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fMRI Analysis of Three Concurrent Processing Pathways

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1. Introduction

Biomarkers are useful measurements to monitor ranges of neurological and biochemical activity. They can be used as warning signs of poor adaptation to changes in either internal or external environments. The eye is an apt structure to use for obtaining biomarkers, since it interacts with multiple systems. For instance, pupil size and response during visual scanning tasks is being touted as a potential biomarker for autism (Martineau, Hernandez et al., 2011), the osmolarity in human corneal tear layer is thought to possibly be a biomarker for dry eye severity (Suzuki, Massingale et al., 2010) and disruptions in rapid eye movement during sleep is found to correlate with amounts of stress (Mellman, Bustamante et al., 2002).

This chapter proposes a use of functional magnetic resonance imaging (fMRI) to obtain a visual stress biomarker in processing pathways. This hypothesized biomarker would use the eye to indicate the relationship between internal adaptation (influenced by conscious and non-conscious filtering and decision-making networks) and external environmental changes. Section two of the chapter simplifies the big picture of brain function into cortical and subcortical interconnected networks that have three concurrent movement pathways; section three emphasizes the eye and how its complex circuitry connects with systems, including motor, sensory and attentional networks linked with those three pathways. Section four describes a proposed visual stress test that could show a dysfunction in the synchrony among those three pathways, thus detecting disease states even before structural changes occur. Implementation of this proposed test might be useful in assessing levels of brain injury, or in early identification of diseases affecting brain circuitry, such as seizure disorders, Alzheimer's, Parkinson's and multiple sclerosis.

Documentation of brain activity can be achieved by various methods, using both functional and anatomical landmarks, which will help to account for individual patient differences. For example, some methods quantify neuronal firing (via electrophysiological tools), others measure oxygen levels in blood (via hemodynamic responses) and still others assess metabolic changes (via optogenetic methods). (Optogenetic methods use genetically engineered proteins to regulate activity of specific types of cells by turning neural circuits on and off through light-activated channels. This new method observes and assesses local networks within the framework of global circuitry.) Often, two or more testing methods are used together to account for limitations in each (Dale and Sereno, 1993). For instance, fMRI maps *where* local neuronal activity is by measuring the hemodynamics of blood flow, and electroencephalograms (EEG) map *when* electrical activity occurs by measuring frequency oscillations of brainwaves. The fMRI and EEG together have high spatial resolution and temporal resolutions respectively, providing more information than either method alone. Combining optogenetics with fMRI technology into an optogenetic fMRI (ofMRI) allows scientists to assess both neuronal activity and its metabolic sequellae, helping to identify, and in some cases treat, underlying disease states (Lee, Durand et al., 2010; Zhang, Gradinaru et al., 2010; Cardin, Carlen et al., 2010).

Although the fMRI is a wonderful diagnostic tool, one limitation is the restriction on patient movement. To address this apparently unchangeable drawback, instead of the patient moving, the external environment can be altered and the patient's adaptation measured. The alterations can be done through the eye by stimulating the retina with lenses, prisms, filters and/or mirrors.

2. Survival functions to executive functions: Brain circuitry

Brain activation involves stimulation, modulation, feedback and feedforward mechanisms in two main groupings: subcortical functions and cortical processing. Each grouping is known to have multiple interconnections, with more pathways being discovered annually. These extensive feedforward and feedback systems allow for interconnectivity of individual structures as well as linkages between movements and thoughts.

Brain activity can be viewed in terms of arousal of, awareness of and attention to both the internal and the external environment. Subcortical activity, such as survival functions (circulation, digestion, respiration, etc.), remain beneath conscious awareness until altered by suprathreshold sensory stimuli, causing distracting cortical activity. An individual with a larger threshold of tolerance to sensory changes would not be burdened by those stimuli, thus allowing more efficient brain function.

In 1973, Ralph Luria wrote about functional systems in the brain that were not in isolation. (Luria, 1973) He proposed that the cortical brain was composed of both units and zones, which, when functioning properly, work together to regulate behaviors, senses and thinking. The units included information handling, tone and regulation of mental activity. The zones included a primary, for information gathering, a secondary, for information processing and programming, and a tertiary, for complex forms of integrated mental activity. He hypothesized that sensation and perception were intimately involved with movement, having afferent and efferent components. He also proposed that the eye, as an extension of the brain, is never passive, and is always actively searching to pick out essential clues from the environment. Now, almost forty years after Luria's theory was first presented, functional organization and anatomical connectivity of regions in the cerebral cortex have been documented through neuroimaging and other techniques.

In the brain, structures are grouped to accomplish specific types of tasks. For instance, in general movement networking, many interacting pathways are involved with the frontal cortices, basal ganglia and cerebellum as the "main players." The frontal cortices plan and organize movement, generating motor programs (with the prefrontal and the premotor regions contributing to different functions), the basal ganglia govern movement intention programs, and the cerebellum is involved in the coordinated adjustment (smoothing out) of movement quality. The prefrontal cortex sends voluntary commands to the basal ganglia so that appropriate movement is selected, and other cortical association areas send the basal ganglia information for acquired (automatized) movement. Sensory signals from cortical processing are sent to the matrix of the basal ganglia, while the striosomal portion of the basal ganglia attaches an "emotional valence" to that sensory information for the purpose of learning.

Fine motor tasks such as eye movements add more "players". The brainstem's oculomotor system receives direct projections from the various eyefields located in their own brain network. Frontal eye fields, parietal eye fields, prefrontal eye fields and supplementary eye fields, each have a region involved in either saccadic or smooth eye movements (Lynch and Tian, 2006; Cui, Yan et al., 2003). Neuroanatomical studies in non-human primates determined that there are several distinct regions in the cerebral cortex (designated eye fields) forming a cortico-cortical network guiding and executing decisions for voluntary, visually guided saccadic and pursuit eye movements. Some of the subcortical structures used in eye movement, for example, involve the superior colliculus and the frontal eye fields integrating information received by the geniculate-striate pathway and contributing to more thinking and movement decisions (Ding and Gold, 2011).

Anatomical patterns of new movements, from initial learning to automation, shift over time as the movement is practiced and developed. The retention of movement schema (praxicons) is in parietal/temporal-parietal circuits and connects with the cerebellum which refines the praxicons and innervatory programs by comparing predicted movement outcome with error. These comparisons are accomplished by the brain via two types of procedures, described by theoretical control models. Forward models predict movement outcomes by projecting signals to parietal and frontal motor regions, allowing for automation and bypassing direct (slower) sensory input. Inverse cerebellar models are initiated outside of conscious awareness and bypass premotor cortex commands, allowing automatic movements. Speed and precise accuracy of intentionally guided actions and predictions is thus developed (Imamizu and Kawato, 2009).

