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ORIGINAL ARTICLE

Reaction time variability and attention-deficit/hyperactivity disorder: is increased reaction time variability specific to attention-deficit/hyperactivity disorder? Testing predictions from the default-mode interference hypothesis

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Abstract
Increased reaction time variability (RTV) is one of the most replicable behavioral correlates of attention-deficit/hyperactivity disorder (ADHD). However, this may not be specific to ADHD but a more general marker of psychopathology. Here we compare RT variability in individuals with ADHD and those with other childhood internalizing and externalizing conditions both in terms of standard (i.e., the standard deviation of reaction time) and alternative indices that capture low-frequency oscillatory patterns in RT variations over time thought to mark periodic lapses of attention in ADHD. A total of 667 participants (6–12 years old) were classified into non-overlapping diagnostic groups consisting of children with fear disorders ($n=91$), distress disorders ($n=56$), ADHD ($n=103$), oppositional defiant or conduct disorder (ODD/CD; $n=40$) and typically developing controls (TDC; $n=377$). We used a simple two-choice reaction time task to measure reaction time. The strength of oscillations in RTs across the session was extracted using spectral analyses. Higher RTV was present in ADHD compared to all other disorder groups, effects that were equally strong across all frequency bands. Interestingly, we found that lower RTV to characterize ODD/CD relative to TDC, a finding that was more pronounced at lower frequencies. In general, our data support RTV as a specific marker of ADHD. RT variation across time in ADHD did not show periodicity in a specific frequency band, not supporting that ADHD RTV is the product of spontaneous periodic lapses of attention. Low-frequency oscillations may be particularly useful to differentiate ODD/CD from TDC.

Keywords Reaction time variability · State regulation · Attentional lapses · Oppositional defiant disorder · Conduct disorder

Introduction

Individuals with attention-deficit/hyperactivity disorder (ADHD) display abnormally high levels of intra-individual reaction time variability (RTV) when performing laboratory tasks (Castellanos and Tannock 2002). This association has been extensively replicated, appears to be genetically based and is found on a variety of cognitive tasks (Kuntsi and Klein 2012). However, the meaning and specificity of RTV in ADHD remain unclear (Kofler et al. 2013). On the one hand, it has been argued that elevated RTV is caused by ADHD-specific neuropsychological processes (Sonuga-Barke and Castellanos 2007). On the other hand, it has been seen as a general marker of psychopathology found across many diagnostic groups (Karalunas et al. 2014).

Adopting the first position, Sonuga-Barke and Castellanos (2007) proposed the default-mode interference hypothesis. This hypothesis postulated that increased RTV in ADHD is a behavioral marker of spontaneous periodic lapses in attention due to the emergence of spontaneous default-mode brain activity during task performance. These lapses would have their effects interfering with attention control processes (Sonuga-Barke and Castellanos 2007), increasing intra-individual RTV. It was predicted that behaviorally this would manifest as occasional clusters of long reaction times (RTs)

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producing cycles of low-frequency oscillations in RT across time (Castellanos et al. 2005).

Traditionally, RTV is assessed by global summary measures, such as the standard deviation of RT (SDRT). Alternative analytical approaches have been employed to test whether RTV in ADHD is distributed differently than in controls in ways that might implicate specific cognitive processes. These include ex-Gaussian models (Hervey et al. 2006; Leth-Steensen et al. 2000; van Belle et al. 2015a, b) and other similar distributional approaches (Williams et al. 2007), the coefficient of variation (Klein et al. 2006), consecutive variance (Klein et al. 2006) and, more recently, diffusion models (Karalunas et al. 2014; Metin et al. 2013; Salum et al. 2014a, b). However, neither these approaches quantify the *periodic nature of fluctuations* in RT data nor can be used to test the default-mode interference hypothesis. For such analyses, the entire RT time series must be examined (Castellanos et al. 2005). In this analysis, the use of signal processing techniques such as fast Fourier or Morlet wavelet analysis to transform the time-series data into the frequency domain to estimate the power and amplitude of oscillations within specific frequency bands (Castellanos et al. 2005) is needed.

Using such an approach on data from an Eriksen flanker task Castellanos et al. (2005) reported that the greatest power to differentiate individuals with ADHD and controls in terms of RT variation was around 0.05 Hz (frequency range 0.02–0.07—i.e., oscillatory peaks occurred roughly every 20 s). It is worth mentioning that differences between ADHD and control participants in frequency bands below 0.07 Hz have also been reported by some investigators (Adamo et al. 2012; Broyd et al. 2009; Di Martino et al. 2008; Johnson et al. 2007; Karalunas et al. 2012a), but not others (Geurts et al. 2008; Johnson et al. 2008). Studies using event rates that allowed a wider frequency range to be sampled also detected higher variability in faster frequencies than 0.07 Hz (Adamo et al. 2012; Helps et al. 2011; Johnson et al. 2007, 2008; Karalunas et al. 2012b). One study found that frequencies as high as 0.20–0.26 Hz were most strongly related to ADHD and that these differences were familial in nature (Helps et al. 2011). Nonetheless, the range of approximately 0.05 Hz, as shown by Castellanos et al. (2005), has been the most well replicated and used in research for the purpose of investigating the default-mode interference hypothesis. However, some previous works in the literature, including two meta-analysis (Karalunas et al. 2012b, Kofler et al. 2013), have shown that RTV in ADHD may not be unique to any specific power spectrum, raising additional concerns on the default-mode interference hypothesis.

