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Mental health problems are associated with low-frequency fluctuations in reaction time in a large general population sample. The TRAILS study

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ABSTRACT

Background: Increased intra-subject reaction time variability (RT-ISV) as coarsely measured by the standard deviation (RT-SD) has been associated with many forms of psychopathology. Low-frequency RT fluctuations, which have been associated with intrinsic brain rhythms occurring approximately every 15–40 s, have been shown to add unique information for ADHD. In this study, we investigated whether these fluctuations also relate to attentional problems in the general population, and contribute to the two major domains of psychopathology: externalizing and internalizing problems.
Methods: RT was monitored throughout a self-paced sustained attention task (duration: 9.1 ± 1.2 min) in a Dutch population cohort of young adults (n = 1455, mean age: 19.0 ± 0.6 years, 55.1% girls). To characterize temporal fluctuations in RT, we performed direct Fourier Transform on externally validated frequency bands based on frequency ranges of neuronal oscillations: Slow-5 (0.010–0.027 Hz), Slow-4 (0.027–0.073 Hz), and three additional higher frequency bands. Relative magnitude of Slow-4 fluctuations was the primary predictor in regression models for attentional, internalizing and externalizing problems (measured by the Adult Self-Report questionnaire). Additionally, stepwise regression models were created to investigate (a) whether Slow-4 significantly improved the prediction of problem behaviors beyond the RT-SD and (b) whether the other frequency bands provided important additional information.
Results: The magnitude of Slow-4 fluctuations significantly predicted attentional and externalizing problems and even improved model fit after modeling RT-SD first (R^2 change = 0.6%, $P < .01$). Subsequently, adding Slow-5 explained additional variance for externalizing problems (R^2 change = 0.4%, $P < .05$). For internalizing problems, only RT-SD made a significant contribution to the regression model ($R^2 = 0.5\%$, $P < .01$), that is, none of the frequency bands provided additional information.
Conclusions: Low-frequency RT fluctuations have added predictive value for attentional and externalizing, but not internalizing problems beyond global differences in variability. This study extends previous findings in clinical samples of children with ADHD to adolescents from the general population and demonstrates that deconstructing RT-ISV into temporal components can provide more distinctive information for different domains of psychopathology.
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1. Introduction

A capacity to sustain attention is essential for adequate information processing and the successful accomplishment of goal-directed tasks. As such, sustained attention is of fundamental importance for general cognitive abilities and daily life skills. Fluctuations in the quality of sustained attention, as manifested by

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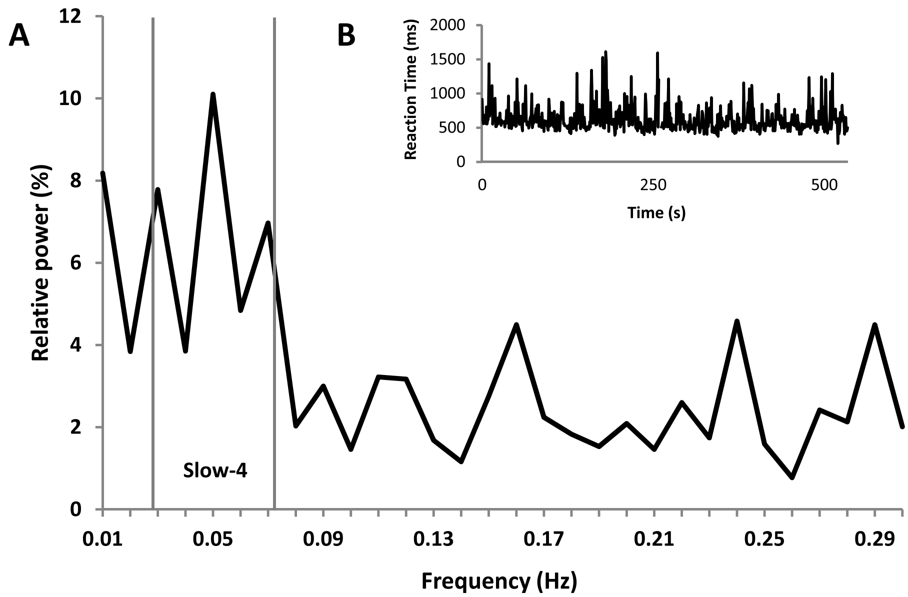

Fig. 1. Frequency spectrum analysis. (A) Frequency spectrum plot and (B) RT series for a particular subject. Note that (A) and (B) contain similar information, but in a different form. A RT series (B) is a complex signal that is set in the time domain (*x*-axis). This signal is transformed to (A) the frequency domain by direct Fourier Transform. This means the RT series is decomposed into a range of frequencies; the relative power on the *y*-axis indicates how strongly fluctuations of a certain frequency are present. This is expressed as the percentage of the total variance in the signal a certain frequency point accounts for. The boundaries of the Slow-4 band (0.027–0.073 Hz) are indicated in gray.

increased intra-subject reaction time variability (RT-ISV), have been documented in various psychiatric disorders, such as ADHD, ASD, bipolar disorder, depression, schizophrenia, and conduct disorder [4,9,15,24,33,52]. These findings seem to suggest that RT-ISV could be "related to pathophysiologic processes cutting across diagnostic boundaries" [p.1417; 8]. RT-ISV has not only been found in psychiatric populations, but has also been associated with both broad categories of problem behaviors in children and adolescents in population samples: internalizing problems, which are related to anxiety and depression, and externalizing problems, related to aggressive and rule-breaking behaviors [5,49]. Therefore, RT-ISV could represent a general marker of maladaptation. The underlying mechanisms of this broad variability measure have, however, remained largely unspecified.