Movement is not in isolation from thoughts; it is one part of a network of functional circuits, each with its own pathway, synchronizing like an orchestra. Concurrent pathways form loops, including sensory stimuli, processing and motor reactions and responses. The processing can be analytical and intentional, or intuitive and habitual, leading to various brain networks, such as, visuo-spatial processing from the parietal lobe, visually guided action from the premotor cortex and navigation, imagination and planning for the future in the prefrontal cortex. (Kravitz, Saleem et al., 2011) Both the mind (cortical) and body (subcortical) systems have to adapt to continual environmental changes, at either a conscious or non-conscious level of awareness. Also, there is substantial integration between subcortical and cortical structures as well as interrelationships and interactions at micro-circuitry levels.

At any given moment, three movement types (reflex, developed and intentional) are the result of three processing pathways, activated by different amounts of stimulation at different speeds, capturing different amounts of attention. Figure 1 highlights the differences between how these movement types are generated. The distinctions are important to our purposes because of the interrelationships among the three separate pathways. Developed movements include learned-orienting and anticipatory pathways. However, orienting movements can also be reflexive. It is possible that during an fMRI, the three processing pathways can be analyzed to assess which one has more of an attentional demand at the expense of the others and determine the location(s) of brain activity occurring.

The following diagram (Figure 1) has much more extensive integration of cortical and subcortical structures than implied by the small arrow, but is a simplification in order to describe the framework of subcortical to cortical shifts in brain activity. All cortical areas have significant inputs and major feedforward and feedback connections to numerous subcortical structures. Some functional networks share similar pathways. For instance, auditory and visual reflexive spatial orienting are controlled by a common underlying neural substrate (Santangelo, Olivetti Belardinelli et al., 2007) and there are subspecialized areas, such as the middle temporal lobe (MT) which, in congenitally blind people, reacts to tactile motion, but in sighted people, reacts to either visual or tactile motion. (Sani, Ricciardi et al., 2010).

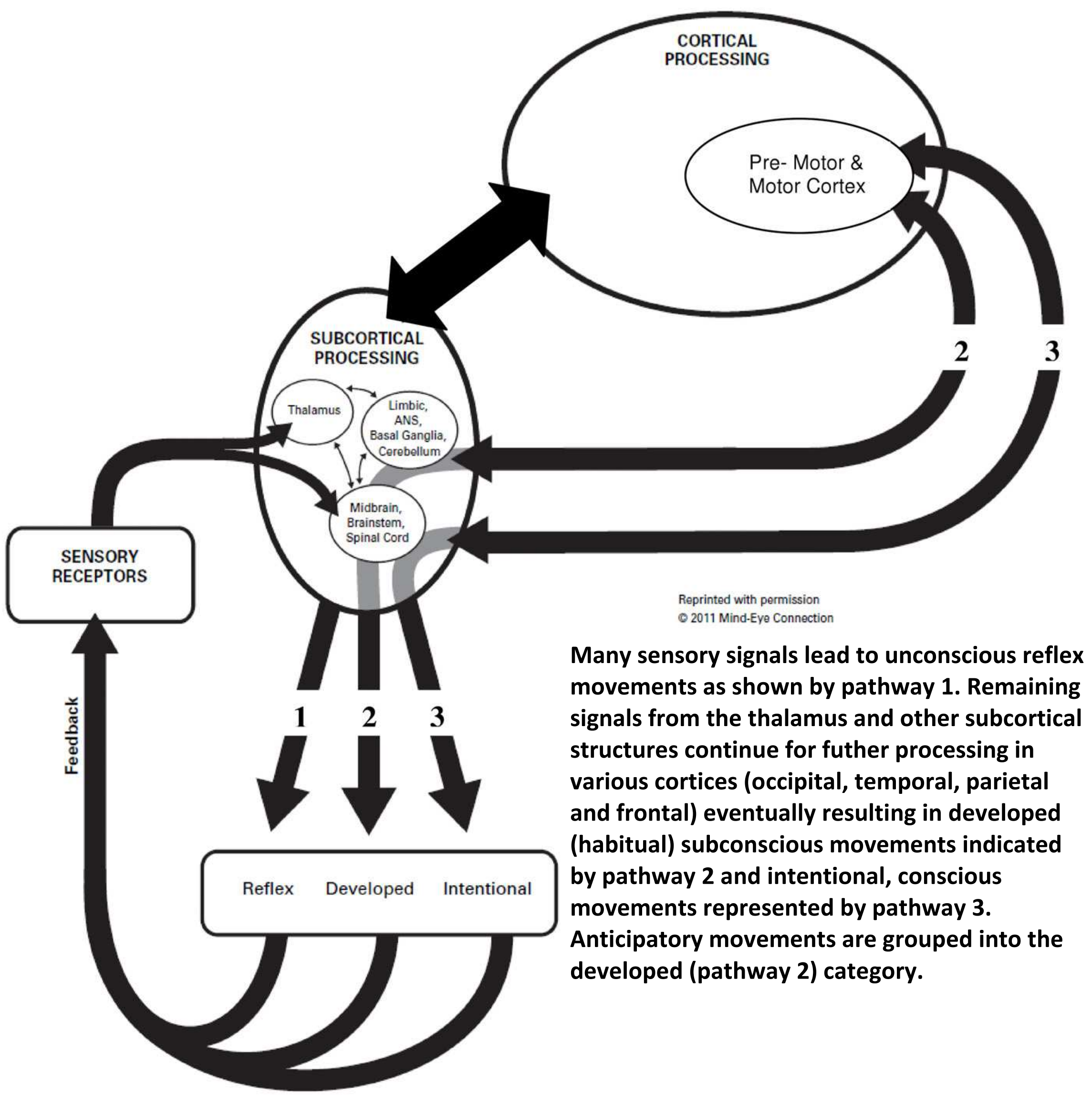

Fig. 1. Simplified Diagram of Three Concurrent Movement Pathways

Whether the paradigm used is anatomical, physiological, psychological, neurological, etc, there is only one brain with parallel systems in action. Below are some ways to view brain activity. Each is a continuum, with a constant two-way exchange of information.

Stimulus Location	Internal External
Processing Mode	Ambient Where Am I* Ambient Where is It?* Focal What is It*
Physiological Pathways	Magnocellular* Koniocellular* Parvocellular*
Anatomical Categories	Subcortical Cortical
Functional Networks	Survival Functions Executive Functions
Psychological Activity	Non-conscious Conscious
Perceptual Activity	Arousal Awareness Attention Intention
Brainwave Type	delta theta alpha beta gamma

Table 1. Simplified continuums in brain function analysis (*discussed in section 3)

Visual, auditory and somatosensory signals are transmitted partly through the thalamus and partly other subcortical regions. From the thalamus, auditory signals travel to the temporal lobe, and visual signals to the occipital lobe, later combining with proprioceptive and somatosensory information from the body in the parietal lobe for higher cortical processing (Williams, 2010).

