The aperiodic exponent of pupil fluctuations in the resting state predicts excitation/inhibition balance in attentional processing

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Abstract

The aperiodic exponent of neural signals in different modalities is associated with the excitation/inhibition balance of the neural system. Given that resting pupil fluctuations contain rich temporal dynamics, we hypothesized that the aperiodic exponent of pupil fluctuations could predict the neural excitation/inhibition balance in attentional processing. The present study was the first attempt to investigate the cognitive significance of the aperiodic exponent of pupil responses. We recorded participants' resting pupil fluctuations and measured their visual attention with a Posner cueing task. Significant correlations were found between the aperiodic exponent of pupil fluctuations and microsaccadic and behavioral responses when stimulus uncertainty was high and thus required a neural excitation/inhibition balance. Furthermore, an independent analysis showed that the aperiodic exponent of pupil fluctuations was predictive of an individual's ADHD symptoms of hyperactivity/impulsivity, suggesting its potential to reflect an individual's trait of attentional processing. These findings highlight the rich information contained in pupil fluctuations and open a new avenue for accessing the neural excitation/inhibition balance in cognitive processing.

Keywords

Aperiodic exponent, pupil size, excitation/inhibition balance, visual attention

Introduction

Brain activities at different spatiotemporal scales often exhibit a 1/f-like power spectrum–power decreases with increasing frequency, which represents aperiodicity of the neural response (He, 2014). Aperiodicity has been demonstrated in the fluctuations of electrocorticography (ECoG, Manning et al., 2009), electroencephalogram (EEG, Waschke et al., 2021), magnetoencephalography (MEG, Dehghani et al., 2010), and functional magnetic resonance imaging (fMRI, He, 2011) signals. Additionally, 1/f-like power spectrums have also been observed in the behavioral recordings of animals (Jones et al., 2023) and humans (Palva et al., 2013). Even though the slopes of the power spectrum are different for different modalities, the aperiodic dynamics of behavioral and neural activities have been found to be strongly related across modalities (Jones et al., 2023), indicating a general cognitive mechanism underlying these dynamics. Evidence has suggested that the slope of the 1/f spectrum (i.e., the aperiodic exponent) tracks the ratio of excitation and inhibition in the underlying neuronal circuits (Gao et al., 2017), such that the general mechanism has been suggested to be the excitation/inhibition balance (E/I balance). For example, causal evidence has been found where the anesthetic drug propofol, which enhances neural inhibition, increases the aperiodic exponent, while the anesthetic drug ketamine, which enhances neural excitation, decreases the slope of the aperiodic exponent (Waschke et al., 2021). Consequently, the aperiodicity has been viewed as a reflection of the E/I balance in neural processing.

Pupil size is usually considered to be related to the state of arousal. Pupil fluctuations contain rich temporal dynamics, which are primarily influenced by two neurotransmitters (Reimer et al., 2016), the locus coeruleus-norepinephrine (LC-NE) and the basal forebrain-acetylcholine (BF-ACh) systems. Pfeffer et al. (2022) found a significant negative correlation between pupil size and the aperiodic exponent of the MEG signal, showing that the larger the pupil, the smaller the aperiodic exponent (i.e., the flatter the spectrum). These results indicate that there may be a relationship between pupil size and E/I balance, i.e., the larger the pupil, the greater the neural excitation and the weaker the neural inhibition. Meanwhile, previous studies have found that the pupil fluctuations, such as hippus (pupil oscillations below 1 Hz), reflect neural excitability better than raw pupil size (Binda & Lunghi, 2017; Pomè et al., 2020). However, previous studies have mainly focused on the periodic features of pupil fluctuations, and no study has investigated the relationship between the

aperiodic component of pupil fluctuations and neural E/I balance.

The present study sought to examine whether the aperiodic component of pupil fluctuations during the resting state could reflect the E/I balance in attentional processing. The LC-NE and BF-ACh systems are related to both pupil control and attentional processing (Thiele & Bellgrove, 2018), which may share common control mechanisms. Furthermore, in the classic Posner cueing task, Yu and Dayan's (2005) study found that both neurotransmitter systems were able to represent and utilize information uncertainty for attentional processing. We therefore hypothesized that the aperiodic component of pupil fluctuations could reflect the E/I balance of attentional processing and that their relationship is modulated by stimulus uncertainty.

E/I balance could be reflected not only in the aperiodic component of neural activities but also in the symptoms of attention-deficit/hyperactivity (ADHD). There is experimental evidence of changes in the spectral slopes of neural signals in ADHD patients, suggesting abnormalities in the neural E/I balance of these patients. For example, Robertson et al. (2019) reported that the spectral slopes were steeper in preschool-age children with ADHD. In addition, children with ADHD have a greater theta-beta ratio (Arns et al., 2013), also implying a steeper spectral slope (Finley et al., 2022). However, there is also inconsistent evidence. Other researchers have found flatter spectral slopes in school-age and adolescent ADHD samples (Ostlund et al., 2021). Karalunas et al. (2022) reconciled this conflict by showing that infants with a family history of ADHD had steeper spectral slopes, whereas adolescents diagnosed with ADHD had flatter slopes, with the trend reversing across age. In addition, multiple pupil indices in the resting state, such as size and hippus, have been associated with symptoms of ADHD in adults (Nobukawa et al., 2021), but to date, no studies have examined the relationship between the aperiodic component of the pupil fluctuations and ADHD symptoms. We further hypothesized that if the aperiodic component of pupil fluctuations during the resting state reflects an individual's trait of E/I balance, then this trait should be reflected in an individual's ADHD symptom level.

To test these hypotheses, the present study examined the relationship between the aperiodic component of the resting pupil and the performance on attentional tasks (including behavioral and microsaccadic responses) and ADHD symptoms. To reflect the E/I balance in attentional processing, we used the exogenous spatial cueing paradigm with different cue-validity (100% and 50%) used by Jia et al. (2017, 2019) (Fig. 1A) and recorded behavioral and microsaccadic responses. ADHD

symptoms were assessed by the Adult Self-Rating Scale for ADHD (ASRS, Kessler et al., 2005). The results showed that the aperiodic exponent of pupil fluctuations in the resting state predicted E/I balance in attentional processing, as evidenced by a significant correlation between the aperiodic exponent and behavioral and microsaccadic responses in the 50%, but not 100%, cue-validity condition. Mediation analyses further indicated that the microsaccadic response in the attention task mediated the effect of the aperiodic exponent on behavioral performance. Finally, the aperiodic exponent of resting pupil fluctuations was predictive of hyperactivity/impulsivity in ADHD symptoms, which supports our second hypothesis. Thus, the present study demonstrates for the first time that the aperiodic exponent of pupil fluctuations reflects neural E/I balance in attentional processing and further suggests that this exponent could be used as a measure of adult ADHD symptoms.

Methods

Participants

Seventy adult volunteers (33 males, 19-25 years old) were recruited. The sample size was chosen based on previous studies, which suggested that this number was adequate for a reliable individual differences approach (Carter Leno et al., 2022; Karalunas et al., 2022). Participants had normal or corrected-to-normal vision, and had no known neurological or visual disorders. The research protocols reported here were approved by a local ethics committee at Hangzhou Normal University. Written informed consents were obtained from all participants prior to the experiment.

