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Pupil constriction via the parasympathetic pathway precedes perceptual switch of ambiguous stimuli

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ABSTRACT

Perceptual rivalry of ambiguous stimuli reflects the interaction of neural activity among multiple cortical regions. However, it remains unclear what drives a spontaneous perceptual alteration. We hypothesized that increased fluctuations in spontaneous neural activity due to arousal reduction drive the perceptual switch. Here, we show that the pupils shrank a few seconds prior to the onset of the spontaneous perceptual switch. Such pupil constriction was not observed before the exogenous perceptual switch. Pharmacological experiments confirmed that the pupil constriction disappeared when the peripheral parasympathetic pathway (pupil sphincter muscle) was blocked, but it remained intact when the peripheral sympathetic pathway (pupil dilator muscle) was manipulated. Furthermore, rapid pupil dilations with behavioral response are also mediated by the peripheral parasympathetic pathway. The present findings suggested that transient arousal drops, as denoted by the autonomic nervous modulation of pupil size, are involved in inducing the spontaneous perceptual switch of bistable stimuli.

1. Introduction

The perception of ambiguous stimuli spontaneously alternates among multiple states without any physical changes in the stimuli. This perceptual transition reflects the interaction of the neural activity among multiple cortical regions, including the prefrontal, parietal, and sensory areas (Leopold and Logothetis, 1999; Lumer et al., 1998; Sterzer and Kleinschmidt, 2007; Watanabe et al., 2014). However, it remains unclear what modulates the cortical interactions and drives the spontaneous perceptual switch. Cortical activity is modulated by the subcortical arousal system through the widespread ascending projections including the noradrenaline and acetylcholine projections. When arousal is prompted by activation of these projections, spontaneous neural activity is suppressed, thereby enhancing the signal-to-noise ratio in cortical processing (Foote et al., 1975; Kimura et al., 2014; Kuo and Trussell, 2011). Conversely, when arousal decreases, the spontaneous fluctuations in cortical activity increases (Ferguson and Cardin, 2020; Liu et al., 2018). Larger volatility in cortical activity should facilitate the transitions among multiple stable states of cortical dynamics (Watanabe et al., 2014). Therefore, we hypothesized that increased fluctuations in spontaneous neural activity due to arousal reduction drive the perceptual switch. To test this possibility, we measured the pupil size as a physiological marker of arousal change, and compared a temporal change in the pupil size before a spontaneous perceptual switch in bistable apparent motion (Bistable) with a change before a stimulus-driven perceptual switch (Replay) (Fig. 1A).

Given that the response to a perceptual switch increases arousal and greatly changes the physiological autonomic activity, it is difficult to segregate whether physiological activities are triggers of perceptual switch or effects of the previous switch. The present study resolved this problem by performing a three-step approach. First, we used a quartet apparent motion stimulus, which has relatively long intervals of perceptual reversals (Sterzer and Kleinschmidt, 2007). Second, in the experiments, the participants with relatively long intervals of perceptual rivalry in a pre-screening test were enrolled. Furthermore, only epochs with an alteration interval of $\geq$10 s were analyzed (46%, Fig. 1B).

We further tried to identify which component of the autonomic nervous system is responsible for controlling pupil size and is associated with perceptual switching during the viewing of ambiguous visual stimuli. To this end, we pharmacologically blocked the peripheral autonomic pathways innervating the iris muscles. The peripheral parasympathetic pathway, innervating the pupil sphincter (constriction)

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muscle, was blocked using a cholinergic antagonist (tropicamide). The peripheral sympathetic pathway, which innervates the pupil dilator muscle, was manipulated by an adrenergic alpha-1 receptor agonist (phenylephrine), instead of an adrenergic antagonist, because adrenergic antagonists for human eye drops are currently unavailable. Since the adrenergic receptors at the neuromuscular junction are already activated by the adrenergic agonist, any changes in the release level of adrenaline due to sympathetic input are not reflected in the pupil diameter (Turnbull et al., 2017). By using these pharmacological blocking methods, we compared the temporal change in pupil size between the treated and non-treated eyes that were viewing bistable apparent motion stimuli. If the peripheral parasympathetic pathway is involved in pupil changes preceding the perceptual switch, the change in pupil size should disappear in the eye treated with tropicamide. Conversely, if the peripheral sympathetic pathway is involved, the change in pupil size should disappear in eyes treated with phenylephrine.

