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Reaction Time Variability in Children Is Specifically Associated With Attention Problems and Regional White Matter Microstructure

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ABSTRACT

BACKGROUND: Increased intraindividual variability (IIV) in reaction times (RTs) has been suggested as a key cognitive and behavioral marker of attention problems, but findings for other dimensions of psychopathology are less consistent. Moreover, while studies have linked IIV to brain white matter microstructure, large studies testing the robustness of these associations are needed.

METHODS: We used data from the Adolescent Brain Cognitive Development (ABCD) Study baseline assessment to test the associations between IIV and psychopathology (n = 8622, age = 8.9–11.1 years) and IIV and white matter microstructure (n = 7958, age = 8.9–11.1 years). IIV was investigated using an ex-Gaussian distribution analysis of RTs in correct response go trials in the stop signal task. Psychopathology was measured by the Child Behavior Checklist and a bifactor structural equation model was performed to extract a general p factor and specific factors reflecting internalizing, externalizing, and attention problems. To investigate white matter microstructure, fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity were examined in 23 atlas-based tracts.

RESULTS: Increased IIV in both short and long RTs was positively associated with the specific attention problems factor (Cohen's d = 0.13 and d = 0.15, respectively). Increased IIV in long RTs was also positively associated with radial diffusivity in the left and right corticospinal tract (both tracts, d = 0.12).

CONCLUSIONS: Using a large sample and a data-driven dimensional approach to psychopathology, the results provide novel evidence for a small but specific association between IIV and attention problems in children and support previous findings on the relevance of white matter microstructure for IIV.

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The transitional period from childhood to adolescence involves continued cognitive development (1,2), neurodevelopment (3,4), and for some, the emergence of mental health problems (5–7). Accuracy and processing speed improve with age, and increased cognitive stability, reflected by decreased intraindividual variability (IIV) in reaction times (RTs), is observed (8,9). IIV is thought to be a marker for the efficiency and stability of top-down attentional control (10,11). High IIV during cognitive tasks may reflect impairments in information processing, failure to maintain attentional control, and difficulties regulating behavior (12,13).

Increased IIV has been suggested as a phenotype, or even an endophenotype of attention-deficit/hyperactivity disorder (ADHD), based on experimental paradigms covering working memory, sustained attention, and interference tasks (13–18). In a review, Karalunas *et al.* (13) found that increased IIV in other disorders was due to comorbid ADHD, but the apparent specific association between IIV and ADHD may be driven by a subset of children. Meta-analyses and other reviews have, however, found that IIV is a common feature of many different disorders, including ADHD, Tourette's disorder, autism spectrum disorder, traumatic brain injury, dementia, and schizophrenia (11,19,20). Therefore, IIV might be a marker of deviations in top-down attentional control across diagnostic categories (13,21), serving as a risk factor for general psychopathology.

Most previous studies on IIV and psychopathology in children have used diagnostic categories and case-control designs, excluding participants with subclinical symptoms, thus not capturing the dimensional nature of psychopathology (22,23). A broad data-driven approach can therefore be informative, with a general factor of psychopathology (p factor) describing the shared variance across diagnostic categories (24,25). Because the p factor alone is insufficient, other dimensions or subfactors, such as internalizing (e.g., anxiousness and sadness) and externalizing (e.g., aggressiveness and delinquency) problems, should also be considered. Additionally, a separate attention problems dimension is often found (26). While the p factor is quantified as the shared variance across different forms of psychopathology, there are several

ways to define the subfactors. The most common models are higher order models, in which the factors can correlate with each other, and bifactor models, in which the subfactors do not correlate and explain unique residual variance.

A central account of IIV is that it reflects failure to maintain attentional control (11,12). Supporting this, IIV has been associated with increased brain activation in the default mode network (DMN), possibly reflecting insufficiency of its suppression (27,28). Sonuga-Barke and Castellanos (29) proposed the default mode interference hypothesis to explain attention fluctuations during task performance in ADHD, and it has later been extended to other disorders (30). The hypothesis postulates that when transitioning from resting state to task, DMN activity decreases and task-related brain activity increases. However, during the task, the DMN activity gradually increases, causing prolonged RTs driving IIV. This is supported by studies reporting decreased dorsolateral prefrontal cortex activity, a task-positive brain region, in relation to increased IIV (31,32). This reflects poorer processing efficiency (13,33–36), associated with altered white matter, as observed in children with ADHD (37). It can therefore be informative to investigate the neural correlates of IIV using diffusion tensor imaging (DTI), of which the most common metrics are fractional anisotropy (FA), mean diffusivity (MD), and axial diffusivity (AD) and radial diffusivity (RD), measuring the degree of anisotropy, the average diffusion, and diffusion along and across the diffusion axis, respectively (38,39).