Apparatus and tools

The visual stimuli were presented on a CRT monitor (resolution: 1024×768; refresh rate: 85 Hz). The MATLAB (The MathWorks) and the Psychophysics Toolbox (Brainard, 1997) were used to present the stimuli and to record the behavioral responses. The experiment took place in a dimly lit and sound-proof room. The participants comfortably seated at a viewing distance of about 70 cm, with their heads stabilized on a chin rest.

Stimuli and procedure

The experiment consisted of a spatial cueing task phase and a resting-state eye-movement recording phase. The spatial cueing task was similar to that in our previous study on attentional shifting (Jia et al., 2017; Lv et al., 2022). Fig. 1A showed the events that occurred on a typical trial. At the beginning of each trial, a central fixation dot (0.16°×0.16°; 0 cd/m^2), flanked by two square place holders (4°×4°; 104 cd/m^2; distance to the fixation dot: 6°), was presented on a gray background (23 cd/m^2) for 1000-1500 ms. Then, the border of one of the placeholders suddenly dimmed to 0 cd/m^2 in luminance for 100 ms, serving as exogenous cueing on the corresponding spatial location. Following an inter-stimulus interval of 1000-1500 ms, a bar (size: 1.30°×0.13°; luminance: 67 cd/m^2) that tilted left or right by 2° appeared in one of the placeholders for 100 ms as a probe. The participants were instructed to report the tilt orientation of the probe by pressing one of two keys within 1000 ms. The participants were required to maintain fixation throughout the whole trial. The cue-validity was manipulated within participants with a block design. Specifically, participants completed two blocks of the spatial cueing task, with the validity of the spatial cue being 100% and 50% in each block, respectively. The assignment of the validity to each block was balanced across participants, and participants were informed about the cue-validity before starting

each block. Each block contained 200 trials, which took about 20 minutes to complete. Participants completed 15 practical trials at the beginning of each block.

After the spatial cueing task, participants underwent a resting-state phase, where their eye movement information was recorded. During this phase, participants were required to look at the fixation point (0.16°×0.16°; 0 cd/m^2) in the center of the gray screen (23 cd/m^2) for 300 s and were told to minimize blinking.

Eye movement recording

Eye movements were recorded binocularly at 1000 Hz with an EyeLink 1000 eye tracker (SR Research, Ottawa) during the whole experiment. A chin rest was used for each participant to maintain good tracking accuracy. The eye tracker was calibrated with a standard 9-point calibration procedure at the beginning of each experiment session.

Microsaccade detection in the spatial cueing task

Microsaccades were detected with an improved version (Engbert & Mergenthaler, 2006) of the algorithm originally proposed by Engbert and Kliegl (2003). Horizontal and vertical eye positions were mapped onto a velocity space, to which a 5 standard deviations threshold was applied to detect saccades. For a detected saccade to be counted as a microsaccade, three criteria must meet: 1) a temporal overlap between the two eyes, 2) a minimum duration of 6 ms, and 3) an amplitude below 1°. Trials that contained saccades larger than 1° were excluded from the analysis. This data cleansing procedure excluded 8% and 10% of the trials from the 100% and 50% cue-validity experiments, respectively.

Microsaccade rate analysis

A rectangular moving window of 100 ms (stepped in 1 ms) was used to examine the microsaccade rate in a time window of 100 ms before and of 1000 ms after the attention cue onset (Engbert & Kliegl, 2003). Considering that a microsaccade could land in the same or opposite hemifield as the cue, we will use “congruent” and “incongruent” to refer to these two types of microsaccades, respectively. The cueing effect was revealed in the rate difference between the congruent and incongruent microsaccades.

Resting-state pupillometry data processing

The PuPl toolbox (Kinley & Levy, 2021) was used for pre-processing of the raw pupil size data, which took the following three steps:

1. Raw pupil size data cleaning. The samples in which pupil size is changing at an implausibly high rate (i.e., where the "dilation speed" is too high) and samples that are small "islands" surrounded by missing data are recognized as outliers and deleted from the recordings (Kret & Sjak-Shie, 2019). The threshold of the dilation speed was set to be the median speed plus 3 times the median absolute deviation. The "islands" were defined as samples with a duration of less than 30 ms and are surrounded by missing data exceeding 25 ms.

2. Blink identification. Blinks were identified with the pupillometry noise method (Hershman et al., 2018). The identified blink samples were deleted from the recordings along with their adjacent data within 50 ms prior to and 150 ms after the identified blinks.

3. Data interpolation, smoothing, and downsampling. The gaps in pupil size data resulting from data cleaning and blink removal were filled in using linear interpolation. High-frequency noises in the pupil size data were removed by data smoothing using a moving mean filter with a 150-ms length Hanning window (Zhao et al., 2019). Finally, the data were downsampled from 1000 Hz to 100 Hz and averaged across two eyes.

Spectral slope and power analysis

The 300-s pre-processed pupil data were first normalized for each participant to remove the mean difference between participants. Then, the power spectral density (PSD) of the normalized pupil data was calculated using the Welch's method with a window length of 5000 data points and 50% overlapping windows. The "Fitting Oscillations and One-Over-f" (FOOOF) toolbox was used to calculate the aperiodic exponent (Donoghue et al., 2020) of the PSDs, which uses a spectral parameterization algorithm to decompose the power spectrum into periodic and aperiodic components via an iterative process of model fitting. Considering that the fluctuations of pupil size are mainly concentrated between 0-1 Hz (Pomè et al., 2020; i.e., pupillary hippus; Turnbull et al., 2017) and that the spectral plateau above 1 Hz could disrupt the estimation of aperiodic exponent (Gerster et al., 2022), we extracted aperiodic exponents from the 0-1 Hz frequency range of each power spectrum (aperiodic_mode = 'fixed', max_n_peaks = 'inf', default settings otherwise). The 'fixed' setting was used given that we did not anticipate a "knee" in the power spectrum. This assumption was supported by visual inspection of each PSD after spectral parameterization via FOOOF.

ADHD symptoms measurement

ADHD symptoms were measured using the World Health Organization adult ADHD Self-Report Scale (ASRS; Kessler et al., 2005), an eighteen-item measure of ADHD symptoms that can be administered verbally or through survey. The "inattention" and "hyperactivity/impulsivity" symptoms were each measured with nine items of the ASRS. Participants select how frequently each statement is true in the past 6 months for them on a five-point scale from 0=never to 4=very often. Higher scores are indicative of more severe symptoms associated with ADHD.

Statistical analysis

Independent samples t-tests were used in tests for differences in behavioral accuracies and the behavioral cueing effects between groups of participants. The cluster-based permutation test (Maris & Oostenveld, 2007) was used to test the between-group differences in cueing effects in the microsaccade rate. Pearson correlation was used for all correlation analyses.

As significant paths were found between the aperiodic exponent and the microsaccadic cueing effect, the aperiodic exponent and the behavioral cueing effect, and the microsaccadic cueing effect and the behavioral cueing effect, a formal participant-wise mediation model was implemented. The indirect path from the aperiodic exponent to the microsaccadic cueing effect (a) and the microsaccadic cueing effect to the behavioral cueing effect (b) was computed, as was the direct path from the aperiodic exponent to the behavioral cueing effect (c'). The indirect path and mediation were computed as the product of $a \times b$, with a resulting 95% confidence interval for each indirect path from 1,000 bootstrapped samples. The total, direct and indirect effects were tested for significance at $P < 0.05$.

