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Response time intra-subject variability: commonalities between children with autism spectrum disorders and children with ADHD

Nicoletta Adamo,

Phyllis Green and Randolph Cōwen Institute for Pediatric Neuroscience, NYU Child Study Center, New York University Langone Medical Center, One Park Avenue, 8th floor, New York, NY 10016, USA

Lan Huo,

Division of Biostatistics, NYU Child Study Center, New York, USA

Samantha Adelsberg,

Phyllis Green and Randolph Cōwen Institute for Pediatric Neuroscience, NYU Child Study Center, New York University Langone Medical Center, One Park Avenue, 8th floor, New York, NY 10016, USA

Eva Petkova,

Division of Biostatistics, NYU Child Study Center, New York, USA; Nathan Kline Institute for Psychiatric Research, Orangeburg, NY, USA

F. Xavier Castellanos, and

Phyllis Green and Randolph Cōwen Institute for Pediatric Neuroscience, NYU Child Study Center, New York University Langone Medical Center, One Park Avenue, 8th floor, New York, NY 10016, USA; Nathan Kline Institute for Psychiatric Research, Orangeburg, NY, USA

Adriana Di Martino

Phyllis Green and Randolph Cōwen Institute for Pediatric Neuroscience, NYU Child Study Center, New York University Langone Medical Center, One Park Avenue, 8th floor, New York, NY 10016, USA

Adriana Di Martino: Adriana.Dimartino@nyumc.org

Abstract

Despite the common co-occurrence of symptoms of attention deficit hyperactivity disorder (ADHD) in individuals with autism spectrum disorders (ASD), the underlying mechanisms are under-explored. A potential candidate for investigation is response time intra-subject variability (RT-ISV), a hypothesized marker of attentional lapses. Direct comparisons of RT-ISV in ASD versus ADHD are limited and contradictory. We aimed to examine whether distinct fluctuations in RT-ISV characterize children with ASD and with ADHD relative to typically developing children (TDC). We applied both a priori-based and data-driven strategies to RT performance of 46 children with ASD, 46 with ADHD, and 36 TDC (aged 7–11.9 years). Specifically, we contrasted groups relative to the amplitude of four preselected frequency bands as well as to 400 frequency bins from 0.006 to 0.345 Hz. In secondary analyses, we divided the ASD group into children with

Correspondence to: Adriana Di Martino, Adriana.Dimartino@nyumc.org.

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and without substantial ADHD symptoms (ASD⁺ and ASD⁻, respectively). Regardless of the strategy employed, RT-ISV fluctuations at frequencies between 0.20 and 0.345 Hz distinguished children with ADHD, but not children with ASD, from TDC. Children with ASD⁺ and those with ADHD shared elevated amplitudes of RT-ISV fluctuations in frequencies between 0.18 and 0.345 Hz relative to TDC. In contrast, the ASD⁻ subgroup did not differ from TDC in RT-ISV frequency fluctuations. RT-ISV fluctuations in frequencies 0.18–0.345 Hz (i.e., periods between 3 and 5 s) are associated with ADHD symptoms regardless of categorical diagnosis and may represent a biomarker. These results suggest that children with ADHD and those with ASD⁺ share common underlying pathophysiological mechanisms of RT-ISV.

Keywords

Autism; ADHD; Reaction-time intra-subject variability; Functional data analysis; Endophenotype

Introduction

Clinical and epidemiological studies have overwhelmingly substantiated the occurrence of symptoms of attention deficit hyperactivity disorder (ADHD) in individuals with autism spectrum disorders (ASD) [1–7]. To date, the underlying mechanisms of the overlap between these disorders remain unclarified. One strategy is to identify intermediate markers that might reveal common pathophysiological mechanisms. A candidate for investigation is response time intra-subject variability (RT-ISV), which measures consistency of performance over time. RT-ISV has been increasingly proposed as a marker of lapses of attention rooted in physiological models [8–11]. RT-ISV is frequently quantified with summary measures such as the RT standard deviation (SD-RT) or coefficient of variation [9, 12, 13]; more recently, frequency analyses of RT time-series have also been employed [9, 14–22]. Increases of commonly used indices of RT-ISV (e.g., SD-RT) have been used to characterize ADHD defined both categorically [23–32] and dimensionally [21, 33, 34]. When compared to typically developing controls (TDC), individuals with ASD have also been found to show abnormally elevated RT-ISV [35–37]. However, direct comparisons between individuals with ASD and those with ADHD have been few and yielded opposite results [38–40].