The integration of somatosensory, auditory and visual inputs is one aspect of determining “Where am I?”. There are also cognitive systems operating to assist in spatial orientation (Arthur, Philbeck et al., 2009). However when using MRI machines to assess brain activity and functional circuitry in thinking and movement pathways, body movement cannot be used because it is restricted. Similarly, auditory testing is difficult to use, because there is ambient noise. Therefore, the obvious choice would be the eye -- easily accessible and directly connected to the brain. It must be noted that recent studies suggest an effect upon the subject’s vestibular system produced by the fMRI magnetic field (Roberts, Marcelli et al. 2011), which could possibly influence eye movement findings. However, the effect was noted during a resting state when the visual system was not provided any meaningful drive.

3. The mind-eye connection: Functional networks

Although eye movement is commonly assessed by fMRI, the complete depth of possibilities has not fully been explored. As has been shown above, the eye is much more than a visual sensory organ; it provides the entrance to a two-way street into the body and the mind. In this chapter, for the sake of simplicity, only three subsystems -- motor, sensory and attention -- will be addressed, while remaining aware that they are part of a much bigger, more complex cortical/subcortical loop with multiple feedback and feedforward channels in a continually adapting dynamic system of metabolic and neurological functional networks.

When the classically understood visual pathway from the eye to the visual cortex is engaged in a conscious activity (i.e. seeing), reflexive and responsive networks are also in use. For instance, the reading process comprises not only the cortical visual activity of seeing (letters on the page), but also a concurrent process creating the foundation for visualization and interpretation. In addition, the mind is on the alert for external and internal sensory signals which may shift mental attention. If a person is reading and a loud noise occurs, attention will tend to shift as many events take place. The head reflexively turns toward the perceived sound location, postural mechanisms maintain balance and respiration, digestion and circulation systems are momentarily disrupted, to name a few. All in all, if processing is disrupted, attention is often hindered.

There are numerous factors affecting visual processing such as internal health, attention, spatial awareness, emotional state, etc., each affecting the functional networking of reflexive, intuitive (developed) and analytical (intentional) processing pathways. If there is a problem in one or more functional networks, the issue could be due to structural damage or inefficient synchronization of systems. For instance, fMRI connectivity analysis demonstrates that auditory and visual cortices are linked; altering one affects the other (Eckert, Kamdar et al. 2008) . Recent studies propose that sensory systems might be able to be used to regulate timing of brainwaves (Hughes, 2008), implying that visual interventions could alter brain circuitry. fMRI testing revealed that in a resting state, activation in specific cortical networks differs between patients with Alzheimer's disease and healthy people. This distinguishing factor of decreased metabolism in certain brain structures can be a potential biomarker for Alzheimer's disease. (Greicius, Srivastava et al. 2004)

Each individual has a unique filtering process that includes simultaneous and sequential processing before decisions are made as to motor output. The mind continually filters external and internal stimuli, choosing how to respond, with a complex series of conscious and non-conscious thoughts and emotions, many of which affect brain networks connected with the eye. (Reactions, on the other hand, are more automatic, occurring without those "decision-making" processes). As will be shown, each of these decisions, reactions and responses can be thought of in terms of "clues, cues and cruise control" and related to the three processing pathways. Consciously used clues lead to intentional movements, inferences of cues accessed beneath conscious awareness lead to habitual responses, and automatic reflex systems on "Cruise Control" lead to reflex movements that function unconsciously.

(This is not a new concept. Dr. A.M Skeffington, the founding father of neuro-optometry, understood that patients' use of visual systems was not a simple, mechanical matter of seeing but instead was a patient's internal engagement with the external environment and desire to explore a spatial world around them. This was extremely evident to him by changes in the retinal reflex during optometric retinoscopy. Decades later, it was demonstrated that conscious perception of the external world activated fast brainwaves, different from the brain activity exhibited when perception of the external surroundings was not high attentional priority (Hughes, 2008).)

Subsections, 3.1, 3.2 and 3.3. describe those processing channels in terms of 1) movements, including eye movements, 2) sensory signal processing, including retinal signals, and 3) attentional factors, modulated by external and internal elements.

3.1 Movement networks: Reactions and responses

There are many measureable motor outputs from the eye, including pupillary reactions, ciliary body activity, eyelid and extraocular muscles (EOM) movement. The intraocular (pupil and ciliary body) and extraocular muscles each use different circuitry (Muri, Iba-

Zizen et al., 1996), often combining with feedback from eye muscle position (proprioceptors) in the eye and neck muscles. Because the purpose is to discuss intentional, habitual (developed) and reflexive movement pathways, this chapter is limited to the related extraocular muscles which can be moved reflexively, habitually (from developed skills) or intentionally. The eyelid will not be included because it is innervated by both smooth and skeletal muscles, and is therefore controlled by different functional networks.

Although the eyes can be moved voluntarily, most eye movements are reflexive (Weir, 2006).

Figure 2 shows reflexive reactions of extraocular muscles include the following, which share many of the same neuronal pathways:

- Vestibulo-Ocular Reflex (VOR) moves the eyes to counteract head movement, allowing the eyes to maintain fixation – a function critical for stabilizing the eyes while the head is moving.
- Optokinetic Nystagmus Reflex (OKN) pathways help eye stabilization during an involuntary fixation of moving objects (Swenson, 2006).
- Reflexive Saccadic eye movements – when the superior colliculus sends signals reflexively pointing the eyes to stimuli of interest, such as flashes of light or loud noises. The superior colliculus contains a spatial mapping of the external environment and receives visual, auditory and somatic sensation from many locations, including the spinal cord, the cerebral cortex and basal ganglia.

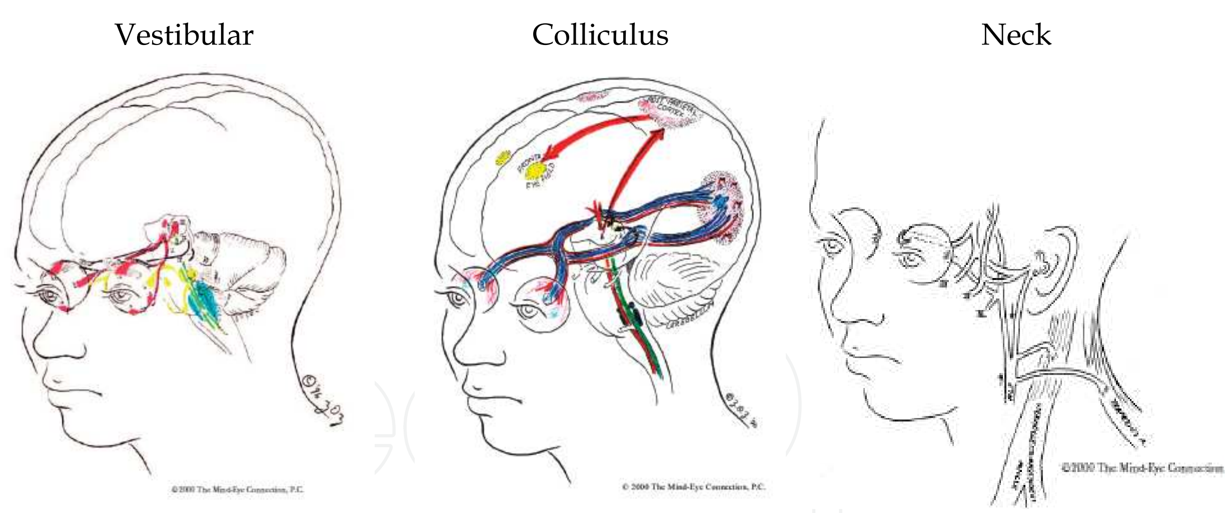

Fig. 2. Reflex pathways of eye movements

Cortical responses of extraocular muscles based on sensory input and attention:

- Non-reflexive saccadic eye movements
- Vergence eye movements – convergence and divergence, aiming the eyes toward a target on the z-axis.
- Smooth Pursuit eye movements – require the eyes to be fixated on a moving external target.
- Fixation eye movements – maintain target in line of central eyesight.

3.2 Sensory networks: Central and peripheral retinal signals

Other neurological sensory input in the visual system includes proprioceptors from the EOM. There are also chemical pathways in the eye that have feedback and feedforward input, such as the consistency of corneal tear layer which varies as the nervous system is stressed, and the chemical gradients in the optic nerve which vary with retinal activity.

The retina itself functions constantly, extraordinarily busy with metabolic and neurological activity, even during sleep. In fact, when eyelids are closed, regardless of the waking state, photic stimulation caused by ambient lighting affects retinal (and brain) processing. Concurrently, there is non-photic stimulation from metabolic activity. Of the multiple sensory networks in the eye, this section will focus on central and peripheral retinal stimulation. (Section 3.1 discussed retinal signals that were transmitted directly through the midbrain's superior colliculus to elicit reflex eye movements. This section emphasizes the retinal signals that synapse at the thalamus' lateral geniculate nucleus (LGN) and continue to the occipital lobe.)

Retinal stimulation occurs in at least three ways: from extrinsic illumination (light or lack of light), from intrinsic chemical changes via circadian rhythms (Tombran-Tink and Barnstable, 2008), or by mechanically induced pressure. The fact that extrinsic illumination stimulates the retina, in easily manipulated ways, will help establish the visual stress biomarker proposed in the beginning of the paper. During an fMRI, the visual stress test determines when the peripheral retinal stimulation reaches its threshold and distracts central retinal attention of details. Central stimulation occurs when the macular region receives light where attention is placed.

Chemically and electrically, there is a monumental amount of internal processing occurring in the retina via the main groups of retinal cells (bipolar, ganglion, horizontal, amacrine, photoreceptor and Mueller), which are subdivided into over a hundred cell types, each performing a different task. This cellular teamwork allows for such functions as luminous efficiency, sensitivities to spectral frequencies and gated signaling channels.

Retinal processing begins at the photoreceptor level when a photon of light is absorbed by the molecule rhodopsin, converting it into an activated state. Subsequently, a cascade of chemical changes occurs in the outer retina, leading to various ion channels opening and closing, eventually eliciting an electrical response in the inner retina, which is monitored by action potentials and calcium regulation pathways. The traveling signals eventually arrive in ganglion cells, continuing through the optic nerve and into the brain (Tombran-Tink and Barnstable, 2008) (See Figure 3).

The superior, inferior, temporal, nasal and macular portions of the retina are developed from completely different sets of chemical pathways and genetic codes, and each of those five geographical sections in the retina is regulated by different transcription factors and develops during different timeframes (DeGrip, Pugh et al., 2000; Tombran-Tink and Barnstable, 2008). This is important, because patterned neuronal activity in the early retina has a substantial influence on the retinotopic organization of the superior colliculus (Mrsic-Flogel, Hofer et al., 2005). Therefore, stimulating selected retinal portions with visual interventions can induce processing changes.

Retinal pathways differ not only in development, but also in function. This has been demonstrated by fMRI testing indicating that nasal and temporal regions vary in melatonin suppression (Ruger, Gordijn et al., 2005). Binasal occlusion on eyeglasses has been used for years to visually treat patients with crossed eyes and brain injuries. Perhaps this occlusion alters the chemical pathways, indirectly affecting neurological circuitry in eye movement control and thus perception of surrounding space (linking motor, sensory and attentional circuitry). Processing also differs between the inferior and superior hemifields of external space (Rubin, Nakayama et al., 1996). For instance, people are generally more attuned to visual information entering from the lower portion of external space (light coming upward stimulating the superior retina) than to light stimulating the inferior retina.

Alteration of retinal stimulation affects both subcortical and cortical processing. Visual processing has been documented in several hundred functional feedback and feedforward brain pathways encompassing almost fifty cortical regions (Klemm, 1996), and fMRI allows for better three dimensional spatial resolution of these pathways. When activated by light, the retina triggers activity at three concurrent levels of processing: analytical (conscious, simultaneous or sequential), intuitive (subconscious) and autonomic (unconscious). Eventually an fMRI database of normal functions can be accumulated so that functional changes during disease processes could be compared to normed data. fMRI usage can thus aid in the differentiation of pathways in concurrent systems during mental activity.