Most studies have used the standard deviation (RT-SD) as a single-point estimate of reaction time variability, which has been taken to reflect a breakdown of top-down control or general noise in the neural transmission of information [2,3,30,47]. The SD-approach typically ignores the fact that attention fluctuates from moment-to-moment. For a full characterization of variability, parameters that define its periodic structure should also be taken into account [8]. RT-ISV could, for instance, represent fast moment-to-moment variations in task performance as well as more slowly evolving fluctuations in attentional control. Deconstructing RT-ISV into different temporal components is a necessary step for RT-ISV to become a more informative marker and requires more advanced methods [24]. Frequency spectrum analysis (Fig. 1) is a sophisticated technique that has recently been successfully applied in the study of RT-ISV in ADHD [8,16,51]. This method allows studying whether the different types of problem behaviors relate to similar or different periodic patterns of response variability.

The neurobiological basis of RT-ISV is still poorly defined, but multiple origins have been suggested [37]. Recent studies suggest that spontaneous fluctuations in human behavior can be accounted for by intrinsic fluctuations within cortical systems [23]. Therefore, the investigation of distinct periodic patterns in attentional performance through frequency spectrum analysis might provide a method for relating RT-ISV to underlying brain processes [8]. Penttonen and Buzsáki defined distinct neurophysiological frequency bands, each supposed to be generated by different mechanisms and serving different functions [43]. Their Slow-4 band (0.027–0.073 Hz, Table 1, Fig. 1) has attracted special interest [16], because its frequencies correspond to the very low-frequency oscillations that characterize the brain's default mode network (DMN, for a review see [21]). The DMN is a distinctive set of widely distributed but functionally highly connected brain regions, which support introspective or self-referential processing [22,45]. DMN activation is typically attenuated during cognitive tasks, which requires an extrospective attentional orientation [18,39,50]. It has recently been suggested that an ineffective shift from the default mode to an active processing mode during cognitive challenges could explain slow periodic fluctuations (< 0.1 Hz) in sustained attention performance [46]. Thus, rather than maintaining focus

Table 1
Frequency band characteristics.

Frequency band	Approximate period (s)	Lower (Hz)	Higher (Hz)	Reference band	Lower (Hz)	Higher (Hz)
Slow-2a	2–3	0.31	0.54	TSa	0.01	0.54
Slow-2b	3–5	0.20	0.30	TSb	0.01	0.30
Slow-3	5–13	0.08	0.19	TSb	0.01	0.30
Slow-4	14–33	0.03	0.07	TSb	0.01	0.30
Slow-5	50–100	0.01	0.02	TSb	0.01	0.30

Note that the Slow-2a band is only applicable to the "fast" sub-group. TSa: Total Slow band encompassing Slow-5 up to Slow-2a; TSa is used as a reference band for Slow-2a and all other Slow bands for the sub analysis on the "fast" group. TSb: Total Slow band covering Slow-5 up to Slow-2b; TSb is the reference band for the main regression analyses on the total sample.

on the task, the mind wanders off during time intervals that are reminiscent of the DMN's intrinsic rhythm [39].

Sonuga-Barke and Castellanos [46] propose that one of the pathways to the sustained attention deficits seen in ADHD could be a disturbance in default mode functioning, which could manifest itself as spontaneous low-frequency RT fluctuations in attention. The underlying mechanism is unknown, but the authors argue that various factors could predispose towards greater default mode interference, including limited effortful control resources (i.e. the ability to regulate attention and behavior), low motivation, and high affinity with the default mode (i.e. resistance to change of this state). These factors are key to ADHD, but associated with externalizing problems as well (e.g. reduced effortful control [41] and high boredom proneness [35]). In addition, there is some preliminary evidence for atypical DMN activity and an uncoupling between the DMN and the attention network in externalizing psychopathology [12,48]. Therefore, default mode interference might not only relate to attentional problems, but also to externalizing problems. It is more difficult to formulate clear expectations for internalizing problems. On the one hand, associations might be weaker or non-existent, because internalizing problems are not as strongly linked to issues of behavioral control in the general population as externalizing problems [19,41]. On the other hand, a dominant default mode has been hypothesized to relate to rumination and an internally focused cognitive style in depression [38]. From this perspective, internalizing problems in the general population might also be linked to more affinity with the default mode and hence, more interference during cognitive tasks.

Recently, an abnormal magnitude of low-frequency RT fluctuations in the Slow-4 band (~ 0.05 Hz) has been demonstrated in attention deficit hyperactivity disorder (ADHD), an attentional disorder characterized by problems with motivation and executive functioning [8,16,51]. Importantly, these low-frequency RT fluctuations added unique information beyond the global increase in RT-SD [16]. It is still unknown whether differences in low-frequency fluctuations also relate to attentional problems in the general population and whether there are associations with internalizing and externalizing problems. In addition, higher frequencies (> 0.1 Hz) have received little attention, but could provide important additional information about the mechanisms underlying RT-ISV.