2. Methods

2.1. Participants

Forty-two healthy volunteers participated in the initial screening experiment. All participants had normal vision, either uncorrected or with correction by contact lenses. Thirty-one participants passed the screening criteria (at least 15 perceptual intervals of ≥10 s in 10 min)

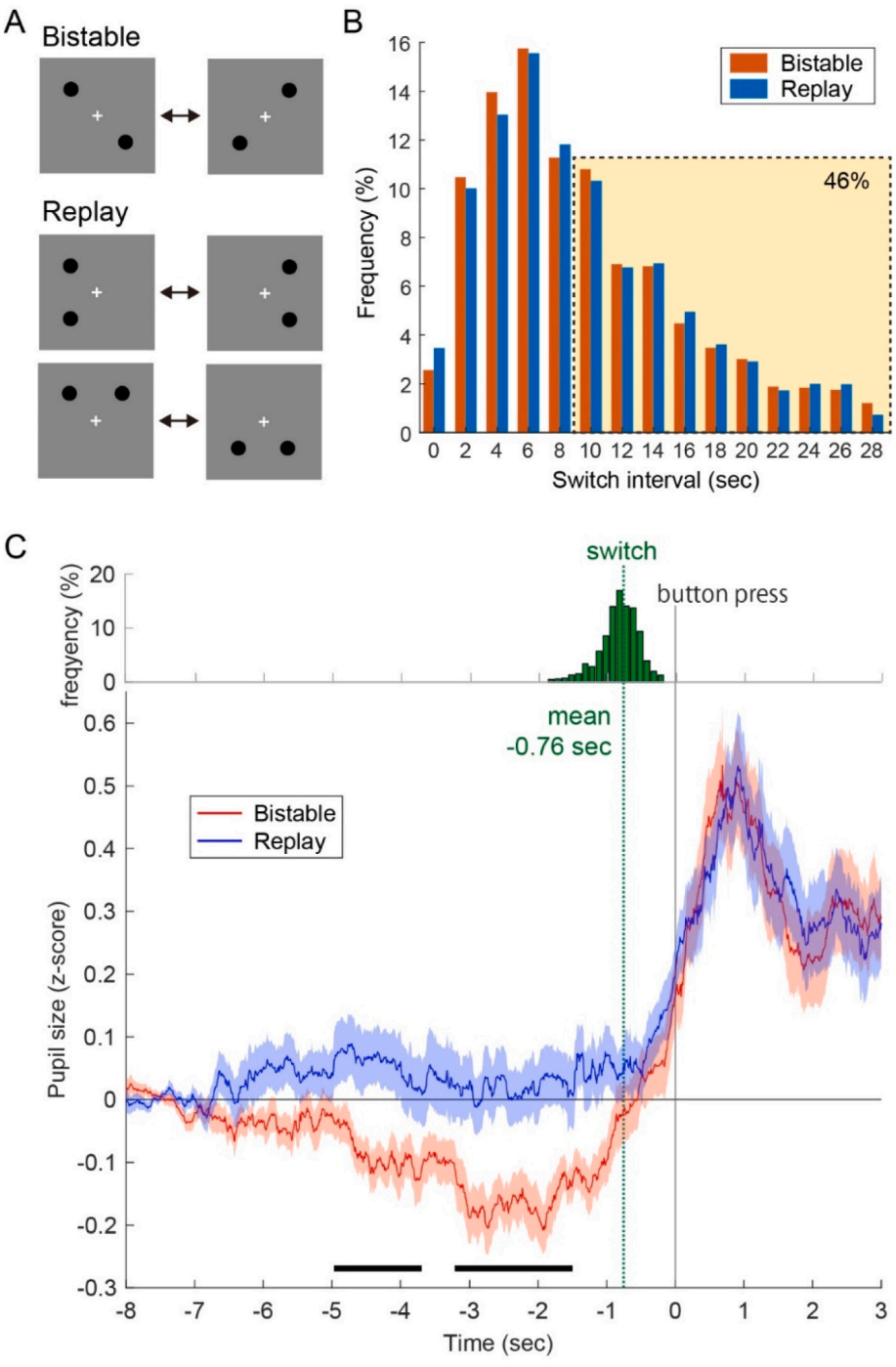

Fig. 1. Pupil size changes preceding a perceptual switch. (A) Apparent motion stimuli. In the Bistable condition, the observer's motion perception is bistable between the vertical and horizontal directions. In the Replay condition, only one direction of movements can be perceived. The sequence of reversals between the vertical and horizontal directions reproduced the one reported in the Bistable condition of each participant. Two frames alternatively displayed at 4 Hz. (B) Distribution of percept duration. Trials longer than 10 s (46%) were used for the pupil analysis. (C) Temporal changes in the pupil diameter around a perceptual switch. The red and blue lines represent the Bistable and Replay conditions, respectively, and the shaded areas denote a standard error. Time zero is the time at which the participant pressed a button to indicate a change in percept. The average pupil size for 7–8 s before button press was used as a baseline adjustment. The black underline denotes a significant difference between the two conditions. The upper panel showed a histogram of the direction switch time in the Replay condition and gives an indication of how long after a percept change the participant presses the button.