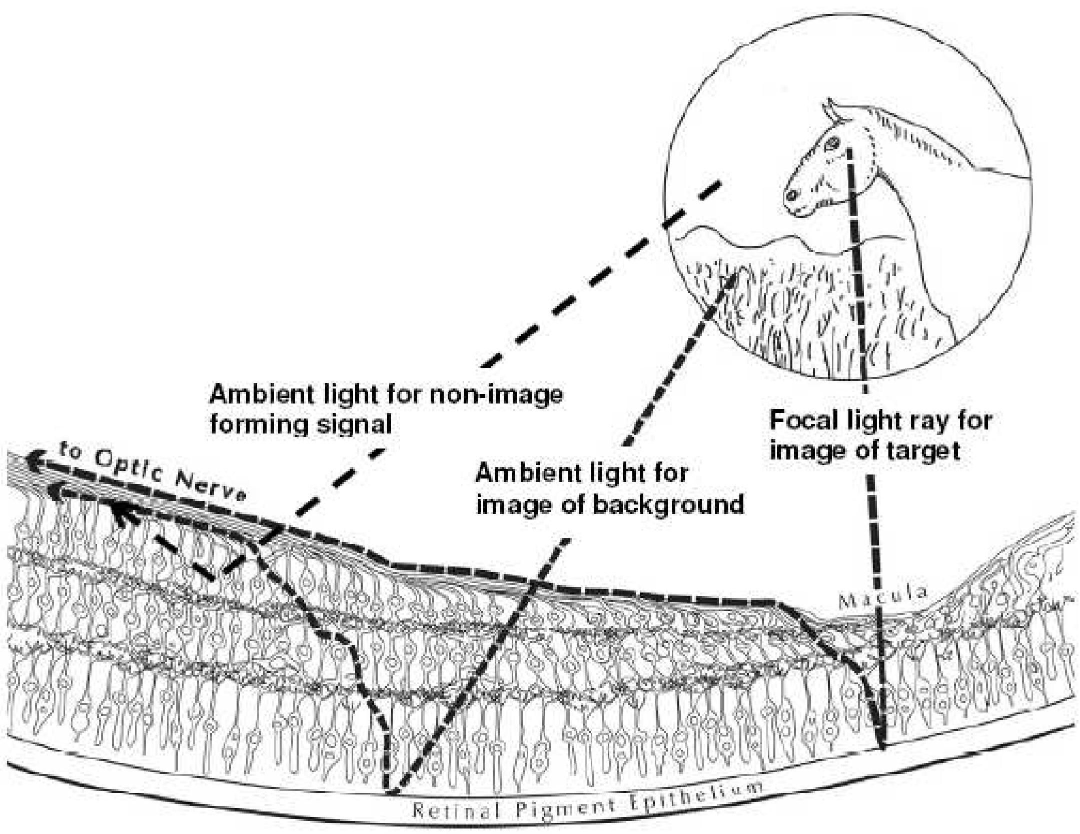

Fig. 3. Central and peripheral light rays striking the retina, exiting the optic nerve. ©2011 Mind-Eye Connection Reprinted with permission. For simplification, the dendrites are drawn in a line, but do vary in length.

3.3 Attentional networks

Retinal stimulation is, of course, only one portion of sensory input to the eye. There are many other sensory signals involved, such as proprioceptor information and signals from corneal receptors. Consider the effect of a small eyelash rubbing against the cornea. During the time when the eyelash is bothersome, reflex tearing occurs, the eyelid reflexively blinks, the extraocular muscles reflexively point the eyes away from the pain, the auditory system's awareness of the surroundings constricts, the pupils change size, etc. If the person wishes to continue to see, he must apply conscious effort. In a stressed condition or diseased state, the need to apply conscious attention will occur sooner and more frequently than under normal conditions. That painful sensory stimulus creates an attentional demand, diverting attention away from the external environment and eyesight. The sensory system and motor systems are not simply mechanical; they are inextricably linked with and influenced by attentional networks.

This process of sensory input via light striking the retina does not take place in a vacuum. Other events may influence the individual's perception, including which details are selectively filtered out from the available information at a given time. The level of awareness an individual is able to experience is dependent not only on the proper functioning of the retina and other structures of the eye, but also on the availability of the mind's attentional networks – neurological and chemical. This fact offers insight into patient function and dysfunction and also presents many possibilities for designing tests to define the normal parameters of conscious attention versus reflexive and habitual activity.

In 1911, an article commented on how retinal reflexes changed depending on attention factors and the angle of the light (Wilson, 1911). A hundred years later, in 2011, a more analytical research project demonstrated the validity of that concept in migraine sufferers (Huang, Zong et al., 2011).

In the 1930's, Dr. A.M. Skeffington, described "vision" as an emergent concept from four intertwining circles (Where am I? Where is it? What is it? and Speech/Auditory). The "Where am I?" relies mainly on subcortical processing, the "Where is it?" "What is it" and "Speech/Auditory" rely mainly on cortical processing. Dr. Skeffington spent years promoting his thoughts that the eye was part of the body, controlled by the brain, and that changing information which entered the eye would affect the entire body (Skeffington, 1957). This pioneering optometrist believed that sensory systems should be evaluated in total rather than in isolation. For instance, he believed that eye aiming and focusing be evaluated together as a team, termed a visual reflex, rather than separately as convergence and accommodation, since they are not separate. One responsibility of optometrists whose work emphasizes neuro-optometry is to measure the function or dysfunction of retinal circuitry. fMRI research demonstrates (decades after Dr. Skeffington's proposals) that the eyes do affect brain and body circuitry. (There is also interplay between an individual's genetic predisposition and their unique experiences, regulating brain circuitry.)

The sensory inputs of both eyes have magnocellular, koniocellular and parvocellular portions, arising from peripheral and central retinal stimulation. The magnocelluar portion is further divided into two smaller parts: non-conscious reflex and developed pathways. Testing the mental shift in attention from ambient processing (magnocellular pathways) to focal processing (parvocellular pathway) is important in differentiating movement pathways.

Magnocellular (M) system provides answers to “Where am I?” and “Where is It?” at a reflexive and a cortical level respectively, beneath conscious awareness, and the parvocellular (P) system answers the meaningful question of “What is It?” at the cortical level.

The fastest retinal signal pathway is the reflexive “Where am I?” portion of the magnocellular (M) pathway involving retinal signals that are processed subcortically. Of the retinal signals continuing through the optic radiations before arriving at the occipital cortex, some originate from macular stimulation (carrying information regarding color and detail) and others from peripheral retinal activation (carrying information regarding such factors as speed, location, size and shape). When entering the occipital lobe’s striate cortex, the information is *spatially* based (externally controlled), with a point to point spatial representation of the external world mapped with pinpoint precision. However, upon exiting the occipital lobe, information is *attentionally* based (internally controlled), with the dorsal stream going on to the parietal lobe (carrying “Where is It?” signals of background information) and the ventral stream continuing to the temporal lobe (carrying “What is It?” signals of target information). Signals from the dorsal and ventral streams integrate, eventually arriving in the frontal lobe. From there, signals are transmitted to cranial nerves III, IV and VI which send signals to the extraocular muscles, resulting in eye movement.

In 2011, it was determined that a Koniocelluar (K) pathway activity might be gating the cortical circuits fed by the M and P pathways and hypothesized that the sensory streams can be adjusted to modify brain rhythms via parallel visual pathways (Cheong, Tailby et al., 2011). Also, each of the two cortical visual streams also have connections with subcortical nuclei (Webster, Bachevalier et al., 1995). These studies seem to provide validity to the concept of a visual stress biomarker.

In addition to the “Where am I?” (subcortical processing), “Where is It?” (dorsal stream) and “What is It?” (ventral stream), hypotheses for When and Why pathways emerged in 2003 (Krekelberg, 2003). In 2011, a study found a “When” pathway and demonstrated its connections between the visual cortex and the temporal lobe (Naya and Suzuki, 2011).

