The Pupil

Determination of the integrity of the pupillary light reflex (PLR) is a critical step in neuroophthalmic evaluation. This reflex is initiated with photic stimulation of the photoreceptors (rods and cones) in the outer retina, which synapse in the bipolar cells of the middle retina, and again in the ganglion cells in the inner retina. Ganglion cell axons comprise the optic nerve, and pass through the fibrous lamina cribosa, posteriorly into the orbit, through the optic foramen to join the opposite optic nerve at the optic chiasm in the cranial fossa. Here, a species-dependent number of axons decussate or cross-over to the contralateral optic tract (primate=50%, feline=65%, canine=75%, equine, bovine, porcine=80-90%, submammalian species=100%), Fibers then course to the ipsilateral or contralateral optic tract, and then project in a topographical fashion to the ipsilateral dorsal lateral geniculate body (dLGB). From here, the majority of fibers (80%) project to the optic radiation and visual cortex. Twenty percent of fibers in the optic tract bypass the LGB project and many of these project to the pretectal nuclei near to rostral colliculi to control pupilomotor function. Note that other fibers bypassing the dLGB synapse in the hypothalamus to regulated circadian rhythm, and the rostral colliculi to elicit the optic dazzle reflex, reflexive redirection of gaze, and stimulation of the reticular activating system. From the pretectal region, the pupillomotor fibers then undergo a second decussation near the caudal commissure, and project to the contralateral parasympathetic nuclei of CN III. This second crossing over is the anatomic basis for the indirect PLR, i.e. unilateral afferent stimuli results in bilateral efferent effect. The number of fibers crossing at the caudal comissure is commensurate with the number crossing over at the chiasm. In humans, the first and second crossing over of fibers amounts to 50% each, with the result being that the direct and indirect PLR are of equal magnitude. In subprimate species, this second crossing over results in more fibers projecting back to the stimulated eye. As a result, in most mammals, the direct PLR being of greater magnitude than the indirect or consensual PLR.

Groundbreaking research over the last 15 years has identified a subset of retinal ganglion cells (RCG) which are photosensitive (depolarize in response to light), with melanopsin as the photosensitive pigment. These *intrinsically photosensitive retinal ganglion cells* (ipRGC) comprise approximately 2% of the overall RCG population, and project to areas of the brain that regulate non imaging forming functions to light.
specifically PLR and circadian related behavior including photoentrainment, regulation of sleep-wake states and latency, acute masking, and acute suppression of pineal melatonin. In the normal retina the input to ipRCGs is predominately from rod/cone photoreceptors, which regulate acute shifts in PLR. ipRCGs themselves appear to modulate sustained size of the pupil in response to ambient light levels. Whereas rod/cone photoreceptors respond only to light shone on a very small spot, ipRCGs respond to light striking a broad expanse of retina from a network of dendrites, which increases efficiency of irradiance detection/monitoring. ipRCGs are capable of generating a PLR without rod/cone input (for example in dogs with PCRD or SARDs). A PLR may be elicited in normal dogs at low light intensity; whereas in SARDS dogs PLR is elicited with blue light (480nm, near the peak sensitivity of melanopsin) at high intensity, but not red light (630nm) even at high intensity. An extension of this finding is that a decreased PLR (or pupillary escape) to blue light at high intensity can indicate RCG degeneration (inner retinal disease).

The efferent pathway of the PLR is comprised of pre-ganglionic fibers in the anteriomedial nucleus and ventrosegmental area (the Edinger-Westphal nucleus). Fibers then exist the mesencephalon with CNIII, also containing motor fibers to the skeletal muscle controlling eyelid and eye movement. Pupillomotor fibers and motor fibers diverge in the orbital cone near the ciliary ganglion, the synaptic ganglion of the efferent pathway. From here, in the dog, 5-8 short ciliary nerves contain mixed parasympathetic (pupillomotor and ciliary muscle), sympathetic, and sensory afferent fibers from CNV and these nerves enter the globe near the posterior pole and project to their respective regions. In the cat, there are only two short ciliary nerves (malar and nasal) that contain only parasympathetic fibers. This later configuration may result in the characteristic “D” shaped, or “reverse D-Shaped” pupil seen in cats with lesions in only one of the two ciliary nerves.

The mammalian iris contains smooth muscle under autonomic control, (iris dilator with norepinephrine as the neurotransmitter; and the iris sphincter with acetylcholine as the neurotransmitter), and a result the PLR has a relatively long latency period in mammals. Conversely, the iris of most submammalian species contains skeletal muscle with a PLR being of short latency, and pupil excursions can be under voluntary control.

A number of other factors influence pupil size and mobility. For example, psychosensory stimulation provides direct, active adrenergic input to the dilator muscle, as well as a reciprocal adrenergic inhibition of the sphincter muscle. Supranuclear inhibition for parasympathetic fibers of CNIII is present, and is lost with sleep, anesthesia, and opioids, resulting in miosis. PLR intensity is also dependent on the intensity of the light source used as a stimulus, and the area of retina stimulated (with the temporal retina, containing the highest concentration of photoreceptor, producing the PLR of greatest magnitude).

When evaluating the PLR, it is important to stimulate different regions of the retina, evaluating both the direct and indirect PLR. In non-primates, a dynamic
contraction anisocoria occurs (direct PLR > indirect PLR) due to unequal decussation of fibers at chiasm and again after pre-tectal nuclei. PLR evaluation should also include the “swinging flashlight test” in which light is alternately shifted from one eye to other. A normal response is characterized by both pupils constricting to equal degree when stimulated, and the illuminated eye produces slightly more constriction. “Pupillary escape” may be seen in which the illuminated pupil dilate slightly after initial contraction, and this phenomena can be normal, representing an adaptation of stimulated retina. Pupillary escape may also be seen with an incomplete unilateral, prechiasmal lesions, or the result of scatter illumination entering a normal fellow eye. A “positive” test (Marcus-Gunn pupil) is abnormal and occurs when the illuminated pupil dilates. In humans, a positive swinging flashlight test indicates a unilateral prechiasmal optic nerve or retinal lesion is present. In subprimates with asymmetrical optic nerve fiber decussation, a positive swinging flashlight test may be seen with both pre and post chiasmal, afferent arm lesions (see appendix with series of slides explaining this phenomena, kindly provided by Dr. Ben Blacklock, Dick White Referrals, Cambridge, UK).

