

Absence of the 7-Repeat Variant of the DRD4 VNTR Is Associated With Drifting Sustained Attention in Children With ADHD But Not in Controls

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Many genetic studies have demonstrated an association between the 7-repeat (7r) allele of a 48-base pair variable number of tandem repeats (VNTR) in exon 3 of the DRD4 gene and the phenotype of attention deficit hyperactivity disorder (ADHD). Previous studies have shown inconsistent associations between the 7r allele and neurocognitive performance in children with ADHD. We investigated the performance of 128 children with and without ADHD on the Fixed and Random versions of the Sustained Attention to Response Task (SART). We employed time-series analyses of reaction-time data to allow a fine-grained analysis of reaction time variability, a candidate endophenotype for ADHD. Children were grouped into either the 7r-present group (possessing at least one copy of the 7r allele) or the 7r-absent group. The ADHD group made significantly more commission errors and was significantly more variable in RT in terms of fast moment-to-moment variability than the control group, but no effect of genotype was found on these measures. Children with ADHD without the 7r allele made significantly more omission errors, were significantly more variable in the slow frequency domain and showed less sensitivity to the signal (d') than those children with ADHD the 7r and control children with or without the 7r. These results highlight the utility of time-series analyses of reaction time data for delineating the neuropsychological deficits associated with ADHD and the DRD4 VNTR. Absence of the 7-repeat allele in children with ADHD is associated with a neurocognitive profile of drifting sustained attention that gives rise to variable and inconsistent performance. © 2008 Wiley-Liss, Inc.

KEY WORDS: endophenotype; response variability; reaction time; executive function; dopamine

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INTRODUCTION

Within the molecular genetics literature of attention deficit hyperactivity disorder (ADHD) an association with the 7-repeat allele of a 48 base-pair (bp) tandem repeat polymorphism of the dopamine D4 receptor gene (DRD4) stands as one of the most consistent findings. This association has been found across both case-control [e.g., LaHoste et al., 1996] and family-based designs [e.g., Swanson et al., 1998], with several meta-analyses confirming a small but statistically significant effect [e.g., Li et al., 2006]. As yet, the functionality of this variant remains uncertain [Wong and Van Tol, 2003]. It has been proposed that the 7-repeat DRD4 allele is associated with 25–50% of the observed cases of ADHD [Grady et al., 2003].

A parallel literature has sought to document the functional significance of this variant from a neuropsychological perspective. A commonly reported finding is the superior neuropsychological performance of ADHD probands who carry the 7-repeat DRD4 allele, relative to probands without this allele [Swanson et al., 2000; Manor et al., 2002; Bellgrove et al., 2005]. This finding is paradoxical however, as it can be argued that the 7-repeat DRD4 allele should confer risk to ADHD, in part through its influence on the development of those cognitive and neural processes supporting attention [Castellanos and Tannock, 2002]. Accordingly, carriers of the 7-repeat DRD4 allele might be expected to perform more poorly on tests of attention than those without this allele.

In order to account for these paradoxical findings Swanson et al. [2000] have proposed that the 7-present ADHD subgroup might have a partial syndrome characterized by behavioral excesses and intact cognition, whereas the 7-absent ADHD subgroup may have a full syndrome characterized by behavioral excesses and cognitive deficits. An unresolved issue, however, is whether the 7-repeat DRD4 allele has comparable effects on cognition in ADHD and non-ADHD samples. Only

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one previous study has compared the vigilant performance of control and ADHD participants genotyped for the DRD4 variable number of tandem repeat (VNTR) and this yielded null results [Barkley et al., 2006].

The present study addressed these issues by examining the influence of the 7-repeat DRD4 allele on sustained attention and reaction-time variability in a large sample of healthy and children with ADHD genotyped for the 48 bp VNTR. Sustained attention refers to the endogenous maintenance of an alert state in the absence of exogenous input and is achieved via a predominantly right-hemisphere network including the right frontal and parietal cortices [Sturm and Willmes, 2001]. A meta-analysis of neuropsychological performance in ADHD suggests that sustained attention deficits are reliably associated with the disorder [Willcutt et al., 2005]. A genetic contribution to sustained attention is suggested by both behavior genetic studies [Groot et al., 2004] and molecular genetic studies that have linked allelic variation in catecholamine genes to sustained attention deficits in ADHD [e.g., Loo et al., 2003].

A ubiquitous finding from reaction time studies of ADHD, including those employing sustained attention tasks, is that of increased response time variability [Johnson et al., 2007a]. Rather than reflecting random noise, it has been suggested that response time variability could be a marker for frontal brain pathology [Stuss et al., 2003; Bellgrove et al., 2004] and it has been advanced as a candidate endophenotype for ADHD [Kuntsi and Stevenson, 2001; Castellanos and Tannock, 2002; Kuntsi et al., 2006; Andreou et al., 2007]. Castellanos et al. [2005] recently suggested that increased response time variability may be a reflection of a catecholaminergic deficiency within frontostriatal structures that impairs the ability to modulate very low-frequency fluctuations in neuronal activity. This scenario could give rise to the relatively frequent lapses of attention that may underpin deficits in sustained attention in ADHD. Heightened RT variability in children with ADHD without the 7-repeat allele has been observed in three out of six studies that have investigated cognitive-genetic (DRD4 VNTR) correlates of ADHD [Swanson et al., 2000; Manor et al., 2002; Bellgrove et al., 2005]. In the other three studies, RT variability was not examined [Langley et al., 2004; Barkley et al., 2006; Kielsing et al., 2006] (see Table I for a summary of these articles).