and participated in the behavioral experiment at a later date. Nine participants were excluded from the analysis due to an unstable pupil diameter measurement ($n = 5$) or an extremely high ratio of short switch intervals ($n = 4$). The final sample, thus, consisted of 22 participants (mean age 21.5 years, range 19–24 years; 8 women). No statistical test was run to determine sample size a priori. The chosen sample sizes are similar to those in previous publications related to pupil activity (Einhauser et al., 2008; Hupe et al., 2009).

In the pharmacological experiment, 14 participants of the behavioral experiment agreed to participate. Two participants were excluded from the analysis due to an extremely high ratio of short switch intervals. The final sample of the pharmacological experiment consisted of 12 participants (mean age, 22.3 years, range 20–24 years; 3 women). The sample size was determined by the power analysis using the effect size of the first experiment (alpha = 0.05, d = 1.05, power = 0.9). All participants had no ocular and central nervous system pathologies, diabetes, and cardiovascular problems. In addition, an ophthalmologist confirmed that their anterior chamber angles were not narrow before the experiment. The review board of Osaka University approved the experimental protocol (FBS2019-13), and our procedures followed the guidelines outlined by the Declaration of Helsinki. All participants provided written informed consent prior to the experiment.

2.2. Stimuli and procedures

We presented an apparent motion stimulus that induces motion perception using a 4-Hz alteration between two images. Each image shows two disks positioned at the corners of a virtual rectangle on a gray background (disk diameter 0.8 degree, luminance of gray background 20 cd/m^2, luminance of black disk 0 cd/m^2). When the disks are located at opposite corners, the perceived direction of apparent motion spontaneously alternates between the vertical and horizontal directions (Fig. 1A, Bistable). On the other hand, when the two disks share a vertical or a horizontal edge, the perceived motion direction is always determined by the visual stimulus (Fig. 1A, Replay). The sequence of reversals reproduced the one reported in the preceding Bistable condition of each participant. The diameter of the disks was 0.8 degree, and the distance they moved was 4 degrees at maximum. Participants sat in a chair in front of a 24-inch liquid crystal display (1920 × 1080 pixels, refresh rate 60 Hz, FlexScan, Eizo, Japan) and stabilized their head position using a chin rest and a forehead rest placed at a distance of 56 cm from the screen. They were requested to fixate on a white cross at the center of the screen (the size of cross 0.5 degree, luminance of the white cross 80 cd/m^2) throughout the experiment and to immediately report perceived changes in motion direction by pressing a button.

The optimal horizontal-to-vertical distance ratio (aspect ratio) of the disks which leads to equal durations of vertical and horizontal motion perceptions varies greatly by person (Genc et al., 2011). Thus, we first optimized the aspect ratio for each participant for maximum ambiguity in the Bistable condition (Genc et al., 2011; Sterzer and Kleinschmidt, 2007). Participants were presented a horizontally or vertically biased apparent motion stimulus (aspect ratio of 0.5 or 1.2, respectively). The aspect ratio gradually increased or decreased by 0.07 degree every 5 s, and they reported when the perceived motion direction changes. This procedure was repeated four times for each biased stimulus, and the optimal aspect ratio was determined by averaging the aspect ratios when the perceived motion direction changed for each person (see Supplementary Fig. 1). This individually optimized aspect ratio (range, 0.78–0.89) was used in all succeeding experiments.

Next, to screen out the participants whose perceptual alteration intervals were too short, the Bistable condition was presented with the optimized aspect ratio for 10 min and the average perceptual alteration interval was calculated. The participants with >15 events in which the same perception lasted for >10 s were enrolled in the main experiment.

In the behavioral experiment, the participants were presented with the Bistable and Replay conditions using the individually pre-optimized aspect ratios. First, the participants reported perceptual alternations of motion direction under the Bistable condition for 10 min. Based on this performance, the timing of motion alternation in the Replay condition was programmed to exactly reproduce the sequence of perceptual alternation intervals of the previous Bistable condition. Participants performed the two task conditions twice each with a 3-min break between sessions. The pupil diameter was recorded using a near-infrared eye tracker (Tobii Pro Spectrum, Tobii AB, Sweden) at a sampling frequency of 120 Hz.