Sensory stimuli are filtered during processing, and decisions are made by the mind based on arousal, attention, awareness, emotions and memories. Conscious attention and awareness are often directed to different volumes of surrounding space which can be expanded or constricted depending on other internal and external signals, including general health and fatigue. Intra-cortical connections are responsible for routing information selectively to progressively higher and higher levels of processing. There is top-down processing from memory circuitry and bottom-up processing from retinal input, with the control of visual attention thought to be found in the pulvinar (the back section of the thalamus) (Olshausen, Anderson et al. 1993). The thalamus is also responsible for mediating the interaction between attention and arousal during perceptual and cognitive tasks (Portas, Rees et al., 1998; Saalmann and Kastner 2009, 2011). Dr. Selwyn Super, an optometrist whose work emphasizes neuro-optometry, discusses intention as a top-down executive function with feedforward and anticipatory circuitry and attention with both top-down and bottom-up connections, competing with each other. In the case of patients with attentional neglect, where internal awareness of surrounding space or of their body is not normal, some are deemed sensory-attentional, others motor-intentional and still others as having representational deficits (Super, 2005).

It is clear that controlled, subtle continual change in retinal stimulation will eventually cause shifts in attentional demands and brain activity as signals trigger shifts from arousal to awareness to attention. This type of controlled change can be produced by optometric methods.

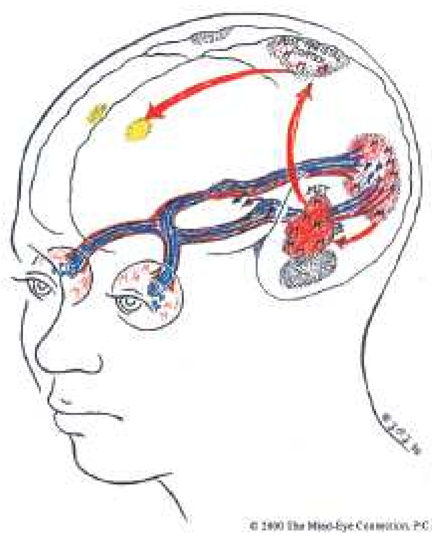

Fig. 4. Magnocellular "Where is It?" pathway signals traveling in middle temporal (MT) and medial superior temporal (MST) lobes.

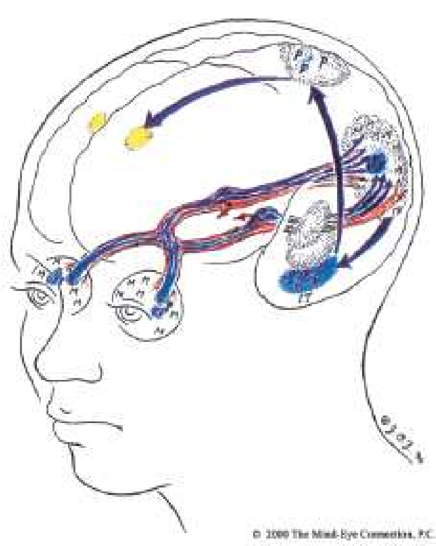

Fig. 5. Parvocellular "What is It?" pathway Signals traveling through the inferior temporal (IT) lobes.

4. Optometric changes to functional networks

Optometric tools, such as prisms, break light into frequencies and spatially distribute the light onto the retina. Each tool stimulates different areas of the retina, and as the eye moves, the optic flow sent to the brain is altered. By relying on the point to point brain mapping from the retina to the visual cortex, and the non-visual pathways from the retina to other brain circuitry, visual intervention could affect fMRI findings.

The visual changes could be accomplished by using combinations of lenses, prisms and filters (including occlusion) to alter entering light. The amount and direction of light input can be a controlled variable, and the patient's reactions to changing environmental stimuli can be measured to determine how well, and in what areas, the subcortical and cortical networks are interacting as well as its tipping point. Circuitry and pathways used for information processing can be identified and modified.

The visual spectrum has more to offer than eyesight alone. For instance, prisms and mirrors together are being developed to render objects invisible to the human eye (Zhang, Luo et al., 2011), and mirrors are being used in rehabilitations in patients with neglect from brain trauma (Ramachandran and Altschuler, 2009).

Intentional eye movements and retinal stimulation are often used to induce changes in brain activity during fMRI testing. Equally as valuable, is an assessment of a patient's adaptation to environmental change. Disruption of mechanisms can lead to disease. If there is significant variation from a normal database, eye movements can be used during fMRIs to detect deviations in information processing, perhaps identifying disease states before structural breakdowns occur.

Visual interventions can be in many forms, each stimulating the retina in a different way.

- Lenses – dispersing light toward the edges or the center of the retina. This change in light mainly alters the balance between central and peripheral circuitry by having the target and background occupy different percentages of the retinal input.
- Yoked Prisms – angling light toward one edge of the retina. This initially affects the body's positional sense, because reflexive eye movements will point the eyes toward the incoming light, triggering internal postural mechanisms in the hips for stability of balance, to counteract the eye movement. Depending on the stability of the person's sense of balance, attention may be then shifted to external targets.
- Non-yoked prisms – angling light toward either nasal or temporal retinal sensors. The eyes will also reflexively point toward the light, but this inward and outward movement stimulates different visual and postural mechanisms (shoulders rather than hips), pulling attention to the object location.
- Filters – altering either spatial or temporal retinal input, thus affecting processing.
- Tints - filtering out specific wavelengths of light, stimulating specific retinal cells, primarily altering internal sensations, via the autonomic nervous system.
- Mirrors – make targets appear farther away than the mirror frame, creating a sensory mismatch between the central (target) and peripheral (background).

Table 2. Optometric tools for non-invasive visual interventions

Movements, sensory inputs and attention can be considered within a broader framework of sensory integration. For instance, just because a person can hear and see does not mean he can simultaneously watch and listen to a moving target such as a teacher in a classroom. Using visual stress tolerated, as a biomarker for normal brain adjustments, will demonstrate adaptation ability (as long as the patient's individual tolerance level and overall physical and mental state is considered).

Eye stimulation can be used for both diagnostic and therapeutic purposes. When a person doesn't appropriately adapt to environmental changes, this proposed biomarker will be outside of a normal range. For instance, adaptation to specific spatial shifts in prisms led researchers to the conclusion that prism adaptation was processed in motor parts of the brain relating to action timing. Patients adapted to the prisms' spatial displacement independent of awareness of subjective timing (Tanaka, Homma et al., 2011).

5. Conclusion: A biomarker for usage of clues, cues and cruise control

The exploration of brain activity following changes in retinal inputs is fundamental for a better understanding of the basic principles governing large-scale neuronal dynamics. The hypo- and hypersensitivity of the retina, even through a closed eyelid, suggest a neurological basis for the diagnostic and therapeutic effect of lenses to consciously and non-consciously alter incoming sensory signals and influence brain processing.

Current functional magnetic resonance imaging vision research tends to focus on perception, or on eyesight and damage in eye structures, such as optic neuritis and macular degeneration. However, the eye offers much more. Its interactions and relationships within, between and among motor, sensory and attentional networks (as well as emotional and cognitive systems) can be documented by controlling external environmental changes and measuring internal adaptation, thus differentiating among the three concurrent processing pathways and movement outputs.

