A circuit for pupil orienting responses: implications for cognitive modulation of pupil size
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Pupil size, as a component of orienting, changes rapidly in response to local salient events in the environment, in addition to its well-known illumination-dependent modulation. Recent research has shown that visual, auditory, or audiovisual stimuli can elicit transient pupil dilation, and the timing and size of the evoked responses are systematically modulated by stimulus salience. Moreover, weak microstimulation of the superior colliculus (SC), a midbrain structure involved in eye movements and attention, evokes similar transient pupil dilation, suggesting that the SC coordinates the orienting response which includes transient pupil dilation. Projections from the SC to the pupil control circuitry provide a novel neural substrate underlying pupil modulation by various cognitive processes.

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Introduction
Efficient visual coding begins in the eye. Light enters the eye through, and is controlled by, the pupil. The pupil constricts in response to an increase of global luminance level, which is typically referred to as the pupillary light reflex, and it dilates for a global luminance decrease, referred to as the darkness reflex [1]. The quality of the signal projected on the retina is already under the control of this simple mechanism. This illumination-dependent pupil modulation is well understood, and thought to regulate the trade-off between sensitivity and sharpness for the optimization of image quality [2,3]. Additionally, pupil dilation has been linked to various cognitive processes [4], which we refer to as cognition-related pupil responses. Over the past decade, a growing body of research has used pupil size to investigate various cognitive processes, demonstrating correlations between pupil size and aspects in cognition such as target detection, perception, learning, memory, and decision making (e.g. [5–12]).

Changes in pupil size have also been associated with the orienting response [13,14], we refer to these responses as orienting-related pupil responses. The presentation of a salient stimulus initiates a series of responses to orient the body for appropriate action, including not only saccades and attentional shifts [15,16], but also transient pupil dilation [1,17,18*,19*]. The function of this pupil dilation is thought to increase visual sensitivity [13], although empirical evidence to support the argument is lacking [20]. The superior colliculus (SC; optic tectum in non-mammals), one of most important structures related to saccadic eye movements and spatial attention [21,22**], may also play a central role in coordinating this orienting-related pupil response [17,18**,23,24**], highlighting a novel neural substrate to possibly coordinate various cognitive processes and pupil diameter. Here, we review the evidence supporting the link of the SC to orienting-related pupil responses, focusing on recent work in monkeys and humans.

Pupil control circuit
Pupil size is controlled by the balanced activity between sympathetic and parasympathetic pathways (Figure 1) that have been identified and reviewed in detail elsewhere [1,25]. Briefly, in the parasympathetic system, retinal ganglion cells project directly to the pretectal olivary nucleus (PON), which in turn projects bilaterally to the Edinger–Westphal (EW) nucleus [26]. Preganglionic parasympathetic neurons in the EW project to the ciliary ganglion to control pupillary constriction muscles of the iris [1]. Pupil size is also controlled by the dilator muscle that is innervated by sympathetic nerves from the superior cervical ganglion (SCG), which is driven by a circuit originating in the hypothalamus via the spinal cord [1,25].

Although the neural substrate mediating cognitive state and pupil dilation is less clear, the locus coeruleus-noradrenaline system (LC-NE) is regularly implicated [70]. Anatomically, the LC has afferent projections to the EW nucleus and the spinal cord [25] to connect with both parasympathetic and sympathetic pathways, respectively (Figure 1). Furthermore, the LC has been associated with many functions related to cognition, arguably via arousal mechanisms [27*]. One important preliminary study has reported a correlation between pupil size and LC activity in monkey single cell recording [28*]. In humans, drugs assumed to alter arousal level via modulating LC activity.
Pupil orienting circuit

The SC has direct connections to the pupil pathways (Figure 1). The SCs projects ipsilaterally to the PON [40]. The SCi receives inputs from the SCs, frontal-parietal areas, and the basal ganglia, as well as the LC [41]. The SCi projects directly and indirectly to the EW [40,42,43], possibly activating and inhibiting parasympathetic pathways, respectively. The SCi could modulate the sympathetic system through efferent projections to the mesencephalic cuneiform nucleus (MCN) [33,44,45], a brainstem area regulating stress-related and defensive responses [46,47]. Stimulation of the MCN activates sympathetic vasomotor outflow [48], including modulation of pupil size [1]. Therefore, the SC has the necessary connections to coordinate orienting-related pupil responses via key inputs to the pupil control circuit.