Despite the advanced literature on the topic, it is worth to mention that previous studies of RT oscillations have some important limitations: (1) Most studies have been restricted to clinical samples and so results may be subject to referral biases (Biederman et al. 2005; Gillberg et al. 2004; Maniadaki et al. 2006); (2) studies derived from medicated referred samples may be subject to important biases concerning the well-documented effects of medications on RTV in ADHD (Bron et al. 2014); (3) even though few studies compared ADHD to other clinical groups and others have compared different indices of RTV in ADHD, no studies so far have compared *low-frequency periodicity* effects in other common comorbid mental disorders such as oppositional defiant disorder/conduct disorder (ODD/CD) or emotional disorders (anxiety or depression); (4) the majority of studies have used relatively complex tasks which means that an artificial reconstruction of the time series using statistical methods is necessary; and (5) for periodicity analyses, only one study (Helps et al. 2011) took into account that the power spectrum of RT data decreases with increasing frequency, i.e., it exhibits 1/*f* noise (Gilden et al. 1995). This might bias data analysis toward identifying power peaks at lower frequencies where none really exists (Helps et al. 2011).

Here we report a study of RTV generated using a simple two-choice reaction time task in a large non-referred sample of non-medicated children assessed for the presence of mental disorders. Previous studies from our research team have also investigated information processing and inhibitory control deficits in this community sample (Salum et al. 2014a, b). This study found poorer processing efficiency to be a specific finding of ADHD and also showed evidence that faster encoding and response style could be used as markers to differentiate ADHD from controls and from children with other symptomatic domains. For this current research, we selected four non-overlapping ('pure' or 'non-comorbid') groups of psychiatric psychopathologies (Fear, Distress, ADHD and ODD/CD) and a group of typically developing controls. We extracted both standard RT measures and those that estimated the strength of oscillations in time-series data in particular frequency domains to investigate the effects related to *periodicity*. Using a simple task to measure RT in a non-referred, non-medicated and non-comorbid sample, the current study addresses the limitations of the previous literature and aims to build upon previous findings to investigate the default-mode interference hypothesis. We hypothesized that (1) increased RTV will be found in non-referred cases of ADHD relative to controls and these effects will be specific to ADHD (i.e., not found in other common psychiatric disorders) and (2) that, consistent with the initial formulation of the default-mode interference hypothesis, time-series RTs in ADHD would be specifically characterized by greater power in specific low-frequency bands with the largest effects seen in around 0.05 Hz.

Methods

Participants

The sample is part of a large community-based study (Salum et al. 2015). The ethics committee of the University of São Paulo approved the study. We obtained written consent from parents of all participants and verbal assent from all children.

The screening phase of the study included children (6–14 years of age) from public schools situated close to research centers in two Brazilian cities: Porto Alegre and São Paulo. We screened 9937 parents using the *Family History Survey* (FHS) (Weissman et al. 2000). From this pool, we recruited two subgroups—one randomly selected ($n=958$) and one high-risk sample ($n=1524$). Selection of the high-risk sample involved a risk-prioritization procedure and was determined by FHS (Weissman et al. 2000), which was used to identify current and/or past history of psychiatric symptoms in the subject and in the subject's family members. This approach was conducted to identify individuals with current symptoms and/or a family history of specific disorders (Salum et al. 2015). Data for the current paper were drawn from 1993 participants (79.3%) with available data on the RT task. A total of 119 participants (4.7%) were excluded due to poor task compliance since RT measures could not be obtained for these children. Five non-overlapping groups (e.g., no comorbidity allowed, pure psychiatric diagnosis) were selected from the remaining sample of 1874 participants according to DSM-IV criteria. Thus, analysis was performed with 667 participants divided within the following groups: (1) *Typical developing controls* (TDC): no psychiatric disorder or any family history of ADHD ($n=377$); (2) *ADHD*—any subtype ($n=103$); (3) *Fear disorders*: separation and social anxiety disorder, specific phobia or agoraphobia ($n=91$); (4) *Distress disorders*: generalized anxiety disorder, depression (major or not otherwise specified) or post-traumatic stress disorder ($n=56$); and (5) *ODD or CD* ($n=40$). The criteria for group separation were adapted from previous research conducted by our research team which showed the empirically derived division of Fear, Distress and Externalizing groups well suited for the description of psychopathology as measured by the DAWBA bands (Martel et al. 2016). Considering the aims of the current study, the externalizing group was subdivided into ADHD and OCD/OD. Exclusion criteria were current use of any psychotropic medication ($n=48$; 2.6%), IQ below 70 ($n=36$; 1.9%), mania ($n=3$; 0.2%), pervasive developmental disorder ($n=9$; 0.6%), tics ($n=15$; 0.8%), eating ($n=8$; 0.5%), obsessive–compulsive ($n=5$; 0.3%) or psychotic disorders ($n=1$; 0.1%).

