Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Neurobiology

A circuit for pupil orienting responses: implications for cognitive modulation of pupil size

Chin-An Wang and Douglas P Munoz

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.

Address
Centre for Neuroscience Studies, Queen's University, Kingston, Ontario, Canada

Corresponding author: Munoz, Douglas P (doug.munoz@queensu.ca)

Current Opinion in Neurobiology 2015, **33**:134–140

This review comes from a themed issue on **Motor circuits and action**

Edited by **Ole Kiehn** and **Mark Churchland**

http://dx.doi.org/10.1016/j.conb.2015.03.018

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]).

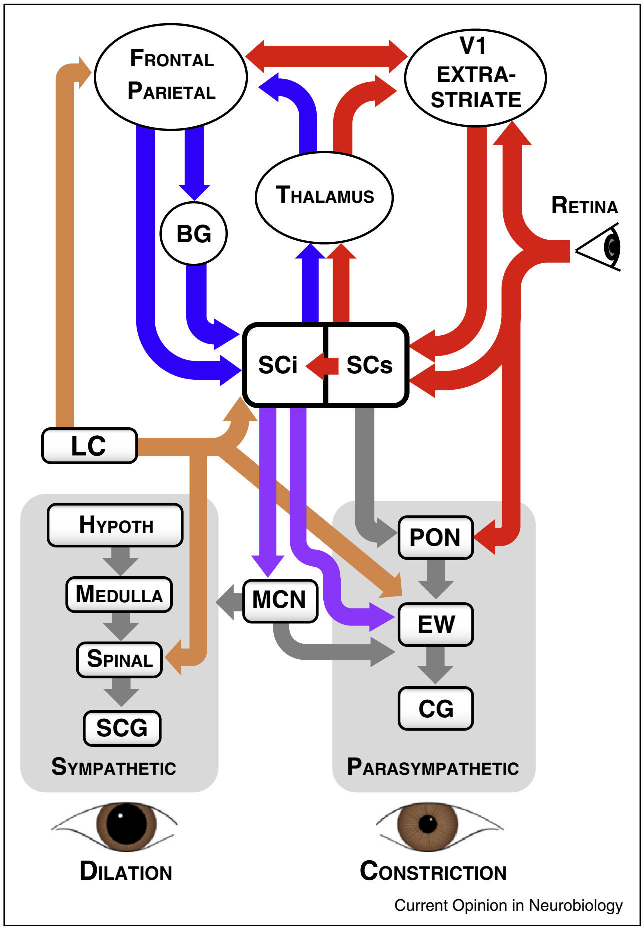
Changes in pupil size have also been associated with the orienting response [13,14], we refer to these responses as orienting-related pupil responses. The presentation of a salient stimulus initiates a series of responses to orient the body for appropriate action, including not only saccades and attentional 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-norepinephrine system (LC-NE) is regularly implicated [70]. Anatomically, the LC has efferent 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

Figure 1



Current Opinion in Neurobiology

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.

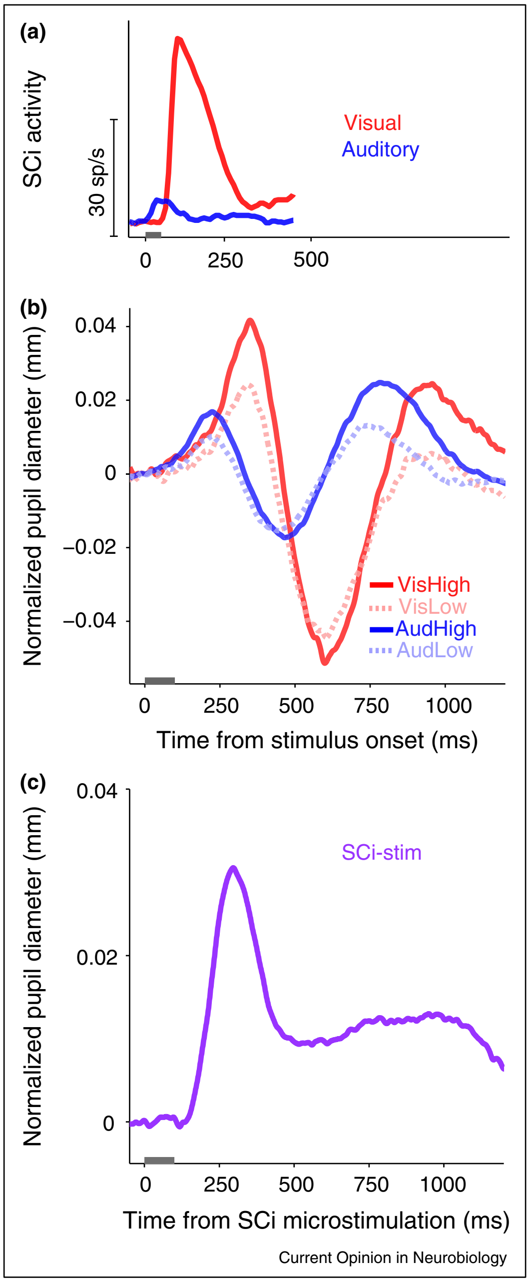
The superior colliculus (SC) is a midbrain structure with neurons organized into a retinotopically coded map of contralateral visual and saccade space. The SC is functionally separated into superficial visual-only layers (SCs) that receive inputs from the retina and visual cortex, and intermediate layers (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].