**Pupil responses to salient stimuli**

Numerous studies have identified a significant effect of stimulus salience on shifts of gaze and attention [15,16], but saliency effects on the orienting-related pupil response are less understood. Stimulus contrast is one of the most primitive saliency components [49], and has been implemented as a component of saliency in a number of computational models [50]. Changing the contrast of a target has dramatic effects on sensory responses in the SCi and ensuing saccadic reaction times (SRT), with faster and greater SCi activity and faster SRTs for higher contrast stimuli [51–53]. Moreover, auditory stimuli tend to induce faster, but smaller sensory responses in the SCi compared to those produced with visual stimuli (Figure 2a) [54*]. If transient pupil dilation is linked to saliency via the SCi, it should occur regardless of stimulus modality, particularly on a salient non-visual (i.e., auditory) stimulus, and the magnitude and timing of evoked pupil responses should scale with the level of stimulus contrast. Recent studies have shown that pupil responses were induced by presentation of visual stimuli, and evoked responses were qualitative similar to those evoked by auditory stimuli (Figure 2b) [18**], suggesting that these responses are dissociable from illumination-dependent pupil responses. Most importantly, the transient pupil responses scaled with stimulus contrast, with faster and greater responses for higher visual stimulus contrast and louder auditory stimuli. Additionally, auditory stimuli evoked faster pupil responses compared

Figure 1  
Schematic of the pupil orienting circuit. See text for details. Abbreviations: BG, basal ganglia; CG, ciliary ganglion; EW, Edinger-Westphal nucleus; Hypoth, hypothalamus; LC, locus coeruleus; MCN, mesencephalic cuneiform nucleus; PON, pretectal olivary nucleus; SCi, intermediate layers of the superior colliculus; SCs, superficial layers of the superior colliculus; SCG, superior cervical ganglion; V1, primary visual cortex.

also change pupil size accordingly [29], and pupil diameter is linked to LC activation in a recent fMRI study [30]. Behavioral studies have shown that the relationship between changes in pupil size and task performances can be well explained by assuming that pupil size reflects LC activity [10,31,32]. Although it is generally accepted that pupil size is modulated by activity in the LC-NE system likely via changing arousal state, there is likely an additional pathway that also mediates cognition-related pupil responses.

The superior colliculus (SC) is a midbrain structure with neurons organized into a retinotopically coded map of contralateral visual and saccade space. The SC is functionally separated into superficial visual-only layers (SCs) that receive inputs from the retina and visual cortex, and intermediate layers (SCi) that receive convergent cognitive, multi-sensory, and motor inputs [33,34]. Moreover, the SCi projects directly to the brainstem premotor circuit to execute orienting responses. An increasing number of studies have suggested that the SCi encodes both stimulus salience and relevance to coordinate various components of orienting [35,36**,37,38], including not only shifts of gaze and attention, but also pupil dilation [17*,18**,23,24**,39].

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to visual stimuli, consistent with modality effects observed in SCI neuronal activity [54\*]. Overall, these results suggest that transient pupil dilation, as one component of orienting, is modulated by stimulus contrast, likely mediated via the SCI.

### Pupil responses to multisensory stimuli

Salient visual and auditory stimuli, when presented alone, elicit transient pupil dilation. This raises an intriguing question of how salient signals from the different modalities (i.e., visual and auditory) are combined to influence pupil dynamics. One hallmark of SCI processing is multisensory integration [55]. If the orienting-related pupil responses are coordinated by the SCI, salient stimuli presented from different modalities should be integrated in the SCI to produce coordinated pupil responses. Because response onset latencies evoked by auditory stimuli in the SCI are faster than those evoked by visual stimuli (Figure 2a) [54\*], the earliest component of pupil responses induced by audiovisual stimuli should be similar to that induced by auditory stimuli, and pupil response magnitude should be enhanced in the audiovisual condition. Consistently, the presentation of combined visual and auditory stimuli induced similar pupil responses in monkeys (Figure 3a), with greater response magnitude, compared to single modality presentation [18**]. Moreover, response latencies in the audiovisual condition were similar to those in the auditory alone condition, but faster than those in the visual alone condition, again suggesting that the SCI is involved in integrating multisensory stimuli for orienting-related pupil responses.

