

# On the Somatosensation of Vision

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## ABSTRACT

The interconnection between vision and somatosensation is already well-established and is further supplemented by the evolutionary link between eyes and photoreceptors, and the functional connection between photosensation and thermoreception. However, our analysis shows that the relation between vision and somatosensation is much deeper and suggests that somatosensation may possibly be the basis of vision. Surprisingly, our photoreceptor itself needs somatosensory proteins for its functioning, and our entire visual pathway depends on somatosensory cues for its functioning.

**KEYWORDS :** Mechanoreception, Photoreception, thermoreception, Nociception, Proprioception, TRP Channels, TREK, TREKK, Degenerins

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## Introduction

Somatosensation, the set of sensory abilities mediating body sensation, comprises of the submodalities: mechanoreception, thermoception, nociception and proprioception, which are together responsible for sensing heat, cold, stretch, pressure, pain and body position.<sup>1</sup> Although it is believed that peripheral stimuli are detected with the help of receptors, transduced into action potentials and conveyed to the central nervous system (CNS), recent studies suggest that even non-neuronal cells could be directly involved in somatosensation.<sup>2</sup>

Recently, there has been a flurry of research about molecules, enzymes, proteins, lipids involved in somatosensation. Especially, with the help of ion channels several somatosensory modalities are sensed; examples of ion channels include, but are not restricted to transient receptor potential (TRP) proteins, degenerins (DEG/MEC), acid sensing ion channels etc (ASICs). Current advances in vision research have also identified these somatosensory enzymes, molecules and channels to be present in the visual pathway and surprisingly in eyes and photoreceptors too (For example, myosin VIIa, integrins).

The links between somatosensation and vision have been well authenticated.<sup>3</sup> Expression of J1- and J3-crystallin genes and PaxB mRNA (messenger Ribose nucleic acid) in *Tripedalia statocysts*, close association of the atonal family of genes in photosensation and mechanosensation,<sup>4</sup> proteins like myosin IIIA, harmonin, Norrin-Frizzled-4 (a presumptive Wnt receptor), the human Choroideremia gene, transcription factors atonal/Math1, which are associated with

vision and hearing in humans reinforce the evolutionary relationship between mechanosensation and vision.<sup>5</sup> Thermal stimulation of the skin thermoreceptors results in a decrease in the mobilization level of the rods of the retina<sup>6</sup> and exposing a subject to illumination results in decreased mobilization of cold receptors in the skin.<sup>7</sup> This functional connection between the optic receptors and thermoreceptors further strengthens the link between somatosensation and vision.

What if there was more to somatosensation and vision than just the links between them? Could somatosensation have a fundamental role in vision? What if each of the somatosensory submodalities was debilitated and the impact on vision studied?

Here, we analyze the significant contribution of somatosensory tools to vision. We consider how the absence of somatosensory modalities impairs vision, how photoreceptors themselves are affected by modified somatosensation, how somatosensory ion channels, molecules, proteins, somatic afferents and efferents are pivotal to vision and visual perception.

## Vision without mechanoreception

The cells in the human body are subject to mechanical pressure and forces which are sensed and transduced into signals that elicit the appropriate response. These mechanical cues are sensed with the help of mechanically gated channels and mechanoreceptors (hair cells in the cochlea and cutaneous mechanoreceptors).<sup>1,2</sup> Low-threshold mechanoreceptors respond to benign touch. When impaired or altered, they could be debilitating, even in case of vision.

The mechanoreceptive Mueller muscles in the eyelid are found to be essential for the contraction of the levator muscles against the weight of the eyelid so that an adequate visual field is maintained.<sup>8</sup> Cornea of rabbits, and cornea, sclera, bulbar conjunctiva, and uvea of cats, consist of elements that respond to mechanical stimuli specifically.<sup>9</sup> Altered mechanoreception in the human trabecular meshwork (HTM) cells increases the intraocular pressure (IOP). Increased oxidative stress inhibits proteasome activity and causes elevated apoptosis. Mechanical stretch, biophysical cues such as cell-cell and cell-matrix interactions control transcription and cause splicing of several mRNAs, and thereby, alter signal transduction, the expression of numerous genes, proteins and matrix metallo proteases (MMPs), remodel and change the composition of the HTM extra-cellular matrix (ECM). These factors in turn modulate the aqueous humour outflow causing glaucoma.<sup>10-12</sup>

Factors such as eyeball shape, relative positions of the eye's surfaces and the perfusion pressure in the eye are influenced by IOP. Apart from causing glaucoma, elevated IOP could modify mechanoreception, causing corneal oedema, iris ischemia, lens opacity, also affecting the retinal circulation. Afferent mechanoreception has been found to exist at the sclera spur and the anterior uvea in the eye.<sup>13</sup>

Retinal ganglionic cell (RGC) apoptosis, is caused by elevated hydrostatic pressure and change in mechanical cues at the lamina cribosa in the eye, which deprives nutritional and structural support to the RGCs and affects axonal transport. Increased mechanical strain on the myo-

fibroblasts of the eye, causes scleral remodelling, affects the mechanotransduction pathway, alters the expression of a multitude of genes, protein kinases, cell receptors, transcription factors and reduces scleral resistance to expansion due to increased IOP resulting in axial myopia.<sup>11</sup>

Retinal angiogenesis *in vivo* is controlled by a pathway affected by ECM elasticity. These biomechanical cues also affect their sensitivity to chemicals. Changes in ECM elasticity, adhesivity or topography, mechanical stresses, cell-generated traction forces change capillary cell shape and function, stimulate expression of growth factors (like VEGFR2), capillary growth and vascular remodelling *in vivo*.<sup>14</sup>

### Mechanosensitive (MS) channels in photoreception

Somatosensory signals are translated by neurons into action potentials, which activate mechanoreceptive nerve endings. The mechanical stimuli at these endings, in turn, open mechanosensitive channels, which convert the mechanical forces to electrical and chemical stimuli and cause depolarization of the terminal. The MS channels are activated by many mechanisms such as membrane bilayer mechanics, stretch of the membrane, fluid shear stress, physical coupling through tethers, osmotic variation, amphipathic compounds, cytoskeletal cues, conformational change in proteins, and by second messengers generated by MS enzymes or receptors. In the following paragraphs, we highlight their significance in our eyes, specifically in photoreception.