A study of adults (40) found a positive relationship between IIV and the DTI indices MD, AD, and RD, and a negative relationship between IIV and FA in widespread brain regions. In an atlas-based DTI study on children, Tamnes *et al.* (9) also found widespread associations, with IIV being linked to lower FA and higher MD, AD, and RD in the corticospinal tract (CST), left superior longitudinal fasciculus (SLF), uncinate fasciculus, forceps minor, and corpus callosum (CC). These results are partly supported by Klarborg *et al.* (41), who reported a link between IIV and lower FA in the SLF and the white matter underlying the superior parietal cortex. The CST is a descending pathway mainly from the precentral motor cortex into the brain stem, propagating signals critical for body movement, including response execution (42). The CC is the main interhemispheric pathway and is important for attention and processing speed (43). These results thus point to a failure in motor systems underlying increased IIV. However, effects were also seen in forceps minor, bilaterally in the uncinate fasciculus, and in the left SLF, all pathways with frontal connections. Considering the lack of associations with median RT (9), this suggests that IIV is not just related to processing speed, but also to cognitive control.

While functional magnetic resonance imaging (MRI) studies mainly propose the DMN as underlying IIV, DTI studies report more widespread results. A possible explanation is that the structure of long-distance connections between neural networks can influence the functional integration of networks, which in turn is associated with behavioral control (44). Interestingly, the uncinate fasciculus is considered one of the main tracts connecting to the DMN (45), creating a possible link between DTI and functional MRI results. All-in-all, this warrants further investigation into the neural underpinnings of increased IIV.

Previous studies mainly investigated IIV as either the standard deviation of RT or as the coefficient of variance. This makes it challenging to make specific inferences about the nature of increased IIV because these measures are a sum of data from many trials rather than providing information about the unimodal, positively skewed distribution observed in RT data (46,47). This is particularly relevant for the default mode hypothesis in which regularly fluctuating RTs would be expected. Contrary to this hypothesis, Salum *et al.* (15) did not find that RTs fluctuate regularly throughout a task when RTs were transformed into frequency bands. Instead, they argue that IIV may be related to random fluctuations in attention. More specifically, studies show that IIV is primarily driven by occasional long responses, which makes it more suitable to use an ex-Gaussian estimation of variability (46,48,49). An ex-Gaussian approach decomposes the RT distribution of each dataset into a normal and an exponential component from which 3 parameters are calculated (19). The variables mu and sigma are extracted, representing the mean and standard deviation of the normal distribution, respectively, while tau describes both the mean and the standard deviation of the exponential component or the tail of the distribution. An advantage of this approach is that by separating tau (slow responses) and sigma (variability in faster responses), both can be estimated more accurately (49).

While previous studies have investigated IIV in ADHD, the present study sought to elaborate on this by testing whether IIV is associated with attention problems specifically or with other dimensions of psychopathology identified with a data-driven approach (n = 8622, age = 8.9–11.1 years). Furthermore, while studies have established an association between IIV and white matter microstructure, there are inconsistencies regarding the regional specificity. Therefore, we sought to test the robustness and regional pattern of the associations between IIV and white matter microstructure in a large sample (n = 7958, age = 8.9–11.1 years). We used data from the Adolescent Brain Cognitive Development (ABCD) Study baseline assessment and decomposed individual RT distributions using an ex-Gaussian approach. It was hypothesized that greater tau and sigma would be associated with both general psychopathology and a specific attention problems factor (13,19). Additionally, we hypothesized that greater tau and sigma would be associated with widespread lower FA and higher MD, AD, and RD (9).