In the pharmacological experiment, two kinds of mydriatic drops (two drops of phenylephrine 5%, NEOSYNESIN® or one drop of tropicamide 0.4%, MYDRIN®-M) were instilled to the participants' eye at different days. Tropicamide is a cholinergic antagonist, and its administration in the eye blocks signal transmission via acetylcholine at the neuromuscular junctions on the iris sphincter muscle. Phenylephrine is an adrenergic alpha 1 agonist, and its administration in the eye saturates signal transmission via noradrenaline at the neuromuscular junctions of the iris dilator muscle. Therefore, these eye drops could prevent signals from the central nervous system from being reflected in the activities of the iris sphincter and dilator muscles. Both drugs are commonly used as mydriatic drops to widen the pupil during ophthalmic examinations. The use of these eyedrops was approved by the review board of Osaka University for the following experimental protocols (FBS2019-13). These mydriatic drops were administered at the same dosage as that used for regular ophthalmic examinations. Participants were healthy adults with no history of ocular and central nervous system pathologies, diabetes, and cardiovascular disease. Before participation, an ophthalmologist confirmed that the participant had no predisposition to increased intraocular pressure and no problem with the administration of mydriatic drops. Until mydriasis was recovered, the participant was advised to refrain from performing dangerous mechanical operations, such as driving a car, and avoid looking directly at the sun or strong light. Pharmaceutical companies reported no side effect or after effect associated with the administration of these mydriatic drops, so participants had no particular disadvantage except the time they spent participating.

The washout period was at least 2 days. The drugs were instilled in the non-dominant eye, and the dominant eye was used as a control eye. Given that the pupil diameters differed between the instilled and intact eyes, the threshold values for both eyes were adjusted separately. Thus, the pupil diameters of both eyes were recorded using two near-infrared camera systems (Eyelink II, SR Research, USA) at a sampling frequency of 250 Hz. Ten out of 12 participants had their vision corrected by wearing contact lenses; the contact lens on the non-dominant eye was taken off throughout the experiment.

Before the instillation of the eye drop, participants were presented with the Bistable condition for 3 min using the individually pre-optimized aspect ratios. Subsequently, the mydriatic drop was instilled into their non-dominant eye, and the participants were asked to close their eyes for 1 min. To fully saturate the effect of the sympathetic α1 stimulant, the experiment was performed after waiting for 40 min after instillation. Then, the participants performed the experiment under the Bistable condition for 10 min for four times with a 5-min break between sessions. The order of the instillation of the two eye drops was counterbalanced across participants.

2.3. Data analysis

All data analyses were conducted using MATLAB (2018b, The MathWorks, Inc., USA). To exclude an artifact due to eye blinks on the pupil data, we first detected the blink onset and offset time by finding a pair of rapid decrease and increase within 500 ms in the pupil diameter, and these artifacts were removed by erasing data for 50 ms before and after the blink. Then, the pupil diameter was converted to a standardized z-score (z = [raw signal – average]/[standard deviation]) for each participant. The pupil response was analyzed by epochs lasting from 8 s

before to 3 s after the time of button press. To avoid the influence of a dramatic pupil change due to perceptual switch or button press, data from 8 to 7 s before button press were used for baseline corrections. To exclude the effects of changes in physical activity associated with motor responses, only the data epochs with perceptual alternation intervals exceeding 10 s were analyzed. The number of total switch events and number of epochs with longer intervals (> 10 s) for each participant are listed in Supplementary Table 1. Longer intervals accounted for 46% and 48% of all intervals in the behavioral and pharmacological experiments, respectively There was no statistical difference in the ratio between the behavioral and pharmacological experiments (paired *t*-test, tropicamide $t_{11} = -0.79$, $p = 0.44$, phenylephrine $t_{11} = -0.28$, $p = 0.78$). We further compared the estimated parameter values of gamma distribution ($y = \frac{1}{b^a \cdot \Gamma(a)} * x^{a-1} e^{-x/b}$) of perceptual switch intervals between them. As summarized in Supplementary Table 2, parameter values did not differ significantly between behavioral and pharmacological experiments (paired t-test, tropicamide, parameter a, $t_{11} = 1.98$, $p = 0.07$, parameter b, $t_{11} = -1.84$, $p = 0.09$; phenylephrine, parameter a, $t_{11} = 1.39$, $p = 0.19$; parameter b, $t_{11} = -1.51$, $0 = 0.16$). These results indicate that pharmacological manipulation of the peripheral autonomic pathway did not appear to influence perceptual dynamics of ambiguous stimuli. To examine the effect of switch report on pupil size, we extracted the data from 2 s before to 4 s after the time of button press for all events. Data from −2 to 1 s before the button press were used for baseline corrections. The timeseries of median pupil size across epochs were calculated for each participant and used in the later statistical analysis. We used the median instead of the mean to reduce the influence of outliers due to artifacts, such as microblinks.