Effects of pupil responses evoked by the presentation of salient stimuli have also been demonstrated in humans and again, the size and magnitude of evoked pupil responses scaled with the level of stimulus contrast [19\*]. Faster pupil responses were induced by auditory, compared to visual stimuli (Figure 3b), and audiovisual stimuli evoked larger pupil response magnitude, compared to visual or auditory alone stimuli [56]. In summary, qualitatively similar pupil modulations have been observed in both humans and monkeys (Figure 3).

### Pupil responses to SC microstimulation

Although the central role of the SCI on shifts of gaze and attention is well-established [21,22**], its role is less clear on other components of orienting such as pupil dilation. SCI microstimulation evokes saccades and deactivation of the SCI interrupts saccades toward the affected location of the visual field [21]. Studies exploring SCI microstimulation on the shift of attention demonstrate facilitative effects for stimuli presented in the stimulated location of the visual field and neurons recorded in the SCI are also modulated by covert shifts of attention [22**]. Recently, it has shown that deactivation of the SCI diminishes covert...
Multisensory integration of orienting-related pupil responses. (a) Monkey transient pupil responses evoked by presentation of visual-alone (red traces), auditory-alone (blue traces), or combined audiovisual stimulus (purple traces) (adapted with permission [18**]). (b) Human transient pupil responses evoked by presentation of visual-alone, auditory-alone, audiovisual stimulus. Gray bar on X-axis indicates the time line of stimulation (100 ms).

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selection of task-required information on the affected location of visual field [57], establishing a causal role of the SC on attention.

Microstimulation of the monkey SCi, subthreshold for saccade initiation, also elicited transient pupil dilation (Figure 2c) [24**]. Similar pupillary dilation was also evoked by microstimulation in the deep layers of the optic tectum in anesthetised barn owls [17*]. Given that pupil dilation was not evoked by weak microstimulation of the SCs [24**], projections from the SCi to the EW and MCN may underlie this pupil response by either inhibiting the parasympathetic pathway, activating the sympathetic pathway, or both. Moreover, the pupil response latency and magnitude evoked by SCi stimulation was similar to that induced by salient auditory and visual stimuli (compare Figure 2b and c). Although there were differences in the sustained portion of the pupil response between salient stimulus presentation versus SCi microstimulation, the initial increase of pupil dilation was comparable and in line with the suggested role of the SCi in driving the initial orienting response. These results also raise one intriguing possibility that pupil dilation evoked by SCi microstimulation may contribute to some facilitative effects in behavior. However, future research is required to address this question in detail.

Modulation of pupil responses by saccade preparation
Pupil responses are also modulated by top-down processes [4], and some of these modulations may be associated with SC-mediated pupil pathways. The anti-saccade task is frequently used to examine voluntary control because subjects are instructed prior to stimulus appearance to either generate a pro-saccade (look at a peripheral stimulus) or an anti-saccade (look in the opposite direction of the stimulus). Unlike the automatic visuomotor response required in the pro-saccade condition, to complete an anti-saccade, subjects must suppress the automatic saccade and generate a voluntary response in the opposite direction of the stimulus. Distinct neural preparatory activity is required to successfully generate pro-saccade versus anti-saccade [58], particularly in the SC and frontal eye field (FEF), with higher inhibition-related fixation activity (rostral SC) in preparation for anti-saccade compared to pro-saccade. Moreover, the level of preparatory activity (caudal SC) related to motor preparation negatively correlated with SRTs [59,60]. Similarly, in human functional magnetic resonance imaging studies, there is higher FEF activation during preparation for anti-saccades compared to pro-saccades [61–63], and this preparatory activity in the FEF negatively correlates with SRTs [64,65].

