Identifying a distinctive familial frequency band in reaction time fluctuations in ADHD

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Abstract

Background: Patients with ADHD are typically more variable in their reaction times (RT) than control children. Signal processing analyses have shown that ADHD children's time-series RT data has a distinctive low frequency periodic structure suggestive of a pattern of occasional spontaneous performance lapses. However, findings have been constrained by task design and analytical techniques. Here we use data derived from a simple attention task with a short inter-stimulus interval combined with a fine grained analysis of spectral power across a broader frequency range to differentiate the periodic qualities of ADHD time series RT data from (i) 1/f noise and (ii) the performance of controls. We also assess the familiality of these frequencies by using a proband-sibling design.

Methods: Seventy-one children with ADHD and one of their siblings, and fifty control participants completed a simple RT task. Power across the RT frequency spectrum was calculated and peaks identified for cases and controls. The frequencies significantly differentiating the two groups were identified. Familiality was assessed in two ways. First, by comparing probands with their unaffected siblings and controls, and secondly by investigating the siblings of neuropsychologically impaired and unimpaired children with ADHD.

Results: Analyses converged to highlight the potential importance of the .20-.26 Hz (4-5 second cycles) band in differentiating the periodic structure of variability in ADHD RT time series data from both 1/f noise and control performance. This frequency band also showed the strongest evidence of familiality.

Discussion: ADHD children's RT performance had a distinctive periodic structure compared to controls. The band identified as most differentiating and familial was at a higher frequency than in most previous reports. This highlights the importance of employing tasks

with faster inter-stimulus intervals that will allow a larger portion of the frequency spectrum to be examined. The possible psychological significance of the findings is discussed.

5 KEY WORDS: Reaction Time Variability, Low Frequency, Attention-Deficit/Hyperactivity Disorder, Endophenotype, Attentional lapses

Introduction

Attention deficit/hyperactivity disorder (ADHD) is a common psychiatric disorder of childhood with a complex, multi-factorial aetiology (Bidwell et al., 2007). One of the most consistent findings across laboratory studies is that individuals with ADHD are more variable in their reaction times (RT) on neuropsychological tasks than control children (e.g. Kalff et al., 2005; Klein et al., 2006; Scheres et al., 2001; van Meel et al., 2005). This heightened degree of intra-individual variability (IIV: typically reported as larger standard deviation (SD) of RT) is as strongly and reliably correlated with ADHD symptoms as are measures of more specific cognitive processes (Epstein et al., 2003; Kunsti et al., 2001). IIV is often related to poor performance on tasks (e.g. Bellgrove et al., 2004), although case/control RTV differences are sometimes seen even when there is no obvious performance deficits on other measures (for a review see Klein et al. 2006). Increased IIV has been said to reflect state regulation deficits (Sergeant et al., 1999), an astrocyte dysfunction (Russell et al., 2006) or default-mode interference (Sonuga-Barke & Castellanos, 2007). However the SD of RT statistic, the most commonly used index of IIV, is unable to capture periodic fluctuations in time series RT data which are important in distinguishing between the predictions made by these different models. Random variability that does not contain a regular or periodic, temporal structure may represent global dysregulation of behaviour – perhaps a non-specific feature of psychopathology (Geurts et al. 2008). Periodicity in IIV, in contrast, is assumed to implicate specific biological mechanisms which exhibit similar temporal frequencies (e.g., lapses in attention due to interference from very low frequency brain oscillations; Castellanos et al., 2005; Sonuga-Barke & Castellanos, 2007; Broyd et al., 2009).

A number of alternative indices of variability to SD of RT have been proposed to explore this issue; here we will review two of these indices and related methods. First, the

ex-Gaussian model (Ratcliff et al., 1979) assumes that the RT distribution can be represented as the sum of a normal (Gaussian) distribution and an independent exponential curve. This model has three parameters, μ, the mean, σ the SD of the normal component, and τ the mean of the exponential component. This allows the mean RT from slower responses (τ) to be calculated independently from RTs in the normal distribution. Ex-Gaussian analyses have demonstrated that ADHD and control children may not differ in terms of the first two parameters; however τ is greater suggesting that they make an unusually high proportion of very slow responses (e.g. Leth-Steensen et al., 2000; Hervey et al., 2004). This has been presented as evidence of periodic attentional lapses. Crucially however, the periodic structure of these occasional long RTs cannot be represented in ex-Gaussian models. Instead, more sophisticated signal processing techniques such as Fast Fourier Transformations (FFT), which can inform about the power and amplitude of specific frequency bands within RT data, are required to capture this aspect of IIV. Castellanos et al. (2005) first employed these techniques on time-series RT data. They found that RT data from an Eriksen flanker task oscillated (i.e. fluctuated periodically) at a distinctive frequency, centred around 0.05 Hz[1] (a cycle on average every 20 seconds) in both ADHD and control children. Greater power at this frequency was seen in the ADHD group than the control group: An effect normalised by methylphenidate. Building on this finding Di Martino et al. (2008) found that power in this frequency band was able to predict the diagnosis of ADHD above and beyond SD of RT. However, not all studies have found supportive evidence that ADHD children's RT fluctuations can be differentiated from controls in terms of power in this frequency band. Geurts et al. (2008) did not find children with ADHD to differ from controls

[1] The frequency of oscillations is described in hertz (Hz), which is a unit of cycles per second.

on measures of IIV (SD of RT, ex-Gaussian measures of μ, σ and τ, or frequency domain specific measures of RT), raising questions about how generalisable these findings are across ADHD samples. Nonetheless, these alternative indices of IIV allow us to explore the temporal structure of RT data more effectively and may provide a useful alternative to global measures of RTV in the investigation of underlying biological mechanisms associated with enhanced IIV in ADHD.

While FFT evidence supporting the existence of low frequency periodicity in Flanker Task RT time-series data in ADHD has provided an important impetus for the development of new models of ADHD performance, it is obvious that the particular frequency band identified by these studies will be constrained in a number of ways by the characteristics of the task and the analysis used. First, the flanker task has a relatively slow event rate (typically an inter-stimulus of 3 seconds) so that the observation of cycles of more than 0.17 Hz (i.e. cycles shorter than 6 seconds) are not possible. In this regard it is interesting that Johnson et al., (2007) identified a different ADHD-differentiating frequency band using a sustained attention task with a shorter ISI of 1.5 second. Second, the Flanker task is a relatively complex task incorporating different stimulus types, with different response demands of varying difficulty (i.e. incongruent vs. congruent trials) so that the time series has to be reconstructed statistically to account for the RT difference between easier and more difficult trials. A recent study highlighted the effect of task difficulty on RT periodicity (Vaurio et al. 2009). On a Go/No-Go task, ADHD patients were best differentiated from controls in a frequency band from .027-.074 Hz, but in a complex version of this task, the ADHD patients were best differentiated from controls in a higher frequency band .074-.202 Hz (Vaurio et al. 2009). Third, previous analyses have summed power across theoretically derived frequency bands (slow 2, 0.2-0.5 Hz; slow 3, 0.06-0.2 Hz; and slow 4, 0.02-0.06 Hz,

see Penttonen & Buzsaki, 2003). However, these boundaries may not capture the functionally important or most statistically significant elements with regard to differences between ADHD cases and controls. Finally, analyses have not taken into account that the power spectrum of human RT data, like periodic data from biological systems such as electrical and electromagnetic brain activity (Demanuele et al. 2007) decreases with increasing frequency: That is, it exhibits 1/f noise (Gilden et al. 1995; Gilden 1997; Gilden and Hancock 2007). Because of this there may be a bias towards identifying power peaks in the lower frequencies if analyses are not adjusted for 1/f properties. This has not been done in previous analyses. In summary, task and methodological parameters, including analysis strategy have implications for, and may constrain, the frequency bands that can be observed and explored by frequency domain analyses.