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 saliency 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 2



Current Opinion in Neurobiology

Effect of contrast-based saliency modulation and SCi microstimulation on transiently evoked pupil responses. **(a)** Population activity recorded from the monkey SCi following the presentation of visual (red trace) or auditory (blue trace) stimuli (adapted with permission [54•]). **(b)** Normalized pupil responses following the presentation of visual or auditory stimuli with two different levels of stimulus contrast (high-visual and low-visual contrast or high-auditory and low-auditory intensity) (adapted with permission [18••]). **(c)** Normalized pupil responses following SCi microstimulation (adapted with permission [24••]). Gray bar on *X*-axis indicates the time line of stimulation (a: 50 ms; b and c: 100 ms). VisHigh: high contrast visual stimulus; VisLow: low contrast visual stimulus; AudHigh: high auditory intensity stimulus; AudLow: low auditory intensity stimulus; SCi: intermediate layers of the superior colliculus.

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

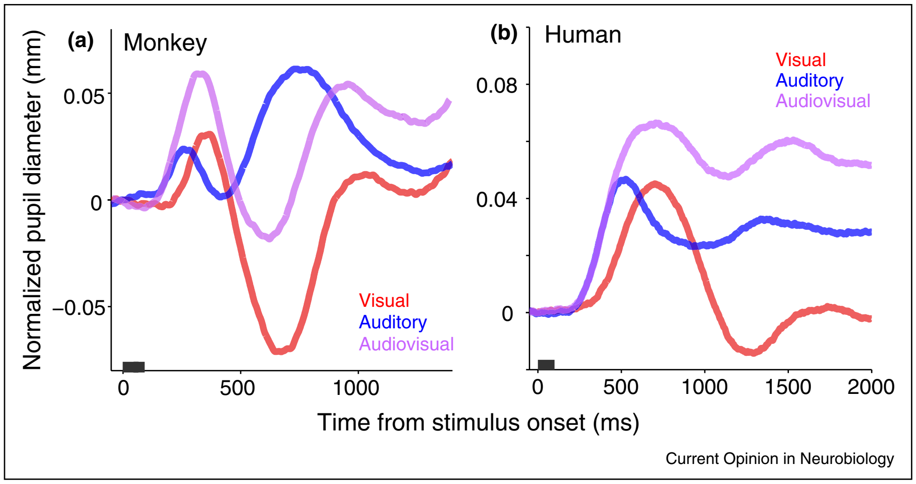
Salient visual and auditory stimuli, when presented alone, elicit transient pupil dilation. This raises an intriguing question of how salient signals from the different modalities (i.e., visual and auditory) are combined to influence pupil dynamics. One hallmark of SCi processing is multisensory integration [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

Figure 3



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).