In this study, we will investigate how the low-frequency RT fluctuations that have been associated with default mode disturbances relate to attentional, internalizing and externalizing behaviors in the general population. To this end, we will apply frequency spectrum analysis to RT series of a lengthy self-paced sustained attention task in a large young adult cohort, which is representative of the full range of mental health problems in the general population [28]. Our main focus will be on the Slow-4 frequency band, but the added value of other frequency bands will also be explored.

2. Subjects and methods

2.1. Study sample

Participants were part of the TRacking Adolescents' Individual Lives Survey (TRAILS), a large representative prospective population cohort study situated in the North of The Netherlands. The TRAILS target sample was selected through primary schools in five municipalities, including both urban and rural areas. The baseline sample comprised 2230 10–12-year-olds (response rate 76%) with diverging socioeconomic backgrounds and academic performance levels. In accordance with the population in the North of The Netherlands, the sample was of predominantly Dutch ethnicity (89.7%). Children of lower socioeconomic background, boys, and children with poor school performance were somewhat less likely to participate, but responders and non-responders did not differ in emotional and behavioral problems [14]. Extensive recruitment efforts were made throughout the assessment waves to ensure that also hard-to-recruit responders were retained in the study ([40], for more details on the sampling procedure and methods [14,28,42]). The present study involved data from the fourth assessment wave (T4) during which the response rate was 84.3% (n = 1881, 52.3% girls) and the mean age was 19.1 ± 0.6 years. We selected participants who successfully completed a sustained attention task (see below) and filled out a self-report questionnaire on problem behaviors at T4 (n = 1455, mean age: 19.0 ± 0.6 years, 55.1% girls, 77.4% of the total T4 TRAILS sample).

2.2. Experimental procedure

2.2.1. Neurocognitive functioning

The sustained attention dot patterns (SAD) task was part of a test battery of five tasks assessing neurocognitive functioning taken from the Amsterdam Neuropsychological Tasks (ANT) battery [13]. During the SAD task, participants had to respond as quickly as possible to patterns with 3, 4 of 5 dots by pressing one of two mouse buttons with the index finger of their dominant hand ("yes" response) when there were 4 dots, and pressing the other mouse button with their non-dominant hand ("no" response) when there were 3 or 5 dots. The three types of dot patterns occurred with equal frequency and were randomly presented across 50 series of 12 trials without breaks. A dot pattern disappeared immediately after a response had been given (valid response window: 200–6000 ms), which means task pace was largely determined by the participant's behavior. In this manner, fluctuations in attention shaped the rhythm of the task rather than the other way around. Each stimulus was followed by a fixed post-response interval of 250 ms.

2.2.2. Mental health problems

Attentional, internalizing and externalizing problems were assessed by the Adult Self-Report (ASR) [1]. Participants rated whether for the past 6 months statements regarding their own adaptive functioning and problems were not true, somewhat or sometimes true, or very or often true. The attentional problem (ATT) scale consists of 15 items (α = 0.84). The internalizing problem (INT) scale is a conjunction of the ASR's withdrawn/depressed (9 items, α = 0.76) and anxious/depressed (18 items, α = 0.91) scales. The externalizing problem (EXT) scale is a conjunction of the ASR's aggressive behavior (15 items, α = 0.85), delinquent behavior (14 items, α = 0.77), and intrusive behavior (6 items, α = 0.68) scales. Missing values on the item level were imputed (if at least half of the scale's items were valid) according to the corrected item mean imputation procedure [27]. For all three scales, the mean item score was calculated.

2.3. Data analyses

2.3.1. Exclusion of participants

Participants were excluded from analyses when their error rate exceeded 15% of trials (90 of 600), when there were task interruptions or response omissions, and in case of multiple (> 4) premature responses below the minimal reaction time of 200 ms for the SAD task, because those subjects probably did not understand task instructions or were insufficiently engaged in the task. In addition, we excluded subjects with a linear time-on-task effect that explained more than 10% of the variance in their time series (time-RT $r > |0.31|$), because frequency analysis can only be performed on stationary signals. In total, 66 datasets were discarded from the eligible sample, which resulted in a sample of 1455 18–20-year-olds who successfully completed the SAD task and questionnaire. Independent sample *t*-tests showed that the excluded subjects did not differ from the included sample on the three outcome domains (all $P > .14$).

2.3.2. Data preparation for frequency spectrum analyses

To prepare the data for frequency spectrum analyses there were three important issues we had to deal with. (1) The wide response window provided leeway for incidental trials with an unusually long RT. This type of trial response can by itself make the variance so large that it obscures any other effects present in the data. Therefore, we defined outliers as RT's that contributed more than 10% to the total variance ($RT\text{-}SD^2$). We calculated the total variance of the RT series and recalculated the variance after removing the largest RT, RTmax, from the RT series. If the new variance was less than 90% of the variance of the original RT series, the RTmax was classified as an outlier. It can be shown that all RT's with a *z*-score (RT-meanRT)/sdRT) higher than 7.8 in the original time series decreased the total variance by 10%; these were classified as outliers. Premature responses and outliers were linearly interpolated, based on the two adjacent trial responses. Only 0.08% of the total number of trials was interpolated. The majority of subjects had no (72.3%) or only one (24.4%) outlier (range: 0–3). (2) RT data typically have a positively skewed distribution. Using a displacement parameter is a normal procedure to benefit optimally from a logarithmic transformation to obtain a normal distribution [16]. Therefore, we applied a displaced natural logarithmic transformation (ln) to approach normality of the distribution (displacement parameter = 150 ms, i.e. the lower limit of probable responses). (3) Trial type (three levels) impacts average RTs. Therefore, we subsequently adjusted the time series for the subjects' average RTs of each stimulus type to regress the impact of trial type on average RT out [16]. The adjusted logarithmic RT series (alnRT) is used in further analyses.