### Transient Receptor Potential (TRP) channels

The TRP family of cation channels has been found to function in sensory processes such as touch, proprioception, osmosensation, hearing and a variety of other physiological processes such as cell volume regulation and ion homeostasis.<sup>15,16</sup>

The founding member of the TRP family, the drosophila TRP (dTRP) has been found in the eye photoreceptor and is essential for mediating phototransduction.<sup>16</sup> Here, several proteins are clustered together to form a huge signalplex for proper localization of all the components and the TRP channels are closed for the efficient termination of the phototransduction pathway, when the illumination of the photoreceptor cells stops. These channels are associated with the actomyosin

cytoskeleton through the scaffold protein INAD (inactivation no afterpotential D), which is the central component of the signalplex and it is these mechanical cues from the cytoskeleton, that are responsible for the movement and activity of the TRP channels in the cells.<sup>17,18</sup>

Recent evidence suggests that not only channel closure, but, the opening of dTRP channels may also be governed by mechanical stimulation, i.e., by lipid binding mechanics during the direct binding of lipids to the channels or by a stretch in the microvillar membrane due to increase in the concentration of these lipids in response to light stimulation subsequently followed by a change in the structure of the signalplex.<sup>19</sup>

A detailed examination of the pathway, thus, accentuates on the dependence of the phototransduction pathway on mechanical cues from the actomyosin cytoskeleton and instigates the thought that the TRP channels in the drosophila eye could be mechanoreceptive. However, further research needs to be carried out to completely understand the interaction between the cytoskeleton and TRP channels, the mechanism of activation of TRP channels and to find out if the Drosophila TRP channels themselves are somatosensory in nature.

The association of TRP channels with the actomyosin cytoskeleton, directly or indirectly (through macromolecular complexes), has also been observed in mammals. Similarly, the molecular coordination and light-induced protein translocation evident in the Drosophila signalplex is also reflected in the rim of vertebrate photoreceptors.<sup>20</sup> Future work could tell us whether these biochemical characteristics of the phototransduction pathway and the dependence of the pathway on mechanical cues could be extended to human eyes too.

### Mechanosensory abnormal/degenerins (MEC/DEG) and sodium (NaC) channels

MEC/DEG and NaC are a family of constitutively active cationic MS channels with diverse functions. These mechanosensors have also been found in the eyes. Amphioxus, which is closely related to the vertebrates, consists of four rows of cells in its frontal eye. The MS sodium channel, AmphiNaC, is expressed in two symmetrical cells in the first two rows (considered as photoreceptors) of the frontal eyes. The paired eyes of the vertebrates have been found to be similar to

the amphioxus frontal eyes. Hence, the presence and role of similar MS channels in vertebrate photoreceptors, if any, needs to be investigated.<sup>21</sup>

Another group of MS channels called the ASICs, belonging to H<sup>+</sup>-gated subgroup of the DEG/ENaC family have been found to function in the rodent retina and photoreceptors.<sup>21</sup> In the retina, acidic transients activate these MS channels and tune visual perception. ASIC1 positively modulates cone phototransduction and adaptation. Inactivation of ASIC2, a negative modulator of rod phototransduction, results in light-induced retinal degeneration.<sup>22</sup> Hence, the MS channels are necessary to maintain the integrity of the retina and their impairment could lead to substantial visual loss. The rodent retina has also been found to harbour the MS epithelial sodium channels (ENaC), although their role in photoreception remains to be proved.<sup>23</sup>

### Vision without MS channels TREK and TRAAK

MS channels TRAAK (found in the retinal neurons and outer photoreceptor layer(OPE)), TREK-1, TREK-2, and K<sup>+</sup> inward rectifying (Kir) channels have been found to be functional in the eye. Removal or impairment of these channels affects osmotic regulation, glial cell homeostasis, destabilizes the membrane potential of Muller cells and affects K<sup>+</sup> clearance in the retina.<sup>24</sup> Defective TRAAK mechanosensitivity affects reception and integration of synaptic signals and neuron survival.<sup>25</sup> Defects in MS volume regulated outwardly rectifying chloride channels affect the clarity of the ocular medium and aqueous humour outflow in mammalian corneal epithelium and trabecular meshwork (TM) cells.<sup>9</sup> Table 1 summarises somatosensory channels in the eyes.