Recent advances in time series analyses, using a fast Fourier transform (FFT), have enhanced our understanding of variability in RT [Castellanos et al., 2005]. Breaking RT variability into slow and fast forms has allowed an analysis of vigilant behavior over longer (slow variability) and shorter moment-to-moment (fast variability) time-frames [Johnson et al., 2007a]. This form of analysis has been particularly useful for understanding the cognitive performance of children with ADHD relative to controls and children with autism [Johnson et al., 2007b]. Crucially, no studies have yet compared FFT measures of reaction time variability as a function of DRD4 genotype. The application of this technique might provide greater sensitivity and help to clarify inconsistencies regarding the functional effect of the 7-repeat allele for cognition in ADHD.

This study investigated sustained attention and response time variability in children with and without ADHD, stratified according to the presence or absence of the 7-repeat DRD4 allele. We predicted poorer cognitive performance of the ADHD cohort, relative to controls, on the Fixed and Random versions of the Sustained Attention to Response Task (SART) [Robertson et al., 1997], a task known to activate the right frontoparietal attentional networks [Manly et al., 2003] that are thought to be dysfunctional in ADHD [Sowell et al., 2003; Silk et al., 2005]. We also predicted a Diagnosis \times Genotype interaction, driven by the poorer performance of the 7-absent ADHD subgroup, potentially supporting the notion that the

latter group is comprised of individuals with other genetic or non-genetic etiologies [Swanson et al., 2000].

MATERIALS AND METHODS

Participants

Sixty-eight children with ADHD and 60 control children participated in the study (see Table II). All children were of Irish descent. There was no significant difference in age between the two groups. The average IQ of the ADHD group was significantly lower than that of the control group, as measured using four subtests (picture completion, vocabulary, information, block design) of the Wechsler Intelligence Scale for Children (WISC) [Wechsler, 1992], [$F(1,126) = 38.909$, $P < 0.001$]. As this research was a follow-on study from previous work [Bellgrove et al., 2005], data from 30 children with ADHD genotyped for the 48 bp VNTR had previously been published. Behavioral data from 44 children with ADHD and 15 controls had previously been published [Johnson et al., 2007a,b].

Exclusion criteria for participation in the study included known neurological conditions, pervasive developmental disorders or serious head injuries. Control children were also excluded if they had first-degree relatives with ADHD. All children scored above 69 on the WISC. Handedness was measured using the Edinburgh Handedness Inventory [Oldfield, 1971].

The participants were recruited as part of ongoing genetic studies. The control children were recruited from Dublin schools. The ADHD participants were either referred by consultant psychiatrists or recruited through support groups. Diagnosis for the ADHD participants was confirmed by psychiatrists using the parent form of the Child and Adolescent Psychiatric Assessment (CAPA) [Angold et al., 1995]. Twenty-four (35%) of the children with ADHD were stimulant naïve. Nineteen (28%) of the children with ADHD were taking stimulant medication around the time of testing; this stimulant medication was withdrawn for at least 24 hr prior to testing. The potential confound of a differential effect on performance of the SARTs due to stimulant drug withdrawal in the 7-repeat allele present ($n = 9$) and absent ($n = 11$) groups was tested. For each measure, there was no significant effect of Genotype. One child received 36 mg per day of Atomoxetine (Strattera), whilst the remainder received Methylphenidate (Ritalin, Concerta; dose range 15–72 mg per day).

At the time of testing, all parents completed the Conners' Parent Rating Scale—Revised: Short Version (CPRS-R:S) [Conners, 1997]. All of the children with ADHD had ADHD Index T-scores greater than 64 (mean 78, SD 6) and all control children had scores less than 60 (mean 45, SD 6). There was a significant difference between the two groups on the Conners' Index T-scores, [$F(1,126) = 926.037$, $P < 0.001$].

After complete description of the study to the subjects, written informed consent was obtained. The experimental work was conducted under the approval of Local Ethical Committees in accordance with the declaration of Helsinki.

Genotyping

The procedures followed for genotyping the ADHD and control samples have been previously published [Hawi et al., 2000]. The participants were grouped according to the presence or absence of the 7-repeat allele (please refer to Table II), as per previous studies [Swanson et al., 2000; Langley et al., 2004; Bellgrove et al., 2005; Barkley et al., 2006; Kielsing et al., 2006]. The frequencies of the DRD4 alleles in the ADHD and control groups are displayed in Table III. All genotypes were in Hardy–Weinberg Equilibrium.

TABLE I. A Review of the Studies Investigating the Performance of Children With Attention Deficit Hyperactivity Disorder (ADHD) on Tests of Cognitive Performance, Sub-Grouped by Possession of the Alleles of the Dopamine D4 Receptor (DRD4) Variable Number of Tandem Repeats (VNTR)

Study	Sample size according to clinical group and possession of DRD4 alleles (n)	Task name and description	Genetic findings
Swanson et al. [2000]	13 ADHD with at least one 7-repeat allele 19 ADHD with no copy of 7-repeat allele 21 controls (not genotyped)	Three tasks were administered, but an overall measure of performance was reported. The three tasks were: A color word task to probe executive function network A cued-detection task to probe the orienting and alerting networks A go-change task to probe the alerting and executive networks	Mean RT: 7p ADHD group did not differ from control group. 7a ADHD group was significantly slower in mean RT than control group and 7p ADHD group (one-tailed test but not two-tailed test) SD of RT: 7p ADHD group did not differ from control group. 7a ADHD group was significantly more variable in mean RT than control group. Any difference between the 7p and 7a ADHD groups was not reported
Manor et al. [2002]	No controls tested 36 ADHD with at least one copy of a long (7-, 8-repeat) allele 96 ADHD with no copy of a long allele	Test of Variables of Attention (TOVA)—a computerized CPT	Commission errors: long DRD4 repeat allele ADHD group made significantly less errors than the short DRD4 repeat allele ADHD group Omission errors: trend for the long DRD4 repeat allele ADHD group to make less errors than the short DRD4 repeat allele ADHD group Mean RT: no significant difference between the two groups SD of RT: long DRD4 repeat allele ADHD group was significantly less variable than the Short DRD4 repeat allele ADHD group
Langley et al. [2004]	For the Matching Familiar Figures Test (MFFT) and CPT 25 ADHD with at least one 7-repeat allele 53 ADHD with no copy of 7-repeat allele 40 controls (not genotyped) For the Go/No-Go and Stop Task 20 ADHD with at least one 7-repeat allele 46 ADHD with no copy of 7-repeat allele 23 controls (not genotyped)	Battery of neuropsychological tests MFFT measuring impulse control Stop Task measuring response inhibition Go/No-Go task measuring response inhibition CPT measuring sustained attention and response inhibition	MFFT—7p ADHD group made significantly more incorrect responses than the 7a ADHD group, which made significantly more incorrect responses than the control group. The 7p ADHD group responded (for correct and incorrect responses) significantly more quickly than the 7a ADHD group, which responded significantly more quickly than the control group Stop Task—7p ADHD group responded significantly more quickly than the 7a ADHD group. Neither ADHD group differed from the control group. There was no difference between the groups in terms of the % of inhibitions Go/No-Go Task—There was no significant difference in RT between the 7p and 7a ADHD groups, or between the 7a and control groups. The 7p ADHD group responded significantly more slowly than the control group. There was no significant difference between the two ADHD groups in terms of the % of inhibitions. No data comparing the ADHD and control groups was provided