2.3.3. Frequency bands

The center frequencies of discrete neurophysiological oscillation bands are assumed to form a linear progression on a natural logarithmic scale [43]. Based on these center frequencies, six different low-frequency bands have been defined (Supplementary data, Table S1) [16,43]. We discarded the lowest frequency band (Slow-6) because of low reliability. According to the Nyquist theorem, the highest frequency that can be coded corresponds to half the sampling frequency of that signal, which is subject-specific in our task design (range: 0.31–0.74 Hz, median = 0.55 Hz). Therefore, we split the highest frequency band (Slow-2) in one band that was applicable to all subjects (Slow-2b: 0.198–0.30) and another band (Slow-2a: 0.31–0.538) that was only applicable to subjects whose maximum frequency was at least 0.54, that is the "fast" group ($n = 807$, 55.5% of the sample). For all subjects, a total slow band (TSb, range: 0.01–0.30) was defined that spanned across bands Slow-5 up to Slow-2b. For the "fast" group, an additional total slow band was defined that also included the Slow-2a band (TSa, range: 0.01–0.54). The software package interpolates the frequency points to create a frequency resolution of 0.01 Hz (Table 1).

2.3.4. Frequency spectrum analysis

First, we calculated the mean (alnRT-mean) and the standard deviation (alnRT-SD). Then, we applied power spectral analysis (Fig. 1) to the adjusted RT data through CARSPAN, a software program that has originally been developed for cardiovascular data analysis [17]. Similar to cardiac interbeat intervals, the self-paced nature of our task resulted in non-equidistant sample intervals. In order to compute the power in each of the previously defined frequency bands, CARSPAN uses estimation techniques based on direct Fourier Transform, which has less restrictions compared to fast Fourier Transform (i.e. 2^n equidistant samples). The power in bands Slow-5–Slow-2b and TSb was calculated for all subjects. For the Slow-2a and TSa bands, power was calculated only for the "fast" group. Normalized power variables were computed by dividing the power in a particular band by the total power in its respective reference band (Table 1) and multiplying by a hundred. The normalized or relative power indicates the percentage of the total variance a certain frequency band accounts for in a particular subject.

2.4. Statistical analyses

2.4.1. Group characteristics

We compared the "fast" and "slow" groups on task duration, mean error rate, internalizing, externalizing, and attentional problems by means of independent sample *t*-tests.

2.4.2. Regression analyses

Separate simple linear regression models were performed examining the association between relative power in the Slow-4 band (NPW_aln_SL4) and each of the three outcome dimensions of problem behavior (ATT, EXT, INT). Additionally, we created a three-step regression model for each outcome domain. By adding alnRT-SD first, and NPW_aln_SL4 second, we tested whether relative power in the Slow-4 band significantly improved the prediction of problem behaviors beyond the general standard deviation. In the third step, we investigated whether bands Slow-5, Slow-3, and Slow-2b provided important additional information, using a stepwise approach. We repeated this analysis for the "fast" group to additionally examine the role of the Slow-2a band.

3. Results

3.1. Group characteristics

For the eligible sample ($n = 1455$), the average task duration was 9 min (547 ± 74 s) with an average trial duration of 666 ms (± 116), average trial variation of 205 ms (± 87), and a mean error rate of 4.02% (± 2.42). The mean item score, SD, and range for each of the outcome domains is displayed in Table 2. The task duration was significantly shorter for the "fast" group (500.8 ± 27.2) compared to the "slow" group (604.0 ± 62.2), $t(846) = 39.3$, $P < .001$. The "fast" group did not differ from the "slow" group on any of the problem domains (all $P > .11$). The "fast" group did have a slightly higher error percentage (4.6 ± 2.52) than the "slow" group (3.3 ± 2.09), $t(1452) = -10.3$, $P < .001$.

3.2. Regression analyses

The Slow-4 band accounted on average for 17.9% (± 3.5) of the total variance in RT with individual values ranging from 9.3–33.5% (see Supplementary data, Table S2 for the power distribution across the frequency bands for the whole sample and the "fast" and "slow" sub-groups). Simple linear regression models showed that relative power in the Slow-4 band significantly predicted attentional

Table 2
Group characteristics.

	Mean	SD	Range
Internalizing problems	0.29	0.28	0.00–1.67
Externalizing problems	0.23	0.20	0.00–1.34
Attentional problems	0.45	0.31	0.00–1.60

Note that the maximum mean item score is 2 for each outcome domain.

Table 3
Three-step regression models for each outcome domain.