METHODS AND MATERIALS

Sample

We used baseline cross-sectional data from the open ABCD Study (https://abcdstudy.org/) (50,51). The total sample consists of 11,878 8.9- to 11.1-year-old children recruited through schools near 21 study sites in the United States (52). See the Supplement for additional information.

The final samples in this study, after quality control (QC), consisted of 8622 participants (4151 females, mean_{age} = 9.9 years, SD = 0.6, range = 8.9–11.1 years) for analyses on the associations between IIV and psychopathology, and 7958 participants (3857 females, mean_{age} = 9.9 years, SD = 0.6, range = 8.9–11.1 years) for analyses on the associations between IIV and white matter microstructure.

Experimental Task

To measure IIV, we used trial-level data from a visual stop signal task (SST) performed while the participants were in the MRI scanner. In short, the task involves a go stimulus and a stop stimulus. The go stimulus requires a fast response while the occasional stop stimulus on a subset of trials following the go stimulus requires the participant to withhold their response. The task is illustrated in Figure 1 and described in detail in the Supplement.

Of the total sample, 10,248 had available baseline trial-level behavioral data from the SST. Of these, 693 were excluded due to missing genetic ancestry factor (GAF) scores (53). The GAF scores are 4 continuous variables, labeled African, American, European, and East Asian, describing proportion of genetic ancestry. The scores are calculated based on the Bayesian clustering results with the 1000 Genomes reference panel.

Of the 9555 datasets with both baseline trial-level behavioral data from the SST and GAF scores, 184 were excluded due to incomplete data. To ensure task compliance and enough trials, participants with accuracy below 60% on go trials were excluded (n = 744), in line with previous literature on children and the ABCD Study sample (54,55). One additional dataset with a negative skew in the distribution was removed because it was unfit for ex-Gaussian distribution analysis. Thus, 8626 participants passed the QC on behavioral data performed prior to separate QC on psychopathology and DTI data.

Prior to extracting the behavioral variables of interest, trials with premature responses (RT $<$ 150 ms) were removed. To account for post-error slowing, a concept of behavioral adaptation and performance monitoring, potentially affecting the results, successful go trials following an error response were excluded to purify our measure of IIV. This resulted in an average of 42.24 correct go trials removed per participant (SD = 14.14, range = 12–181) and an average of 219.98 correct go trials retained (SD = 34.20, range = 75–276).

From these trials, mu, sigma, and tau were extracted as behavioral variables of interest. The ex-Gaussian distribution analysis was performed using the function timefit from the retimes toolbox (56) implemented in R (57), with bootstrap resampling with 1000 iterations and using the maximum likelihood method for parameter estimation.

Parent-Reported Child Psychopathology

Child psychopathology was measured using the Child Behavior Checklist (CBCL) (age 6–18 years form) (58), which consists of 119 items scored on a 3-point Likert scale ranging from 0 (not true) to 2 (very true or often true). The items describe behaviors (e.g., "Destroys others' things") that the parents rate. Previous studies have shown evidence supporting the reliability and validity of CBCL (59). To obtain broad dimensional factors of psychopathology, we based our analyses on Clark *et al.* (26). Based on model 4, a bifactor model (Figure S1), we separated the items into the specific,