Psychiatric diagnosis Psychiatric disorders were diagnosed using the Development and Well-Being Assessment (DAWBA) (Goodman et al. 2000), a structured interview applied by trained lay interviewers. The DAWBA is a clinically valid tool for assessing childhood psychiatric disorders (Angold et al. 2012; Foreman et al. 2009), in which all questions are closely related to DSM-IV diagnostic criteria. The DAWBA was administered to biological parents in accordance with previously reported procedures (Goodman et al. 2000). A team of nine psychiatrists supervised by a senior child psychiatrist rated data from these interviews. Child probabilistic diagnosis was established using diagnostic probability bands (Goodman et al. 2000), which represent computer-generated categories based on answers to the DAWBA questions that inform the rater about the probability of a positive diagnosis ($\sim 0.1, \sim 0.5, \sim 3, \sim 15, \sim 50$ and $> 70\%$, coded as 0 [0.1%] to 5 [> 70%]). DAWBA bands have shown good concordances with clinician-rated diagnosis, with Kappas ranging between .4 and .7, sensitivities .4 and .8 and specificities .98 and .99 (Goodman et al. 2011).

Measures

Intelligence IQ was estimated using the Vocabulary and Block Design subtests of the Wechsler Intelligence Scale for Children, 3rd edition—WISC-III (Wechsler 2002) using the Tellegen and Briggs method (Tellegen and Briggs 1967) and Brazilian norms (Figueiredo 2001).

Two-Choice Reaction Time Task 2C-RT This task measures the ability to perform simple decision about the direction an arrow on the screen is pointing (Hogan et al. 2005). A total of 100 arrow stimuli were presented, half requiring left and half requiring a right button press. The inter-trial interval was 1500 ms, and stimulus duration was 100 ms.

Preparation of 2C-RT data For each participant and each trial, responses with latencies before 100 ms or scores higher than 3 SDs above the group mean were replaced by the group mean. These procedures have been previously used to prepare 2C-RT data in other RTV ADHD studies (Helps et al. 2011). In addition, the first three trials from each series, which tended to be aberrant, were discarded.

Statistical analysis

Classical analysis took into account the percentage of correct responses; RT data (RT mean and SDRT) were the dependent measures in a multivariate analysis of covariance (MANCOVA) and analyses of covariance (ANCOVA) with the group as the between-subject variable and with the site (Porto Alegre and São Paulo), sex, age and IQ as covariates.

Spectral analysis of 'periodic oscillations'

For frequency power analyses, task constraints (ISI 1500-ms and 150-s block) allowed us only to investigate frequencies from 0.013 to 0.33 Hz. For each subject, the spectral power of the RT series in each frequency band was obtained (Gescheider et al. 2005) and power within each frequency band was compared between groups using two approaches: *First,* we compared groups on theoretically defined frequency bands by summing power for four frequency bands: slow-5 (0.01–0.027 Hz), slow-4 (0.027–0.073 Hz), slow-3 (0.073–0.198 Hz) and slow-2 (0.198–0.25 Hz) (Buzsaki and Draguhn 2004; Penttonen and Buzsáki 2003). *Second,* power within each frequency band was compared between TDC and each clinical group using a *z* score statistics. To maintain the structure of the RT data series, missing responses were interpolated using a linear interpolation implemented in *R* ('fSeries'). Missing responses at the beginning or the end of the RT series were also replaced by the group mean. To remove the impact of response accuracy on the RT data series, errors were regressed out and unstandardized residuals used in subsequent analyses.

Differences in mean spectrum power were investigated using a mixed design 4 × 5 ANOVA with the band as a within-subject variable (4 levels: slow-5, slow-4, slow-3 and slow-2), and the group as a between-subject variable (5 levels: TDC, ADHD, Fear, Distress and ODD/CD). In addition to the theoretically defined levels, we analyzed the data across the whole continuum using *z* score statistics to compare TDC and each clinical group regarding power within each frequency band.

1/*f* modeling

In the 1/*f* analysis, for each subject's RT series, the following model was employed:

$$Spectral\ Power\ (f) = 1/f^{\alpha} + \beta$$

by using the spectral regression estimator of Geweke and Porter-Hudak (Gescheider et al. 2005) in which *f* refers to the frequency, α the decay parameter of 1/*f* (based on a log regression) estimated for each individual, and β the amplitude of a white noise component. We then contrasted the mean α between each group and the TDC using *t* tests. Estimated values of mean α for each subject were also used for correlations with measures of psychopathology.

