PLASTICITY AND MACULAR DEGENERATION:

THE REORGANIZATION OF ADULT CORTICAL TOPOGRAPHY

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PLASTICITY AND MACULAR DEGENERATION:

THE REORGANIZATION OF ADULT CORTICAL TOPOGRAPHY

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SUMMARY

This study evaluated whether cortical reorganization occurs in response to macular degeneration (MD), a progressive disorder of the retina that results in central vision loss. Past research has observed the ability of V1 to adapt to retinal damage, demonstrating that deafferented cortex is activated by the stimulation of intact retinal areas. It is still unclear, however, if and to what degree cortical reorganization is associated with specific forms of the eye disease macular degeneration (MD). This study evaluated the retinal health of MD participants (both age-related and juvenile) as well age-matched controls with computerized microperimetry. Contrast-reversing stimuli were then presented to different parts of the visual field while participants were scanned with functional magnetic resonance imaging (fMRI). For MD participants, stimulation of peripheral retinal areas elicited activation in deafferented cortex. This activation occurred for retinal areas adapted for eccentric viewing (preferred retinal locations), but not in preserved retina at the same eccentricity. These findings add to the scientific knowledge of plasticity in sensory systems by supporting an input driven understanding cortical of reorganization. They could also have a meaningful impact on how the AMD and other forms of macular degeneration are treated by informing the design of therapeutic training regimes.

CHAPTER 1: INTRODUCTION

Plasticity [. . .] means the possession of a structure weak enough to yield to an influence, but strong enough not to yield all at once. . . Organic matter, especially nervous tissue, seems endowed with a very extraordinary degree of plasticity of this sort; so that we may without hesitation lay down as our first proposition the following, that the phenomena of habit in living beings are due to the plasticity.

-William James, *Principles of Psychology*

The above quote by William James demonstrates a profound insight into what would become one of the most essential elements of psychology: the ability of the nervous system, and by consequence, the organism, to adapt structurally and functionally to an ever changing world. James uses the world "plasticity" to express the flexibility of the nervous system in response to varying environmental conditions. Changes in exogenous input yield changes in nervous tissue. These neural modifications, in turn, affect the organism's experience of the world and, ultimately, its behavior within it.

Contemporaries and successors of James would go on to elaborate on the theory of plasticity in more biological terms. In his *Textura del Sistema Nervioso*, Santiago Ramon y Cajal wrote that behavioral change must be rooted in "the formation of new [neural] pathways through ramification and progressive growth of the dendritic arborization and the nervous terminals" (as cited in Kandel, 2000). This view conceptualizes plasticity as a type of structural modification, a physical property of neurons and their connections.

Later, the mid 20th century, the Polish psychologist, Jerzy Konorski (1948), advanced another version, stating that plasticity is the "permanent functional transformations [that] arise in particular systems of neurons as a result of appropriate stimuli and their combinations". Konorski's understanding is more operative in nature,

emphasizing the selective strengthening of synapses as an agent of plasticity and, consequently, learning. This conception emerged independently in the West in the form the Hebbian synapse (Hebb, 1949).

On a fundamental level, all of these theorists wrote of a marked connection between behavior and the environment, one that is mediated by a malleable and reactive nervous system. The exploration of this relationship between brain, behavior, and environment would go one to be a mainstay of neuroscience and psychology. While the latter two elements have been explored in depth by the first century of psychology, the inclusion of the brain is only now forging beyond the level of structural neuroanatomy, particularly in humans. The advent and development of imaging technologies towards this aim is promising. However, they are still in their infancy.

Undoubtedly there are still theoretical and technical advancements to be made, but perhaps researchers can take confidence in James's logic: If organisms are capable of responding to the environment in a timely and appropriate fashion, there must be some aspect of their biology that adjusts in accordance. Changes in behavior and cognition must be mirrored by changes in the brain. Science is now directing its attention toward these changes in an effort to discover what they are and how they fit into the psychological experience of human beings.

CHAPTER 2: THEORETICAL FOUNDATIONS

2.1 The Concept of Plasticity

The history of research on brain plasticity was originally developmental and neuropsychological in nature. Initial findings in lesioned animals demonstrated that the immature brain is more likely than the fully developed to regain lost motor capacities (Kennard, 1938). Research from the nineteen-sixties through the seventies sought to examine the critical periods and limitations associated with plasticity in humans by exploring the recovery of function after traumatic and acquired (e.g. stroke, meningitis) brain injury. Investigators documented the recovery of cognitive and language abilities after brain injuries suffered at different maturational periods. These studies generally reported that the earlier the age of injury the more likely the recovery of function (for a review see, Stiles, 2000).

Plasticity in the sensory systems has also been a prominent area of investigation. The architecture of the sensory cortices generally develop along a prescribed path, both prenatally and after birth (Swindale, 1996). However, research has demonstrated windows in the development of somatosensory systems that are amenable to plasticity (for review see O'Leary et. al., 1994). Most notably, the work by Hubel, Wiesel and colleagues has demonstrated the existence of critical periods in the maturation of visual pathways that are crucial for development of visual preferences and skills (Bauer & Held, 1973; Hein, Held, & Gower, 1970; Hubel, Wiesel, & LeVay, 1977; Wiesel & Hubel, 1965). For example, lesioning the eye of a cat during such a critical period results the preferential representation of the remaining eye in the visual pathway, a state called ocular dominance (Hubel, Wiesel & LeVay, 1977). Other research has demonstrated

similar windows of plasticity in the development of the somatosensory (Fox, 1992) and the auditory cortices (Illing, 2004).

Most early research has viewed plasticity as a reactive system, one that comes into play when principal connections are perturbed in some way. Under this conceptualization, plasticity was not necessarily viewed as a normal part of cortical functioning. Researchers generally agreed that it served an adaptive function and was more prominent in the juvenile brain (Stiles, 2000). It was understood, however, that adult brains must display some form of "plasticity" in response to sensory experience. After all, adult humans and animals are capable of sensory and motor learning that must reflect a functional neuronal change on some level. However, many theorists believed this type plasticity was located in "higher" perceptual processing areas, not in the primary sensory and motor cortices (Das, 1997).

Recent years have seen more detailed studies on the neurobiological underpinnings of plasticity. However, the range of research scenarios has lead to confusion on how to exactly define the phenomenon. For example, the term "plasticity" has been used to describe changes at the synaptic level induced by environmental conditions (Greenough & Chang, 1989), in the reorganization of somatosensory representations after severing efferent nerves (Merzenich & Jenkins, 1983), and in the topographic relocation of sensory modalities via the rewiring of afferent pathways (Sur, Garraghty, & Roe, 1988).

Moreover, new research is beginning to suggest that plasticity is not just an ancillary property of the juvenile brain but can occur in adults as well. Such studies have observed the reorganization of cortical maps in the visual, auditory, and somatosensory

cortices of adult animals (for a review see Buonomano & Merzenich, 1998). These investigations indicate there may be more to plasticity than originally conceived; that it is not just a reactive process of the immature brain, but a commonplace aspect of neural processes.

In an effort to place early and more recent research on the same theoretical footing, Stiles (2000) proposed a conceptual modification of plasticity, extending its role beyond reparative processes and specific developmental windows. Specifically, she stressed the inclusion of plasticity as a normal part of brain functioning, a fundamental property that mediates the relationship between brain and environment. In this framework, plasticity is viewed as a dynamic feature of the brain that reflects the systematic relationship between input and neurological functioning. Plasticity is a part of learning, the acquisition of motor and perceptual skills, as well as strategy and problem solving, and, perhaps most importantly, it occurs throughout the lifespan.

Advancing a similar idea, Das (1997) submitted that plasticity might be a key element in the neurological substrate that underlies sensory processing. In particular, he proposed the well-defined cortical representations of the retina and skin sections may not be the result of hard-wired neural architectures, but the dynamic interaction of cortical neurons. The boundaries of these representations are the result of a balance between inhibition and excitation. Altering this equilibrium by changing inputs can result in the reorganization of cortical maps. In his view, plasticity is a continuously active component of sensory processing, capable of altering processing patterns and cortical topography in response to input change.

The proposals of Stiles and Das point to a current reformation in the understanding of plasticity. There is no doubt that physiological research has expanded plasticity's theoretical scope considerably. However, the challenge of making substantial connections between neural dynamics and psychological principles remains. As described next, this avenue of research may be best pursued using a sensory modality that has a history of both exacting behavioral and physiological research, namely vision.

2.2 The Visual Modality

We overwhelmingly rely on vision for our interaction with the world. This dependence is reflected in human neuroanatomy. Neural pathways extending to the auditory cortex have approximately 30,000 fibers while those to the occipital cortex contain over 1 million (Wurtz & Kandel, 2000). In the primate brain, visual processing takes place over a diffuse and highly interconnected series of cortical areas (Felleman & van Essen, 1991). A century of perceptual research attests to vision's ability to parse, interpret, and learn from the measureless amounts of information in the visual world (Gibson, 1967). In short, out of all the senses, vision has the most sensitive and discriminating relationship with the environment, and for this reason, it seems the ideal candidate for the exploration the new conception of plasticity.

As with other traditional approaches to plasticity, early sensory research on visual plasticity was conducted under a developmental paradigm (for reviews see Boothe, Dobson, & Teller, 1985; Movshon & Slutyers, 1981). Models of plasticity in the primary visual cortex have focused on the development of orientation maps in the immature brain (Swindale, 1996). However, these developmental models do not address visual processing, only the formation and mutability of cortical features during development. In

contrast, models of processing in visual cortex often assume neurons are elements with fixed properties that do not change in response to exogenous pressure (Heeger et. al., 1996).

Unfortunately, developmental and process-oriented models of vision have developed largely independently. Das (1997) has proposed that forging connections between these domains may be fostered under the recent understanding of dynamic cortical plasticity. If this is possible, it would yield a foundation for understanding vision in terms of both developmental and process mechanisms. The key to doing this is demonstrating the applicability of plasticity, formally limited to developmental frameworks, to the physiological substrates and psychological characteristics of normal visual processing. Methodologically, this means examining plasticity in adult brains in addition to juveniles, establishing plasticity as an intermediary in input and response relationships, and modeling it in a time frame that corresponds with behavioral adaptation.

The challenge of this approach is that it necessitates observing plastic changes on a smaller physical and temporal scale than traditional investigations. Plasticity in the juveniles can yield very prominent neural and behavioral changes. Within the critical periods of the immature brain, plasticity can influence thalamic inputs and affect fundamental aspects of vision such as orientation preference, ocular dominance (Hubel & Wiesel, 1982), even the cortical location of modalities (Sadato et al., 2002). In contrast, plastic changes in the adult brain seem to be limited to intracortical connections and characterized by the reorganization of receptive fields (Das, 1997). This form of plasticity, referred to as cortical reorganization, may take months to become permanent

(for a review see Kaas, 1991), but immediate changes in receptive field size have been observed in response to discrimination tasks (Weinberger, 1995) and the controlled presentation of sensory inputs (Pettet & Gilbert, 1992).

The extension of plasticity to the adult cortex means its redefinition at the cellular level of neural organization. However, this can only be accomplished if our structural and functional levels of description are commensurate. Fortunately, the relationship between the retina and visual cortex in the primate brain is such that fine discriminations in organization and function are possible. There is, for example, a well understood correspondence between the stimulation of the retina and corresponding locations of activation in the primary visual cortex (for a review see, McFadzean, Hadley, & Condon, 2002). A solid understanding of the topographic relationship between visual stimulation and cortical activity makes evidence of plasticity in the visual cortex potentially more observable and conclusive.

Vision researchers, then, may be uniquely poised to add to the growing body of knowledge on cortical plasticity in the adult brain. Indeed, recent research spanning methodologies from controlled lesioning in animals to neuroimaging in humans seems to indicate the visual cortex's capacity to reorganize to changes in retinal input (Kaas et al., 1990; Darian-Smith & Gilbert, 1995; Calford et al., 2000; Baker et al., 2005). This body of research is not without its detractors (Horton & Hocking, 1998; Smirnakis, et al., 2005) or unanswered questions (Sereno, 2005). Still, a solid path has been laid by vision research for pursuing a more complete understanding of cortical plasticity.

2.3 Current Directions

Interests in basic science aside, a concrete understanding of visual plasticity could hold great value for the treatment of human visual ailments. If the primary visual cortex is able to respond in ways that allow adaptation to trauma or disease, then an understanding how such processes take place can inform therapies for those afflicted with visual impairments. The existence of a class of ocular diseases called retinopathies, for example, lends an important clinical dimension to research on visual plasticity.

One such disease is macular degeneration (MD). MD destroys retinal photoreceptors and causes the deafferentation (lack of input) of cortex representing the macular area of the retina. The condition ultimately results in central vision loss. A specific form of MD, age-related macular degeneration (AMD), is growing concern among health professionals due to its increasing rate of occurrence in the aging population (Eye Disease Prevalence Research Group, 2004). If a connection can be demonstrated between the progression of AMD and the factors dictating cortical reorganization, it could prove beneficial in developing treatment options for a condition that as no known cure (Foundation for Fighting Blindness, 2005).

Recently, Cheung and Legge (2005) published a review calling attention to the application of advancements in neuroimaging and ocular perimetry (a technique for assessing the health of the retina) to studying cortical reorganization. They argue that the combination of neuroimaging and perimetry technology can be used to launch a detailed exploration of the nature of cortical reorganization in the AMD population. Research under this framework has the unique distinction of possessing both strong basic and applied values. The knowledge acquired could meaningfully contribute to an

understanding of cortical reorganization in the visual system as well as aid efforts to develop treatments and therapies to combat macular degeneration.

Following this lead, the research described in this paper sought to draw on the relationship between the retina and primary visual cortex in order to shed light on the nature of cortical reorganization in individuals with macular degeneration. The findings are presented in supplement to the growing body of research on neural plasticity in the adult brain. The goal at this point was directed more toward basic science than clinical techniques. However, it is also hoped that any or all of the findings may prove useful in the treatment of MD.

CHAPTER 3: LITERATURE REVIEW

3.1 Macular Degeneration

The number of people over the age 65 in the U.S. will rise from 1.75 to nearly 3 million by the year 2020 (Cheung & Legge, 2005). In such a population, the ailments of old age are a prominent societal concern. Age-related macular degeneration is increasingly becoming a prevalent disorder among the United States' growing senior population. With 12% of people over the age of 80 afflicted with AMD, it is the most common cause of blindness in the elderly (Eye Disease Prevalence Research Group, 2004). In addition, a similar genetic variant, known as juvenile macular degeneration (JMD), targets the younger population. JMD develops during childhood and is sometimes present at birth. It affects over 25,000 Americans.

Both AMD and JMD are life altering. The consequences of their progression leads to difficulty performing all the everyday tasks that require focal vision: driving, reading, computer use (Decarlo, 2003; Fletcher, 1999; Jacko, Vitense, Scott, 2003). In short, due to their gravity and increasing prevalence, both AMD and JMD pose debilitating health problems with the potential to reduce the quality of life for millions of people.

3.1.1 Pathology

MD affects the macula of the eye, a 15 mm area of the retina representing the central 15 – 20° of the visual field (Cheung & Legge, 2005). The fovea, an area of the retina used specifically in focal vision, lies in the macula's bounds. Macular vision is characterized by higher acuity than that of the peripheral retina. This discrepancy is due to physiological characteristics such as the concentration of cone photoreceptors and one-

to-one mapping with ganglion cells (Tessier-Levigne, 2000). The functional consequence of this structure is that the macula acts as an area of high spatial resolution for use in central vision. The very reason MD is so debilitating is its effect is on this select but essential part of the retina.

MD pathology is characterized by the deterioration of macular photoreceptors, the neurons that transduce light into neural signals. Photoreceptor loss results in the formation of a scotoma, an area of the visual field distinguished by the progressive and untreatable loss of visual perception (Cheung & Legge, 2005). As MD progresses, fixating on stimuli in the central visual field becomes increasingly difficult if not impossible. Though vision loss can be profound, people with scotomata often demonstrate some residual light sensitivity in the afflicted macula (Cheung & Legge, 2005). Perhaps more importantly, many with MD maintain preserved photoreceptors in the peripheral areas of the retina. These areas come to shoulder a greater functional load for those afflicted with MD. Figure 1 illustrates a healthy retina and one scarred due to MD.

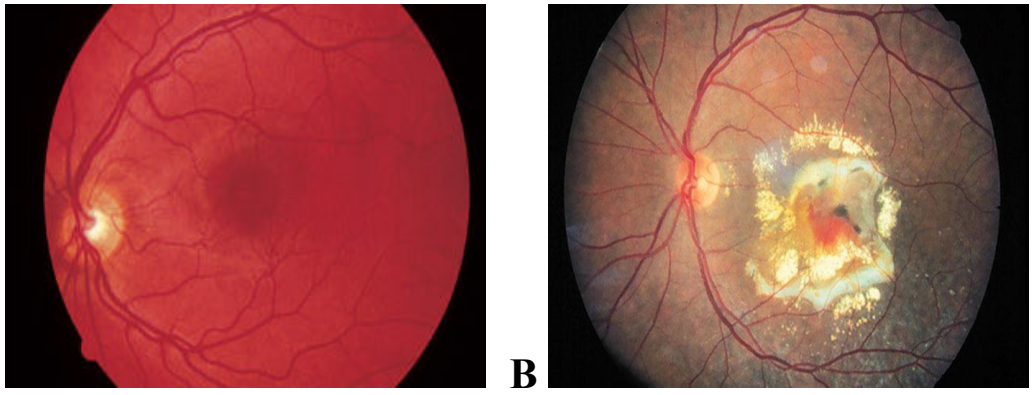


Figure 1. Healthy Retina (A) and Retina with MD (B)

In Figure B scarring is the result of choroidal neovascularization in MD. Notice how the damage is confined to the central part of the retina. The periphery is largely unaffected.

3.1.2 Wet and Dry AMD

MD can be categorized as wet or dry, based on pathological distinctions (Ambati et al., 2003; Chopdar et al., 2003). Dry MD is characterized by localized cell death on the retinal pigment epithelium (RPE), a vessel-rich layer that supports the metabolic needs of photoreceptor cells. This retinal deterioration is due to the build up of acellular debris called drusen. The accumulation of drusen underneath the RPE leads to the death of epithelium cells and eventually the disfunction of overlying photoreceptors. Vision loss resulting from dry MD is directly related to the amount and location of drusen (Bressler, 1994). Most cases of AMD, approximately 85% to 90%, are atrophic or "dry" macular degeneration (Seddon, 2001).

Wet or exudative MD stems from choroidal neovascularization (CNV) or the overgrowth of new blood vessels in the RPE. These blood vessels can penetrate the retinal epithelium and damage photoreceptors through the leakage of blood and lipids (Cheung & Legge, 2005). CNV progression can be classified as classic or occult. The classic form results in the formation of a distinct scotoma due to blood or fluid build up under the retina. Less leakage is involved in occult cases and, as a result, its effects are sometimes less apparent. Wet AMD is often more serious than dry because it progresses faster. In addition, individuals with the occult form sometimes do not notice the onset of wet AMD until neovascularization becomes more substantial (Fine, 1986).

3.1.3 Scotomata

Scotomata often appear as dark or blurry areas in the central field of view. They can be spotted or solid a mass as well as take on a variety of shapes: irregular, ring, horseshoe (Fletcher, 1999). A longitudinal study by Sunness et al. (1999) showed that approximately half the individuals with AMD had a solid scotoma. Over a period of three

years the approximate diameter of scotomata in their sample increased by a median of 5.69°. Scotomata will continue to grow if left unchecked. To make matters worse, they often form in both eyes at the same time (Schuchard et al., 1999). These bilateral scotomata are a particularly hampering condition, due to the fact one eye can compensate for other's deficit.