	Attentional problems			Externalizing problems			Internalizing problems		
	B	SE B	β	B	SE B	β	B	SE B	β
Step 1									
Constant	0.37	0.05		0.16	0.03		0.18	0.04	
alnRT-SD	0.26	0.14	.05[a]	0.23	0.09	.06*	0.35	0.13	.07**
F(1,1453)	3.40			5.83			7.13		
R^2 (%)	0.2[a]			0.4*			0.5**		
Step 2									
Constant	0.23	0.07		0.07	0.04		0.19	0.06	
alnRT-SD	0.30	0.14	.06*	0.25	0.09	.07**	0.34	0.13	.07**
NPW_aln_SL4	6.91	2.36	.08**	4.69	1.54	.08**	−0.25	2.14	−.00
F(2,1452)	6.00			7.54			3.57		
ΔR^2 (%)	0.6**			0.6**			0.0		
Step 3									
Constant				0.01	0.05				
alnRT-SD				0.29	0.10	.08**			
NPW_aln_SL4				4.95	1.55	.08**			
NPW_aln_SL5				3.32	1.38	.06*			
F(3,1451)				6.98					
ΔR^2 (%)				0.4*					

Three-step regression models were used to examine the added predictive value of Slow-4 and other bands beyond the global standard deviation. In step 1, only the standard deviation of the adjusted logarithmic reaction time series (alnRT-SD) was included. In step 2, relative power in the Slow-4 band was added to the model. In step 3, the Slow-5, Slow-3 and Slow-2b bands were added to the model if significant. The regression coefficient B and its standard error (SE) for alnRT-SD and power in the bands were multiplied by 10^3. R^2 indicates the percentage of explained variance, ΔR^2 the percentage of added explained variance compared to the previous step.
[a] $P = .07$
* $P < .05$.
** $P < .01$

problems, F(1,1453) = 7.47, $P < .01$, and externalizing problems, F(1,1453) = 7.73, $P < .01$, but not internalizing problems, F(1,1453) = 0.14, $P = .71$. Power in the Slow-4 band accounted for 0.5% of the variation in attentional and externalizing problems. Adding power in the Slow-4 band to initial regression models based on alnRT-SD indicated that Slow-4 improved the prediction of attentional and externalizing problems beyond the general standard deviation; the Slow-4 band accounted for an additional 0.6% of the variation in attentional and externalizing problems (ΔR^2 in Table 3). The Slow-5 band explained another 0.4% of the variation in externalizing problems, but no band beyond Slow-4 added predictive power for attentional problems. For internalizing problems, only the standard deviation had significant predictive value; Slow-4 nor any of the other bands added predictive value beyond the standard deviation. Similar regression analyses in the "fast" group did not show added predictive value of the Slow-2a band for any of the outcome domains.

4. Discussion

In this study, we set out to investigate whether low-frequency RT fluctuations (< 0.1 Hz) that have been associated with default mode disturbances relate to mental health problems in the general population. To this end, we applied a frequency spectrum approach to RT series of a self-paced sustained attention task in which participants' attentional fluctuations drove the rhythm of the task. The three outcome domains were associated with RT variability in their own unique way: internalizing problems only with RT-SD, attentional problems with RT-SD and Slow-4, and externalizing problems with RT-SD, Slow-4, and Slow-5. For none of the outcome domains, additional information was gained by including higher frequency bands in the model. Thus, together with the SD, frequencies below 0.1 Hz seem to pick up on all psychopathology-relevant intra-individual variability.

The finding that relative power in the Slow-4 band significantly predicted attentional problems is consistent with recent studies that found increased low-frequency fluctuations in behavioral performance in children with ADHD [8,16,31,32,51]. Our finding that Slow-4 independently contributed to the prediction of attentional problems, on top of RT-SD, is also in harmony with the earlier finding that this band provides unique information for the differentiation of children with and without ADHD [16]. Thus, Slow-4 seems to be an informative marker of inter-individual variability in attentional problems, which should be obtained alongside the general RT-SD. Our findings extend prior findings in children with ADHD to young adults in the general population. This suggests that an inability to modulate Slow-4 RT fluctuations represents a fundamental process that affects individuals to the extent they experience mental health problems, such as difficulty sustaining attention and forgetfulness. This resonates with recent appeals for a more dimensional approach in the study of mental domains (e.g. NIMH's Research Domain Criteria). The exact brain behavior relationship of Slow-4 fluctuations is not yet clear, but default mode interference has been suggested to cause the performance variability assumed to underlie these ADHD-related symptoms [8,46]. In support of this idea are reports of DMN-abnormalities in ADHD [10,20,26] and findings that medication that increases attention and concentration (i.e. methylphenidate) attenuates both low-frequency RT fluctuations and DMN activity during cognitive tasks in individuals with ADHD [8,36,44]. At this stage, we should, however, be careful with causal inferences given the cross-sectional nature of our study design.