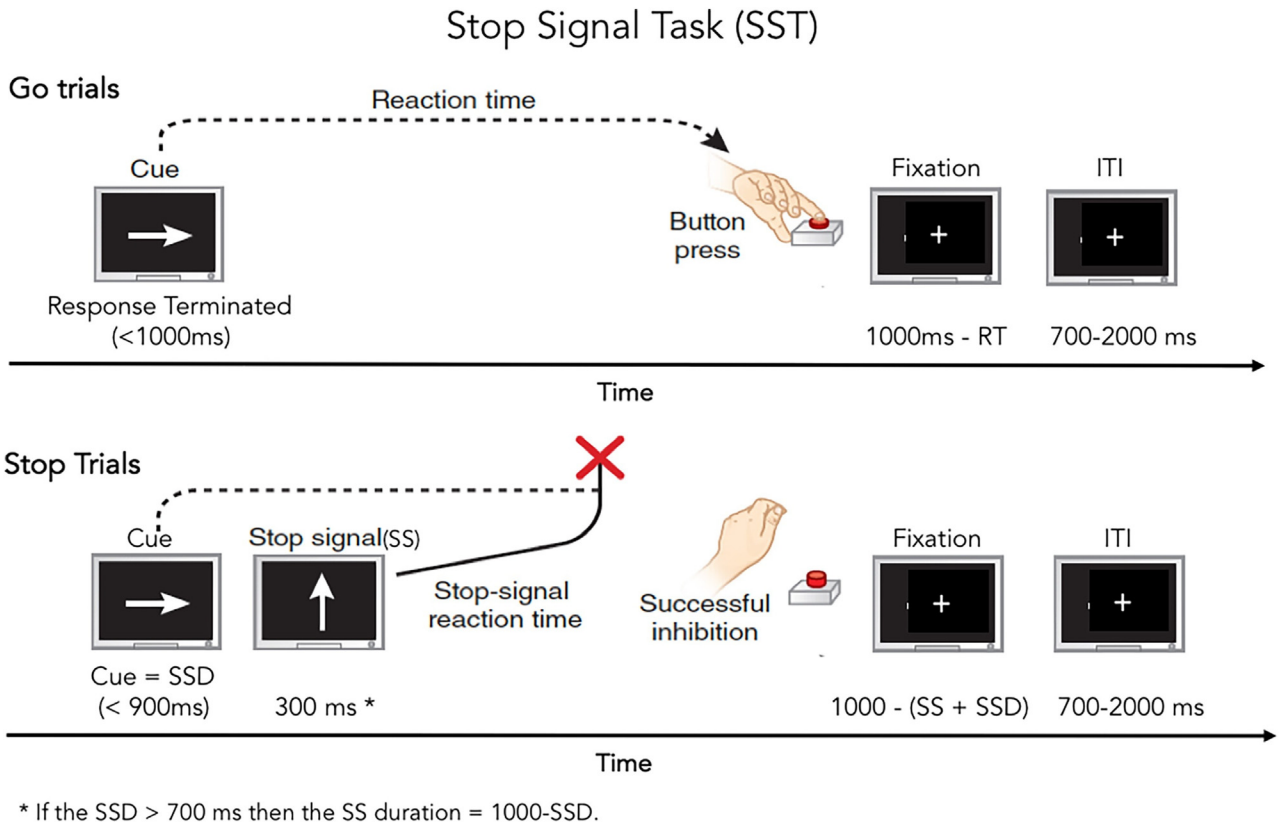

Figure 1. Illustration of the stop signal task. ITI, intertrial interval; RT, reaction time; SSD, stop signal delay. [Reproduced with permission from Casey *et al.* (61).]

residualized subfactors, internalizing, externalizing, and attention problems. The model has been reported with adequate fit (root-mean-square error of approximation = 0.07, indicator level explained common variance = 0.79). Next, a graded response model was performed in Mplus (60). As in Clark *et al.* (26), items about substance abuse (items 2, 106, and 112) were removed due to low endorsement. Of the 8626 datasets that passed QC on behavioral data, 4 were excluded due to incomplete CBCL data, yielding a final sample of 8622 for analyses on associations between IIV and psychopathology. The items' factor loadings are provided in the Supplement.

MRI Acquisition and Processing

The imaging data in the ABCD Study is acquired across 21 sites and 29 scanners (61). For the present analyses, we used tabulated diffusion MRI data from a high angular resolution diffusion imaging sequence with multiple b-values and fast integrated B0 distortion correction (reversed polarity gradient method). White matter tracts were segmented based on the probabilistic atlas AtlasTrack (62). The processing steps are described elsewhere (63). For our analyses, we included the following major fiber bundles: cingulate cingulum, parahippocampal cingulum, corticospinal/pyramidal, anterior thalamic radiations, uncinate, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, CC, SLF, superior corticostriatal, striatal inferior frontal cortex, and inferior frontal superior frontal cortex. All tracts were bilateral except for the CC, yielding 23 tracts of interest in which we examined mean FA, MD, AD, and RD.