### Vision without thermoception

Thermoception, the process of sensing the presence or absence of heat (coldness) in the vicinity, takes place with help of temperature-gated channels (like the TRP channels) and thermoreceptors, generally present in the skin. However, functional thermoreceptors have also been found in the face and eyes. Different thermosensitive fibres encode a wide range of temperatures.<sup>2</sup>

Ocular areas exposed to external temperature changes (such as, cornea, limbus) are filled with cold-activated thermosen-

Table 1. A summary of somatosensory channels in the eyes

Channels involved in somatosensati on	Presence in tissue or organ (related to vision)	Associated pathology or physiology
NOMPC	Drosophila	Proprioception touch and
(TRPN)	compound eye bristles	audition
dTRP	Drosophila eye	Mechanotransduction in photoreception ?
TRPML3	Retina cells	Maturation. (mechanosensory role ?)
TRPP3	Retina	Retinal (mechanosensory role?) and hair cell development
ASIC2	Eye neurons and photoreceptors	Negative modulation of rod phototransduction
ASIC1a	cones	Positive modulation of phototransduction, inactivation can cause light-induced retinal degeneration
ASIC3, ASIC4	retina	Mechanosensation & nociception?
ASIC2b	retina	Modulation of ASIC3 & ASIC2a
AmphiNaC	Amphioxus frontal eyes	?
ENaC	Retina photoreceptors	Mechanotransduction in photoreception?
TRAAK	RGC axons, OPE, retina	Osmotic regulation, cell homeostasis, K <sup>+</sup> clearance, synaptic transmission
TREK-1, TREK-2	eyes	Osmotic regulation, cell homeostasis, K <sup>+</sup> clearance
Outward rectifying chloride channels	Corneal epithelium, TM cells	Ocular medium clarity and aqueous humour outflow maintenance
P2X3, P2X7 & P2X5	Rat retina	Mechanotransduction in photoreception?
P2X2, P2X4	Rat retina & choroid	Mechanotransduction in photoreception?
Unclassified Stretch activated channels (SACs)	Human retinal muller cells, TM cells, choroid plexus epithelium	Mechanotransdcution?
CAT-50	Frog lens	Mechanotransdcution

sors which detect external temperature variations. Cold-sensory fibres (A $\delta$  or C) with spotlike receptive fields are distributed throughout the surface of the eye, with higher density in the perilimbal episclera and the posterior segment, and their functions are similar to thermosensors found in other parts of the body, which accentuates on their importance in vision. Reduction in ocular blood flow causes temperature variations and activates these receptors which may be responsible for thermosensation in the eye and face and in blinking due to ocular surface evaporation. These thermosensors have low mechanical sensitivity, may signal blood flow variations and help regulate regional temperature and blood flow. Their impairment could lead to loss of useful information and affects retinal function and vision.<sup>26</sup>

Mutations in a recently identified gene hclA coding for an ionotropic histamine

receptor subunit in *Drosophila melanogaster*, leads to defects in the visual system, neurologic disorders and changed responsiveness to neurotoxins.<sup>27</sup> The same gene is considered to be a potential player in thermosensation too.<sup>28</sup>

#### Vision without nociception

Nociception, the neural process by which we sense harmful stimuli, is initiated by pain receptors which detect chemical, mechanical and thermal stimuli above a certain threshold and send signals to the brain and spinal cord. They are found mostly in the skin and to a lesser extent in the internal surfaces such as, periosteum and joint surfaces.

It is a little known fact that cornea is the most densely innervated tissue in the body, with four types of nociceptors innervating its epithelium. Mechano-nociceptors respond to sharp mechanical forces acting on the cornea and protect it from injury.

Polymodal nociceptors help sustain the pain caused by harmful high threshold mechanical, chemical and thermal stimuli. Cold nociceptors detect low temperatures and mediate cooling sensations. Silent nociceptors respond to local inflammation and chemical stimuli. Without these nociceptors, integrity of the ocular surface would be lost and corneal wound healing may not be possible. The nociceptors are distributed homogeneously throughout the cornea and their density is a measure of corneal sensitivity.<sup>29</sup> They are important for a healthy cornea and their loss will lead to 'dry eye' which could decrease the corneal sensitivity or erode its epithelium. Their loss could result in irreparable damage to the cornea, eventually resulting in blindness.<sup>30</sup>

Mechano, polymodal and cold nociceptors are also functional in the episclera, sclera, bulbar conjunctiva, iris and in the ciliary body. Damage to the nociceptive

nerves, as in the case of a surgery, could affect their threshold level, sensitivity, and they may become hypoaesthetic or even anaesthetic, depending on the type and extent of damage. The subject may have decreased lacrimal secretion and may experience acute or chronic pain of variable duration.<sup>31</sup>

### Vision without proprioception

Sensory receptors in the inner ear (labyrinth receptors), muscles (Muscle spindle), tendons (golgi tendon), joints inform us about motion or relative position of our body or body parts by responding to stimuli arising internally. These receptors are called proprioceptors and the process is called proprioception.

Proprioceptors play a crucial role in vision and visually guided behaviour. Proprioceptive inputs are necessary for oculomotor control, maintenance of binocular vision and spatial localization. In animals, experimental removal of these inputs led to deterioration in depth perception, affected fixation stability and ocular alignment, caused deviation of eye position, modified eye movements and optokinetic responses, and altered the vestibulo-ocular reflex (VOR) and the vestibulocollic reflex.<sup>32,33</sup>

In an experiment involving hooded rats, albino rats, and dystrophic and non-dystrophic Royal college of surgeon (RCS) rats, it was observed that dystrophic RCS rats alone failed to orient themselves to a visual stimulus and spent less time under the dark while compared to others, when placed under different illumination levels. The somatosensory defect also prevented the dystrophic RCS rats from reaching criterion levels in the visual discrimination test, reflecting the effect of proprioceptive loss on vision.<sup>34</sup>

Proprioception influences human vision too. Altered proprioception modifies ocular alignment, static eye position as well as eye movements such as saccades and smooth pursuit.<sup>35</sup> Modified extra ocular muscle (EOM) proprioception affects visuomotor behaviour and may be a factor in the cause and treatment of eye ailments like strabismus and nystagmus.<sup>32,33</sup> Signals from EOM proprioceptors are involved in constructing the registered direction of gaze and vision, and in visual information processing in the brain. They are also associated with the development of visual properties of the visual cortex

neurons such as stereoacuity and orientation selectivity.<sup>32</sup>

Recently, it has been proved that proprioceptive inputs during passive eye movements play a significant role in the reduction of perceived motion smear, disproving previous notions of negligible proprioceptive contribution to extra-retinal information and clarity.<sup>36</sup> Disturbing the proprioceptive input from the innervated myotendinous cylinders (IMCs) in the EOMs leads to oculomotor disorder and interferes with normal binocular vision and spatial localization.<sup>37</sup> Proprioceptive inputs have also been found to contribute to the self-recognition of active movement visually, called the "sense of agency".<sup>38</sup>