Figure 2. Normal Vision (A) Scotoma Obstructing Central Vision (B)

From National Eye Institute, www.nei.nih.gov

3.1.4 Preferred Retinal Locations

The gradual loss of vision in MD allows individuals to alter behavioral patterns associated with vision in order to adapt to their condition. Because MD's initial affect is on the macula, patients often begin to utilize other parts of the retina to focus and fixate in the absence of central vision. A peripheral area of the retina, often immediately adjacent to the degraded retina, is sometimes adopted as a substitute to the macula (Cheung & Legge, 2005). This area, the preferred retinal location or PRL, is key in an

adaptive technique called eccentric viewing, where individuals reorient their eyes in such a way that images fall on the PRL and not the damaged macula (Timberlake, Peli, Essock, & Augliere, 1987; Von Noorden & Mackensen, 1962). Often times, this is the only way those afflicted with MD can salvage some of their former visual abilities (Altpeter, Mackeben, & Trauzettel-Klosinski, 2000).

The utility of the PRL as an alternate area of fixation has been of particular interest to vision researchers. Fuchs was the first to discover the existence of the PRL while researching individuals with hemianopia (as cited in Cheung & Legge, 2005). His analysis of what he called a "pseudo-fovea" depicted an area in peripheral vision that adopts the functions of the fovea when macular areas of the retina are damaged. Further research on the PRL has indicated that it has lower resolution and functionality compared to the macula. Studies have shown that the fixation ability within the PRL is substantially less than the normal fovea (Schuchard & Fletcher, 1994). For example, the diameter of the fixation area for a PRL is between 1 and 9 degrees, substantially larger than the 0.2 to 0.5 degree area of the fovea (Schuchard, 1999). In addition, use of the normal fovea yields 3-4 times better fixation than a PRL (Sansbury, 1973).

The reduced ability to fixate using a PRL is a direct consequence of a general lack of acuity associated with the peripheral areas of the retina. In the periphery, several photoreceptors map to a single ganglion cell rather than the one to one correspondence found in the fovea (Tessier-Levigne, 2000). This means that input proceeding to the brain from the periphery has lower resolution. This is a limitation of peripheral vision inherent in the biology of the retina and visual pathways, no amount of training or experience with a PRL can change this structure. However, frequent use of a PRL may eventually yield

top-down or cortical influences that enhance its performance beyond normal capabilities. For example, Casco et al. (2003) showed the ability of a patient with JMD to better attend to peripheral retinal locations than normally sighted controls.

It has been observed that PRLs tend to form in certain parts of the retina. A number of factors could influence this tendency, such as properties of the retina and cortex as well as the functional necessity of common tasks such as reading. For example, functional explanations of PRL formation involve learning to read "around" scotomata. Nilsson et al. (1998, 2003) demonstrated that MD patients can regain the ability to read after the development of a trained retinal location (TRL). The necessity of relearning such tasks as reading may influence PRL development, trained or not, but it is likely that other factors contribute the formation of a PRL. Fletcher and Schuchard (1997) found that many patients develop left-field PRLs even though they impair the reading of English text.

Evidence indicates that certain biological factors may contribute to the location of a PRL. There are natural differences in peripheral retinal sensitivity that could influence this process (Wertheim, 1891). Altpeter and colleagues reported that attention capabilities vary according to locations on the peripheral retina (2000). Both low vision and normal sighted participants prefer horizontal, peripheral locations above those in the vertical plane. In further support of biological causes, the response of the visual cortex to the 'geographic' distribution of the damage on the retina could be a possible factor. Research has shown that PRLs tend to develop on average no more than 2-2.5° from the peripheral border of a central scotoma, an indication that cortical restructuring affects their initial development (Fletcher & Schuchard, 1997; Sunness et. al., 1996).

3.1.5 Impact of MD

MD can cause a substantial reduction in the quality of life for the people it afflicts (Brown et. al., 2002). For example, individuals with AMD have difficulty reading (Fletcher, 1999), and those with bilateral scotomata are less likely to drive (Decarlo, 2003). In light of such consequences, there is a great need to fully understand the etiology and progression of MD in order to develop ways to combat the condition. Work is under way on promising treatments, but as of now there is no cure for macular degeneration. One relatively unexplored area of research, however, focuses on the neurological consequences of the MD, how the visual cortex responds to sensory deprivation caused by scotomata (Cheung & Legge, 2005).

Due to retinal deafferentation, MD patients initially have large regions of inactive visual cortex that correspond to the scotomatous retina (Sunnes, Lui, & Yantis, 2004). It is possible that MD's affect on visual input may lead to structural modifications in visual processing, specifically, the topographic reorganization of the visual cortex. To establish a theoretical grounding for this question it is necessary to draw on two bodies of research, an older literature regarding the relationship between the retina and visual cortex and more recent research exploring the idea of cortical reorganization itself.

3.2 Retinotopic Organization

The connection between the retina and primary visual cortex (also called V1) has been examined for over a century. The structural location of V1 is along the calcarine sulcus, a landmark running from the caudal area of the occipital lobe to just below the corpus callosum, where it intersects with the parietooccipital fissure (Duvernory, 2000; Tailariach & Tourneax, 1988). Visual space is represented over this surface in the form of

a topographic map. Studies examining the relationship between the calcarine sulcus and the visual field describe an exact relationship between the stimulation of certain retinal areas and activity localized to specific parts of the sulcus (for a review see McFadzean et al., 2002).

This relationship can be described by three general retinotopic principles: eccentricity, polar angle, and cortical magnification. *Eccentricity* refers to a spatial correspondence between areas of retinal stimulation and the location of activity along the calcarine sulcus. Stimulation of the fovea and other central areas of the retina elicit activation in the posterior calcarine sulcus. As stimulation moves toward the periphery of the retina, cortical activation proceeds anteriorly. *Polar angle* refers to the relationship between the banks of the calcarine sulcus (dorsal and ventral) and the superior and inferior aspects of the visual field. The deepest part of the sulcus represents the horizontal meridian of the visual field. Surface area on the dorsal bank corresponds to the lower visual field, while the ventral surface represents the upper.

Another principle*, cortical magnification*, describes the disproportionate amount of cortex devoted to central vision. The surface area of cortical activation becomes smaller as stimulation moves to the periphery of the retina. In contrast, stimulation of retinal locations closer to the fovea elicit progressively larger areas of cortical activation. In fact, though estimates vary, stimulation of the fovea accounts for the majority of activation in the primary visual cortex. The most posterior part of the calcarine sulcus represents just the fovea and is referred to as the occipital pole. The amount of cortical area representative of the fovea reflects its functional importance as an area for central vision (Azzopardi & Cowey, 1993).

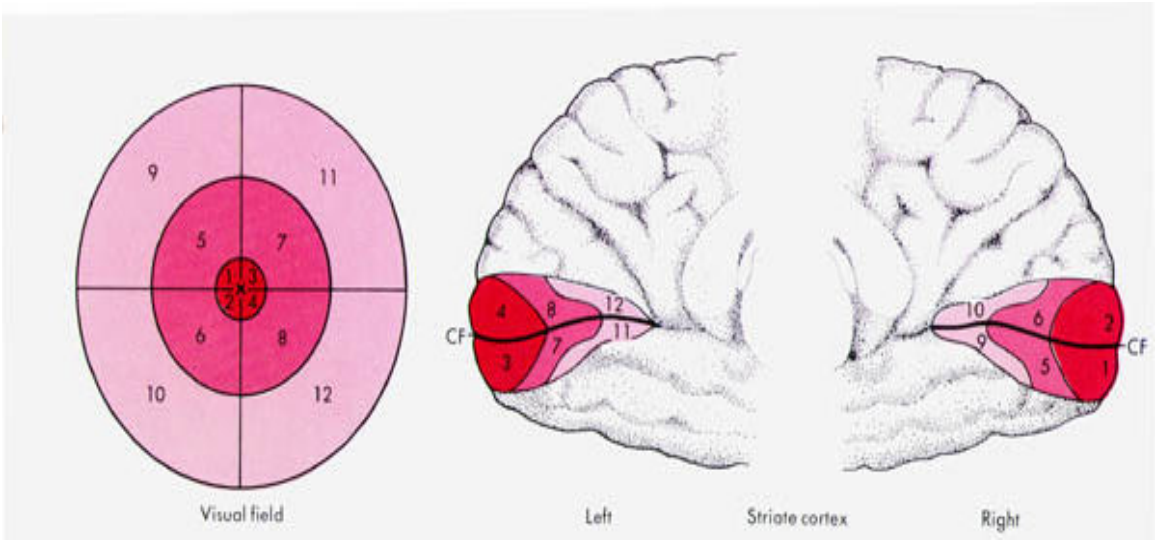


Figure 3. Retinotopic Organization of the Calcarine Sulcus

The central field of view occupies the majority of the calcarine sulcus. Cortical area diminishes for locations in the peripheral retina.

3.2.1 Neuropsychological Research

Early work examining the connection between the visual cortex and the retina involved the neuropsychological examination of war injured soldiers. During the Russo-Japanese war, the physician Tatsuji Inouye examined visual deficits resulting from head wounds. The straight trajectories of the bullets and conventional x-rays allowed Inouye to accurately approximate the location of brain damage and then compare this information with patients' reports of visual field deficits. His examination localized V1 to the calcarine sulcus as well as identified retinotopic principles such as the posterior to anterior mapping and the disproportionate relationship between central visual field and the posterior cortex. Inouye's findings demonstrate the first account of a mapping between the visual field and the calcarine sulcus (Glickstein, 1988).

Similar results were compiled by two British doctors, Gordon Holmes and William Lister, during World War I. Assigned to military hospitals, Holmes and Lister's investigation proceeded in much the same way as Inouye's, documenting the visual capacities of soldiers that had suffered gun shot and other war-related injuries to the occipital cortex (Holmes & Lister, 1916). Their work would gain widespread acceptance, eventually leading to the first retinotopic map of the human calcarine sulcus (Holmes, 1945). The map quantified the amount of cortex representative of the macular visual field. Holmes projected that 25 % of the calcarine sulcus was devoted to processing input from the central 15° vision. These results were later confirmed by other neuropsychological examinations (Spalding, 1952).

Technological advancement brought more methodical ways to investigate retinotopy, though brain injured patients were still key subjects. Brindley and Lewin (1968) used cortical stimulation on a patient who had become blind later in life. They found that stimulation of areas around the calcarine sulcus produced the perception light spots or phosphenes in different parts of his visual field. The relationship they observed was consistent with Holmes' mapping. The 1970's and 80's saw the pairing visual field perimetry with computerized tomography (CT) in investigation patients with various occipital lesions and infarctions (Kattah et. al., 1981; McAuley & Russell, 1979; Orr et. al., 1977; Spector et. al., 1981). Again, these results largely supported the parameters of Holmes' original map.

Almost fifty years later, however, Horton and Hoyt (1991) presented research that lead to the popular revision of the Holmes map. Employing participants with occipital damage, they used modern perimetric techniques to map visual deficits and then

magnetic resonance imaging (MRI) to locate lesions along the calcarine. Comparing this information, the authors concluded that Holmes actually underrepresented the size of the cortical magnification factor by over half. Their revised map allocated 50% of the calcarine sulcus to the first 10° of the visual field. Further research by McFadzean et al. (1994) corroborated these findings. The revisions by Horton and Hoyt were also based on previous retinotopic research in non-human primates. This use of animal subjects, as detailed in the next section, afforded greater experimental control and accuracy in the investigation of retinotopy.

3.2.2 Animal Research

The cellular architecture of non-human primates has been extensively compared to that of humans revealing fundamental similarities (Zilles & Clarke, 1997). Accordingly, the flexibility of animal models has substantially added to an understanding of the relationship between the retina and visual cortex. Animal studies are experimentally stronger than neuropsychological investigations because they do not rely on inferential associations between the visual field and cortical damage. Instead they involve experimental manipulations, like recording changes in brain activity in response to stimulus presentation.

Employing micro-electrode recordings and controlled lesioning in macaques, Talbot and Marshall (1941) revised early estimates of cortical magnification, showing that the active area of cortex representing the fovea is 40 times greater than the cortical area representing the retina at 60 degrees eccentricity. Using micro-electrodes other research have reported similar findings, suggesting that over 70% of the calcarine is

representative of the first 15° of central vision in macaques (Daniel & Whitteridge, 1961; Dow et al., 1985; Van Essen, Newsome, & Maunsell, 1984).

Retinotopy has also been investigated using tracing techniques in animals. Tootell et al. (1988) injected macaques with a glucose infusion, C-2-deoxy-d-glucose (DG) that forms visually identifiably marks on areas of tissue that metabolically incorporates it. The authors presented macaques with high contrast concentric rings and radial lines at varying eccentricities. The animals were sacrificed and their visual cortices were flattened and examined for 2-DG marks, the location of which would indicate the areas of the cortex that were activated by the stimuli. The results demonstrate an analog of Holmes map in monkeys, showing a cortical magnification of 15mm/deg at the fovea. In addition Tootell et al. found that the cortical magnification factor was larger along the vertical meridian compared to the horizontal.

In another tracing study, Azzopardi and Cowey (1993) used a retrograde transneuronal tracer (agglutinin-horseradish peroxidase) in macaques to determine how many cortical neurons connect to ganglion cells from the fovea and peripheral retinal areas. They found that 3.5 to 5.9 more cortical neurons correspond to ganglion cells from the fovea than the periphery. Their results indicate that more cortex is devoted to the representation of the fovea than would be expected from the distribution of ganglion cells alone, another indication of cortical magnification in the primary visual cortex.

Animal research on retinotopy has supported the initial scheme of Holmes map, but has evidenced a larger cortical magnification factor. These results would later on influence Horton and Hoyt's revision, though this was primarily a neuropsychological

study. The experimental examination of human retinotopy would have to await the advent of neuroimaging methodologies.

3.2.3 Neuroimaging

Human research employing positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have substantially contributed to our knowledge of retinotopic organization. The first of such studies were executed using PET. PET involves tracking cerebral blood flow by radioactively labeling the oxygen atom in water molecules. The influx of oxygenated blood in specific areas of the cortex is an indication of cellular metabolism and increased neuronal activity. Fox et al. (1987) used PET to examine cortical activity in participants presented with circular annuli which stimulated macular, peri-macular, and peripheral retinal areas. Their results confirmed previous findings that increasingly peripheral stimulation corresponds to anterior activation in the visual cortex.

The advent fMRI has allowed researchers to dynamically image the relationship between neural activity and cognitive tasks over time (Vellringer, 2000). Functional MRI measures blood oxygenation level dependence (BOLD). Neural activity is extrapolated from the overcompensation of oxygenated blood necessary to support neural metabolism (Fox & Raichle, 1986; Fox et al., 1988). fMRI has enough temporal resolution to allow researchers to explore relationships between the brain and cognitive processes on a finer time scale. PET integrates brain activity over intervals of one minute or longer while the temporal resolution of fMRI is on the order of seconds (Saper, Iversen, & Frackowiak, 2000).

Researchers in the nineties began to use fMRI to study retinotopic organization in healthy human volunteers. Engle et al. (1994) employed an expanding annulus to selectively stimulate different cortical areas. The annulus was animated with an alternating checkerboard pattern and gradually expanded from a central fixation point to the periphery of the visual field. This property allowed cortical stimulation to be phase encoded to the annulus's location in the visual field. The result was a time course that related cortical activation with stimulation of different parts of the retina. Another stimulus for mapping cortical activation was developed by DeYoe et al. (1996). They used a rotating, checkered half-circle to map the response of the cortex in terms of polar coordinates.

More ambitious mapping studies have been undertaken using neuroimaging to precisely define to degree of cortical magnification in the human visual cortex. Sereno et al. (1995) as well as Engle, Glover, and Wandell (1997) demonstrated cortical magnification in humans using both annuli and rotating half-circles while scanning with fMRI. Both studies were able to map cortical activation to specific retinal areas with a high degree of accuracy. Duncan and Boyton (2003) used the same techniques and concluded on cortical magnification factors of 18.5, 8.4, and 1.4 mm/deg for 0, 1, and 10 degrees of eccentricity, respectively. In general, the results of these studies are a more precise confirmation of earlier neuropsychological and animal research on the functional topography of V1.

3.3 Cortical Reorganization

As discussed previously, a seminal attribute of the nervous system is its ever changing structure. The brain's capability to alter neural configurations in response to environmental pressures allows organisms to adapt and respond in ways not hardwired by their genomes. This fundamental property, recognized by some of the earliest researchers in neuroscience and psychology, has been resurrected in recent years to address a new understanding of neural plasticity: one that expands its operation beyond injury response in juveniles.

3.3.1 Reorganization due to Surgical Amputation

Reorganization of somatosensory cortex has been examined in adult animals (for a review see Kaas, 1991). Many of these studies have involved the surgical manipulation of peripheral nerves in some way, whether by amputation (Rasmusson, 1982; Rasmusson & Turnbull, 1983; Kelahan & Doetsch, 1984), the transplantation of a patch of skin (Merzenich et al, 1988), or suturing digits together (Clark et al., 1988). These experiments then use micro-electrode arrays to record neural signals from representative cortex. Often times, substantial changes in RFs are observed, such as their initial silencing in cortex representative of an amputation and then their eventual expansion.

Cortical reorganization of the somatosensory cortex has been examined in humans as well. In a series of papers Ramachandran and colleagues examined the perceptual experiences of post-operative amputees (Ramachandran, 1993; Ramachandran, Rogers-Ramachandran, Stewart, 1992; Ramachandran, Stewart, & Rogers-Ramachandran, 1992). A systematic relationship was observed between the stimulation of specific areas on the

face and the perception of phantom limb phenomena for different parts of an amputated hand (Ramachandran, 1993).

When patient's cheeks were touched they felt the sensation in both the cheek and phantom thumb. When their chins were touched, they reported the sensation in the chin and as well as the fifth digit of the removed hand. These relationships are consistent with the topographic organization of the somatosenory cortex. Areas afferented with pathways from the hand and fingers are normally juxtaposed to those from the face. It seems that cortex that normally corresponds to the hand was marshaled to process input to its closest topographical location, the face.

3.3.2 Reorganization Due to Training

Cortical reorganization in response to training regimes has been observed both behaviorally and biologically (Das, 1997). Tactile discrimination tasks in animals have offered some of the best evidence of the reorganization of the somatosensory cortex. Training of a single digit results in improved discrimination as well as the expansion of corresponding cortical areas in the somatosensory cortex (Recanzone et al, 1992, a-b). Interestingly, attention seems to be a critical determinant in this expansion. Animals trained the same way but distracted by another task (auditory discrimination) do not show the same cortical expansion (Recanzone et al, 1992c).

Training methodologies using human subjects have reported similar results. Pascual-Leone et al. (2005) investigated plasticity in response to training. These experiments used transcranial magnetic stimulation (TMS) of the motor cortex to demonstrate that the locus of neural activation associated with a manual task (playing a series of keys on a piano) becomes heighten and expands with practice sessions over the

course of a week (Pascual-Leone, et. al., 1995; Pascual-Leone, et. al., 1996). The practice-related activation returns to a baseline levels with the cessation of the task. Amazingly this change in activation even occurs when participants refrain from actually performing the task and only think about performing it. Other findings include dramatic changes in activation between pre-practice and post-practice states in the first week of a training regime, but less pronounced differences after the fifth week. Pascual-Leone and colleagues (2005) believe this distinction may indicate a two-step process in cortical plasticity, first the excitation of dormant connections then the eventual growth of new axonal connections.

Psychophysical evidence from visual discrimination tasks also support a dynamic interpretation of adult cortical organization. Using behavioral measures, these studies evidence that the changes in characteristics of human and animal perceptual performance must be located in V1 (Gilbert, 1994). Visual perception in humans improves substantially with training. Moreover, the improvement is selective. Training a specific area of the visual field in a discrimination task (determining stimulus position or orientation) does not extend to other areas of the retina (Schoups et al., 1995) nor to different discriminations tasks (Crist et al., 1996; Fahle & Morgan, 1996). Top-down affects from higher processing stages can not account for the selective strengthening of a specific part of the visual field. The receptive fields in higher visual areas are larger than those of V1. There must be plasticity at the level of the primary visual cortex that allows such specificity in perceptual training. The structures and activity patterns that may allow this selective enhancement in V1 are discussed next.

3.4 Reorganization of the Primary Visual Cortex

Training regimes and surgical alteration indicate the power of input to affect a neural change. Perhaps the most interesting aspect of many of these studies is that they were performed on adults, whose brains, by convention, are less susceptible to change. Though adult plasticity may be limited to the reorganization of neural topography, it seems clear that the adult brain is capable of adapting to changes in external input, as reflected in the alterations of neural structure and activity patterns.