We address these limitations in the current study. First, the task used to generate the time-series RT data is a simple choice RT task with a relatively short ISI (1500 ms). This allows an analysis across a broader frequency range (i.e. 0.01 to 0.30 Hz). Second, we employ a fine grained analysis of spectral power across a broader frequency range unconstrained by the theoretically-derived frequency band boundaries. Finally, we incorporate an assessment of spectral power peaks relative to 1/f noise.

We also assess the familiality of low frequency periodicity in ADHD RT fluctuations. Given the probability that ADHD is genetically heterogeneous (Bidwell et al., 2007), there is a need to find endophenotypes or biological markers associated with etiologically more homogenous and simpler forms (e.g. Doyle et al., 2005). Some data support increased IIV, in general, as an endophenotype of ADHD. Groups of unaffected relatives of probands with ADHD, who share susceptibility genes for the disorder but do not express the disorder themselves, have been shown to demonstrate increased IIV (SD of RT) compared to controls

groups, including dizygotic twin pairs discordant for ADHD (Bidwell et al., 2007; Rommelse et al., 2007; Uebel et al., 2010). Furthermore Nigg et al. (2004) have demonstrated that familial patterns of impairment segregate within ADHD families. When their sample of ADHD children was divided into two groups on the basis of whether they showed excessive IIV, they found that the relatives of those with high levels of IIV also had higher levels of IIV than a group of controls. Siblings of those ADHD patients without high IIV were no different from controls. The value of specific frequency bands of periodic fluctuations in RT as putative endophenotypes (i.e., their familiality) has not been examined. In this paper we report the first analysis of familiality of IIV, in terms of power in low frequency fluctuations in RT time series data.

In summary, in the present study we employ a fine grained analysis of spectral power across a broader frequency range in time series RT data derived from a simple task with a short ISI to; (i) isolate "peaks" in low frequency power that significantly differ from 1/f noise in cases and controls separately and (ii) identify ADHD-differentiating frequency bands. Heritability of ADHD-differentiating frequency bands will be measured by comparing ADHD probands with their unaffected siblings and controls and also the siblings of neuropsychologically impaired and unimpaired subgroups of ADHD. Through these analyses we aim to identify ADHD-differentiating frequencies in the RT time series that differ significantly from 1/f noise and are familial and so likely to be important mediators of aetiological processes.

Method

Methods for the present study have been described elsewhere in three separate publications (see Bitsakou et al., 2008; Bitsakou et al., 2009; Sonuga-Barke et al., 2010a) and will be described only briefly here.

Participants

Seventy-one families with at least one child with ADHD and one sibling were initially recruited into the University of Southampton contribution to the International Multicentre ADHD Genetics study (IMAGE) database. Control participants were recruited from local primary and secondary schools. The ADHD, sibling and control samples are identical to the samples reported in Bitsakou et al. (2008), Bitsakou et al. (2009) and Sonuga-Barke et al. (2010a). Participants who made >15% omission errors on the task were not considered to be sufficiently engaged in the task and were excluded from further analysis (see Di Martino et al., 2008). Seven children from the ADHD group and six children from the sibling group were excluded on this basis. Excluded children were younger (F[1,189] = 9.64, p = .002) and had greater conduct problems (F[1,189] = 6.17, p = .014) than not-excluded children. Data failed to record for two children in the sibling group. Six siblings of the ADHD probands were also affected by ADHD, and were included in the ADHD group in any case/control analyses but were excluded from familiality analyses. Therefore, 69 cases with ADHD, 56 unaffected siblings of a subset of these cases, and 50 controls were included in various analyses. Inclusion criteria for ADHD cases was a research diagnosis of ADHD and inclusion criteria for both ADHD cases and controls was IQ > 70, age 6-17 years, and no other major mental health problems.

Diagnostic Criteria

The clinical diagnosis of ADHD-combined type was validated in all cases using the IMAGE project clinical algorithm, which are described in detail elsewhere (see Brookes et al.,

2006). In brief, probands and siblings with Conners' ADHD subscales T scores > 63 were administered the *Parental Account of Childhood Symptoms* (PACS; Taylor et al., 1991) - a semi-structured clinical interview developed to provide a research-based diagnosis of ADHD and related disorders (i.e. conduct disorder). Parent and teacher report on the Conners long-version rating scales (Conners, 1996), the *Strengths and Difficulties Questionnaire* (SDQ; Goodman, 1997), and Social Communication Questionnaire (Berument et al., 1999) were also used to quantify comorbid symptoms and to identify 'above cut-off' levels of impulsivity or hyperactivity in control children.

Procedure

The University of Southampton IMAGE neuropsychology protocol was approved by both the University of Southampton and local NHS medical-ethics committees. Any ADHD medication was discontinued for at least 48 hours before testing. All participants and parents gave their informed consent to participate in the study. The parent was administered the PACS during the children's neuropsychological testing (no PACS interview was undertaken with the healthy control children or non-ADHD siblings (i.e. Conners' T score < 63)). Each testing session lasted between 2 and 2.5 hours and children were allowed short breaks, the experimenter remained with each child throughout the task. All children received a £5 voucher for their participation.

Task & Measures

All participants completed a simple *two-choice response RT task (2CR-RT;* Hogan et al., 2005) as part of the larger test battery. In this task children were presented with 100 green left- or right-pointing arrows (left- and right- pointing arrows were presented with equal probability [50:50] in random order: 1500 ms ISI, 100ms stimulus presentation) in the centre of a computer monitor. Children were instructed to indicate the direction of each

arrow as quickly and as accurately as possible by a button press of the left or right computer mouse button.

Wechsler Intelligence Scales for Children (WISC-III; Wechsler, 1991) were used to estimate full-scale IQ in all children. The vocabulary and block design subsets were used; this short form of the WISC-III is frequently used as a screening measure in research and has been shown to have good reliability (r = .911) and validity (r = .862) (Sattler, 1992). The sum of the scaled score from these two subtests was converted into an estimated full-scale IQ deviation quotient using the conversion reported in Sattler (1992).

