics (Table 1).

TABLE 2. COGNITIVE MEASURES DURING THE OPEN LABEL PHASE

	Assessment				*Effects*			
	Week				*Task manipulation*		*Assessment*	
Task variables	*0*	*4*	*8*	*24*	p[a]	η^2	p[a]	η^2
A. Focused Attention	*M (SD)*[d] n = *15*[b]	*M (SD)*[d] n = *15*[b]	*M (SD)*[d] n = *15*[b]	*M (SD)*[d] n = *16*[b]		n = *11*[c]		
RTRT/PM	1415 (352)/0	1179 (332)/3.3	1127 (347)/3.6	1074 (329)/0.1			0.02	0.46
RTRNT/PFN	1661 (436)/0	1285 (410)/0	1239 (475)/0	1142 (411)/1.4			0.02	0.43
RTIT/PFI	1754 (509)/7.1	1358 (399)/7.1	1159 (310)/7.1	1229 (370)/0.1			0.001	0.69
RTIT vs. RTRT (Relevance 1)					0.004	0.59	0.02	0.46
RTIT vs. RTRNT (Relevance 2)					0.39	0.07	0.26	0.13
B. Divided Attention	*M (SD)/Med*[d] n = *14*[b]	*M (SD)/Med*[d] n = *14*[b]	*M (SD)/Med*[d] n = *18*[b]	*M (SD)/Med*[d] n = *16*[b]		*n = 11*[c]		
RTHL1/PM1	1154 (337)/5	1027 (242)/0	1118 (390)/5	1062 (346)/6.3			0.38	0.08
RTCRL1/PF1	1314 (359)/1.8	1112 (326)/0	1265 (576)/0	1201 (491)/5.9			0.72	0.01
RTHL2/PM2	1653 (502)/11	1369 (415)/8	1292 (431)/5	1236 (448)/10			0.001	0.71
RTCRL2/PF2	1873 (507)/2.5	1498 (457)/0	1541 (637)/2.5	1589 (720)/0			0.17	0.18
RTHL1 vs RTHL2 (Load)					<0.001	0.78	0.002	0.65
Load x Target					0.14	0.21	0.14	0.21

Note that effect sizes of η^2 (partial eta squared) ≥ 0.14 are high-, $\eta^2 \geq 0.06$ and $\eta^2 < 0.14$ are medium-, and $\eta^2 < 0.06$ are small-effect sizes according to Cohen (Stevens 2002).

[a]*p* values from repeated measures analyses of variances; tested two-sided.

[b]Number of participants with valid measures.

[c]Number of participants with valid measures at all timepoints during the open label phase.

[d]In milliseconds.

PM = percentage of misses
PFN = percentage of false alarms nontargets
PFI = percentage of falst alarms irrelevant targets
PM1 = percentage of misses load 1
PM2 = percentage of misses load 2
PF1 = percentage of false alarms load 1
PF2 = percentage of false alarms load 2
RTRT = reaction time relevant targets
RTRNT = reaction time relevant non-targets
RTIT = reaction time irrelevant targets
RTHL1 = reaction time hits load 1
RTHL2 = reaction time hits load 2
RTCRL1 = reaction time correct rejections load 1
RTCRL2 = reaction time correct rejections load 2