One of the reasons plasticity may be observable within a short time span for the somatosensory and motor cortices, is that sudden changes in the environment necessitate adaptation from these systems. If this is true, it seems reasonable that other sensory modalities may also have the same quick acting ability in response to environmental input. Due to the relationship between the retina and V1, a topic of interest is whether damage to the retina may result in timely reorganization of V1. The visual system of both humans and animals often suffer injuries that warrant reorganization. In the case of a lesion or malformation of the retina, neurons in the corresponding parts of the visual cortex are deafferented, that is, they lack visual input. The question is whether V1 can respond to this lack stimulation and reorganize as does the somatosensory cortex.

3.4.1 Structure of V1

As perceptual training studies indicate, the locus of reorganization in the human visual system is the primary visual cortex. The size of RFs in higher processing areas makes their involvement in cortical reorganization unlikely. The only subcortical intermediary between the eye and cortex is the Lateral Geniculate Nucleus (LGN). However, it is unlikely that LGN facilitates reorganization because its involvement would

yield larger RFs than psychophysical and physiological studies demonstrate (Gilbert, 1992). Many LGN fibers connect to single cortical neurons in V1. However, these neurons do not have comparable receptive fields. In fact, their RFs are small enough to suggest a single afferent. This may mean that the majority of the connections from the LGN are modulatory in nature. Moreover, studies examining reorganization after retinal lesions have shown that while the deafferented cortex begins to respond to stimulation outside of its receptive field, activity in the LGN remains silent even after cortical recovery (Gilbert & Wiesel, 1992; Darian-Smith & Gilbert, 1995). These findings suggest the LGN has little to no involvement in cortical reorganization.

The primary visual cortex possesses at structure amenable to the process of reorganization. The neurons of V1, pyramidal cells, are arranged in cortical columns with inputs from the LGN but also extensive horizontal connections between columns (Rockland & Lund, 1982; Martin & Whitteridge, 1984). This plexus of horizontal connections is achieved through the collateral branching of axons extending up to 6 mm into the surrounding cortex (reviewed in Gilbert & Wiesel 1992).

Moreover, connections are segregated to neurons with the same RF properties (Gilbert & Wiesel, 1989; Livingstone & Hubel, 1984). In addition to retinotopy, other mappings specific to color, orientation, and directionality characterize the surface of primary visual cortex (Blasdel & Salama, 1986; Ts'o et al*,* 1990). Pyramidal cells sensitive to color, for example, connect to other color sensitive cells in adjacent columns. These interconnections are both excitatory and inhibitory in nature, yielding an overall subthreshold effect (Hirsch & Gilbert, 1991; Ts'o et al., 1986; Weliky et al., 1995). The primary visual cortex, then, has the physical capacity of selectively altering the size and

shape of receptive fields. It is capable of the dynamic interactions that characterize cortical reorganization.

3.4.2 The Process of Reorganization

Evidence from anatomical and physiological studies indicates that the visual cortex may be able to respond to retinal deafferentation by reorganizing. This reorganization takes the form of an expansion of the receptive fields for neurons in the lesion projection zone (LPZ), the area of cortex deafferented by the lesion. Activity here is often ectopic; it is elicited by stimulation outside normal receptive fields. Resumption of ectopic activity in the LPZ may occur in two stages: first a short term step characterized by the immediate expansion of the receptive fields of deafferented neurons, then long term stage that involves the growth of axons and the formation of new neural connections (Pettet & Gilbert, 1992).

Short term reorganization can occur almost immediately because it involves the unmasking of existing horizontal connections. Research using lesioning techniques, manipulation of the optic disk, and artificial scotomas induced by flooding the peripheral retina with over-stimulation, have evidenced an immediate change in receptive field size as the first response to retinal deafferentation (Fiorani et al., 1992; Schmid et al., 1995; Schmid et al., 1996). This expansion has been shown to occur within minutes (Gilbert & Wiesel, 1992; Pettet & Gilbert, 1992).

Research on long term reorganization implicates the arborization of new horizontal connections. Studies using the antegrade label biotcytin (Gilbert & Weisel, 1992; Darian-Smith & Gilbert, 1995) have demonstrated that, in a matter of months, suprathreshold activity in lateral connections leads to new axonal sprouting. The

synaptogenesis of new axons is also evidenced by the presence of neurotrophins and insulin growth factors (IGF-1) in the plexus of horizontal connections, which encourage the growth and differentiation of new cells (Obata, et. al., 1999). Their presence indicates that deafferented neurons are forming new physiological connections in the surrounding tissue.

3.4.3 Physiological Evidence

The nineties saw physiological research demonstrating that the visual cortex can functionally adapt to lesions of the retina. Kaas et al. (1990) induced lesions in the eyes of cats and then monitored the activity of corresponding cortical neurons by single cell recording. After 2-6 months, deafferented neurons were responsive to stimulation of retinal areas on the border of the lesion. This was compelling evidence that the topography of the adult visual cortex may actually change in response to an alteration of inputs. Further research found that the expansion of receptive fields occurs initially at the perimeter of the LPZ and then spreads toward the center, although cortex corresponding to the very center may never respond to ectopic stimulation (Heinen & Skavenski, 1991).

Research has also examined specifically whether patterns of neural activity induced by cortical reorganization differ from that of the normal cortex. Calford et al. (2000) lesioned the retinas of cats and examined the neurons of the LPZ. They found that after 24 weeks, stimulation of the intact retina produced ectopic activity in the neurons of the LPZ. The size of the discharge fields was similar to that of normal cells, although discharge rates were weaker. These results indicate that, for the most part, the characteristics of reorganized activity are no different from that of normal cortex, just located in areas not ascribed by retinotopy.

Other studies, however, has argued against long term, permanent reorganization of the primary visual cortex. Murakami et al. (1997) found no evidence of reorganized receptive fields to lesioning the macaque eye. They offer that perceptual recovery is due to a "filling in" process similar to that which masks the blind spot, not reorganization. In another study, Horton and Hocking (1998) lesioned a part of one eye in adult macaques and enucleated the other. Using levels cytochrome oxidase as an indicator of cellular metabolism, they found significant rise in LPZ activity after nearly five months, but they argue that perceived "reorganization" of the visual cortex is actually a consequence of retinal healing.

Forgoing eletctrophysiology for fMRI, Smirnakis et al. (2005) lesioned the eyes of adult macaques and examined the BOLD response for reorganized activity. They found no evidence of reorganization in the LPZ even 7.5 months after the surgery. They contend that previous electrophysiological studies have selectively observed neurons. However, larger ensembles of cells, like those examined by fMRI, do not demonstrate reorganization. The studies discussed next challenge this claim. As to why these researchers did not find evidence of cortical reorganization is unclear. It could be that reorganization is dependent on number of factors (lesion characteristics, time, visual input, etc) that may interact to afford a wide variety of results.

3.4.4 Neuroimaging Evidence

Imaging technology has been employed to address the question of cortical reorganization in humans. Baseler et al. (2002) assessed cortical activity in rod monochromats and normally sighted controls. Because rod monochromats have nonfunctional cone photoreceptors and the central retina is comprised almost entirely of

cones, these individuals effectively have a small scotoma on the fovea. Using fMRI to measure cortical activation, they found that cortical areas corresponding to the fovea were responsive to stimulation from peripheral parts of the retina. In similar research, Morland et al. (2001) used fMRI to evidence cortical reorganization in response to other visual abnormalities such as lesions to the white matter and abnormal decussation of the optic chiasm.

The demonstration of cortical reorganization in response to various types of retinopathy suggests that it may also occur in MD. Sunness, Lui, and Yantis (2004) investigated this idea with an fMRI study of a single individual with AMD. They found an unresponsive area in the primary visual cortex corresponding to the location of the scotoma. Though these results seem to suggest that cortical reorganization does not occur in response to AMD, only one participant was tested and she had symptoms of AMD for only three years. In fact, the authors considered their paper an indication of the feasibility of using technology such as fMRI for the assessment of cortical reorganization in response to macular degeneration, rather than definitive statement against it.

A recent study by Baker et al. (2005) employed fMRI to investigate the cortical activity in two individuals with macular degeneration. In both the onset of the degeneration was in adolescence and had progressed for over ten years. When the authors presented them with whole screen pictures (places and faces) that stimulated the entire visual field they observed activity in areas of V1 that represented the degraded retina. Because this part of the cortex was deafferented, the authors' reasoned that the activation must be the result of cortical reorganization. In further examination, they located the participant PRLs and selectively stimulated them. Again, activation occurred in the

deafferented areas of V1. This was the first neuroimaging evidence of cortical reorganization in response to MD.

Shortly after, preliminary research has provided evidence both for and against reorganization of V1 in MD patients. Dilks et al. (2006) imaged six individuals with AMD, three with absolute scotomata on the fovea showed large scale reorganization, while the others with residual central vision did not. Masuda et al (2006), however, imaged individuals with both AMD and JMD but did not observe cortical reorganization in any participant. At present, researchers seem to agree that while cortical reorganization may be possible in those with MD, time since diagnosis, severity, age of onset, and other disease related factors may play a prominent role in whether or not reorganization is observed.

3.5 Literature Summary

Investigations of cortical reorganization are now moving beyond animal models in an effort to study how reorganization may manifest in the human brain. At present, the most appropriate focus for such research is on vision and its cortical representation in V1. This is partly due to advancements in technology such as fMRI and improved ocular perimetry. In addition, primate retinotopy, provides a solid neural foundation on which to examine cortical reorganization. This is complimented by the wealth of information from visual psychophysics and ophthalmology. In short, converging knowledge garnered from behavioral, clinical, and neurological approaches set vision science in a prime position to address the possibility and scope of reorganization in the human brain. The following research description hopes to add to this endeavor as well inspire future investigations.

CHAPTER 4: CURRENT STUDY

4.1 Research Goals

People with MD must deal the loss of high-acuity, central vision. The formation of a scotoma results in a substantial area of deafferented visual cortex that may grow with advancement of the disease. To cope, MD patients often begin to retrain their visual habits so that they are able fixate with a PRL instead of the diseased macula. Neurologically, these conditions could lead to a change in the relationship between retinal input and V1. Areas of the retina that had formally been the largest contributors to cortical afferentation (macula) are now silent, while input from peripheral areas (PRL) are more prominent. The interaction of these two factors: unused cortex and eccentric viewing, may be favorable to the reorganization of processing in V1.

Animal and human studies provide evidence that the visual cortex is able to reorganize in response to retinal deafferentation (Kaas, et al., 1990; Darrian-Smith & Gilbert, 1995; Calford, et al., 2000, Morland et al., 2001; Baseler, et al., 2002). However, research on whether cortical reorganization occurs in humans with MD has been equivocal (Baker et al., 2005; Heinen & Skavenski, 1991; Dilks et al., 2006; Masuda et. al., 2006; Sunness et al., 2004). Moreover, recent research has simply attempted to show that cortical reorganization occurs in response to MD, not make empirical clams on critical factors affecting onset or progression.

In light of these remaining questions, the goal of the present research was to investigate whether cortical reorganization occurs in response to the presence of MD, and more specifically, whether or not reorganization may be linked to physical and functional

attributes of the retina. Accordingly, this research addressed the relationship between different parts of the retina and the presence and/or extent of cortical reorganization.

4.2 Hypotheses

This research examined three hypotheses. The first is simply that activation in the primary visual cortex should mirror retinal health. The stimulation of retinal areas affected by scotomata should show reduced activation in the primary visual cortex compared to stimulation of the intact retina. This result would replicate earlier findings (Sunness, Liu, & Yantis, 2004).

Secondly it was hypothesized that deafferented cortical areas in MD patients would show activation in the posterior calcarine sulcus to stimulation of the PRL. Because the PRL is in the peripheral retina, activity in the posterior calcarine would indicate the expansion of receptive fields for deafferented cortex and evidence cortical reorganization. In contrast, PRL stimulation in Controls should not elicit activation in the posterior calcarine because the normal structure of retinotopy is maintained in these subjects. These results would indicate that reorganization is taking place in the MD group, not the Controls, and confirm the findings of Baker et al. (2005).

A final goal of this study was to specifically examine the relationship between the PRL and cortical reorganization. The proposed procedure allows for an analysis of how PRLs affect reorganization in relation to other retinal areas. The use of a PRL may induce cortical reorganization beyond that associated with the preserved retina in general. It was hypothesized that stimulation of a patient's PRL will result greater activation in the posterior calcarine than other preserved retinal locations at the same eccentricity.

CHAPTER 5: METHODOLOGY

5.1 Participants

Fourteen individuals participated in this study. All provided written, informed consent and were compensated for their participation. Six were MD patients at the Emory University Eye Center. One patient had JMD since birth, the others developed AMD as adults and had lived with the condition for a maximum of ten years. The remaining eight participants were age-matched controls with normal or corrected to normal vision.

Eligibility for the MD group was contingent on the diagnosis of exudative (e.g., wet) or atrophic (e.g., dry) forms of MD, defined by clinical characteristics within a 3,000 μm radius of the fovea, including presence of drusen, evidence of changes in the retinal pigment epithelium, geographic atrophy, and choroidal neovascularization. The distinction between individuals with JMD and AMD was based on the age of disease diagnosis (typically, within 1st or 2nd decade of life for JMD individuals versus the 4th to 7th decade of life for AMD individuals). Control group participants were selected based on age-matching criteria. Control participants did not have MD or any other eye disease that severely affected their vision.

Certain ineligibility criteria applied to all participants, regardless of the experimental group. All potential participants with visual acuity (corrected) worse than 20/400 were disqualified, as were participants with significant media opacities such as cataract, glaucoma, and corneal scarring. Minor cataract and pseudophakia were allowed to the extent that it does not preclude ocular testing or ability to view visual stimuli. The visual health and other pertinent characteristics for all participants are shown in Table 1.

Table 1. Participant Demographics

Participant	Group	Age/Sex	Time since Onset	Eye Used
CO	JMD	63/M	R: Birth, L: Birth	Left
HG	AMD	82/F	R: ~ 10 yrs, L: ~ 10 yrs	Left
JJ	AMD	75/M	R: 3 yrs, L: 3 yrs	Left
JR	AMD	78/F	R: ~ 2 yrs, L: ~ 6 yrs	Right
SL	AMD	72/M	R: ~ 1 yrs, L: ~ 5 yrs	Right
RD	AMD	71/M	R: ~ 2 yrs, L: ~ 2 yrs	Left
AF	Control	72/M	N/A	Right
AK	Control	48/F	N/A	Right
AS	Control	75/M	N/A	Right
BA	Control	71/M	N/A	Right
BR	Control	78/F	N/A	Right
EJ	Control	82/F	N/A	Right
JT	Control	63/M	N/A	Left
RP	Control	81/M	N/A	Left

Time since onset is approximated in the table. The values (i.e. R: ~10 yrs, L: ~10 yrs) better reflect the time of diagnosis. The actual onset of disease is likely to have occurred before diagnosis. The far right column indicates the eye with the best visual acuity. It was identified for each participant and was used in subsequent phases of the experiment (e.g. MP-1, fMRI). Although AK was run, her match in the MD group cancelled. As a result her data was not used in the analyses. She is included in the table for documentation purposes.

5.2 Apparatus

An MP-1 microperimeter (Nidek Inc.) was used to identify the location and extent of scotomata and PRL locations in MD participants. It was also used to confirm that control participants have normal vision. Functional MRI using a Siemens 3T magnet was employed to acquire functional brain images of participants while they viewed the presentation of stimuli to different parts of their visual field.

5.2.1 Microperimetry

The MP-1 microperimeter (Nidek, Inc) was employed to evaluate the health of participants' retinas. It uses fundus tracking microperimetry and color digital photography to produce highly accurate assessments of retinal sensitivity and preferred fixation. The MP-1's strength over more traditional methods of perimetry lies in its ability to determine the position of the retina despite eye movements. Traditional perimetry requires a stable fixation, which is often lacking in individuals with MD (Anderson, 2003). Newer microperimetry technology, like the MP-1, uses a low power laser that sweeps over the retina and continuously collects data on the position of anatomical structures (Webb et. al., 1980; Sharp et. al., 2004). Active tracking in reference to biological landmarks allows visual field testing to be performed accurately even though the eye may have difficulty fixating.

The MP-1 takes a continuously updated infrared image of the retina. The operator uses this image to accurately present stimuli at varying intensities to select parts of the retina. The luminous intensity of the stimuli varies on a logarithmic scale denoted by values ranging from 0 dB, the brightest stimulus (127 cd/m^2), to 20 dB, the dimmest

(1.27 cd/m^2). During examination, luminance is varied by a thresholding strategy that determines the dimmest detectable stimulus for a specific retinal location.

Two examination procedures were performed using the MP-1: an examination of retinal sensitivity to 20° eccentricity and a smaller more specific examination of PRLs in MD participants. The 20° test indicated the location of scotomata and/or healthy retina. In the fixation test, MD participants were allowed to fixate normally, naturally using their PRL. The MP-1 operator then performed a 12° sensitivity test on the location. This procedure provided evidence of the PRL's location through fixation as well as detailed analysis of its sensitivity. Data from the visual field testing was then superimposed onto the fundus photograph allowing a diagnostic assessment of retinal sensitivity.

5.2.2 fMRI

A Siemens 3T Magnetom Trio fMRI scanner was used for neuroimaging of participants. The Magnetom Trio is a full-body scanner equipped with a Siemens radiofrequency (RF) head coil. The body coil was used for RF excitation and the head coil for signal detection. A BOLD echoplanar sequence was used with a TR of 2000 ms, TE of 30 ms, and a flip angle of 90°. Scans had a base resolution of 64 voxels and a voxel size of 3.4 × 3.4 × 3.4 mm. Each functional volume consisted of 33 slices. Data were acquired across six runs. Each run collected 194 volumes. Wedge functional scans lasted 6 minutes and 32 seconds; section scans, 8 minutes and 8 seconds.

After functional scanning, a T1, 3D, structural image was obtained for each participant. The structural scans consisted of a single slab oriented to sagittal plane and divided into 192 slices. The echoplanar sequence had a TR of 2300 ms and a TE of 3.93 ms. Contrast parameters of the scan consisted of a TI 1100 ms and a flip angle of 8°. The

scans had a base resolution of 256 voxels and a voxel size of 1.0 × 1.0 × 1.0 mm. A total of 123 volumes were collected. Structural scans lasted 7 minutes and 23 seconds.

5.3 Stimuli

The stimulus presentation was programmed and presented on E-Prime software (version 1.1, Schneider, Eschman, & Zuccolotto, 2002) running on a 1GHz Pentium 3 computer. During scanning, participants viewed two types of stimuli: wedge and section. Both were composed of contrast reversing black and white checks. All stimuli were presented over a homogenous, gray background. Fixation stimuli consisted of four red or black crosses on the vertical and horizontal meridians. Participant preference determined both cross color and eccentricity. Fixation stimuli were present during both stimulus trials and inter-stimulus intervals.

5.3.1 Stimulus Construction

The construction of all stimuli was based upon a template composed of 5 concentric circles and 12 radii (Figure 4). Division by the radii alone produced 12 equivalent wedges. The intersection of concentric circles and radii produced 60 sections (The innermost sections were cone shaped because of the convergence of radii). In order to induce the same amount of cortical activity from peripheral and central stimulation, sections were scaled so that larger stimuli were presented in the periphery of the visual field. Scaling was accomplished by adjusting the diameters of the five concentric circles according to the human cortical magnification factor (Horton & Hoyt, 1991). The following equation was used to calculate the diameter in degrees of visual angle for each of the circles (Baseler, Sutter, Klein, & Carney, 1994).

$$E(n) = e^{n/2.76} - 1$$

Degrees of visual angle for the innermost to outermost circles were 7.79, 11.63, 17.14, 25.07, and 36.45 respectively. These values were then used to calculate the diameters of the circles in inches. A diameter of 8 inches was set for the fifth and outermost circle. The length of the diameters for each of the remaining 4 circles was then calculated from their corresponding visual angles. Table 2 indicates the visual angle, diameters and radii in inches for the nine base rings.