An alternative to swinging flashlight test is the “cover-uncover” test, which is performed by covering one eye with a card, then swinging the card to cover the fellow eye. This test is similar to swinging flashlight test, with the ambient light acts as differential light source in uncovered eye, instead of active stimulation with a light source. If the uncovered eye dilates without any constriction this constitutes a “positive test.” The cover-uncover test eliminates the possibility of scatter illumination creating pupillary escape.

Chromatic testing of PLR is based on the presence of ipRGCs and involves stimulating the retina with high intensity blue (480nm) and red (630nm) light. The normal eye has a positive PLR with both of these wavelengths; with photoreceptor disease (SARDs, PRA) the PLR is negative with red light and positive with blue light; with retinal ganglion cell or optic nerve disease, the PLR is negative with both wavelengths.

The dark adaptation test involves evaluation of pupil size after five minutes in the dark. The pupil size is evaluated by viewing the pupil and fundic reflection with a direct ophthalmoscope held at an arm’s distance from the patient. In the normal eye, the pupils dilate fully and symmetrically. With a mechanical problem of the iris, the pupils fail to dilate. An afferent arm lesion will also be associated with full dilation. With a unilateral efferent arm lesion, the response differs between dogs and cats. For example, a nuclear or preganglionic lesions in both dogs and cats fully dilate, a postganglionic lesion in the cat shows full dilation, but the latter lesion in a dog produces a smaller pupil ipsilateral to the lesion, owing to the fact that sympathetic fibers are also affected. The dark adaptation test is very useful for establishing a tentative diagnosis of Horner syndrome (discussed below), as the anisocoria is accentuated by dark adaptation, with the effected eye retaining the miosis and unaffected eye dilating fully. When a PLR deficit is noted, it is important to first rule-out rule out non-neurologic disorders such a mechanical or structural iris abnormalities, and pharmacologic blockade with parasympatholytic agents such as atropine. Depending on the location of the lesion, PLR abnormalities may result in
abnormalities in pupillary diameter or shape, response to dark adaptation testing, pupillary light reflex, and vision (if afferent arm lesion prior to LBG).

A broad characterization of PLR abnormalities is as follows: 1) with afferent arm lesions, both vision and PLR are abnormal, 2) with cortical lesions, vision is affected but PLRs are normal, and 3) with efferent arm lesions, PLR is abnormal and vision is unaffected. An important caveat here is that PLRs are often maintained even with advanced outer retinal lesions (owing to the ipRCG cited earlier and/or the presence of some functional photoreceptors), and objective quantification of PLR is difficult in a clinical setting in animals.

A unilateral retinal or prechiasmal optic nerve lesion will be characterized by lack of direct and consensual (to fellow eye) PLR, a positive swinging flashlight test (Marcus-Gunn pupil), and visual deficits/blindness. In these instances, a thorough funduscopic examination should be performed to rule out any obvious retinal or intraocular optic nerve diseases. Recall that PLRs and dazzle reflex may persist with advanced outer retinal disease with visual deficits owing to the ipRCGs.

A unilateral optic tract lesion will produce similar clinical signs with the exception that the dilated pupil is contralateral to lesion, the anisocoria may be subtle, there is a positive swinging flashlight test (in subprimates), and the more miotic pupil persists in the same eye regardless of which eye is stimulated. The visual field contralateral to affected tract is diminished or lost (visual fields discussed later), and this is referred to as a contralateral homonymous hemianopia. A corollary to this is that the vision loss is most obvious in eye contralateral to lesion.

A bilateral retinal, optic nerve, optic chiasmal, optic tract, or posterior commissure lesion will produce complete loss of PLR and vision, with mydriasis in ambient light. Lesions that affect the central chiasm (certain types of intracranial neoplasia) and that affect only the crossed fibers will produce equal, but larger than normal pupil size and may produce a “paradoxical pupil” whereby the direct and consensual PLRs are present, but the more constricted pupil is opposite the side stimulated (i.e. the consensual response is greater than the direct response). Chiasmal lesion from compression from pituitary gland tumors are commonly associated with PLR deficits in humans; these tumors are less common causes of optic chiasmal compression in dogs as the pituitary stalk is located and angles more caudally than in humans.

Interestingly, cerebellar lesions may also influence PLR and resting pupil size, for reasons not entirely understood. It is known that the cerebellum influences autonomic functions, and a unilateral fastigial nucleus ablation produces contralateral pupillary dilation and partial protrusion of ipsilateral nictitans. A lesion in the nucleus interpositus may produce a larger pupil ipsilateral to lesions, contralateral nictitans protrusion, and ipsilateral loss of tactile placing reflexes. Generalized cerebellar dysfunction produces bilateral mydriasis and PLR deficits.
Internal ophthalmoplegia refers to impairment of pupillary function and may be the result of impairment of the sphincter muscle, presence of an atropine-like drug, or a lesion in the parasympathetic innervation or efferent arm of the PLR (CNIII parasympathetic nuclei, intracranial CNII, orbital cranial nerve III or ciliary ganglion, short ciliary nerves). Within CNII, the pupillomotor fibers are located superficially, and as a result may be preferentially damaged with no motor dysfunction. An efferent pathway lesion is characterized by ipsilateral dilated pupil, hemipupil in cats if postganglionic, a nonreactive pupil to direct and indirect light, and supersensitivity to parasympathomimetics such as dilute pilocarpine. With postganglionic lesions (cranial to ciliary ganglion) in the cat, full dilation occurs with dark adaptation, whereas in the dog, the ipsilateral pupil is smaller with dark adaptation due to concurrent involvement of sympathetic fibers (concurrent Horner syndrome).