Similarly, using frequency analyses, increased RT-ISV fluctuations have been consistently observed in children with ADHD compared to TDC [9, 14–20, 22]. In contrast, studies directly comparing children with ADHD to those with ASD and to TDC have yielded opposite results. In one study, only children with ADHD showed increases in fluctuations encompassing a wide range of frequencies above and below 0.07 Hz [41]. Another study reported increased RT-ISV fluctuations (0.03–0.13 Hz) in children with ASD relative to both ADHD and TDC groups, which did not differ from each other [42]. Thus, whether RT-ISV fluctuations in specific frequency bands distinguish ASD from ADHD remains unknown.

Examinations of low-frequency fluctuations of RT-ISV [9, 14–22] have been motivated by the hypothesis that attentional lapses reflect interference between the brain's default network [43] and fronto-parietal networks associated with top-down cognitive control [10, 11]. The extent of coordination or inter-regulation between the default network and the cognitive control network was found to be inversely correlated with RT-ISV in healthy adults [44]. In turn, abnormalities involving the default network and other large-scale networks have been reported in both ADHD and ASD (for reviews, see [45, 46]). These large-scale networks have traditionally been identified using fluctuations in spontaneous blood oxygen level dependent (BOLD) signals at frequencies below 0.1 Hz [47] these overlap with RT-ISV

fluctuations. Frequency analyses of the amplitude of spontaneous low-frequency fluctuations in the BOLD signal found an intriguing frequency-specific spatial distribution, for example, the frequency band centered at 0.05 Hz was specifically detected in basal ganglia, thalamus, and sensorimotor cortex [48]. In sum, these lines of evidence underpinned our examination of low-frequency oscillations of neuropsychological performance in both ADHD and ASD.

Accordingly here, we aimed to examine patterns of RT-ISV fluctuations in children with ASD, relative to those with ADHD and TDC who completed a Go/No-Go task, the fixed version of the Sustained Attention to Response Task (SART: [18, 19, 20, 49]). We explored group differences in RT-ISV fluctuations using two analytical strategies. One employed frequency bands selected a priori based on biological models of frequency distribution [50, 51], the other examined 400 frequencies within the measured spectrum. With the a priori approach, consistent with prior examinations [14, 16, 21, 22], we selected four frequency bands based on the model that biologically relevant frequencies are organized at regular intervals along the natural logarithmic scale [51], presumably reflecting distinct neuronal oscillators [50, 51]. The second exploratory approach was motivated by recent demonstrations that data-driven strategies can reveal ADHD-related abnormalities not otherwise detectable with a priori constrained frequency bands [17]. Accordingly, we used the functional data variant of Analysis of Variance [52] in which frequency amplitudes were treated as a function of all measured frequencies. Thus, the three groups were compared with respect to the entire function as opposed to reducing the function to a small number of frequency bands as in our first approach.

Finally, the influence of ADHD comorbidity on RT-ISV fluctuations in individuals with ASD is under-explored. The only study contrasting children with ASD with and without ADHD comorbidity reported increased RT-ISV in both ASD subgroups regardless of the occurrence of ADHD symptoms [42]. Thus, to further examine the role of ADHD comorbidity in ASD, we identified a subgroup of children with ASD and ADHD-like symptoms (ASD⁺), and explored their patterns of RT-ISV fluctuations.

Methods and materials

Participants

We collected RT data from 159 children aged between 7.0 and 11.9 years who participated in ongoing studies at the NYU Child Study Center and analyzed RT experiments from 128 children (46 with ADHD, 46 with ASD and 36 TDC, Table 1) who completed at least 85 % of the task (see task details below).

Children with ADHD and ASD were recruited through referrals from the NYU Child Study Center Child and Family Associates, parent support groups, newsletters, flyers, and web/newspaper advertisements. TDC were recruited from the local community through flyers, advertisements and word of mouth.

