

Commentary

Pupil tracks statistical regularities: behavioral and neural implications

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Pupillary light reflex adjusts the amount of light reaching the retina. Recent work suggests that the brainstem pupillary light reflex pathway is controlled by the environment's internal models derived from higher-order temporal statistics. This finding has implications at the behavioral and neural levels. Pupillary changes in response to statistical regularities could be a metric constituting the precision with which the internal models are represented. These pupillary changes may aid in information processing through attentional mechanisms. One possible region that mediates descending cognitive inputs to pupil cycling is locus coeruleus. Here we propose a unified framework of locus coeruleus' role in modulating pupillary change, which successfully explains current and previous findings. The locus coeruleus could have multiple subsystems selectively (but not exclusively) driven by behavioral relevance and statistical learning to regulate pupillary change.

Keywords

Statistical learning; pupil dilation; locus-coeruleus; attentional mechanisms

Statistical regularities are aspects of the environment that are repeated over space and time (Turk-Browne, 2012). For instance, the building landscape changes in a similar manner from a city to its outskirts, and the pedestrians tend to cross the road when the red signal is on. This ability to extract spatio-temporal patterns within the environment is fundamental to human behavior. Identifying the mechanisms through which these regularities are extracted and consequently used in forming internal models of the environment is central to statistical learning research (Fiser and Aslin, 2002). The majority of the research in statistical learning has used offline measures that expose participants to sequences of stimuli containing statistically reliable spatio-temporal regularities and subsequently assess their ability to detect them (Barakat et al., 2013). The ongoing research aims to identify the potential online measures that track statistical learning.

Pupillometry is an online measure of pupil size and reactivity to various stimuli. Pupillary changes (dilation and constriction) respond to the global luminance levels and adjust the amount of light reaching the retina. These changes are known as *pupillary light re-*

flexes (PLR), which were traditionally considered lower-level reflexes. Converging evidence indicates the possibility that pupillary changes involve descending projections from various cortical and subcortical regions, including locus coeruleus (LC), thalamus, inferior and superior colliculus, anterior (ACC) and posterior cingulate cortex (PCC), orbitofrontal cortex (OFC), right anterior insular cortex (rAIC) and superior frontal gyrus (SFG) (DiNuzzo et al., 2019; Joshi et al., 2016), which makes pupil size an ideal candidate that reflects on a wide range of cognitive functioning (Mathôt and van der Stigchel, 2015).

In a recent study, Schwiedrzik and Sudmann (2020) demonstrated that the brainstem PLR pathway that accounts for pupil dynamics adjustment is controlled by the environment's internal models derived from higher-order temporal statistics. Pupil recordings of humans and monkeys were made as they viewed faces with and without statistical regularities, referred to as random and structured streams of faces, respectively. In the random condition, faces were presented at a fixed temporal rate (2 Hz) whereas, in the structured condition, faces were presented at the same rate but were grouped into pairs such that the first face in a pair predicted the identity of the second face, giving rise to a pair rate of 1 Hz. This way, the luminance-induced pupil variations in random conditions (2 Hz) were dissociated from the pair-induced pupil variations in structured conditions (1 Hz), which contained statistical regularities.

Human participants performed a 1-back repetition detection task to ensure that they were paying attention while monkeys passively viewed the faces with a reward for accurately fixating at the center. This difference in tasks did not lead to any difference in pupil signal spectral power between the two primates. Subsequent experiments on humans included: (i) a rapid serial visual presentation (RSVP) task to assess participants' ability to retain the statistical structure they have been exposed to, (ii) a card-sorting task that tested participants' awareness of the statistical structure, and (iii) a disk-detection task having a briefly presented disk embedded within the structured and random streams of faces to assess the consequence of pupil entrainment associated with the statistical structure on visual sensitivity.

The results revealed a distinct peak in pupil signal spectral power at the image rate (2 Hz) in both structured and random conditions. Interestingly, an additional distinct peak was observed at

the pair rate of 1 Hz in the structured condition. This suggests that the pupil can track statistical regularities that are not attributable to a luminance-based effect. This pupil entrainment to regularities was not an artifact arising from any eye movement signals or blinks. The same results were found in monkeys, suggesting that monkeys and humans exhibited similar pupillary dynamics to environmental statistics. Importantly, human participants showed faster and more accurate responses to the paired faces than the novel faces in the RSVP task, suggesting that they retained the face sequences' statistical structure. This pupillary entrainment to regularities occurred in the absence of explicit awareness of regularities as subjects failed to reproduce the original pairs in the card-sorting task. This entrainment had direct perceptual consequences by enhancing visual sensitivity within a pair in the disk-detection task.

Pupil entrainment induced by statistical regularities may aid in information processing through attentional mechanisms. For instance, statistically structured sequences of information receive attentional priority, thereby invoking an implicit attentional bias for the regularities (Zhao et al., 2013). Pupillary changes in response to violated regularities (Alamia et al., 2019) and predicted stimuli (Richter and de Lange, 2019) are attention-dependent. Predicted stimulus elicits a reduced pupil dilation following statistical learning (Richter and de Lange, 2019), which could be regarded as a pupil-based sensory attenuation. However, the present study did not show any attenuation in pupil responses for the second predicted face than the first face of a pair.