(Continued)

TABLE I. (Continued)

Study	Sample size according to clinical group and possession of DRD4 alleles (n)	Task name and description	Genetic findings
Bellgrove et al. [2005]	20 ADHD with at least one 7-repeat allele 31 ADHD with no copy of 7-repeat allele 39 control children (not genotyped)	Sustained Attention to Response Task (random version)—a measure of sustained attention and response inhibition.	<p>CPT—There was no significant difference between the two ADHD groups in terms of commission errors; both groups made more errors than the control group. There was no significant difference between the two ADHD groups in terms of omission errors; the 7a ADHD group made significantly more omission errors than the control group and there was a trend suggesting a difference between the 7p ADHD and control groups</p> <p>Commission errors: 7a ADHD group made significantly more errors than the control group. 7p ADHD group did not differ from the control group. It is not reported if the two ADHD groups differed significantly</p> <p>Omission errors: 7a ADHD group made significantly more errors than the 7p ADHD group. It is not reported if the 7a and 7p ADHD groups differed from the control group</p> <p>Mean RT: No difference between the three groups</p> <p>SD of RT: 7a ADHD group was significantly more variable in RT than the 7p ADHD group and the control group, which did not differ</p>
Kieling et al. [2006]	No controls tested 7-repeat grouping 26 ADHD with at least one 7-repeat allele 64 ADHD with no copy of the 7-repeat allele	CPT—test of sustained attention and response inhibition	<p>7-repeat grouping</p> <p>Commission errors: 7p ADHD group made significantly more commission errors than the 7a ADHD group</p> <p>Omission errors: No significant difference between the two ADHD groups</p> <p>4-repeat grouping</p> <p>Commission errors: Non-4/4 ADHD group made significantly more commission errors than the 4/4 ADHD group</p> <p>Omission errors: Non-4/4 ADHD group made significantly more omission errors than the 4/4 ADHD group</p>
Barkley et al. [2006]	46 ADHD with at least one 7-repeat or higher allele 30 ADHD with 2 copies of 6 or fewer repeats (no 7-repeat) 26 controls with at least one 7-repeat or higher allele 14 controls with 2 copies of 6 or fewer repeats (no 7-repeat)	Adolescent testing Gordon Diagnostic System—a CPT-like task measuring commission and omission errors Matching Familiar Figures Test-20 (MFFT)—a test of impulse control Wisconsin Card Sort Task (WCST)—a test of higher executive functions including abstract reasoning and problem solving measuring total number of errors, perseverative errors, categories successfully achieved	<p>There were no significant main effects involving genetic grouping on any of the measures of any of the tasks, at either adolescent or adult testing. When the participants were grouped into those with at least one copy of the 7-repeat allele with those with no copy of the 7-repeat allele, again, no significant differences were found</p>

Adult testing
 Gordon Diagnostic System—a CPT-like
 task—Cancellation task
 and omission errors
 Card playing test—a test of response
 perseveration and/or a diminished
 sensitivity to punishment measuring number
 of cards played and earnings

CPT = Continuous Performance Task; 7p = 7-repeat allele present; 7a = 7-repeat allele absent; RT = reaction time; SD of RT = standard deviation of reaction time; MFFT = Matching Familiar Figures Test.

Apparatus and Procedure

Participants performed the Fixed and Random versions of the SART, presented on a laptop computer [Robertson et al., 1997]. In the Fixed version, a repeating fixed sequence of digits (1–9) was presented. In the Random version, the digits appeared in a pseudorandom order. A single digit appeared on the screen for 313 msec; a mask was then presented for 125 msec, after which a response cue (a bold cross) appeared for 63 msec, followed by a second mask for 375 msec and a fixation cross for 563 msec. The total inter-stimulus interval was 1439 msec (digit onset to digit onset). Participants were instructed to respond, using a button press, to every digit (go-trial) except ‘3’ (no-go trial). They were asked to respond when the response cue appeared on screen 125 msec after the digit was extinguished, or 438 msec from the start of the trial. The response cue was used to limit the impulsive response style of the ADHD children and to reduce any speed/accuracy trade-offs. Both the Fixed and Random versions of the SART consisted of 225 trials, representing 25 runs of the 1–9 sequence, each lasting approximately 5.5 min. The presentation of the tasks was counterbalanced across participants.

Data Analysis

Errors of *commission* (responses made on digit 3) and *omission* (non-responses on every other digit) and the *mean* of the RTs on the go-trials were calculated.