Analytical Strategy

Task performance – RT and SD of RT

Impossible responses (<100 ms) for each participant were removed. The number of omission errors and directional errors for each participant was calculated. Consistent with previous research, Mean RT and SD of RT for each participant was calculated from correct responses only (see Di Martino et al., 2008). For each measure, any outliers (individual's score > 3 SD from the group mean) were replaced by the group mean for that measure. Differences between groups in task performance were assessed using independent samples t-tests. The effect of comorbidities in ADHD cases (i.e. oppositional defiant disorder [ODD], conduct disorder [CD], and anxiety disorder [AD]) was assessed by comparing comorbid and non-comorbid cases using t-tests.

RT data series pre-processing and signal processing analysis

To remove the impact of response type (correct or incorrect) on the RT data series, errors were regressed out and the unstandardised regression residuals were used in subsequent frequency domain analyses (see Helps et al., 2009). To maintain the structure and validity of the RT data series critical for FFT analysis, missing responses were

interpolated using a linear interpolation (SPSS version 15). For the frequency analysis, the 1500 ms ISI allowed for a frequency resolution of up to 0.33 Hz, while the 150 sec block length determined the lower boundary of 0.013 Hz. FFT analyses were conducted (using 60 point Hamming windows with 20 sample overlap) and two separate analyses were then performed on these data.

Identifying frequency bands that distinguish periodic structure of RT data from 1/f noise

First, we identified power peaks in the frequency domain that differentiated the periodic structure of RT time-series data from 1/f noise for cases and controls separately. To achieve this we first fitted a $1/f^{\alpha} + \beta$ model to the mean FFT for each group using EzyFit curve fitting software (version 2.30; see http://www.fast.u-psud.fr/ezyfit/). Previous work suggests that a $1/f^{\alpha} + \beta$ model provides a good fit to RT data where f refers to frequency, α refers to a spectral component and β represents the amplitude of a white noise component. Although Gilden and Hancock (2007) have shown that these components may vary with group status (i.e. participants with attention deficits have a different frequency structure relative to controls), the $1/f^{\alpha} + \beta$ model successfully captured and accounted for this difference, providing a good fit for both groups[2]. We then compared each group's FFT score at each data point to the value predicted by the model, using a one-sampled t-test to identify peaks in the data that differed significantly from the 1/f distribution. As this large number of tests (total number = 8192 tests) would increase the number of false positives occurring by chance, we adopted a stringent criteria for identifying peaks differing from the 1/f noise with 500 consecutive significant results required (see Smith et al., 2007). This represented a frequency band of minimum bandwidth, 0.02 Hz.

[2] As with Gilden and Hancock (2007) $1/f^{\alpha} + \beta$ provided the best fit to our data (Control R = .748, ADHD R = .909)

Identifying frequency bands that distinguish ADHD from controls

Second, using identical significance criteria as above, we attempted to identify frequency bands that differentiated ADHD from control individuals by directly comparing the frequency spectrum of each group. The statistical significance of differences between the ADHD and controls for each point in the whole frequency spectrum was tested using t tests, and the frequency bands that best differentiated the groups identified. Power was calculated as the area under the curve within each of these ADHD-differentiating bands for each of the groups, and as power is not normally distributed these data were (natural) log transformed. The effect of comorbidities in ADHD cases (i.e. oppositional defiant disorder [ODD], conduct disorder [CD], and anxiety disorder [AD]) was assessed by comparing comorbid and non-comorbid cases using t-tests.

Familiality of power within ADHD-differentiating frequency bands was assessed using one-way ANOVA to compare ADHD probands with their unaffected probands and the controls. Following Nigg et al., (2004) we divided the siblings into two groups – those with proband siblings who had high power within these bands (scored in the worst 20th percentile for control children) which we called "impaired" and those that did not meet this inclusion threshold, which we called unimpaired probands. It was predicted that to show familiality, siblings of "impaired" ADHD cases would not differ from ADHD cases in terms of the power in ADHD-differentiating frequency bands but would differ from controls, while the opposite would be the case for the siblings of the "unimpaired" probands.

Results

ADHD cases and controls did not differ in age or gender. The ADHD cases had lower estimated full scale IQ, had more symptoms of ADHD and higher levels of conduct problems (see Table 1). On the 2-CR RT task, the ADHD cases and controls showed similar mean RTs.

ADHD cases were found to make more errors and had higher SD of RT. These effects were unchanged after controlling for IQ.

Figure 1 plots the grand average FFTs of the time-series RT data for ADHD cases and controls superimposed on the 1/f distribution along with the p values for 1 sample t tests of FFT against 1/f values. For controls significant differences from the 1/f model did occur at a number of frequencies (.16 - 17 Hz and .20 -.26 Hz) but only band .20-.26 Hz met the stringent criteria used here. For ADHD cases nominal significant differences ($p < 0.05$) from the 1/f model were identified in the bands .16-.19 Hz, .23 - .26 Hz and .28-.30 Hz in the ADHD FFT. Only the frequency bands .16-.19 Hz and .23-.26 Hz met our stringent criteria.

Figure 2 directly compares the grand average FFTs of the time-series RT data for ADHD cases and controls and plots the p values for differences between the two groups at each point in the frequency spectrum. Differences reached nominal statistical significance ($p < 0.05$) in a number of bands (06-.07 Hz, .14-.16 Hz, .20-.26 Hz, .30 -.32Hz). Only bands .14-.16Hz (cycles 6-7 seconds: 1022 consecutive significant results) and .20-.26 Hz (cycles 4-5 seconds: 1656 consecutive significant results) met the stringent criteria. Table 1 reports the case control differences for the area under the curve of the different ADHD-differentiating frequency bands. There were no significant differences between comorbid and non-comorbid cases for any of these disorders in any of the outcome variables.

Familiality Analysis: Probands, unaffected siblings and controls did not differ in age. Although there was a smaller proportion of boys in the sibling group compared to the proband or the control group (see Table 2), a multivariate ANOVA with gender entered as the independent variable found no significant effect of gender on any of the measures of variability ($F(1,173) = .547$, p = .461 *ns*). Siblings were reported to have more ADHD symptoms and conduct difficulty scores at intermediate levels between probands and

controls scores. Siblings generally displayed IIV scores that were intermediate between probands and controls (SD of RT and differentiating frequencies). These results were unchanged by statistically controlling for IQ. When we looked at the siblings of "impaired" and "non-impaired" probands we found evidence for within family correlations on SD of RT and the frequency band from .20-.26 Hz (see Table 3). That is, in both cases "impaired" children differed significantly from controls but not from probands in terms of IIV, while the reverse was the case for the unimpaired children. These effects remained significant after controlling for age and IQ.

