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Spotlight

Renewed Attention on the Pupil Light Reflex

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In a recent study, Ebitz and Moore described how subthreshold electrical microstimulation of the macaque frontal eye fields (FEF) modulates the pupillary light reflex. This elegant study suggests that the influence of the FEF and prefrontal cortex on attentional modulation of cortical visual processing extends to the subcortical circuit that mediates a very basic reflex, the pupillary light reflex.

While we are most familiar with the constriction of the pupil that occurs with light, the pupil modulates due to other factors. For example, many studies have documented that pupil dilation accompanies mental effort or increased attention, while pupil constriction occurs when we are sleepy [1]. Furthermore, pupil dilation as a signal of heightened vigilance and arousal has been suggested to increase attractiveness [hence the use during the Italian Renaissance of the plant, *Atropa belladonna* (beautiful woman) whose active agent atropine is a pupil dilator]. As an extreme case, Richard Gregory, a renowned vision scientist of the mid-20th century, showed that the pupils of a talking parrot were modulated only slightly by light, but modulated significantly during the attention required for vocalization or the recognition of known words from humans [2].

Light- and arousal-related pupil responses are counted among the most basic behaviors in the repertoire of many diverse species. Their neural pathways are known in some detail, and involve a circuit from the retina thorough the mesencephalon [olivary pretectal nucleus (OPN) encoding retinal illumination] to the pupilloconstrictor preganglionic neurons of the Edinger–Westphal nucleus, and a sympathetic component responsible for arousal effects [1]. As Ebitz and Moore [3] point out, there has recently been a renewed interest in pupillary responses in nonhuman primates related to orienting responses and task conflict [4,5]. In addition, three laboratories working with human participants have shown a new kind of attentionally driven pupil behavior: without any change of light level, covertly attending to a brighter region of the visual field is sufficient to drive a pupillary constriction [6,7] and, when a light increment does occur, the evoked pupillary constriction is enhanced when the light stimulus is attended versus ignored [8].

The neural substrates of this attentional modulation of the pupillary light response were unknown until Ebitz and Moore [3] identified a key component of the underlying circuit: the FEF, a prefrontal cortical area implicated in the control of eye movements and attention [9]. Their main finding is that the amplitude of a pupil response depends on the coincidence between the light stimulus and subthreshold FEF electrical microstimulation, precisely as it depended on the coincidence between stimulus and attention in experiments on human participants. While monkeys maintained fixation, a peripheral light stimulus was presented either inside or outside the movement field of the stimulated site, as previously defined by suprathreshold microstimulation; the light always evoked pupillary constriction, but the constriction was stronger when the stimulus was inside the movement field of the stimulated site; it was weaker when the stimulus was 180° to, and at the same eccentricity as, the movement field of the stimulated site. Furthermore, the FEF microstimulation was only effective when it preceded the visual probe by 40 ms, and not by 80 or 160 ms.

Given the spatial and temporal specificity of this response modulation, these effects cannot be dismissed as dependent on cognitive load or arousal, or explained by a change in sympathetic tone. There are other known cortical influences on pupil size, but these also fail to explain this attentional modulation (Box 1). For example, there is the 'pupillary near response', a pupillary constriction that accompanies the ocular convergence and change in focus required to view a near object, which involves pathways from regions of visual and frontal cortex to neurons in the midbrain near response region that then project to pupilloconstrictor neurons within the Edinger–Westphal nucleus [1]. One might wonder whether this response could explain the effects of attention or FEF stimulation, because both these manipulations might induce near viewing. However, if this were the case, FEF stimulation should induce pupil constriction irrespective of the presence or location of the light stimulus, which is not what Ebitz and Moore [3] found. Human data also suggest that the effect of attention cannot be explained by the pupillary near response. The key finding is that attention also enhances the pupillary

Box 1. Pupil Responses in Blindsight

Subthreshold FEF microstimulation as well as the actual execution of a saccade modulates pupil size. It is interesting to note, as Ebitz and Moore point out [3], that the dynamic of this response changes depending on the task and the stimulus set. Far from being just an artifact to be controlled for, perisaccadic pupil modulations might represent a new and rich source of information for monitoring visual processing during saccade planning and execution; for example, to understand the processing of intrasaccadic signals and their suppression from conscious awareness [11], following the seminal work of Sahraie and colleagues [12] who found that pupillary 'onset responses', objectively measured with relative ease, predict one of the most elusive phenomena: blindsight in patients with cortical lesions.

dark response: increasing dilation in response to a luminance decrement [10].