Inclusion as a child with ADHD required a DSM-IV-TR diagnosis of any of the three subtypes of ADHD supported by administration of the Schedule of Affective Disorders and Schizophrenia for Children—Present and Lifetime Version (K-SADS-PL: [53]) to the parent/legal guardian and separately to the child. To minimize potential confounds, we only included children with ADHD and with a parents Social Responsiveness Scale (SRS [54, 55]) total score inconsistent with autistic traits (i.e., T -score <65).

Within the ASD group, trained clinicians classified children as having DSM-IV-TR diagnoses of autistic disorder, Asperger's disorder, or Pervasive Developmental Disorder

Not Otherwise Specified ($n = 34$, $n = 4$, and $n = 8$, respectively) based on the child's history combined with the Autism Diagnostic Observation Schedule, Module 3 (ADOS, $n = 46$; research reliable $n = 45$), and available Autism Diagnostic Interview-Revised (ADI-R, $n = 43$; research reliable $n = 29$). One child had clinical but not research reliable ADI-R and ADOS scores. Assessment of comorbid disorders in ASD was based on administration of the K-SADS-PL (parents only [$n = 18$], parent-child dyads [$n = 11$]), or unstructured psychiatric interviews with parent(s) [$n = 17$]).

For both clinical groups, comorbidity and psychotropic medication use are summarized in Table 1. Briefly, 18 children (40 %) with ADHD and 25 (54 %) children with ASD presented with comorbid Axis-I disorders; 34 children with ADHD (74 %) and 33 with ASD (72 %) were naïve to psychotropic medications. Participants taking stimulants were asked to suspend their medications for at least 24 h prior to task administration.

The TDC group included children with no history of Axis-I psychiatric disorders and with T -scores below 65 on all four ADHD-summary scales on the Conners Parent Rating Scale—Revised: Long Version (CPRS-R:L [56, 57]) and on the SRS total T -score. Absence of psychiatric diagnoses was confirmed by K-SADS-PL administration to both parent(s) and child in 31 subjects (86 %), with a parent only in one (2 %), and with a child only in four (11 %).

For all children, absence of neurological disorders and estimates of full-scale IQ (FSIQ) 80 per Wechsler Abbreviated Scale of Intelligence were required. We collected information to compute socio-economic status from all parents but nine (four, three, and two in the TDC, ADHD, and ASD groups, respectively) [58].

The study procedures were approved by the institutional review board of the NYU School of Medicine. Prior written informed consent/assent from parents and children, respectively, were obtained. Each family received a reimbursement of up to \$60 for participation in this portion of the study.

Task administration

Participants completed a fixed sequence version of the Sustained Attention to Response Task (SART [16, 18–20, 49]). As detailed elsewhere [16, 18–20, 49], task trials consisted of the digits ‘1’–‘9’ appearing on the screen in ascending order for 25 repeated sequences in one block. Children were instructed to respond to the target stimulus—a cross following each digit—by pressing a mouse button for all digits of the sequence (Go trials), except for the digit ‘3’ (No-Go trials). After performing an initial 1.5 min practice session, all children were administered a 5.5 min session including 225 trials presented with an inter-stimulus-interval (ISI) of 1.45 s. We applied frequency analyses on all experimental trials independent of the trial type (e.g., “Go” and “No-Go” trials). As mentioned before, only the RT experiments from the participants completing at least 85 % of the total trials were included in the analyses. Based on this criterion, a significantly higher number of children with ADHD ($n = 24$), relative to those with ASD and TDC ($n = 1$ and 3, respectively) were excluded from analyses ($\chi^2_{(2)} = 25.8$; $p < 0.0001$). Children with ADHD who were excluded were significantly younger than those who were included, but they did not differ significantly on any measures of ADHD severity or sex distribution.

Task performance

RT speed and accuracy—For each participant included in analyses ($n = 128$), we computed mean (M-RT) and standard deviation of RT (SD-RT) over all responses.

Accuracy measures included number of omissions for Go trials and commission errors (i.e., responses on the No-Go trials).