Friedrich ataxia (FRDA), a hereditary disease characterized by the impairment of proprioception and hence difficulty in walking, lurching gait, absence of deep tendon reflexes and others, has a role in visual loss too. FRDA results in defective visual fields, progressive loss of RGCs and causes considerable damage to the optic nerve. Loss of visual acuity, damage to the optic disk and even loss of central vision were sometimes encountered because of the ataxia.<sup>39</sup> The visual evoked potentials were abnormal in most of the cases. Other symptoms included fixation instability, ocular flutter, impaired VOR and abnormal saccadic movements and smooth pursuit.<sup>40</sup>

The superior colliculus or optic tectum, a component of the mid-brain which plays a critical role in visual reception, is sensitive to proprioceptive inputs and manipulation of these inputs alters the visual response.<sup>32,41</sup>

### Visual perception without somatosensation

EOM proprioceptive cues control muscular activity of the neck muscles and head movement and thereby, participate in body orientation and visual perception.<sup>31</sup>

Somatosensory cues modulate visual slant perception,<sup>42</sup> Hering and Wundt illusions<sup>43</sup> and suppress illusory visual motions such as autokinesis,<sup>44</sup> and oculogyral vision.<sup>45</sup>

Recently, tactile stimulation alone has been found to activate the dorsal region of the lateral occipital cortex (LOC), an important visual area for object recognition, even in cases where object recognition through visual stimulation alone was not possible.

Also, the LOC was activated by tactile input directly and therefore, tactile activation is not secondary to visual activation of LOC. This evidence suggests an important role for tactile stimuli in visualization.<sup>46</sup>

Our brain relies on haptic information to resolve visual mislocalizations. Somesthetic cues to the somatosensory cortex influence the visual cortex via the parietal lobe and this is important for spatial attention during vision.<sup>47</sup> Somesthetic cues stimulate the middle superior temporal (MST) area<sup>48</sup> in the middle temporal visual area and strongly influence perception of structure from motion.<sup>49</sup> Right somatosensory-related cortices are required for visual recognition of emotion.<sup>50-52</sup> Somatosensory information inhibits visually elicited avoidance behaviour and this is necessary in natural situations, such as, mating.<sup>53</sup> Impaired somatosensation could affect natural behaviour, visual recognition of emotion and visual conflict may not be resolved.

### Vision without somatic afferents and efferents

Special somatic afferents (SSA) mediates special sensations of vision from retina.<sup>41</sup> Severing or subjecting the optic nerve (an SSA) to increased pressure, could lead to ipsilateral blindness, a choked optic disc and axonal degeneration. Similarly damage to the general somatic efferents (GSE) such as the trochlear nerve, the abducens nerve and the oculomotor nerve (consists of a GSE and a general visceral efferent), causes a variety of visual disorders such as drooping of the upper eyelid, dilated and fixed pupil, paralysis of accommodation, inability to focus the eye, double vision, slight protrusion of the eyeball and strabismus.<sup>54</sup> Also, somatosensory loss to the trigeminal nerve (general somatic afferent) injures the cornea.<sup>55</sup> Table 2 gives us a gist of the somatosensory signals involved or modified during vision with their associated pathologies and physiologies.

### Are MS purinergic receptors essential in the retina?

Purinergic receptors (P2X & P2Y) have been found in abundance in the retina. They are a family of ligand-gated ion channels responsive to ATP and a few related nucleotides. Their presence in nociceptive<sup>56</sup> and mechanosensitive afferents<sup>57,58</sup> and hence, their involvement in somatosensation in the periphery as well as the CNS has been authenticated. Receptors P2X3, P2X7 & P2X5 have been found in the rat retina alone, while P2X2 and P2X4 exist in

**Table 2. A summary of the somatosensory signals involved or modified during vision with their associated pathologies and physiologies**

Type of somatosensory signal involved or modified	Tissue or organ involved or affected during vision	Associated physiology or pathology
Mechanoreception at mueller cells	eyelid	Levator muscle contraction for adequate visual field maintenance
Mechanoreception at the HTM cells	eye	Modified signal transduction, modulated aqueous humour outflow, leads to glaucoma
Mechanoreception	cornea	Increased fluid content in the cornea, causing reduction in visual acuity
Mechanoreception	iris	Loss of blood supply to the iris
Mechanoreception	Eye lens	Opacity
Afferent	Sclera, anterior	?
Mechanoreception	uvea	
Mechanical cues at lamina cribosa	Retinal ganglion cells ( RGCs)	Deprivation of support to RGCs, axonal transport affected, followed by RGC cell death
mechanical stress on myofibroblasts	Sclera	Alters expression of genes. Results in axial myopia
Mechanical cues (ECM elasticity)	Retina	Change in capillary cell shape and function, formation of new blood vessels in retina
Thermosensation	Cornea, limbus	Detection of external temperature variations
Thermosensation (cold-sensory fibres)	Posterior segment, perilimbal episclera	Maintenance of regional temperature, blood flow and hence, retinal integrity.
Nociception (Mechano-nociceptors)	Cornea, episclera, iris, sclera, ciliary body, bulbar conjunctiva	Protection from injury
Nociception (Polymodal nociceptors)	Cornea, episclera, iris, sclera, ciliary body, bulbar conjunctiva	Pain sustenance
Nociception (Cold-nociceptors)	Cornea, episclera, iris, sclera, ciliary body, bulbar conjunctiva	Cooling sensations
Nociception (Silent nociceptors)	Cornea	Response to inflammation, chemicals
Proprioception (Palisade nerve endings in IMCs of EOMs)	Optic tectum, sclera, eye ( in general)	Visual and spatial localization, oculomotor control, normal eye position and movements, stable fixation, binocular vision, visual clarity, agency, visual response
Somatosensory proprioceptive cues	Visual processing regions in brain	Modulating Perception and suppressing illusory visual motions
Tactile stimuli	Lateral occipital cortex	Object recognition during Visualization
Haptic signals	Parietal lobe, visual cortex, MST	Spatial attention during vision, perception of structure from motion, resolving visual conflict
Right somatosensory related cortices	Visual processing regions in brain	Visual recognition of emotion
Somatic afferents and efferents	Cranial nerves involved in vision	Blindness, axonal damage, accommodation and focus problems, corneal damage, strabismus, eyeball

