

# Temporal dynamics of auditory bistable perception correlated with fluctuation of baseline pupil size

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## Abstract

A dynamic neural network change, accompanied by cognitive shifts such as internal perceptual alternation in bistable stimuli, is reconciled by the discharge of noradrenergic locus coeruleus neurons. Transient pupil dilation as a consequence of the reconciliation with the neural network in bistable perception has been reported to precede the reported perceptual alternation. Here, we found that baseline pupil size, an index of temporal fluctuation of arousal level over a longer range of timescales than that for the transient pupil changes, relates to the frequency of perceptual alternation in auditory bistability. Baseline pupil size was defined as the mean pupil diameter over a period of 1 s prior to the task requirement (i.e., before the observation period for counting the perceptual alternations in Experiment 1 and reporting whether participants experienced the perceptual alternations in Experiment 2). The results showed that the baseline pupil size monotonically increased with an increasing number of perceptual alternations and its occurrence probability. Furthermore, a cross-correlation analysis indicates that baseline pupil size predicted perceptual alternation at least 35 s before the behavioral response and that the overall correspondence between pupil size and perceptual alternation was maintained over a sustained time window of 45 s at minimum. The overall results suggest that variability of baseline pupil size reflects the stochastic dynamics of arousal fluctuation in the brain related to bistable perception.

## KEYWORDS

auditory stream segregation, baseline pupil size, bistable perception, perceptual alternation, pupillometry

## 1 | INTRODUCTION

Pupillary changes function as an adjustment of light entering the eyes mediated by the autonomic nervous system (ANS) (Beatty & Lucero-Wagoner, 2000; Goldwater, 1972;

Granholm & Steinhauser, 2004; Irene et al., 1993; Samuels & Szabadi, 2008). The sympathetic and parasympathetic divisions of the ANS are controlled by the acetylcholine and noradrenergic system. Norepinephrine (NE) is used as a neurotransmitter of noradrenergic neurons released

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from the locus coeruleus (LC). The neurons project to a major part of the brain, the so-called locus coeruleus noradrenergic system (LC-NE system). Pupillary changes are thought to reflect changes in neural activity via the LC-NE system, which has been shown to be involved in a broad range of cognitive processes.

A dynamic neural network change accompanied by a cognitive shift is reconciled by the discharge of noradrenergic LC neurons in a manner of both inhibition or excitement (Bouret & Sara, 2005). The noradrenergic projection throughout the central nervous system suppresses neurons in most cases, whereas it exceptionally functions to accentuate a novel stimulus (Zerbi et al., 2019). Corresponding to this, the LC neuron activities are classified into tonic and phasic patterns, which have different timescales of neuron firing. The fluctuations in the tonic activity occur in a longer range of timescales than the phasic activity. It is well known that the tonic LC activity is related to cognitive task performance in an inverted U-shaped manner (Aston-Jones & Bloom, 1981). Furthermore, changes in neuromodulators of the NE level in the brain (i.e., fluctuation of tonic LC activity) are cross-correlated with fluctuation of baseline pupil size as evidenced from animal studies (Aston-Jones & Cohen, 2005; Rajkowski et al., 1993; Reimer et al., 2016). Based on the correlation between the changes in pupil size and LC-mediated NE release, several previous studies have reported that the baseline pupil size correlates to various aspects of cognitive and behavioral performance (Aminihajibashi et al., 2020; Eldar et al., 2013; McGinley et al., 2015; Schneider et al., 2016).

Pharmacologically elevating the tonic NE level in humans increases the intrinsic behavioral variability in perceptual alternations (Pfeffer et al., 2018). Although relative-phase distributions for perceptual alternations have certain stochastic dynamics approximated to gamma distributions (Logothetis et al., 1996), the relationship between temporal dynamics of tonic NE level change and internal neural network stochastics as a perceptual alternation is still poorly understood. Since the connectivity among brain functions is correlated with pupil size via a role in the modulation of neural gain in the LC (Shine et al., 2016), the dynamics of the internal brain state through is expected to reflect the frequency of perceptual alternation. In other words, if the changes in the tonic arousal level through the LC-NE system involves intrinsic perceptual alternation, the baseline pupil-like arousal should reflect a dynamic neural network change with an intrinsic perceptual shift in bistable perception. Along this line, the transient pupil dilation response has been observed around the occurrence of perceptual alternation (Einhäuser et al., 2008; Grenzebach et al., 2021; Hupé et al., 2009; Sato et al., 2020). However, whether there is a

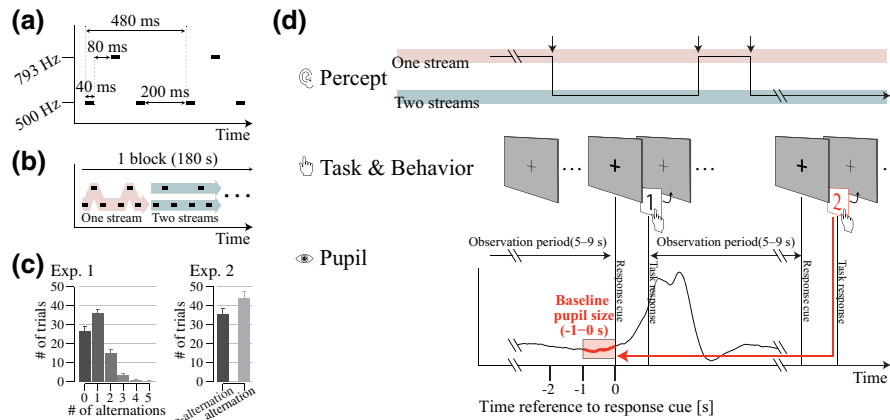
relationship between the baseline pupil size as a proxy of the tonic arousal state and the perceptual alternation over timescales longer than a single trial is unknown.