Attentional and externalizing problems are often co-morbid, and issues of behavioral control are central to both of them. Our finding of increased Slow-4 power for externalizing problems further supports the hypothesis that the degree of default mode interference relates to individual differences in effortful control resources [46]. Importantly, Slow-5 power provided additional information for externalizing problems. Possibly, amplified Slow-4 and Slow-5 power both index increased default mode interference (DMN-oscillations have generally been related to frequencies below 0.1 Hz, [11,22]). However, Slow-5 power explained variance for externalizing problems beyond Slow-4. This suggests that externalizing problems are related to an additional neurophysiological process driving slow RT fluctuations. Each frequency band is assumed to be generated by different mechanisms and to serve different physiological functions, with the slowest rhythms integrating the largest neural networks [6,43]. Recent studies show that low-frequency oscillations in the Slow-5 band might be most robust in default mode structures, such as the medial prefrontal cortex and posterior cingulate cortex, whereas Slow-4 oscillations might be strongest in the basal ganglia [25,29,53]. This suggests that while externalizing problems might involve more widespread brain dysregulation, a dysfunction of the basal ganglia could be more central to attentional problems. The basal ganglia are indeed seen as a key site of dysfunction in ADHD [7] and increased Slow-4 power in ADHD has been suggested to represent a catecholaminergic deficiency [8]. Future work should combine neurophysiological measures, such as EEG and fMRI with behavioral measures of task performance to elucidate the exact neural basis of distinct profiles of low-frequency RT fluctuations. Our findings suggest there are both shared and distinct sources of RT-ISV for attentional and externalizing problems.

In line with a previous study in preadolescents, we found that RT-SD predicted internalizing problems in young adults [49]. We did not find evidence for an association between internalizing problems and specific RT fluctuations over and above RT-SD. The finding that the internalizing domain, in contrast to the other two domains, was not associated with low-frequency RT fluctuations is consistent with the finding that internalizing problems are less strongly associated with low effortful control than externalizing problems [19,41]. Possibly, internalizing problems are predominantly associated with task behaviors that are not periodic in nature. Alternatively, low-frequency RT fluctuations might only be related to internalizing problems during tasks that evoke emotional responses or negative rumination, or in patients with a specific diagnostic profile, such as major depressive disorder [38]. Based on the present study, we can nonetheless conclude that default mode interference as assessed by low-frequency RT fluctuations does not seem to be associated with broadly defined internalizing problems in adolescents from the general population.

We should note that, in general, the effects in our study were of modest size. Slow-4 power, for instance, uniquely explained only 0.6% of the variation in attentional problems. This is, however, not unexpected given the multifactorial etiology of mental health problems and our focus on a relatively healthy cohort. A recent meta-analysis of 8 studies suggests there is a moderate effect size across the low frequencies in ADHD (Hedge's $g = 0.39$) [34]. Possibly, larger effect sizes will also be seen at the extreme end of the behavioral spectrum for other psychiatric disorders (e.g. conduct disorder). Importantly, although the effects of the low frequencies were small, they had a stronger impact than the widely used RT-SD (e.g. 1% vs 0.4% for externalizing problems).

Because theory and research have mainly emphasized low-frequency bands in ADHD so far, the primary focus of our study were the Slow-4 (and Slow-5) fluctuations, which have been associated with default mode disturbances. The meta-analysis indicated that faster frequency bands may also be implicated [34], but these higher frequency bands were not related to attentional or other mental health problems in this study. This discrepancy may be explained by the hierarchical nature of our models: higher frequency bands did not provide any *additional* information re attentional problems beyond the lower frequency bands, suggesting they are either irrelevant or redundant (i.e. explained by a similar source). Clearly, more research is warranted into the neurobiological basis of the different components to investigate whether similar or different neurobiological mechanisms affect RT variability in multiple frequency bands.

5. Conclusion

Together, these findings show that RT-ISV contains specific temporal components with potential relevance for psychopathology. While increased global variability in task performance (RT-SD) has been found in many forms of psychopathology, we show domain-specific associations with the slowest temporal components. Thus, a deconstruction of RT-ISV into different temporal components seems to provide an important step for RT-ISV to become a more informative marker. As a second step, future studies will need to address whether different temporal profiles of RT-ISV relate to distinctive underlying neurophysiological processes. It is still unknown whether the temporal patterns of the other spectral bands reflect relevant neural oscillations that occur at similar frequencies, but Slow-4 and Slow-5 power might provide easily acquired proxies for DMN function. This study demonstrated that deconstructing RT-ISV in temporal components opens up new possibilities to investigate the (potentially different) underlying neurophysiological mechanisms of fluctuations in sustained attention in different domains of psychopathology.

Disclosure of interest

J.A.B., A.M.R., A.J.O. No conflict of interest.

J.K.B. has been in the past 3 years a consultant to/a member of the advisory board of/and/or a speaker for Janssen Cilag BV, Eli Lilly, Bristol-Myer Squibb, Shering Plough, UCB, Shire, Novartis and Servier. He is neither an employee nor a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, and royalties.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eurpsy.2014.03.005.

References

[1] Achenbach TM, Rescorla L. Manual for the ASEBA school-age forms & profiles: an integrated system of multi-informant assessment.. Burlington, Vermont: University of Vermont, Research Center for Children, Youth and Families; 2001