the rat retina as well as choroids.<sup>59,60</sup> Also, ATP-gated channels with properties of Purinergic receptors have been found only in RGCs.<sup>61</sup> These receptors have also been found in bipolar, amacrine and mueller cells of the retina.<sup>62</sup> Their expression in various cells of the retina is indicative of a strong role of these MS receptors in phototrans-

duction. However, only future work will substantiate this claim.

#### **Photoreception with altered/absent mechanotransduction**

The vertebrate photoreceptors involve the formation of a molecular complex and light-induced protein translocation evi-

dent in the signalplex of the *Drosophila* phototransduction pathway. We also know that the actomyosin cytoskeleton interacts with the *Drosophila* TRP channels and provides mechanical signals mandatory for phototransduction. It is possible that similar channels exist in the vertebrate phototransduction pathway too.

The photoreceptors of each human eye synthesizes *de novo* some 10 billion opsin molecules per second. It is critical for phototransduction that the opsin molecules synthesized in the inner segment be transported to the outer segment. This is mediated by myosin VIIa, an actin-based mechanoenzyme found in the cilium of vertebrate photoreceptors.<sup>34,63</sup> Myosin VIIa, similar to the myosin III in drosophila eye, possibly forms a complex with other proteins and their interactions provide mechanical signals necessary for the translocation of opsin to the OS<sup>34,63</sup> thereby, playing a crucial role in phototransduction in humans. Hence, the alteration or absence of these mechanical cues during mutation in myosin VIIa, could causes blindness, as in the case of Usher's syndrome.<sup>64</sup>

The fact that mutations in myosin VIIA also cause deafness in Usher's syndrome

(a deafness-blindness disease) due to defective mechanotransduction,<sup>65</sup> suggests a possibility that myosin VIIa mediates a mechanotransduction pathway in photoreceptors too, and blindness is caused when mutation in myosin VIIa disturbs the mechanotransduction pathway, thereby reflecting a possible role for mechanotransduction in photoreception.

Myosin VIIa has also been found in cilia present in the eyes. Cilia are organelles consisting of a microtubule-based axonemal structure that emerge from the basal bodies and are found on cell surfaces in almost all mammalian cells. They may be motile, nodal or non-motile (primary cilia). It is a well-known fact that primary or non-motile cilia generally function as mechanosensors or chemosensors (nociceptors) or both,<sup>66</sup> reflecting their somatosensory nature. It has been found that the outer segments (OS) of the photo-

receptors are modifications of these primary cilia. The cilia also connect the OS segment to the inner segment and function in retinal photoreception, suggesting another mechanosensory function in vision.<sup>67</sup> Further research on these organelles could help us accentuate on their importance in vision. Table 3 gives us a list of various somatosensory elements, proteins and molecules which would affect/probably affect vision.

**Future perspectives and conclusions**

It is common knowledge that mechanosensory interommatidial bristles (presence of Nomp C mechanoreceptors)<sup>68</sup> exist in the compound eye of the drosophila<sup>69</sup> and their high density perfectly matches the number of facets at the centre of the eye. However, the reasons for their presence in the eye in spite of the presence of photoreceptors and their role in vision, if at all any, are yet to be found. The neurons of these bristles

**Table 3. A summary of the various somatosensory elements, proteins and molecules which would affect/probably affect vision**

Other molecules/elements present/probably present in the eyes with a direct or indirect somatosensory role	Associated physiology
Mechanical signals (from actomyosin cytoskeleton)	TRP channel gating and movement during phototransduction. (in Drosophila eye)
Plasma-membrane bound enzymes (phospholipase A2 & C)	Increase their activity causing more phosphorylation and help mediate mechanotransduction
Cytoskeletal complex	Delayed channel activation following stimulus, Modulation of MS channel activity.
Tethers, Mechanical cues (From cell-cell interations), viscoelasticity of actin	Gating of ion channels
Mechanical signals from Focal adhesion proteins-(Focal Adhesion Kinase, paxilin, and the adaptor protein p130Cas), cadherin, integrins, myosin VIIa, NINAC	Mechanotransduction, Activation of intracellular signaling pathways
Lipid bilayer physical changes, membrane stretch	Generation of mechanical cues for mechanotransduction
Fatty metabolites, Ca2+(second messenger), ATP, membrane kinases), prostaglandins, alpha B crystallin	Mediating mechanotransduction pathway in phototransduction?
Fatty acids, trinitrophenol, lysolecithin,	Plasma membrane crenation enhancing SAC activity
Chlorpromazine, tetracaine	Cup-fomration in membrane inhibiting SAC activity
Gadolinium, amiloride, barium	Block TRAAK
Stomatin-related protein (SLP-3)	Bind to ASICs 2 & 3 to mediate mechanotransduction
Mechanical signals (from actomyosin cytoskeleton)	TRP channel gating and movement during phototransduction. (in Drosophila eye)
Plasma-membrane bound enzymes ( phospholipase A2 & C)	Increase their activity causing more phosphorylation and help mediate mechanotransduction
Cytoskeletal complex	Delayed channel activation following stimulus, Modulation of MS channel activity.
Tethers, Mechanical cues (From cell-cell interations), viscoelasticity of actin	Gating of ion channels