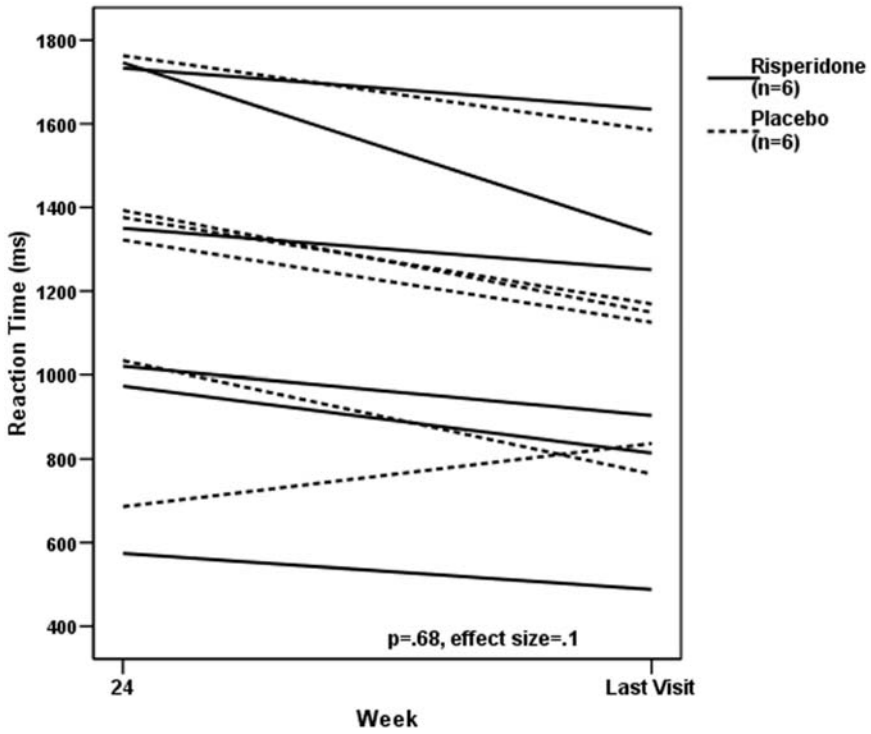

FIG. 1. Focused attention task: Reaction times irrelevant targets (RTIT) for each subject in the discontinuation phase.

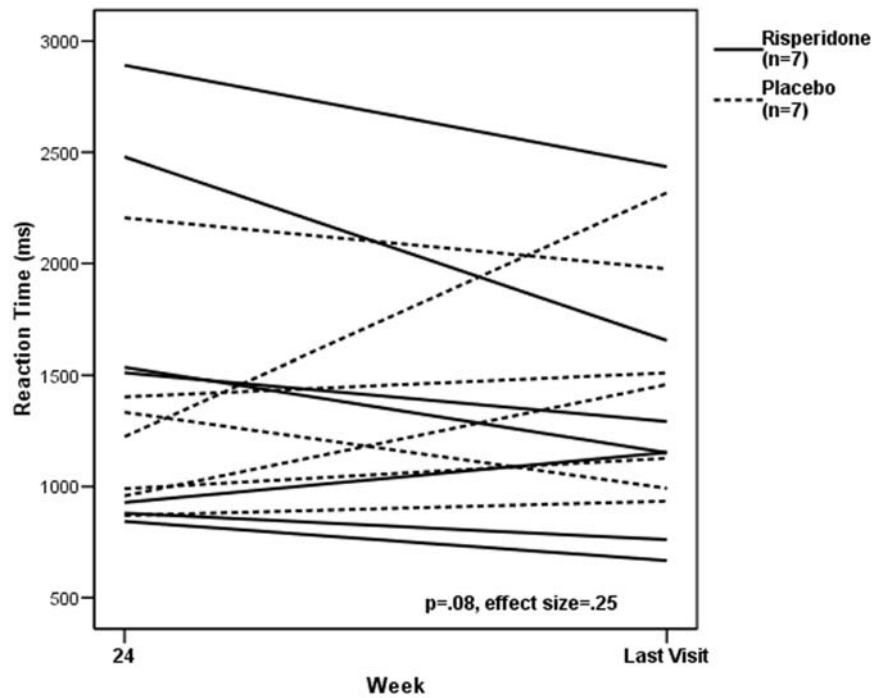

FIG. 2. Divided attention task: Reaction times correct rejections high-load condition (RTCRL2) for each subject in the discontinuation phase.