[2] Baumeister AA. Intelligence and the "personal equation". Intelligence 1998;26:
255–65.
[3] Bellgrove MA, Hester R, Garavan H. The functional neuroanatomical correlates of response variability: evidence from a response inhibition task. Neuropsychologia 2004;42:1910–6.
[4] Brotman MA, Rooney MH, Skup M, Pine DS, Leibenluft E. Increased intrasubject variability in response time in youths with bipolar disorder and at-risk family members. J Am Acad Child Adolesc Psychiatry 2009;48:628–35.
[5] Brunnekreef A, De Sonneville LMJ, Althaus M, Minderaa RB, Oldehinkel AJ, Verhulst FC, et al. Information processing profiles of internalizing and externalizing behavior problems: evidence from a population-based sample of preadolescents. J Child Psychol Psychiatry 2007;48:185–93.
[6] Buzsáki G, Draguhn A. Neuronal oscillations in cortical networks. Science 2004;304:1926–9.
[7] Castellanos FX, Tannock R. Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. Nat Rev Neurosci 2002;3:617–28.
[8] Castellanos FX, Sonuga-Barke EJS, Scheres A, Di Martino A, Hyde C, Walters JR. Varieties of attention-deficit/hyperactivity disorder-related intra-individual variability. Biol Psychiatry 2005;57:1416–23.
[9] Castellanos FX, Sonuga-Barke EJS, Milham MP, Tannock R. Characterizing cognition in ADHD: beyond executive dysfunction. Trends Cogn Sci 2006;10: 117–23.
[10] Castellanos FX, Margulies DS, Kelly C, Uddin LQ, Ghaffari M, Kirsch A, et al. Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder. Biol Psychiatry 2008;63:332–7.
[11] Cordes D, Haughton VM, Arfanakis K, Carew JD, Turski PA, Moritz CH, et al. Frequencies contributing to functional connectivity in the cerebral cortex in "resting-state" data. AJNR Am J Neuroradiol 2001;22:1326–33.
[12] Dalwani MS, Tregellas JR, Andrews-Hanna JR, Mikulich-Gilbertson SK, Raymond KM, Banich MT, et al. Default mode network activity in male adolescents with conduct and substance use disorder. Drug Alcohol Depend 2014;134: 242–50.
[13] De Sonneville LMJ. Amsterdam Neuropsychological Tasks: a computer-aided assessment program. In: den Brinker BPL, Beek PJ, Brand AN, Maarse SJ, Mulder LJM, editors. Cognitive ergonomics, clinical assessment and computer-assisted learning: Computers in Psychology. Lisse, The Netherlands: Swets & Zeitlinger; 1999. p. 187–203.
[14] De Winter AF, Oldehinkel AJ, Veenstra R, Brunnekreef JA, Verhulst FC, Ormel J. Evaluation of non-response bias in mental health determinants and outcomes in a large sample of pre-adolescents. Eur J Epidemiol 2005;20:173–81.
[15] Depp CA, Savla GN, de Dios LAV, Mausbach BT, Palmer BW. Affective symptoms and intra-individual variability in the short-term course of cognitive functioning in bipolar disorder. Psychol Med 2011;42:1409–16.
[16] Di Martino A, Ghaffari M, Curchack J, Reiss P, Hyde C, Vannucci M, et al. Decomposing intra-subject variability in children with attention-deficit/hyperactivity disorder. Biol Psychiatry 2008;64:607–14.
[17] Dietrich A, Riese H, van Roon AM, van Engelen K, Ormel J, Neeleman J, et al. Spontaneous baroreflex sensitivity in (pre)adolescents. J Hypertens 2006;24: 345–52.
[18] Eichele T, Debener S, Calhoun VD, Specht K, Engel AK, Hugdahl K, et al. Prediction of human errors by maladaptive changes in event-related brain networks. Proc Natl Acad Sci U S A 2008;105:6173–8.
[19] Eisenberg N, Valiente C, Spinrad TL, Liew J, Zhou Q, Losoya SH, et al. Longitudinal relations of children's effortful control, impulsivity, and negative emotionality to their externalizing, internalizing, and co-occurring behavior problems. Dev Psychol 2009;45:988–1008.
[20] Fassbender C, Zhang H, Buzy WM, Cortes CR, Mizuiri D, Beckett L, et al. A lack of default network suppression is linked to increased distractibility in ADHD. Brain Res 2009;1273:114–28.
[21] Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 2007;8: 700–11.
[22] Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A 2005;102:9673–8.
[23] Fox MD, Snyder AZ, Vincent JL, Raichle ME. Intrinsic fluctuations within cortical systems account for intertrial variability in human behavior. Neuron 2007;56:171–84.
[24] Geurts HM, Grasman RPPP, Verté S, Oosterlaan J, Roeyers H, van Kammen SM, et al. Intra-individual variability in ADHD, autism spectrum disorders and Tourette's syndrome. Neuropsychologia 2008;46:3030–41.
[25] Han Y, Wang J, Zhao Z, Min B, Lu J, Li K, et al. Frequency-dependent changes in the amplitude of low-frequency fluctuations in amnestic mild cognitive impairment: A resting-state fMRI study. NeuroImage 2011;55:287–95.
[26] Hoekzema E, Carmona S, Ramos-Quiroga JA, Richarte Fernández V, Bosch R, Soliva JC, et al. An independent components and functional connectivity analysis of resting state fMRI data points to neural network dysregulation in adult ADHD. Hum Brain Mapp 2013;35:1261–72.
[27] Huisman M. Imputation of missing item responses: some simple techniques. Qual Quant 2000;34:331–51.