To identify statistically significant differences in the temporal variation of physiological activity between two conditions, we conducted a cluster-based permutation test for correcting for multiple comparisons along the time dimension. First, the t-value was calculated using a paired, two-tailed *t*-test at each time point across participants, and the sum of the t-values for clusters (i.e., with *p*-values continuously <0.05) was calculated. Next, the data were shuffled between the two conditions in each participant, and the statistical test was repeated. The maximum value of the total t-values was held constant by a scaling procedure. By repeating the shuffling procedure 1000 times, the distribution of the total t-values using randomized data was obtained. The total t-value corresponding to a two-tailed alpha level of 0.05 was then used as the statistical threshold in analyzing the original data set.

3. Results

Twenty-two participants reported perceptual switches of the Bistable and Replay conditions for 20 min each. The pupils gradually shrink several seconds prior to the spontaneous perceptual switch (red line in Fig. 1C), but such pupil constriction was not observed in the stimulus-driven perceptual switch (blue line in Fig. 1C). On the other hand, the pupil dilation in association with the button presses was observed in both conditions. A significant difference between the two conditions was detected at 5.0–3.7 and 3.2–1.5 s before the switch report (cluster-based permutation test, $p < 0.05$). The distribution of mean pupil size across a significant time period for each participant is shown in Supplementary Fig. 2. We presume that this pupil constriction occurs prior to the awareness of perceptual reversal because the mean latency of the switch report from the stimulus changes was 0.76 s in the replay condition (green bars in Fig. 1C).

It may be argued, however, that arousal reduction or drowsiness due to prolonged same perception biases the response criterion for spontaneous perceptual switches, such as delayed responses. To test this possibility, we compared the distributions of percept durations between high and low arousal states, divided according to the pupil size, for 1–2 s before the button press (Supplementary Fig. 3). Although the ratio of short intervals at 2 s in the high arousal state was higher than that in the low arousal state, the distributions did not statistically differ between high and low arousal states (two-sample Kolmogorov-Smirnov test, $p = 0.91$). Even in a high arousal state, 38% of perceptual durations were longer than 10 s. Therefore, it is unlikely that the pupil constriction was caused by changing the response criterion due to a decrease in arousal level.

It is a well-known fact that voluntary eye movements or eye blinks sometimes trigger the perceptual switch.(Leopold and Logothetis, 1999) It is thus possible that it is not the change in the arousal level per se but some changes in voluntary eye movements or eye blinks associated with the arousal level that actually triggered the perceptual switch. However, the gaze activity did not change before the perceptual switch in the present study (Supplementary Fig. 4). In addition, the blink rates did not differ between the Bistable and Replay conditions before the perceptual switch (Supplementary Fig. 5). These results clearly show that the transient arousal reduction per se was involved in inducing a spontaneous perceptual switch.

The pupil diameter is controlled by equilibrium of the sympathetic and parasympathetic systems. We then identified which autonomic nervous pathway was involved in pupil constriction preceding the perceptual switch by blocking the neuromuscular junction with two types of mydriasis eye drops. Each participant was administered eye drops twice with a different type applied each time. The drugs were applied to a single eye, and the other eye was used as simultaneous control (Fig. 2A). Before application of eye drops, we confirmed that both eyes showed a similar pattern of pupillary response with and without contact lenses (see Supplementary Fig. 6). At 40 min after the instillation, 12 participants reported spontaneous perceptual switches of the Bistable condition for 40 min with a five-minute break every 10 min. In both drugs, mydriasis occurred in the drugged eye until the end of the experiment, and the control eye showed miosis to adjust the amount of light entering the eyes (Fig. 2B). Although pupil constrictions before the perceptual switch were observed in the control eye, it disappeared in the drugged eye where the central parasympathetic signals were blocked (red line in Fig. 2C). The significant difference in the pupil size between the drugged and control eyes was detected 4.0–1.4 s before the switch report (cluster-based permutation test, $p < 0.05$). The distribution of mean pupil size across a significant time period for each participant is shown in Supplementary Fig. 7A. Such difference was not observed between the drugged and control eyes when the central sympathetic signals were inhibited (Fig. 2D). These results demonstrate that pupil constriction before the spontaneous perceptual switch was mediated by the peripheral parasympathetic pathway in particular.