External ophthalmoplegia refers to dysfunction of the motor fibers of CNIII, and is characterized by ptosis (from effect on levator superioris mm.), lateral strabismus, inability to rotate the globe dorsally, ventrally, or medially, and +/- internal ophthalmoplegia. Isolated external ophthalmoplegia is rare and generally seen with central lesions, affecting the motor portion of the CNIII nucleus. Concurrently internal and external ophthalmoplegia is referred to as total ophthalmoplegia and is almost always preganglionic, and the result of an intracranial lesion, for example cavernous sinus syndrome.

Pharmacologic testing may aid in localization of efferent arm lesions, and two topical agents may be used: 0.5% physostigmine (indirect parasympathomimetic, allows buildup of acetylcholine at the synaptic ending) and 2% pilocarpine (a direct parasympathomimetic). With 0.5% physostigmine, and with postganglionic efferent lesions, no constriction occurs, whereas with preganglionic lesions constriction occurs 40-60 minutes before the control eye. An effect of 2% topical pilocarpine (direct parasympathomimetic), confirms the lesion is neurologic rather than structural, and the affected pupil constricts sooner than the control pupil. Dennervation hypersensitivity is characteristic of efferent arm ganglion or postganglionic lesions, and the affected pupil will respond to dilute concentrations of pilocapine (0.1-0.2%) that do not affect the normal pupil.

Two specific diseases that affect the efferent arm in cats include feline dyautonomia and feline spastic pupil syndrome. With the former, decreased lacrimation, mydriasis, anisocoria, prolapsed nictitans, photophobia and blepharospams occur, and are associated with a more widespread degeneration of the autonomic nervous system. (I.e. clinical signs seen reflect both parasympathetic and sympathetic denervation). With feline spastic pupil syndrome, there is inconsistent/alternating anisocoria that persists with dark adaptation. This syndrome is seen in association with FeLV infection and is thought to be a manifestation of viral neuritis of sympathetic/parasympathetic innervation or both. Spastic pupil syndrome is thought to be a risk factor for the development of multicentric lymphosarcoma.
The oculosympathetic pathway to the globe, orbit, and adnexal structures takes a long and convoluted course, and is therefore denervation (Horner syndrome) is associated with lesions in a variety of anatomic sites along this pathway. First order neurons arise in the hypothalamus and course down the lateral tectotegmentospinal tract, descend ipsilaterally through the brain stem and lateral funiculus of spinal cord, and synapse in preganglionic cell bodies in gray matter of intermediolateral column of spinal cord T1-T4. Second order neurons arise in the rami communicans, pass through ventral roots, course through the thoracic sympathetic trunk, cervicothoracic and middle cervical ganglia, cervical sympathetic trunk, and synapse in cranial cervical ganglion (caudomedial to tympanic bullae) with postganglionic sympathetic neurons. Postganglionic fibers join the tympanic branch of CN IX to form caroticotympanic nerves, course over promonotory of middle ear and exit the middle ear and enter cavernous sinus to join CN V. Most fibers pass through the ophthalmic division of CNV, to the nasociliary nerve (to innervate the upper eyelid, dilator mm. and smooth mm. of orbit). Innervation to the dilator mm. of the iris enters the globe via long ciliary nerve (recall the difference between the cat vs. dog), and travel through the suprachoroidal space to anterior segment. Additionally, some fibers pass through the maxillary division of CNV to infraorbital/zygomatic nerve to supply the lower nictitans and lower eyelid.

The classical findings of sympathetic denervation of the eye include ptosis, enophthalmos, miosis and nictitans protrusion. In small animals, miosis is often the most prominent and dramatic finding, and recovery of pupillary function is more likely with preganglionic vs. postganglionic lesions. Anisocoria is generally obvious and dark adaptation, and excitement accentuate the difference in pupil size. Drooping of the upper lid (ptosis) and slight elevation of the lower lid “reverse ptosis” may be apparent, resulting in a narrowed palpebral fissure. Enophthalmos may or may not be present, and so called “apparent” enophthalmos is caused by the narrowed palpebral fissure. Protrusion of nictitans may be accentuated by the enophthalmos.

In large animals, the clinical signs of Horner syndrome may be subtler than in dogs and cats. Sympathetic ptosis is the most consistent finding. Cutaneous facial and cervical hyperthermia occurs, and in the horse, facial sweating is often seen from vasodilatation and increased blood flow from decreased vasomotor tonus. In cattle, the effect is opposite and lack of sweating on the affected side is seen (as sweating in cattle is mediated by alpha adrenergic receptors). Vascular engorgement of pinna may also be seen in cattle.

Pharmacologic testing for diagnosis and lesion localization of Horner syndrome is sometimes clinically useful. Testing should take into account the response in the control eye (normal fellow eye), quantity of drug applied, whether there is disruption of the corneal epithelium influencing drug penetration, and any prior topical agents given (for example, tropicamide). 6% topical cocaine (blocks reuptake of norepinephrine) would result in no mydriasis in Horner syndrome, and helps to confirm the diagnosis, but is not necessarily localizing. Hydroxyamphetamine (causes release of norepinephrine) will cause no or incomplete mydriasis with postganglionic lesions, while preganglionic lesions will dilate. Hydroxyamphetamine is no longer commercially available and must
be compounded by a pharmacist. 10% phenylephrine will cause mydriasis in 5-8 minutes with postganglionic lesions (owing to denervation hypersensitivity), as well as retraction of nictitans and resolution of ptosis. It should be noted that denervation hypersensitivity is a variable phenomena, occurs with some extent with pre-ganglionic lesions, is a time-dependent phenomena, and partial lesions may produce partial hypersensitivity.