Here, we examined whether the fluctuation of tonic pupil size is correlated with the frequency of perceptual alternations. In two experiments, consecutive auditory tone sequences which can produce two different patterns of perceptual experience, the so-called auditory stream segregation, were employed to elicit bistable perception (e.g., Bregman, 1990; van Noorden, 1975). To address the question of whether a stochastic fluctuation of baseline pupil size is associated with the number of perceptual alternations, we monitored baseline pupil size while participants listened the auditory stimulus and engaged in the following task: In Experiment 1, they reported the number of perceptual alternations every few seconds from 0 to 5 (Figure 1d). In Experiment 2, participants were asked to simply detect whether a perceptual alternation occurred or not (yes or no). It should be noted that Experiment 1 requested the participant to keep counting and memorizing the number of alternations throughout the observation period. Thus, there was a concern that the participant would take on a stronger perceptual load when holding a larger number of perceptual alternations in mind in Experiment 1, as it has been shown that higher mental effort on working memory increases baseline pupil size (Aminihajibashi et al., 2020; Schneider et al., 2016). The yes/no paradigm in Experiment 2 served as a control test to evaluate the confounding effect of this task-related perceptual load. Results showed that baseline pupil size was monotonically correlated with the number of perceptual alternations (Experiment 1) and its occurrence probability (Experiment 2). Furthermore, a cross-correlation function between the baseline pupil size and number of perceptual alternations revealed the temporal aspects of baseline pupil change on perceptual alternations over timescales longer than a single trial.

## 2 | METHOD

### 2.1 | Participants

All experimental procedures were performed in accordance with the ethical principles outlined in the Research Ethics Committee of Nippon Telegraph and Telephone Corporation (NTT) Communication Science Laboratories. All participants provided written informed consent. Twenty-three volunteers (6 men, 17 women; age range of 27–49 years; mean age = 39.8) participated in both Experiments 1 and 2. The order of participation in Experiments 1 and 2 was counterbalanced across participants (twelve participants started with Experiment 1 and the rest of them started with Experiment 2).



**FIGURE 1** Experimental design. (a) Time configuration of the ABA\_ pattern. (b) Consecutive auditory tone sequences which can produce two different patterns of a single galloping or two isolated rhythms. (c) Averaged trial numbers among responses in experiments 1 and 2 (d) participants listened to a series of two tones with different frequencies (see “methods”). Participants were asked to count the number of perceptual alternations in Experiment 1 (i.e., number of black arrows in top panel; the trace here is an example for explanation purposes) or report whether they experienced a perceptual alternation in Experiment 2 while a narrow fixation cross was presented, which is referred to as the observation period. Once the fixation cross became thicker (i.e., response cue), participants pressed a corresponding button depending on the task (i.e., number keys from 0 to 5 in Experiment 1 and yes/no in Experiment 2). All pupil changes illustrated here are averaged data across participants and alternation cases from Experiment 1. To avoid the effect of the motor responses (i.e., button press) or its preparation on the pupil size, the baseline pupil size was defined as the mean pupil size over  $-1000$  to  $0$  ms to the response cue onset (period marked in red in the graph), and was labeled according to the subsequent participants’ task answer (the red line with arrows) for subsequent baseline pupil size and cross-correlation analysis

One participant in Experiment 1 and four participants in Experiment 2 were excluded from pupil analyses due to eyeblinks on more than 40% of trials. The sample size was determined by a priori power analysis using G\*Power, considering a power of 0.8, type I error level of 0.05, and expected effect size of 0.3 (Faul et al., 2007). These parameter settings led to a minimum sample size of 20 participants. All participants were tested by standard hearing screening to ensure that their audiometric thresholds did not exceed a hearing level of 25-dB at 0.25, 0.5, 1, 2, 4, and 8 kHz. Experimental data and analysis code are available at <https://github.com/suzuki970/PupilAuditoryStreaming>.

## 2.2 | Stimulus and apparatus

In the experiments, we used the classic ABA\_ auditory sequence (van Noorden, 1975) consisting of repeated cycle of an ABA triplet (A and B referring to tone-bursts with different frequencies) followed by a blank (indicated by \_). The frequencies of the A and B tones were 500 and 793 Hz, respectively (five semi-tone separation). The tones and the blank of ABA\_ (A, B, and \_) had 40-ms duration and were separated with an 80-ms silent interval (Figure 1a). Thus, the duration of the one cycle of the ABA\_ pattern was 480 ms. The auditory stream pattern elicits alternating percepts of a single galloping-rhythm auditory stream

(ABA\_, ABA\_, ...) or two isolated rhythms (A\_A\_A\_A\_..., B\_B\_B\_B\_...) as illustrated in Figure 1b. The stimulus was generated digitally with a sampling rate of 44.1 kHz and presented diotically via headphones (MDR-7506, Sony) at the A-weighted sound pressure level of 65 dB.

The luminance of the background and fixation cross were 4.5 and 0.07  $\text{cd}/\text{m}^2$ , respectively, which was calibrated using a spectro-radiometer (LS-100, KONICA MINOLTA). An LCD monitor (Flex Scan L985EX, EIZO) with a resolution of  $1600 \times 1200$  and a refresh rate of 60 Hz was used in the experiment. The fixation cross was located at 0.1 degrees from the center. The line widths of the fixation cross for indicating the experience period and response cue were 2 and 5 pixels, respectively. Each participant’s chin was fixed at a viewing distance of 700 mm. The task was conducted in a dark room and executed using MATLAB2019a (MathWorks) using Psychtoolbox (Brainard, 1997).