Sensitivity to the no-go “3” target (d') and response bias (*criterion*) measures were calculated using simple choice (yes/no) signal detection theory.¹ A hit was characterized as a correct no-go response, a miss was a commission error, a false alarm was an omission error and a correct rejection was a correct go response. The hit rate was determined by calculating the number of hits and dividing this by the addition of the number of hits and the number of misses. The false alarm rate was determined by calculating the number of false alarms and dividing this by the addition of the number of false alarms and the number of correct responses. The false alarm and hit rates were corrected to account for floor and ceiling effects using the $[1/(2 \times 200)]^2$ and $[1 - 1/(2 \times 25)]^3$ standard corrections. To calculate d' , a z -transform of the false alarm rate was subtracted from the z -transform of the hit rate. To calculate the criterion, -0.5 was multiplied by the addition of the z -transforms of the hit and false alarm rates. d' represents a person's sensitivity to stimulus identity: the higher the d' value, the better the discrimination between a target and a non-target. d' combines the data of the omission and commission errors into one metric, thus providing a measure of a person's sensitivity to the stimuli. According the signal detection theory, the criterion is independent of d' and represents the person's bias in response: as the bias to respond “yes that was a target” to a stimulus increases, the criterion approaches 0 and an unbiased observer will have a criterion of 1.

The sequence of 225 RTs per SART type was analyzed using a FFT, following the methodology of Johnson et al. [2007a, b]. Grand average FFT spectra were also calculated per group for descriptive purposes (see Figs. 1 and 2). A detailed description of data preparation and the procedures for derivation of the FFT spectra can be found in Johnson et al. [2007b].

Data preparation for FFTs. To calculate the FFTs, the RTs for the digit 3 and RTs of less than 100 msec were linearly

¹Please refer to Macmillan NA, Creelman CD. 1991. Detection Theory: A User's Guide. New York: Cambridge University Press for an explanation of signal detection theory.

²Where 200 is the maximum number of false alarms in the SART.

³Where 25 is the maximum number of hits in the SART.

TABLE II. Information on the ADHD and Control Children

Group	ADHD	Control
Number	68	60
Age (mean, SD)	11.4 (2.3)	11.8 (3.2)
IQ (mean, SD)	93.3 (13.9)*	108.5 (13.6)
Left-handers	11	2
DSM-IV Combined Type/Hyperactive-Impulsive/Inattentive diagnosis	57/4/7	
Oppositional defiant disorder co-morbidity	37	
Conduct disorder co-morbidity	10	
Conners' ADHD Index (mean, SD)	77.9 (6.4)*	45.3 (5.7)
Conners' Hyperactive Subscale (mean, SD)	83.6 (8.0)*	48.6 (7.6)
Conners' Restless/Impulsive Subscale (mean, SD)	81.2 (6.8)*	47.1 (6.6)
At least one copy of the 7-repeat allele of DRD4 VNTR	28	15
Zero copies of the 7-repeat allele of DRD4 VNTR	40	45
No. included in FFAUS analysis	58	59
No. included in SFAUS analysis	55	58

ADHD = Attention Deficit Hyperactivity Disorder; IQ = intelligence quotient; SART = Sustained Attention to Response Task; FFAUS = Fast Frequency Area Under the Spectra; SFAUS = Slow Frequency Area Under the Spectra.

*Significant difference between ADHD and controls; alpha level set at 0.05.

TABLE III. Frequencies and Percentages of DRD4 Alleles for 68 Children With ADHD and 60 Control Children

DRD4 alleles	2	3	4	7	8	Total
ADHD frequency	8	5	91	31	1	136
ADHD percentage	6%	4%	67%	23%	1%	100%
Control frequency	5	13	82	20	0	120
Control percentage	4%	11%	68%	17%	0%	100%

interpolated from the immediately preceding and following RTs. For the fast-frequency area under the spectra (FFAUS), individual RT data were detrended, subtracting out any linear components.

Derivation of FFT Spectra. The RT data were analyzed according to Welch's averaged, modified periodogram method. The RT data were analyzed over the entire trial (225 data points per individual). The time-series was first divided into 7 segments of 75 data points, with an overlap of 50. Each segment was Hamming-windowed and zero-padded to length 450.⁴ The FFT was then calculated for each segment. The FFT for each segment was averaged across the seven segments to provide a spectrum per individual. All RT data points were represented in this analysis, due to the 50 data point overlap. Any segments of 75 data points where there were over 10 errors of omission (not necessarily occurring together) were excluded in the FFT. Subsequently a small number of participants were excluded (see Table II).

By calculating the area under the spectrum (AUS) over a broad band of interest, the power (overall variance) in the RT signal may be measured. Information contained within the original RT series remains after the FFT. If the power over the entire frequency range is integrated, this will equate to the overall variance in the data. Consistency and distinctiveness of a particular RT pattern is measured by the peak power at a particular point in the spectrum. Healthy adult control subjects often show a slowing in RT on digit 1 relative to digits 9 and 2 in preparation for the upcoming no-go response on the fixed SART. If this average pattern is consistently reproduced

on every 1–9 sequence, a peak in the spectra at 0.0772 Hz is found (reciprocal of 9 digits \times 1.439 sec inter-stimulus interval; see dotted line in Fig. 1). This peak was used as a marker to divide the variability into the Fast Frequency and Slow Frequency Area under the Spectra.

The *Fast-Frequency Area Under the Spectra* (FFAUS) encompassed all sources of variability faster than once per SART cycle (0.0772 Hz; area under curve to the right of dotted line in Figs. 1 and 2). Trial-to-trial or moment-to-moment variability was captured in this calculation. The *Slow Frequency AUS* (SFAUS) encompassed all sources of variability slower than once per SART cycle (area under curve to the left of dotted line in Figs. 1 and 2). Variability that occurred over any time period greater than one SART cycle was captured in this calculation. To ensure that all low frequencies were encompassed in the SFAUS, the time series was not divided into segments. Any RT time series where there were greater than five errors of omission in a row were excluded in the FFT for the SFAUS measure (see Table II). The data were not detrended in the SFAUS analysis, allowing an analysis of the linear components of the RT variation.