Results

The aperiodic exponent of resting pupil fluctuations correlates with the attentional cueing effect

Fig. 1B shows that the pupil size in the resting state gradually decreased over time during the 300-s recording phase. The power spectral density (PSD) of the pupil size fluctuations (Fig. 1C) roughly followed a 1/f power law distribution, with the power being higher at lower frequencies and decreasing rapidly with increasing frequency. The decrease in power was roughly linear in the double logarithmic coordinates (Fig. 1C). We used the FOOOF algorithm (Donoghue et al., 2020) to separate the aperiodic and oscillatory components of the pupil spectrum, which found that only 30 of the 70 participants (43% of the participants) had periodic oscillations in their pupil data. The remaining 40 participants (57% of the participants) did not have any oscillatory component in their pupil fluctuations (Fig. 1D) despite the fact that the parameters were set to allow the algorithm to detect any possible oscillatory component. Therefore, we extracted the oscillatory component from the pupil data of the 30 participants who had oscillatory component. Results showed that the oscillatory frequency of the pupil was concentrated around 0.3 Hz (Fig. 1E), consistent with previous studies (Bouma & Baghuis, 1971; Turnbull et al., 2017; Ukai et al., 1997). Next, our analysis focused on the relationship between aperiodic exponent of pupil fluctuations and the behavioral performance in the attention task.

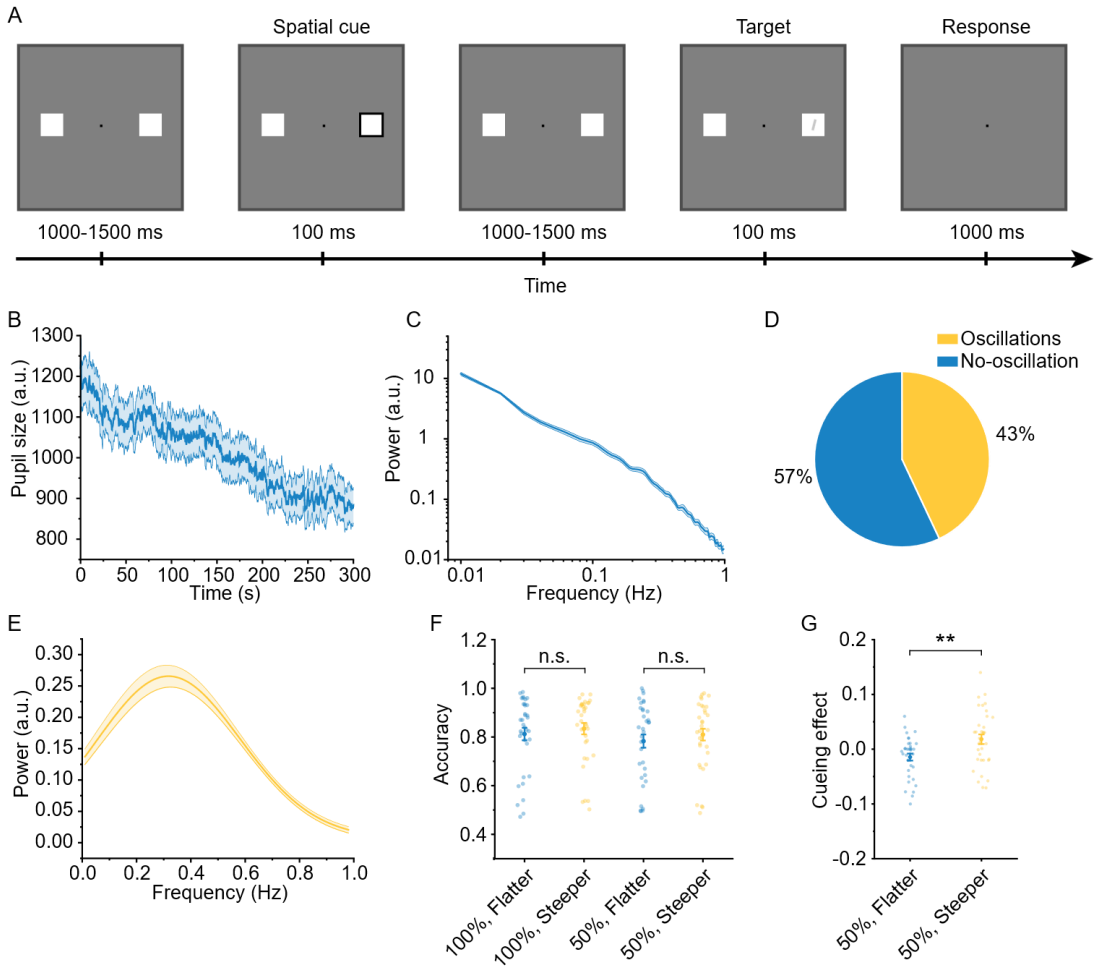

Fig. 1. Trial structure of the experimental task and pupil fluctuations in the 300-s resting state. (A) Trial structure for a valid-cue condition of the experimental task. A fixation dot flanked by two placeholders (white squares) was first presented on the screen. After 1000-1500 ms, the border of one placeholder turned into black for 100 ms (spatial cue). After another interval of 1000-1500 ms, the probe appeared briefly in one of the placeholders. The probe was a bar tilted left or right by 2°, and participants judged the tilt orientation by a keypress within 1000 ms. The cue predicted the probe location on 100% and 50% of the trials in the two blocks of the experiment, respectively. (B) Fluctuations of the raw pupil size in the 300-s resting state. (C) PSD of the resting-state pupil fluctuations shown in the double logarithmic coordinates. (D) The proportion of participants with and without periodic oscillations in the pupil fluctuations. (E) PSD of the pupil oscillations within 0 - 1 Hz. (F) Behavioral response accuracy in the 100% and 50% cue-validity experiments for participants with flatter and steeper spectral slopes. (G) Spatial cueing effects in the 50% cue-validity experiment for the two groups of participants, i.e., participants with flatter or steeper spectral slopes. The shaded areas in B, C, E and the error bars in F, G indicate the standard

error of the mean (SEM).

To examine the relationship between the aperiodic exponent of pupil fluctuations (i.e., the slope of the spectrum) and the behavioral performance, we divided the 70 participants into two halves based on the median value of the aperiodic exponent. The slope of the spectrum was relatively steeper in participants with a high aperiodic exponent and relatively flatter in participants with a low aperiodic exponent. In the experiment with 100% cue-validity, both groups of participants had high response accuracies ($M \pm SD$: flatter group, 0.81±0.15; steeper group, 0.83±0.14) and there was no significant difference between the two groups ($t(68) = -0.63$, $P = 0.529$, Cohen's $d = -0.15$; Fig. 1F). For the 50% cue-validity experiment (i.e., where the cue failed to predict where the probe would appear), the two groups of participants also had high response accuracies ($M \pm SD$: flatter group, 0.78±0.16; steeper group, 0.81±0.14), which did not differ significantly between groups ($t(68) = -0.73$, $P = 0.468$, Cohen's $d = -0.17$; Fig. 1F), either. These results suggest that the aperiodic component of pupil fluctuations is not predictive for the overall accuracy in attentional tasks, either in the 100% or 50% cue-validity conditions.