Results

Group differences in demographics, psychopathology and traditional task variables are depicted in Table 1. Distress disorders had a higher proportion of females than the TDC group [$x^2(5) = 13.71$, $p = 0.018$; adjusted residuals = 2.7]. The ADHD group had significantly lower IQ than TDC [$F(5,702) = 3.14$, $p = 0.008$]. Groups did not differ significantly in age [$F(5,700) = 1.91$, $p = 0.09$].

Did individuals with ADHD have higher RTV in terms of RTSD then TDC and other diagnostic groups?

MANOVA demonstrated an effect of group [$F(12,1953) = 3.57$, $p < 0.001$, $\eta_p^2 = .021$] *on standard measures*—accuracy, mean RT and SRDT. ADHD showed higher SDRT than TDC, ODD/CD and Fear groups (Fig. 1, panel C). Furthermore, for accuracy, ADHD had a significantly lower number of correct responses than the TDC and Fear groups (Fig. 1, panel A). ODD/CD had a significantly lower mean RT if compared to the other groups (Fig. 1, panel B).

Did individuals with ADHD display a greater power of oscillations specifically on lower-frequency bands (slow-4; around 0.05 Hz frequency)?

The mixed design ANOVA was performed combining spectral power as commonly defined in the literature. In this analysis, there was a main effect of group [$F(4,657) = 16.75$, $p < 0.001$, $\eta_p^2 = 0.093$], a main effect of band [$F(3,1971) = 485.6$, $p < 0.001$, $\eta_p^2 = 0.425$] and band by group interaction [$F(12,1971) = 2.10$, $p = 0.014$, $\eta_p^2 = 0.013$]. Given the presence of the group by band interaction, between-group differences were performed in each band using Bonferroni adjustment. This analysis revealed that ADHD has higher spectrum power than all other groups across all frequency bands (except for differences from distress group in the slow-5 band, $p = 0.081$), whereas ODD/CD has lower spectrum power than distress and ADHD in slow-5; lower spectrum power than Fear, Distress and ADHD in slow-4; lower spectrum power than distress and ADHD in slow-3; and lower spectrum power than ADHD in slow-2 (Fig. 1, panel D).

In addition, power within each frequency band compared between TDC and each clinical group using a *z* score statistics, allowing the whole frequency continuum to be explored, with no need to specify theoretically defined frequency bands. Figure 2 shows the difference in power for each frequency band for each disorder. Concordant with our previous analysis individuals with ADHD displayed greater

Table 1 Psychiatric and demographic characteristics of typically developing controls and psychopathological groups

	TDC ($n=377$)		Fear ($n=91$)		Distress ($n=56$)		ADHD ($n=103$)		ODD/CD ($n=40$)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
DSM-IV diagnosis										
Separation	–	–	32	35.2	–	–	–	–	–	–
Specific phobia	–	–	50	54.9	–	–	–	–	–	–
Social phobia	–	–	14	15.4	–	–	–	–	–	–
PTSD	–	–	–	–	7	12.5	–	–	–	–
GAD	–	–	–	–	19	33.9	–	–	–	–
Major dep	–	–	–	–	26	46.4	–	–	–	–
Other dep	–	–	–	–	3	5.4	–	–	–	–
Undiff anx/dep	–	–	–	–	2	3.6	–	–	–	–
ADHD-C	–	–	–	–	–	–	26	25.2	–	–
ADHD-I	–	–	–	–	–	–	43	41.7	–	–
ADHD-H	–	–	–	–	–	–	19	18.4	–	–
ADHD NOS	–	–	–	–	–	–	15	14.6	–	–
ODD	–	–	–	–	–	–	–	–	29	72.5
CD	–	–	–	–	–	–	–	–	9	22.5
Other disruptive	–	–	–	–	–	–	–	–	3	7.5
Demographics										
Gender (male)	204	54.1	41	45.1	20	35.7	60	58.3	26	65.0
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Age (years)	9.49	1.91	9.56	1.93	10.21	1.96	9.50	1.74	9.75	2.02
IQ	105.6	16.09	101.2	16.96	101.1	17.17	99.99	17.06	101.6	13.35
SES (score)	20.72	4.68	20.15	4.21	19.25	4.76	20.64	5.26	19.40	4.75
Neuropsychology	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
2C-RT										
% Correct	78.7	13.7	78.0	14.3	77.8	17.1	72.0	14.7	75.6	14.5
Mean RT	484.0	110.6	504.4	110.2	491.0	94.2	500.7	104.1	445.0	101.7
SD RT	171.8	75.4	179.7	64.4	183.2	86.6	220.3	94.9	170.0	102.3
Spectrum power ($e10^4$)										
Slow-5	3.74	2.97	4.42	3.29	4.94	3.96	6.52	5.61	2.55	2.11
Slow-4	3.10	2.14	3.72	2.62	3.87	2.88	5.41	4.04	2.26	2.01
Slow-3	2.05	1.27	2.26	1.18	2.60	1.95	3.44	2.06	1.50	9.73
Slow-2	1.42	8.57	1.644	9.10	1.66	9.45	2.32	1.59	1.15	5.81