It is worth noting that pupil dilation in association with the button press for switch report showed different temporal patterns between the drugged and control eyes (Fig. 2C, D). To further examine this tendency, we analyzed the temporal change in pupil size related to all button press events using the data just before the button press as the baseline (−2 to 1 s). When the peripheral parasympathetic signals were blocked, the peak latency of pupil dilation was significantly delayed in the drugged eye compared to the control eye (Fig. 3A, −0.32 to 0.95 s, cluster-based permutation test, $p < 0.05$). The distribution of mean pupil size across a significant time period for each participant is shown in Supplementary Fig. 7B. On the other hand, when the peripheral sympathetic signals were blocked, the peak latency did not differ between the eyes (Fig. 3B). These results suggest that the rapid pupil dilatation was mainly mediated by the deactivation of the peripheral parasympathetic nervous system. It was also noted that the magnitude of pupil dilation associated with the reporting of perceptual switch was smaller in the pharmacological experiment compared to that in the behavioral experiment. There are several interpretations of this. First, given that all participants of the pharmacological experiment had performed the same task in the previous behavioral experiment, familiarity with the ambiguous visual stimuli might have attenuated the arousal response in the pharmacological experiment. Another interpretation is that since mydriasis caused by eye drops had caused abundant light uptake, a mechanism

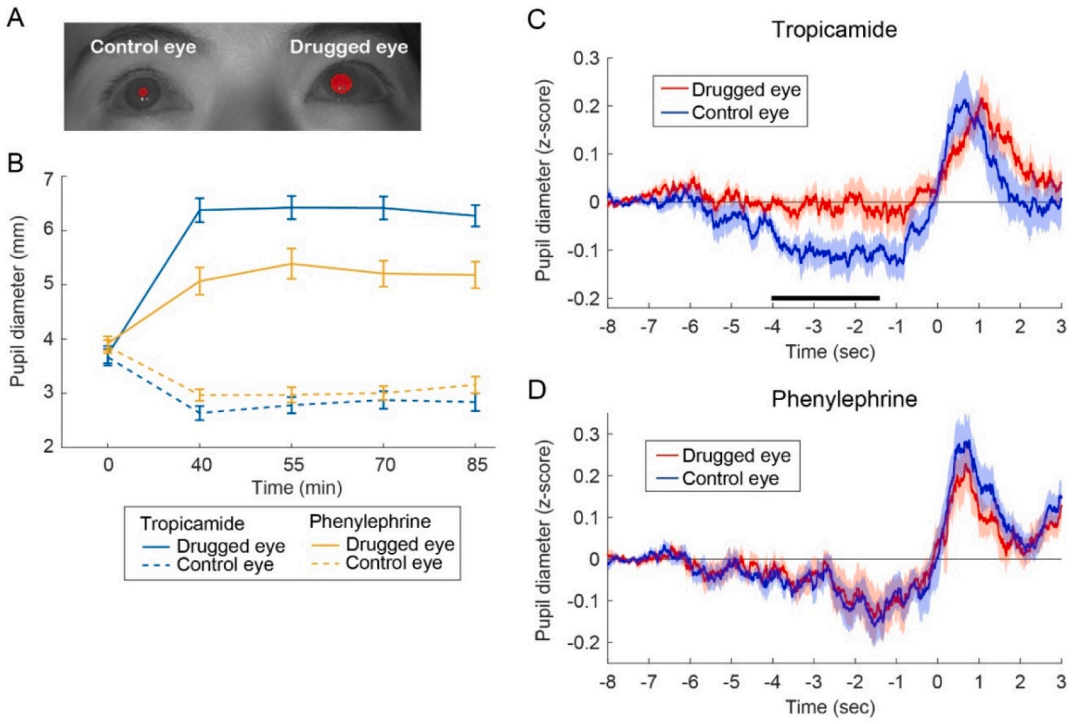

Fig. 2. Effects of the mydriatic drops on pupil activity.
(A) Images of the pupil in the intact and instilled eyes. (B) Pupil diameter comparison of the eyes at baseline (0 min), during tropicamide installation (blue line), and during phenylephrine installation (yellow line). The dotted lines represent the pupil diameter of the intact eyes. The error bar represents a standard error. (C) Pupil diameter changes in the intact (blue) and tropicamide-instilled (red line) eyes around a perceptual switch. (D) Pupil diameter changes in the intact (blue) and phenylephrine-instilled (red) eyes around a perceptual switch. The shared areas represent a standard error. The black underline denotes a significant difference between the two conditions.

suppressed pupil dilation to regulate the amount of light uptake.