In ophthalmic practice, Horner syndrome is most often postganglionic (otitis, idiopathic), while in neurologic practice, more cases of preganglionic and central Horner syndrome are seen. Also note that with early otitis, ipsilateral dilation may be present from irritation of nerve fibers. In this instance, the dilation may be distinguish from internal ophthalmoplegia as no parasympathetic hypersensitivity is present with Horner syndrome.

See Appendix II for summary of characteristics of anisicoria, bilateral miosis, and bilateral mydriasis.

Vision and Visual Pathways

The visual pathways and afferent PLR pathways are identical up to the lateral geniculate body, where 80% of optic tract fibers course to the dorsolateral LGB in a topographic manner (in other words, maintaining spatial organization present in the retina). Visual fibers then ascend through the optic radiation to the occipital cortex, maintaining and enhancing this topographical organization. Visual segregation occurs such that each cerebral hemisphere receives information from contralateral visual field (visual field being defined at the area in space viewed by regions of both retinas simultaneously). This occurs as nasal retinal fibers decussate at the optic chiasm, whereas temporal retinal fibers do not. This results in the right nasal hemiretinal fibers crossing over to project to left cerebrum, while the right temporal fibers remain uncrossed and project to right cerebrum. As a result, a target in right half of visual field (right visual hemifield) projects onto the right nasal retina and left temporal retina, then course to the left optic tract, the left dLGN and the left cerebral hemisphere. In other words, objects in the right visual hemifield project to the right nasal hemiretina and left temporal hemiretina and ultimately the information is received by the left cerebrum.

Assessment of vision in animals is often subjective and crude when compared with humans. Vision and visual pathway testing may be performed by one of several methods including evaluation of the PLR (as visual and PLR fibers share a common path until the LGB), menace response, dazzle reflexes, visual cliff testing, visual placing reaction, and photophic and scotopic obstacle course testing. Visual cliff testing involves testing an animal’s ability to visualize a drop-off (i.e. from a table edge) with a plexiglass/table edge interface. Visual cliffs are an indicator of visual system and other areas of cortex, and in large animals this response is present at birth, whereas in dogs/cats the ability to respond to a visual cliff begins at about 4 weeks of age. Visual placing reaction tests similar regions in the visual system and cortex, and involves holding the animal in the air, and advancing towards a table edge. If the animal visualizes the table
edge, both forelegs will extend. Lesions in rostral portion of striate cortex or foreleg region of motor cortex will abolish visual placing reaction in contralateral visual field.

Other more objective means of assessing the visual pathways include the electrodiagnostic testing including electronegretinography, and visually-evoked response. (discussed elsewhere in the course)

The menace response is a cortically mediated eyelid closure +/- head withdrawal and eyeball retraction that occurs when the animal is confronted with a visual threat. The pathways involved and response are complex, and not true reflex but response. The clinician must take care not to create wind currents that the animal can detect, and a plexiglass windshield should be used if necessary. The menace response requires an intact optic nerve, central visual pathway, and connections with cerebrum and CN VII pathway. Lesions along any part of this pathway will cause menace response deficits, and cortical lesions causes loss of contralateral visual field menace response. For poorly understood reasons, cerebellar (corticocorticopontocerebellar) lesions may cause ipsilateral menace response loss with normal vision.

The dazzle reflex, unlike the menace response is a subcortically-mediated reflex. The effect is a partial eyelid blink in response to bright light, and the eyelids may open then close. A contralateral closure may sometimes be present but is of lesser magnitude that in the stimulated eye. The pathway involves the retina, optic nerve to midbrain region, with input to the supraoptic nuclei and rostral colliculi. The efferent pathway is CN VII that controls obicularis oculi function. Interestingly, some mesencephalic lesions may demonstrate loss of dazzle reflex in absence of other neurologic signs. While not fully documented, my experience and observations by others (A. Komorany) suggests that the ipRCGs are thought to be capable of eliciting a dazzle reflex.

As a result of this visual segregation, an unilateral lesions along the visual pathway that is posterior to the optic chiasm (optic tract, optic radiation, visual cortex) will produce a homonymous heminopia, defined as a loss of one hemivisual field (e.g. loss of right visual field from loss of nasal retinal fibers in right eye and temporal fibers in left eye). Loss of two hemivisual fields (e.g. loss of both temporal visual fields from loss of both nasal retinal fibers) may occur with a chiasmal lesions if only crossed fibers are affected. This “heteronymous hemianopia” is also seen in Siamese cats with congenital misrouting of optic nerve fibers, producing a binasal hemianopia. A quadrantic heminopia in which only a quadrant of a visual field is loss, would occur with a partial unilateral lesion caudal to chiasm and could only be documented with objective visual field testing.

Lesions in the retina and pre-chiasmal optic nerve will produce characteristic clinical signs including lack of direct and consensual (to fellow eye) PLRs, a positive swinging flashlight test/cover uncover (Marcus-Gunn pupil) and visual deficits or blindness. It is important to note, however, that some PLR is often maintained (and because of the difficulty in objectively quantifying PLR in animals, may appear normal) in animals with even very advanced outer retinal disease (from ipRCGs).
Total lesions in the optic chiasm may result in total lesions cause bilateral PLR and visual deficits. With chiasmal lesions, PLR deficits are often recognized before visual deficits, and because of the proximity to the hypothalamus, abnormalities in behavior, appetite, temperature regulation, and endocrine function may concurrently present. As mentioned previously, subtotal lesions affecting the central chiasm may cause a heteronymous heminopia (bitemporal hemianopia) from effects on the crossing fibers from nasal hemiretina, with subsequent loss of both temporal visual field and the so-called “paradoxical pupil” whereby the consensual PLR is greater than the direct PLR.