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

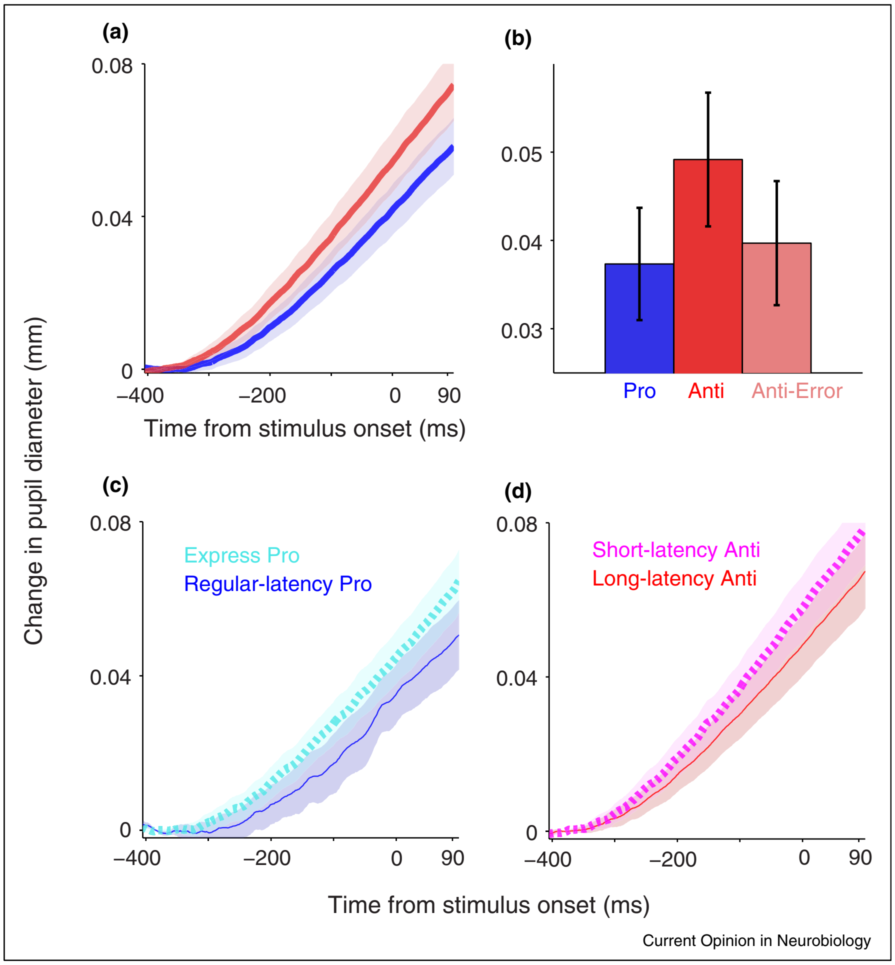
Microstimulation of the monkey SCi, subthreshold for saccade initiation, also elicited transient pupil dilation (Figure 2c) [24••]. Similar pupil dilation was also evoked by microstimulation in the deep layers of the optic tectum in anesthetised barn owls [17•]. Given that pupil dilation was not evoked 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.

Figure 4



Current Opinion in Neurobiology

Effects of saccade preparation on pupil size (adapted with permission [66•]. **(a)** Change in pupil diameter for correct pro-saccade and anti-saccade trials before stimulus appearance. **(b)** Pupil dilation size (50 ms before to stimulus presentation) among trials with correct pro-saccade, correct anti-saccade, or erroneous anti-saccade. **(c)** Pupil response for correct short-latency express and regular-latency pro-saccades prior to stimulus appearance. **(d)** Pupil response for correct short- and long-latency anti-saccades prior to stimulus appearance. In (a, c, d), the shaded colored regions surrounding the pupillary response represent ± standard error range (across participants) for different conditions. In (b), the error-bar represents ± standard error across participants. Pro: correct pro-saccade trials; Anti: correct anti-saccade trials; Anti-error: erroneous anti-saccade trials.

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 fronto-parietal 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 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.

Acknowledgements

This work was supported by Canadian Institutes of Health Research Grant (MOP-136972). D.P.M. was supported by the Canada Research Chair Program.

References and recommended reading

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

- • of special interest
- •• of outstanding interest

1. Loewenfeld IE: *The Pupil: Anatomy, Physiology, and Clinical Applications*. Boston: Butterworth-Heinemann; 1999.

2. Campbell FW, Gregory AH: **Effect of size of pupil on visual acuity**. *Nature* 1960, **187**:1121-1123.

3. Laughlin SB: **Retinal information capacity and the function of the pupil**. *Ophthalmic Physiol Opt* 1992, **12**:161-164.

4. Beatty J: **Task-evoked pupillary responses, processing load, and the structure of processing resources**. *Psychol Bull* 1982, **91**:276-292.