TABLE 3. COGNITIVE MEASURES DURING THE DISCONTINUATION PHASE

	Assessment				*Effects*			
	Week 24 risperidone		*Last visit risperidone*		*Task manipulation*		*Medication × assessment*	
Task variables	*Discontinuation*	*Maintenance*	*Discontinuation*	*Maintenance*	p[a]	η^2	p[a]	η^2
A. Focused Attention	*M (SD)*[c] n = *6*[b]	*M (SD)*[c] n = *6*[b]	*M (SD)*[c] n = *6*[b]	*M (SD)*[c] n = *6*[b]				
RTRT	1021 (302)	1078 (408)	1042 (269)	1169 (578)			1.06	0.05
RTRNT	1196 (553)	1050 (401)	1061 (265)	1099 (497)			0.98	0.06
RTIT	1262 (369)	1192 (475)	1105 (292)	1267 (699)			0.68	0.1
RTIT vs. RTRT (Relevance 1)					0.02	0.45	0.5	0.06
RTIT vs. RTRNT (Relevance 2)					0.03	0.42	0.78	0.01
	M (SD)[c]	*M (SD)*[c]	*M (SD)*[c]	*M (SD)*[c]				
B. Divided Attention	n = *7*	n = *7*	n = *7*	n = *7*				
RTHL1	980 (369)	983 (309)	999 (298)	775 (181)			0.04	0.36
RTCRL1	1059 (275)	1211 (653)	1119 (309)	932 (248)			0.04	0.37
RTHL2	1108 (232)	1142 (502)	1239 (279)	954 (230)			0.10	0.23
RTCRL2	1283 (453)	1581 (815)	1474 (518)	1302 (598)			0.08	0.25
RTHL1 vs. RTHL2 (Load)					0.002	0.60	0.84	0.004
Load × Target					0.14	0.24	0.96	0

Note that effect sizes of η^2 (partial eta squared) ≥ 0.14 are high-, $\eta^2 \geq 0.08$ and $\eta^2 < 0.14$ are medium-, and $\eta^2 < 0.08$ are small-effect sizes according to Cohen (Stevens 2002).[a]*p* values from repeated measures analyses of variances, adjusted for Mental Age and tested two-sided.

[b]Number of participants with valid measures at week 24 and last visit.

[c]In milliseconds.

RTRT = reaction time relevant targets
RTRNT = reaction time relevant non-targets
RTIT = reaction time irrelevant targets
RTHL1 = reaction time hits load 1
RTHL2 = reaction time hits load 2
RTCRL1 = reaction time correct rejections load 1
RTCRL2 = reaction time correct rejections load 2

Mean RTs increased from week 24 to the last visit assessment for only the placebo group, whereas a further decrease in the group that continued on risperidone was observed (Fig. 2). The greatest increase was observed for the high-load exhaustive memory search condition (RTCRL2). The corresponding interaction ("medication by assessment"), however, showed a smaller effect size than the interaction corresponding with changes in low load RTs (RTL1). Yet, the latter interactions were actually caused by relatively greater RT decreases in the risperidone group than increases shown in the placebo group. When testing the changes in the high-load nontarget search condition (RTCRL2) for both groups separately, we found a nonsignificant increase ($p = 0.34$) with yet a high-effect size ($\eta^2 = 0.15$) for the placebo group, and a trend-level significant decrease for the risperidone group ($p = 0.06$; $\eta^2 = 0.46$). However, the above-suggested larger effect on especially the high-load conditions was not confirmed by three- or four-way interactions including the task variable "load" (Table 3B).

DISCUSSION

This study was the first to have evaluated neuropsychological effects of risperidone in children and adolescents with PDDs. Our results suggest a beneficial effect of long-term treatment with risperidone on cognitive functioning, especially with regard to processes that make a demand on working memory.

For both the focused and divided attention tasks, it was demonstrated that the manipulations of, respectively, distractibility by irrelevant information and working memory-related serial search processes were successful, showing that task performances indeed were valid with the consequence that assessment-related changes could be interpreted in terms of the measurement pretensions.