[28] Huisman M, Oldehinkel AJ, de Winter A, Minderaa RB, de Bildt A, Huizink AC, et al. Cohort profile: the Dutch "TRacking Adolescents" Individual Lives' Survey'; TRAILS. Int J Epidemiol 2008;37:1227–35.
[29] Hutchison WD, Dostrovsky JO, Walters JR, Courtemanche R, Boraud T, Goldberg J, et al. Neuronal oscillations in the basal ganglia and movement disorders: evidence from whole animal and human recordings. J Neurosci 2004;24:9240–3.
[30] Jensen AR. The importance of intraindividual variation in reaction time. Pers Individ Dif 1992;13:869–81.
[31] Johnson KA, Kelly SP, Bellgrove MA, Barry E, Cox M, Gill M, et al. Response variability in attention deficit hyperactivity disorder: evidence for neuropsychological heterogeneity. Neuropsychologia 2007;45:630–8.
[32] Johnson KA, Robertson IH, Kelly SP, Silk TJ, Barry E, Dáibhis A, et al. Dissociation in performance of children with ADHD and high-functioning autism on a task of sustained attention. Neuropsychologia 2007;45:2234–45.
[33] Kaiser S, Roth A, Rentrop M, Friederich H-C, Bender S, Weisbrod M. Intra-individual reaction time variability in schizophrenia, depression and borderline personality disorder. Brain Cogn 2008;66:73–82.
[34] Karalunas SL, Huang-Pollock CL, Nigg JT. Is reaction time variability in ADHD mainly at low frequencies? J Child Psychol Psychiatry 2012;54:536–44.
[35] Krueger RF, South SC. Externalizing disorders: cluster 5 of the proposed metastructure for DSM-V and ICD-11. Psychol Med 2009;39:2061–70.
[36] Liddle EB, Hollis C, Batty MJ, Groom MJ, Totman JJ, Liotti M, et al. Task-related default mode network modulation and inhibitory control in ADHD: effects of motivation and methylphenidate. J Child Psychol Psychiatry 2011;52:761–71.
[37] MacDonald SWS, Nyberg L, Bäckman L. Intra-individual variability in behavior: links to brain structure, neurotransmission and neuronal activity. Trends Neurosci 2006;29:474–80.
[38] Marchetti I, Koster EHW, Sonuga-Barke EJ, Raedt RD. The default mode network and recurrent depression: a neurobiological model of cognitive risk factors. Neuropsychol Rev 2012;22:229–51.
[39] Mason MF, Norton MI, Van Horn JD, Wegner DM, Grafton ST, Macrae CN. Wandering minds: the default network and stimulus-independent thought. Science 2007;315:393–5.
[40] Nederhof E, Jörg F, Raven D, Veenstra R, Verhulst FC, Ormel J, et al. Benefits of extensive recruitment effort persist during follow-ups and are consistent across age group and survey method. The TRAILS study. BMC Med Res Methodol 2012;12:93.
[41] Oldehinkel AJ, Hartman CA, De Winter AF, Veenstra R, Ormel J. Temperament profiles associated with internalizing and externalizing problems in preadolescence. Dev Psychopathol 2004;16:421–40.
[42] Ormel J, Oldehinkel AJ, Sijtsema J, van Oort F, Raven D, Veenstra R, et al. The TRacking Adolescents' Individual Lives Survey (TRAILS): design, current status, and selected findings. J Am Acad Child Adolesc Psychiatry 2012;51:1020–36.
[43] Penttonen M, Buzsáki G. Natural logarithmic relationship between brain oscillators. Thalamus Relat Syst 2003;2:145–52.
[44] Peterson BS, Potenza MN, Wang Z, Zhu H, Martin A, Marsh R, et al. An FMRI study of the effects of psychostimulants on default-mode processing during Stroop task performance in youths with ADHD. Am J Psychiatry 2009;166:1286–94.
[45] Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci U S A 2001;98:676–82.
[46] Sonuga-Barke EJS, Castellanos FX. Spontaneous attentional fluctuations in impaired states and pathological conditions: a neurobiological hypothesis. Neurosci Biobehav Rev 2007;31:977–86.
[47] Stuss DT, Murphy KJ, Binns MA, Alexander MP. Staying on the job: the frontal lobes control individual performance variability. Brain 2003;126:2363–80.
[48] Tang Y, Jiang W, Liao J, Wang W, Luo A. Identifying individuals with antisocial personality disorder using resting-state FMRI. PLoS One 2013;8:e60652.
[49] Van Deurzen P, Buitelaar J, Agnes Brunnekreef J, Ormel J, Minderaa R, Hartman C, et al. Response time variability and response inhibition predict affective problems in adolescent girls, not in boys: the TRAILS study. Eur Child Adolesc Psychiatry 2012;21:277–87.
[50] Weissman DH, Roberts KC, Visscher KM, Woldorff MG. The neural bases of momentary lapses in attention. Nat Neurosci 2006;9:971–8.
[51] Yordanova J, Albrecht B, Uebel H, Kirov R, Banaschewski T, Rothenberger A, et al. Independent oscillatory patterns determine performance fluctuations in children with attention deficit/hyperactivity disorder. Brain 2011;134: 1740–50.
[52] Zahn TP, Kruesi MJ, Rapoport JL. Reaction time indices of attention deficits in boys with disruptive behavior disorders. J Abnorm Child Psychol 1991;19: 233–52.
[53] Zuo X-N, Di Martino A, Kelly C, Shehzad ZE, Gee DG, Klein DF, et al. The oscillating brain: complex and reliable. Neuroimage 2010;49:1432–45.