## 2.3 | Procedure

All participants sat in front of the computer screen with their chin in a chin rest to prevent head movement. Each block was started with a standard five-point calibration. One block lasted 180 s and consisted of 19 to 24 trials depending on the trial durations, which were jittered randomly (see below). Each trial started with the bold fixation

cross transformed into the narrow cross. During presentation of the narrow fixation cross, referred to as the *observation period*, with its duration randomly selected from a uniform distribution between 5 and 9 s, participants were instructed to count the number of perceptual alternations in Experiment 1 (i.e., a continuous version of the “counting” condition in the Einhäuser et al., 2008 study) and detect whether they experienced any perceptual alternation in Experiment 2, without any voluntary effort to control them. When the fixation cross changed to bold (referred to as the *response cue*), they gave their answer by pressing a corresponding button depending on the task (i.e., a number from 0 to 5 in Experiment 1 and yes/no in Experiment 2) using a keypad. The fixation cross changed back to the narrow cross as soon as their response was detected. This was the cue for the start of the next observation period or trial, and participants started the counting or detection task in Experiments 1 and 2, respectively. They were instructed to fixate the central fixation cross throughout the whole block of trials. The auditory stream stimulus was presented continuously regardless of the response delay during the whole block. Each participant performed four blocks in each experiment.

## 2.4 | Pupillometry analysis

Pupil size was measured using an eye-tracking system (EyeLink 1000, SR Research) at a sampling rate of 1000 Hz. The tracking was performed based on pupil diameter using the centroid mode throughout the study. Pupil diameter estimates were generated by the device in pixels. As in previous studies (e.g., Einhäuser et al., 2008), the major analyses in the present study were based on pupil diameters calculated in z-scores ( $z$ ) within the whole experiment (four blocks) for each participant. Because we recognize that some studies in this field chose to analyze non-normalized (i.e., not z-transformed) pupil diameter (e.g., Sato et al., 2020), we also conducted analyses based on diameters converted to millimeters from pixels (the results are described in the Figure S1). Essential conclusions drawn from the results are unaltered by the data normalization. Pupil data during eyeblinks, which were obtained as the values of zero in the data and more than  $\pm 3$  standard deviation ( $\sigma$ ) of the first derivative of pupil data within the whole experiment for each participant, were interpolated by cubic hermite interpolation. Trials with additional artifacts, in which the velocity change in pupil size was more than 40 [z/s], were excluded from the analysis (the averages of rejected trials were 5.6% in Experiment 1 and 5.9% in Experiment 2 out of all trials per participant).

To avoid the motor and/or decision-making artifacts in the pupil size, the baseline pupil size associated with

a given trial was computed as the average of samples collected during the 1-s period prior to the onset of the response cue for the previous trial (Figure 1d, red line). We also counted the number of transient pupil dilation or constriction (transient PD/PC) events during the early 4-s part of the observation period as follows (Zhao et al., 2019): pupil slope was computed using second-order central differences after a 1-s window of a smoothing filter had been applied within a trial. Transient PD/PC events were defined as local maximum positive and negative values of the slope, separated by  $\geq 300$  ms (Joshi et al., 2016; Zhao et al., 2019). The transient PD/PCs in the observation period were counted from 0 to 4 s after the task response cue of the previous trial. This time window was chosen due to the limit of the inter-trial interval. The participants were assigned the task for over a period of at least 5 s until the next trial (i.e., the period from the button press to the appearance of the next response cue). The window of 0–4 s covers the period immediately from the response and before 1 s prior to the next response cue for all trials and thus enables us to exclude the “baseline pupil size” period from the PD/PC analyses. For each trial, the number of PD and PC events were summed, respectively, and then averaged across trials separately for alternation and no-alternation trials for each participant. The alternation and no-alternation trials here correspond to the trials with  $\geq 1$  and 0 alternation responses in Experiment 1. The number of PD and PC events corresponded to the subsequent participants' task answer, the same as in the baseline pupil size analysis.

## 2.5 | Cross-correlation function

For the results of Experiment 1, the cross-correlation function (CCF) was calculated between the baseline pupil size and the z-scored number of perceptual alternations over 80 trials, which was chosen as it was the minimum of the total trial number throughout the four-block experiment for all participants. The series of the baseline pupil size and the number of perceptual alternations were aligned when the baseline pupil size was obtained 5–9 s before the perceptual alternation response (i.e., lag = 0 condition refers to the correspondence of the trial structure as illustrated in Figure 1d). As a control, a “shuffled” cross-correlation was calculated and compared with the raw cross-correlation results, in which the pupil data from one block were paired and aligned with the behavioral responses (i.e., the number of perceptual alternations) from a randomly selected different block. The cross-correlations for all possible paired block combinations out of four blocks [i.e., 21 combinations = 24 combinations – 3 successive paired

blocks (e.g., 4, 1, 2, 3)] were calculated for each participant and averaged for a given combination. Person's correlation coefficients were calculated between the baseline pupil size and perceptual alternation response across the entire referred trails for each participant. The  $p$  values for Pearson's correlation were corrected by the false discovery rate (FDR) for multiple comparisons at each referred trial lag by using the Benjamini and Hochberg method (Benjamini & Hochberg, 1995).