M mean, *SD* standard deviation, *SES* socioeconomic status, *IQ* intelligence quotient, *RT* reaction time, *2C-RT* two-choice RT task, *TDC* typically developing controls, *PTSD* post-traumatic stress disorder, *GAD* generalized anxiety disorder, *Undiff* undifferentiated, *anx* anxiety, *dep* depression, *ADHD* attention-deficit/hyperactivity disorder, *-C* combined, *-I* inattentive, *-H* hyperactive, *NOS* not otherwise specified, *ODD* oppositional defiant disorder, *CD* conduct disorder, *TDC* typically developing controls

power across all frequency bands compared to typically developing controls and other psychopathological groups (Fig. 2). Individuals with ODD/CD showed decreased power in specific frequency bands across the spectrum.

Supplementary analysis: taking 1/*f* noise into account

Frequency domain analyses showed that spectral power decreased as a function of increasing frequency, resembling 1/*f* noise (Fig. 3). To take account of this, a 1/*f* model was adjusted for each subject to determine whether the mean decay parameter (α) differed between groups. No group effects in this parameter were seen for Fear, Distress or ADHD groups (all p values higher than 0.05). In contrast, ODD/CD differed from TDC in the mean decay parameter (mean ODD/CD alpha compared to TDC, 0.31 vs. 0.24, respectively; $p=0.03$). This demonstrates that the decrease in power (as a function of frequency) of ODD/CD deviates from that seen in TDC. Therefore, differences between ODD/CD and TDC (that overall indicate a lower variability for ODD/CD) became less pronounced at higher frequencies. As