Statistics

All dependent variables were calculated per participant. All measures were analyzed in a Diagnosis (ADHD vs. control) by SART (Fixed vs. Random) by Genotype (7-present vs. 7-absent) three-way mixed factorial ANOVA design. The alpha level was set at 0.05.

RESULTS

There was a significant association between possession of the 7-repeat allele and diagnosis [$\chi^2(1) = 3.739$, $P < 0.040$], with more of the children with ADHD in possession of the 7-repeat allele (28 out of 68) than the control group (15 out of 60).

⁴Please refer to Oppenheim AV, Schafer RW, Buck JR. 1999. Discrete-time signal processing. New Jersey: Prentice Hall for an explanation of the steps involved in time-series analysis, including Hamming-windows and zero-padding.

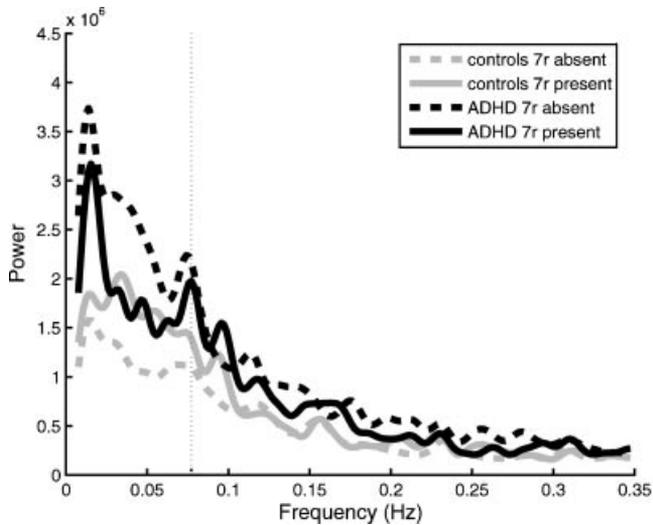


Fig. 1. Grand average of the fast Fourier transform (FFT) of the mean response time (RT) data on the Fixed Sustained Attention to Response Task (SART) for the children with attention deficit hyperactivity disorder (ADHD) and control children with at least one copy of the 7-repeat allele of the dopamine receptor D4 (DRD4) variable number of tandem repeats (VNTR; 7r present) and with no copies of the 7-repeat allele (7r absent). The Y-axis represents the power of periodic changes in RT data. The X-axis represents the different temporal frequencies, in Hertz (Hz). The dotted line represents the point dividing the measures of slow and fast frequency variability. It is at 0.0772 Hz (one SART cycle), the reciprocal of $9 \text{ digits} \times 1.439 \text{ sec}$ inter-stimulus interval of the SART. Grand average spectra were calculated per group using the FFT function in MatLab, 2006b (The MathWorks, Natick, MA).

Commission Errors

The ADHD group (mean 10.8, SD 6.3) made significantly more commission errors than the control group (mean 7.5, SD 5.4), [$F(1,124) = 19.626$, $P < 0.001$]. Both groups made more errors on the Random SART (mean 12.7, SD 5.7) than on the Fixed SART (mean 5.7, SD 4.2), [$F(1,124) = 216.279$, $P < 0.001$]. There was no significant main effect or interaction involving Genotype.

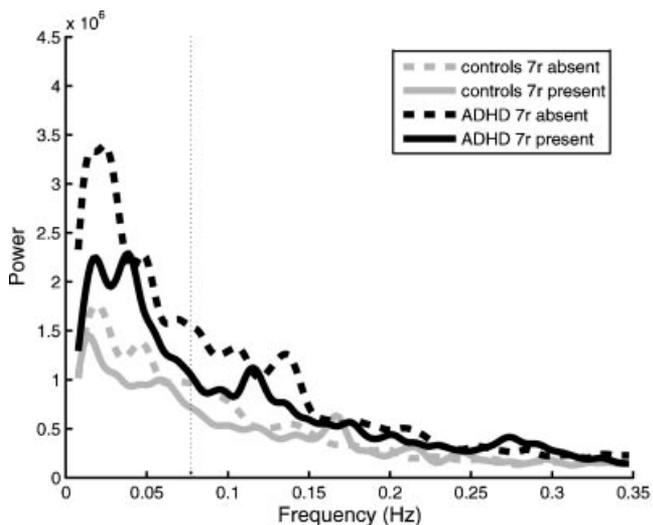


Fig. 2. Grand average of the fast Fourier transform (FFT) of the mean response time (RT) data on the Random Sustained Attention to Response Task (SART) with the same participants as per Figure 1.

Omission Errors

No main effect of Genotype was found, however a significant main effect of Diagnosis was further explained by a significant Diagnosis by Genotype interaction, [$F(1,124) = 5.317$, $P < 0.023$] (see Fig. 3). The 7-absent ADHD group (mean 14.7, SD 15.8) made significantly more omission errors than the 7-present ADHD group (mean 9.9, SD 10.3; $P < 0.05$). The 7-absent ADHD group made significantly more omission errors than the 7-absent control group (mean 4.9, SD 6.3; $P < 0.001$). There was no significant difference in the number of omission errors made between the 7-absent and 7-present (mean 9.1, SD 9.8) control groups ($P > 0.05$). There was no significant difference in the number of omission errors made by the 7-present ADHD and the 7-present control groups. The high number of omission errors made by the 7-absent ADHD group was driving this interaction. There was no significant difference between the number of omission errors made in the Fixed and Random SARTs.

Mean RT

There was no significant difference in mean RT between the ADHD (mean 481 msec, SD 113) and control (mean 517 msec, SD 121) groups. There was no significant difference in mean RT between the 7-absent (mean 488 msec, SD 121) and 7-present (mean 510 msec, SD 110) groups. There was no significant difference in mean RT between the Fixed (mean 490 msec, SD 111) and the Random SARTs (mean 508 msec, SD 123). There were no significant interactions.