4. Discussion

The present study revealed that a transient drop of arousal, which was reflected by pupil constriction, occurred several seconds prior to the spontaneous perceptual switch of ambiguous stimuli. By contrast, pupils did not shrink prior to the perceptual switches that were driven by overt changes in stimuli which took place after the same intervals as those of the spontaneous switches. Therefore, pupil constriction before the spontaneous perceptual switch did not occur due to tiredness after the prolonged current perception, but rather it was associated with the induction of the spontaneous perceptual switch. This pupil constriction preceding the spontaneous perceptual switch disappeared when the peripheral parasympathetic pathway (pupil sphincter muscle) was blocked by the cholinergic antagonist. In contrast, manipulating the peripheral sympathetic pathway (pupil dilator muscle) had no effect on it. The present findings suggest that transient arousal drops are involved in induction of the spontaneous perceptual switch of bistable stimuli, as denoted by pupil constriction via the peripheral parasympathetic pathway.

It is worth noting that the present study revealed that blocking the peripheral parasympathetic pathway (pupil sphincter muscle) affected not only pupil constriction preceding the perceptual switch but also pupil dilation associated with reporting of the perceptual switch. In contrast, inhibiting the peripheral sympathetic pathway (pupil dilator muscle) had no effect on pupil constriction and had a weak effect on pupil dilation. Previous human pharmacological studies consistently reported that when the peripheral parasympathetic pathway is blocked, pupil dilation associated with cognitive task difficulty and spontaneous fluctuations in pupil size, known as hippus, disappear, while inhibiting the peripheral sympathetic pathway did not have any such effect on pupil size (Steinhauer et al., 2004; Turnbull et al., 2017). This evidence suggests that the pupil sphincter muscle, under the influence of central parasympathetic activity and central sympathetic activity, is involved in the adjustment of pupil size. In fact, animal physiological studies have revealed that there is a neural circuit connecting the central sympathetic system to the peripheral parasympathetic pathway. The Edinger-Westphal (EW) nucleus, which contains parasympathetic preganglionic neurons that innervate the pupil sphincter muscle, receives inhibitory inputs from the locus coeruleus (LC) nucleus via an alpha-2 adrenoreceptor (Koss, 1986; Szabadi, 2018). As there is a close association between pupil diameter and neural activity in the LC nucleus, which is the center of noradrenergic projections (Joshi et al., 2016; Murphy et al., 2014), the release of noradrenaline from the LC suppresses the neural activity in the EW nucleus, resulting in pupil dilation due to relaxation of the pupil sphincter muscle. Conversely, decreased activity of the LC neurons weakens the inhibition of the EW nucleus and leads to constriction. Converging this evidence, we assume that changes in pupil size via the peripheral parasympathetic pathway reflect fluctuations in arousal level modulated by the LC-noradrenaline system. If this speculation/hypothesis is true, then the pupil constriction before the perceptual switch might be due to a combination of increased parasympathetic drive plus transient attenuation of the activity in the LC-noradrenaline system.

This raises the question of how arousal reduction due to the LC-noradrenaline system induces the perceptual transitions of ambiguous stimuli. The noradrenaline projection from LC modulate the signal-to-noise ratio of cortical processing by suppressing the spontaneous cortical activity (Ferguson and Cardin, 2020; Foote et al., 1975; Kimura et al., 2014; Kuo and Trussell, 2011). Therefore, when arousal is prompted, the current perceptual state might become stable. In fact, a previous study reported that the larger the pupil size at the onset of each perceptual switch of ambiguous stimuli, the longer the duration of the