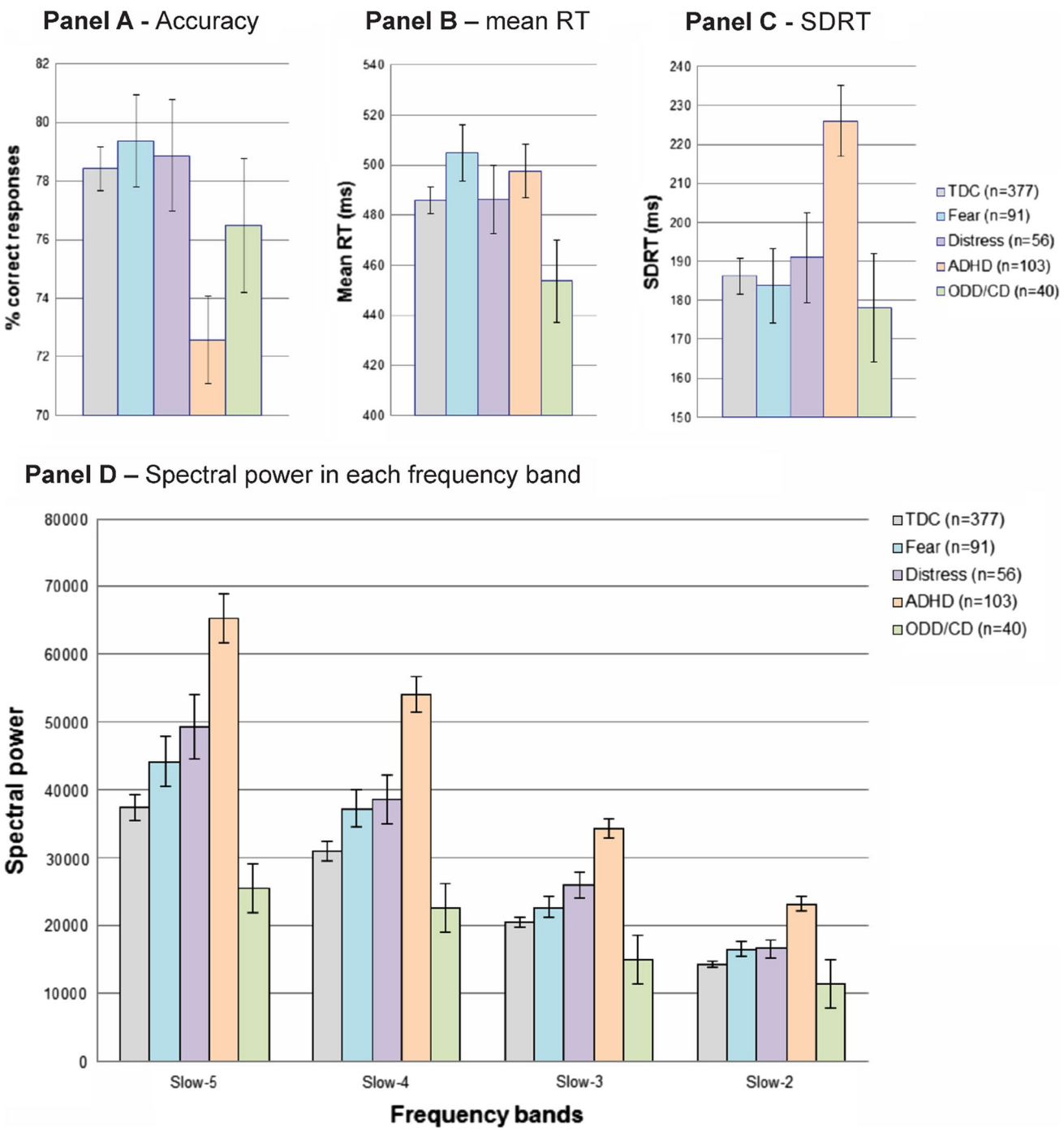

Fig. 1 Between-group differences in traditional parameters of the two-choice reaction time task and in power spectrum bands. *TDC* typically developing children; *ADHD* attention-deficit/hyperactivity disorder; *ODD/CD* oppositional defiant disorder/conduct disorder; *RT* reaction time; *SDRT* intra-subject standard deviation of the reaction time; *theoretically defined bands*: slow-5 (0.01–0.027 Hz), slow-4 (0.027–0.073 Hz), slow-3 (0.073–0.198 Hz) and slow-2 (0.198–0.25 Hz)

a supplemental analysis the alpha parameter was extracted from the model for each subject, and this parameter was used to compare levels of alpha power among oppositional and conduct DAWBA bands, an ordered categorical measure of psychopathology (Goodman et al. 2011). This allows us to have a more fine-grained measure that captures subthreshold manifestations of both ODD and CD. Using this analysis, no between-group differences emerged for alpha power among DAWBA bands for either ODD [$F(4,635) = 0.62$, $p = 0.65$] or CD [$F(6,635) = 0.50$, $p = 0.74$].

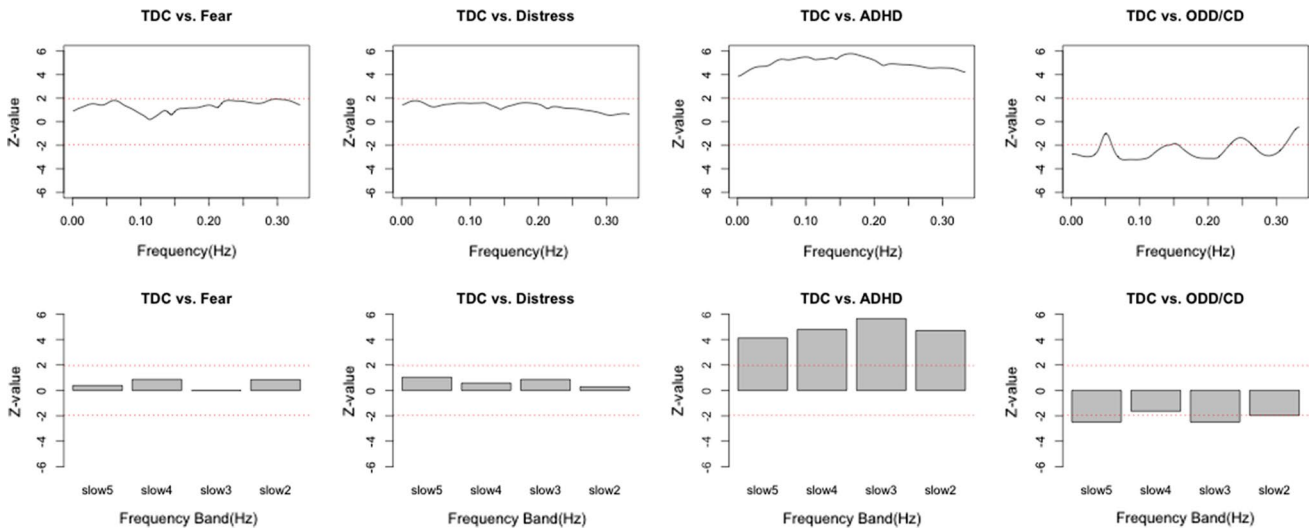

Fig. 2 Contrasts between each psychopathological group (Fear, Distress, ADHD and ODD/CD) versus typically developing children across all frequency bands (top panel) and clustered according to theoretically defined bands (bottom panel). Data are demonstrated in form of group subtractions. Note: *TDC* typically developing children; *ADHD* attention-deficit/hyperactivity disorder; *ODD/CD*, oppositional defiant disorder/conduct disorder. Top panel: Solid lines crossing the red dotted line (z scores higher than 1.96 and lower than −1.96) represent significant between-group differences in that specific part of the spectrum. Bottom panel: group differences between TDC and each group according to theoretically defined frequency bands: slow-5 (0.01–0.027 Hz), slow-4 (0.027–0.073 Hz), slow-3 (0.073–0.198 Hz) and slow-2 (0.198–0.25 Hz). Z value was Bonferroni corrected for 4 bands