Fast Frequency Area Under the Spectra (FFAUS)

The ADHD group (mean 577,623; SD 372,259) was significantly more variable in moment-to-moment fast variability than the control group (mean 386,494; SD 274,455), [$F(1,124) = 19.626$, $P < 0.001$] (see Fig. 4). There was no significant difference in fast frequency variability between the Fixed and Random versions of the SART. There was no significant difference between the 7-absent and 7-present Genotype groups and no significant interaction between Diagnosis and Genotype [$F(1,113) = 1.680$, $P > 0.198$].

Omission errors

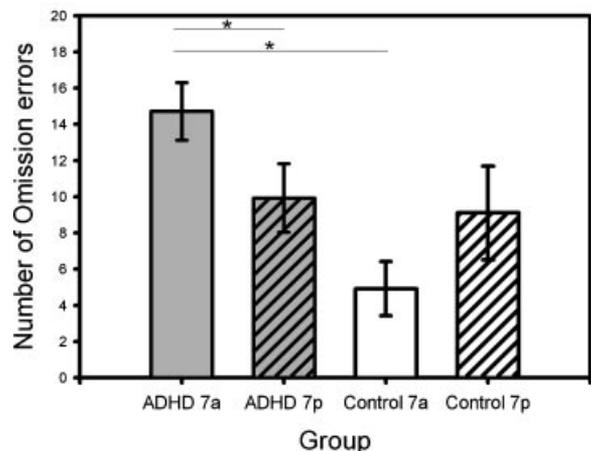


Fig. 3. Mean number of omission errors made in the Sustained Attention to Response Task (SART) by the children with attention deficit hyperactivity disorder (ADHD) and control children, divided into those with at least one copy of the 7-repeat allele of the dopamine receptor D4 (DRD4) variable number of tandem repeats (VNTR; ADHD $n = 28$; control $n = 15$) and those with no copies of the 7-repeat allele (ADHD $n = 40$; control $n = 45$).

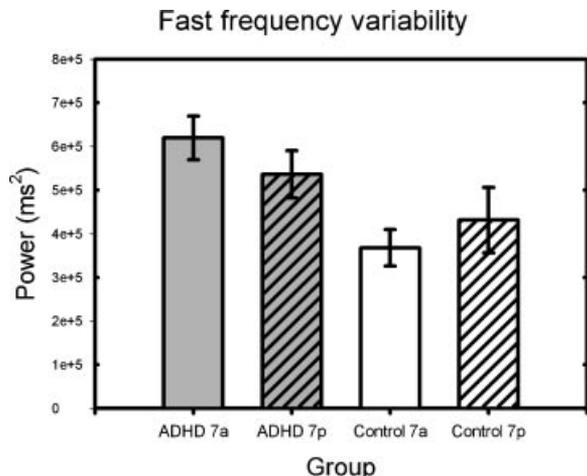


Fig. 4. Mean power of the fast frequency area under the spectra (FFAUS), encompassing all sources of variability faster than once per Sustained Attention to Response Task (SART) cycle (area under curve to the right of dotted line in Fig. 1), for the children with attention deficit hyperactivity disorder (ADHD) and control children, divided into those with at least one copy of the 7-repeat allele of the dopamine receptor D4 (DRD4) variable number of tandem repeats (VNTR; ADHD n = 27; control n = 14) and those with no copies of the 7-repeat allele (ADHD n = 31; control n = 45).

Slow Frequency Area Under the Spectra (SFAUS)

No Genotype main effect was found, however a significant Diagnosis main effect was further explained by a significant Diagnosis by Genotype interaction, [$F(1,109) = 6.581, P < 0.012$] (see Fig. 5). The 7-absent ADHD group (mean 789, SD 619) was significantly more variable in the slow frequency domain than the 7-present ADHD group (mean 495, SD 479; $P < 0.010$). The 7-absent ADHD group was significantly more variable than the 7-absent control group (mean 318, SD 246; $P < 0.001$). There was no significant difference in the slow frequency variability of the 7-absent and 7-present (mean 451, SD 576) control groups ($P > 0.05$). There was no significant

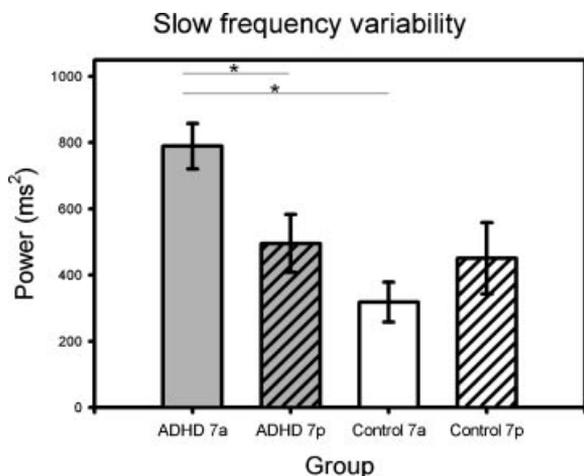


Fig. 5. Mean power of the slow frequency area under the spectra (SFAUS), encompassing all sources of variability slower than once per sustained attention to response task (SART) cycle (area under curve to the left of dotted line in Fig. 1), for the children with attention deficit hyperactivity disorder (ADHD) and control children, divided into those with at least one copy of the 7-repeat allele of the dopamine receptor D4 (DRD4) variable number of tandem repeats (VNTR; ADHD n = 21; control n = 14) and those with no copies of the 7-repeat allele (ADHD n = 34; control n = 44).

difference in the slow frequency variability of the 7-present ADHD and the 7-present control groups. The significantly greater slow variability in RT of the 7-absent ADHD group drove this interaction. There was no significant difference between the slow variability in RT and the Fixed and Random SARTS.