We then calculated the spatial cueing effect (i.e., difference between the response accuracy in the cued direction and that in the uncued direction) in the 50% cue-validity experiment. The results showed that the cueing effect was numerically lower than 0 ($M \pm SD$: -0.02±0.04) for participants with a flatter slope (lower aperiodic exponent), but was numerically greater than 0 ($M \pm SD$: 0.02±0.05) for participants with a steeper slope (higher aperiodic exponent). Furthermore, there was a significant difference in the cueing effect between the two groups ($t(68) = -3.00$, $P = 0.004$, Cohen's $d = -0.72$; Fig. 1G). The significant relationship between the aperiodic exponent and the attentional cueing effect, rather than the overall accuracy, may be due to the fact that the attentional cueing effect more closely reflects the balance of attention in the cued and uncued directions.

The aperiodic exponent of the resting pupil fluctuations correlates with microsaccadic IOR in high stimulus uncertainty

Attentional effects elicited by exogenous cues are reflected by dynamic changes in the microsaccade rate (Laubrock et al., 2005; Lv et al., 2022). The microsaccade after the presentation of an exogenous cue is oriented more in the opposite direction of the cue, reflecting a microsaccadic inhibition of return (IOR). We examined the relationship between the aperiodic exponent of the

pupil fluctuations and the microsaccadic response. As in the analyses above, we divided the participants into two groups according to the aperiodic exponent value and examined the microsaccadic responses of each group of participants. We calculated the cueing effect for the microsaccade rate by subtracting the rate of microsaccade in the cued direction by that in the uncued direction. For the 100% cue-validity experiment, the cueing effect of the microsaccade rate was negative after cue presentation (Fig. 2A), replicating the classic microsaccadic IOR effect (Laubrock et al., 2005; Lv et al., 2022). Critically, the cueing effect of the microsaccade rate was not significantly different between the two groups of participants with high and low aperiodic exponents. To further validate the results of median splitting, we extracted the microsaccadic cueing effect in 200-500 ms for all participants and calculated its correlation with the aperiodic exponent of the pupil fluctuations (Fig. 2B). We found that the aperiodic exponent was not significantly correlated with the microsaccadic cueing effect in the 100% cue-validity experiment ($r = 0.01$, $P = 0.946$). For the 50% cue-validity experiment, the cueing effect of microsaccade was also negative after cue presentation (Fig. 2C). However, the cueing effect of microsaccade was significantly different between the two groups of participants (from 216 to 381 ms), with the participants having lower aperiodic exponent (i.e., flatter spectrum) showing greater microsaccadic IOR. To validate the results of median splitting, we extracted the microsaccadic cueing effect in 200-500 ms for all participants and calculated its correlation with the aperiodic exponent of the pupil fluctuations (Fig. 2D). We found that the aperiodic exponent was significantly correlated with the microsaccadic cueing effect in the 50% cue-validity experiment ($r = 0.36$, $P = 0.002$). These results replicated those of behavioral performance, showing that the aperiodic exponent was associated with microsaccadic and behavioral responses only at 50% cue-validity, i.e., when stimulus uncertainty was high. More importantly, these results further demonstrate that participants with low aperiodic exponent exhibit hyperexcitability to nonpredictive cues and fail to suppress automatic microsaccadic responses to nonpredictive cues. The behavioral and microsaccade results provide direct evidence for the first hypothesis of this study.

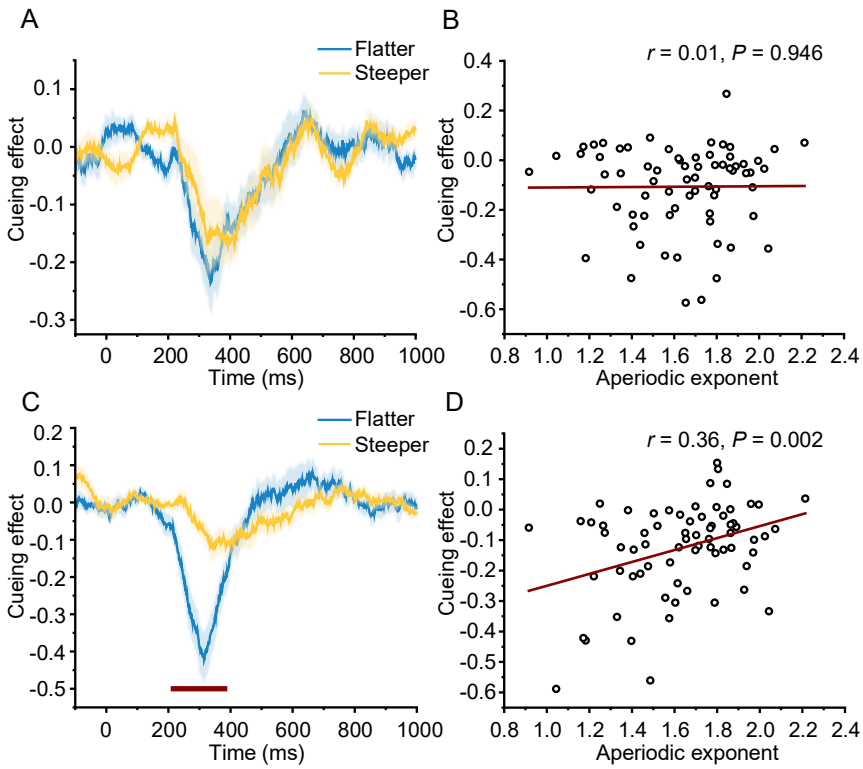

Fig. 2. Relationship between the pupillary aperiodic exponent and the cueing effect in microsaccade rate. (A) Microsaccadic cueing-effects for two groups of participants with flatter and steeper spectral slopes in the 100% cue-validity experiment. (B) Correlation between the microsaccadic cueing effect and aperiodic exponent in the 100% cue-validity experiment. (C) Microsaccadic cueing effects for two groups of participants with flatter and steeper spectral slopes in the 50% cue-validity experiment. (D) Correlation between the microsaccadic cueing effect and aperiodic exponent in the 50% cue-validity experiment. The shaded areas indicate the SEM.

To explore whether the prediction of the microsaccadic cueing effect in the 50% cue-validity experiment was selective to the aperiodic exponent of the pupil fluctuations, we further median-split the participants using the mean, variance, and hippus power of the raw pupil size data. We found no significant differences between the microsaccadic cueing effects of the three median-split halves of participants (Fig. 3). This result further suggests that the aperiodic exponent of the pupil fluctuations predicts the neural E/I balance better than the raw pupillary measurements.

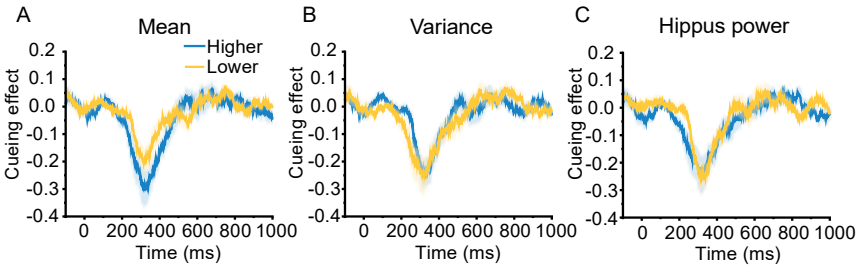

Fig. 3. Differences of microsaccadic cueing-effects in the 50% cue-validity experiment using mean (A), variance (B), and hippus power (C) of the pupil size data to median-split the participants. The shaded areas indicate the SEM.