Discussion

This study replicates previous findings of increased IIV (SD of RT) in ADHD and suggests that this variability has a low frequency periodic structure that is distinctive relative to controls. One band in particular (.20-.26 Hz: cycles 4-5 seconds) seemed especially important given that it demonstrated the greatest difference in the FFT spectrum between ADHD cases and controls and overlapped with a band on which ADHD cases power differed significantly from the predicted 1/f distribution, suggesting that this power peak could not be accounted for by 1/f noise. Finally, this band provided the strongest evidence of familiality.

This frequency band is somewhat higher than that typically found to differentiate ADHD children from controls in previous studies (Castellanos et al. 2005; Di Martino et al. 2008). However these analyses have used data from the Eriksen flanker task and this task may not be ideally placed to assess periodicity in time series data. It places high demands on interference control, has multiple trial types of varying difficulty (three different stimulus types and two different directions for each stimulus), and samples performance infrequently (3 second ISI). Crucially because of its slow ISI our ADHD-differentiating frequency (.20 -.26

Hz) cannot be observed in the data obtained from the Eriksen Flanker task given its temporal parameters (i.e. only frequencies lower than .17 Hz could be identified given a 3 second ISI). Interestingly Johnson et al. (2007) who used a sustained attention task with a similar ISI to the task we use here, reported that the RT fluctuations in a group of impaired-ADHD children (defined by the number of commission errors) were best distinguished from an unimpaired-group and controls by power in the frequency band of .07-.33Hz (cycles 3–14 seconds) – importantly, the band found in the current study overlaps with the frequency band identified in prior work. Furthermore, although Di Martino et al. (2008) controlled for multiple trial types by regressing out their effects from the RT time-data series, the impact of these methods on the FFT is unclear. Although, investigations of frequency domain variability in RT data must allow sufficient time for participant responses, which means that stimuli cannot be presented at extremely fast rates, utilising tasks with faster ISIs will allow a larger portion of the frequency spectrum to be examined and this will clarify the frequency bands which are able to best distinguish between ADHD cases and controls. The best possible tasks are probably those with continuous rather than discrete measures of performance. For instance, deviation from target plotted against time on a visual tracking task may provide the optimal measure of the periodic nature of performance lapses in ADHD.

The proband-sibling analysis provided evidence about the potential importance of this ADHD differentiating-frequency band as a putative endophenotype. First we examined the differences in the power in this band between probands, unaffected siblings and controls. Second we looked at whether this measure was specifically related to RT variability in unaffected family members. The findings were consistent with previous research (e.g. Nigg et al., 2004) in showing evidence for familiality for SD of RT: unaffected siblings of

children with ADHD were found to exhibit intermediate SD of RT scores between probands and control children (the difference between unaffected sibilings and controls was non-significant), and siblings of probands who showed impaired SD of RT also exhibited greater SD of RT than control children or siblings of unimpaired-probands. We extended this analysis by showing a very similar familial pattern in terms of spectral power in the frequency band .20 - .26 Hz. These data provide the first evidence that lower frequency fluctuations in RT data may be familial, and because siblings had intermediate scores between probands and controls, may have value as an ADHD endophenotype. Future research needs to extend this design to genetically informative-designs and studies to establish its relationship with measures of genetic and environmental risk.

The current study differed from previous studies in that it used a data driven approach to identify the boundaries to ADHD-differentiating frequency bands rather than theoretically pre-defined frequency bands founded upon mathematical models of the properties of RT spectra and other physiological systems such as neuronal oscillations (see Penttonen and Buzsáki 2003; Buzsáki and Draguhn 2004). The ADHD-differentiating band found in the current study overlapped with these bands to some degree (i.e. .20-.26 Hz overlaps with the slow 2 frequency band [0.2-0.5 Hz]). The convergence of mathematical model-based and data-driven approaches to defining frequency band boundaries is an important consideration for future research, with particular relevance for concurrent RT and physiological data recordings, such as EEG.

The finding of periodic fluctuations in RT in the current study is in keeping with models that see ADHD as the result of alterations in context-dependent dynamic processes (Sonuga-Barke et al. 2010b). In general, IIV in RT performance in ADHD is theoretically rather non-specific. It has been argued at different times to reflect deficits in state-

regulation (Sergeant et al. 1999; Sonuga-Barke et al. 2010b), time perception (Castellanos and Tannock 2002) and executive dysfunction (Barkley, 1997). The current finding and those previously reported of a low frequency periodic signature to this variability, while potentially consistent with all these models, is specifically predicted by a recent neuro-biological model of attentional lapses in impaired states and systems, such as that seen in ADHD. In this model, periodic spontaneous lapses in attention occur when very low frequency brain activity typically seen in the default network of the resting brain (for a review see the following: Raichle et al. 2001; Fox and Raichle 2007; Sonuga-Barke and Castellanos 2007; Broyd et al. 2009) is not effectively attenuated during the transition from rest to task, and thus intrudes into and interferes with brain processes required for performance (e.g. Sonuga-Barke and Castellanos 2007). Indeed imaging studies have shown increased SD of RT in patients with ADHD is associated with reduced deactivation of the default network (Fassbender et al. 2009; Helps et al. 2009; Helps et al. 2010). Likewise EEG studies have shown reduced attenuation of resting state very low frequency EEG activity in ADHD participants with the onset of tasks (Helps et al. 2009; Helps et al. 2010), and that this low frequency activity is synchronised with RT fluctuations to a greater extent for participants who do not deactivate 'default-mode' activity effectively and who exhibit high levels of ADHD symptoms (Helps et al. 2009). In the current study, the frequency band that best differentiated patients from controls and provided the most convincing evidence of familiality is faster (.20 to .26 Hz; cycles of 4-5 seconds) than the neuronal oscillations typically associated with the default-mode network, as defined by hemodynamic and electrophysiological recordings (<0.1 Hz, see Fox and Raichle 2007; Helps et al. 2008; Helps et al. 2009; Helps et al. 2010). Nevertheless, a direct assessment of the relationship between these faster neuronal oscillations (4-5 second cycles) using EEG or BOLD signal data

(which is limited to very low frequency bands by its sampling rate) and 4-5 second cycle fluctuations in RT data, has yet to be conducted. Future research utilising tasks with fast ISIs and concurrent EEG recordings will be able to answer these questions more directly.

In sum, we have shown that children with ADHD exhibit greater IIV than controls: More specifically, they show periodic fluctuations in RT in time-series data. We highlight the potential importance of a particular frequency band (.20-.26 Hz: cycles 4-5 seconds) that strongly differentiated ADHD cases from controls, was different from 1/f noise and showed evidence of heritability.

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Reference List

Barkley, R. A. (1997). Inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. *Psychological Bulletin, 121*, 65-94.

Bellgrove, M.A., Hester, R. & Garavan, H. (2004).The functional neuroanatomical correlates of response variability: evidence from a response inhibition task. *Neuropsychologia, 42*(14)*,* 1910-6.