d'

No Genotype main effect was found, however a significant Diagnosis main effect was further explained by a significant Diagnosis by Genotype interaction, [$F(1,124) = 7.058, P < 0.009$] (see Fig. 6). The d' of the 7-absent ADHD group (mean 1.7, SD 1.1) was significantly lower than that of the 7-present ADHD group (mean 2.3, SD 1.1; $P < 0.05$). d' of the 7-absent ADHD group was significantly lower than that of the 7-absent control group (mean 2.8, SD 0.9; $P < 0.001$). There was no significant difference in d' between the 7-absent and 7-present (mean 2.5, SD 1.1) control groups. There was no significant difference in d' between the 7-present ADHD and the 7-present control groups. The low sensitivity to stimulus identity (low d') of the 7-absent ADHD group drove this interaction. A SART main effect was also found, [$F(1,124) = 124.125, P < 0.001$]. d' for the Fixed SART (mean 2.8, SD 1.0) was significantly higher than for the Random SART (mean 1.9, SD 1.0), suggesting that sensitivity to the stimuli was greater during the Fixed compared with the Random SART, which most likely reflects the predictability of the stimuli in the Fixed SART.

Criterion

There was no significant Diagnosis or Genotype main effect or interaction. The criterion of the 7-absent ADHD (mean 0.8, SD 0.4), the 7-present ADHD (mean 0.8, SD 0.4), the 7-present control (mean 0.7, SD 0.4) and 7-absent control (mean 0.7, SD 0.4) groups did not differ significantly. A SART main effect was found, [$F(1,124) = 156.083, P < 0.001$]. The criterion for the Fixed SART (mean 0.5, SD 0.3) was significantly lower than for the Random SART (mean 1.0, SD 0.3), suggesting all participants shared a similar response bias, in that they were more readily responding affirmatively to the target during the Fixed SART, compared with the Random SART.

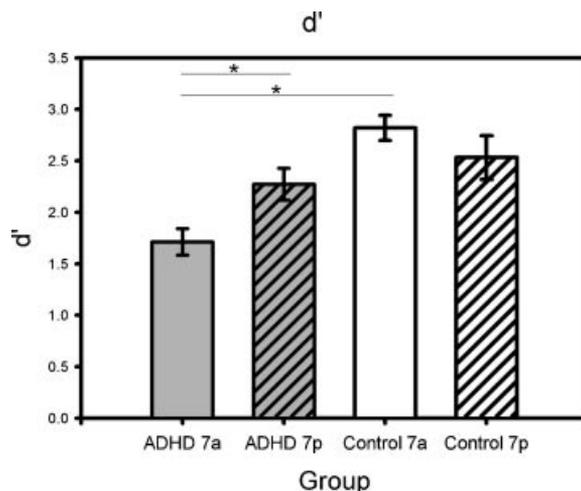


Fig. 6. d' results of the children with attention deficit hyperactivity disorder (ADHD) and control children, divided into those with at least one copy of the 7-repeat allele of the dopamine receptor D4 (DRD4) variable number of tandem repeats (VNTR; ADHD n = 28; control n = 15) and those with no copies of the 7-repeat allele (ADHD n = 40; control n = 45).

DISCUSSION

This study examined the influence of the 7-repeat allele of the DRD4 VNTR on neurocognitive performance in ADHD, utilizing time-series analyses of reaction time data for the first time. Across two tasks of sustained attention, we found that the 7-absent ADHD group performed significantly more poorly in terms of the number of omission errors, the slow frequency variability and sensitivity to discriminating between the target and non-target stimuli compared with the 7-present ADHD and the control groups, all of which did not differ significantly. We suggest that drifting sustained attention, mediated by underlying low arousal levels, gives rise to heightened omission errors and slow frequency variability and decreased sensitivity to stimulus identity (d'). The counter-intuitive finding of relative deficits in 7-repeat allele-absent children with ADHD, even though the 7-repeat allele is significantly associated with ADHD clinical status, has previously been reported (see Table I). Performance in terms of commission errors and moment-to-moment fast frequency variability—measures which we have argued reflect the top-down cortical control of attention [Johnson et al., 2007a,b]—was not modified by DRD4 genotype: for both measures, children with ADHD were impaired relative to controls. This dissociation between the measures that represent moment-to-moment top-down attention control and gradual drifting of sustained attention, according to the presence or absence of the 7-repeat allele in ADHD, suggests that the 7-absent group may represent a subgroup with a specific deficit in drifting sustained attention and arousal. This novel hypothesis derives directly from the sensitivity of the time-series analysis and highlights the utility of a componential approach to reaction time variability. That the ADHD children with the 7-repeat allele performed comparably with controls suggests that other genetic and non-genetic factors may also be involved in conferring risk to ADHD.

Interestingly, we did not find a main effect of DRD4 genotype on the neurocognitive performance of the healthy control children. Previous studies have reported discrepant results regarding the cognitive control of healthy children and adults with respect to their DRD4 genotype. Fossella et al. [2002] showed a modest effect of the 4-repeat allele on measures of executive conflict resolution in healthy adults, with those carrying the 4-repeat having poorer neurocognition than those who were homozygous for either the 2- or 7-repeats. Congdon et al. [2007] showed that adults who carried the 7-repeat allele had poorer response inhibition, as measured using the stop-signal task, than those without the allele. A reported interaction between eye-blink response, attentional flexibility and possession of at least one copy of the 7-repeat [Dreisbach et al., 2005] was not replicated in a larger sample size [Muller et al., 2007]. Froehlich et al. reported an interaction between possession of the 7-repeat allele and poorer spatial working memory. Interestingly, in boys alone, increased blood lead levels correlated with poorer performance on rule learning and reversal and spatial span in those lacking a copy of the 7-repeat allele [Froehlich et al., 2007]. The lack of a main effect of DRD4 genotype on the cognitive performance of the control children in the present study may have been due to low power. The calculation of the effect sizes associated with DRD4 genotype for omission errors, slow variability and d' (signal detection) in control children yielded Hedge's g scores of 0.56, 0.37 and 0.31, respectively. We estimate that sample sizes of 80, 184 and 258 (one-tailed) would be required to attain significant differences between the 7-absent and 7-present control group for errors of omission, slow variability and d' , respectively.