Of the 8626 datasets that passed QC on behavioral data and GAF, further exclusions were for missing scanner serial number (n = 1), missing DTI data (n = 161), and not passing recommended QC (automatic and manual; n = 506), yielding a final sample of 7958 for analyses on associations between IIV and white matter microstructure. To correct for scanner effects, we used neuroComBat (64) in R (57), an adaptation of ComBat (65), a batch-effect correction tool (Figure S2). The adjustments were made before the main analyses and with age, sex, GAF, mu, sigma, and tau as covariates. These were, as recommended, the same variables as those in the main analyses. neuroComBat works well for harmonization of DTI data (66).

Statistical Analyses

All statistical analyses were performed using the Permutation Analysis of Linear Models toolbox (67). Six analyses were run, testing the associations between 1) mu and psychopathology, 2) sigma and psychopathology, 3) tau and psychopathology, 4) mu and DTI, 5) sigma and DTI, and 6) tau and DTI. The psychopathology factors (p, internalizing problems, externalizing problems, and attention problems) and the DTI metrics (FA, MD, AD, and RD in 23 tracts of interest) were included as separate modalities in their respective analyses. All analyses were performed with age and sex as covariates to avoid potential spurious associations driven by age and sex effects and, additionally, including the 4 GAFs to minimize spurious associations due to population stratification (68). The p values were computed using permutation testing across 10,000 iterations. Because the sample contains related subjects, including twins, a complex block exchangeability restriction was added during permutation (69). Block restriction was based on 8 unique family types (i.e., family decomposition), with additional within family shuffling based on sibling status. Furthermore, familywise error correction was applied across contrasts (70) and modalities (71) to control for multiple comparisons, with a significance threshold of $p < .05$. The analysis code is available: https://osf.io/x36qt/.

RESULTS

Descriptive Analyses

Descriptive statistics on the behavioral measures, psychopathology factors, and mean DTI metrics are shown in Table 1 and separately for the sexes in Tables S1 and S2. For the behavioral measures of interest, mu, sigma, and tau, only correct response go trials were included. Participants with an accuracy below 60% on go trials were excluded, but after trial exclusions, the accuracy was recalculated for the included trials only, explaining the observed accuracies below 60%. The 2 samples (IIV-CBCL and IIV-DTI, age: 8.9–11.1 years) did not significantly differ in terms of the main behavioral scores (mu: $t = -0.08$, $p = .937$; sigma: $t = -0.08$, $p = .936$; and tau: $t = -0.43$, $p = .665$). Correlations and t tests for age and sex differences, respectively, are found in the Supplement.

Associations Between IIV and Psychopathology

To examine the relationships between IIV and broad dimensions of psychopathology, we separately tested the associations between mu, sigma, and tau and a general p factor and specific uncorrelated subfactors of internalizing, externalizing, and attention problems (Table 2). Age, sex, and the 4 GAFs were included as covariates and relatedness was accounted for. The analyses showed a significant positive association between sigma and the attention problems factor ($t = 6.06$, $p = .010$, Cohen's $d = 0.13$) indicating that more variability in RTs within the normal distribution was associated with more attention problems. Additionally, we found a significant positive association between tau and the attention problems factor ($t = 6.71$, $p = .021$, Cohen's $d = 0.15$) indicating that more long RTs were associated with more attention problems. Scatterplots of the significant associations are shown in Figure 2. All other results from these analyses were nonsignificant.

Associations Between IIV and White Matter Microstructure

To examine the relationships between IIV and white matter microstructure, we performed similar analyses as described above for associations between IIV and psychopathology, separately testing the associations between mu, sigma, and tau and regional DTI metrics (FA, MD, AD, and RD in 23 tracts of interest: Tables S6–S8). Age, sex, and the 4 GAFs were included as covariates and relatedness was accounted for.

The results showed that tau had a significant positive association with RD in the left ($t = 5.28$, $p = .013$, Cohen's $d = 0.12$) and right ($t = 5.19$, $p = .020$, Cohen's $d = 0.12$) CST, indicating that a longer tail of RTs in the RT distribution was related to increased RD bilaterally in that tract. Scatterplots of the significant associations are shown in Figure 3. All other results from these analyses were nonsignificant.