## 2.6 | Statistical analysis

Mean baseline pupil size was subjected to a one-way repeated-measures analysis of variance (ANOVA) with the number of alternations as the within-subject factor in Experiment 1. A paired  $t$ -tests was applied to the mean baseline pupil size between the presence (alternation) and absence (no- alternation) of perceptual alternations in Experiment 2. The level of statistical significance was set to  $p < .05$  for all analyses. Pairwise comparisons of the main effects were corrected through multiple comparisons using the Bonferroni-Holm method. Effect sizes were given as partial  $\eta^2$ ;  $\eta_p^2$  for ANOVA and as Cohen's  $d_z$  for  $t$ -tests (Cohen, 1988, p. 48; Lakens, 2013). Greenhouse-Geisser corrections were performed when the results of Mauchly's sphericity test were significant. To quantify the evidence in the data, we performed Bayesian paired  $t$ -tests and computed Bayes factors (BF) using a Cauchy prior width of  $r = 0.707$  for effect size by the BayesFactor package (v0.9.12-4.2) (Morey, 2019) for the R software (Version 3.6.3) (R Core Team, 2020). BF estimates the relative weight of the evidence in favor of  $H_1$  over  $H_0$  as  $BF_{10}$ .

For baseline pupil size bin analysis, for each participant, all trials were sorted in ascending order based on the baseline pupil size and divided into five equally populated bins. This procedure led to an equal trial number in each pupil size bin. The number of perceptual alternations (Experiment 1) and the z-scored probability of perceptual alternation (Experiment 2) was averaged and fitted by the following two models to assess whether the behavioral variability ( $Y$ ) can be explained by a monotonic fitting or second-order polynomials.

$$\text{Model 1: } Y \sim \beta_0 + \beta_1 P.$$

$$\text{Model 2: } Y \sim \beta_0 + \beta_1 P + \beta_2 P^2$$

where  $\beta$  represents regression coefficients, and  $P$  represents the baseline pupil response bins. The models were quantified using the Akaike information criterion (AIC), which specifies the evidence of goodness of fit for a model.

## 3 | RESULTS

### 3.1 | Experiment 1

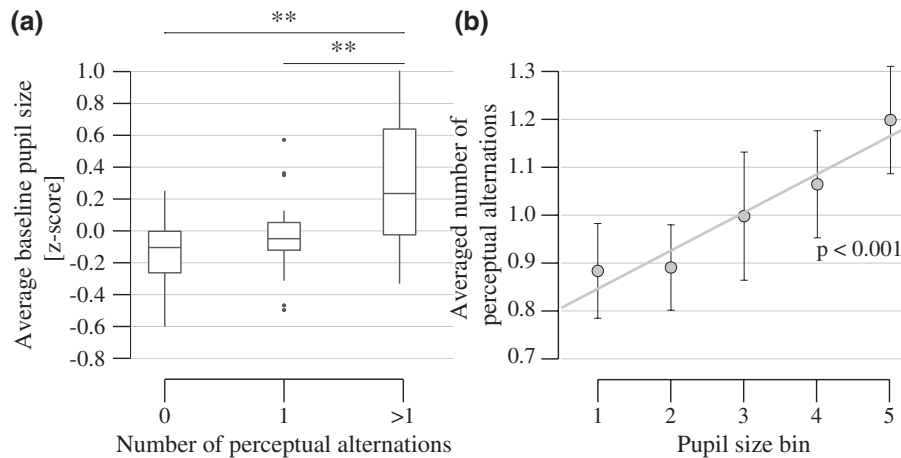
#### 3.1.1 | Behavioral response

Participants reported the number of perceptual alternations from 0 to 5. As the trial numbers were unbalanced among these responses (Figure 1c), we classified the number of alternation responses into 0, 1, and more than 2 times (hereafter, referred to as 0-, 1-, >1-alt cases, respectively). The average numbers of trials were  $26.27 \pm 12.4$ ,  $35.59 \pm 10.18$ , and  $14.68 \pm 9.83$ , respectively ( $F(1.84,38.62) = 15.427$ ,  $p < .001$ ,  $\eta_p^2 = 0.424$ ,  $BF_{10} = 1.50 \times 10^5$ ). Post analysis showed that the number of trials for 1-alt cases was significantly larger than for 0- and >1-alt cases ( $t(21) = 2.614$ ,  $p = .016$ , Cohen's  $d_z = 0.557$ ,  $BF_{10} = 3.331$ ;  $t(21) = 6.143$ ,  $p < .001$ , Cohen's  $d_z = 1.31$ ,  $BF_{10} = 4741.359$ ) and that for 0-alt cases was larger than for >1-alt cases ( $t(21) = 2.703$ ,  $p = .013$ , Cohen's  $d_z = 0.576$ ,  $BF_{10} = 3.921$ ) at alpha level of 0.05/3 corrected by the Bonferroni-Holm method. RTs of each response category were  $1.24 \pm 0.501$ ,  $1.129 \pm 0.401$ , and  $1.209 \pm 0.864$  s ( $F(1.24,26.09) = 0.307$ ,  $p = .633$ ,  $\eta_p^2 = 0.014$ ,  $BF_{10} = 0.156$ ). Although the observation period was jittered from 5 to 9 s, the number of perceptual alternations was not determined by the observation time ( $F(1.55,32.58) = 1.213$ ,  $p = .301$ ,  $\eta_p^2 = 0.055$ ,  $BF_{10} = 0.317$ ).