The above specifications produced a template used to create all other stimuli. The major divisions of the template produced 12 wedges and 60 sections. Both stimulus types were composed of alternating black and white checks. The checkered pattern was created by the placement of equidistant circles and radii between the major divisions of the template. Three equidistant circles and radii between each of the major divisions resulted in a total of 48 radii, 21 concentric circles, and 1860 alternating checks. Figure 4 shows the stimulus template and the major divisions of wedge and section stimuli.

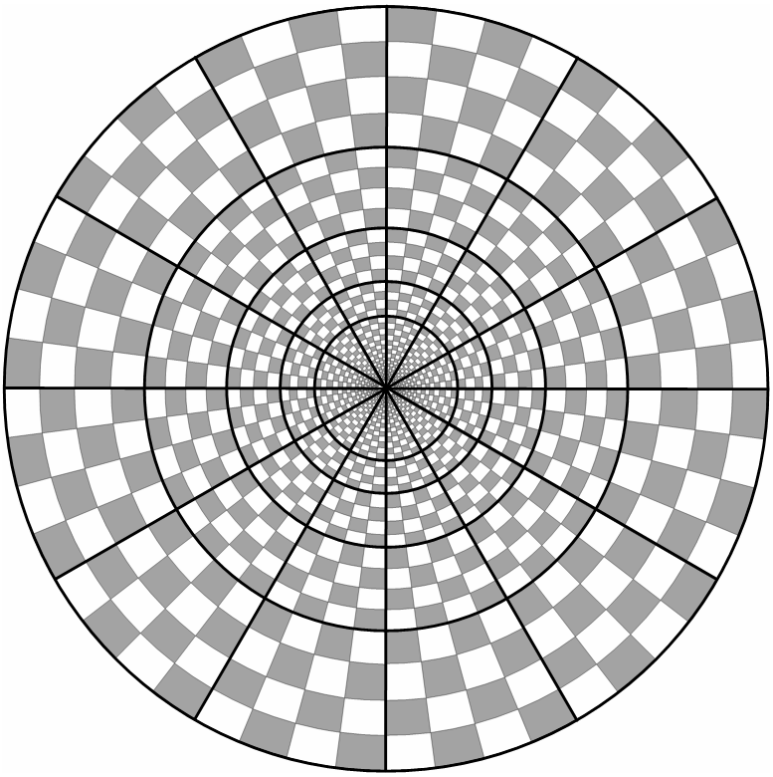


Figure 4. Stimulus Template

Major divisions are indicated by the black lines in bold. In this depiction, the checks are gray so that the divisions are clearly distinguishable. The central most sections are actually wedge shaped due to the intersection of radial divisions.

Table 2. Stimulus Template Characteristics

Ring	Eccentricity (Visual Angle)	Diameter
1	7.79°	1.48"
2	11.63°	2.23"
3	17.14°	3.34"
4	25.07°	5.07"
5	36.45°	8.00"

5.3.2 Wedges

Wedge stimuli (Figure 5) were used to stimulate the retina from the central part of the visual field to the periphery. The stimulus template was divided into 12 separate wedges. The major radii of the stimulus template were the boundaries of the wedges, each subtending 36.45° of visual angle toward the periphery of the display and converging at the center. The divergent ends were connected by a 30 degree arc, corresponding to the outermost circle. Each wedge also had four main internal arcs corresponding to the 4 remaining concentric circles. Equidistant arcs and radii between the major divisions resulted in 80 checks for each wedge.

5.3.3 Sections

Section stimuli (Figure 5) were used to stimulate more specific areas of the retina. The stimulus template was divided into 60 sections, 5 sections in each of the wedges. Each section was bounded by two radii and circles from the major divisions. Sections were also divided by equidistant arcs and radii to produce a total of 16 checks in each section.

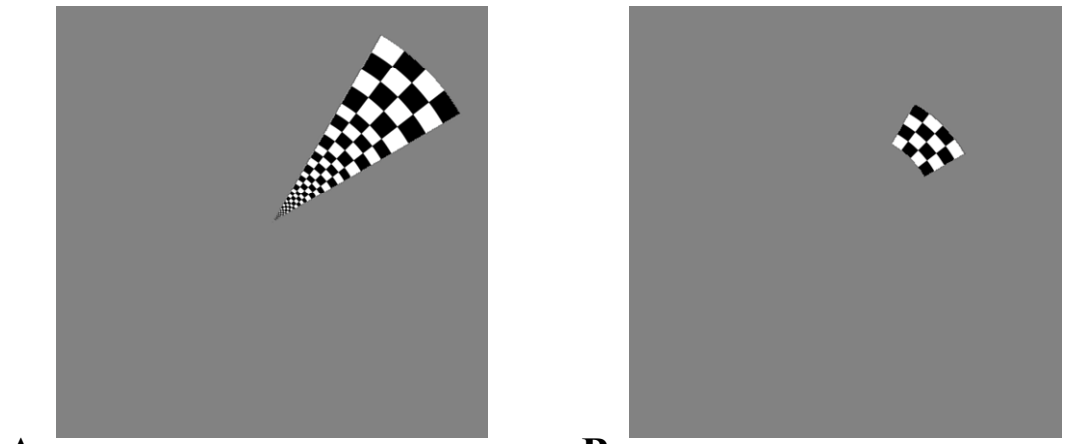


Figure 5. Wedge Stimulus (A) Section Stimulus (B)

5.3.4 Stimulus Presentation

Separate scanning runs were used to collect data from wedge and section stimuli. Each stimulus run began with the presentation of fixation crosses then the random presentation of either wedge or section stimuli. Wedge and sections were presented over the fixation crosses, partially occluding them on some trials. However, because stimuli were presented one at a time, no more than one of the crosses was occluded on any one trial.

Each stimulus was presented for 1512 milliseconds. The contrast-reversing quality of the stimuli was created by the rapid, successive presentation of two forms for each stimulus. Every stimulus was actually composed of two contrasting images in which all the white checks in one image corresponded to the all the blacks checks in the other. Each image was presented in the same location for 63 ms, alternating 12 times to produce a stimulus contrast reversing at 8 Hz. At the end of each stimulus presentation the fixation crosses remained on the screen until the next presentation.

The presentation of stimuli was synchronized with the onset of the functional volumes from the scanner. The inter-stimulus interval (ISI) varied randomly between 2, 4, or 8 seconds. The 2 second intervals comprised 50% of ISIs while 4 and 8 second intervals comprised 25% each. The use of variable inter-stimulus intervals was based on a research showing that ISI length varied according to a Poisson distribution reduces residual activity across stimulus trials (Ollinger, Shulman, & Corbetta et al., 2001 a & b). The 48 wedge stimuli were presented randomly with four repetitions of each wedge within each fMRI run. The 60 section stimuli were presented randomly once per run. The presentation of stimuli during the scanning session is depicted in Figure 6.

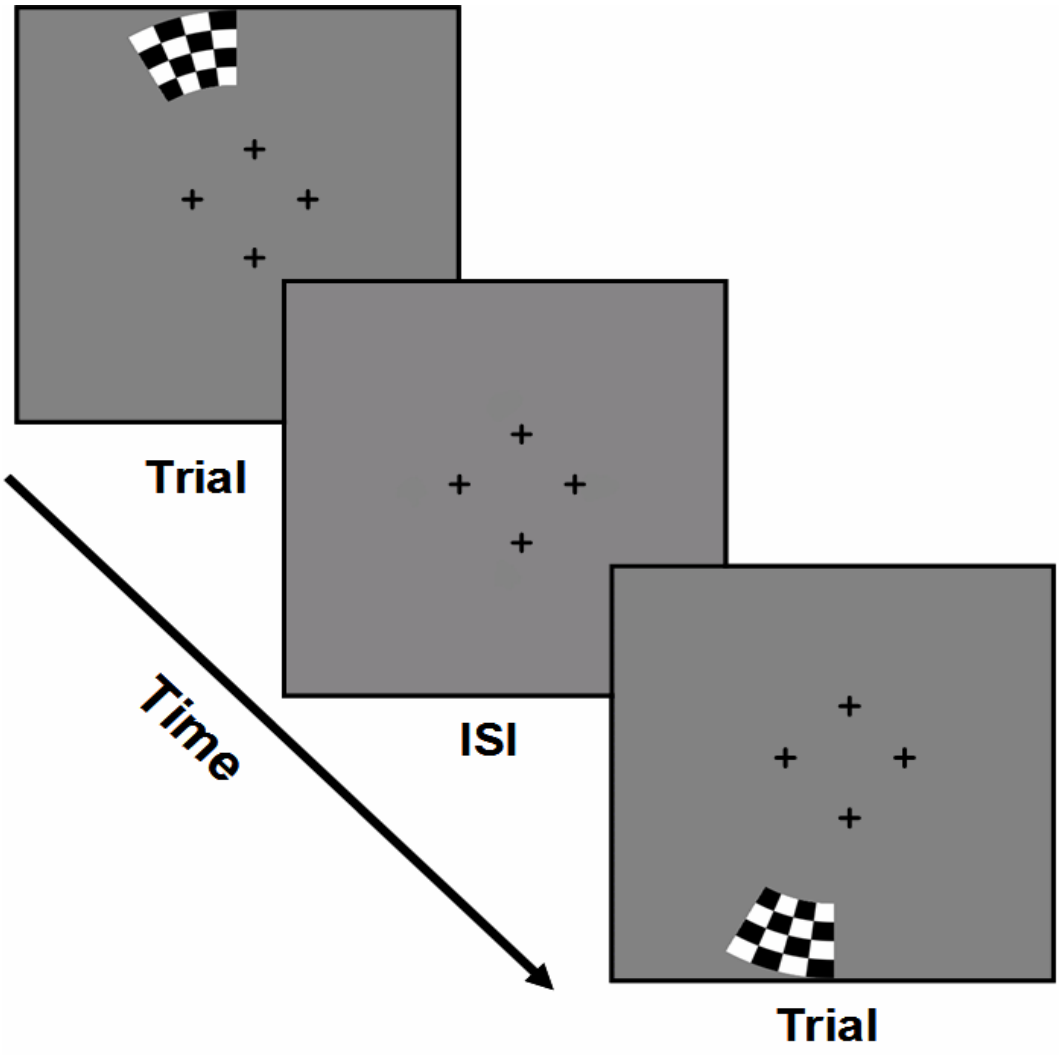


Figure 6. Stimulus Presentation

An event-related fMRI design was used. Stimuli were presented for ~ 1.5 seconds. The inter-stimulus interval varied between 2, 4, and 8 seconds. Stimulus presentation was synchronized with the collection of volumes. On a few trials volume collection was out of sync with the stimulus presentation; this was corrected by modifying the reference function in during data analysis

5.4 Procedure

Before microperimetery and neuroimaging all participants underwent a standard ophthalmologic examination to assess visual function. Participants were evaluated with the MP-1 then scanned with fMRI. The entire session took approximately three hours.

5.4.1 Ophthalmologic Exam

Patient and control participants both had an eye exam consisting of assessments of visual acuity, contrast sensitivity, and color vision. The eye with best vision was determined by patient charts and corroborated with acuity tests. This eye was subsequently assessed by the MP-1 and used in the fMRI phase. In the case of MD participants, all had established medical files documenting previous eye exams. Native or corrected visual acuity was also assessed using vision charts and automatic testing of lens refraction (Frederick & Bailey, 1996; Ferris, et al., 1982).

Contrast sensitivity, the ability to differentiate between degrees of luminosity in a fixed image, was tested using the Pelli-Robson chart (Pelli, Robson, & Wilkins, 1988). It presents a series of letters of constant size that decrease in contrast as the participant reads from top to bottom. Color sensitivity in all patients was tested using the Farnsworth Dichotomous Test for Color Blindness, Panel D15 (Farnsworth, 1947). The test assesses color sensitivity by having participants arrange an array of colored disks. The obtained order is an indicator of a participant's ability to discriminate colors. Table 3 depicts the ophthalamological exam results.

Table 3. Ophthalmologic Exam Results

Participants	Visual Acuity/Eye	Contrast Score	Farnsworth Test Order
MD			
CO	20/100 (Left)	1.20	1,2,3,4,7,6,5,14,15,13,10,12,11,9,8
HG	20/400 (Left)	1.20	1,2,3,4,5,6,15,7,14,13,8,10,9,12,11
JJ	20/250 (Left)	0.15	1,2,4,5,3,6,14,13,15,7,9,8,1,1,12,10
JR	20/100 (Right)	1.20	2,1,3,5,6,4,7,8,9,11,10,13,1,3,14,15
RD	20/160 (Left)	1.20	1,2,3,5,4,6,7,8,9,12,11,10,13,14,15
SL	20/200 (Right)	1.50	1,2,3,4,5,6,7,11,10,13,12,14,9,8,15
Control			
AF	20/20 (Right)	1.65	1,2,3,4,5,6,7,8,9,10,11,12,13,14,15
AS	20/40 (Right)	1.65	1,2,3,4,5,6,7,10,11,12,13,14,15,8,9
BA	20/25 (Right)	1.65	1,2,3,4,5,6,7,8,9,10,11,12,13,14,15
BR	20/32 (Right)	1.50	1,2,3,4,5,6,7,8,9,10,11,12,13,14,15
EJ	20/20 (Right)	1.65	1,2,6,7,5,4,3,8,9,14,15,10,11,12,13
JT	20/32 (Left)	1.65	1,2,3,4,5,6,7,8,9,10,11,12,13,15,14
RP	20/25 (Left)	1.50	1,2,3,4,5,6,7,8,9,10,11,12,13,14,15

Visual acuity scores are standard Snellen fractions. Normal values for contrast scores in the older adults ranges from 1.6 to 1.7, where a higher score indicates better contrast sensitivity. In the Farnsworth Dichotomous Test, a correct consecutive ordering (i.e. 1, 2, 3) would indicate normal discrimination of colors. Aberrations of this order indicate a deficiency in color vision.

5.4.2 Microperimetry

Assessment of visual field and retinal health involved a computerized microperimetry protocol. The stimuli used in the perimetry exam consisted of a 20° circular pattern of 76 Goldmann III stimuli (white, circular light) centered on the fovea and spaced approximately 2° apart. Each stimulus was presented individually to a specific part of the retina for 200 msec.

Four fixation crosses, each 3° in diameter, positioned 10° apart in the horizontal and vertical planes. Participants were instructed to fixate centrally by looking at an imaginary point resulting from the logical intersection of these red crosses. Despite the lack of central vision, MD participants were able "fixate" on this imaginary center point and keep their eyes remarkably still during microperimetry. Both MD and control participants fixated centrally (not using PRLs) during the microperimetry exam. Participants were instructed to respond to the presence of a stimulus by pressing a handheld switch.

Retinal sensitivity was measured in units of dB ($dB = 10 \log_{10} (L_{max}/L_{stim})$, where L_{max} is the maximum stimulus luminance of the instrument and L_{stim} is the luminance of the presented stimulus). The MP-1 initially measures sensitivity at each testing location by varying the luminous intensity of the stimulus, the brightest level of which is 127 cd/m^2, the dimmest level 1.27 cd/m^2. It then converts threshold values into dB units (0 to 20).

A thresholding strategy was used to determine retinal sensitivity values. Stimuli were presented using a 4-2 staircase method that varied luminance based on participant responses. If a stimulus was detected, the threshold algorithm decreased luminance for the next presentation to the same location by 2 dB. Conversely, if a stimulus was missed, the algorithm increased luminance by 4 dB until it was detected. This procedure was iterated until a threshold value for retinal sensitivity was established at each of 76 stimulus locations.

5.4.3 Neuroimaging

Scanning sessions began by orienting participants in the scanner. Foam padding was used to restrict head movement and head phones allowed communication from the control room. A patch was placed over the eye with worse vision. Once participants were comfortably positioned in the scanner, the stimulus template appeared on the screen. The mirror was adjusted so participants could see as much of the display as possible. For MD participants, central parts were often occluded by scotomata, but the mirror was adjusted so that they could see the edges of the template. Fixation crosses were then presented in different colors (red or black) and at different eccentricities. The crosses were moved toward the periphery until MD participants indicated they could see them. Participants also chose the most discernable color (Table 4).

Table 4. Participant Fixation and Stimulus Preference

Participant	Fixation Cross Color	Eccentricity
MD		
CO	Red	11°
HG	Black	25°
JJ	Red	25°
JR	Black	30°
RD	Red	7°
SL	Red	7°
Control		
AS	Red	7°
AF	Red	7°
AK	Red	7°
BA	Red	7°
BR	Red	7°
EJ	Red	7°
JT	Black	7°
RP	Red	7°

Participants choose between red and black fixation crosses. Red crosses were programmed in the original design because the fixation crosses in the MP-1 procedure are red. However, some participants had to wear stock frames in the scanner that did not match their exact prescription. For this reason black fixation crosses were added because they might be more discernable. The eccentricity of the crosses was adjusted between the following values in degrees of visual angle (viz. 7°, 11°, 25°, 30°). Participants selected the value at which they could see the best. Notice how the controls all selected the lowest setting (7°). Only two MD patients selected this setting.

As in the mictoperimetry exam, participants were then instructed to "focus" on the logical intersection of these crosses and try to remain fixated in that position during the scanning runs. Eye movements were monitored throughout the scan with video equipment. If participants moved their eyes during the scan, they were encouraged to remain focused on the intersection of the fixation crosses. The stimuli were presented on a screen behind the head of participants and viewed through an angled mirror. Functional runs began with the wedge stimuli and then two consecutive runs with the sections. This order was repeated to complete the six functional runs. The structural scan was obtained last. Table 5 indicates functional and structural run characteristics.

Table 5. Scan Run Characteristics

Run Type	Trial Number	Volumes	Duration (min)
Wedge 1	48	194	6:32
Section 1	60	194	8:08
Section 2	60	194	8:08
Wedge 2	48	194	6.32
Section 3	60	194	8:08
Section 4	60	194	8:08
Structural	N/A	123	7.23

All participants with the exception of BA completed the entire scanning procedure. BA's scan was aborted at her request. However, before this happened, both wedge scans and two of the section scans (1 and 2) were obtained. These data were analyzed with the rest.

CHAPTER 6: DATA ANALYSIS

6.1 Preprocessing

Data analysis was performed with SPM2 software. Preprocessing involved the coregistration and reslicing of functional images to their respective structural scans. After reconstruction, head-motion artifacts were corrected to the last functional scan with a least squares approach using a six-parameter, rigid-body transformation algorithm (Friston et al., 1995). Slice acquisition timing differences were corrected and images coregistered to the T1 structural scan.

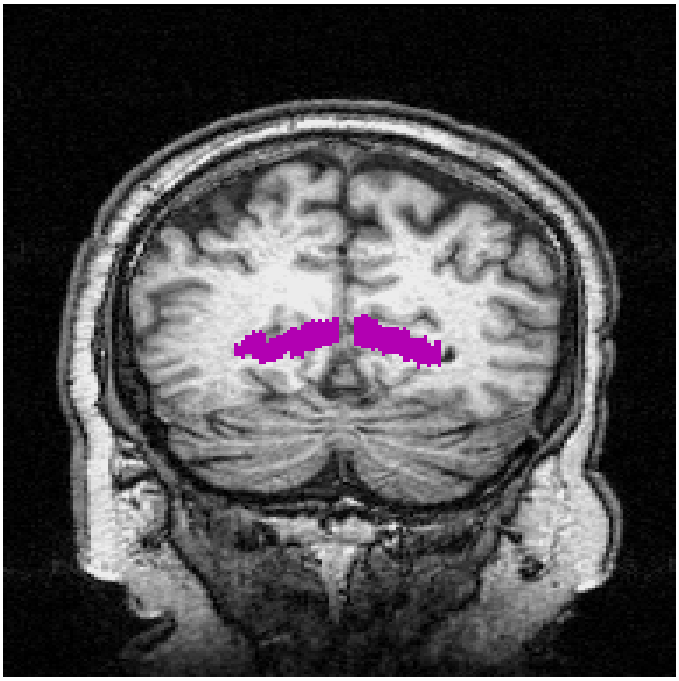
6.2 GLM Analysis and Normalization

A modified general linear model was used to analyze the data (Worsley & Friston, 1995). Contrast files were created for each wedge and section relative to baseline. There were 60 total contrasts for the sections and 12 for the wedges. Contrast files were coregistered to structural images. An idealized hemodynamic response function and high-pass filter removed frequencies below .0078 Hz. For display purposes, certain covariates were normalized to the Montreal Neurological Institute reference brain.