5. de Gee JW, Knapen T, Donner TH: **Decision-related pupil dilation reflects upcoming choice and individual bias**. *Proc Natl Acad Sci USA* 2014, **111**:E618-E625.

6. Einhauser W, Stout J, Koch C, Carter O: **Pupil dilation reflects perceptual selection and predicts subsequent stability in perceptual rivalry**. *Proc Natl Acad Sci USA* 2008, **105**:1704-1709.

7. Eldar E, Cohen JD, Niv Y: **The effects of neural gain on attention and learning**. *Nat Neurosci* 2013, **16**:1146-1153.

8. Goldinger SD, Papesh MH: **Pupil dilation reflects the creation and retrieval of memories**. *Curr Dir Psychol Sci* 2012, **21**:90-95.

9. Naber M, Frassle S, Rutishauser U, Einhauser W: **Pupil size signals novelty and predicts later retrieval success for declarative memories of natural scenes**. *J Vis* 2013, **13**:1-20.

10. Nassar MR, Rumsey KM, Wilson RC, Parikh K, Heasly B, Gold JI: **Rational regulation of learning dynamics by pupil-linked arousal systems**. *Nat Neurosci* 2012, **15**:1040-1046.

11. Privitera CM, Renninger LW, Carney T, Klein S, Aguilar M: **Pupil dilation during visual target detection**. *J Vis* 2010, **10**:1-14 3.

12. Wierda SM, van Rijn H, Taatgen NA, Martens S: **Pupil dilation deconvolution reveals the dynamics of attention at high temporal resolution**. *Proc Natl Acad Sci USA* 2012, **109**:8456-8460.

13. Lynn R: *Attention, arousal and the orientation reaction*. Oxford, UK: Pergamon Press; 1966.

14. Sokolov EN: **Higher nervous functions; the orienting reflex**. *Annu Rev Physiol* 1963, **25**:545-580.

15. Carrasco M: **Visual attention: the past 25 years**. *Vis Res* 2011, **51**:1484-1525.

16. Kowler E: **Eye movements: the past 25 years**. *Vis Res* 2011, **51**:1457-1483.

17. • Netser S, Ohayon S, Gutfreund Y: **Multiple manifestations of microstimulation in the optic tectum: eye movements, pupil dilations, and sensory priming**. *J Neurophysiol* 2010, **104**:108-118.

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.

18. •• Wang CA, Boehnke SE, Itti L, Munoz DP: **Transient pupil response is modulated by contrast-based saliency**. *J Neurosci* 2014, **34**:408-417.

This paper showed that transient pupil dilation 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.

19. • Wang CA, Munoz DP: **Modulation of stimulus contrast on the human pupil orienting response**. *Eur J Neurosci* 2014, **40**:2822-2832.

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.

20. Nieuwenhuis S, De Geus EJ, Aston-Jones G: **The anatomical and functional relationship between the P3 and autonomic components of the orienting response**. *Psychophysiology* 2011, **48**:162-175.

21. Gandhi NJ, Katnani HA: **Motor functions of the superior colliculus**. *Annu Rev Neurosci* 2011, **34**:205-231.

22. •• Krauzlis RJ, Lovejoy LP, Zenon A: **Superior colliculus and visual spatial attention**. *Annu Rev Neurosci* 2013, **36**:165-182.

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.

23. Netser S, Dutta A, Gutfreund Y: **Ongoing activity in the optic tectum is correlated on a trial-by-trial basis with the pupil dilation response**. *J Neurophysiol* 2014, **111**:918-929.

24. •• Wang CA, Boehnke SE, White BJ, Munoz DP: **Microstimulation of the monkey superior colliculus induces pupil dilation without evoking saccades**. *J Neurosci* 2012, **32**:3629-3636.

This paper demonstrated that, in awake monkeys performed the task, transient pupil dilation 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.

25. Szabadi E: **Modulation of physiological reflexes by pain: role of the locus coeruleus**. *Front Integr Neurosci* 2012, **6**:94.

26. Gamlin PD: **The pretectum: connections and oculomotor-related roles**. *Prog Brain Res* 2006, **151**:379-405.

27. • Sara SJ, Bouret S: **Orienting and reorienting: the locus coeruleus mediates cognition through arousal**. *Neuron* 2012, **76**:130-141.