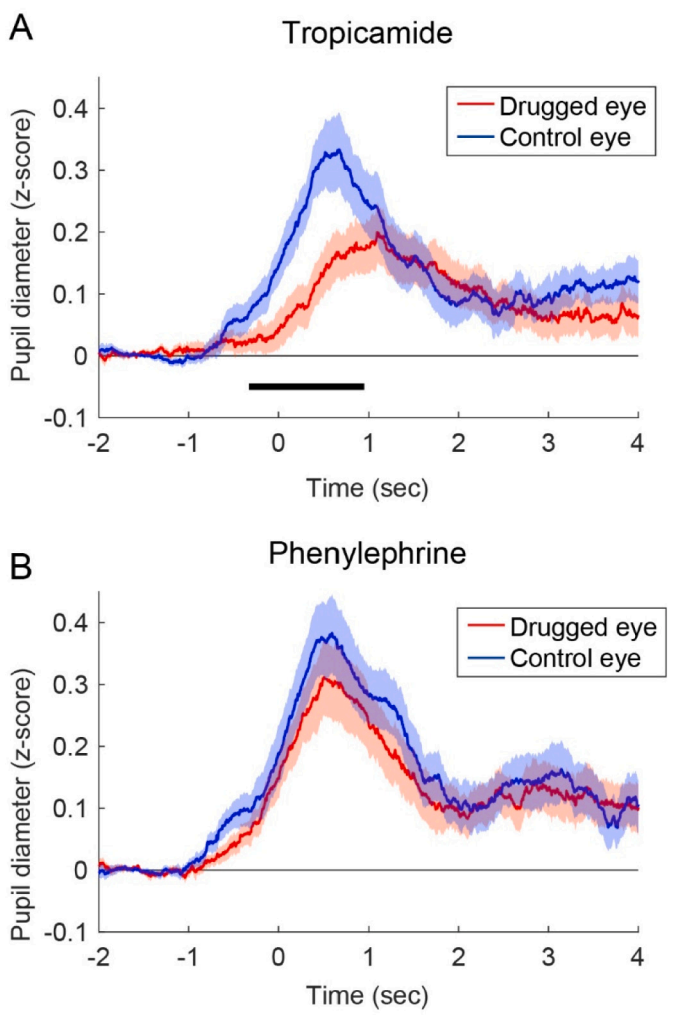

Fig. 3. Effects of the mydriatic drops on pupil dilation.
(A) Pupil diameter changes in the intact (blue line) and tropicamide-instilled (red line) eyes after the button press for a switch report. (B) Pupil diameter changes in the intact (blue line) and phenylephrine-instilled (red line) eyes after the button press. The shared areas represent a standard error. The black underline denotes a significant difference between the drugged and control eyes.

perception (Einhauser et al., 2008). Contrary to arousal enhancement, arousal reduction denotes a diminished activity of the LC-noradrenaline system and accompanies an increased spontaneous activity in the cortical neurons (Ferguson and Cardin, 2020). A recent brain imaging study revealed that the transient arousal drops during a resting state induces a spontaneous activation in the global cortical areas with deactivation in the subcortical regions (Liu et al., 2018). An increased spontaneous cortical activity enhances the fluctuations in the cortical interactions, thereby destabilizing the current perception. Therefore, we infer that a transient arousal reduction due to decreased activity in the LC-noradrenaline system drives the spontaneous perceptual switch of the ambiguous stimuli.

It has been proposed that various factors influence the perceptual switch rate of ambiguous stimuli (Leopold and Logothetis, 1996). For example, a study revealed that presentation of flash triggered a perceptual switch (Kanai et al., 2005). Meanwhile, another study showed that observers can voluntarily bias perceptual switch rates by controlling attention toward the stimuli (Meng and Tong, 2004). These studies suggest that both bottom-up and top-down attention systems are involved in perceptual switching. Additionally, the present study provides a new insight that not only attention but also intrinsic arousal change is involved in inducing perceptual switch. Although the present study examined pupillary responses to the apparent motion stimulus, the same tendency was observed in pupillary responses to other types of ambiguous stimuli (e.g., the Necker cube) in a previous study (Einhauser et al., 2008). Therefore, we speculate that transient arousal reduction is one of the principal factors that cause perceptual switch in general bistable perception. However, it should be noted that the present study collected data from slow switchers and focused on a state where the alteration interval was >10 s. Thus, the present study alone cannot tell us whether transient arousal reduction is also involved in the perceptual switch with short intervals. In fact, a previous study reported that fast and slow switchers have a different inhibitory tone at the level of the primary visual cortex (van Loon et al., 2013). A future study is required to compare the effect of arousal changes on fast switchers.

In summary, this study revealed that transient arousal reduction, as denoted by pupil constriction, precedes the onset of perceptual switch of ambiguous stimuli. It also becomes clear that the peripheral parasympathetic pathway is involved in controlling the pupil size for both dilation and constriction under the influence of the brain arousal system. Taken together, this study suggests that arousal fluctuations in central autonomic nervous activity continually modulate our visual awareness.

Declaration of competing interest

Authors have no competing interests.

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Appendix A. Supplementary data

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