The results of the current study show that the effects of the DRD4 VNTR are conditional upon diagnostic status and that the effects are quite specific in terms of drifting

sustained attention (omission errors, slow frequency variability, reduced sensitivity). The 7-absent ADHD subgroup may be associated with a range of other genetic (and non-genetic) abnormalities that together confer risk for deficits in drifting attention. This deficit may occur in addition to more general deficits in top-down control of attention, here reflected in the increased number of commission errors and moment-to-moment variability in RT (FFAUS) that characterize the ADHD group generally. Although drifting sustained attention and reduced sensitivity to stimuli [Oades, 2000; Johnson et al., 2007b] is a feature of the ADHD group as a whole, our results demonstrate that this deficit is particularly pronounced in those without the 7-repeat allele. Stratifying large collaborative ADHD samples according to this phenotype may provide the necessary power required to examine gene-gene interactions in this subgroup and thus clarify hypotheses regarding the nature of other genetic abnormalities in this group.

The functional role of the variants of the DRD4 VNTR remains unclear. The 7-repeat allele is associated with a diminished response of the dopamine D4 receptor to dopamine [Asghari et al., 1995] (although see Kazmi et al. [2000]) and a significantly larger amount of MPH is needed to achieve symptom normalization in children with ADHD with at least one copy of the 7-repeat allele, suggesting a poorer response to MPH administration [Hamarman et al., 2004]. Based on these reports, one might expect that children with ADHD with at least one copy of the 7-repeat allele (and therefore a blunted response to dopamine) would demonstrate deficits in the measures of top-down control of attention, as dopamine is thought to be a key neurotransmitter involved in executive attention [Posner and Rothbart, 2006] and maintenance of performance on CPTs [Levy and Hobbes, 1996]. The findings from this study, however, suggest that there is no specific effect of the DRD4 VNTR on the measures of top-down attention control (commission errors and moment-to-moment variability in RT). Altered functioning in some other dopaminergic mechanisms may be contributing to the ADHD group's poor performance on these measures.

The findings from this study suggest that an absence of the 7-repeat allele is associated with drifting sustained attention in ADHD that may be potentially linked to diminishing arousal. Noradrenaline is a key neurotransmitter of the alerting attentional system [Posner and Rothbart, 2006]. Animal work with behaving monkeys suggests that the prefrontal cortical (PFC)-locus coeruleus (LC) noradrenaline system is extremely sensitive to attentional state, with LC neurons responding poorly to targets and well to distractors during drowsy states [Rajkowski et al., 1998]. We have recently shown that errors of omission and slow frequency variability measures in medication naive children with ADHD are not changed by a 6-week treatment with MPH [Johnson et al., 2008]. In contrast, robust improvement with MPH was seen for errors of commission and fast frequency variability, suggesting that the moment-to-moment top-down control of executive attention may be more conducive to catecholaminergic (both dopamine and noradrenaline) manipulation than the omission error and slow frequency variability measures.

These findings lead us to speculate that the D4 receptor may play a role in controlling the release of NA in the prefrontal cortex. NA receptors are widely located within the prefrontal cortex and NA is believed to be heavily involved in attentional capabilities [Arnsten and Li, 2005]. On NA pre-junctional neurons, the alpha-2 autoreceptor controls the release of both NA and dopamine into the synaptic cleft [Starke, 2001; Devoto et al., 2004] through the cAMP second messenger system. Whilst D4 receptors appear to be predominantly located on GABA and glutamate neurons in the frontal cortex, it has also been reported that D4 receptors are located on tyrosine hydroxylase (TH) positive neurons [Svingos et al.,

2000]. It remains to be elucidated if these TH positive neurons are dopaminergic or noradrenergic. One can speculate, however, that if D4 receptors were to be located pre-synaptically on NA neurons that it may play a similar autoreceptor role to the alpha-2 autoreceptor. Both of these receptors share a common signaling pathway in that they negatively couple to adenylate cyclase. Specifically, we speculate that the dopamine acting on the D4 receptor on pre-synaptic NA neurons will reduce cAMP concentrations, and this action may lead to a decrease in the release of NA. A decrease of NA in the prefrontal cortex may weaken activity within the LC, thus impacting upon arousal levels. Those children with ADHD *without* the 7-repeat allele may be more greatly affected by this D4 autoreceptor role on the release of NA, thus making them *more* susceptible to decreasing arousal levels. Ultimately this may manifest in increased omission errors, heightened slow frequency variability and reduced target sensitivity. In contrast, the children with ADHD and at least one copy of the 7-repeat may have a diminished second messenger response to dopamine, causing less down-regulation of NA release via the D4 autoreceptor, thus supporting relatively better attentional performance. Although this hypothesis may account for the cognitive deficit of the 7-absent group, it does not explain the mechanism by which the 7-repeat allele might confer risk to ADHD.

In conclusion, the 7-absent subgroup of children with ADHD made significantly more omission errors, was significantly more variable in the slow frequency domain and demonstrated less sensitivity to discriminating between the target and non-target stimuli compared with the 7-present ADHD sub-group. Both ADHD groups made more commission errors and were more variable in moment-to-moment fast frequency RT than the control groups; DRD4 allele status played no significant role on these measures. DRD4 allele status did not account for significant variance in the performance of the healthy control children. Absence of the 7-repeat allele in children with ADHD is therefore associated with specific neurocognitive impairment associated with drifting sustained attention.

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