Explanations rooted in attentional and reward-based accounts could elucidate the reasons for the enlarged pupillary response of the second predicted image. First, attention can potentially reverse the attenuating effect of prediction by boosting predictions' precision (Kok et al., 2012). Second, as attention gets biased towards statistically reliable stimuli (Zhao et al., 2013), this biased attention may allocate more attentional resources for processing the predicted second face, thus enhancing the second face's internal representation in a pair (Barakat et al., 2013). Alternatively, the second face's internal representation can get enhanced due to perceptual learning caused by the intrinsic reward of meeting expectation and pair completion (Barakat et al., 2013).

Pupillary changes in response to statistical regularities could be a metric constituting the precision with which the internal models are represented. Indirect evidence exists for how pupil diameter is responsive to manipulation of various regularities present in the environment. For instance, pupil diameter is sensitive to the uncertainty of event's probability (Friedman et al., 1973), deviancy from stimulus property (Liao et al., 2016), various structural (Alamia et al., 2019; Zhao et al., 2019) and temporal violations (Raisig et al., 2010), and reflects dynamically updated beliefs associated with the precision of stimulus distributions (Vincent et al., 2019). Together, these findings suggest that pupil size reliably varies with the sudden changes in the environment's causal statistical structure. Schwiedrzik and Sudmann (2020) also highlight the critical finding that pupil dynamics adjust to the environment's temporal regularities. However, the way statistical regularities impact pupillary changes lacks consistency. In the condition with regularities, pupil dilation following the first face is smaller than the predicted second face.

The most crucial finding of Schwiedrzik and Sudmann (2020) is that the brainstem PLR pathway is under the influence of brain areas that can extract environmental regularities. One possible site that mediates descending cognitive inputs to pupil cycling is locus coeruleus (LC). The LC, a subcortical brain structure and origin of norepinephrine (NE), is considered a key node within the neural circuitry that controls the iris's muscles (Samuels and Szabadi, 2008). The LC-NE system is often implicated in various cognitive processes from selective attention (Sara and Bouret, 2012), surprise (Avery and Krichmar, 2017), and reward processing during decision making to tracking and evaluating the statistics of unfolding sensory signals (Zhao et al., 2019). Event-related measures indexing the activity in the LC-NE system (Murphy et al., 2011) are also linked with statistical learning (Jost et al., 2015), providing indirect evidence for LC role in statistical learning. However, Schwiedrzik and Sudmann (2020) suggest that their results are dissociable from the noradrenergic effects of the LC-NE system based on the argument that pupil cycling is primarily under parasympathetic control. Given the inconsistency in how regularities impact the pupillary changes, we propose another possible mechanism that interfaces pupil cycling by LC and explains the present findings, displaying a lack of pupil-based attenuation to predicted stimulus.

A few findings exist in supporting LC to have multiple subsystems selectively (but not exclusively) driven by behavioral relevance and statistical learning in regulating pupillary changes. Recent studies have identified anatomical and functional heterogeneity within the LC and its connectivity patterns (Breton-Provencher and Sur, 2019; Uematsu et al., 2017). A primary association between pupil and LC can correspond to a secondary association between pupil and targets of LC-NE neuromodulation (Joshi and Gold, 2020; Joshi et al., 2016) which are cognitively-mediated. It has been shown that behavioral relevance exerts a significant influence on pupillary dynamics (Zhao et al., 2019). Because implicit statistical learning may not be as behaviorally (task) relevant as a violated prediction of learned regularities or unanticipated events, pupillary response to these violations may involve different subsystems within LC. This could be the reason why Schwiedrzik and Sudmann (2020) did not find any evidence for surprise-based pupil dilation of the first face or prediction-based sensory attenuation of the second face. Thus, distinct subsystems within LC driven by behavioral relevance or statistical structure may subserve pupillary changes to facilitate information processing.

In conclusion, Schwiedrzik and Sudmann (2020) reveal that pupillary adjustments, which were once thought to be a lower-level reflex, are under the influence of brain areas that can extract regularities and form internal models of the environment. Pupil keeps track of the changes in the environment and actively uses this information to enhance visual sensitivity. Pupillary entrainment to these regularities may involve attentional mechanisms for better stimulus representation. Given recent findings related to functional and anatomical heterogeneity in LC and its putative role in cognitively induced pupillary changes, we suggest, based on extraneous information missed by Schwiedrzik and Sudmann (2020), that LC could mediate these pupillary changes employing different subsystems within it. This notion of distinct subsystems within LC driven by behavioral relevance serving different pupillary changes

is based on the available evidence, and future studies should focus on experimental investigation to verify it. However, it provides additional directions in establishing pupillometry as an online measure to track statistical learning. More work is needed to establish clarity on pupillary entrainment mechanisms in response to internal models and their interaction with other cognitive processes at the structural and functional levels.

Author contributions

SW and SP wrote the manuscript. Both authors contributed to editorial changes.

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Conflict of Interest

The authors declare no competing financial interests.

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