Because pupil dilation is evoked by microstimulation of both rostral and caudal SC [24**], pupil size should reflect both types of preparatory activity. Consistently, human pupil size was larger in preparation for correct anti-saccades, compared to correct pro-saccades and erroneous pro-saccades made in the anti-saccade condition (Figure 4a and b) [66*]. Furthermore, larger pupil dilation prior to stimulus appearance accompanied saccades with faster reaction times (Figure 4c and d), together suggesting that pupil size is an effective proxy of neural activity related to preparation of pro-saccade and anti-saccade.
Conclusions and clinical applications
The orienting-related pupil response has the potential to be used as a biomarker for clinical investigation because of the proposed link of top-down processes in the frontoparietal cortex and basal ganglia to the pupil control circuit via the SCi (Figure 1). We propose that dysfunction in the frontoparietal cortex and basal ganglia can lead to altered pupil responses in cognitive tasks. For example, the ability to recognize stimulus saliency is impaired among patients with neurological disorders [67] and these effects could be mediated via the SCi. It has been suggested that low salient stimuli could induce maximal dopamine released as high salient stimuli in schizophrenia [68]. Therefore, modulations of stimulus salience on pupil size should be greatly reduced in schizophrenia. Because autism participants show less interesting to eye-face stimuli [69], pupil responses induced by the presentation of eye-face stimuli should also be attenuated accordingly. A simple orienting task requiring no saccadic eye movements could easily be completed by young children and more severely affected patients, and could be helpful for diagnoses of such disorders.

The SCi receives multisensory-related, arousal-related, cognition-related signals from cortical and subcortical structures, and projects directly to the brainstem premotor circuit to coordinate the orienting response (Figure 1). We reviewed a compelling set of results, showing transient pupil dilation evoked by both salient sensory stimuli (visual, auditory, and audiovisual) and SCi microstimulation, and we argue for a key role of the SCi in coordinating changes in pupil diameter (mm) with respect to stimulus onset (ms).
the orienting-related pupil response. Moreover, pupil size was modulated by preparatory activity related to saccade generation (top-down signal). The SCi is a key locus for convergence of bottom-up sensory information and top-down goal-directed signals that are critical for orienting [36,37]. The SC-mediated pupil pathways could provide the substrate required for pupil size modulation by various cognitive processes.

**Conflict of interest statement**

Nothing declared.

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**References and recommended reading**

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest


This paper showed that pupil dilation, as a component of orienting, is evoked by microstimulation of the optic tectum in barn owls, providing converging evidence from different animals.


This paper showed that transient pupil dilations in monkeys is evoked by presentation of visual, auditory, or audiovisual stimuli, and transient component of pupil responses evoked by stimulus presentation is similar to that evoked by SCI microstimulation, together suggesting an involvement of the SCI on evoked pupil responses.


This paper demonstrated that pupil dilation in humans is transiently evoked by presentation of visual stimuli, and the timing and the size of evoked responses are systematically modulated by stimulus contrast.


This paper reviewed recent findings that highlight a causal involvement of the SC on spatial attention, independent of the modulation of attention in visual cortex, suggesting novel possibilities to understand the brain mechanisms that enable spatial attention.


This paper demonstrated that, in awake monkeys performed the task, transient pupil dilution is evoked by weak electrical microstimulation in the SCI, but not in the SCs, suggesting a coordinated role of the SCI on the orienting response including pupil dilation.


This review argued a critical role of the locus coeruleus on cognition mediating through arousal.


This is the first study to provide neurophysiological evidence on the correlation between pupil size and activity in the locus coeruleus in nonhuman primate performed behavioral tasks.


36. Cornell BD, Munoz DP: Overt responses during covert orienting. Neuron 2014, 82:1220-1243. This paper reviewed recent findings to support that the SCI coordinates various components of the orienting response, including saccadic eye movements, neck and limb muscle recruitment, pupil dilation, and microsaccade, highlighting potential implications to provide oculomotor biomarkers in health and disease.


This paper showed sensory activities induced by visual or auditory stimuli in the SCI with faster and weaker SCI responses evoked by auditory compared to visual stimuli.


This paper showed modulation of pupil size by active preparation for pro-saccade versus anti-saccade, with larger pupil dilation in preparation for correct anti-saccades, compared to correct pro-saccades and erroneous anti-saccades. Larger dilation prior to stimulus appearance accompanied saccades with faster reaction times, together suggesting that pupil size is an effective proxy of neural activity related to saccade preparation.