Other molecules/elements present/probably present in the eyes with a direct or indirect somatosensory role	Associated physiology
Mechanical signals from Focal adhesion proteins-(Focal Adhesion Kinase, paxilin, and the adaptor protein p130Cas), cadherin, integrins, myosin VIIa, NINAC	Mechanotransduction, Activation of intracellular signaling pathways
Lipid bilayer physical changes, membrane stretch	Generation of mechanical cues for mechanotransduction
Fatty metabolites, Ca <sup>2+</sup> (second messenger), ATP, membrane kinases), prostaglandins, alpha B crystallin	Mediating mechanotransduction pathway in phototransduction?
Fatty acids, trinitrophenol, lysolecithin,	Plasma membrane crenation enhancing SAC activity
Chlorpromazine, tetracaine	Cup-fomration in membrane inhibiting SAC activity
Gadolinium, amiloride, barium	Block TRAAK
Stomatin-related protein (SLP-3)	Bind to ASICs 2 & 3 to mediate mechanotransduction

include thermoreceptive TRP channels encoded by the pyrexia gene, suggesting another somatosensory role in vision.<sup>18</sup> Also, the photoresponse mechanism is similar to that in mammalian intrinsically photosensitive retinal ganglionic cells.<sup>70</sup> Further research needs to be carried out to know if presence of mechanosensory organs (such as, the bristles in the drosophila eye) can be extended to human eyes too.

Photoreceptors themselves are believed to receive directional inputs from mechanosensors, as in the case of the crayfish caudal photoreceptors (CPRs), which are primary photoreceptors in the crayfish Central nervous system (CNS).<sup>71</sup> Is it possible that even human photoreceptors require somatosensory inputs?

All cells across the evolutionary spectrum, from the primitive to the most complex, need to be somatosensitive for survival. Cellular homeostasis needs osmosensation, mechanosensation, thermosensation, and chemosensation. Though photoreceptor is an epitome of a complex sensor, it must first fulfil the basic sensory demands for homeostasis. Somatosensation at the cellular level is essential to developmental pathways and to normal tissue homeostasis, in our case ocular tissues, primarily in the maintenance of tissues in which cellular adaptive responses are crucial to counteract substantial variations from normal conditions. At the tissue level, somatosensory cues are generated by cell-cell and cell matrix interactions mediated by focal adhesion kinases, integrins and other mechanoproteins. It is possible that all the molecular events in the eye and in the visual system, in general, rely on somatosensory cues or pathways for their function.

Vision, which is possible only at the systemic level, needs to adapt to the constant demands of the changing physical environment to maintain homeostasis. However, somatosensation exists even at the lower levels of hierarchy (cellular and molecular levels) in a living system and hence, it is plausible that somatosensation is fundamental to the existence of vision and probably, other senses too.

Although the recent discovery of many somatosensory molecules, enzymes, and proteins involved in vision tempts us to conclude that vision cannot exist without somatosensation, further research needs to be carried out to fetch more concrete evidences to support our hypothesis and shed light on somatosensory involvement in the functioning of other senses too.

Subjecting any cell to mechanical, thermal, chemical, and electrical forces stimuli (both internal and external) activates its somatosensory receptors, which translate the stimuli into biosignals, which in turn initiate a plethora of physiological responses, necessary for our survival. Probably, not only vision, life itself would cease to exist without somatosensation.

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## References

1. Ellen AL and Diana MB. Feeling the pressure in mammalian somatosensation. *Curr Opin Neurobiol* 2005; 15: 382–388.

2. Ellen AL and Michael JCT. Mechanisms of sensory transduction in the skin. *Nature* 2007; 445: 858–865.
3. Roger NN, John VH and Stephen RJ. Links between vision and somatosensation: Vision can improve the felt position of the unseen hand. *Curr Biol* 2001; 11(12): 975–980.
4. Fritzsche B, Beisel KW, Pauley S *et al.* Molecular evolution of the vertebrate mechanosensory cell and ear. *Int J Dev Biol*. 2007; 51(6–7): 663–78.
5. Joram P and Zbynek K. Cubozoan jellyfish: an Evo/Devo model for eyes and other sensory systems. 2004; 48: 719–729.
6. Kurilova LM. Effect of thermal stimulation of the skin on the functional state of the optic analyzer. *Byulleten' t~ksperimental'noi Biologii i Meditsiny* 1963; 56(9): 17–21.
7. Kurilova LM. Effect of the conditions of adaptation of the optic analyzer to the function of the thermoreceptors of the human skin. Translated from *Byulleten' t~ksperimental'noi Biologii i Meditsiny* 1964; 57(3): 3–6.
8. Kiyoshi M. Stretching of the Mueller Muscle Results in Involuntary Contraction of the Levator Muscle. *Ophthal Plast & Recons* 2002; 18(1): 5–10.
9. Tan JCH, Kalapesi FB and Coroneo MT. Mechanosensitivity and the eye: cells coping with the pressure. *Br. J. Ophthalmol.* 2006; 90: 383–388.
10. Darrell WD. Mechanobiology of trabecular meshwork cells. *Exp Eye Res*, 2009; 88(4): 718–723.
11. Diana EJ and Jan L. Mechanotransduction gone awry. *Nat Rev Mol Cell Bio* 2009; 10: 63–73.
12. Joshua ZG and Paul R. Biological properties of trabecular meshwork cells. *Exp Eye Res* 2009; 88(4): 671–675.
13. Freny BK, James CHT and Minas TC. Stretch-activated channels: a mini-review. Are stretch-activated channels an ocular barometer? *Clin.*