Selective chiasmal lesions may produce characteristic clinical findings. For example, rostral chiasm lesions with asymmetric involvement of rostral chiasm may present as ipsilateral blindness (from effects on the ipsilateral optic nerve) progressing to temporal visual field loss in contralateral eye (from effects on the crossed fibers at the chiasm). Dorsal chiasmal lesions, because this area is in direct contact with lateral ventricle and CSF may be associated with hydrocephalus or meningitis. Pituitary tumors are common causes of optic chiasmal dysfunction in humans, but much less common in dogs owning to a species difference in the anatomic relationship between the pituitary stalk and optic chiasm.

Unilateral optic tract lesions will produce similar clinical signs as unilateral retinal or prechiasmal optic nerve but the more dilated pupil will be contralateral to lesion, the anisocoria may be subtle, there is a positive swinging flashlight test (not in humans the swinging flashlight test is normal with optic tract lesions), and the more miotic pupil persists in the same eye regardless of which eye is stimulated. The visual field contralateral to affected tract is diminished or lost (contralateral homonymous hemianopia), and while some vision loss is present in both eyes, the vision loss is most obvious in eye contralateral to lesion. Because the proximity of the optic tract to the internal capsule (all afferent and efferent fibers to and from cortex), contralateral postural reaction deficits with normal gait may be seen. Canine distemper virus may have a select tropism for this anatomic region of the brain.

Unilateral lesions the optic radiation will produce a contralateral homonymous hemianopia. Extensive or complete lesions in this region may also affect the caudal limb of internal capsule and result in a contralateral hemiplegia and hemianesthesia.

Unilateral visual cortex lesions will also produce a contralateral homonymous hemianopia. In humans, and experimental animals (cats), the striate and extastriate visual cortex has selective procession and control of visual function. For example, the rostral and medial regions control stereopsis and processing, analysis, form, pattern, and texture. The rostral region controls visual placing, while the caudal and lateral regions are involved with menace blink response. The caudal and medial regions mediate conjugate eye movements (orientation and attention of eyes to visual target) and project corticocortical pathways directly to brainstem to control these eye movements. Selective lesions in these areas may cause deficits in one of more of these functions. Complete lesions will produce loss of menace blink response in contralateral visual field,
loss of conjugate eye movements and loss of contralateral visual placing. The visual cortex has extensive connections to other areas of the brain, including projections to 1) the opposite visual cortex via the corpus callosum, 2) the motor cortex of both cerebral hemispheres, 3) the cerebellum by way of the pons, and 4) the rostral colliculi and CNIII, VI, VI nuclei, directly or indirectly through the rostral colliculi. As a result of the latter, the visual cortex and rostral midbrain have extensive interaction in mediating visually guided behavior.

Visual cortex lesions are seen with a variety of conditions including intracranial neoplasia, hypoxia or anoxia as a complications of anesthesia, polioencephlomalacia (thiamine deficiency), lead intoxication in ruminants, and metabolic storage diseases in dogs and cats.

Lesions in the parietal lobe, between the visual and motor cortex, may result in loss of the menace response in the contralateral visual field, no loss of vision, and subcortical reflexes that remain intact (dazzle/PLR). Lesions in the motor cortex may cause abnormal menace blink (if eyelid region of motor cortex involved), abnormal visual placing reaction with contralateral loss of visual placing (if foreleg region of motor cortex involved), but will not result in abnormalities in conjugate gaze (orientation and attention to target stimuli) which is mediated by corticotectal pathways descending directly from the visual cortex to the brainstem, and not through the motor cortex.

**Eye Movement:**

Eye movement consists of both dynamic (voluntary eye movements, vestibular responses, and saccadic movement) and static (ocular alignment) components, and are mediated by the 6 extraocular muscles and retractor bulbi muscle, which are innervated by CN III, IV, and VI. CNIII (oculomotor nerve) innervates the medial, dorsal, and ventral rectus and ventral oblique mm, as well as levator superioris mm. The nuclei of CNIV (trochlear nerve) is found in the mesencephalon at the caudal border of CNIII nuclei, and innervates the contralateral dorsal oblique muscle. The trochlear nerve is unique in that is contains the fewest axons, longest intracranial course of all cranial nerves, and is the only cranial nerve to exit on the dorsal aspect of the brainstem and to completely decussate. CN VI (abducens nerve) innervates the lateral rectus, and retractor bulbi, and controls eyeball retraction (retractor bulbi mm.), and conjugate horizontal eye movements. 70% of fibers of CNVI course to the ipsilateral lateral rectus m, through the medial longitudinal fasiculis (MLF), and 30% of fibers contacts contralateral oculomotor (CNIII) medial rectus motor neurons. In this manner, CNVI coordinates abducting of ipsilateral lateral rectus and adduction of contralateral medial rectus.

Abnormal eye movement or position may be classified as resulting from muscle paresis (palsy) vs. mechanical restriction (restrictive). The latter is assessed by a forced duction (traction) testing, in which, following topical anesthesia, the conjunctiva is grasped with fine forceps and the globe mechanically moved to varying positions. Muscle paresis may be supranuclear (cortex/brain stem) or peripheral (infranuclear or in the
respective cranial nerve itself). The vestibulocular reflex (VOR, discussed below) may be useful to distinguish these two locations, as if the VOR is present, the paresis is likely supranuclear in location. The vergence of the two eyes (alignment along a central axis) is best evaluated using the corneal (light) reflex. With this test, the eye is illuminate with small light source, and spots of light (reflections) visible on anterior corneal surface. The spots of light should fall within the constricted pupil with normal ocular vergence (in the cat these light reflexes fall slightly medial to constricted pupil).