Berument, S.K., Rutter, M., Lord, C., Pickles, A. & Bailey, A. (1999). Autism screening questionnaire: diagnostic validity. *British Journal of Psychiatry, 175,* 444-51.

Bidwell, L.C., Willcutt, E.G., DeFries, J.C. & Pennington, B.F. (2007). Testing for neuropsychological endophenotypes in siblings discordant for attention-deficit/hyperactivity disorder. *Biological Psychiatry, 62*(9), 991-8.

Bitsakou, P., Psychogiou, L., Thompson, M. & Sonuga-Barke, E.J.S. (2008). Inhibitory deficits in attention-deficit/hyperactivity disorder are independent of basic processing efficiency and IQ. *Journal of Neural Transmission, 115*(2), 261-8.

Bitsakou, P., Psychogiou, L., Thompson, M. & Sonuga-Barke, E.J.S. (2009). Delay Aversion in Attention Deficit/Hyperactivity Disorder: An empirical investigation of the broader phenotype. *Neuropsychologia, 47*(2), 446-56.

Brookes, K., Xu, X., Chen, W., Zhou, K., Neale, B., Lowe, N., Aneey, R., Franke, B., Gill, M., Ebstein, R., Buitelaar, J., Sham, P., Campbell, D., Knight, J., Andreou, P., Altink, M., Arnold, R., Boer, F., Buschgens, C., Butler, L., Christiansen, H., Feldman, L., Fleischman, K., Fliers, E., Howe-Forbes, R. et al. (2006). The analysis of 51 genes in

DSM-IV combined type attention deficit hyperactivity disorder: association signals in DRD4, DAT1 and 16 other genes. *Molecular Psychiatry, 11*(10), 934-53.

Broyd, S., Demanuele, C., Debener, S., Helps, S., James, C.J. & Sonuga-Barke, E.J.S. (2009). Default-mode brain dysfunction in mental disorders: A systematic review. *Neuroscience and Biobehavioural Reviews, 33*(3), 279-96.

Buzsáki, G. & Draguhn, A. (2004). Neuronal oscillations in cortical networks. *Science, 304,* 1926-1929.

Castellanos, F.X., Sonuga-Barke, E.J.S., Scheres, A., Di Martino, A., Hyde, C. & Walters, J.R. (2005). Varieties of attention-deficit/hyperactivity disorder-related intra-individual variability. *Biological Psychiatry, 57,* 1416-23.

Castellanos, F. X. & Tannock, R. (2002). Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. *Nature Reviews Neuroscience,* 3, 617-628.

Conners, K. (1996). Rating scales in ADHD. Durham NC, Duke University Medical Centre.

Demanuele, C., James, C. J. & Sonuga-Barke, E.J.S. (2007). Distinguishing low frequency oscillations within the 1/f spectral behaviour of electromagnetic brain signals. *Behavioral and Brain Functions,* 3, 62.

Doyle, A.E., Willcutt, E.G., Seidman, L.J., Biederman, J., Chouinard, V.A., Silva, J. & Faraone, S.V. (2005). Attention-deficit/hyperactivity disorder endophenotypes. *Biological Psychiatry, 57*(11), 1324-35.

Di Martino, A., Ghaffari, M., Curchack, P., Reiss, C., Hyde, C., Vannucci, E., Petkova, D., Klein, D. & Castellanos, F.X. (2008). Decomposing Intra-Subject Variability in Children with Attention-Deficit/Hyperactivity Disorder. *Biological Psychiatry, 64*(7), 607-14.

Epstein, J.N., Erkanli, A., Conners, C.K., Klaric, J., Costello, J.E. & Angold, A. (2003). Relations between continuous performance test performance measures and ADHD behaviors. *Journal of Abnormal Child Psychology, 31*(5), 543-54.

Fassbender, C., Zhang, H., Buzy, W. M., Cortes, C. R., Mizuiri, D., Beckett, L., & Schweitzer, J. B. (2009). A lack of default network suppression is linked to increased distractibility in ADHD. *Brain Research, 1273*, 114-128.

Fox, M. D. & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonanceimaging. *Nature Reviews Neuroscience, 8,* 700-711.

Geurts, H.M., Grasman, R.P.P.P., Verte, S., Oosterlaan, J., Roeyers, H., van Karnmen, S.M. & Sergeant, J.A. (2008). Intra-individual variability in ADHD, autism spectrum disorders and Tourette's syndrome. *Neuropsychologia, 46*(13), 3030-41.

Gilden, D. L. (1997). Fluctuations in the time required for elementary decisions. *Psychological Science, 8*(4), 296-301.

Gilden, D. L., & Hancock, H. (2007). Response varability in attention-deficit disorders. *Psychological Science, 18*(9), 796-802.

Gilden, D. L., Thornton, T., & Mallon, M. W. (1995). 1/f noise in human cognition. *Science, 267*(5205), 1837-1839.

Goodman, R. (1997). The strengths and difficulties questionnaire: A research note. *Journal of Child Psychology & Psychiatry, 38*(5), 581-6.

Helps, S., James, C., Debener, S., Karl, A., & Sonuga-Barke, E. J. S. (2008). Very low frequency EEG oscillations and the resting brain in young adults: A preliminary study of localisation, stability and association with symptoms of inattention. Journal of Neural transmission, 115, 279-285.

Helps, S. K., Broyd, S. J., James, C. J., Karl, A., Chen, W., & Sonuga-Barke, E. J. S. (2010). Altered spontaneous low frequency brain activity in Attention Deficit/Hyperactivity Disorder. Brain Research, 1322, 134-143.

Helps, S. K., Broyd, S. J., James, C. J., Karl, A., & Sonuga-Barke, E. J. S. (2009). The attenuation of very low frequency brain oscillations in transitions from a rest state to active attention. Journal of Psychophysiology, 23(4), 191-198.

Hervey, A.S. (2004). Reaction time distribution analysis on Conners' continuous performance test as a function of ADHD diagnosis and symptomatology. *Dissertation Abstracts International: Section B: The Sciences and Engineering, 65*(6), 3162.

Hogan, A.M., Vargha-Khadem, F., Kirkham, F.J., & Baldeweg, T. (2005). Maturation of action monitoring from adolescence to adulthood: an ERP study. *Developmental Science, 8*(6), 525-34.

Johnson, K.A., Kelly, S.P., Bellgrove, M.A., Barry, E., Cox, M., Gill, M. & Robertson, I.H. (2007). Response variability in Attention Deficit Hyperactivity Disorder: Evidence for neuropsychological heterogeneity. *Neuropsychologia, 45*(4), 630-8.