- Experiment. Ophthalmol. 2005; 33(2): 210–217.
14. Mammoto A, Connor KM, Mammoto T *et al.* A mechanosensitive transcriptional mechanism that controls angiogenesis. *Nature* 2009; 457: 1103–08.
  15. Matthieu R, Lise RD, Nathalie A *et al.* Mechanosensor Channels in Mammalian Somatosensory Neurons. *Sensors* 2007; 7(9): 1667–82.
  16. Robert AC, Michelle A, Diana B *et al.* A Double TRPtych: Six Views of Transient Receptor Potential Channels in Disease and Health. *J Neurosci* 2008; 28(46): 11778–11784.
  17. Kristopher C, Jeroen M and Frank NL. Interplay between TRP channels and the cytoskeleton in health and disease. *Eur J Cell Biol* 2008; 87(8-9): 631–640.
  18. Lee Y, Lee Y, Lee J *et al.* Pyrexia is a new thermal transient receptor potential channel endowing tolerance to high temperatures in *Drosophila melanogaster*. *Nat Genet* 2005; 37: 305–310.
  19. Ricardo D and Juan B. Unitary Recordings of TRP and TRPL Channels From Isolated *Drosophila* Retinal Photoreceptor Rhabdomeres: Activation by Light and Lipids. *J Neurophysiol.* 2009; 101: 2372–2379.
  20. Stephan F. Primary processes in sensory cells: current advances. *J Comp Physiol A Neuroethol Sens Neural Behav Physiol.* 2009; 195(1): 1–19.
  21. Simona C, Diana O, Manuela P *et al.* Expression of AmphiNaC, a new member of the amiloride-sensitive sodium channel related to degenerins and epithelial sodium channels in amphioxus. *Int J Biol Sci.* 2006; 2(2): 79–86.
  22. Eric L. Acid-sensing Ion Channels in Sensory Perception. *J. Biol. Chem.* 2007; 282(24): 17325–17329.
  23. Stephan K and Laurent S. Epithelial Sodium Channel/Degenerin Family of Ion Channels: A Variety of Functions for a Shared Structure. *Physiol. Rev.* 2002; 82(3): 735–767.
  24. Skatchkov SN, Eaton MJ, Shuba YM *et al.* Tandem-pore domain potassium channels are functionally expressed in retinal (Müller) glial cells. *Glia* 2005; 53(3): 266–276.
  25. Reyes R, Lauritzen I, Lesage F *et al.* Immunolocalization of the arachidonic acid and mechanosensitive baseline traak potassium channel in the nervous system. *Neuroscience*, 2000; 95: 893–901.
  26. Juana G, Carmen AM, and Carlos B. Activation of Scleral Cold Thermoreceptors by Temperature and Blood Flow Changes. *Invest Ophth Vis Sci* 2003; 44(2): 697–705.
  27. Iovchev M, Boutanaev A, Ivanov I *et al.* Phylogenetic shadowing of a histamine-gated chloride channel involved in insect vision, *Insect Biochem Mol Biol.* Jan 2006; 36(1): 10–7.
  28. Hong ST, Bang S, Paik D *et al.* Histamine and its receptors modulate temperature preference behaviors in *Drosophila*. *J Neurosci* 2006; 26(27): 7245–7256.
  29. Situ P, Simpson TL, Fonn D. Eccentric variation of corneal sensitivity to pneumatic stimulation at different temperatures and with CO<sub>2</sub>. *Exp Eye Res* 2007; 85: 400–405.
  30. Fengfu L, David C, Chris L *et al.* Cellular and nerve regeneration within a biosynthetic extracellular matrix for corneal transplantation. *PNAS* 2003; 100(26): 15346–51.
  31. Carlos B, Carmen AM and Juana G. Neural basis of sensation in intact and injured corneas. *Exp Eye Res* 2004; 78: 513–525.
  32. Donaldson IM. The functions of the proprioceptors of the eye muscles. *Philos Trans R Soc Lond B Biol Sci.* 2000; 355(1404): 1685–1754.
  33. Weir C, Knox P, and Dutton G. Does extraocular muscle proprioception influence oculomotor control? *Br J Ophthalmol.* 2000; 84(9): 1071–1074.
  34. Leonard H, Malcolm B, Peter, JC *et al.* Sensory Capacity of the Royal College of Surgeons Rat. *Invest Ophthalmol Vis Sci.* 2000; 41: 3979–3983.
  35. Lewis RF, Zee DS, Gaymard BM *et al.* Extraocular muscle proprioception functions in the control of ocular alignment and eye movement conjugacy *J Neurophysiol* 1994; 72(2): 1028–1031.
  36. Jianliang T Scott, BS, Harold EB. Signals of eye-muscle proprioception modulate perceived motion smear. *J Vision* 2008; 8(14): 1–6.
  37. Sung EP, Ho SS, Sei YO. Innervated Myotendinous Cylinders Alterations in Human Extraocular Muscles in Patients With Strabismus. *Korean J Ophthalmol.* 2009; 23(2): 93–99.
  38. Daniela B, Jonathan C and Miall RC. Proprioception Contributes to the Sense of Agency during Visual Observation of Hand Movements: Evidence from Temporal Judgments of Action. *J Cognitive Neurosci* 2007; 19(9): 1535–1541.
  39. Fortuna F, Barboni P, Liguori R *et al.* Visual system involvement in patients with Friedreich's ataxia. *Brain* 2009; 132(1): 116–23.
  40. Fahey MC, Cremer PD, Aw ST *et al.* Vestibular, saccadic and fixation abnormalities in genetically confirmed Friedreich ataxia. *Brain* 2008; 131(4): 1035–45.
  41. Subhash CB. Neuroscience for the Study of Communicative Disorders, Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia 2008.
  42. Ernst MO, Banks MS and Bulthoff HH. Touch can change visual slant perception. *Nat Neurosci* 2000; 3: 69–73.
  43. Keiko O, Norimichi K, Yuji W. Haptics can modulate the Hering and Wundt illusions. *Jpn Psychol Res* 2007; 49(1): 79–85.
  44. Lackner JR and Zakbar J. Proprioceptive information about target location suppresses autokinesis. *Vision Res.* 1977; 17: 1225.
  45. Lackner JR and Evanoff JN. Some proprioceptive influences on the spatial displacement component of the oculogyral illusion. *Percept Psychophys* 1988; 43: 526.
  46. Harriet AA and Glyn WH. Direct Tactile Stimulation of dorsal Occipito-Temporal Cortex in a Visual Agnostic. *Curr Biol* 2009; 19: 1–6.
  47. Emiliano M, Chris DF, Jon D. Modulation of Human Visual Cortex by Cross-modal Spatial Attention. *Science* 2000; 289(5482): 1206–1208.
  48. Michael SB, Nafi EY, Neel K *et al.* Human MST But Not MT Responds to Tactile Stimulation. *J Neurosci* 2007; 27(31): 8261–8267.
  49. Blake R, Sobel KV, James TW. Neural synergy between kinetic vision and touch. *Psychol Sci.* 2004; 15(6): 397–402.
  50. Adolphs, R. Neural systems for recognizing emotion. *Curr Opin Neurobiol.* 2002; 12(2): 169–77.
  51. Ralph A, Hanna D, Daniel T *et al.* A Role for Somatosensory Cortices in the Visual Recognition of Emotion as revealed by three-dimensional lesion mapping. *J Neurosci* 2000; 20(7): 2683–2690.
  52. Ralph A. Neural systems for recognizing emotion. *Curr Opin Neurobiol* 2002; 12(2): 169–177.
  53. Tsurudome K, Li X, Matsumoto N. Intracellular and current source density analyses of somatosensory input to the optic tectum of the frog. *Brain Res.* 2005; 1064(1–2): 32–41.
  54. Fix JD, Neuroanatomy, Harwal Publishing, Philadelphia (1992).
  55. Møller AR, Neural plasticity and disorders of the nervous system, Cambridge University Press, Cambridge 2006.
  56. Kazuhide I. P2 receptors and chronic pain. *Purinerg Signal* 2007; 3: 135–144.
  57. Boris AC and Peter Illes. P2X Receptors and Nociception. *Pharmacol Rev* 2001; 53(4): 553–568.
  58. Burnstock G. P2X receptors in sensory neurons. *Brit J Anaesth* 2000; 84(4): 476–488.
  59. Uwe B, Elke G, Claudia I *et al.* Gene expression of the P2X receptors in the rat retina. *Molecular Brain Research* 1998; 59(2): 269–272.
  60. Uwe B, Konrad K and Thomas HWS. Expression of the P2X<sub>2</sub>-receptor subunit in neurons of the rat retina. *Mol Brain Res* 1998; 62(1): 106–109.
  61. Taschenberger H, Jüttner R and Grantyn R. Ca<sup>2+</sup>-Permeable P2X Receptor

