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Keeping a large-pupilled eye on high-level visual processing

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The pupillary light response has long been considered an elementary reflex. However, evidence now shows that it integrates information from such complex phenomena as attention, contextual processing, and imagery. These discoveries make pupillometry a promising tool for an entirely new application: the study of high-level vision.

The long-standing view of pupil control

Constriction of the pupil in response to light may be the simplest visually evoked behavior [1]. The basis for this response has little to do with the visual system as we usually think of it (forming an image of the world). In large part, it is a simpler and archaic 'sense of light' used for systemic adjustments, such as adapting rhythmic physiological functions (e.g., sleep) to the local environment. It depends primarily on a special class of retinal cells that contain melanopsin and project almost exclusively to subcortical targets, making little or no contribution to the canonical image forming visual pathway to the cortex [2].

When light level is constant, another archaic circuit – the autonomic system – induces fluctuations of pupil size [1]. In humans, the balance between sympathetic and parasympathetic activity varies in complex ways with the cognitive and emotional status of the subject, and this has led to the realization that non-light-dependent pupil dilations could correlate with such constructs as cognitive load and decision making, as described in several reviews and recently revisited experimentally [3,4].

New evidence that complex vision influences the pupil

Rapidly accumulating evidence suggests that these two circuits are not the only contributors to pupil control. Specifically, pupillary light responses may integrate signals from the more complex image forming system. Evidence for this comes from the study of three phenomena that are characteristic of cortical visual processing: attention, contextual modulations, and mental imagery. All three affect pupil size in a predictable and systematic way. Covertly shifting attention to a brighter region of an image produces pupillary constriction, despite the fact that the cognitive load and pattern of retinal illumination remain constant [5]. Pupillary constriction is also evoked by contextual information that is usually associated with high light levels, such as a picture of the sun, even if the actual luminance of the image is the same as in control stimuli [6,7]. Moreover, mentally visualizing a bright scene (compared with a darker scene) produces pupillary constriction [8]. Although surprising for many, these recent findings connect with research from more than 50 years ago, showing that pupillary light responses are inhibited when perceptual sensitivity is transiently suppressed [9]. Together, these results suggest that, while the subcortical non-image forming system may be responsible for the largest part of pupillary light responses, there is also a contribution of other (likely cortical) signals.

What is the functional significance of these effects? In other words, does the fact that complex visual processing modulates pupil diameter serve any purpose? To answer this question, the size of these effects must be considered. In humans, light can change pupil diameter between approximately 2 and 8 mm, with small but measurable consequences on visual sensitivity, acuity, and depth of field [1]. Pupil dilations related to arousal are more modest, of the order of 1 mm, and pupil changes with shifts of attention and context are often just a fraction of a millimeter. Many have speculated on how these tiny pupil modulations may enhance vision (e.g., attention may improve acuity at the behaviorally relevant light level). However, no direct evidence has been provided so far and, extrapolating from data with larger pupil changes, one would predict close to un-measurable effects on visual performance. This opens intriguing questions about the origin of the modulations (Box 1). However, no matter how subtle their impact on vision is, these pupil modulations might be symptomatic of a general phenomenon – the ubiquity of top–down influences on sensory processing – and thereby serve as a sensitive, noninvasive tool for its study.

Pupillary modulation as a tool for studying sensory processing

One key feature of pupillary responses is that they are overt and easily measurable, much like behavioral performance and perceptual reports. Unlike direct reports, however, pupil size is an objective parameter, and it can be acquired with minimal cooperation on the part of the subject.

One area where these features are particularly valuable is the clinical evaluation of visual loss. Standard methods require patients to perform a demanding detection task,

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Box 1. Origins of the contextual modulations of the pupillary light response

If small pupil size changes are unlikely to enhance vision in any meaningful way, what is the purpose of having such tight control over pupil size? Why do we need to modulate the simple pupillary light response by taking into account complex factors such as attention and context? One possibility is that pupillomotor nuclei are functionally linked to nearby oculomotor nuclei that are well known to integrate cortical signals, for example, those controlling the optokinetic reflex. Another hypothesis is that the origin of high level influences dates far back in phylogeny; they may be 'vestigial' in humans, but have developed in species with enhanced pupil mobility. In fact, pupils come in a variety of sizes and forms, and some of these allow for more obvious changes in retinal illumination and image blur. An ancient origin would suggest that, like the basic 'reflex' light response, high level effects are shared across several species. By contrast, if these effects were by-products of other circuits for oculomotor control, they might be specifically associated with particular patterns of eye movement, and associated with foveal vision. Preliminary insight into these questions might come from studies that test the relationship between pupillary responses and eye movements, for example, by juxtaposing the effects of attention to spatial and non spatial (feature-based) attributes [15].

and this is not always possible and reliable. However, pupillary responses can be recorded rapidly while the patient simply stares at a screen, and the results for mapping visual field loss in several retinal pathologies this way are encouraging [10]. Importantly, given the evidence suggesting that pupillary light responses integrate high level information, these methods could be extended to blindness of nonretinal origin. For example, patients with lesions of early visual cortex may experience blindsight, or an inability to consciously perceive stimuli in part of the visual field; however, some retained the ability to correctly guess their features. Quantifying this ability is notoriously challenging and relies on the patients' capability and willingness to report on sensations that they don't consciously experience. However, recent research [11,12] indicates that a reliable index of this phenomenon can be obtained by comparing pupillary responses to stimuli in the 'blind' versus spared visual fields.