Assessment of the three different levels of eye movement and adaptation to change is important for diagnosis of systems' instability or dysfunction, with the ultimate goal to measure shifts in attention and compare to a normed database. Thoughts and movements are integrated via:

- Consciously used **clues**, leading to intentional **movements**
- Inferences of **cues** accessed beneath conscious awareness, leading to developed or habitual actions
- Automatic reflex systems on "**Cruise Control**" leading to movements that function unconsciously

Thus, visual systems involve not solely what the eyes see, but the integration of neural pathways. When observed during fMRI, eye motor responses offer insight into brain activity and can be helpful to further categorize and appropriately treat the increasing incidence of degenerative and other conditions. Specifically, a visual stress test can influence brain circuitry via alterations of retinal input during an fMRI procedure (using lenses, prisms, mirrors and/or filters) and can have the potential for revealing dysfunction in such pathways as information processing, attention, movement and other interconnected sensory systems. Imaging techniques are useful ways to demonstrate dysfunctional circuitry, both in grey and white matter, but sometimes the dysfunction has to be stressed before a breakdown can be observed. Clinical applications could include assessments of functional breakdowns in disease states, e.g., seizure disorders, memory deficits and visuo-cognitive abilities in patients with Alzheimer's disease and eye movement control and balance in patients with traumatic brain injuries or Parkinson's disease.

Retinal pathway changes and impairments have been noted in patients with epilepsy, Parkinson's and Alzheimer's along with other diseases (van Baarsen, Porro et al., 2009; Altintaş, Iseri, et al., 2008; Cubo,Tedeio, et al. 2010; Parisi V, 2003). Cortical atrophy in Alzheimer's patients can be seen years before cognitive impairment becomes evident (Dickerson, Stoub et al. 2011), yet cognitive impairment is not always the first symptom of Alzheimers disease (38% of people have vision, behavior or other warning signs (Balasa, Gelpi, et. al. 2011) and that the default network brain activity differs in people with Alzheimer's (Shin J., Kepe, V. et al., 2011). This paper hypothesizes that shifts in cognitive and attentional systems can be observed even earlier, using neuro-optometric interventions during fMRI, in combination with other testing methods, to measure an abnormal functional shift in either default attentional networks or cognitive networks, before the structural atrophy occurs. A defect in functional connectivity would be a valuable biomarker.

Embracing a viewpoint of brain circuitry and metabolism could shift optometry toward a profession of selective neurological and biochemical pathway stimulation. Using the eye as a portal to the nervous system, measurements of internal reactions and responses to external changes can be made, in hopes of providing a useful visual stress biomarker for future disease research and eventual interventions for preventive healthcare.

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7. References

Altintaş O, Işeri P, et al. (2008). "Correlation between retinal morphological and functional findings and clinical severity in Parkinson's disease." Doc Ophthalmol. 2008 Mar;116(2):137-46. Epub 2007 Oct 26.

Arthur, J. C., J. W. Philbeck, et al. (2009). "Non-sensory inputs to angular path integration." *J Vestib Res* 19(3-4): 111-125.

Balasa, M, E. Gelpi, et al. (2011). "Clinical features and APOE genotype of pathologically proven early-onset Alzheimer disease." Neurology May 17, 2011 vol. 76 no. 20 1720-1725

Cardin, J. A., M. Carlen, et al. (2010). "Targeted optogenetic stimulation and recording of neurons in vivo using cell-type-specific expression of Channelrhodopsin-2." *Nat Protoc* 5(2): 247-254.

Cheong, S. K., C. Tailby, et al. (2011). "Slow intrinsic rhythm in the koniocellular visual pathway." *Proc Natl Acad Sci U S A*.

Cubo E, Tedejo RP, et al. (2010). “Retina thickness in Parkinson's disease and essential tremor.” Mov Disord. Oct 30;25(14):2461-2. PMID:20669291

Cui D. M., Yan Y. J., and Lynch, J.C. (2003). Pursuit subregion of the frontal eye field projects to the caudate nucleus in monkeys. *J of Neurophysiol, 89*: 2678-2684.

Dale, A.M., Sereno, M.I. (1993) Improved localization of cortical activity by combining EEG and MEG with MRI cortical surface reconstruction: a linear approach. "*J of Cog. Neuroscience* 5(2): 162-176.

DeGrip, W. J., E. N. Pugh, et al. (2000). *Molecular mechanisms in visual transduction*. Amsterdam ; New York, Elsevier.

Dickerson, B. C., T. R. Stoub, et al. (2011). "Alzheimer-signature MRI biomarker predicts AD dementia in cognitively normal adults." *Neurology* 76(16): 1395-1402.

Ding, L. and J. I. Gold (2011). "Neural Correlates of Perceptual Decision Making before, during, and after Decision Commitment in Monkey Frontal Eye Field." *Cereb Cortex*.

Eckert, M. A., N. V. Kamdar, et al. (2008). "A cross-modal system linking primary auditory and visual cortices: evidence from intrinsic fMRI connectivity analysis." *Hum Brain Mapp* 29(7): 848-857.

Greicius, M. D., G. Srivastava, et al. (2004). "Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI." *Proc Natl Acad Sci U S A* 101(13): 4637-4642.

Huang, J., X. Zong, et al. (2011). "fMRI evidence that precision ophthalmic tints reduce cortical hyperactivation in migraine." *Cephalalgia* 31(8): 925-936.

Hughes, J. R. (2008). "Gamma, fast, and ultrafast waves of the brain: their relationships with epilepsy and behavior." *Epilepsy Behav* 13(1): 25-31.

Imamizu, H. and M. Kawato (2009). "Brain mechanisms for predictive control by switching internal models: implications for higher-order cognitive functions." *Psychol Res* 73(4): 527-544.

Klemm WR. (1996). Understanding neuroscience. St. Louis (MO): Mosby; p.151–52.

Kravitz, D. J., K. S. Saleem, et al. (2011). "A new neural framework for visuospatial processing." *Nat Rev Neurosci* 12(4): 217-230.

Krekelberg, B. (2003). "Sound and vision." *Trends Cogn Sci* 7(7): 277-279.

Lee, J. H., R. Durand, et al. (2010). "Global and local fMRI signals driven by neurons defined optogenetically by type and wiring." *Nature* 465(7299): 788-792.

Luria, A.R. (1973). The working brain: an introduction to neuropsychology. Penguin Books

Lynch, J. C. and J. R. Tian (2006). "Cortico-cortical networks and cortico-subcortical loops for the higher control of eye movements." *Prog Brain Res* 151: 461-501.

Martineau, J., N. Hernandez, et al. (2011). "Can pupil size and pupil responses during visual scanning contribute to the diagnosis of autism spectrum disorder in children?" *J Psychiatr Res* 45(8): 1077-1082.