#### 3.1.2 | Baseline pupil size

Figure 2a illustrates the grand-averaged baseline pupil changes across participants before the response cue onset, as a function of perceptual alternations number. The one-way repeated measures ANOVA revealed a significant main effect on the number of perceptual alternations ( $F(1.52,31.91) = 11.424$ ,  $p < .001$ ,  $\eta_p^2 = 0.352$ ,  $BF_{10} = 1316.731$ ). The post-hoc multiple comparisons showed that the baseline pupil size in the >1-alt case was significantly larger than in the 0- and 1-alt cases ( $t(21) = 3.66$ ,  $p = .001$ , Cohen's  $d_z = 0.78$ ,  $BF_{10} = 25.712$ ;  $t(21) = 3.954$ ,  $p = .001$ , Cohen's  $d_z = 0.843$ ,  $BF_{10} = 47.379$ , respectively), indicating that the baseline pupil size, prior to counting the number of alternations, was related to a subsequent number of perceptual transitions.

The answered number of trials was significantly different among the 0-, 1-, and >1 cases as shown above. Such unbalanced trial numbers can cause biases in the statistical analysis and decreased statistical power. Thus, we performed an alternative analysis to avoid this potential statistical problem. We segregated the trials equally into five bins based on the rank order of baseline pupil size. Results are shown



**FIGURE 2** Baseline pupil size in the number of perceptual alternations. (a) Averaged baseline pupil size from  $-1000$  ms to the response cue onset (see ‘methods’). Boxplots show median values, the interquartile range (IQR),  $IQR \times 1.5$ , and outliers. (b) Relationship between baseline pupil size and number of perceptual alternations classified by equal size bins. Error bars indicate the standard error of the mean. Asterisks (\*) indicate statistical significance at  $*p < .05$ , and  $**p < .01$

in Figure 2b. The data were fitted by a simple regression model ( $y = 0.079x + 0.76$ ,  $R = 0.119$ ,  $t = 5.1447$ ,  $p < .001$ ). Consistent with the previous results, the number of alternations monotonically increased with the baseline pupil size.

## 3.2 | Experiment 2

### 3.2.1 | Behavioral response

The average number of ‘yes’ and ‘no’ trials (presence and absence of perceptual alternations, respectively) were  $36 \pm 13.66$  and  $44.89 \pm 15.3$ , respectively ( $t(18) = -1.448$ ,  $p = .165$ , Cohen’s  $d_z = 0.332$ ). The observation time could not explain the number of ‘yes’ or ‘no’ trials ( $t(18) = -0.157$ ,  $p = .877$ , Cohen’s  $d_z = 0.036$ ). RT in the answer ‘yes’ ( $1.236 \pm 0.44$  s) was significantly faster than ‘no’ ( $1.236 \pm 0.44$  s) ( $t(18) = 5.724$ ,  $p < .001$ , Cohen’s  $d_z = 1.313$ ). This could be because, the participant in the ‘yes’ trial would have been ready to respond as soon as the first occurrence of a perceptual alternation before the response cue was presented, whereas the participant had to wait until the cue to say ‘no’. It is important to note, therefore, that the perceptual load and/or mental effort is expected to be lower in the ‘yes’ trials than in the ‘no’ ones.

### 3.2.2 | Baseline pupil size

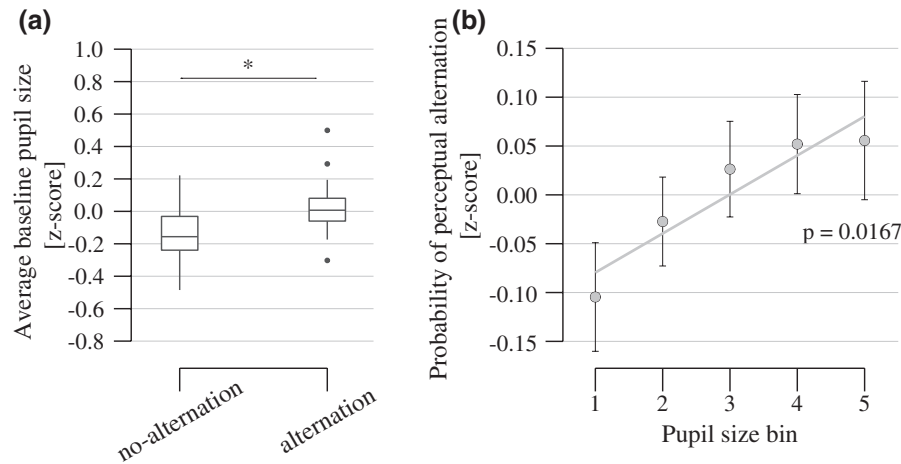
Figure 3a shows the grand-averaged time-course of baseline pupil changes parameterized by alternation cases (yes or no). Consistent with Experiment 1, a paired t-test for averaged changes in baseline pupil size from  $-1000$  ms

to the response cue onset for each answer (i.e., the presence or absence of perceptual alternation) showed that the baseline pupil size in the presence of a perceptual alternation was significantly larger than in the absence of perceptual alternation ( $t(18) = -2.508$ ,  $p = .022$ , Cohen’s  $d_z = 0.575$ ,  $BF_{10} = 2.73$ ).