Microsaccadic response mediates the effect of the aperiodic exponent of resting pupil fluctuations on the attentional effect

Since the aperiodic exponent of the resting pupil fluctuations was correlated with microsaccadic IOR and behavioral performance in the 50% cue-validity experiment, we explored whether the aperiodic exponent of the resting pupil fluctuations serves as an individual trait that influences the microsaccadic IOR to the stimulus, which then influences the behavioral response to the stimulus. Supporting this hypothesis, participant-wise mediation analyses revealed that the relationship between the aperiodic exponent of resting pupil fluctuations and the behavioral cueing effect was fully explained by the microsaccadic IOR (Fig. 4; indirect effect: $b = 0.02$, $P = 0.043$; direct effect: $b = 0.03$, $P = 0.166$; total effect: $b = 0.05$, $P = 0.018$). The total and indirect effects were significant in the mediation, but the direct effect was not significant. These outcomes indicate that the aperiodic exponent of resting pupil fluctuations influences individuals' microsaccadic responses to the cue which then influence the behavioral performance. These results support the hypothesis that aperiodic exponent of resting pupil fluctuations could reflect individuals' trait of attentional processing that affect behavioral outcomes by influencing microsaccadic responses.

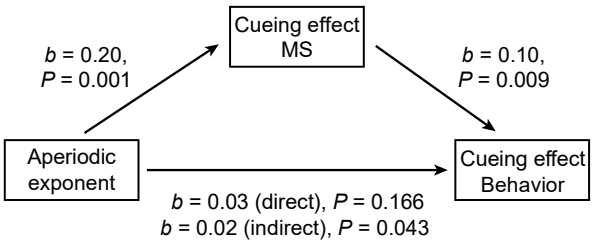

Fig. 4. Participant-wise mediation model for pupil and behavioral data from the 50% cue-validity experiment. The cue effect of microsaccade mediates the relationship between the

aperiodic exponent and the cue effect of behavior.

The aperiodic exponent of the resting pupil fluctuations predicts ADHD symptoms

Finally, if the aperiodic exponent of pupil fluctuations could reflect the trait of attentional processing, we predicted that such a trait should correlate with the level of ADHD symptoms. To test this point, we calculated correlations between the aperiodic exponent and the ADHD symptoms measured by ASRS (Kessler et al., 2005). We calculated the correlation between the aperiodic exponent and the total ADHD score as well as its inattention and hyperactivity/impulsivity subcomponents. We found a significant negative correlation between the aperiodic exponent and the total ADHD score (Fig. 5A; $r = -0.27$, $P = 0.023$), suggesting that a lower aperiodic exponent (flatter slope) is accompanied by more severe ADHD symptoms. While a negative correlation was observed in both subcomponents, the correlation was significant between the aperiodic exponent with hyperactivity/impulsivity (Fig. 5B; $r = -0.35$, $P = 0.003$) but not with inattention (Fig. 5C; $r = -0.10$, $P = 0.472$). Therefore, a lower aperiodic exponent is accompanied by more severe hyperactivity/impulsivity symptoms. This result suggests that the aperiodic exponent of the pupil fluctuations primarily reflects the hyperactivity/impulsivity trait of attentional processing.

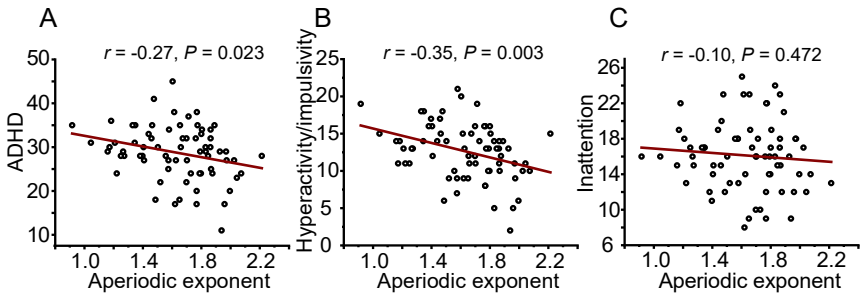

Fig. 5. Correlations between aperiodic exponent and ADHD (A), hyperactivity/impulsivity (B), and inattention (C) symptoms.

As a control analysis, we calculated the correlation between the total ADHD score and the mean, variance, and hippus power of the pupil fluctuations, but found significant correlations in none of the analyses (Fig. 6). This result further confirmed that the aperiodic exponent is more predictive for the trait of attentional processing than other raw indices of pupil size, strengthening the reflecting effect of the aperiodic exponent for the E/I balance of attention.

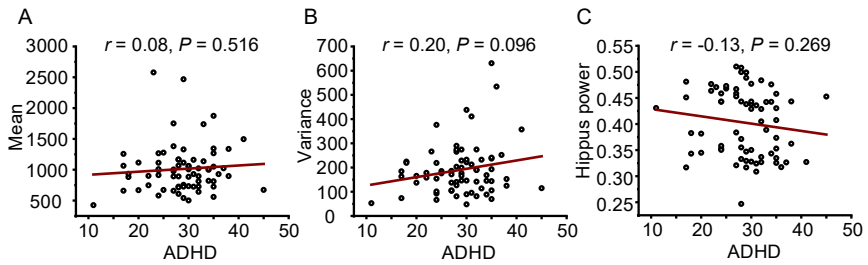

Fig. 6. Correlations between the total ADHD score and mean (A), variance (B), and hippus power (C) of pupil size.

Discussion

The present study explored the cognitive function of the aperiodic exponent of pupil fluctuations and the potential of using it as a reflection of E/I balance in visual attention. We recorded pupil size of a group of participants in the resting state and examined the attentional E/I balance with an attentional task and estimated the participants' attentional traits with an ADHD self-report scale. The aperiodic exponent of pupil size fluctuations correlated with the behavioral and microsaccadic cueing effects in the 50% cue-validity condition when the stimulus uncertainty is high. Specifically, a greater aperiodic exponent was accompanied by a larger cueing effect of behavior and a lower microsaccadic IOR. A mediation model further identified that the microsaccadic IOR mediated the effect of the aperiodic exponent on the behavioral cueing effect, suggesting that the aperiodic exponent of the resting pupil fluctuations reflects individuals' trait associated with attentional processing. Finally, and specifically, we revealed that participants with a lower hyperactivity/impulsivity ADHD symptom exhibited a greater aperiodic exponent in their pupil fluctuations. Notably, because the pupil size information was recorded offline, these correlations were free from contaminations due to simultaneous recording. Control analyses further showed that the prediction of the attentional effects and symptoms above did not exist in other indices of the raw pupil size data. Taking these results together, the fluctuation information of pupil sizes is likely to reflect important cognitive functions and its aperiodic exponent in particular may reflect attentional E/I balance.