Cortical input is also involved in another subtle, but consistent, pupil behavior: the transient pupil constriction at the onset of any equiluminant visual stimulus (i.e., stimuli that do not change luminance [1]). This 'onset response' is likely included in all pupillary responses measured in attention studies as well as by Ebitz and Moore [3], and the neural circuits explaining the two effects are likely to be partially overlapping. Yet, again, the two are not identical: in humans, the effect of attention is not explained by adding an 'onset' constriction component, but comprises a gain increase in the pupillary response to both light and dark: enhanced constriction in response to light increments and, symmetrically, enhanced pupillary dilation in response to light decrements [10]. Note that Ebitz and Moore [3] did not investigate whether FEF stimulation also enhances dilation in response to dark, as attention does; perhaps a future study will clarify this point.

How, then, could FEF activity affect the subcortical reflex circuit mediating the pupillary light response? To account for the enhancement of pupillary light response, it is necessary that FEF stimulation enhances a neural encoding of brightness that, in turn, drives pupillary constriction. Figure 1 shows two possible pathways. FEF stimulation could directly modulate the olivary pretectal nucleus, which encodes retinal illumination and directly activates the pupilloconstrictor pathway (Figure 1, broken blue line). Alternatively, or in addition, FEF might act indirectly through occipital visual cortical areas, whose visual response is modulated by FEF [9] and might participate in the pupillary light reflex (Figure 1, continuous blue lines) by projecting to the mesencephalic pupil light reflex circuit, either to the olivary pretectal nucleus, or to pupilloconstrictor neurons within the Edinger–Westphal nucleus. Consistent with this former suggestion, Clarke and colleagues reported that some neurons in the macaque olivary pretectal nucleus receive apparent cortical inputs [1]. In a conceptually similar model, the role of occipital visual areas could be replaced or supplemented by the superior colliculus, which has all the necessary cortical and subcortical connectivities to modulate pupillary responses [5].

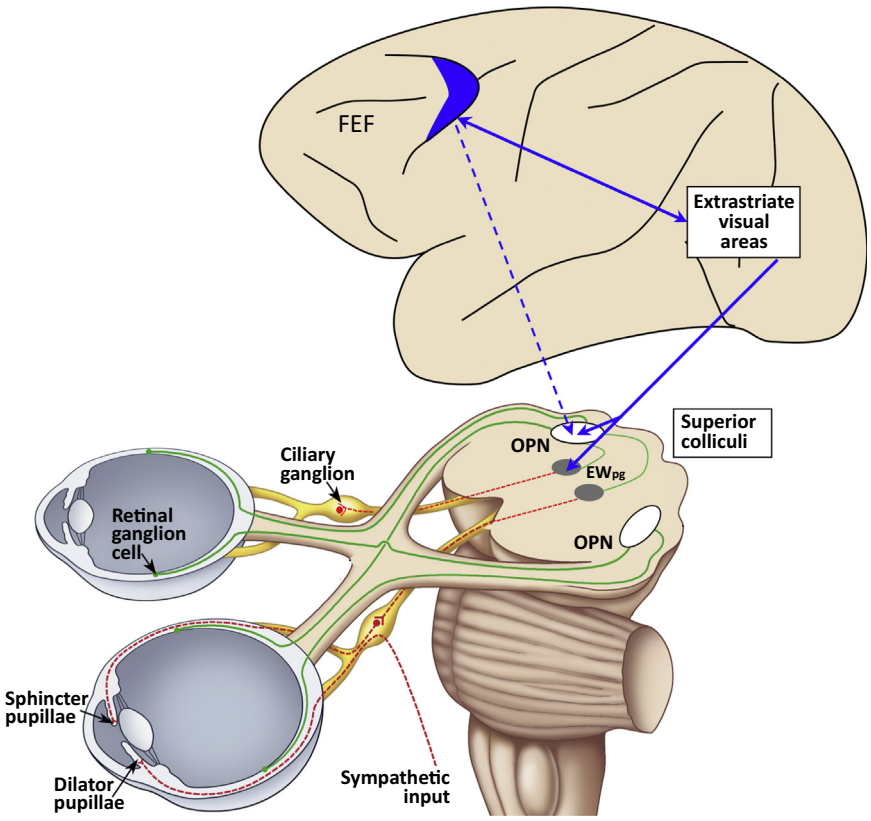

Figure 1. Cortical and Subcortical Structures That Might Be Involved in the Attentional Modulation of the Pupillary Light Response. Green lines show the retinal input and red lines the pupillomotor output. Blue lines show hypothetical cortical projections. Luminance-encoding elements are represented as white boxes. For simplicity, connections and projections are represented for one side only. Abbreviations: EWpg, Edinger–Westphal preganglionic subdivision; FEF, frontal eye fields; OPN, olivary pretectal nucleus.

As evident from this overview and the recent report of Ebitz and Moore [3], far from being a simple light-evoked reflex, pupillary responses are modulated in a well-defined fashion by attention, fatigue, arousal, ocular convergence and accommodation, among others. We still know little of the central mechanisms that control these responses, but renewed attention to the pupil light reflex in both humans and nonhuman primates will hopefully lead to other important discoveries.

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