Table 1. Descriptive Statistics

	Sample for IIV-CBCL Analyses, n = 8622				Sample for IIV-DTI Analyses, n = 7958			
Variable	Mean	SD	Min	Max	Mean	SD	Min	Max
Age, Years	9.93	0.63	8.92	11.08	9.94	0.63	8.92	11.08
goRT, ms	550.83	90.84	292.15	1032.73	550.41	90.97	292.15	1032.73
goAcc, %	73.33%	11.40%	25%	92%	73.45%	11.35%	25%	92%
Mu	386.53	84.08	154	964.42	386.43	84.21	154	962.42
Sigma	72.58	30.74	2.84	400.46	72.54	30.72	2.84	400.46
Tau	164.39	46.41	14.81	370.68	164.08	46.49	14.81	370.68
p Factor	−0.03	0.91	−1.77	3.26	–	–	–	–
Internalizing Problems	0.02	0.75	−2.73	3.68	–	–	–	–
Externalizing Problems	−0.02	0.71	−2.61	2.98	–	–	–	–
Attention Problems	−0.03	0.78	−2.22	2.96				
FA	–	–	–	–	0.47	0.016	0.39	0.53
MD, $\times 10^{-3}$ mm^2/s	–	–	–	–	0.78	0.019	0.70	0.87
AD, $\times 10^{-3}$ mm^2/s	–	–	–	–	1.23	0.023	1.07	1.32
RD, $\times 10^{-3}$ mm^2/s	–	–	–	–	0.56	0.020	0.48	0.65

FA, MD, AD, and RD represent the mean values across all tracts.

AD, axial diffusivity; CBCL, Child Behavior Checklist; DTI, diffusion tensor imaging; FA, fractional anisotropy; goAcc, accuracy on go trials; goRT, reaction time on go trials; IIV, increased intraindividual variability; MD, mean diffusivity; Min, minimum; Max, maximum; RD, radial diffusivity.

DISCUSSION

The results of the present study showed that increased IIV in short (sigma) and long (tau) RTs were positively associated with attention problems in a large population–based sample of children ages 8.9 to 11.1 years. Additionally, we found that tau was positively associated with RD in the left and right CST. Overall, the findings indicate a small but specific association between IIV and attention problems in children and support previous findings on the relevance of white matter microstructure for IIV.

Previous research has reported inconsistent results on whether increased IIV is specific to ADHD or a marker of attentional control difficulties across diagnostic categories (13–15,19). We used a data-driven dimensional approach to psychopathology and found that IIV was specifically associated with attention problems in a large population–based sample of children. Notably, in our bifactor model, this specific attention problems factor explained unique variance beyond a general p factor, and we found no associations between IIV and the p factor or the subfactors, internalizing or externalizing problems. Moreover, using an ex-Gaussian approach, we distinguished between standard deviation within the normal distribution (sigma) and the tail of the RT distribution (tau) and found that attention problems were associated with both. This is in contrast to previous research showing that increased IIV is primarily driven by long RTs or tau (46,48,49). Tau has been argued to reflect attention lapses (16,46,48), and the finding is therefore in line with studies on children and adolescents diagnosed with ADHD (16,46,72,73). However, while tau is linked to attentional lapses, attentional lapses have been found to be insufficient to explain IIV (13,19,74), indicating that the conceptualization of IIV is still unclear.

Relatedly, Karalunas *et al.* (13) reported that the observed increased IIV in children with ADHD was driven by a subset of children with extreme values. This can perhaps partly explain the small effect sizes observed in the present study because the associations may be stronger in samples with higher overall symptom levels. Moreover, while tau may be associated with symptom severity in children with ADHD (16), both sigma and tau may be associated with attention problems in a population-based sample of children. Additionally, the age range, 8.9 to 11.1 years, can possibly explain our lack of findings in relation to other dimensions of psychopathology, particularly internalizing problems, because these symptoms typically present later in adolescence (75). This is supported by the positive association between age and internalizing in this study (see the Supplement). The relationship between IIV and internalizing problems may therefore be of interest in later releases of the ABCD Study.