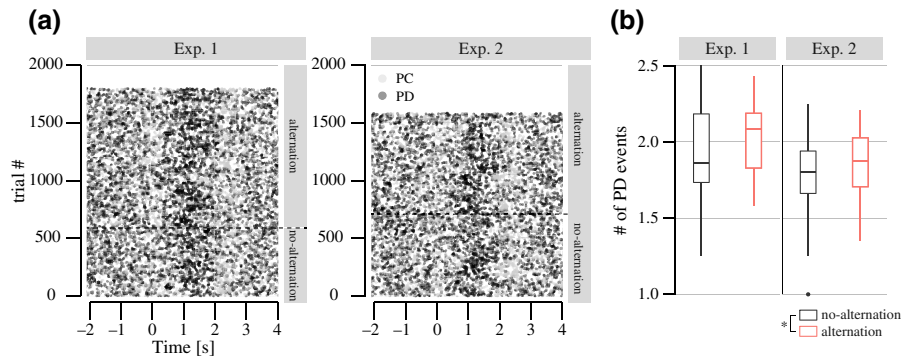
Following the same analysis procedure as in Experiment 1, we segregated the trials into five bins based on the ranked order of the normalized baseline pupil size. For each participant, we normalized the probability of perceptual alternation by z-scores and averaged them in each pupil size bin (Figure 3b). The model fitted by a simple regression showed the significance ( $y = 0.04x + -0.12$ ,  $R = 0.228$ ,  $t(18) = 2.4301$ ,  $p = .0167$ ).

### 3.2.3 | Transient pupil dilation/constriction (PD/PC)

To assess the relationship between perceptual alternations and transient pupil change reported previously (Einhäuser et al., 2008; Grenzbach et al., 2021; Turi et al., 2018), we calculated the rate of PD/PC events (see Methods). Figure 4a shows the occurrence of PD/PC events for each trial across all subjects, over a period of 2 s before the task response in the previous trial to 4 s after it. We averaged the number of PD events over a period of 4 s after the task response in the previous trial (Figure 4b). To compare by the within-subject design, the participants who were not rejected in both Experiments 1 and 2 were examined in the following analysis. Two-way repeated measures ANOVAs on the averaged PD events with the response content and experiment as within-subject factors revealed that the average number of PD events was



**FIGURE 3** Baseline pupil size parameterized by alternation cases. (a) Averaged baseline pupil size from  $-1000$  ms to the response cue onset (see ‘Methods’). Boxplots show median values, the interquartile range (IQR),  $IQR \times 1.5$ , and outliers. (b) Relationship between baseline pupil size and probability of perceptual alternation classified by equal size bins. Error bars indicate the standard error of the mean. The asterisk (\*) indicates statistical significance at  $p < .05$



**FIGURE 4** Pupil dilation/constriction rates in experiments 1 and 2. (a) Raster plots of pupil dilation/constriction events around task responses. In the result of Experiment 1 (left panel of a), answer of 0 labeled as “no-alternation” vs. more than 1 labeled as ‘alternation’. Black and white dots indicate the inflection point of pupil dilation and constriction in each single trial. (b) Average number of pupil dilation events within the time range from 0 to 4 s for alternation and no-alternation trials. Boxplots show median values, the interquartile range (IQR),  $IQR \times 1.5$ , and outliers

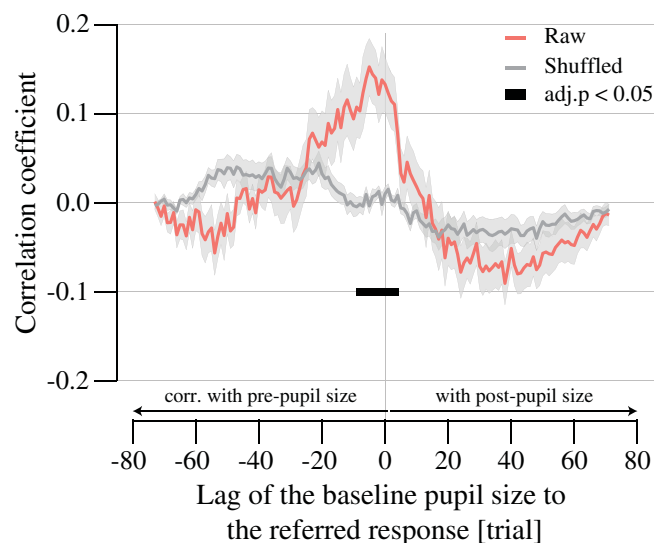
significantly larger in alternation trials than in no-alternation trials ( $F(1,18) = 5.973$ ,  $p = .025$ ,  $\eta_p^2 = 0.249$ ,  $BF_{10} = 2.186$ ), consistent with the previous studies (Einhäuser et al., 2008; Grenzebach et al., 2021). The number of PD events was larger in Experiment 1 than in 2 ( $F(1,18) = 7.77$ ,  $p = .012$ ,  $\eta_p^2 = 0.302$ ,  $BF_{10} = 17.622$ ), which could be explained by the higher task demand in Experiment 1, as the LC-NE system reflects a broad range of cognitive processes. There was no interaction between the response content and experiment ( $F(1,18) = 0.226$ ,  $p = .64$ ,  $\eta_p^2 = 0.012$ ,  $BF_{10} = 0.332$ ). Two-way repeated measures ANOVAs on the averaged PC showed that there were no significant main effect and interaction ( $F(1,18) = 1.183$ ,  $p = .291$ ,  $\eta_p^2 = 0.062$ ,  $BF_{10} = 0.405$ );  $F(1,18) = 2.372$ ,  $p = .141$ ,  $\eta_p^2 = 0.116$ ,  $BF_{10} = 0.874$ ;

$F(1,18) = 0.004$ ,  $p = .948$ ,  $\eta_p^2 = 0$ ,  $BF_{10} = 0.315$ , respectively). There was a concern that the PD events and observed baseline pupil size were not sufficiently independent measures. For example, if the transient pupil dilation had a sufficiently slow time decay, the apparent baseline diameter would build up with accumulated PD events. To address this concern that the baseline pupil size might be affected by the PD events, we calculated the number of PD events in the baseline pupil size analysis in every 1-s time bin (Figure S2) and the correlation between the baseline pupil size and number of transient PD events (Figure S3). Note that the number of PD events during the early 4-s part of the observation period were summed and their order ranked across trials for each subject. The baseline pupil size after the window for calculating the number of PD events was parameterized by the rank order of

the PD events. The results revealed that there was no statistical evidence that increasing the number of PD events can explain the baseline pupil size in both experiments.