Mellman, T. A., V. Bustamante, et al. (2002). "REM sleep and the early development of posttraumatic stress disorder." *Am J Psychiatry* 159(10): 1696-1701.

Mrsic-Flogel, T. D., S. B. Hofer, et al. (2005). "Altered map of visual space in the superior colliculus of mice lacking early retinal waves." *J Neurosci* 25(29): 6921-6928.

Muri, R. M., M. T. Iba-Zizen, et al. (1996). "Location of the human posterior eye field with functional magnetic resonance imaging." *J Neurol Neurosurg Psychiatry* 60(4): 445-448.

Naya, Y. and W. A. Suzuki (2011). "Integrating what and when across the primate medial temporal lobe." *Science* 333(6043): 773-776.

Olshausen, B. A., C. H. Anderson, et al. (1993). "A neurobiological model of visual attention and invariant pattern recognition based on dynamic routing of information." *J Neurosci* 13(11): 4700-4719.

Parisi V. (2003). "Correlation between morphological and functional retinal impairment in patients affected by ocular hypertension, glaucoma, demyelinating optic neuritis and Alzheimer's disease." Semin Ophthalmol. Jun;18(2):50-7.

Portas, C. M., G. Rees, et al. (1998). "A specific role for the thalamus in mediating the interaction of attention and arousal in humans." *J Neurosci* 18(21): 8979-8989.

Ramachandran, V. S. and E. L. Altschuler (2009). "The use of visual feedback, in particular mirror visual feedback, in restoring brain function." *Brain* 132(Pt 7): 1693-1710.

Roberts, D.C., V. Marcelli, et al. (2011). "MRI magnetic field stimulates rotational sensors of the brain." Curr Biol 21(19): 1635-1640.

Rubin, N., K. Nakayama, et al. (1996). "Enhanced perception of illusory contours in the lower versus upper visual hemifields." *Science* 271(5249): 651-653.

Ruger, M., M. C. Gordijn, et al. (2005). "Nasal versus temporal illumination of the human retina: effects on core body temperature, melatonin, and circadian phase." *J Biol Rhythms* 20(1): 60-70.

Saalmann, Y. B. and S. Kastner (2009). "Gain control in the visual thalamus during perception and cognition." *Curr Opin Neurobiol* 19(4): 408-414.

Saalmann, Y. B. and S. Kastner (2011). "Cognitive and perceptual functions of the visual thalamus." *Neuron* 71(2): 209-223.

Sani, L., E. Ricciardi, et al. (2010). "Effects of Visual Experience on the Human MT+ Functional Connectivity Networks: An fMRI Study of Motion Perception in Sighted and Congenitally Blind Individuals." *Front Syst Neurosci* 4: 159.

Santangelo, V., M. Olivetti Belardinelli, et al. (2007). "The suppression of reflexive visual and auditory orienting when attention is otherwise engaged." *J Exp Psychol Hum Percept Perform* 33(1): 137-148.

Shin J., Vladimir Kepe, et al. (2011) Multimodal Imaging of Alzheimer Pathophysiology in the Brain's Default Mode Network SAGE-Hindawi Access to Research International Journal of Alzheimer's Disease Volume 2011, Article ID 687945, 8 pages doi:10.4061/2011/687945

Skeffington, A. M. (1957). "The totality of vision." *Am J Optom Arch Am Acad Optom* 34(5): 241-255.

Super, S. (2005). *Intention, attention, inattention & neglect*. Santa Ana, CA, Optometric Extension Program.

Suzuki, M., M. L. Massingale, et al. (2010). "Tear osmolarity as a biomarker for dry eye disease severity." *Invest Ophthalmol Vis Sci* 51(9): 4557-4561.

Swenson, R.S. (2006) Review of functional neuroscience Chapter 8D Eye movements Dartmouth medical school. Accessible at: http://www.dartmouth.edu/~rswenson/NeuroSci/chapter_8D.html

Tanaka, H., K. Homma, et al. (2011). "Physical delay but not subjective delay determines learning rate in prism adaptation." *Exp Brain Res* 208(2): 257-268.

Tombran-Tink, J. and C. J. Barnstable (2008). *Visual transduction and non-visual light perception*. Totowa, N.J., Humana Press.

van Baarsen K.M., Porro G.L., et al. (2009). "Epilepsy surgery provides new insights in retinotopic organization of optic radiations. A systematic review." Curr Opin Ophthalmol. Nov;20(6):490-4.

Webster, M. J., J. Bachevalier, et al. (1995). "Transient subcortical connections of inferior temporal areas TE and TEO in infant macaque monkeys." *J Comp Neurol* 352(2): 213-226.

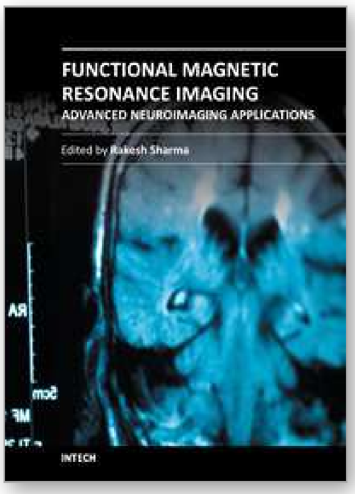
Weir, C.R. (2006). "Proprioception in extraocular muscles." *J Neuroophthalmol* 26(2): 123-127.

Williams, A. L. and A. T. Smith (2010). "Representation of eye position in the human parietal cortex." *J Neurophysiol* 104(4): 2169-2177.

Wilson, J. A. (1911). "Retinoscopy without Atropine, and Some Observations on Ocular Headaches." *Br Med J* 2(2640): 258-259.

Zhang, B., Y. Luo, et al. (2011). "Macroscopic invisibility cloak for visible light." *Phys Rev Lett* 106(3): 033901.

Zhang, F., V. Gradinaru, et al. (2010). "Optogenetic interrogation of neural circuits: technology for probing mammalian brain structures." *Nat Protoc* 5(3): 439-456.



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"Functional Magnetic Resonance Imaging - Advanced Neuroimaging Applications" is a concise book on applied methods of fMRI used in assessment of cognitive functions in brain and neuropsychological evaluation using motor-sensory activities, language, orthographic disabilities in children. The book will serve the purpose of applied neuropsychological evaluation methods in neuropsychological research projects, as well as relatively experienced psychologists and neuroscientists. Chapters are arranged in the order of basic concepts of fMRI and physiological basis of fMRI after event-related stimulus in first two chapters followed by new concepts of fMRI applied in constraint-induced movement therapy; reliability analysis; refractory SMA epilepsy; consciousness states; rule-guided behavioral analysis; orthographic frequency neighbor analysis for phonological activation; and quantitative multimodal spectroscopic fMRI to evaluate different neuropsychological states.