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

28. • Rajkowski J, Kubiak P, Aston-Jones G: **Correlations between locus coeruleus (LC) neural activity, pupil diameter and behavior in monkey support a role of LC in attention**. *Soc Neurosci Abstr* 1993, **19**:974.

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.

29. Hou RH, Freeman C, Langley RW, Szabadi E, Bradshaw CM: **Does modafinil activate the locus coeruleus in man? Comparison of modafinil and clonidine on arousal and autonomic functions in human volunteers**. *Psychopharmacology (Berl)* 2005, **181**:537-549.

30. Murphy PR, O'Connell RG, O'Sullivan M, Robertson IH, Balsters JH: **Pupil diameter covaries with BOLD activity in human locus coeruleus**. *Hum Brain Mapp* 2014, **35**:4140-4154.

31. Gilzenrat MS, Nieuwenhuis S, Jepma M, Cohen JD: **Pupil diameter tracks changes in control state predicted by the adaptive gain theory of locus coeruleus function**. *Cogn Affect Behav Neurosci* 2010, **10**:252-269.

32. Jepma M, Nieuwenhuis S: **Pupil diameter predicts changes in the exploration-exploitation trade-off: evidence for the adaptive gain theory**. *J Cogn Neurosci* 2011, **23**:1587-1596.

33. May PJ: **The mammalian superior colliculus: laminar structure and connections**. *Prog Brain Res* 2006, **151**:321-378.

34. White BJ, Munoz DP: **The superior colliculus**. In *Oxford Handbook of Eye Movements.* Edited by Liversedge S, Gilchrist I, Everling S. Oxford University Press; 2011:195-213.

35. Boehnke SE, Munoz DP: **On the importance of the transient visual response in the superior colliculus**. *Curr Opin Neurobiol* 2008, **18**:544-551.

36. Corneil BD, Munoz DP: **Overt responses during covert**
•• **orienting**. *Neuron* 2014, **82**:1230-1243.

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.

37. Fecteau JH, Munoz DP: **Salience, relevance, and firing: a priority map for target selection**. *Trends Cogn Sci* 2006, **10**:382-390.

38. Mysore SP, Knudsen EI: **A shared inhibitory circuit for both exogenous and endogenous control of stimulus selection**. *Nat Neurosci* 2013, **16**:473-478.

39. Dutta A, Gutfreund Y: **Saliency mapping in the optic tectum and its relationship to habituation**. *Front Integr Neurosci* 2014, **8**:1.

40. Harting JK, Huerta MF, Frankfurter AJ, Strominger NL, Royce GJ: **Ascending pathways from the monkey superior colliculus: an autoradiographic analysis**. *J Comp Neurol* 1980, **192**:853-882.

41. Edwards SB, Ginsburgh CL, Henkel CK, Stein BE: **Sources of subcortical projections to the superior colliculus in the cat**. *J Comp Neurol* 1979, **184**:309-329.

42. Edwards SB, Henkel CK: **Superior colliculus connections with the extraocular motor nuclei in the cat**. *J Comp Neurol* 1978, **179**:451-467.

43. Grantyn A, Grantyn R: **Axonal patterns and sites of termination of cat superior colliculus neurons projecting in the tecto-bulbo-spinal tract**. *Exp Brain Res* 1982, **46**:243-256.

44. Huerta M, Harting J: **Connectional organization of the superior colliculus**. *Trends Neurosci* 1984, **7**:286-289.

45. Harting JK: **Descending pathways from the superior colliculus: an autoradiographic analysis in the rhesus monkey (*Macaca mulatta*)**. *J Comp Neurol* 1977, **173**:583-612.

46. Korte SM, Jaarsma D, Luiten PG, Bohus B: **Mesencephalic cuneiform nucleus and its ascending and descending projections serve stress-related cardiovascular responses in the rat**. *J Auton Nerv Syst* 1992, **41**:157-176.

47. Dean P, Redgrave P, Westby GW: **Event or emergency? Two response systems in the mammalian superior colliculus**. *Trends Neurosci* 1989, **12**:137-147.

48. Verberne AJ: **Cuneiform nucleus stimulation produces activation of medullary sympathoexcitatory neurons in rats**. *Am J Physiol* 1995, **268(3 Pt 2)**:R752-R758.