6.3 Regions of Interest

Regions of interest (ROI) representing the calcarine sulcus were drawn on structural images of each participant using the freeware MRIcro. Anatomical atlases were used to guide the drawing of ROIs in the sagittal plane (Duvernory, 2000; Tailariach & Tourneax, 1988). The region of interest spanned the calcarine sulcus from the occipital pole to the parietooccipital fissure. This ROI was then sliced into separate ROIs along the sagittal plane, each ROI 2 mm thick (Figure 7). Parameter estimates were extracted from these ROIs using the covariates represented in the contrast files.

A



B

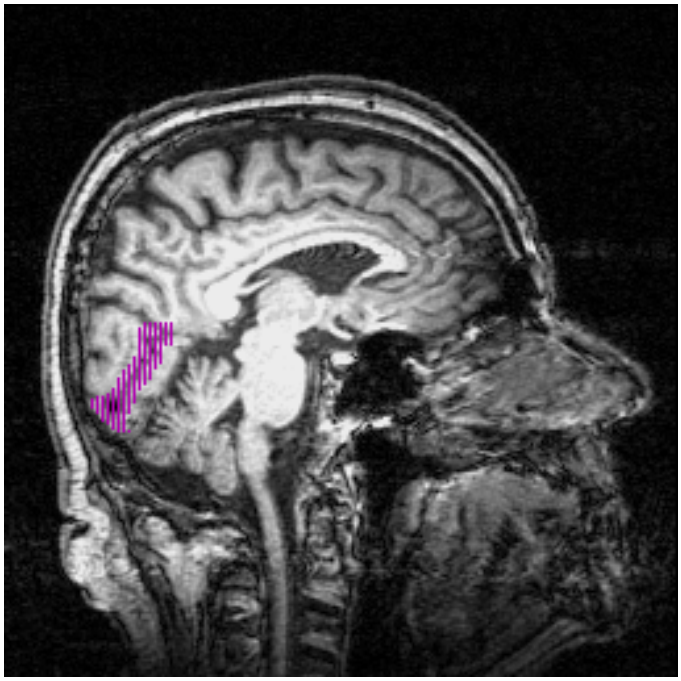


Figure 7. Regions of Interest Across the Calcarine Sulcus

Figure A depicts a single ROI slice in the coronal plane. Figure B shows several slices in the sagittal plane extending the length of the calcarine sulcus. The total number of ROI slices depended on individual neuroanatomy. Most participants had between 15 and 20.

CHAPTER 7: RESULTS

7.1 Microperimetry Data

The MP-1 microperimeter produced functional maps of retinal sensitivity for each participant. Analysis of the functional maps required associating specific retinal areas with the sections and wedges presented during the neuroimaging phase of the study. This was accomplished by overlaying a numbered depiction of the stimulus template onto the retinal maps. Figure 8 shows an example of a retinal map and color-coded sections that correspond to Scotoma, PRL, and Non-PRL areas of the retina (Non-PRL sections are explained below). The outlines of PRL and Non-PRL sections for MD participants are shown overlaid on the retinal maps in Figure 9. Table 6 shows the PRL and Non-PRL sections selected for MD and Control participants.

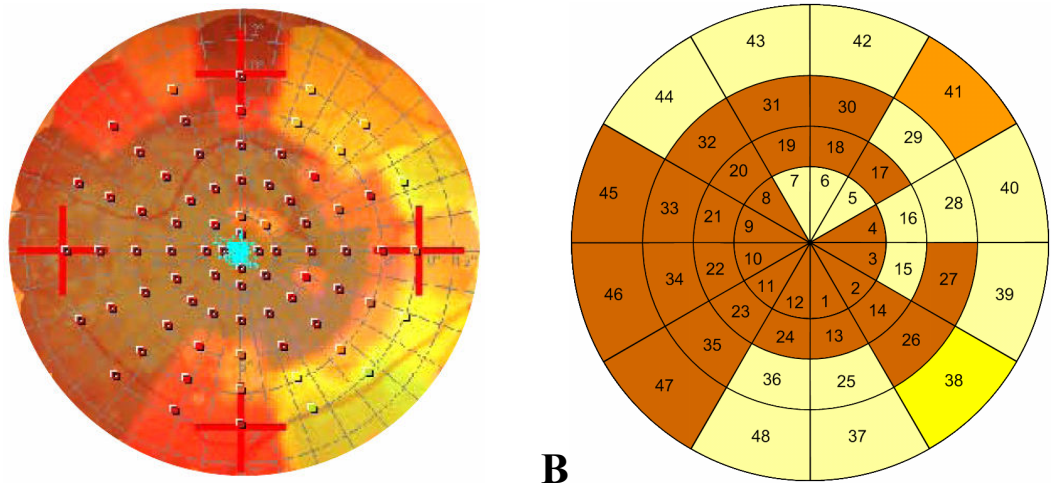


Figure 8. Symbolic Retinal Map (A) and Color-Coded Sections (B)

Section 38 (yellow) is the PRL. Section 48 (orange) is the Non-PRL. Scotoma sections are in brown.

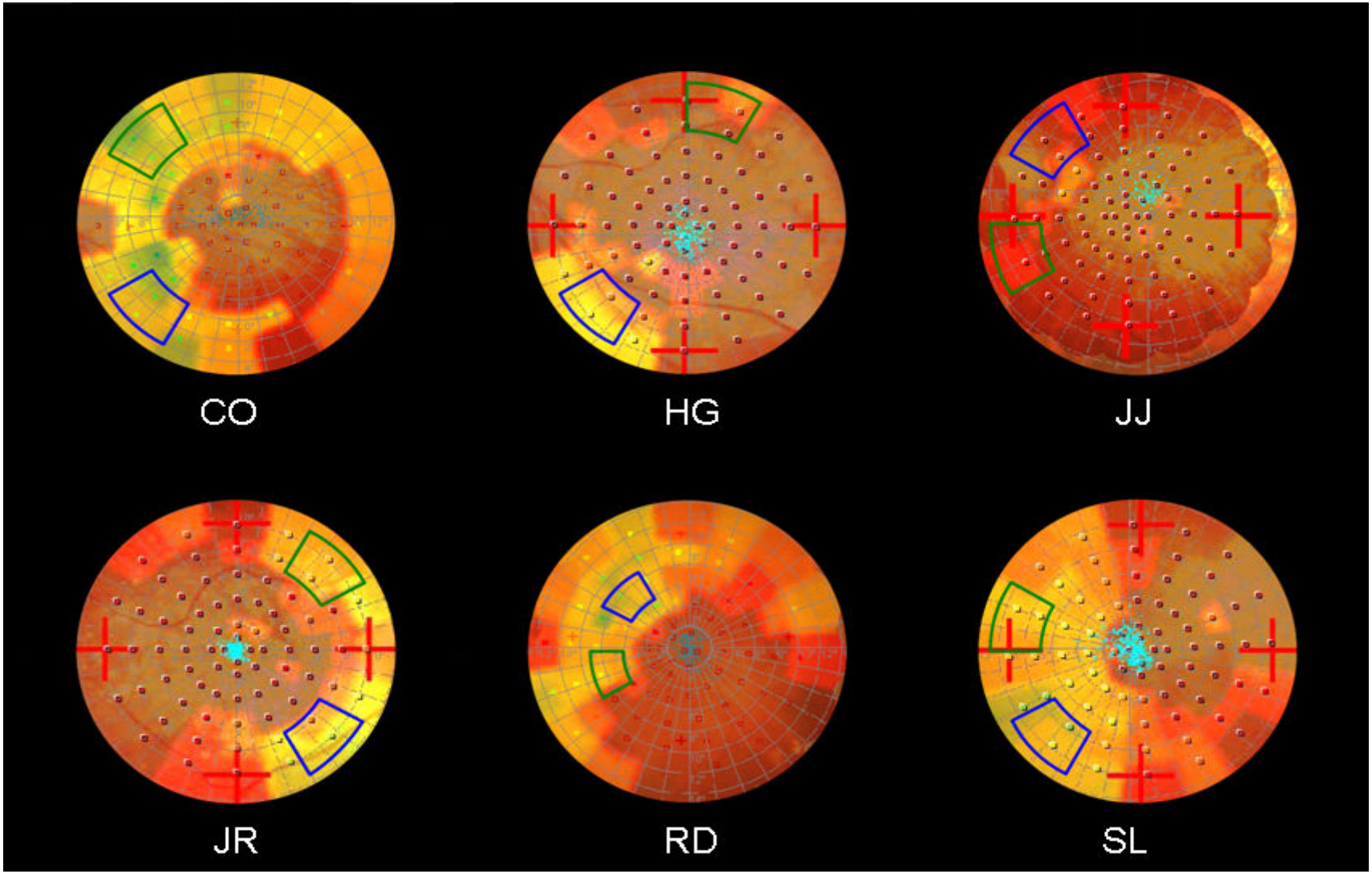


Figure 9. PRL and Non-PRL Sections over MD Retinal Map

Retinal sensitivity maps for the 6 MD participants. Blue sections represent the PRL, green sections, the Non-PRL.

Table 6. PRL and Non-PRL Retinal Sections

Participants		PRL Section	Non-PRL Section
MD	*Control*		
CO	JT	47	44
HG	EJ & RP	47	42
JJ	AS	44	46
JR	BR	38	41
RD	BA	32	34
SL	AF	47	45

7.1.1. Scotomata

Sections corresponding to scotomata were identified on the template overlay for each participant. Sections were designated as part of a scotoma if stimuli within their bounds did not elicit a hit response from participants even at the highest levels of stimulus luminance (0 dB). On the symbolic retinal maps (Figure 8), these areas assumed a brownish color. For example, areas representing the scotoma correspond mostly to sections in the left half of the picture (viz. 8 to 12, 32 to 25, 32 to 36 and 45 to 47). In contrast, areas of preserved retinal sensitivity appeared in beige.

7.1.2. PRL

The fixation test during the microperimetry examine allowed localization of the PRL to a specific retinal quadrant (i.e. upper left, lower left, upper right, lower right). Within this quadrant the section with the highest retinal sensitivity was selected as the best representative of the PRL. PRLs usually assumed a yellow or greenish color on the retinal maps produced by the MP-1. They are yellow in the color coded representation (Figure 8). Control participants do not have actual PRLs, but for comparative purposes

PRLs were selected for controls based on those identified in the matched MD participants (see Table 6).

7.1.3. Non-PRL

Non-PRL sections were defined as areas of preserved retina at the same retinal eccentricity as the PRL. In order to make valid comparisons between PRL and Non-PRL areas, an effort was made to select sections away from the PRL. This is because the extent of the PRL is unknown. It is possible that sections adjacent to the PRL would actually serve the same functional role (e.g. they are actually part of the PRL). Therefore, Non-PRL sections outside of the PRL's quadrant were selected. Non-PRL sections are orange in the color-coded representations (Figure 8). In Controls, Non-PRLs were determined the same way as PRLs, based on MD matches.

7.1.4 Retinal Sensitivity T-Tests

Individual variability in MD's progression prevented an exact match between PRL and Non-PRL retinal sensitivity. For MD participants, the mean retinal sensitivity was 9.5 ± 3.7 dB for PRL sections and 6.8 ± 5.1 dB for Non-PRL sections. These values were significantly different $t(5) = 2.96$, $p < .05$ (Figure 11). In Controls, PRL and Non-PRL sections were not significantly different: PRL = 14 ± 4.5 dB; Non-PRL = 13.4 ± 4.9; $t(6) = 0.56$, $p > .5$. Retinal sensitivity was highest in the PRL sections of Controls. It was lowest in Non-PRL sections of the MD participants. Table 7 shows the retinal sensitivity for PRL, Non-PRL, and Scotoma sections in both MD and Control participants. Figure 11 depicts the difference between PRL and Non-PRL sections in MD participants

Table 7. Retinal Sensitivity (dB) in MD and Controls

Participant	Scotoma	PRL	Non-PRL
MD			
CO	0	13	14
HG	0	7	2
JJ	0	4	0
JR	0	8	7
RD	0	13	9
SL	0	12	8.5
Control			
AF	18.19	15	16
AS	16.67	15.5	16
BA	15.14	16.5	18
BR	9.95	4	5
EJ	15.79	17	15
JT	15	*	*
RP	14.96	15	8

* Participant JT had difficulty performing the MP-1 task. As a consequence, less MP-1 data was collected and PRL and Non-PRL means could not be calculated.

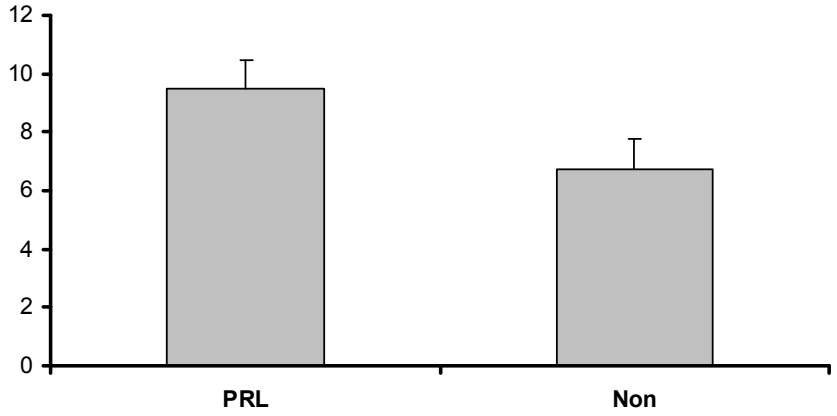


Figure 10. Average Retinal Sensitivity for PRL and Non-PRL Sections (MD)

7.2 Wedge Activity

Wedge analyses were designed to indicate whether there are differences in activity across the retina. Data were grouped into covariates based on wedge location. For example, the data from wedges 1-3 were grouped together into a covariate that represents the lower left of the retina (lower left quadrant). The same procedure was used to create quadrant covariates for wedges 4-6 (upper left quadrant), 7-9 (upper right quadrant), and 10-12 (lower right quadrant). Average retinal sensitivity values collected from the MP-1 were used to rank order the sensitivity of the quadrants, where a rank of 1 indicates the most sensitive and 4 the least (Figure 11). Within group analyses of these quadrants, for the most part, did not show a significant differences in their cortical activity.

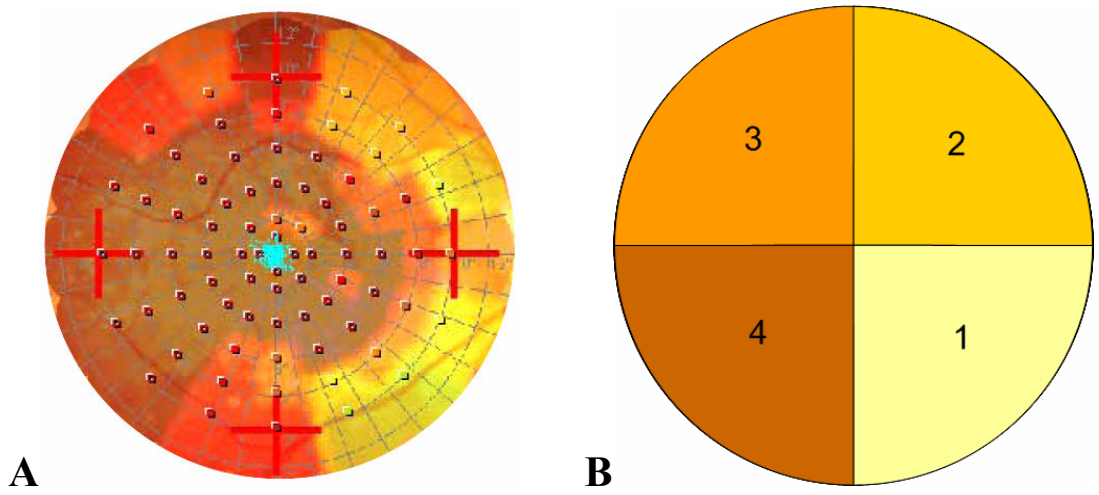


Figure 11. Quadrants Representing Retinal Sensitivity

Figure A is a retinal map. Figure B represents a rank ordering of retinal quadrants base on their retinal sensitivity. The lower right quadrant (1) has the highest sensitivity.

7.2.1 MD Wedge Activity

A repeated measures ANOVA did not show significant differences in activation across ROIs, F(3, 29) = .656, *p*= .592. Figure 12 depicts activation from quadrant covariates. Additional paired samples t-tests showed no significant differences between the quadrant covariates (Table 7).

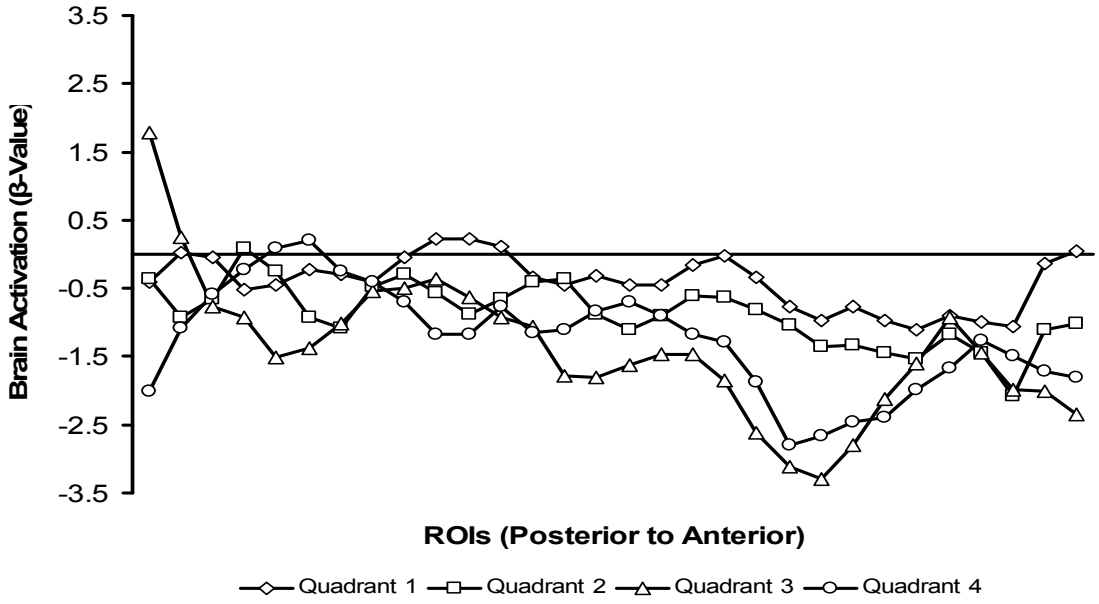


Figure 12. MD Wedge Activity

Table 7. MD Wedge Paired Samples T-Tests

Quadrant	*M*	*SD*	*SE*	*t*	*df*	*Sig*
1/2	0.475	2.463	1.005	0.427	6	0.328
1/3	0.995	2.355	0.961	1.035	6	0.174
1/4	0.845	1.763	0.720	1.174	6	0.146
2/3	0.520	1.295	0.528	0.984	6	0.185
2/4	0.370	1.827	0.746	0.496	6	0.320
3/4	-0.149	1.360	0.555	-0.270	6	0.394

7.2.2 Control Wedge Activity

A repeated measures ANOVAs for Control participants did not show significant differences in activation across ROIs, $F(3, 29) = 2.429$, $p = .099$. Figure 13 depicts activation from quadrant covariates. Additional paired samples t-tests showed significant differences between Quadrant 1 and other quadrants, but no significant differences otherwise (Table 8).