The present study analyzed the aperiodic exponent of pupil fluctuations during the resting state and explored its potential functions in reflecting E/I balance. Our focus on the aperiodic exponent instead of raw pupil size data is inspired by the widely demonstrated aperiodic exponents in neural signals and behavioral responses. For example, 1/f-like power spectrum has been reveal in EEG (Waschke et al., 2021), MEG (Dehghani et al., 2010), ECoG (Manning et al., 2009), and fMRI (He, 2011) data. Functionally significant aperiodic exponents have also been found in the analysis of human behavioral responses (Palva et al., 2013). Critically, these components have been shown to be related to the E/I balance (Gao et al., 2017), with a greater aperiodic exponent, i.e., a steeper spectrum, indicates more neural inhibition while a lower aperiodic exponent, i.e., a flatter spectrum, indicates more neural excitation. Here, we further showed that the aperiodic exponent of pupil fluctuations was also associated the neural E/I balance. Specifically, we estimated the microsaccadic

responses and behavioral performance in an attentional cueing task and found a significant correlation between the aperiodic exponent of pupil fluctuations and these attentional measures under uncertain condition. Further, we revealed that the aperiodic exponent of pupil size also predicted individuals' ADHD symptoms of hyperactivity/impulsivity, further confirming its reflection of E/I balance in attention.

Excitation and inhibition are two fundamental processes that govern the flow of information in the brain. The balance between excitation and inhibition is critical for many brain functions, including attention (Deiber et al., 2020). Attention is the ability to focus on a specific stimulus or task while ignoring others. It is a selective process that allows us to filter out task-irrelevant information and focus on what is important. The E/I balance thus plays a key role in attention by helping to select the task-relevant stimuli for processing. The E/I balance is also important for maintaining attention over time. When we first attend to a stimulus, the E/I balance is tipped in favor of excitation. This allows us to process the stimulus quickly and efficiently. However, over time, the balance gradually shifts back towards inhibition. This keeps our attention from being depleted on one stimulus, providing the opportunity to move on to other possible targets in the environment (Jia et al., 2019; Lv et al., 2022). In the present two tasks, to maintain fixation after cue onset, participants must suppress the automatic microsaccadic responses toward exogenous cues (Rolfs et al., 2004). Consequently, the automatic microsaccades towards the cue are suppressed, and the microsaccades opposite to the cue are enhanced. The response properties of microsaccade directly reflect the degree of neural excitation and inhibition in participants during the attentional tasks. Meanwhile, we found that participants with the low aperiodic exponent of pupil fluctuations exhibit hyperexcitability to the exogenous cues and fail to suppress automatic microsaccadic responses to the cues. These results reveal an association between the aperiodic exponent of pupil fluctuations and E/I balance.

In the present results, the aperiodic exponent of resting pupil fluctuations correlated with microsaccadic IOR in the 50% cue-validity experiment but not in the 100% cue-validity experiment. We speculate that this is because participants were certain about where the probe would appear in the 100% cue-validity experiment, such that participants did not need to suppress the automatic microsaccadic response in the direction of a predictive cue. In contrast, in the 50% cue-validity experiment, participants were completely uncertain about where the probe would appear, rendering participants to suppress the automatic microsaccadic response in the direction of a nonpredictive

cue. Consequently, the neural E/I balance is critical for response control in the 50% cue-validity experiment. These results replicate the previous findings that the E/I balance in attention is sensitive to stimulus uncertainty (Feldman & Friston, 2010; Yu & Dayan, 2005) and demonstrate that the aperiodic exponent of resting pupil fluctuations reflects the neural E/I balance in attention better when under uncertain condition.

Research in both animals and humans suggests that variations in pupil size are reliably associated with locus coeruleus norepinephrine (LC-NE) system activity (Reimer et al., 2016), which is known to modulate attention (Strauch et al., 2022; Thiele & Bellgrove, 2018). Variation in pupil size is related to the spatial distribution of attention (Brocher et al., 2018) and the dynamic allocation of attention over time (Wierda et al., 2012). Recent studies illustrated that pupillary responses are involved in specific attention networks, including arousal (Aston-Jones et al., 1999), orienting (Gabay et al., 2011), and executive functions (Strauch et al., 2022). In the present study, we demonstrated for the first time that the aperiodic exponent of resting pupil fluctuations was associated with individuals' trait of attentional processing. Interestingly, via a mediation model, we found that the association between the aperiodic exponent and the behavioral performance in the attention task was fully mediated by the microsaccadic responses in the attention task. This may because different trait of neural E/I balance led to different suppression of automatic microsaccadic responses to the cue, which in turn led to different attentional effects in behavior.

Previous studies have found a strong relationship between the aperiodic exponent of neural signals and ADHD symptoms, although in opposite trends across ages (Karalunas et al., 2022; Ostlund et al., 2021; Robertson et al., 2019). However, no previous studies have examined the aperiodic exponent of pupil fluctuations or its relationship with ADHD. A recent study has explored the association between pupil size and ADHD symptoms but focused on the raw pupil size data (Bellato et al., 2023). Consistent with our results, their results showed that the raw pupil size failed to predict ADHD symptoms. Here, by extracting the aperiodic exponent of the pupil fluctuations, we revealed a significant association between aperiodic exponent and the hyperactivity/impulsivity of ADHD symptoms. This finding highlights the critical functional significance of temporal dynamics in pupil size in comparison with raw pupil size (Binda & Lunghi, 2017). Notably, the pupil size data in the present study were merely recorded offline during a 300-s resting phase. It, therefore, provides a possibility that offline eye recording may be able to provide important

information about cognitive functions and even traits associated with those functions. In fact, considering that the E/I balance indexed by the aperiodic exponent of neural signals has been found to be associated with a variety of neurological disorders, including ASD (Bast et al., 2023), ADHD (Karalunas et al., 2022), and Parkinsonism (Wiest et al., 2023), the present method may provide a promising measure for these neurological traits as well.

Conclusion

In conclusion, this study employed independent assessments of microsaccadic and behavioral responses during an attention task, self-reported ADHD symptoms, and pupil fluctuations during rest. The findings provide strong and consistent evidence for a link between the aperiodic exponent of pupil fluctuations and E/I balance in attention. The demonstration of the aperiodic exponent in pupil size and its advantage over raw pupil size data in reflecting attentional processes highlights the importance of analyzing the temporal dynamics of pupil size. This approach offers a potentially valuable index for investigating neural E/I balance and neurological disorders associated with E/I balance.

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Author contributions

Rongwei Wang: Investigation, Formal analysis, Visualization, Writing.

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Declaration of Competing Interest

The authors declare that they have no known competing interests.

Reference

Arns, M., Conners, C. K., & Kraemer, H. C. (2013). A Decade of EEG Theta/Beta Ratio Research in ADHD: A Meta-Analysis. *Journal of Attention Disorders*, *17*(5), 374–383. https://doi.org/10.1177/1087054712460087

Aston-Jones, G., Rajkowski, J., & Cohen, J. (1999). Role of locus coeruleus in attention and behavioral flexibility. *Biological Psychiatry*, *46*(9), 1309–1320. https://doi.org/10.1016/S0006-3223(99)00140-7

Bast, N., Boxhoorn, S., Supér, H., Helfer, B., Polzer, L., Klein, C., Cholemkery, H., & Freitag, C. M. (2023). Atypical Arousal Regulation in Children With Autism but Not With Attention-Deficit/Hyperactivity Disorder as Indicated by Pupillometric Measures of Locus Coeruleus Activity. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *8*(1), 11–20. https://doi.org/10.1016/j.bpsc.2021.04.010

Bellato, A., Arora, I., Kochhar, P., Ropar, D., Hollis, C., & Groom, M. J. (2023). Relationship between autonomic arousal and attention orienting in children and adolescents with ADHD, autism and co-occurring ADHD and autism. *Cortex*, *166*, 306–321. https://doi.org/10.1016/j.cortex.2023.06.002

Binda, P., & Lunghi, C. (2017). Short-Term Monocular Deprivation Enhances Physiological Pupillary Oscillations. *Neural Plasticity*, *2017*, 1–10. https://doi.org/10.1155/2017/6724631

Bouma, H., & Baghuis, L. C. J. (1971). Hippus of the pupil: Periods of slow oscillations of unknown origin. *Vision Research*, *11*(11), 1345–1351. https://doi.org/10.1016/0042-6989(71)90016-2

Brainard, D. H. (1997). The Psychophysics Toolbox. *Spatial Vision*, *10*, 433–436.