### 3.2.4 | Cross-correlation function

The cross-correlation analysis (Figure 5) revealed that the baseline pupil size and the number of perceptual alternations had a significant positive correlation over the range of nine trials;  $-6$  to  $+3$  trials with a lag of around 0. This result can be interpreted as indicating that the baseline pupil size at least 35 s ( $=5$  s  $\times$  6 trials  $+5$  s; see below) before the behavioral response predicts perceptual alternation and the overall correspondence between pupil size and the number of perceptual alternations is sustained for at least 45 s ( $5$  s  $\times$  9 trials). It should be recalled that for a given trial (or the lag of 0 in Figure 5), the window for deriving the baseline pupil size preceded the corresponding response by the duration of the observation period (therefore, an additional 5 s was included to derive the 35-s period), and that the observation period was varied randomly between 5 and 9 s (Figure 1d, red line). Thus, the 35 and 45-s durations shown above are conservative estimates, with the assumption that the representative observation period was the minimum of the randomization range.



**FIGURE 5** Cross correlation function between the number of perceptual alternation and baseline pupil size. The red line indicates raw cross-correlations. The gray line indicates block-shuffled cross-correlations. Lag 0 refers to the correspondence of the trial structure as illustrated in Figure 1b in that the baseline pupil size was obtained 5–9 s before the response (i.e., the correlation with post-pupil size when lag  $>1$ ). The horizontal black line indicates the range of significant difference between raw and shuffled functions (corrected by FDR). Shading indicates the standard error of the mean

## 4 | DISCUSSION

In the current study, we investigated the relationship between baseline pupil size and stochastic dynamics of perceptual alternation using auditory stream segregation. We found that baseline pupil size was monotonically correlated with the frequency of perceptual alternations in Experiment 1. In Experiment 2, we replicated this finding by demonstrating that baseline pupil size reflected simply the occurrence of perceptual alternation. Furthermore, the fluctuations of baseline pupil size over a broad range were cross-correlated with the number of perceptual alternations. These findings represent the first demonstration of the correlation between tonic baseline pupil size as an index of arousal level via NE mediated by the LC (Aston-Jones & Cohen, 2005; Breton-Provencher & Sur, 2019; Joshi et al., 2016) and the perceptual alternation rate.

NE release through activation of LC neurons facilitates a reorganization of neural networks (Bouret & Sara, 2005). Based on the assumption that tonic baseline pupil changes are interpreted as a fluctuation of regular LC activity-mediated arousal and attention levels, we hypothesized that the network reorganization that creates the perceptual state shift could be observed as changes in baseline pupil size. As expected, the number and probability of perceptual alternations were correlated with baseline pupil size (Figures 2b and 3b). These correlations indicate that the current network state facilitated/inhibited by the LC-NE system in the brain may determine the upcoming perceptual event, although such causality is not fully supported by the present data. Furthermore, when we aligned the timing of behavioral response and pupil size throughout the experimental session, the cross-correlation function showed that the number of alternations was positively correlated with pupil size up to six trials (nearly 30 to 40 s) ahead of the response time (Figure 5a). Recent studies suggest that dynamic changes in the noradrenergic circuit over time ensure that cognitive function is flexible to novel sensory input or adapts efficiently to the varied environment patterns in terms of brain network topology (Shine, 2019; Yu & Dayan, 2005). Along this line, noradrenergic tonic activity in the LC with a high firing rate is thought to facilitate a “network reset” to sensory input with dynamic coordination of the functional brain network (Bouret & Sara, 2005). Our overall results suggest that the higher the baseline pupil size-linked arousal is, the more frequent the reconstruction of the stochastic dynamics of the brain network fluctuation, presumably indexed by the number of perceptual alternations.

The PD events rate (Figure 4b) as transient pupil changes were higher when perceptual alternation occurred, which is in line with the previous studies (Einhäuser et al., 2008;



Grenzebach et al., 2021). As these transient PD and baseline pupil changes related to cognitive shift are thought to reflect the different LC firing patterns or neural pathways, event-related changes in pupil size may be triggered by stimulus saliency or surprise upon perceptual transition (Kloosterman et al., 2015). Our results cannot be attributed to concerns that the baseline pupil size might be affected by the PD events (see Figure S2). However, it is premature to conclude such a causal relationship: it is still unclear whether these baseline and transient pupillary changes can be explained by common mechanisms or there are independent pathways that affect the perceptual alternations. As in the case of the LC-NE system in terms of baseline pupil size, the basal forebrain-acetylcholine (BF-ACh) system has been reported as evidence for correlations between the BF-ACh and pupil size (Reimer et al., 2016). Future studies focusing on the differences in these two types of pupillary changes could explore the neuromodulatory mechanisms of perceptual alternations.