**CNIII** lesions (oculomotor nerve, medial, ventral, dorsal rectus, ventral oblique and levator superioris) affect PLR, eyelid movement and ocular motility. With complete, total lesions, an ipsilateral ptosis, inability to rotate eye up, down or in, a dilated and nonresponsive pupil, and divergent strabismus (when normal eye directed straight) is present.

**CNIV** lesions result in exotorsion of contralateral eye, and in humans, a vertical diplopia (double vision), from misalignment of the two globes from effects on the dorsal oblique mm. Subtle exotorsion is best detected by examining the fundus in dogs, and evaluating the position of the dorsal retinal venule, which should be directed towards the 12:00 position. Exotorsion may be detected in cats due to the misalignment of the slit pupil. CNIV lesion may be cause by intracranial neoplasia, trauma, or hemorrhage and in general, other mesencephalic disease is generally present.

**CNVI** lesions (abducens nerve, lateral rectus and retractor bulbi mm.) produce an ipsilateral ventrolateral strabismus and/or an ipsilateral palsy of horizontal gaze. Some CNVI nuclear lesions won’t affect the retractor bulbi mm function, whereas lesions in the peripheral CN VI cause paralysis of both lateral rectus and retractor bulbi (retractor bulbi function is mediated by an accessory abducens nuclei).

Cavernous sinus syndrome is generally caused by neoplasia on the ventral intracranial vault, and often effects CN III, CN IV, CN VI (adjacent to cavernous sinus), CN V (ophthalmic and mandibular branches) producing total ophthalmoplegia, mydriasis, paralysis of ocular movement, abnormal corneal blink reflex, and absent eyeball retraction.

The normal vestibulo ocular reflex (VOR, oculocephalic reflex, doll’s head reflex) is elicited with head movement and serves to maintain a steady image on the retina, and produce a jerk phase to preview the upcoming visual scene. A rapid side-to-side head movement will elicit a horizontal jerk nystagmus, and dorsoventral flexion of the head and neck a vertical nystagmus. The VOR consists of a slow drift to maintain the image on the retina, followed by a rapid, corrective phase to returns the eyes to the normal primary gaze position to preview the upcoming visual image. During the slow phase, there is an equal and conjugate movement of both eyes, opposite the direction of head movement, while the fast or jerk phase is in the direction of the head rotation.

Postrotary nystagmus is another type of vestibular ocular movement and is eliciting by spinning the animal 6-8 rotations, stopping, and observing the ocular
movements. Normally, this is characterized by a quick phase jerk nystagmus in the direction opposite the rotation.

The smooth pursuit eye movement (eye tracking) is employed when the eye is following a moving object. Once a visual target is fixated, the smooth pursuit motor system causes the eye to move reflexively to tract the target. The smooth pursuit movement requires a visual target and cannot be initiated voluntarily. The saccadic eye movement is the fastest eye movement, and involves movements that redirect the line of sight even without head movement. These may be involuntary, i.e. the quick phase of vestibular nystagmus that redirects the eyes during passive head movements; or voluntary, i.e. redirection of eye position to objects of interest. Unlike humans, the latter (viewing objects of interest) often occurs with head movement in dogs. The saccadic eye movement may be evaluated by assessing the VOR, or by having dog visually fix on different objects.

Vestibulo-ocular reflexes are mediated through the peripheral vestibular system, including the membranous labyrinth of the inner ear, with afferents through cerebello-pontine angle to the vestibular nuclei and cerebellum. From here, central connections are made with vestibular nuclei, to ocular motor nuclei that innervate extraocular muscles. Neurons of horizontal eye movements are located in CN VI, and neurons of vertical eye movements to CN III and IV. Extensive connections between these three nuclei are present in the medial longitudinal fasciculus.

Nystagmus refers to an involuntary, repetitive to-and-for movement of eyes and include a pendular nystagmus (smooth sinusoidal oscillations) or a jerk nystagmus (alternation of slow drift phase and a corrective quick phase). Any nystagmus is abnormal when the head is motionless. A unilateral vestibular disease will produce a jerk nystagmus. For example, with a right sided vestibular disorder, there is decreased activity in right vestibular system, and the left vestibular system drive the eyes in a slow phase to the right, with the quick phase directed to left, away from lesion (the rapid phase of nystagmus is contralateral to the lesion with peripheral vestibular disease). Central vestibular disease may cause positional nystagmus. Peripheral vestibular disease may also be evaluated with postrotational jerk nystagmus (quick phase opposite direction of rotation). This nystagmus may be decreased when rotated opposite to the side of peripheral vestibular disease, and any difference in response between the two directions of rotation might be indicative of vestibular disease.

Strabismus may be caused by a number of different neurologic and non-neurologic conditions including lesions in the vestibular pathway, lesions in the cranial nerves involved with ocular movement (III, IV, VI) and their interconnections, congenital misrouting of optic nerve axons (Siamese cats), physical displacement of the globe, proptosis, and fibrosing extraocular muscle myositis.
**Lacrimation**

Lacrimation is intimately tied to the trigeminal nerve, which conducts sensory stimuli centrally from lacrimal gland, adnexa, and eye; and stimulates sensory induced reflex tearing mediated through ophthalmic division (lacrimal n.) and first branch of maxillary division (zygomatic n.). The afferent fibers have cell bodies in the trigeminal ganglion, near the petrous temporal bone lateral to cavernous sinus and near middle ear.

CN V also distributes autonomic nervous system fibers to lacrimal gland and face. The parasympathetic innervation to the lacrimal gland originates in the parasympathetic nuclei of CN VII, and courses through the major petrosal nerve (petrous temporal bone and eustachian tube), nerve of pterygoid canal (with sympathetic fibers), synapsing in the pterygopalatine ganglion (orbit), to the zygomatic nerve (CN V), zygomaticotemporal nerve and finally to the lacrimal gland acinar cells. A similar innervation occurs to the lateral nasal gland to stimulate nasal secretions…..after the pterygopalatine ganglion in the orbit, parasympathetic fibers run through the caudal nasal nerve to lateral nasal gland.