Kalff, A.C., De Sonneville, L.M.J., Hurks, P.P.M., Hendriksen, J.G.M., Kroes, M., Feron, F.J.M., Steyaert, J., Van Zeben, T.M.C.B., Vles, J.S.H., Jolles, J. (2005). Speed, speed variability, and accuracy of information processing in 5 to 6-year-old children at risk of ADHD. *Journal of International Neuropsychology Society, 11*(2), 173-83.

Klein, C., Wendling, K., Huettner, P., Ruder, H. & Peper, M. (2006). Intra-subject variability in attention-deficit hyperactivity disorder. *Biological Psychiatry, 60*(10), 1088-97.

Kuntsi, J., Oosterlaan, J. & Stevenson, J. (2001). Psychological mechanisms in hyperactivity: I response inhibition deficit, working memory impairment, delay aversion, or something else? *Journal of Child Psychology & Psychiatry, 42*(2), 199-210.

Leth-Steensen, C., Elbaz, Z.K. & Dougla,s V.I. (2004). Mean response times, variability, and skew in the responding of ADHD children: a response time distributional approach. *Acta Psychologica, 104*(2), 167-90.

Nigg, J.T., Blaskey, L.G., Stawicki, J.A. & Sachek, J. (2004). Evaluating the endophenotype model of ADHD neuropsychological deficit: Results for parents and siblings of children with ADHD combined and inattentive subtypes. *Journal of Abnormal Psychology, 113*(4), 614-25.

Penttonen, M. & Buzsaki, G. (2003). Natural logarithmic relationship between brain oscillators. *Thalamus & Related Systems, 2,* 145-52.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America, 98*(2), 676-682.

Ratcliff, R. (1979). Group reaction time distributions and an analysis of distribution statistics. *Psychological Bulletin, 86,* 446-61.

Rommelse, N.N.J., Oosterlaan, J., Buitelaar, J., Faraone, S.V. & Sergeant, J.A. (2007). Time reproduction in children with ADHD and their nonaffected siblings. *Journal of American Academy of Child and Adolescent Psychiatry, 46*(5), 582-90.

Russell, V., Oades, R., Tannock, R., Killeen, P., Auerbach, J., Johansen, E. & Sagvolden, T. (2006). Response variability in Attention-Deficit/Hyperactivity Disorder: a neuronal and glial energetics hypothesis. *Behavioural Brain Function, 2*(1), 30.

Sattler, J.M. (1992). *Assessment of children: WISC-III and WPPSI-R Supplement.* San Diego, CA: Sattler, J. M.

Scheres, A., Oosterlaan, J. & Sergeant, J.A. (2001). Response execution and inhibition in children with AD/HD and other disruptive disorders: The role of behavioural activation. *Journal of Child Psychology & Psychiatry, 42*(3), 347-57.

Sergeant, J., Oosterlaan, J. & van der Meere, J. (1999). Information processing and energetic factors in attention-deficit/hyperactivity disorder. In: Quay HC, Hogan A, editors. *Handbook of disruptive behavior disorders*. (pp: 75-104). New York: Plenum Press.

Smith, J.L., Johnstone, S.J. & Barry, R.J. (2007). Response priming in the Go/NoGo task: The N2 reflects neither inhibition nor conflict. *Clinical Neurophysiology, 118*(2), 343-55.

Sonuga-Barke E.J.S, Bitsakou, P. & Thompson, M. (2010a). Beyond the Dual Pathway Model: Evidence for the Dissociation of Timing, Inhibitory, and Delay-Related Impairments in

Attention-Deficit/Hyperactivity Disorder. *Journal of American Academy of Child & Adolescent Psychiatry, 49*(4), 345-55.

Sonuga-Barke, E. J. S., Wiersema, J. R., van der Meere, J. J., & Roeyers, H. (2010b). Context dependent-dynamic processes in attention deficit/hyperactivity disorder: differentiating common and unique effects of state regulation deficits and delay aversion. *Neuropsychological Review, 20*(1), 86-102.

Sonuga-Barke, E.J.S. & Castellanos, F.X. (2007). Spontaneous attentional fluctuations in impaired states and pathological conditions: A neurobiological hypothesis. *Neuroscience & Biobehavioural Reviews, 31*(7), 977-86.

Taylor, E., Sandberg, G., Thorley, G. & Giles, S. (1991). The epidemiology of childhood hyperactivity. *Maudsley Monograph,* No. 33 ed. Oxford: Oxford University Press.

Uebel, H., Albrecht, B., Asherson, P., Borger, N.A., Butler, L., Chen, W., Christiansen, H., Heise, A., Kuntsi, J., Schafer, U., Andreou, P., Manor, I., Marco, R., Miranda, A., Mulligan, A., Oades, R.D., van der Meere, J., Faraone, S.V., Rothenberger, A., Banaschewski, T. (2010). Performance variability, impulsivity errors and the impact of incentives as gender-independent endophenotypes for ADHD. *Journal of Child & Adolescent Psychiatry, 51*(2), 210-218.

van Meel, C.S., Oosterlaan, J., Heslenfeld, D.J. & Sergeant, J.A. (2005). Motivational effects on motor timing in attention-deficit/hyperactivity disorder. *Journal of American Academy of Child & Adolescent Psychiatry, 44*(5), 451-60.

Vaurio, R., Simmonds, D. & Mostofsky, S.H. (2009). Increased intra-individual reaction time variability in attention-deficit/hyperactivity disorder across response inhibition tasks with different cognitive demands. *Neuropsychologia, 47*(12), 2389-96.

Wechsler D. (1991). *Wechsler Intelligence Scale for Children*. 3rd ed. San Antonia, Tx: Psychological Corporation.

Table 1: Group characteristics and task performance for cases and controls

	Cases (N=69) Mean (SD)	*Controls (N=50) Mean (SD)*	*Test*	*df*	*Test statistic*	*p*	*Effect size (Cohen's d)*
% Boys	81%	66%	χ^2	1	3.53	.060	
Age	11.66 (1.74)	12.16 (2.25)	*t*	117	.588	.558	
IQ (WISC)							
Vocabulary score	8.80 (2.88)	9.82 (3.47)	*t*	117	1.75	.082	
Performance score	9.23 (2.52)	10.48 (2.57)	*t*	117	2.64	.009	
Estimated Full Score	90.0 (13.4)	101.0 (15.2)	*t*	117	2.63	.010	
SDQ							
Parent Reported							
Hyperactivity	8.20 (1.87)	1.98 (1.68)	*t*	117	18.7	<.001	
Conduct Problems	5.64 (2.36)	1.32 (1.71)	*t*	117	11.0	<.001	
Total difficulties	22.1 (6.53)	6.38 (4.41)	*t*	117	14.6	<.001	
Teacher Reported	N=59	N=37					
Hyperactivity	6.78 (2.85)	1.35 (1.36)	*t*	94	10.8	<.001	
Conduct problems	2.72 (2.36)	.32 (.709)	*t*	94	6.00	<.001	
Total difficulties	14.86 (7.56)	3.65 (3.29)	*t*	94	8.51	<.001	
Scores from RT task							
Number directional errors	30.0 (13.67)	18.7 (15.1)	*t*	117	4.24	<.001	1.43
Number omission errors	6.16 (4.45)	2.18 (3.16)	*t*	117	4.05	<.001	1.05
Mean RT (ms)	363 (75.4)	366 (76.1)	*t*	117	.162	.872	.04
Mean SD of RT (ms)	164 (75.6)	104 (47.0)	*t*	117	4.97	<.001	.98
Mean power .06-.07 Hz	6.57 (1.42)	5.56 (1.55)	*t*	117	4.05	<.001	.68
Mean power .14-.16 Hz	6.81 (1.09)	6.08 (1.03)	*t*	117	3.91	<.001	.69
Mean power .20-.26 Hz	7.58 (.884)	6.97 (.910)	*t*	117	3.95	<.001	.68
Mean power .30-.32 Hz	5.36 (1.08)	4.81 (1.09)	*t*	117	3.10	.002	.51