Table 2. Results From Permutation Analyses on Increased Intraindividual Variability and Psychopathology

	p Factor			Internalizing Problems			Externalizing Problems			Attention Problems		
Variable	t	p	d	t	p	d	t	p	d	t	p	d
Mu	0.05	≈1.000	0.001	−1.93	≈1.000	−0.04	−1.32	≈1.000	−0.03	1.74	.863	0.04
Sigma	3.81	.986	0.08	−2.58	≈1.000	−0.06	0.69	≈1.000	0.02	6.06	.010[a]	0.13
Tau	5.41	.748	0.12	−3.01	≈1.000	−0.07	3.53	≈1.000	0.08	6.71	.021[a]	0.15

p Values were corrected using familywise error rate and corrected across modalities (psychopathology factors) and contrasts (positive and negative).

[a]Significant p values.

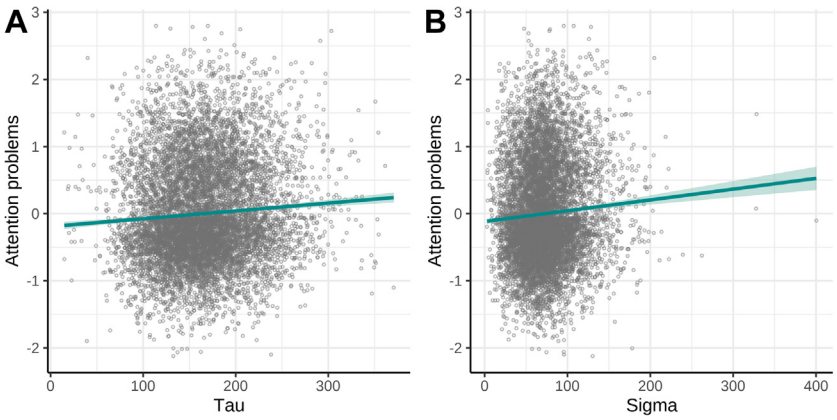

Figure 2. Associations between increased intraindividual variability and attention problems factor. **(A)** Scatterplots of the positive association between sigma and attention problems and **(B)** tau and attention problems. Each dot represents an individual participant. The y-axis is residualized for age, sex, and the 4 genetic ancestry factor scores.

While we hypothesized that increased IIV would be associated with both *p* factor and attention problems, we only found significant results for the latter. This may highlight the underlying mechanisms for the association between increased IIV and ADHD in previous research (13–16). It has, however, been argued that increased IIV in ADHD stems from hyperactivity and not inattention (19,76), but few studies distinguish between the two. Of importance, the CBCL items loading on the attention problems factor measure a mixture of attention problems, hyperactivity, impulsivity, and compulsiveness symptoms. In other words, the associations in the present study may not be solely attributed to attention problems. Furthermore, Buzy *et al.* (76) report that the effect was more pronounced with increased cognitive load in their working memory task. Further research across different cognitive tasks and different clinical and nonclinical samples is warranted.

Our results showed positive associations between tau and RD of the left and right CST in line with previous literature demonstrating the role of the CST in processing speed and execution of motor responses (9,42). Because typical neurodevelopment involves increases in FA and decreases in MD and RD (77), this result might indicate that increased IIV, driven by a longer tail in the distribution of RTs, is related to locally less mature white matter microstructure. However, this does not explain why CST was not associated with mu and sigma because these variables also represent motoric mechanisms. Using functional data or further deciphering the conceptualization of the ex-Gaussian components, e.g., by looking at trial history and occurrence of errors, may further clarify the present findings.

Though we hypothesized that greater tau and sigma would be associated with widespread lower FA and higher MD, AD, and RD, the data did not support this. Interestingly, the significant results show effect sizes of $d > 0.10$, but several tracts demonstrate effect sizes around 0.10 without reaching statistical significance.

The results of the present study should be interpreted considering some limitations. First, there are design issues with the SST, as discussed by Bisset *et al.* (78). However, by only looking at RTs from go trials derived from trial-level data, we have bypassed most of the issues because they were mainly concerning the stop trials and the calculation of accuracies. Nonetheless, the literature shows that in RT tasks that are not pure, e.g., in which a stop signal can occur, participants slow down their RTs in anticipation of a possible stop signal, meaning that RTs increase as a function of stop signal probability (79,80). In the current SST, the stop signal probability is lower than recommended (81), which might be a benefit