Lesions the efferent arm of lacrimation pathway (parasympathetic nucleus of facial nerve, pterygopalatine ganglion, preganglionic or postganglionic parasympathetic fibers) characteristically result in the concurrent findings of ipsilateral dry eye and dry nasal passage (xeromycteria), and these two clinical findings together should always be considered suggestive of *neurogenic keratoconjunctivitis sicca*.

Lesions in floor of middle fossa and major petrosal nerve may affect the trigeminal ganglion or its three main divisions and cause KCS and xeromycteria, and sometimes facial anesthesia, neurotropic keratitis (ophthalmic branch of CN V) and/or medial half of eyelids (ophthalmic) and/or lateral half of periocular adnexa and nasal cavity (maxillary branch of CN V).

Preganglionic lesions in the parasympathetic innervation to the lacrimal gland that occur in the extraperiobital sheath or pterygopalatine ganglion (orbital region), may cause KCS, xeromycteria, and anesthesia to lateral upper and lower eyelids. KCS and anesthesia of lid with no xeromycteria may be seen if the lesions is more cranial in periobita involving the zygomaticotemporal nerve. As a result, it is important to examine the sensation to the eyelids in all cases of KCS where etiology not identified.

Neurogenic KCS is generally non-responsive to topical cyclosporin A, and oral pilocarpine therapy to maximum tolerable level is the preferred treatment. Oral pilocarpine (a parasympathomimetic) directly stimulates the dennervated gland. The treatment regime includes an initial oral dose (in the food) of 2% pilocarpine/2drops/20 pounds/2x daily. The dosage is increased by 1-2 drops every week until signs of systemic toxicity are seen (vomiting or diarrhea), then the dosages decreased to the next lowest level. Some, but not all cases require lifelong therapy.
The petrous temporal bone (PTB) in the middle fossa and middle and inner ear region is an extremely important anatomic region with regards to the eyes as a result of a number of structures coursing through this region. These include CN V, CN VII, CN IX, and ocular sympathetic fiber and parasympathetic fibers. Additionally, the trigeminal ganglion (rostral PTB), and CN VI (rostral PTB) are proximate to the PTB. As a result, lesions in this region have possible effects on lacrimation, blinking, third eyelid retraction, corneal sensation, pupillary dilation, and salivary secretion. Characteristic clinical findings with lesions in this area may include xeromycteria (CN VII), xerostomia (CN VII, CN IX), facial palsy (CN VII), facial anesthesia (CN V), nasal cavity anesthesia (CN V), loss of taste (CN VII, CN IX), and Horner syndrome (oculosympathetics).

Eyelid Neurology:

Motor control of the eyelids is controlled by CNIII (levator superioris mm.) for elevation of the upper lid, and CNVII (obicularis oculi mm.) for closure of the eyelids. Sympathetic innervation exists for smooth muscle in the upper, and lesser extent, lower eyelids which accentuates eyelid opening.

Sensory afferent innervation to the globe and adnexa occur through the ophthalmic and maxillary divisions of CNV. The ophthalmic division has three major branches. 1) the frontal n which innervates the upper eyelid, forehead, and frontal sinus, 2) the lacrimal n which innervates the lateral orbit, lacrimal gland, upper eyelid, and lateral canthus, and 3) the nasociliary n. The latter has two major branches including the long ciliary nerve (cornea, iris, ciliary body, sclera, sympathetics and parasympathetics), and the infratrochlear n (medial canthal skin, medial conjunctiva, sympathetics to upper Muller’s m. The maxillary division of CNV, through the zygomatic n (branches into the zygomaticofacial and zygomaticotemporal) innervates portions of the upper and lower eyelid, conjunctiva, and sympathetics to lower Muller’s m.

Reflex closure of the eyelids may be initiated by ocular pain (reflex blepharospasm, CN V inducing blepharospasm), tactile stimuli (corneal blink reflex and palpebral reflex, mediated by CNV), bright light stimuli (dazzle reflex), and auditory stimuli (mediated by the caudal colliculi).

The corneal blink response is a subcortical reflex closure of eyelids in response to tactile/painful stimuli. Because the reflex is subcortical, there is a short latency period, and the fellow eye sometimes responds with blink of lower amplitude. The afferent pathway is the ophthalmic branch of CN V, and the efferent pathway is CN VII (facial nerve). A head withdrawal with subsequent (cortical) perception is sometimes also evoked. It is important to perform this test outside the visual field to not elicit a menace response.
Neurologic abnormalities of eyelid manifest as ptosis (drooping of upper eyelid), inappropriate closure (spasm), or paralysis (from effects on the facial nerve). Ptosis may be the result of paresis/paralysis of motor function of CNIII, which innervates the levator superioris mm. The levator mm. (s) are innervated by a single midline nucleus of CNIII (caudal central nucleus), and as a result, a midline mesencephalic lesion may result in bilateral ptosis. As pupillomotor and levator mm. fibers are proximate in CNIII, ptosis is often seen concurrently with internal ophthalmoplegia. As discussed previously, ptosis and reverse ptosis may result from sympathetic denervation (Horner syndrome).

Hemifacial spasm occurs from an irritative lesion to CN VII, and results in spasmic, inappropriate blepharospasm. Horner’s syndrome may accompany hemifacial spasm, as it often results from otitis media. Hemifacial spasm may progress to facial paralysis with more profound lesions. The eyelid manifestations of the latter include a widened palpebral fissure, increased visibility of the sclera, and an illusion of proptosis. As discussed below, concurrent neurogenic KCS may result if the lesion is the result of otitis or other petrous temporal bone abnormalities. If neurogenic KCS and no facial nerve paralysis is present, the lesion is likely distal to genu of facial canal of petrous temporal bone. Conversely, if facial nerve paralysis and no neurogenic KCS is present, the lesions is most likely in the peripheral CN VII.