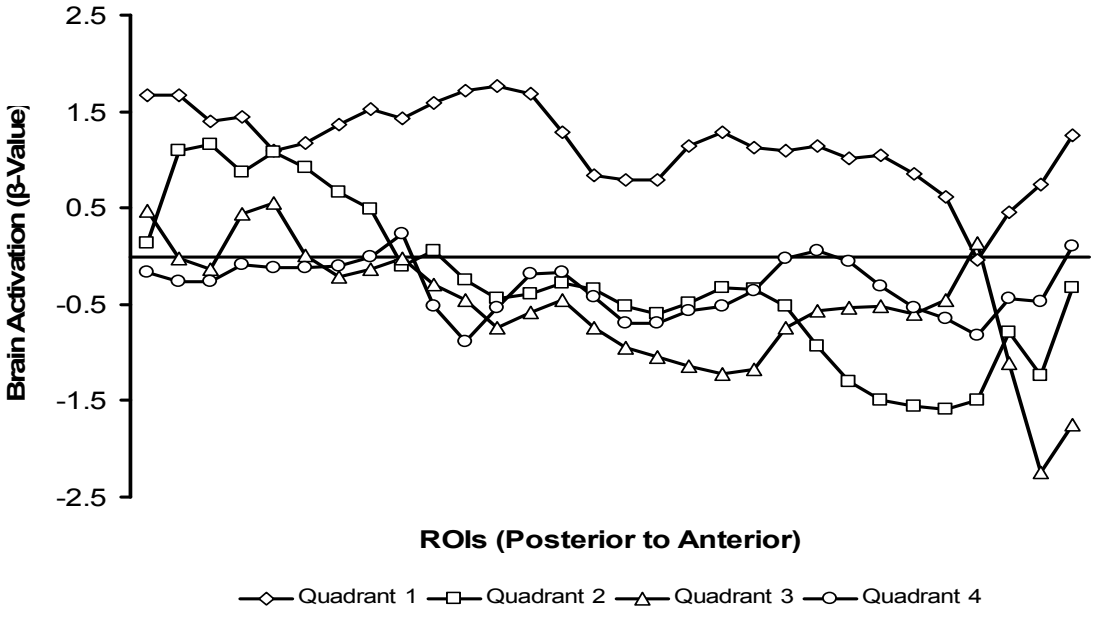


Figure 13. Control Wedge Activity

Table 8. Control Wedge, Paired Samples T-Tests

Quadrant	*M*	*SD*	*SE*	*t*	*df*	*Sig*
1/2	1.457	1.542	0.582	2.532	6	0.022†
1/3	1.708	2.114	0.799	2.138	6	0.038†
1/4	1.528	2.054	0.776	1.968	6	0.048†
2/3	0.237	1.779	0.672	0.346	6	0.370
2/4	0.052	1.969	0.744	0.070	6	0.473
3/4	-0.180	1.888	0.713	-0.253	6	0.404

† $p < .05$, one-tailed.

7.3 PRL vs Scotoma Activity

The previous analyses showed that quadrants affected by scotomata do not result in reduced activity compared to sections with preserved retina. However, the wedges contain both scotomatous and preserved retinal areas. They offer a rough depiction of the effect of scotomata on activity in V1. The next analyses tested the same premise, but in a more exact way, by comparing sections that specifically correspond to the scotoma and PRL. Activity from PRL sections were compared to the average activity of scotoma sections from each "ring" of the stimulus template (Figure 14).

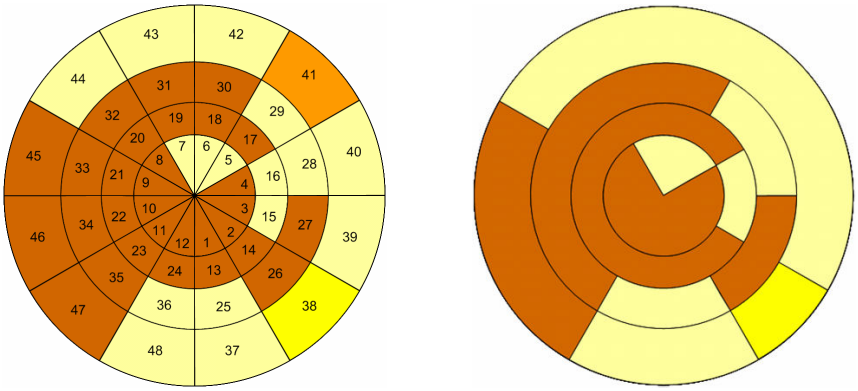


Figure 14. The PRL and Scotoma Rings

7.3.1 MD Participants: PRL vs Scotoma Activity

In MD participants, a repeated measures ANOVA on PRL sections showed there was a significant difference of between ROIs, $F(4, 29) = 1.736$, $p = .018$. The PRL sections produced differential activity across the calcarine sulcus. To better localize where this difference occurs, ROIs were categorized into bins. Each bin contained 10 ROIs and was representative of the Posterior, Middle, and Anterior calcarine sulcus. Pair-wise comparisons showed that parameter estimates from the Posterior bin ($M = 6.14$) were significantly higher than those from the Anterior bin ($M = .005$), $t(5) = 2.523$, $p =$

.02. This result indicates that PRL stimulation causes significantly more activity in posterior ROIs than anterior ROIs. Other bin comparisons (e.g. Posterior/Middle: $t(5) = 0.645$, $p = .27$ and Middle/Anterior: $t(5)$ 1.882, $p = .059$) were not significantly different.

In further analyses, activity in the PRL sections was compared to scotoma sections. ROIs for the scotoma sections were categorized into bins representing the Posterior, Middle, and Anterior calcarine. Pair-wise comparisons demonstrated that parameter estimates in the Posterior PRL bin ($M = 6.14$) were significantly greater than parameter estimates in the Posterior Scotoma bin ($M = -0.819$), $t(5) = 2.860$, $p = .01$. Comparison of PRL and Scotoma sections in Middle and Anterior bins were not found to be significantly different (Middle: $t(5) = 1.322$, $p = .12$, Anterior: $t(5) = -0.209$, $p = .42$). These results indicate that the most prominent difference in activity between PRL and scotoma sections is in posterior calcarine. Figure 15 shows PRL and Scotoma parameter estimates as a function of ROI location on the calcarine sulcus.

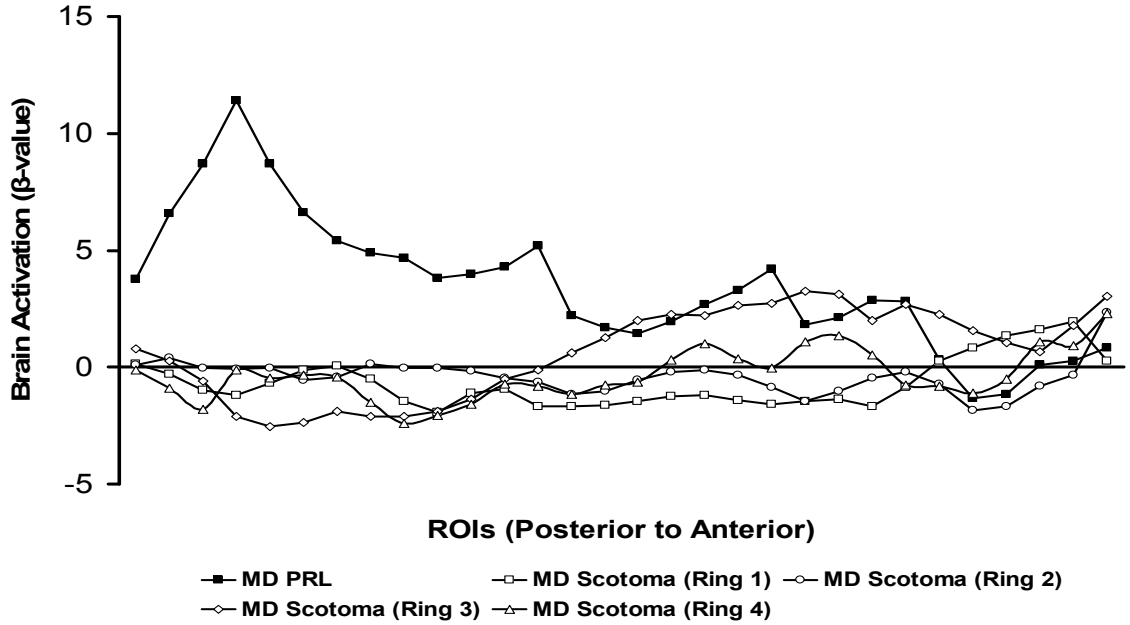


Figure 15. MD PRL vs Scotoma Activity

7.2.2 Control Participants: PRL vs Scotoma Activity

A repeated measures ANOVA on control participants showed there was a significant effect of ROI across the calcarine sulcus, $F(4, 29) = 1.553$, $p = .053$. However, pair-wise comparisons on ROI bins showed that there were not significant differences between Posterior, Middle, and Anterior ROI bins (Posterior/Middle: $t(6) = 1.661$, $p = .07$; Posterior/Anterior: $t(6) = 0.715$, $p = .25$; Middle/Anterior: $t(6) = .-0.282$, $p = .39$). It seems that the significant main effect was a result of arbitrary differences between ROIs and not a systematic difference in parameter estimates across the calcarine sulcus. Activity in PRL sections were also compared to scotoma sections. Pair-wise comparisons showed there were no significant differences between PRL and scotoma bins (Posterior: $t(6) = .141$, $p = .44$; Middle: $t(6) = -.518$, $p = .31$; Anterior: $t(6) = -.123$, $p = .45$. Figure 16 depicts PRL and scotoma parameter estimates graphed across the calcarine sulcus.

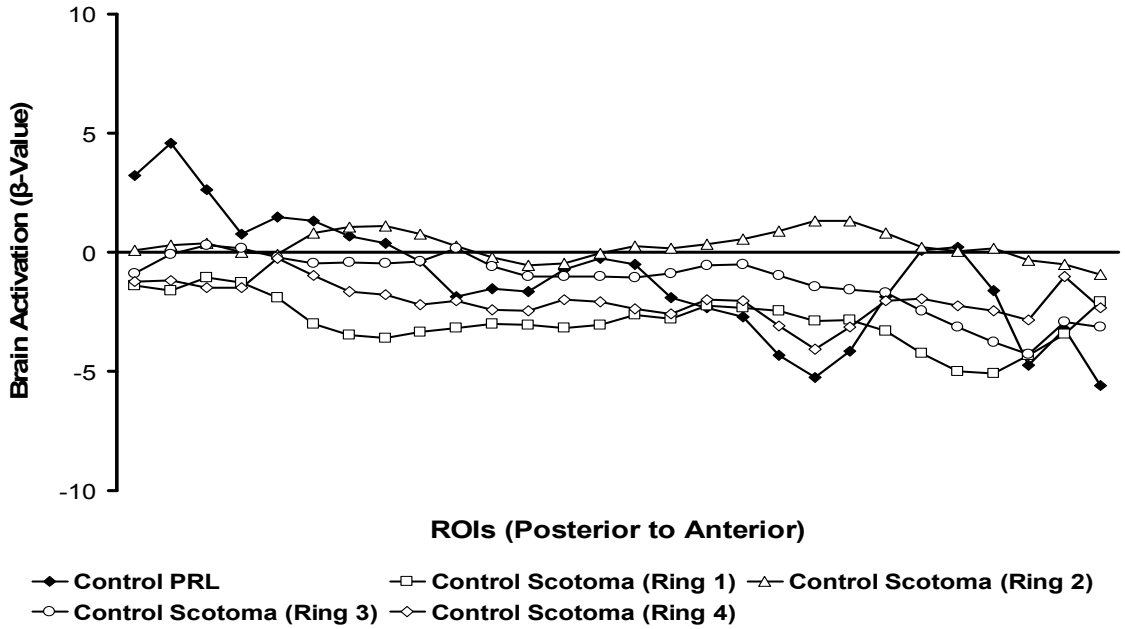


Figure 16. Control PRL vs. Scotoma Activity

7.3 MD vs Control

Between group comparisons investigated whether activity induced by PRL sections differed between MD and Control groups. The PRL holds functional significance in MD participants. In Controls, however, it simply represents another part of the retina with no additional functional purpose. Analyses compared the activity elicited by PRL stimulation in MD and Control participants. Figure 17 depicts the PRL isolated form the color-coded map.

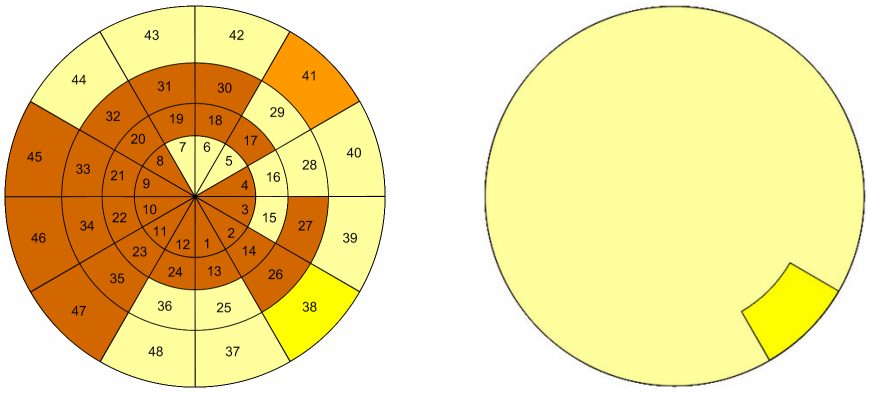


Figure 17. PRL Color-Coded Section

7.3.1 MD vs Control ANOVA

PRL sections from MD participants were compared to corresponding sections from the Controls. A repeated measures ANOVA with ROI as the within-subject variable and Group (MD and Control) as the between-subjects factor did not find a significant effect between ROIs, $F(1, 29) = 0.930$, $p = .57$. There was not a significant between-group effect, $F(1, 29) = 1.033$, $p = .33$, nor a significant interaction effect, $F(1,29) = 0.593$, $p = .99$. Figure 18 depicts the parameter estimates of the MD and Control groups for ROIs across the calcarine sulcus.

7.3.2 MD vs Control T-Tests

The lack of difference between MD and Control groups could be due to the fact that cortical reorganization may be localized to the posterior area of the calcarine sulcus. A difference here would not necessarily yield significant results if the entire calcarine is assessed. To examine possible differences more closely, the ROIs were again divided into Posterior, Middle, and Anterior bins, and differences in activation between MD and Control groups were assessed with independent samples t-tests. Significant differences were not observed for any of the three ROI groups; Posterior: $t(8.11) = 1.247$, $p = .12$; Middle: $t(9.96) = .965$, $p = .35$; Anterior: $t(8.805) = .191$, $p = .42$.

The greatest mean difference, however, was in the posterior ROI group (MD $M = 6.14$, Control $M = 0.886$). This might indicate a real difference between groups that did not rise to the level of statistical significance. Additional independent samples t-tests were performed on the first 10 ROIs in the Posterior bin. Two of the ROIs compared (4 and 5) were significantly different between the MD and Control groups; ROI 4: $t(7.93) = 2.265$, $p = 0.02$; ROI 5: $t(6.20) = 1.987$, $p = 0.04$. ROI 6 approached significance, $t(6.758) = 1.732$, $p = 0.06$. In all cases, the mean of the MD group was larger than that of the Control. These significant and marginally significant ROIs comprise the greatest difference in activation between the two groups (Table 9).

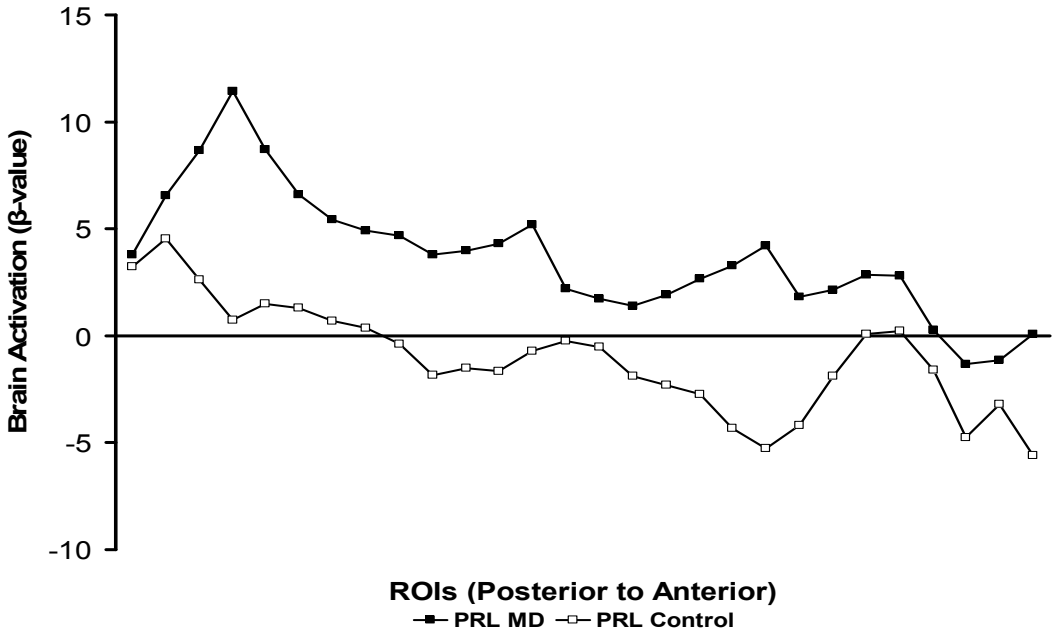


Figure 18. PRL MD vs Control

Table 9. MD vs Control Independent Samples T-tests

ROI	*M* diff	*SE* diff	*t*	*df*	Sig
1	2.309	6.919	0.334	8.523	0.373
2	2.492	6.631	0.376	8.680	0.358
3	5.916	4.161	1.422	6.407	0.101
4	10.672	4.712	2.265	7.939	0.027†
5	8.506	4.281	1.987	6.200	0.046†
6	6.076	3.508	1.732	6.758	0.064†
7	4.544	3.997	1.137	9.068	0.142
8	3.660	4.478	0.817	9.659	0.216
9	3.703	4.566	0.811	8.468	0.220
10	4.663	4.727	0.986	7.166	0.178

† $p < .05$, one-tailed. Analyses did not pass Levene's tests so significant values do not assume equal variances.

7.4 PRL vs Non-PRL

Behavioral research indicates that stimulation of the PRL, because of its functional relevance, may demonstrate more reorganization than other retinal areas (Altpeter, Mackeben, Trauzettel-Klosinski, 2000). In the following analyses, activation elicited by PRL and Non-PRL stimulation was compared in MD participants. Figure 19 depicts PRL and Non-PRL sections. Figure 20 shows the average activity they produce across the calcarine sulcus.

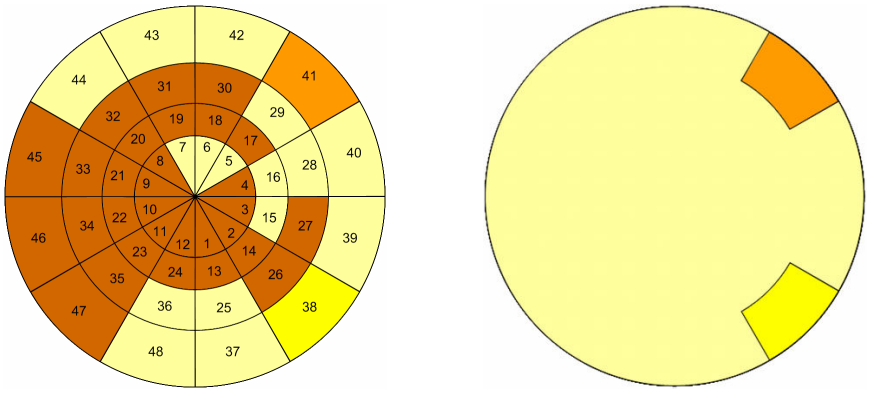


Figure 19. PRL and Non-PRL Color-Coded Sections

7.4.1 PRL vs Non-PRL T-tests

As in the other analyses, PRL and Non-PRL ROIs were divided into three bins representing the Posterior, Middle, and Anterior calcarine. Paired t-tests revealed that there was a significant difference between PRL and Non PRL sections in the posterior part of the calcarine, $t(5) = 3.05$, $p = 0.014$. The Middle bin also demonstrated a significant difference between PRL and Non-PRL groups, $t(5) = 3.209$, $p = 0.012$. However, the Anterior bin did not, $t(5) = 0.459$, $p = 0.33$. Further t-tests on the first 10 ROIs in the Posterior bin reveal that 8 of the ROIs show significant differences between PRL and Non-PRL groups. Table 10 shows significance values for the first 10 ROIs.