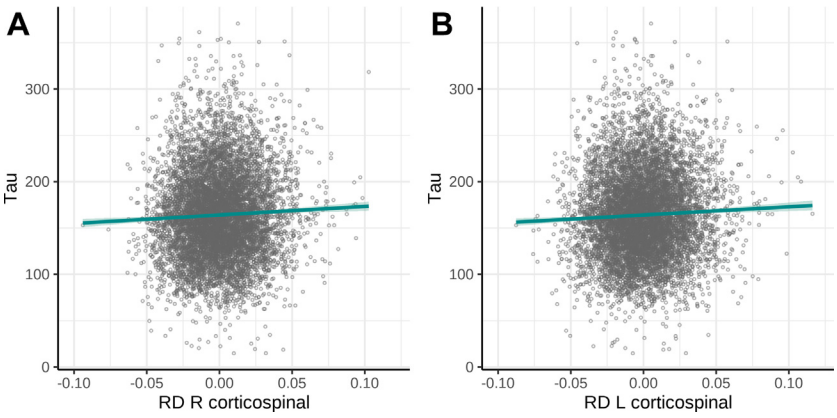

Figure 3. Associations between increased intraindividual variability and diffusion tensor imaging metrics. Scatterplots of the positive associations between tau and radial diffusivity (RD) in the right **(A)** and left **(B)** corticospinal tract. Each dot represents an individual participant. The x-axis is residualized for age, sex, and the 4 genetic ancestry factor scores. L, left; R, right.

in the present study because this should interfere less with the RTs. Furthermore, by looking at IIV with an ex-Gaussian approach, allowing the separation of long and short RTs, and by all participants receiving the same stop signal probability, the present results should be less contaminated by stop signals. Second, further investigations into the conceptualization of the parameters in the ex-Gaussian distribution, e.g., through looking at trial history, are needed to provide more insight into how the parameters could be influenced by stop signals. Third, the specific factors in bifactor models can be difficult to interpret (82), may have less variance, and be more unstable (83). Fourth, our methodological choices may have increased the chance for type II errors or false negatives. This is apparent when considering the strict block exchangeability restriction and multiple comparisons correction applied in the permutation analyses. Fifth, the *t* values and effect sizes are small, though it has been argued that effect sizes are particularly interesting in well-powered studies with large samples, such as in the ABCD Study (84). Owens *et al.* (85) investigated effect sizes in the ABCD Study and demonstrated that even small effect sizes can be relevant. Several studies also discuss how true brain-behavior relationships are smaller than previously described and that small effects should not be dismissed because they can be important clinically or for public health (84,86).

Future research could use longitudinal data to investigate how IIV interacts with psychopathology and white matter over time, during development, and, for instance, during psychological and pharmacological treatment. Future studies could also examine alternative methods for segmenting RTs to investigate IIV and other behavioral attributes related to cognitive processing and decision making (e.g., drift diffusion, frequency analysis, RTs in relation to errors). Some work has already been done on the ABCD Study dataset to compare different ways to calculate IIV (54); however, more work is needed to clarify the sensitivity of different methods for measuring IIV in relation to psychopathology and its neural correlates.

In conclusion, the present study found that IIV is associated with attention problems and regional white matter microstructure in a population-based sample of children ages 8.9 to 11.1. Leveraging a large sample, an ex-Gaussian approach to segment RTs, and a data-driven dimensional approach to psychopathology, the current study built on existing literature, supporting increased IIV as a cognitive phenotype specifically associated with attention problems in children. Moreover, increased IIV driven by long RTs was associated with white matter microstructure bilaterally in the motoric CST. This knowledge can contribute to further understanding of the cognitive mechanisms underlying attention problems in children. Further studies are needed to delineate how such difficulties develop and potentially change during treatment.

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ABCD consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in the analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or ABCD consortium investigators.

Parts of this work were presented as a poster during the Flux Congress in September 2022 in Paris.

Data used in the preparation of this article were obtained from the ABCD Study (https://abcdstudy.org), held in the National Institute of Mental Health Data Archive. This is a multisite, longitudinal study designed to recruit more than 10,000 children ages 9 to 10 years and follow them over 10 years into early adulthood.

A full list of supporters is available at https://abcdstudy.org/federal-partners.html. A listing of participating sites and a complete listing of the study investigators can be found at https://abcdstudy.org/consortium_members/.

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