Repeated testing during the open-label phase resulted in improved performance, indicating that potentially sedating side effects do not impair attention-related information processing during a treatment period of several months. The improved performance could be due to practice effects, maturity, or effects of risperidone over time. Because of the uncontrolled nature of the first part of the study, it was not possible to conclude which element or combination of elements was responsible. However, regarding divided attention in the controlled discontinuation phase, the children maintained on risperidone performed better than those switched to placebo, suggesting at least some long-term drug effect in enhancing working memory performance.

A risperidone-associated effect on focused attention was not apparent from our data. Here, a significant assessment-dependent decrease in the effect of distracting information was found on processing times during the open-label phase, whereas, however, reaction times did not significantly worsen in the placebo group during the discontinuation part. This suggests that the use of risperidone does not interfere with learning to neglect irrelevant information when such a task is repeatedly administered. Interestingly, focused attention has repeatedly been found unaffected in children with PDDs while using similar task paradigms (Althaus et al. 1996; Ozonoff and Jensen 1999). This may explain the lack of regression in the placebo group: If these children (just as those of the other group) did not start with an essentially deficient level of distractibility, they just might have remained at the level reached by learning.

Some of the deterioration in the discontinuation phase might have been due to acute withdrawal effects rather than simply the absence of risperidone. However, as previously described (Troost et al. 2005), time between week 24 and last visit was, on average, 6 ± 1 weeks for placebo and 7 ± 1 for risperidone, making deterioration due to acute withdrawal effects after 3 weeks of gradual taper and another 3 weeks of completely stopping risperidone less likely.

Deficient working memory performance has repeatedly been suggested to characterize children with a PDD (Althaus et al. 1996; Bennetto et al. 1996; Pennington and Ozonoff 1996; Landa and Goldberg 2005) and may arise from structural or functional deviations of the anterior cingulate gyrus (Posner and Raichle 1994;

Haznedar et al. 2000; Luna et al. 2002; Levitt et al. 2003; Koshino et al. 2005; Zarahn et al. 2005). The anterior cingulate gyrus has a high serotonin receptor density (Haznedar et al. 1997), and an imbalance in serotonin neurotransmission has been associated with cognitive and behavioral manifestations of autism (Piven et al. 1991). In this context, it could be speculated that a possible role of risperidone (a potent postsynaptic dopamine and serotonin receptor blocker) in enhancing working memory processes in PDDs may be mediated through a serotonergic effect in this brain area.

A clear limitation of this study was that a large proportion of the children was not able to perform the two tasks well enough to be considered valid task performers. The children with nonvalid measures were of younger chronological and mental age and had lower adaptive skills. This demonstrates that younger children with PDDs and co-morbid disruptive behavior who show lower levels of adaptive skills are less capable of performing adequately on the computerized tasks as used in this trial. Their drop-out from further analyses not only led to relatively small sample sizes (although effect sizes still were high), but also may have confined the generalizability of the results to children of older age with higher levels of functioning. These findings clearly need replication with larger samples, using carefully selected cognitive measures. However, given that cognitive function is one of the more difficult domains to engage in PDDs, the testable rate of approximately 50% still is very favorable and probably would have been lower if a larger proportion of the children in this sample had an autistic disorder. Therefore, these preliminary findings certainly contribute to the sparse literature on the cognitive effects of risperidone in children with PDDs and demonstrate that many such children are in fact testable.

In conclusion, the present study suggests a possible additional benefit of risperidone in low-to-intermediate doses in enhancing working memory performance in children with PDDs. This may be associated with improvements in social, communicative, and academic functioning.

DISCLOSURES

Dr. Buitelaar has been a consultant to/member of advisory board of/and/or speaker for Janssen Cilag BV, Eli Lilly, Bristol-Myer Squibb, UBC, Shire, Medice, Dr. Minderaa is a paid consultant to Eli Lilly and Janssen Cilag BV, and Drs. Troost and Hoekstra have received support from Eli Lilly. Drs. Lahuis and Althaus have no financial ties with for-profit enterprises.

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