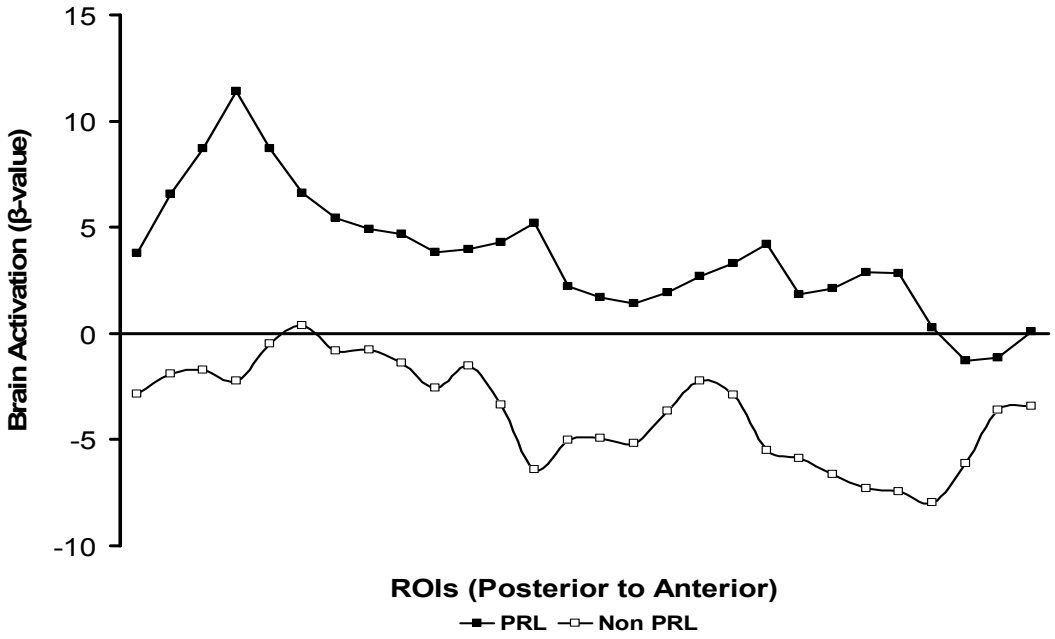


Figure 20. MD PRL vs Non-PRL

Table 10. MD PRL vs Non-PRL Paired Samples T-tests

ROI	*M*	*SD*	*SE*	*t*	*df*	Sig
1	5.174	12.059	4.923	1.161	5	0.140
2	7.947	11.249	4.592	1.731	5	0.072
3	15.294	7.441	3.037	5.035	5	0.002†
4	13.353	9.403	3.838	3.478	5	0.009†
5	9.991	10.086	4.117	2.426	5	0.030†
6	6.801	7.722	3.152	2.157	5	0.041†
7	4.934	10.405	4.247	1.162	5	0.149
8	11.038	7.659	3.126	3.530	5	0.008†
9	8.488	9.993	4.080	2.081	5	0.046†
10	4.205	10.710	4.372	0.962	5	0.190

† $p < .05$, one-tailed. Analyses did not pass Levene's tests so significant values do not assume equal variances.

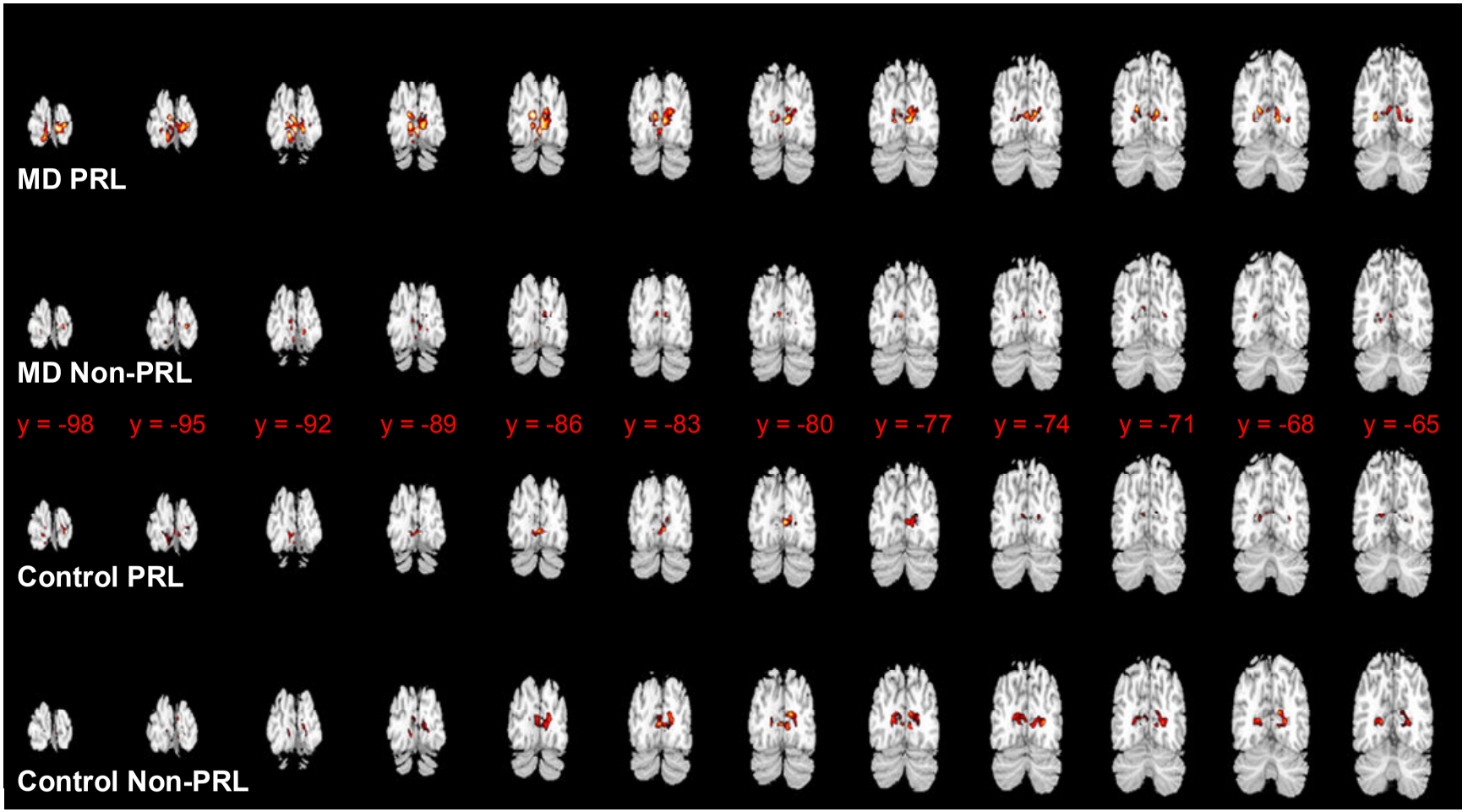


Figure 21. PRL and Non-PRL Activity

Group analyses were performed on normalized contrast images. They produced images for sections representing the PRLs and Non-PRLs in MD participants as well as PRLs in the Controls. Previous analyses indicate that these covariates are significantly different from one another. The group analysis was done to produce functional brain images to depict these differences. Because groups were composed of sections across participants, normalization of the contrasts was necessary for comparison. The functional images were overlaid onto the Montreal Neurological Institute's reference brain. MN1 coordinates are given in red. The images show more activity in posterior slices for the MD PRL array, indicating activity in the deafferented cortex is elicited by the PRL.

CHAPTER 8: DISCUSSION

8.1 Conclusions

Analysis of MD and control participants showed that both PRL and scotoma sections resulted in activity across the calcarine sulcus. However, PRL sections produced significantly more activity in the posterior calcarine for MD participants (Figure 15). There was no such difference in controls (Figure 16). Further analyses showed that sections representing the PRL in MD participants produced greater activation than the same sections in controls (Figure 18). This difference was localized to certain ROIs in the posterior calcarine. Finally, comparison of PRL and Non-PRL sections within the MD participants revealed that PRL sections produced significantly more activity, also localized to the posterior calcarine (Figure 20).

Concerning the PRL and scotoma comparisons, it is not surprising that scotoma sections resulted in some activity in the calcarine sulcus. Scotomata are not necessarily characterized by the absolute degeneration of all photoreceptors within their bounds. It is likely that some photoreceptors remain functional and elicit activity, however modest, in the visual cortex. However, because scotoma sections represent diseased retina in MD participants, their activity should be less than that of the PRLs.

PRL sections did, in fact, elicit more activity than scotoma sections in the posterior calcarine of MD participants (Figure 15). No such difference was observed between PRL and scotoma sections in the controls (Figure 16). These results demonstrate a meaningful connection between retinal sensitivity and the magnitude of activation in the calcarine sulcus and corroborate previous research that scotomata result in a reduction

of activity in the calcarine sulcus compared to preserved retina (Sunness, Lui, & Yantis, 2002).

Cortical reorganization was assessed by comparing the activity from PRL stimulation in MD participants and corresponding sections in controls. The MD group produced significantly more activity in the posterior calcarine than the controls (Figure 18). This difference was pinpointed to four specific ROIs in the posterior bin. Greater activity in the MD group is an indication of the expansion of receptive fields and cortical reorganization. The fact that this activity was elicited by sections presented to the periphery of the retina is further evidence that the visual cortex has reorganized in compensation for retinal deafferentation.

Analyses within the MD group compared the activity elicited by PRL and Non-PRL sections. PRL sections produce more activity in the posterior calcarine than Non-PRLs (Figure 20). This result indicates a relationship between cortical reorganization and the functional role of preserved retina. The increased use of the PRL in MD participants may result in more cortical reorganization. This result supports an understanding of cortical reorganization as an interaction between external input and activity patterns in the visual cortex.

These results supplement growing evidence that the human visual cortex is able to reorganize in response to changes in retinal input. Moreover, the results indicate that the degree of reorganization differs between preserved retinal areas, evidencing a connection between incidence of use and the extent of reorganization.

8.2 Implications

What do these results mean for our understanding of cortical reorganization as a form of plasticity? To begin with, it is evidence that visual reorganization in the adult human can occur within a short time frame. Pervious thought on this matter has categorized reorganization as a decades-long process (Sereno, 2005). Evidence of cortical reorganization within months has been observed in animal studies (Kaas, 1990). However, human research on the matter has been equivocal. For example, Dilks et al. (2006) found evidence of cortical reorganization in individuals who had AMD for less than ten years. However, Masuda et. al. (2006) did not demonstrate the same results for a similar AMD group.

The present research conforms to the findings of Dilks et al. (2005) and Baker et al. (2006). Individuals in this study had MD for ten years or less. Evidence of cortical reorganization from this group lends support to the idea that reorganization yield changes in a matter of a few years, rather than decades. However, though fast reorganization seems possible, it may be dependent on the interaction of several factors (i.e. age, time since onset, disease severity, etc).

The finding that the PRL induces more reorganization than other peripheral areas of the retina also holds many theoretical implications. It is an indication that the process of reorganization is intimately tied to environmental input. Theories have been advanced to suggest how PRLs develop in patients with MD (reviewed in Cheung & Legge, 2005). Differential sensitivity of the retina, changes in input due to training, and cortical factors have been proposed. While the present research supports a connection between PRL

development and cortical reorganization, there are still unanswered questions as to how this process develops.

It seems logical, however, that reorganization must begin with input. The functional difference between a healthy macula, a scotoma, and PRL lies in the amount of input they provide primary visual cortex, whether that is due to adaptation or natural distinction. An input driven explanation of cortical reorganization means that the primary determinant of how reorganization proceeds is where on the retina a MD patient is able to obtain usable visual information. Factors such as the extent and severity of the scotoma, the sensitivity of the peripheral retina, and training by the patient are all contributing elements, but they ultimately interact to determine how V1 receives input.

Another important consideration of an input-driven understanding is its directionality. The development of a PRL may elicit adaptation of neural processing in primary visual cortex. The structure of primary visual cortex seems to suggest that it has the capacity to deal with whatever changes the environment might bestow. This is evidenced by the extensive plexus of horizontal connections that pervade V1. Where ever damage might occur on the retina, and however training, necessity, and additional factors influence the development of PRLs, the primary visual cortex may respond accordingly, because, ultimately, it is the mutable actor in the relationship.

However, this relationship is not definitive. Alternatively, the capacity for reorganization of V1 neurons representing particular part of the visual field regions may drive the development of a PRL in that region. The directionality of reorganization remains unclear and will require more research investigation of the progression of functional reorganization and PRL development. Nonetheless, these findings offer

compelling evidence that, no matter the direction, a connection exists between the functional and cognitive adaptation and the neuronal reorganization in patients with MD.

A final consideration that this research brings to light is how reorganization might proceed. An interesting aspect of our current results is the lack of activity along the extent of calcarine sulcus. The evidence reported here shows that the most posterior aspect of the calcarine sulcus responds actively to peripheral retinal stimulation. However, this activity is isolated.

If the expansion of receptive fields is responsible for cortical reorganization, one might expect intermediary cortical areas, those in between the PRL and occipital pole, to be activated. This was not the case and indicates that the connection between PRL and macular cortex cannot be described by what is currently known about receptive fields and cortical physiology. For example, the range of connections between individual cortical columns is limited to 6 to 8 mm, not long enough to yield posterior activation observed in this study.

Interestingly, in the investigations Baker et al. (2005) also found macular activity out of the range of the collateral connections. They postulated that there might be an additional type of physiological connection that would allow selective, long range reorganization. This connection might only manifest after a long enough period allows for the synaptogesis of new axons or the permanence of long-range connections that remain in the wake of the initial expansion of receptive fields.

8.2 Limitations

This research employed a different method for data analysis than previous work on visual reorganization in humans. Most research on retinotopy has employed flat-

mapping in order to visualize activation in V1. In this process, the cortex is digitally unfolded and flattened so that researchers are able to establish the extent of activity across the cortex without the distortions caused by cortical folding (Wandell, Chial, Backus, 2000).

In contrast, this study created individuals ROIs that spanned the length of the calcarine sulcus and examined activity differences between them for evidence of cortical reorganization. This method certainly has it advantages over whole brain analyses in that it finds the average activation over a specific area (each ROI). However, how it compares to flat mapping procedures is undetermined. ROIs were drawn and divided in the coronal plane. Because the calcarine does not have substantial folds in the coronal plane, the accuracy of the present results is not questioned. However, flat mapping, may prove a more sensitive technique overall.

This study also used structural guides to draw the ROIs, limiting them to areas immediately adjacent to the calcarine sulcus. Studies have shown that V1 activity can often occur far way from the calcarine, closer to higher processing areas on the occipital (Dougherty, 2003). Phase encoded retinotopy has been used as a means of identifying activity representative of V1 and that of other higher processing areas (V2, V3, V4). This study did not employ phase-encoded retinotopy to distinguish V1 form other visual processing areas. In order to insure examination of just V1, ROIs were drawn in close adherence to the morphology of the calcarine sulcus. This tactic reduced the likelihood of including areas other than V1 but likely resulted in the exclusion of V1 areas not localized around the calcarine.

Eye tracking was not employed to monitor participants' fixation as they were scanned. Though possible, eye tracking of individuals with MD is difficult. In addition, a number of other technical problems resulted in forgoing eye tracking and informally monitoring the eyes with a video camera. Accurate data in this study depended on participants keeping their eyes fixated and immobile while stimuli are presented. If a participant focused on a peripheral stimulus with their fovea (in the case of controls) or their PRL (in the case of MD patients) then the activation observed along the calcarine sulcus would not have a true correspondence to the position of the stimulus.

Eye tracking data would indicate which trials participants' eyes strayed. Lacking eye tracking, participants were instructed to perform the same type of fixation during scanning as they did during the MP-1 evaluation. The MP-1 fixation data showed that participants, even MD group, were able keep their eyes still while focusing on the logical intersection of the fixation crosses. The success at performing this task during the MP-1 is an indication of participants' ability to perform it during scanning. Moreover, video monitoring revealed that participants were able to keep their eyes stable.

Moreover, the data suggest that eye movements are unlikely to have contributed to the reported results. Increased brain activity in posterior calcarine sulcus was observed when patients' PRLs were stimulated. Ancillary eye movements are least likely in this condition because the stimulus falls within the most stable region of fixation in MD participants. These results then are likely due to the reorganization of cortical activation within posterior calcarine sulcus and not an artifact of extraneous eye movements.

Finally, although the study produced significant results indicative of cortical reorganization, noise in the data was an issue. There was a general trend across

participants towards activation in the posterior calcarine from peripheral stimuli. However, on an individual basis, not all stimuli demonstrated this. In the future, noise in the data could be reduced in a number of ways. More trials could be run in a session. Although lengthening the time a participant must spend inside the scanner is not desired. In the future, exploratory trials, such as the Wedge scans, could be scarified to make room for more Section trials. Another way of improving the quality of the data is to strengthen the signal-to-noise ration (SNR) of the volumes. This research used a standard circularly polarized (CP) head coil. Future research may employ an 8-channel surface coil to image just the occipital lobe and improve SNR.

8.3 Future Directions

The results of this study have implications for understanding plasticity in the visual cortex. The observance of cortical reorganization in individuals diagnosed with macular degeneration for less than ten years (discounting participant CO) indicates that reorganization can occur on a short time frame in individuals with AMD. However, how factors such as the maturity of the brain, severity of the disease, and training may contribute to the extent and rate of reorganization is largely unknown. This study presents one of the first steps in a vein of research that will examine these issues. Future research will attempt to explicitly describe the progression of reorganization in terms of both exogenous and endogenous factors. Understanding how neurophysiology and environmental factors contribute to reorganization has implications for both basic science and clinical therapy.

Reorganization may also have implications beyond V1. The idea that cortical reorganization may be tied PRL use is consistent with existing behavioral research

demonstrating a functional relationship between cognitive processing and PRL use in MD patients. For example, it has been shown that the PRL location may be related to variability in attentional acuity across a patient's visual field (Altpeter, Mackeben, & Trauzettel-Klosinski, 2000). It has also been demonstrated that patients' ability to attend to and use stimuli from multiple sensory channels strengthens with MD disease progression (Jacko et al., 2003). Such results may mean that reorganization has a demonstrable effect on higher order perceptual and attention processes. Future work will examine these behavioral effects in the context of reorganization.