Neurotropic keratitis is caused by a lesion in the ophthalmic division of CN V, and results in loss of corneal sensation and ulcerative keratitis. The corneal lesions are the result primarily from an absence of the normal tropic influence of the trigeminal nerve on corneal metabolism, rather than reduced blink rate or other factors directly related to corneal sensation. If concurrent Horner syndrome is present, the lesion is distal to trigeminal ganglion along ophthalmic branch (sympathetic fibers enter CN V after trigeminal ganglion).

The smooth muscle of the nictitans is connected to the medial and ventral rectus and dorsal oblique mm. through facial sheaths. In the cat, slips of striated muscle extend from the lateral rectus and levator muscle to attach to the ventral and dorsal nictitans respectively. As a result, in dogs, nictitans protrusion is passive by globe retraction (retractor bulbi, CNVI) or contraction of other EOM. In cats there is an additional active component from the striated muscle connections, and may occur independent of globe movement or retraction (and occur voluntarily). Sympathetic efferent to the nictitans is through branches of the ophthalmic division of CNV (infraorbital n), and maxillary division of CNV (infraorbital and zygomatic branches). Variation in the clinical signs of Horner syndrome may be seen depending on how distal along the sympathetic efferent pathway the lesion resides.
Suggested Reading:


Miller PE, Murphy CJ. Vision in Dogs. JAVMA. 1995; 207: 1623.


Berson, DM, Dunn FA, Takao, M. Phototransduction by retinal ganglion cells that set the circadian clock. Science 2002; 295: 1070-3

Appendix I
Swinging Flashlight Test in Subprimate Species
Courtesy Dr Ben Blacklock

optic nerve – optic chiasm – optic tract – synapse bilaterally on neurons in the pretectal nucleus – axons from each pretectal nucleus relay to both right and left parasympathetic nuclei of CN III (oculomotor) – synapse in ciliary ganglion and then to iris – miosis quoted that Marcus Gunn sign or swinging flashlight test positive is pathonomonic for a pre-chiasmal lesions – ie retina and optic nerve....
HUMAN (50% decussation) – post-chiasmal lesion results in equal miosis
optic nerve – optic chiasm – optic tract – synapse bilaterally on neurons in the pretectal
nucleus – axons from each pretectal nucleus relay to both right and left parasympathetic
nuclei of CN III (oculomotor) – synapse in ciliary ganglion and then to iris – miosis
quoted that Marcus Gunn sign or swinging flashlight test positive is pathonomonic for a
pre-chiasmal lesions – ie retina and optic nerve....
CANINE normal (80% decussation)
showing proportion of nerve fibres which decussate and then are responsible for miosis... (assuming the same 80/20 split at the pretectal nucleus)
Post chiasmal lesion in CANINE ipsilateral to illuminated eye, illustrating proportion of innervation driving miosis in each pupil
Post chiasmal lesion in CANINE contralateral to illuminated eye, illustrating proportion of innervation driving miosis in each pupil
So.. In humans, regardless of which side the post chiasmal lesion affects, the pupils receive the same ‘amount’ of innervation (ie. 25%)
But... in dogs, as the flashlight swings, the ‘amount’ of innervation decreases to a quarter, resulting in a dilation of the pupil... Ie. A positive Marcus-Gunn sign in dogs can be caused by a post-chiasmal lesion
Appendix II

Characteristics of Pupillary Abnormalities


Unilateral Mydriasis:

Efferent Arm
- more obvious anisocoria v. afferent arm
- direct PLR deficit, normal indirect PLR from affected to normal eye
- concurrent external ophthalmoplegia if intracranial lesion
- May have “D” or “reverse D” pupil in cat if postganglionic
- supersensitivity to parasympathomimetics esp. if postganglionic

Afferent Arm
- less obvious anisocoria v. efferent arm (bilateral afferent input)
- direct and indirect PLR deficit if prechiasmal
- more mydriatic pupil and PLR deficit contralateral if postchiasmal
- positive Swinging Flashlight Test with pre and post chiasmal lesions in dogs/cats (only pre chiasmal in humans)
- menace response and dazzle reflex deficits if before lateral geniculate body

Cerebellar lesions
- generally contralateral mydriasis +/- ipsilateral nictitans protrusion
- both pupils respond to light stimuli

Acute Cerebral Swelling
- ipsilateral mydriasis from compression of CNIII

Unilateral Miosis:

Efferent Sympathetic
- ipsilateral miosis
- anisocoria accentuated by dark adaptation
- further constriction on light stimulation
- other findings of Horner Syndrome
- pharmacologic localization may be useful

Other Localizing Findings:
- cervical spinal cord = tetraparesis
-C6-T2 spinal segments = forelimb monoparesis with reduced spinal reflexes
-cervical sympathetic trunk = no other deficits
-inner/middle ear = possible CN V, VI, VII, VIII, IX deficits, possible neurogenic KCS (CN VII parasympathetic nuclei)
-cavernous sinus = possible CN III, IV, V, VI deficits
-orbit = possible concurrent parasympathetic denervation, possible CN II, III, IV, V, VI

**Bilateral Mydriasis:**

Bilateral afferent:
- retinal disease more common than (> optic chiasm > bilateral optic nerve
> bilateral caudal commissure> bilateral optic tract
- concurrent menace/dazzle deficits

Bilateral efferent:
- bilateral CNIII rare
  - e.g. midline brainstem lesions affecting both CNIII parasympathetic nuclei

**Bilateral Miosis**

Loss of supranuclear inhibition of CNIII:
- sleep, opioids, general anesthesia
- extensive cerebral cortical lesion

Experimental reported with rostral collicular lesions in dogs