Estimating the amplitude of RT-ISV fluctuations—We analyzed the RT time-series as previously described [14, 16]. Specifically, to obtain continuous time-series of RT for each subject, we interpolated all missing and anticipatory responses (RT = 100 ms) by replacement with the average RT of the immediate neighbor data points. As in prior work [14, 16], we then transformed each child's RT time-series into time–frequency amplitude matrices (scalograms) using the continuous Morlet wavelet transform [400 scales (or frequencies) and half-length 20] implemented in the Matlab Time–Frequency Toolbox (The MathWorks, Natick, Massachusetts: <http://tftb.nongnu.org>). Per the Nyquist theorem, the ISI (Δt) and task duration ($n\Delta t$: where n is the number of trials) allowed us to examine the frequency range from 0.006 (i.e., $1/2\Delta t$) to 0.345 Hz (i.e., $1/[n\Delta t/2]$).

Identifying frequency targets—To comprehensively examine patterns of RT-ISV fluctuations among groups within the sampled frequency spectrum (0.006–0.345 Hz), we used two complementary approaches, one a priori and the other data-driven. Under the first approach, four frequency bands were used as variables of interest for group comparisons. As detailed in prior work [14, 16, 17, 22], these bands, selected based on biological models [50, 51], included Slow-5 (0.010–0.027 Hz), Slow-4 (0.027–0.073 Hz), Slow-3 (0.073–0.2 Hz), and Slow-2 (0.2–0.345 Hz). For each interval, the frequency amplitude was averaged across time. Of note, as the fixed sequence of the SART produces trial type effects with a spectral peak at 0.077 Hz, we excluded five frequencies above and below that peak [19, 41]. For the data-driven approach, we computed the average amplitude, across time, for each of the 400 frequencies in the examined spectrum. A function of all estimated frequency amplitudes was used for group comparisons as detailed below. We note that for consistency with prior work [14, 16], in main analyses we averaged frequency information over time. Secondary analyses were conducted to examine the potential effect of time on task. Specifically, we split the task into two halves and compared their SD-RT as well as the amplitude of the low-frequency bands within each group with repeated measures ANOVA. Results indicated neither significant differences in SD-RT nor RT-ISV fluctuation over time (Supplementary Fig. 1).

Statistical analyses

Participants characteristics and overall task performance—We evaluated between-group differences in age, IQ estimates, and parent ratings using analysis of variance (ANOVA). Differences for categorical variables were assessed by χ^2 . We compared the three groups (ADHD, ASD and TDC) with respect to M-RT, SD-RT and task accuracy using analysis of covariance (ANCOVA) adjusting for age to address expected developmental changes in task performance [59].

Analyses on a priori selected frequency bands—Given that the frequency intervals are not independent from each other, we first used multivariate ANOVA (adjusting for age: MANCOVA) to test whether differences between groups depended upon a frequency band. Specifically, testing the significance of the frequency band by diagnostic group interaction would indicate whether differences between groups occur equally for all bands (i.e., non-significant interaction) or depend on a specific frequency band (i.e., significant interaction). In this latter case, we performed separate tests for each individual band using ANCOVA adjusting for age. Significant diagnostic group effects were followed by pair-wise comparisons.

Data-driven discovery analyses—To ensure that a priori identification of frequency bands did not limit the detection of group differences, we repeated the pair-wise group comparisons using a functional data analysis (FDA, [52]) approach to regression. The FDA can be thought of as a generalization of multivariate analysis that takes advantage of the specific structure of the multiple observations, such as their temporal or spatial (or frequency) order. We fitted “functional linear models” using as the outcome the amplitude function over the entire range of sampled frequencies (0.006–0.345 Hz). As each subject's amplitude function is observed at 400 frequencies, the FDA reduces the effective dimension of these functions by assuming them to be smooth and hence representable by a smaller number (here $n = 40$) of spline basis functions [48, 56]. The results from fitting a regression model to the entire function $f(\omega)$ are: (1) a coefficient function $b(\omega)$ representing the group effect, with (2) standard error function $SE(\omega)$ and (3) $(1 - \alpha) \%$ confidence interval, all of which are functions of ω . The analysis was performed using the algorithm of Reiss et al. [60], using the function `fosr` (function-on-scalar regression) available in the R package *refund* [<http://cran.rproject.org/web/packages/refund/refund.pdf>]. The function `fosr` also allows the inclusion of covariates and estimates their regression coefficient functions. The smoothed curve functions of the 400 frequencies for each subject were submitted to pair-wise comparisons of the three groups.