Table 2: Group characteristics and task performance for probands, siblings and controls

	Probands (N=64) Mean (SD)	*Siblings (N=56) Mean (SD)*	*Controls (N=50) Mean (SD)*	*Test*	*df*	*Test statistic*	*p*	*Post-hoc comparisons*	*Effect size (Cohen's d)*
% Boys	84%	52%	66%	χ^2	2	13.5	.001		
Age	12.09 (2.28)	11.91 (2.99)	12.16 (2.25)	*F*	2,167	.138	.871		
IQ (WISC)									
Vocabulary score	8.10 (2.68)	9.32 (2.31)	9.82 (3.47)	*F*	2,167	2.22	.112	C > P	.56
Performance score	9.23 (2.40)	9.54 (2.78)	10.48 (2.57)	*F*	2,167	3.45	.034	C > P	.50
Estimated Full Score	93.8 (12.0)	96.67(12.5)	101.0 (15.2)	*F*	2,167	4.18	.017	C > P	.53
SDQ									
Parent Reported									
Hyperactivity	8.28 (1.86)	3.64 (2.61)	1.98 (1.68)	*F*	2,167	162	<.001	P >S , C	2.08, 3.56
Conduct Problems	5.70 (2.30)	2.32 (2.45)	1.32 (1.71)	*F*	2,167	64.6	<.001	P >S > C	1.42, .48
Total difficulties	22.41 (6.43)	9.11 (7.62)	6.38 (4.41)	*F*	2,167	107.4	<.001	P >S > C	1.89, .45
Teacher Reported	N=54	N=44	N=37						
Hyperactivity	6.85 (2.73)	3.52 (2.71)	1.35 (1.36)	*F*	2,131	59.5	<.001	P >S > C	1.22, 1.07
Conduct problems	2.72 (2.33)	1.43 (1.91)	.32 (.709)	*F*	2,131	18.2	<.001	P >S > C	.61,.85
Total difficulties	14.87 (7.27)	7.84 (6.62)	3.65 (3.29)	*F*	2,131	38.0	<.001	P >S > C	1.01, .85
Scores from RT task									
No. of directional errors	29.3 (13.5)	19.5 (11.7)	18.7 (15.1)	*F*	2,167	11.6	<.001	P > S, C	.78, .74
No. of omission errors	4.92 (4.30)	3.02 (3.61)	2.18 (3.16)	*F*	2,167	8.06	<.001	P > S, C	.48, 0.74
Mean RT (ms)	357 (74.0)	399 (88.8)	366 (76.1)	*F*	2,167	4.53	.012	S > P, C	.52, .40
Mean SD of RT (ms)	157 (70.8)	127 (60.3)	104 (47.0)	*F*	2,167	10.60	<.001	P > S > C	.46,.43
Mean power .06-.07 Hz	6.57 (1.42)	6.02 (1.39)	5.56 (1.55)	*F*	2,167	6.91	.001	P > S, C	.39, .68
Mean power .14-.16 Hz	6.81 (1.09)	6.43 (1.03)	6.08 (1.03)	*F*	2,167	6.31	.002	P > C	.69
Mean power .20-.26 Hz	7.58 (.884)	7.25 (.925)	6.97 (.910)	*F*	2,167	6.52	.002	P > C	.68
Mean power .30-.32 Hz	5.36 (1.08)	5.03 (1.01)	4.81 (1.09)	*F*	2,167	3.92	.022	P > C	.51

Note. Post-hoc comparisons are shown where $p < .05$; P = proband, S = sibling, C = control

Table 3: Variability scores in frequencies of significance for probands, impaired- and unimpaired-sibs, and controls.

								Group comparisons and effect size (Cohen's d)		
	Probands Mean (SD)	*Impaired-sib Mean (SD)*	*Unimpaired-sib Mean (SD)*	*Controls Mean (SD)*	*Test*	*df*	*Test statistic*	*p*	*P > C*	*I-S > C*	*U-S >C*
Mean SD of RT	157 (70.8)	147 (75.2)	127 (64.6)	104 (47.0)	*F*	3,174	5.89	.001	✓ .90	✓ .70	× .41
Power .06 -.07 Hz	6.57 (1.42)	5.90 (1.63)	6.04 (1.34)	5.56 (1.55)	*F*	5, 159	4.05	.008	✓ .68	× .22	× .33
Power .14 - .16 Hz	6.81 (1.09)	6.36 (1.19)	6.46 (.998)	6.08 (1.15)	*F*	5, 159	3.99	.009	✓ .65	× .20	× .35
Power .20 - .26 Hz	7.58 (.883)	7.43 (1.01)	7.21 (.893)	6.97 (.910)	*F*	5, 159	3.80	.011	✓ .68	✓.48	× .27
Power .30 - .32 Hz	5.36 (1.08)	4.97 (.772)	5.12 (1.11)	4.81 (1.09)	*F*	5, 159	2.30	.080	✓ .51	× .17	× .28

Note. P = proband, I-S = Impaired-sibling, U-S = unimpaired-sibling, C = control. All analyses control for IQ. ✓ indicates significant group difference ($p < .05$) × indicates non-significant group difference ($p > .05$)