- Channels in Cultured Rat Retinal Ganglion Cells. *J Neurosci* 1999; 19(9): 3353–3366.
62. Thomas HW, Katja Marquardt, Konrad Kohler *et al.* Identification of purinergic receptors in retinal ganglion cells. *Mol Brain Res* 2001; 92(1-2): 177–180.
63. Xinran L, Igor PU, Stephen DMB *et al.* Myosin VIIa participates in opsin transport through the photoreceptor cilium. *J Neurosci* 1999; 19(15): 6267–74.
64. Gibbs D, Azarian SM, Lillo C *et al.* Role of myosin VIIa and Rab27a in the motility and localization of RPE melanosomes. *J Cell Sci* 2004; 117: 6473–6483.
65. Ulrich M. Cadherins and mechanotransduction by hair cells. *Curr Opin Cell Biol* 2008; 20(5): 557–566.
66. Charles TA, Alesha BC, Samantha AB *et al.* Primary Cilia: Cellular Sensors for the Skeleton. *Anat Rec* 2008; 291: 1074–78.
67. James RD and Bradley KY. An incredible decade for the primary cilium: a look at a once-forgotten organelle. *Am J Physiol Renal Physiol* 2005; 289: F1159–F1169.
68. Sergei S and Andriy A. Mechanosensitive channels: what can we learn from ‘simple’ model systems? *Trends Neurosci* 2004; 27(6): 345–351.
69. Garcia-Alonso LA. Postembryonic sensory axon guidance in *Drosophila*. *Cell Mol Life Sci.* 1999; 55(11): 1386–1398.
70. Tao Wang and Criag M. Phototransduction and retinal degeneration in *Drosophila*, *Eur J Physio* 2007; 454(5): 821–847.
71. Bahar S, Alexander N Lon AW *et al.* Phase synchronization and stochastic resonance effects in the crayfish caudal photoreceptor. *Phys. Rev.* 2002; E 65(5): 059011–059014.