We note that while untransformed RT data are not normally distributed, the distributions of derivatives such as values averaged over time do not deviate sufficiently from normality to invalidate the inferences from the statistical analyses we conducted.

Finally, consistent with the literature [2–6], based on parent ratings on the CPRS-R:L, clinically significant ADHD symptoms were identified in 23 children with ASD (ASD⁺) in contrast with the remaining 23 who were classified as ASD⁻ (See Supplementary Table ST1). To explore the extent to which RT-ISV in ASD⁺ resembles that in ADHD, secondary analyses compared the three clinical groups and the TDC using the two approaches described above.

Results

Participant characteristics and overall task performance

As shown in Table 1, groups did not differ from each other with respect to age, estimates of IQ, and socio-economic status. As expected, parent ratings on all clinical indices were significantly elevated in probands (i.e., ADHD and ASD) relative to TDC. While the two clinical groups did not differ from each other with respect to indices of hyperactive and disruptive behaviors (e.g., ADHD-related indices at CPRS-R:L and Externalizing scores at the CBCL), the ASD group showed significantly higher *T*-scores for Internalizing Problems (CBCL) and SRS total score relative to the children with ADHD and TDC. The three groups did not differ significantly in M-RT, SD-RT or in accuracy (number of omissions and commission errors). See Supplementary Table ST2.

Amplitude of RT fluctuations

A priori selected frequency bands—While SD-RT did not reveal statistically significant group differences, comparison of the amplitude of frequency fluctuations did. Specifically, MANCOVA for group differences across specific frequency bands was significant ($p = 0.0007$), so we proceeded with group comparisons relative to each band separately. Increased amplitude in Slow-2 and Slow-3 characterized children with ADHD relative to both those with ASD and TDC. Yet, the *F* test revealed a significant effect of group only for Slow-2 with a moderate effect size ($p = 0.013$, $\eta^2 = 0.07$, Table 2; Fig. 1). Planned pair-wise comparisons confirmed that RT-ISV in Slow-2 was greater for children

with ADHD relative to TDC ($p = 0.003$, Supplementary Table ST3). To facilitate comparisons with prior studies using Cohen's d , pair-wise group comparisons are also provided in Supplementary Table ST3 (for classification of ES, see [61, 62]). While children with ASD showed Slow-2 and Slow-3 amplitudes intermediate between those of children with ADHD and TDC, they did not differ significantly from these groups in pair-wise comparisons.

With regard to Slow-4, children with ADHD presented the highest amplitude and children with ASD the lowest, while TDC were intermediate. However, the F test did not reach statistical significance ($p = 0.055$, $\eta^2 = 0.05$, Table 2; Fig. 1). The amplitude of RT-ISV at Slow-5 did not show any significant effects of group.

Data-driven analyses of 400 frequencies—As summarized in Fig. 2, consistent with the a priori approach, children with ADHD relative to TDC showed increased mean amplitudes in frequencies between 0.14 and 0.345 Hz, as shown by a 95 % point-wise confidence interval above zero. Children with ASD neither differed from those with ADHD in the mean amplitude at any frequencies, nor from the TDC except for five frequencies (0.33–0.345 Hz). Given the narrow width of this frequency band, we defer interpreting this finding pending independent replication.

Secondary analyses on ADHD comorbidity in ASD

We divided children with ASD into those with ADHD-like symptoms (ASD⁺) and without (ASD⁻) based on CPRS:R-L ratings. While significant increases in amplitudes of RT fluctuations were not evident for ASD when considered as a single group, significant differences emerged in secondary group comparisons including ASD⁺ and ASD⁻. This was evident both for the a priori frequency band comparisons and for the FDA-based pair-wise comparisons. Specifically, increased Slow-2 and frequencies > 0.14 Hz characterized both children with ASD⁺ and ADHD relative to TDC. This pattern was not observed in children with ASD⁻. In ASD⁻, we observed smaller amplitudes in these frequencies relative to the ADHD group as shown in Fig. 3; Supplementary Table ST4.