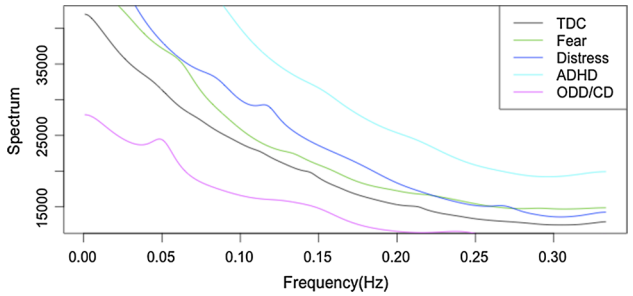

Fig. 3 Power spectrum in each group for each frequency in the 2-choice reaction time showing spectral power decreased as a function of increasing frequency, resembling 1/*f* noise. Note: *TDC* typically developing children; *ADHD* attention-deficit/hyperactivity disorder; *ODD/CD* oppositional defiant disorder/conduct disorder

Discussion

The current results extend previous research demonstrating that participants with ADHD had more variable RTs than TDC. Specifically, we observed that these effects occurred in non-referred unmedicated individuals without any psychiatric comorbidity and were specific to ADHD. No *periodicity* effects characterized ADHD in this sample, contradicting predictions from the default network interference theory.

The finding that RTV is a specific marker of ADHD psychopathology which was absent in other common psychiatric disorders such as ODD/CD or emotional disorders (anxiety or depression) is of particular interest in advancing our understanding of the specificity of pathophysiological mechanisms within childhood psychopathology (Kapur et al. 2012). Since clinical samples are highly comorbid, assessing a non-referred community sample allowed us to define subsamples without comorbidity to investigate the distinct contributions of various clinical presentations.

Using sophisticated time-series analyses to examine *periodicity* effects, we did gain some further insights into the nature of increased RTV in ADHD. The study shows that RTV in ADHD may be related to random/spontaneous rather than periodic fluctuations of attention. This is consistent with previous findings (Karalunas et al. 2012b and Kofler et al. 2013) and shows that the absence of confirmation of the default-mode interference hypothesis may not be attributed to limitations of the previous works, including referral bias and medication effects. The frequency domain analysis revealed that differences between ADHD and TDC occurred across the whole spectrum of frequency bands and were not specific to any subset of frequency bands. Evidence has been mixed with regard to this point, but several studies found differences between ADHD and controls in low frequency ranges (Adamo et al. 2012; Broyd et al. 2009; Di Martino et al. 2008; Johnson et al. 2007; Karalunas et al. 2012b) as well as at somewhat faster frequencies (periods less than 14 s) (Adamo et al. 2012; Helps et al. 2011; Johnson et al. 2007, 2008; Karalunas et al. 2012b). A meta-analysis also

found differences at both slow and fast frequency bands (Karalunas et al. 2012b). These data contradict the original default-mode interference hypothesis formulation which predicted periodic lapses in attention synchronized with fluctuations in brain activity believed to occur predominantly at low frequencies (Sonuga-Barke and Castellanos 2007). However, the recent application of sophisticated frequency domain analytical methods to extensive resting state multimodal data has demonstrated that the 1/*f* spectral property of BOLD intrinsic fluctuations likely reflects hemodynamic temporal blurring. Instead, when the underlying neural processes are deconvolved, the frequency response is flat throughout the measured frequency range from 0.0001 to 0.2 Hz (Fransson et al. 2007). Thus, the flat frequency curve of RT time series in ADHD may well be related to spontaneous neural fluctuations, which are also present throughout a broad frequency range and possibly impact attentional processes.

Interestingly and unexpectedly, we found that lower variability for ODD/CD relative to TDC became significantly less pronounced in higher frequencies. Therefore, lower-frequency bands may be of special importance for differentiating ODD/CD from other clinical conditions, revealing the importance of specific periodicity for this group. This finding is particularly interesting since prior studies (including Kofler's meta-analysis) have found increased RTV in OCD/CD, similarly to what happens to ADHD. However, it is important to underscore that our sample is particularly unique with respect to lack of comorbidity. This allows us to disentangle specific contributions of two different behavioral manifestations. However, a close inspection of the performance data suggests that accuracy rates were equivalent in ODD/CD and TDC groups, but children with ODD/CD were faster than TDCs. This brings up the issue of potential speed-accuracy trade-off effects (SATO). Indeed, our previous analysis using diffusion models, which are able to disentangle processing efficiency, SATO and motor components in RT performance, revealed SATO effects to be a specific marker of ODD/CD in the 2C-RT (Salum et al. 2014a, b). Therefore, such strategic response strategies might be driving between-group differences in the alpha decay parameter, given that there is a significant correlation between alpha and the SATO parameter from the diffusion model (boundary separation), with a small effect size ($r = 0.163$, $p < 0.001$). These results must be interpreted with caution given that a fine-grained analysis with DAWBA ODD and CD bands failed to find any between-group differences. Therefore, results might be due to arbitrary diagnostic thresholds.