Brocher, A., Harbecke, R., Graf, T., Memmert, D., & Hüttermann, S. (2018). Using task effort and pupil size to track covert shifts of visual attention independently of a pupillary light reflex. *Behavior Research Methods*, *50*(6), 2551–2567. https://doi.org/10.3758/s13428-018-1033-8

Carter Leno, V., Begum-Ali, J., Goodwin, A., Mason, L., Pasco, G., Pickles, A., Garg, S., Green, J., Charman, T., Johnson, M. H., Jones, E. J. H., the EDEN, Vassallo, G., Burkitt-Wright, E., Eelloo, J., Gareth Evans, D., West, S., Hupton, E., Lewis, L., … Taylor, C. (2022). Infant excitation/inhibition balance interacts with executive attention to predict autistic traits in childhood. *Molecular Autism*, *13*(1), 46. https://doi.org/10.1186/s13229-022-00526-1

Chica, A. B., Lupiáñez, J., & Bartolomeo, P. (2006). Dissociating inhibition of return from endogenous orienting of spatial attention: Evidence from detection and discrimination tasks. *Cognitive Neuropsychology*, *23*(7), 1015–1034. https://doi.org/10.1080/02643290600588277

Dehghani, N., Bédard, C., Cash, S. S., Halgren, E., & Destexhe, A. (2010). Comparative power spectral analysis of simultaneous elecroencephalographic and magnetoencephalographic recordings in humans suggests non-resistive extracellular media. *Journal of Computational Neuroscience*, *29*(3), 405–421. https://doi.org/10.1007/s10827-010-0263-2

Deiber, M.-P., Hasler, R., Colin, J., Dayer, A., Aubry, J.-M., Baggio, S., Perroud, N., & Ros, T. (2020). Linking alpha oscillations, attention and inhibitory control in adult ADHD with EEG neurofeedback. *NeuroImage: Clinical*, *25*, 102145. https://doi.org/10.1016/j.nicl.2019.102145

Donoghue, T., Haller, M., Peterson, E. J., Varma, P., Sebastian, P., Gao, R., Noto, T., Lara, A. H., Wallis, J. D., Knight, R. T., Shestyuk, A., & Voytek, B. (2020). Parameterizing neural power spectra into periodic and aperiodic components. *Nature Neuroscience*, *23*(12), 1655–1665. https://doi.org/10.1038/s41593-020-00744-x

Engbert, R., & Kliegl, R. (2003). Microsaccades uncover the orientation of covert attention. *Vision Research*, *43*(9), 1035–1045. https://doi.org/10.1016/S0042-6989(03)00084-1

Engbert, R., & Mergenthaler, K. (2006). Microsaccades are triggered by low retinal image slip. *Proceedings of the National Academy of Sciences*, *103*(18), 7192–7197. https://doi.org/10.1073/pnas.0509557103

Feldman, H., & Friston, K. J. (2010). Attention, Uncertainty, and Free-Energy. *Frontiers in Human Neuroscience*, *4*. https://doi.org/10.3389/fnhum.2010.00215

Finley, A. J., Angus, D. J., Van Reekum, C. M., Davidson, R. J., & Schaefer, S. M. (2022). Periodic and aperiodic contributions to theta-beta ratios across adulthood. *Psychophysiology*, *59*(11). https://doi.org/10.1111/psyp.14113

Gabay, S., Pertzov, Y., & Henik, A. (2011). Orienting of attention, pupil size, and the norepinephrine system. *Attention, Perception, & Psychophysics*, *73*(1), 123–129. https://doi.org/10.3758/s13414-010-0015-4

Galfano, G., Betta, E., & Turatto, M. (2004). Inhibition of return in microsaccades. *Experimental Brain Research*, *159*(3), 400–404. https://doi.org/10.1007/s00221-004-2111-y

Gao, R., Peterson, E. J., & Voytek, B. (2017). Inferring synaptic excitation/inhibition balance from field potentials. *NeuroImage*, *158*, 70–78. https://doi.org/10.1016/j.neuroimage.2017.06.078

Gerster, M., Waterstraat, G., Litvak, V., Lehnertz, K., Schnitzler, A., Florin, E., Curio, G., & Nikulin, V. (2022). Separating Neural Oscillations from Aperiodic 1/f Activity: Challenges and Recommendations. *Neuroinformatics*, *20*(4), 991–1012. https://doi.org/10.1007/s12021-022-09581-8

He, B. J. (2011). Scale-Free Properties of the Functional Magnetic Resonance Imaging Signal during Rest and Task. *The Journal of Neuroscience*, *31*(39), 13786–13795. https://doi.org/10.1523/JNEUROSCI.2111-11.2011

He, B. J. (2014). Scale-free brain activity: Past, present, and future. *Trends in Cognitive Sciences*, *18*(9), 480–487. https://doi.org/10.1016/j.tics.2014.04.003

Hershman, R., Henik, A., & Cohen, N. (2018). A novel blink detection method based on pupillometry noise. *Behavior Research Methods*, *50*(1), 107–114. https://doi.org/10.3758/s13428-017-1008-1

Jia, J., Fang, F., & Luo, H. (2019). Selective spatial attention involves two alpha-band components associated with distinct spatiotemporal and functional characteristics. *NeuroImage*, *199*, 228–236. https://doi.org/10.1016/j.neuroimage.2019.05.079

Jia, J., Liu, L., Fang, F., & Luo, H. (2017). Sequential sampling of visual objects during sustained attention. *PLOS Biology*, *15*(6), e2001903. https://doi.org/10.1371/journal.pbio.2001903

Jones, S. A., Barfield, J. H., Norman, V. K., & Shew, W. L. (2023). Scale-free behavioral dynamics directly linked with scale-free cortical dynamics. *eLife*, *12*, e79950. https://doi.org/10.7554/eLife.79950

Karalunas, S. L., Ostlund, B. D., Alperin, B. R., Figuracion, M., Gustafsson, H. C., Deming, E. M., Foti, D., Antovich, D., Dude, J., Nigg, J., & Sullivan, E. (2022). Electroencephalogram

aperiodic power spectral slope can be reliably measured and predicts ADHD risk in early development. *Developmental Psychobiology*, *64*(3). https://doi.org/10.1002/dev.22228

Kessler, R. C., Adler, L., Ames, M., Demler, O., Faraone, S., Hiripi, E., Howes, M. J., Jin, R., Secnik, K., Spencer, T., Ustun, T. B., & Walters, E. E. (2005). The World Health Organization adult ADHD self-report scale (ASRS): A short screening scale for use in the general population. *Psychological Medicine*, *35*(2), 245–256. https://doi.org/10.1017/S0033291704002892