Discussion

Increasing reports of overlap between ADHD and ASD in multiple domains [63–65] motivated our investigation of RT-ISV, a proposed marker of lapses of attention [8, 10]. Based on emerging evidence of the potential association of specific ranges of low-frequency fluctuations in the BOLD signal and distinct brain regions [48, 66], we sought to examine oscillatory patterns in similar frequency bands in RT-ISV in both ADHD and ASD. In these data, children with ADHD could reliably be distinguished from TDC with respect to RT-ISV fluctuations faster than 0.14 Hz (extending from the upper range of Slow-3 into Slow-2). By contrast, children with ASD showed amplitudes that were intermediate between children with ADHD and TDC at these frequencies, without differing significantly from either group. However, when children with ASD were separated into those with and without ADHD symptoms (ASD⁺ and ASD⁻, respectively), we noted increased RT-ISV fluctuations in the ASD⁺ subgroup comparable to those in the ADHD group: both groups showed increased amplitude in frequencies > 0.18 Hz (mostly in Slow-2). These findings were robust to analytical strategy utilized, whether based on a priori selected frequency intervals or on a data-driven examination of all sampled frequencies.

Increased RT-ISV fluctuations in ADHD have been observed in a range of low-frequency bands, such as Slow-5 and Slow-4, and in relatively higher frequencies, i.e., Slow-3 and Slow-2 [9, 14–22, 41]. We did not detect significant differences in the slowest frequency bands in either ADHD or ASD groups, relative to TDC. Recent work has highlighted

somewhat faster frequencies in RT-ISV studies of ADHD, extending up to 0.3 Hz [15–19, 21, 41] and up to 0.2 Hz in large-scale brain networks [67, 68]. Thus, as recently summarized [15], accumulating evidence does not support the hypothesis that RT-ISV fluctuations below 0.1 Hz would represent a biomarker of ADHD [10]. Here we have extended this observation to individuals with ASD⁺, i.e., children with co-occurring ADHD-related symptoms.

Our finding of increased Slow-3 and Slow-2 in ADHD, as in prior ADHD studies [16, 17], was extended to ASD⁺. Shared RT-ISV abnormalities in Slow-2 and Slow-3 between ADHD and ASD⁺ and absence of such abnormalities in ASD⁻ suggest that elevated RT-ISV at these frequencies is a marker of ADHD regardless of ASD diagnostic status. The potential endophenotypic value of Slow-2 is supported by the observations that (a) genetic effects were strongest on cost-efficiency metrics of intrinsic brain fluctuations in the Slow-2 frequency band [66] and (b) increased Slow-2 RT-ISV showed the greatest evidence of familiarity in siblings of children with ADHD [17].

Considering our findings of RT-ISV fluctuations in ASD in the context of earlier studies [41, 42], our results of increased RT-ISV fluctuations in relatively fast frequencies, but only for the ASD⁺ subgroup, are in contrast with the findings of Geurts et al. [42]. They reported increases in both slow and fast frequencies in children with ASD regardless of ADHD comorbidity, albeit with a larger effect in ASD⁺. They used a brief (64 trials, 182 s) two-choice simple response task. We used the same version of the SART as Johnson et al. [41] who also found that children with autism did not differ statistically from TDC. Future studies with larger samples and multiple tasks are required to resolve these discrepancies.

While our analyses revealed shared abnormalities between ADHD and ASD⁺, we did not find disorder-specific patterns of RT-ISV fluctuations. However, we note that the children with ASD⁻ (without ADHD comorbidity) generally showed lower amplitudes of RT-ISV fluctuations across the measured frequencies relative to both TDC and children with ADHD. Thus, we conclude tentatively that children with ASD without substantial ADHD symptomatology do not present with elevated RT-ISV fluctuations on the SART, consistent with Johnson et al. [41].

Limitations of this study are worth noting. Although the female:male ratio was higher in TDC than in the two clinical groups, limiting analyses to males revealed substantially unchanged results (data not shown). With regard to our secondary analyses, identification of children with ASD and comorbid ADHD (ASD⁺) was based only on parent ratings. However, clinician's diagnosis of comorbid ADHD in children with ASD⁺ agreed with parent reports in 74 % of the cases. In contrast with prior work examining the temporal dynamics of behavioral measures (e.g., errors) using longer tasks and multiple blocks [69], our task was too brief to permit adequate analysis of the temporal dynamics of frequency variations in RT. Thus, while we averaged over time to reduce data complexity as in prior efforts [14, 16, 22], future studies would benefit from longer task lengths.