The increased RTV in ADHD has also been ascribed to poorer processing efficiency (Huang-Pollock et al. 2012; Karalunas et al. 2012a, 2014; Salum et al. 2014a, b), which might be linked to deficient activity of the dorsolateral prefrontal cortex (Kuhn et al. 2011; Philiastides et al. 2011) and is associated with less mature myelination (Nagel et al. 2011), both processes that have been linked to ADHD pathophysiology. In fact, recent studies showed that RTV might be a general marker of neural development, mimicking neurodevelopmental differences in ADHD (van Belle et al. 2015a, b). RTV may also reflect other context-dependent dynamic processes involving mechanisms that occur upstream, predisposing to lapses in attention when energetic or motivational aspects do not match the current organism's goals or 'value systems' (Sonuga-Barke 2011). The investigation of the neural underpinnings of ADHD-related variability is in its infancy (Kofler et al. 2013; Kuntsi and Klein 2012), and a number of additional hypotheses can be made including primary deficits in temporal processing (Castellanos and Tannock 2002) and altered motivational processes such as reinforcement and extinction (Sagvolden et al. 2005). Other works even question the role of RTV as a primary neurocognitive indicator, suggesting that it may be secondary to deficits in executive working memory (Kofler 2014).

Our study has a number of strengths. We used sophisticated statistical analyses to assess *periodicity,* and our spectral analyses robustly demonstrate that increased variability was not constrained to a specific frequency band, contradicting the predictions made by the default-mode interference theory. In addition, this is the first study investigating the specificity of such findings compared to other common and highly comorbid psychiatric disorders, such as distress disorders or ODD/CD. Our study was able to disentangle specific effects of ADHD and ODD/CD comparing groups not confounded by comorbidity. This distinction is particularly important since ADHD and ODD/CD are known to be highly comorbid and are found to have additive effects on information processing (Salum et al. 2014a, b). This approach allowed us to point out a potential role of *periodicity* in ODD/CD in the opposite direction to what was found in ADHD (lower variability specifically in low-frequency oscillations). Still, this novel finding must be replicated before it can be interpreted with confidence.

Our results must also be considered in the light of some limitations. First, we only used one task to assess RT *periodicity* effects in children with ADHD and specific effects in some frequency bands may vary with task complexity (Karalunas et al. 2012a). Nevertheless, we were able to investigate a reasonable range of frequency bands. Another advantage of simple reaction time tasks is that the time series does not need to be reconstructed statistically as is required in more complex tasks. Second, data collection was based only on parent reports. Even though they might be the most reliable way to assess psychopathology in younger children, self-reports would be valuable instruments for assessing symptoms of older children and to limit shared variance from the same information source. However, in the context of this study, this limitation may

not be as relevant since the previous meta-analysis studies on this topic have not found systematic differences between studies based on single versus multiple informant methods (Kofler et al. 2013). Third, our investigation was restricted to common psychiatric disorders. Important forms of psychopathology, such as autism or reading disorders, were not evaluated here (Karalunas et al. 2014). Some disorders have also been linked to RTV, as it is the case for schizophrenia (Karantinos et al. 2014) and autism (Tye et al. 2016). Some studies, however, found RTV to be a marker of comorbid ADHD in autism disorders (Adamo et al. 2014), increasing the possibility that RTV functions as a more specific marker of ADHD. Nevertheless, we used an empirically derived taxonomy investigating differences among Fear, Distress, ADHD and ODD/CD, common psychiatric domains with significant prevalence in our cohort. Fourth, the evaluation of non-comorbid diagnosis groups raises questions concerning external validity. However, despite the fact that psychiatric diagnosis often co-occurs (Kessler et al. 2005), the main objective of this current study was to determine the specificity of RTV as a correlate of ADHD and the validity of the default-mode interference hypothesis. These objectives could not be achieved without the separation of non-comorbid groups. Lastly, it is described by previous literature that low frequencies are the most susceptible to artifacts in the spectrum (Gilden 2009). This is important considering our results concerning ODD/CD, increasing the importance of further research to replicate those findings. This possible limitation, however, would not diminish the likelihood of our findings in the increased RTV of children with ADHD, since this was a common finding throughout the spectrum.

In summary, we demonstrated that RTV is a core, specific characteristic of non-referred and non-medicated cases of ADHD, a relevant finding to further research on the yet not entirely known cognitive mechanisms underlying ADHD. Increased variability in non-comorbid ADHD is not limited to low-frequency oscillations, contradicting the predictions made by the default-mode interference theory. In contrast, the periodicity may characterize decreased RTV in ODD/CD, an observation worth replicating and understanding.

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Compliance with ethical standards

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Research involving human participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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