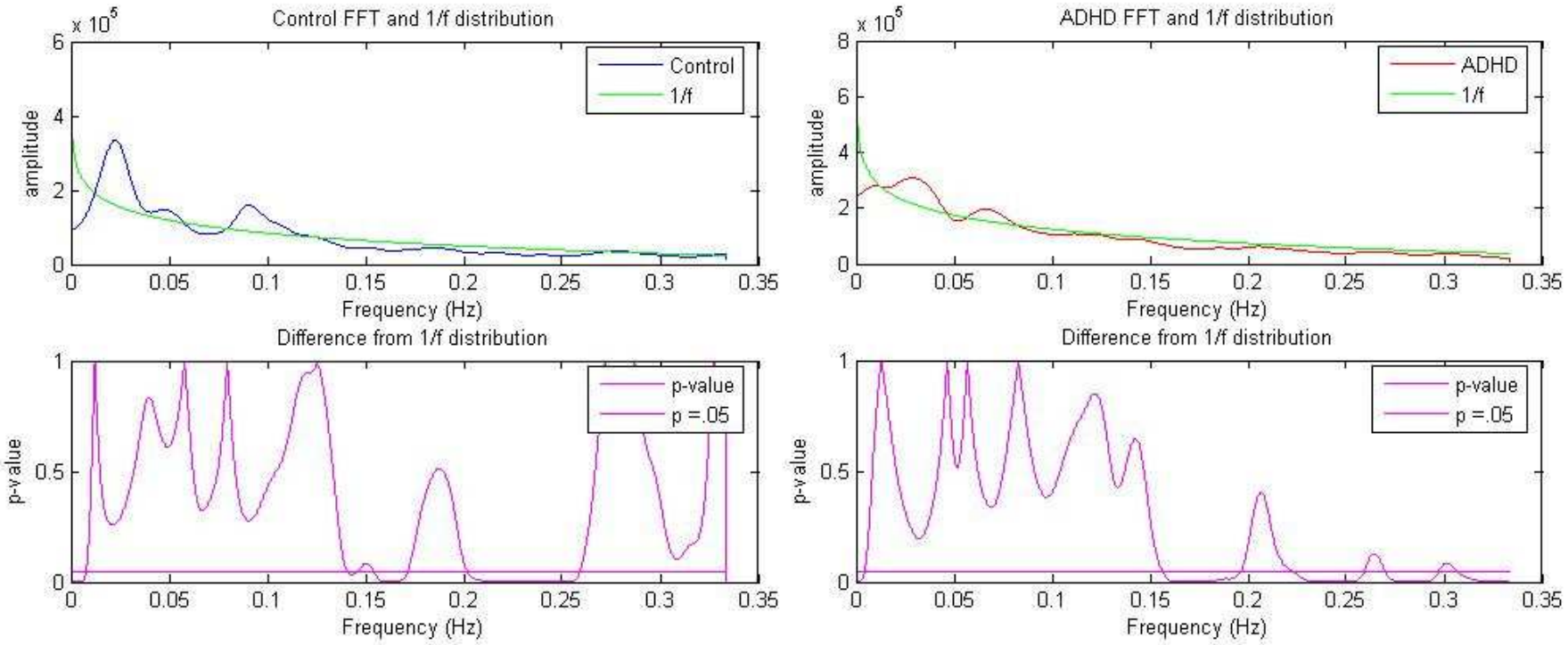

Figure 1: Mean FFT and fitted 1/f function for control (top left) and ADHD groups (top right), and the probability of the FFT differing from the predicted model (one sampled t-tests) for controls (bottom left) and ADHD groups (bottom right)

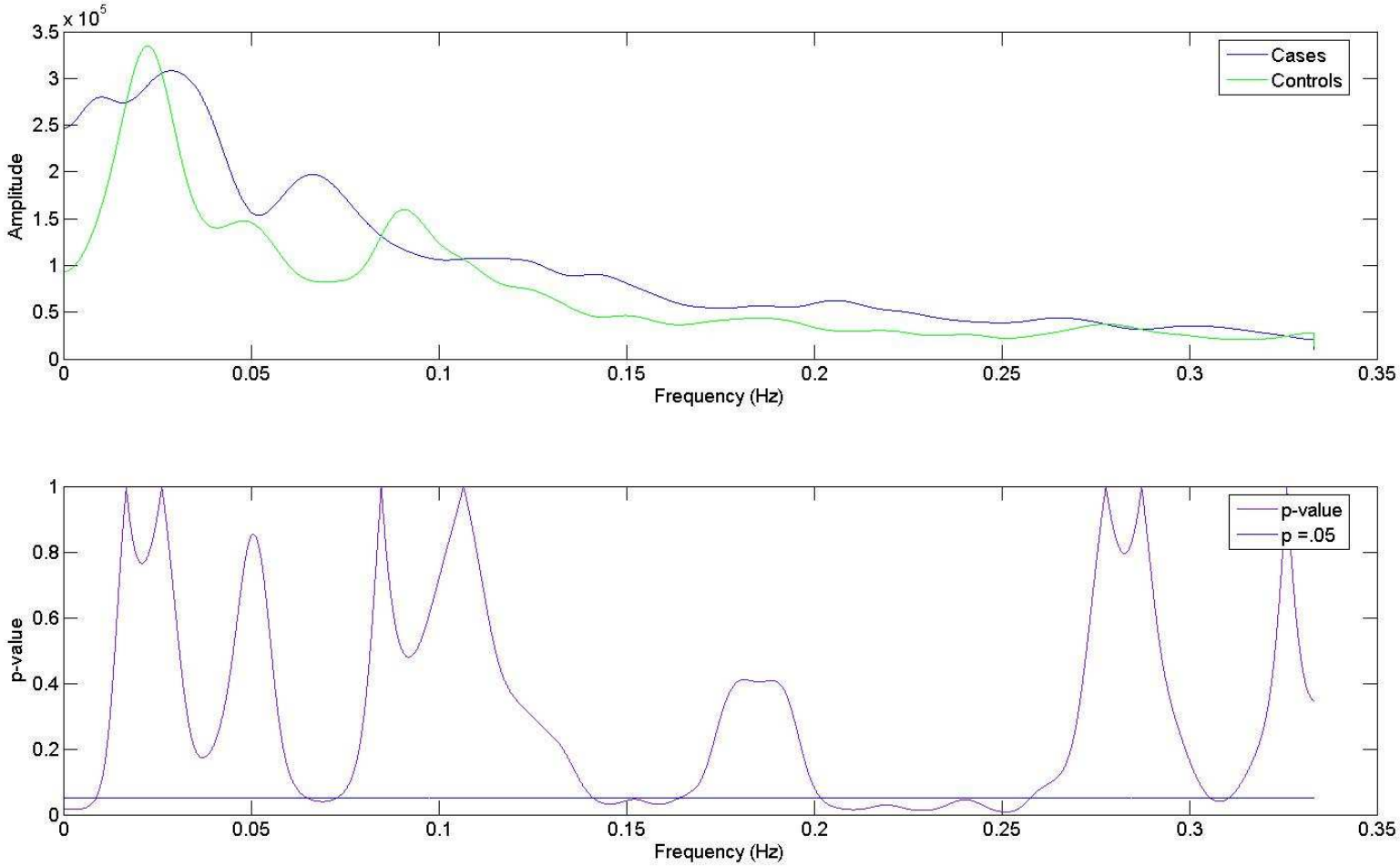

Figure 2: FFT of RT data for cases and controls (above), and the t statistic p value for each difference (below)