In summary, based on two complementary frequency analyses, RT-ISV fluctuations at Slow-2 frequencies (0.20–0.345 Hz, i.e., periods of 3–5 s) are associated with ADHD symptoms regardless of the primary diagnostic classification. If replicated, our findings add to the growing clinical [1–7], molecular [70–73], and neuro-imaging evidence [74–76] of commonalities between ADHD and ASD. Contrasting children with ASD to children with ADHD without ASD allowed us to account for the heterogeneity of ASD and obtain more fine-grained information about the role of increased RT-ISV in these clinical populations. The importance of accounting for clinical heterogeneity in ASD, particularly by considering ADHD symptomatology, is also suggested by recent findings of abnormalities in intrinsic

functional connectivity that are shared by children with ADHD and ASD [76]. Future explorations of brain– behavior relationships in RT-ISV fluctuations in ADHD and ASD are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Average amplitude of each frequency examined with the SART for the ADHD (*red*), ASD (*green*) and TDC (*blue*) groups. Amplitude of the sampled frequency spectrum (0.006–0.345 Hz) for each group including typically developing children (TDC, *blue*), attention deficit hyperactivity disorder (ADHD, *red*), and autism spectrum disorders (ASD, *green*). The amplitude of each frequency is plotted on the X-axis, and the a priori selected frequency bands are delimited by *dashed lines*. The *gray panels* indicate the frequencies that are not included in the analyses: any frequency <0.010 Hz because not included in Slow-5 and the frequencies between 0.071 and 0.083 Hz thought to be associated to the task design. Of note, all groups showed a peak of elevated amplitude around 0.077 Hz, the expected SART generated peak, but they did not significantly differ in the amplitude of this frequency range

Fig. 2.

Differences between diagnostic groups (adjusted for age) with respect to the amplitude of frequencies in the interval 0.006–0.345 Hz based on Functional Data Analysis (FDA). In each panel, regression coefficient functions representing the difference between groups are represented for the entire frequency spectrum (*continuous line*) along with the 95 % point-wise confidence intervals (CIs, *dashed lines*). Frequency ranges where the 95 % CIs do not include a coefficient function of zero represent statistically significant group differences (*shaded areas*)

Fig. 3.

Pair-wise group differences (adjusted for age) of the amplitude of each frequency examined (0.006–0.345 Hz) using functional data analysis (FDA) including children with ASD⁺ and with ASD⁻. In each panel, regression coefficient functions representing the group effect for each comparison are depicted for the entire frequency spectrum (*continuous line*) along with the 95 % point-wise confidence intervals (CIs, *dashed lines*). Frequency ranges where the 95 % CIs do not include a coefficient function of zero represent statistically significant group differences (*shaded areas*)

Table 1

Sample Characteristics

	TDC (<i>n</i> =36)		ADHD (<i>n</i> =46)		ASD (<i>n</i> =46)		Group comparisons	
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	$\chi^2_{(2)}$	<i>p</i>
Boys, <i>n</i> (%)	19 (53)		39 (85)		42 (91)		19.40	<0.0001
SES range 4 or 5, <i>n</i> (%)	22 (48)		34 (74)		32 (71)		6.26	n.s.
							AVONA	Post Hoc
Age (years)	10	1	10	1	10	1	0.02	0.976
Verbal IQ	113	14	107	12	106	15	2.82	0.064
Performance IQ	109	14	104	14	110	19	1.63	0.200
Full-scale IQ	112	14	106	12	109	17	1.71	0.185
CPRS-R:L								
DSM-IV inattention	45	5	68	9	65	11	77.99	<0.0001
DSM-IV hyperactivity/impulsivity	47	6	65	13	66	12	35.90	<0.0001
DSM-IV total	46	6	68	10	67	11	69.40	<0.0001
CBCL-syndrome scale parent								
CBCL internalizing problems	45	10	54	10	65	10	43.44	<0.0001
CBCL externalizing problems	43	9	57	12	59	9	26.20	<0.0001
CBCL total problems	42	10	60	8	66	9	73.18	<0.0001
SRS-parent scale total	45	7	53 <i>n</i> (%)	8	76 <i>n</i> (%)	13	115.52	<0.0001
ADHD subtype <i>n</i> (%)								
Combined	–		32 (70)		–		–	–
Predominantly inattentive	–		12 (26)		–		–	–
Predominantly hyperactive-impulsive	–		2 (2)		–		–	–
Comorbidity <i>n</i> (%)								
More than one comorbidity	–		2 (4)		8 (17)		–	–
Anxiety disorders ^a	–		3 (6)		9 (20)		–	–
Disruptive behavior disorders ^b	–		8 (17)		3 (6)		–	–
Speech-language/learning disorders	–		4 (9)		–		–	–