Pupillometry may also have a major impact on research in nonclinical populations, supporting the investigation of conscious perception and the related construct of attention. Specifically, it may be important for linking behavioral and neurophysiological levels of investigation. For example, we have shown that pupillary responses to light are attenuated when the light stimuli are not attended [5]. This modulation of the pupillary light response provides a quantitative, graded, and time-continuous index of how attention to a stimulus enhances its processing; that is, an index that shares key features with neurophysiological measures (including independence from response criterion, since pupillary responses are involuntary), while correlating tightly with behavioral performance [13]. If attention affects pupillary light responses, then the modulation of these responses can also indicate how attention is deployed across the visual scene, provided that the scene contains a range of luminances. This measure has important advantages over other overt parameters. First, it is acquired without interfering with the subject's behavior or the deployment of attention itself, unlike measuring behavioral performance on a secondary task or at invalidly cued locations. Second, the measured pupil variations *per se* are expected to have minimal or no impact on visual performance (see above), unlike overt shifts of attention (eye movements) that shift the fovea and change the spatiotemporal pattern of visual sensitivity.

It is important to note that actual online tracking of attention (trial-by-trial, millisecond-by-millisecond) by pupillometry is not quite possible yet, mainly because of the difficulty in parsing the multiple factors affecting pupil

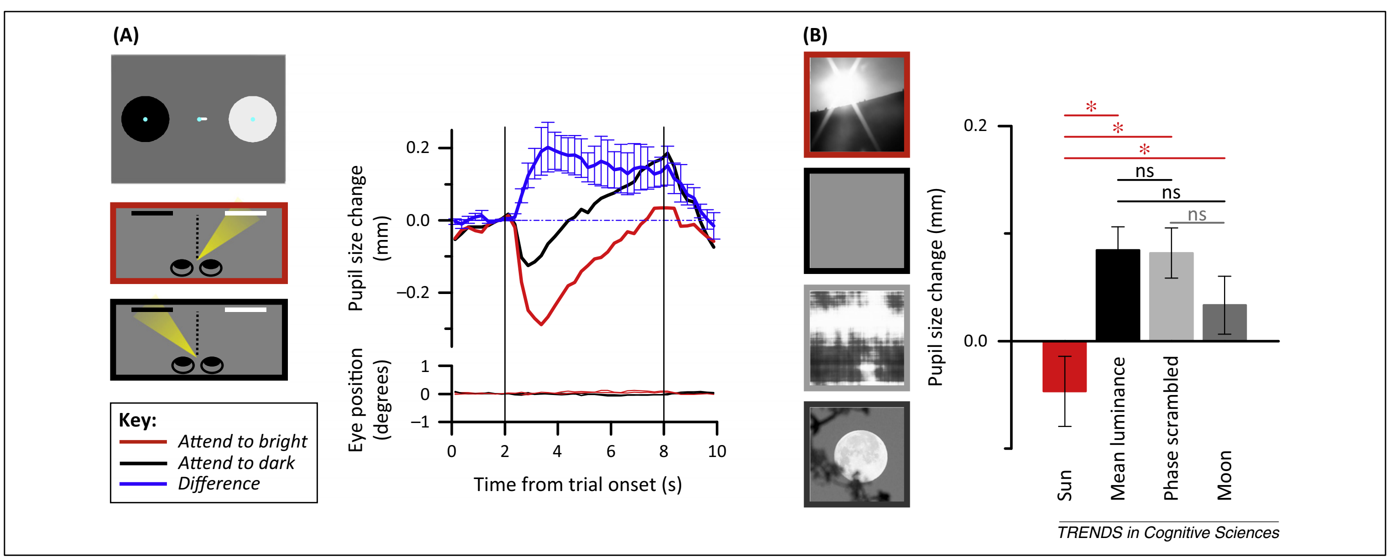

Figure 1. Constriction from attention to brightness and pictures of bright scenes. **(A)** The stimulus display comprised two luminance disks, one brighter and one darker than the gray background. Subjects were cued to covertly attend to the right or left disk. As covert attention shifted (yellow shaded area in icons), eye position remained fixed at the center of the display (broken line), so that retinal stimulation was the same across trials. However, pupil size was smaller when the brighter disk was attended, across the several seconds when the disks were shown and the task was performed (onset and offset marked by vertical unbroken lines). Adapted, with permission, from [5]. **(B)** Subjects were shown grayscale pictures of the sun and three controls with identical mean luminance: uniform gray squares, phase-scrambles of the sun pictures (same contrast), and pictures of the moon (similar level of complexity). The luminance of the pictures was always lower than their bright white background, implying that pupil dilation was expected. However, the pictures of the sun induced significant pupillary constriction relative to all controls. Adapted, with permission, from [6].

traces: light and its interaction with attention, plus cognitive effort, effects of transients and general arousal. However, several approaches to overcome this challenge are becoming available, including computational modeling [4].