Kinley, I., & Levy, Y. (2021). PuPl: An open-source tool for processing pupillometry data. *Behavior Research Methods*. https://doi.org/10.3758/s13428-021-01717-z

Kret, M. E., & Sjak-Shie, E. E. (2019). Preprocessing pupil size data: Guidelines and code. *Behavior Research Methods*, *51*(3), 1336–1342. https://doi.org/10.3758/s13428-018-1075-y

Laubrock, J., Engbert, R., & Kliegl, R. (2005). Microsaccade dynamics during covert attention. *Vision Research*, *45*(6), 721–730. https://doi.org/10.1016/j.visres.2004.09.029

Lee, C., Rohrer, W. H., & Sparks, D. L. (1988). Population coding of saccadic eye movements by neurons in the superior colliculus. *Nature*, *332*(6162), 357–360. https://doi.org/10.1038/332357a0

Lv, X., Cheng, S., Wang, Z., & Jia, J. (2022). The dynamics of microsaccade amplitude reflect shifting of covert attention. *Consciousness and Cognition*, *101*, 103322. https://doi.org/10.1016/j.concog.2022.103322

Manning, J. R., Jacobs, J., Fried, I., & Kahana, M. J. (2009). Broadband Shifts in Local Field Potential Power Spectra Are Correlated with Single-Neuron Spiking in Humans. *The Journal of Neuroscience*, *29*(43), 13613–13620. https://doi.org/10.1523/JNEUROSCI.2041-09.2009

Maris, E., & Oostenveld, R. (2007). Nonparametric statistical testing of EEG- and MEG-data. *Journal of Neuroscience Methods*, *164*, 177–190. https://doi.org/10.1016/j.jneumeth.2007.03.024

Munoz, D. P., & Istvan, P. J. (1998). Lateral Inhibitory Interactions in the Intermediate Layers of the Monkey Superior Colliculus. *Journal of Neurophysiology*, *79*(3), 1193–1209. https://doi.org/10.1152/jn.1998.79.3.1193

Nobukawa, S., Shirama, A., Takahashi, T., Takeda, T., Ohta, H., Kikuchi, M., Iwanami, A., Kato, N., & Toda, S. (2021). Identification of attention-deficit hyperactivity disorder based on the complexity and symmetricity of pupil diameter. *Scientific Reports*, *11*(1), 8439. https://doi.org/10.1038/s41598-021-88191-x

Ostlund, B. D., Alperin, B. R., Drew, T., & Karalunas, S. L. (2021). Behavioral and cognitive correlates of the aperiodic (1/f-like) exponent of the EEG power spectrum in adolescents with and without ADHD. *Developmental Cognitive Neuroscience*, *48*, 100931. https://doi.org/10.1016/j.dcn.2021.100931

Palva, J. M., Zhigalov, A., Hirvonen, J., Korhonen, O., Linkenkaer-Hansen, K., & Palva, S. (2013). Neuronal long-range temporal correlations and avalanche dynamics are correlated with behavioral scaling laws. *Proceedings of the National Academy of Sciences*, *110*(9), 3585–3590. https://doi.org/10.1073/pnas.1216855110

Pfeffer, T., Keitel, C., Kluger, D. S., Keitel, A., Russmann, A., Thut, G., Donner, T. H., & Gross, J. (2022). Coupling of pupil- and neuronal population dynamics reveals diverse influences of arousal on cortical processing. *eLife*, *11*, e71890. https://doi.org/10.7554/eLife.71890

Pomè, A., Burr, D. C., Capuozzo, A., & Binda, P. (2020). Spontaneous pupillary oscillations increase

during mindfulness meditation. *Current Biology*, *30*(18), R1030–R1031. https://doi.org/10.1016/j.cub.2020.07.064

Reimer, J., McGinley, M. J., Liu, Y., Rodenkirch, C., Wang, Q., McCormick, D. A., & Tolias, A. S. (2016). Pupil fluctuations track rapid changes in adrenergic and cholinergic activity in cortex. *Nature Communications*, *7*(1), 13289. https://doi.org/10.1038/ncomms13289

Robertson, M. M., Furlong, S., Voytek, B., Donoghue, T., Boettiger, C. A., & Sheridan, M. A. (2019). EEG power spectral slope differs by ADHD status and stimulant medication exposure in early childhood. *Journal of Neurophysiology*, *122*(6), 2427–2437. https://doi.org/10.1152/jn.00388.2019

Rolfs, M., Engbert, R., & Kliegl, R. (2004). Microsaccade Orientation Supports Attentional Enhancement Opposite a Peripheral Cue: Commentary on Tse, Sheinberg, and Logothetis (2003). *Psychological Science*, *15*(10), 705–707. https://doi.org/10.1111/j.0956-7976.2004.00744.x

Strauch, C., Wang, C.-A., Einhäuser, W., Van der Stigchel, S., & Naber, M. (2022). Pupillometry as an integrated readout of distinct attentional networks. *Trends in Neurosciences*, *45*(8), 635–647. https://doi.org/10.1016/j.tins.2022.05.003

Thiele, A., & Bellgrove, M. A. (2018). Neuromodulation of Attention. *Neuron*, *97*(4), 769–785. https://doi.org/10.1016/j.neuron.2018.01.008

Turnbull, P. R. K., Irani, N., Lim, N., & Phillips, J. R. (2017). Origins of Pupillary Hippus in the Autonomic Nervous System. *Investigative Opthalmology & Visual Science*, *58*(1), 197. https://doi.org/10.1167/iovs.16-20785

Ukai, K., Tsuchiya, K., & Ishikawa, S. (1997). Induced pupillary hippus following near vision:

Increased occurrence in visual display unit workers. *Ergonomics*, *40*(11), 1201–1211. https://doi.org/10.1080/001401397187441

Waschke, L., Donoghue, T., Fiedler, L., Smith, S., Garrett, D. D., Voytek, B., & Obleser, J. (2021). Modality-specific tracking of attention and sensory statistics in the human electrophysiological spectral exponent. *eLife*, *10*, e70068. https://doi.org/10.7554/eLife.70068

Wierda, S. M., van Rijn, H., Taatgen, N. A., & Martens, S. (2012). Pupil dilation deconvolution reveals the dynamics of attention at high temporal resolution. *Proceedings of the National Academy of Sciences*, *109*(22), 8456–8460. https://doi.org/10.1073/pnas.1201858109

Wiest, C., Torrecillos, F., Pogosyan, A., Bange, M., Muthuraman, M., Groppa, S., Hulse, N., Hasegawa, H., Ashkan, K., Baig, F., Morgante, F., Pereira, E. A., Mallet, N., Magill, P. J., Brown, P., Sharott, A., & Tan, H. (2023). The aperiodic exponent of subthalamic field potentials reflects excitation/inhibition balance in Parkinsonism. *eLife*, *12*, e82467. https://doi.org/10.7554/eLife.82467

Yu, A. J., & Dayan, P. (2005). Uncertainty, Neuromodulation, and Attention. *Neuron*, *46*(4), 681–692. https://doi.org/10.1016/j.neuron.2005.04.026

Zhao, S., Chait, M., Dick, F., Dayan, P., Furukawa, S., & Liao, H.-I. (2019). Pupil-linked phasic arousal evoked by violation but not emergence of regularity within rapid sound sequences. *Nature Communications*, *10*(1), 4030. https://doi.org/10.1038/s41467-019-12048-1