49. Itti L, Koch C: **Computational modelling of visual attention**. *Nat Rev Neurosci* 2001, **2**:194-203.

50. Borji A, Sihite DN, Itti L: **Quantitative analysis of human-model agreement in visual saliency modeling: a comparative study**. *IEEE Trans Image Process* 2013, **22**:55-69.

51. Marino RA, Munoz DP: **The effects of bottom-up target luminance and top-down spatial target predictability on saccadic reaction times**. *Exp Brain Res* 2009, **197**:321-335.

52. Marino RA, Levy R, Boehnke S, White BJ, Itti L, Munoz DP: **Linking visual response properties in the superior colliculus to saccade behavior**. *Eur J Neurosci* 2012, **35**:1738-1752.

53. Stanford TR, Quessy S, Stein BE: **Evaluating the operations underlying multisensory integration in the cat superior colliculus**. *J Neurosci* 2005, **25**:6499-6508.

54. Bell AH, Fecteau JH, Munoz DP: **Using auditory and visual**
• **stimuli to investigate the behavioral and neuronal consequences of reflexive covert orienting**. *J Neurophysiol* 2004, **91**:2172-2184.

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.

55. Stein B, Meredith M: *The Merging of the Senses*. Cambridge, MA: MIT; 1993.

56. Wang CA, Munoz DP: **The role of the superior colliculus in the coordination of the pupil orienting response**. *Soc Neurosc Abstr* 2014, **238**:5054.

57. Zenon A, Krauzlis RJ: **Attention deficits without cortical neuronal deficits**. *Nature* 2012, **489**:434-437.

58. Munoz DP, Everling S: **Look away: the anti-saccade task and the voluntary control of eye movement**. *Nat Rev Neurosci* 2004, **5**:218-228.

59. Everling S, Dorris MC, Munoz DP: **Reflex suppression in the anti-saccade task is dependent on prestimulus neural processes**. *J Neurophysiol* 1998, **80**:1584-1589.

60. Everling S, Dorris MC, Klein RM, Munoz DP: **Role of primate superior colliculus in preparation and execution of anti-saccades and pro-saccades**. *J Neurosci* 1999, **19**:2740-2754.

61. Connolly JD, Goodale MA, Menon RS, Munoz DP: **Human fMRI evidence for the neural correlates of preparatory set**. *Nat Neurosci* 2002, **5**:1345-1352.

62. DeSouza JF, Menon RS, Everling S: **Preparatory set associated with pro-saccades and anti-saccades in humans investigated with event-related FMRI**. *J Neurophysiol* 2003, **89**:1016-1023.

63. Manoach DS, Thakkar KN, Cain MS, Polli FE, Edelman JA, Fischl B, Barton JJ: **Neural activity is modulated by trial history: a functional magnetic resonance imaging study of the effects of a previous antisaccade**. *J Neurosci* 2007, **27**:1791-1798.

64. Alahyane N, Brien DC, Coe BC, Stroman PW, Munoz DP: **Developmental improvements in voluntary control of behavior: effect of preparation in the fronto-parietal network?** *Neuroimage* 2014, **98**:103-117.

65. Connolly JD, Goodale MA, Goltz HC, Munoz DP: **fMRI activation in the human frontal eye field is correlated with saccadic reaction time**. *J Neurophysiol* 2005, **94**:605-611.

66. Wang CA, Brien DC, Munoz DP: **Pupil size reveals preparatory**
• **processes in the generation of pro- and anti-saccades**. *Eur J Neurosci* 2015 http://dx.doi.org/10.1111/ejn.12883. in press.

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.

67. Winton-Brown TT, Fusar-Poli P, Ungless MA, Howes OD: **Dopaminergic basis of salience dysregulation in psychosis**. *Trends Neurosci* 2014, **37**:85-94.

68. Grace AA: **Ventral hippocampus, interneurons, and schizophrenia a new understanding of the pathophysiology of schizophrenia and its implications for treatment and prevention**. *Curr Dir Psychol Sci* 2010, **19**:232-237.

69. Klin A, Jones W, Schultz R, Volkmar F: **The enactive mind, or from actions to cognition: lessons from autism**. *Philos Trans R Soc Lond B Biol Sci* 2003, **358**:345-360.

70. Aston-Jones G, Cohen JD: **An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance**. *Annu Rev Neurosci* 2005, **28**:403-450.