In addition to its challenges, the multifactorial nature of pupil constriction can also be advantageous for its use as a research tool. A good example is the phenomenon of binocular rivalry, in which the two eyes are shown different images and these alternate in conscious perception. While perception oscillates, two effects are seen at the level of the pupil: light responses indicate which eye is currently dominant [9], and transient dilations precede each switch in perception, probably indexing a peak of norepinephrine release [3]. Thus, pupil size effectively monitors both sensory processing and neurochemical equilibrium, possibly providing a new tool for exploring their relationship.

Finally, ease of recording, objectivity, and minimal task requirements make pupillometry a promising tool for comparative study across populations.

There is a precedent for the use of pupillometry to compare cognitive strategies in toddlers with autism spectrum disorder and controls [14]. Measuring pupillary responses to images such as those in Figure 1B (in a simple passive viewing paradigm) could give new insight into another much debated area of research on autism spectrum disorder: contextual processing, or whether context has an anomalous influence on perception from a very young age.

Revived interest in pupillary light responses has also been recently motivated by its use in the comparative study of melanopsin-dependent retinal transmission across mammals [2]. Testing responses to stimuli more complex than light flashes, such as those in Figure 1, could additionally provide us with an index of brightness illusions and attentional boost mechanisms – an index that would be directly comparable across species, even when their phylogenetic distance makes it difficult both to establish homologies between neural recording sites and to meaningfully adapt behavioral paradigms.

Concluding remarks

Pupil size changes are simple, overt physiological responses that can be recorded noninvasively and in a relatively inexpensive and straightforward way. Despite this apparent simplicity, pupillary light responses integrate information from multiple brain processes, including complex ones such as attention and contextual modulation of perception. Thus, they provide a window to these constructs that still awaits full exploitation.

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References

1 Loewenfeld, I. (1993) *The Pupil: Anatomy, Physiology, and Clinical Applications*, Wayne State University Press
2 Lucas, R.J. (2013) Mammalian inner retinal photoreception. *Curr. Biol.* 23, R125–R133
3 Einhauser, W. *et al.* (2008) Pupil dilation reflects perceptual selection and predicts subsequent stability in perceptual rivalry. *Proc. Natl. Acad. Sci. U.S.A.* 105, 1704–1709
4 de Gee, J.W. *et al.* (2014) Decision-related pupil dilation reflects upcoming choice and individual bias. *Proc. Natl. Acad. Sci. U.S.A.* 111, E618–E625
5 Binda, P. *et al.* (2013) Attention to bright surfaces enhances the pupillary light reflex. *J. Neurosci.* 33, 2199–2204
6 Binda, P. *et al.* (2013) Pupil constrictions to photographs of the sun. *J. Vis.* 13, art. 8, http://dx.doi.org/10.1167/13.6.8
7 Laeng, B. and Endestad, T. (2012) Bright illusions reduce the eye's pupil. *Proc. Natl. Acad. Sci. U.S.A.* 109, 2162–2167
8 Laeng, B. and Sulutvedt, U. (2014) The eye pupil adjusts to imaginary light. *Psychol. Sci.* 25, 188–197
9 Zuber, B.L. *et al.* (1966) Saccadic suppression of the pupillary light reflex. *Exp. Neurol.* 14, 351–370
10 Sabeti, F. *et al.* (2014) Multifocal pupillography in early age-related macular degeneration. *Optom. Vis. Sci.* 91, 904–915
11 Sahraie, A. *et al.* (2013) Pupil response as a predictor of blindsight in hemianopia. *Proc. Natl. Acad. Sci. U.S.A.* 110, 18333–18338
12 Tamietto, M. *et al.* (2010) Collicular vision guides nonconscious behavior. *J. Cogn. Neurosci.* 22, 888–902
13 Naber, M. *et al.* (2013) Tracking the allocation of attention using human pupillary oscillations. *Front. Psychol.* 4, 919
14 Blaser, E. *et al.* (2014) Pupillometry reveals a mechanism for the autism spectrum disorder (ASD) advantage in visual tasks. *Sci. Rep.* 4, 4301
15 Binda, P. *et al.* (2014) Pupil size reflects the focus of feature-based attention. *J. Neurophysiol.* Published online September 17, 2014, http://dx.doi.org/10.1152/jn.00502.2014