Event-related transient pupil dilations, as an index of phasic LC activity, have been observed by changes in cognitive state such as attentional shift, effort, and decision making (de Gee et al., 2014; Mathôt, 2020; Suzuki et al., 2018) as well as perceptual alternations (Einhäuser et al., 2008; Grenzebach et al., 2021; Sato et al., 2020; Turi et al., 2018). Nevertheless, another explanation of the transient pupil dilations, instead of their being caused by perceptual alternation, could be that they are caused by decision making and/or motor responses such as button-press responses (Einhäuser et al., 2010; Grenzebach et al., 2021; Hupé et al., 2009). To avoid the influence of motor responses or its preparation on the pupil responses, we analyzed baseline pupil size obtained before participants pressed a button or before they were asked to respond (Figure 1d). Another experimental design-related issue concerns the effect of perceptual load on pupil dilation due to the task of counting the number of alternations in Experiment 1, as resting-state (i.e., baseline) pupil size is associated with the performance level of working memory tasks and high perceptual load (Aminihajibashi et al., 2020; Oliva, 2019; Schneider et al., 2016). Thus, we changed the task to a forced-choice one (i.e., yes or no) in Experiment 2 so that the difference in perceptual load between the cases (i.e., whether perceptual alternation occurred or not) was assumed to be more equivalent compared with the difference among the cases in Experiment 1 (i.e., counting and holding the number of perceptual alternations). As we observed similar results in both experiments, we therefore conclude that the effect of the intrinsic perceptual load, such as working memory or effort for counting, on pupil size is unlikely to explain the baseline effect on perceptual alternations. However, we cannot exclude the effect of the expectation of the task cue in

Experiment 2 (e.g., preparing for 'yes'). Making the decision before the task cue might increase the pupil size (de Gee et al., 2014; Mill et al., 2016). Since the baseline pupil size was defined before task assignment, if the decision-making affects to the baseline pupil size, it lasts longer than a single trial. Further studies are needed to assess the temporal aspect of the decision-related pupil dilation.

The frequency of the two tones and the duration between them affect the distributions of relative phases for perceptual alternations (Yamagishi et al., 2017). The effect of these physical parameters of stimuli can affect the perceptual alternations via bottom-up pathways. Besides that, selective attention through top-down modulation influences the build-up phenomenon in which the probability of hearing segregated stream increases over time (Carlyon et al., 2001; Jones et al., 1999; Macken et al., 2003). It has been found that perceptual alternation trials, compared with no-alternation ones, induce stronger negative event-related potentials (Higgins et al., 2020) and more synchronized transient BOLD signal in the auditory cortex (Schadwinkel & Gutschalk, 2011). These findings suggest that both sensory input and cortical activities are involved in perceptual alternation via bottom-up and top-down neural pathways. Furthermore, neurological and neurocognitive studies showed that the duration of a perceptual alternation is associated with GABA/Glx ratios in the auditory cortex (Kondo et al., 2018; Van Loon et al., 2013). Because there is a trade-off relationship between GABA and NE levels, our findings that baseline pupil size as a proxy of the increase in the NE level relates to the perceptual alternation is consistent with the elevating GABA level related to a lower probability of perceptual alternation. This is supported by an inverse correlation between GABAergic neurons in the LC and LC-NE response evidenced from pupil size (Breton-Provencher & Sur, 2019).

As described in the introduction, the present study was motivated by the recent arguments on the role of the LC-NE system, and the above interpretations are made in line with those arguments. It should be noted, however, that pupil responses can also be modulated by more diverse brain areas. The BF-ACh system involved with neural activities in the superior colliculus (SC), the frontal eye field (EFE), and the lateral intraparietal area (LIP) are associated with cognitive processes such as top-down attention (Basso & May, 2017). Wang et al. (2012) found that pupil size was increased by electrical microstimulation of the intermediated layers of the SC (SCi). As several studies have shown the attentional effect on auditory stream segregation (e.g., Snyder et al., 2006; Thompson et al., 2011), brain areas, in particular the SCi, may also be involved in determining the relationship between baseline pupil size and perceptual alternation. In addition, observed perceptual alternations



might modulate the neuronal network(s)/system(s) reflected by baseline pupil diameter. For instance, the LC is projected by the ventral tegmental area (VTA) and the prefrontal cortex (PFC) (Ornstein et al., 1987). Since the PFC has been reported to be related to perceptual alternation (Vernet et al., 2015), activities in the brain area might affect both perceptual alternation and baseline pupil size via a major noradrenergic hub system.

The current study underscores that baseline pupil size predicts the occurrence of perceptual alternations in auditory sequence tones. Perceptual alternations are influenced not only by an event-related transient pupil change (Einhäuser et al., 2008) but also by variability of baseline pupil change that reflects the probable neuromodulatory mechanisms involving the LC-NE system. Although it remains unclear whether the perceptual alternations related to tonic and phasic pupillary changes involve the same neural mechanisms, and what specific causal relationship underlie the observations, our results demonstrate that the stochastic dynamics of neural networks in the brain can be explored by analyzing the successive baseline pupil changes with behavioral responses.

## CONFLICT OF INTEREST

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## AUTHOR CONTRIBUTIONS

**Yuta Suzuki:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; validation; visualization; writing – original draft; writing – review and editing. **Hsin-I Liao:** Conceptualization; investigation; methodology; supervision; writing – review and editing. **Shigeto Furukawa:** Conceptualization; funding acquisition; project administration; supervision; writing – review and editing.

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