	TDC (<i>n</i> = 36)	ADHD (<i>n</i> = 46)	ASD (<i>n</i> = 46)	Group comparisons	
				$\chi^2_{(2)}$	<i>p</i>
Mood disorders ^c	–	1 (2)	4 (9)	–	–
Adjustment disorder	–	1 (2)	–	–	–
Enuresis/encopresis ^d	–	2 (4)	5 (11)	–	–
Trichotillomania	–	1 (2)	–	–	–
ADHD but for criterion E in ASD	–	–	17 (37)	–	–
Medication status <i>n</i> (%)					
Medication-naïve	–	34 (74)	33 (72)	–	–
Not naïve but off medication(s) ^e	–	12 (26)	13 (28)	–	–
Prior history of medications ^f	–	1 (2)	6 (13)	–	–
Current stimulant treatment ^g	–	10 (21)	6 (13)	–	–
Current non-stimulant treatment ^h	–	1 (2)	1 (2)	–	–

ADHD attention deficit hyperactivity disorders, ASD autism spectrum disorders, CBCL child behavior checklist, CPRS-R:L Conners' parent rating scale-revised: long version, SES socio-economic status, high class = 4,5 versus low class = 1,2,3 based on the Hollingshead Index of Social Position [53]. SRS social responsiveness scale, TDC typically developing children, post hoc Bonferroni-corrected post hoc pair-wise comparisons

^a Anxiety disorders included Specific Phobia (ADHD: *n* = 1; ASD: *n* = 3), Separation Anxiety Disorder (ADHD: *n* = 2; ASD: *n* = 1), Generalized Anxiety Disorder (ASD: *n* = 3), and Social Phobia (ASD: *n* = 2)

^b Disruptive Behavior Disorders included Oppositional Defiant Disorder (ADHD: *n* = 8; ASD: *n* = 1) and Disruptive Behavior Disorder Not Otherwise Specified (ASD: *n* = 2)

^c Mood Disorders included Dysthymia (ADHD: *n* = 1) and Mood Not Otherwise Specified (ASD: *n* = 4)

^d Two children with ADHD and four children with ASD had Enuresis, one child with ASD had Encopresis (*n* = 1)

^e Treatment suspended for at least 24 h prior to task administration

^f Prior treatment included SSRIs (*n* = 1 in ADHD) and stimulants (*n* = 6 with ASD)

^g One or more psychostimulant medication

^h Treatment included atomoxetine (*n* = 1 in ADHD), Guanfacine and Sertraline (*n* = 1 in ASD)

Table 2
Group comparisons on amplitude of RT-ISV fluctuations in frequency bands defined a priori

	TDC (<i>n</i> = 36)		ADHD (<i>n</i> = 46)		ASD (<i>n</i> = 46)		Group comparisons ANCOVA _{age}		
	Mean	SD	Mean	SD	Mean	SD	<i>F</i> _(2,124)	<i>p</i>	η^2
Slow-2 (0.20–0.345 Hz)	25,580	12,370	36,454	19,578	32,422	16,626	4.5	0.013	0.07
Slow-3 (0.083–0.20 Hz)	71,916	39,883	88,148	42,878	75,485	43,604	1.8	0.171	0.03
Slow-4 (0.023–0.071 Hz)	167,428	118,872	178,556	107,653	128,483	83,398	3.0	0.055	0.05
Slow-5 (0.010–0.027 Hz)	189,150	160,386	178,189	116,233	176,678	184,673	0.1	0.914	0.001

Amplitudes (ms/Hz2) of each frequency band measured with the Continuous Morlet Wavelet Transform for the SART. ADHD attention deficit/hyperactivity disorder, ASD autism spectrum disorders, TDC typically developing children