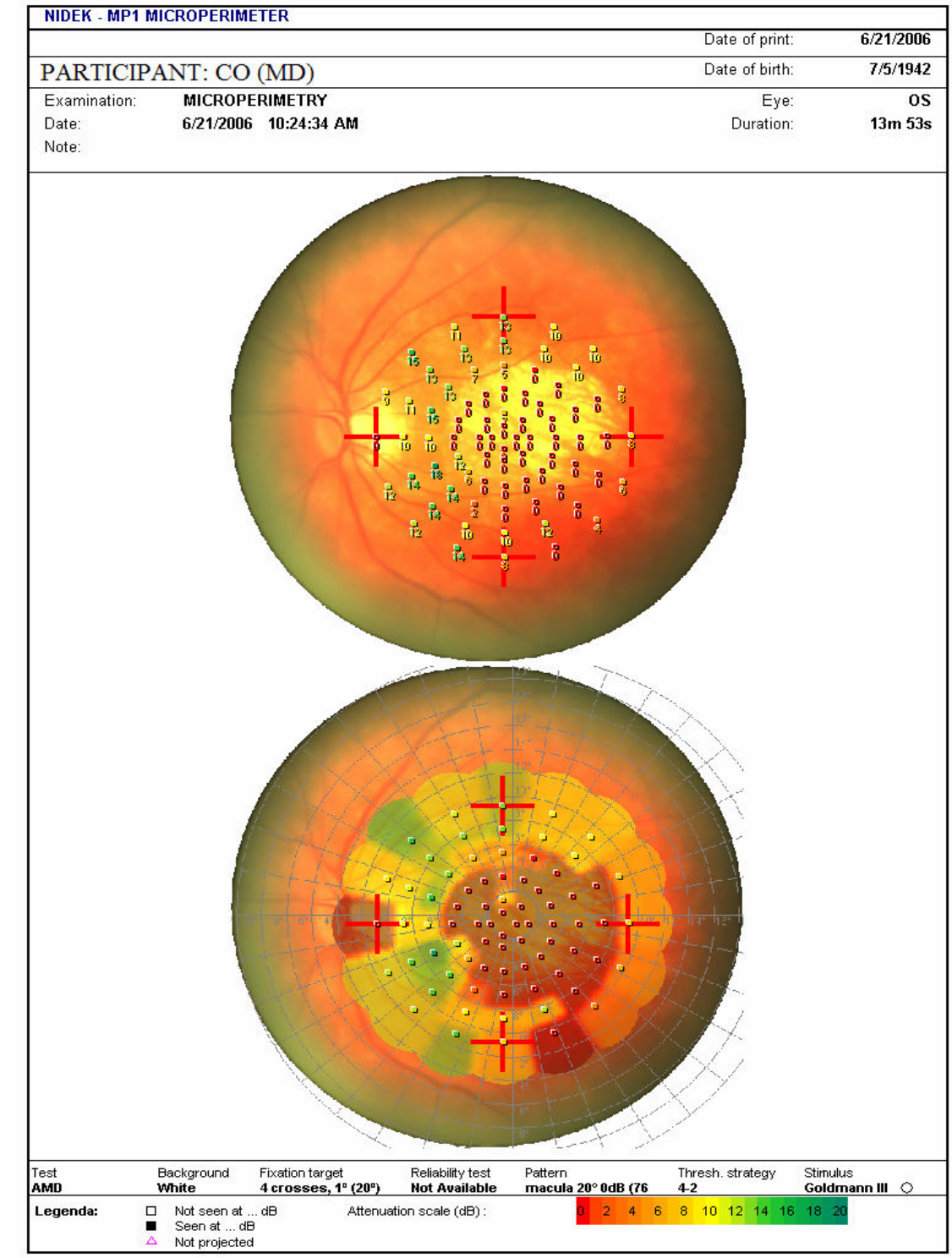
Finally, knowledge of the development of cortical reorganization could inform the design of training regimes and other therapies used to improve the visual capacity of individuals with MD. For example, rehabilitation programs for early-stage MD patients could help induce and direct cortical reorganization toward the formation of an optimal PRL. The extent or rate of cortical remapping in such therapies could be monitored by fMRI techniques and the efficacy of training evaluated by behavioral standards. Further studies may help better understand how and why cortical reorganization occurs and how it can aid the MD population. This research hopes to be the first step on path toward an extensive investigation of how reorganization occurs in the primary visual cortex and how it affects both low and high level vision. It is believed that such knowledge would have far reaching basic and clinical implications.

8.4 Concluding Remarks

Investigation of cortical reorganization has great potential for the extension of neural plasticity into new theoretical domains. The development of models describing the relationship between environmental input, neural change, and psychological experience is an approach at the very core of neuroscience and psychology. This hoped that this document is only the beginning, a first step toward a comprehensive program of research that will inform visual neuroscience and help, in some small way, usher in a new understanding of cortical plasticity.

APPENDIX A

MP-1 OUTPUT (MD PARTICIPANTS)



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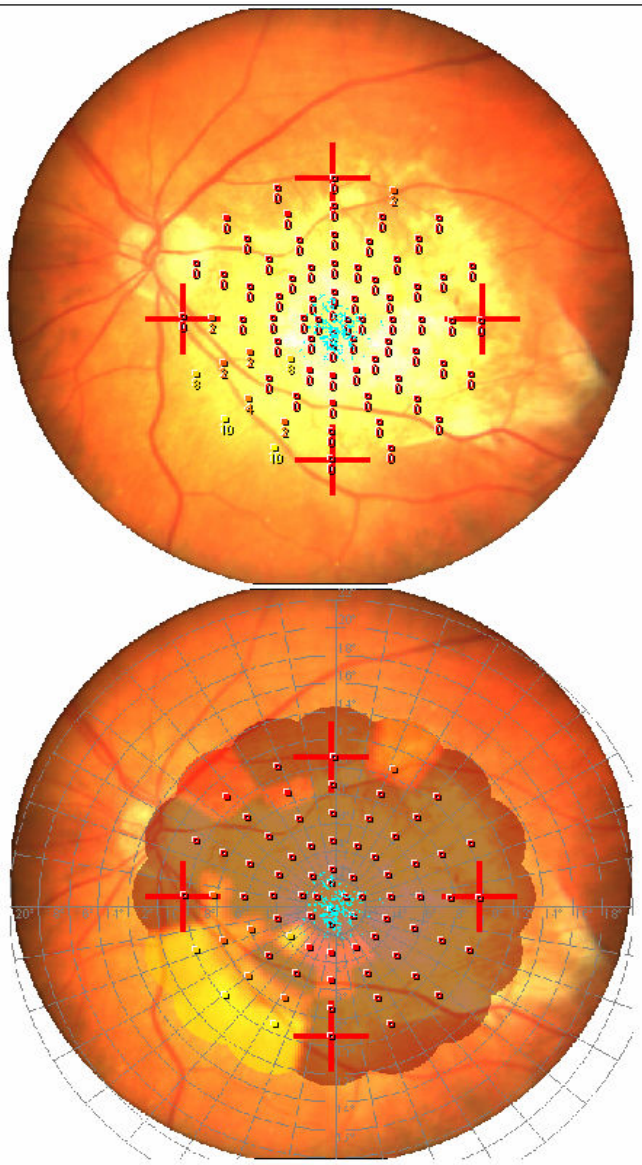

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Legenda:
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- ■ Seen at ... dB
- △ Not projected

Attenuation scale (dB): 0 2 4 6 8 10 12 14 16 18 20

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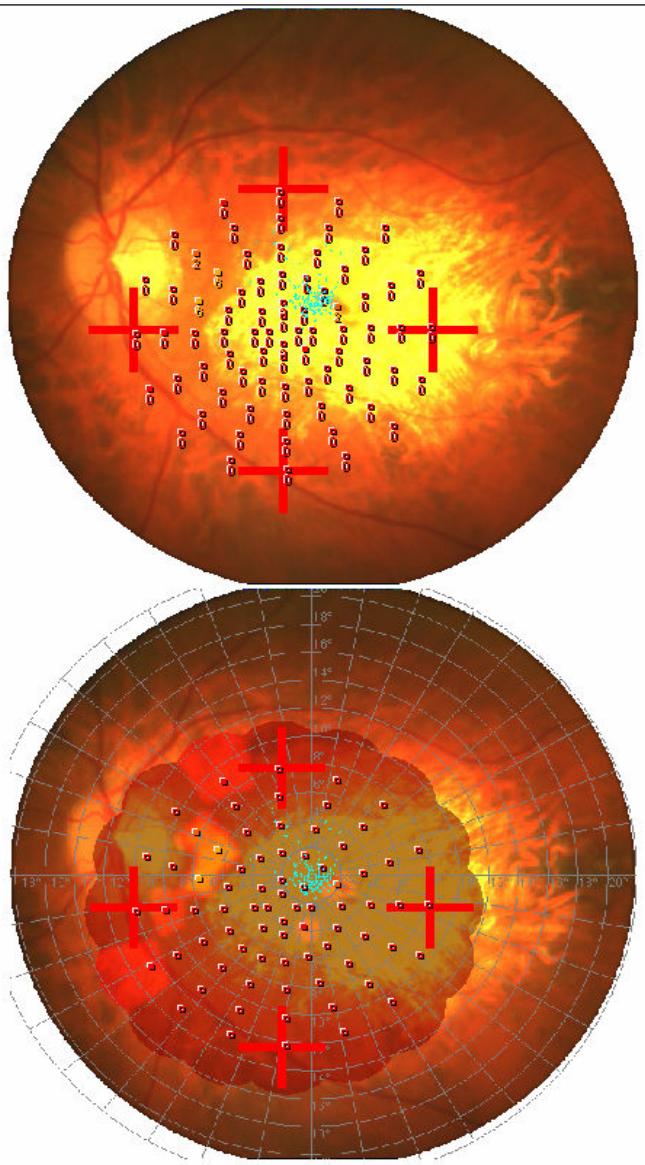

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Attenuation scale (dB) : 0 2 4 6 8 10 12 14 16 18 20

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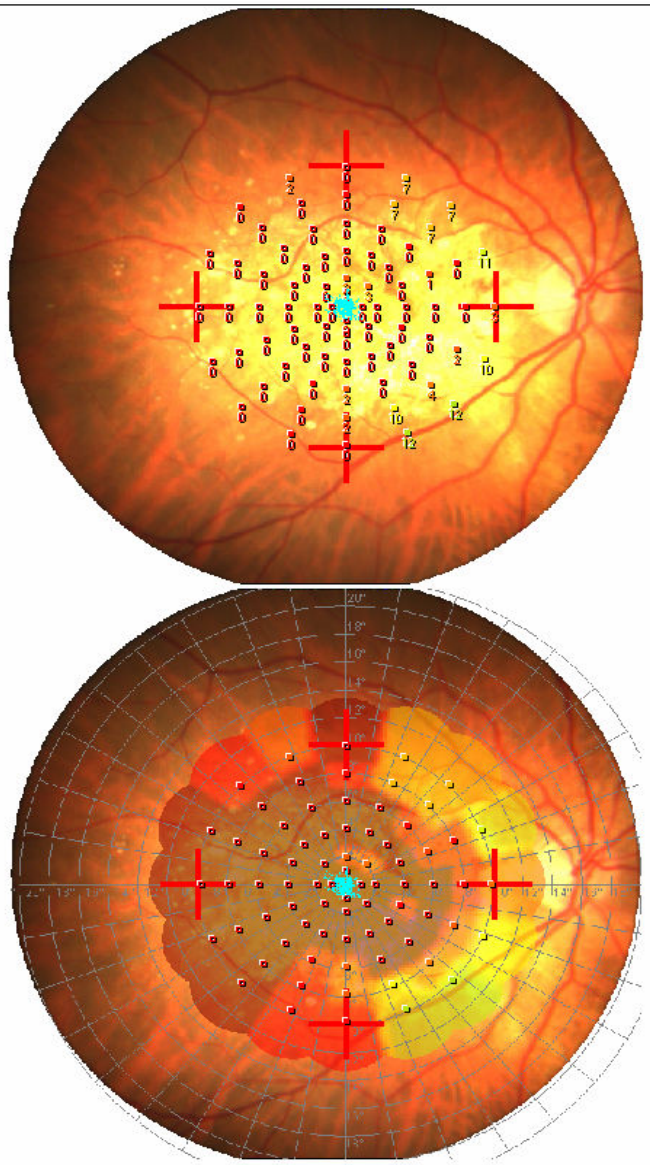

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Legenda:
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- △ Not projected

Attenuation scale (dB) : 0 2 4 6 8 10 12 14 16 18 20

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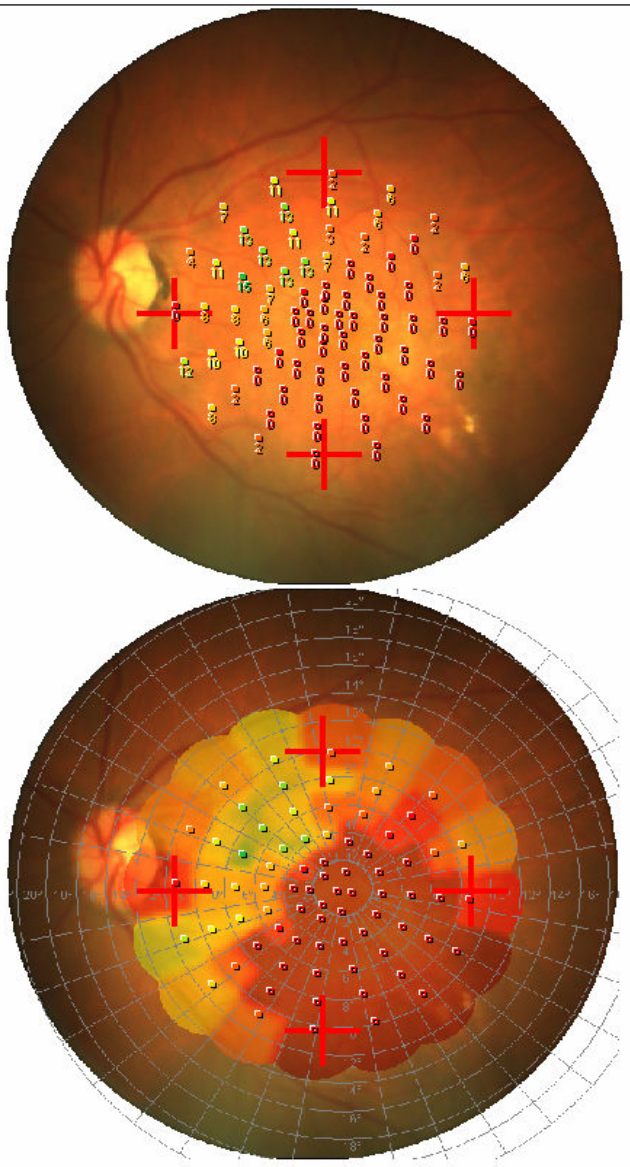

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Legenda: □ Not seen at ... dB ■ Seen at ... dB △ Not projected

Attenuation scale (dB) : 0 2 4 6 8 10 12 14 16 18 20

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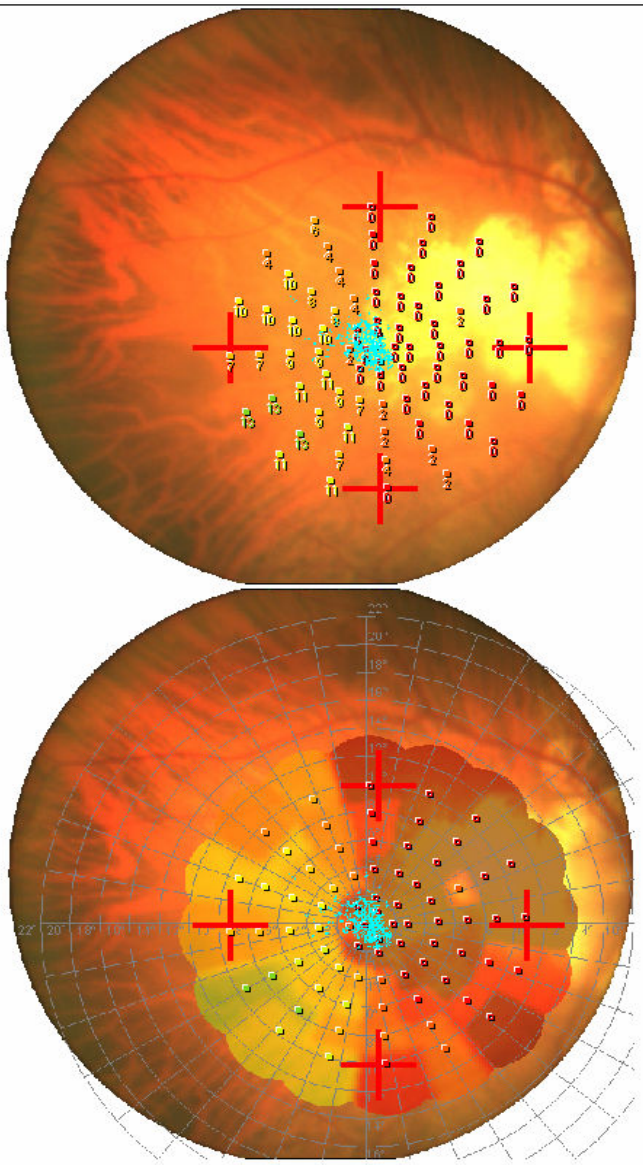

Test	Background	Fixation target	Reliability test	Pattern	Thresh. strategy	Stimulus
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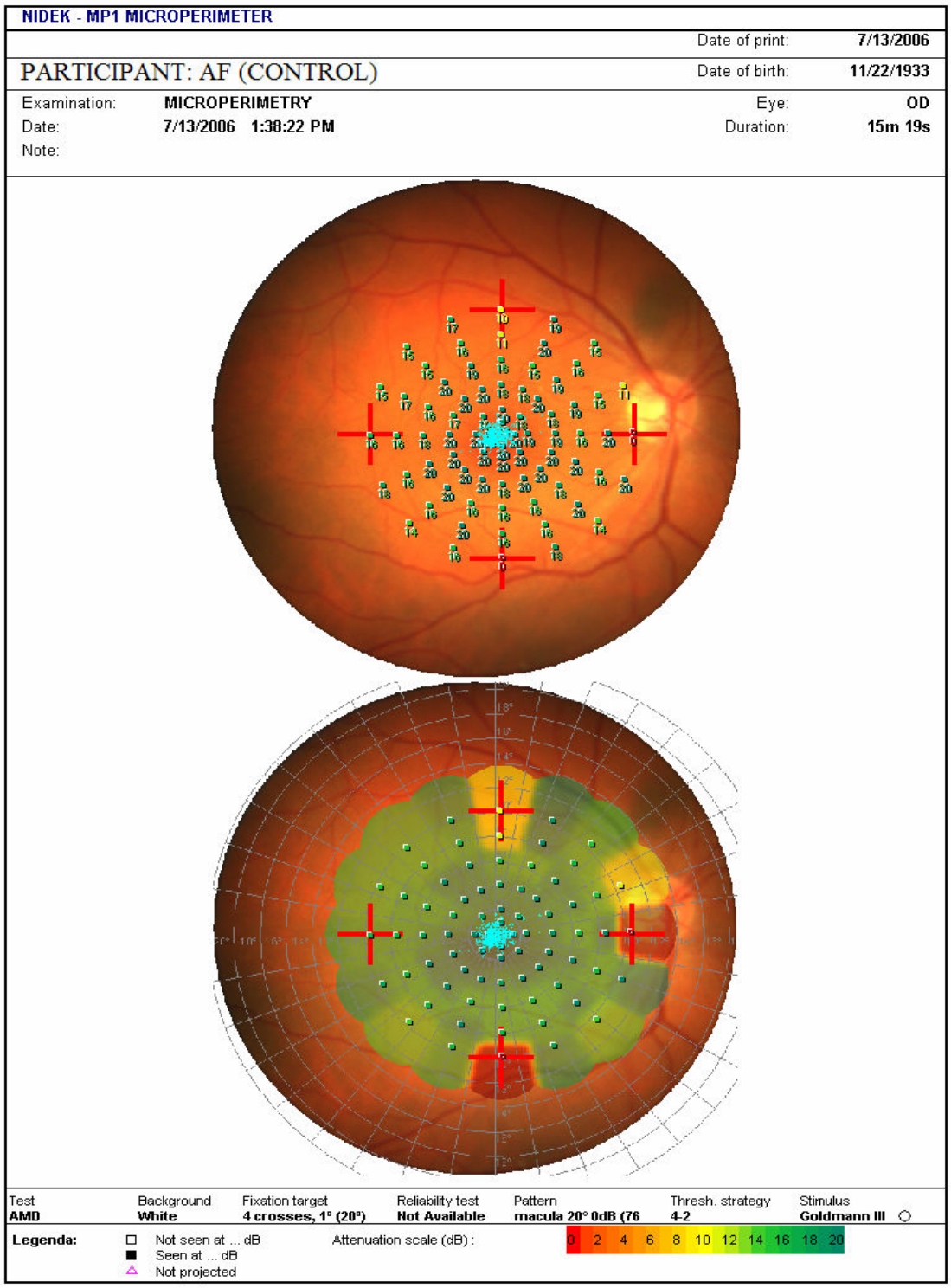
Legenda: □ Not seen at ... dB ■ Seen at ... dB △ Not projected

Attenuation scale (dB) : 0 2 4 6 8 10 12 14 16 18 20

APPENDIX B

MP-1 OUPUT (CONTROL PARTICIPANTS)



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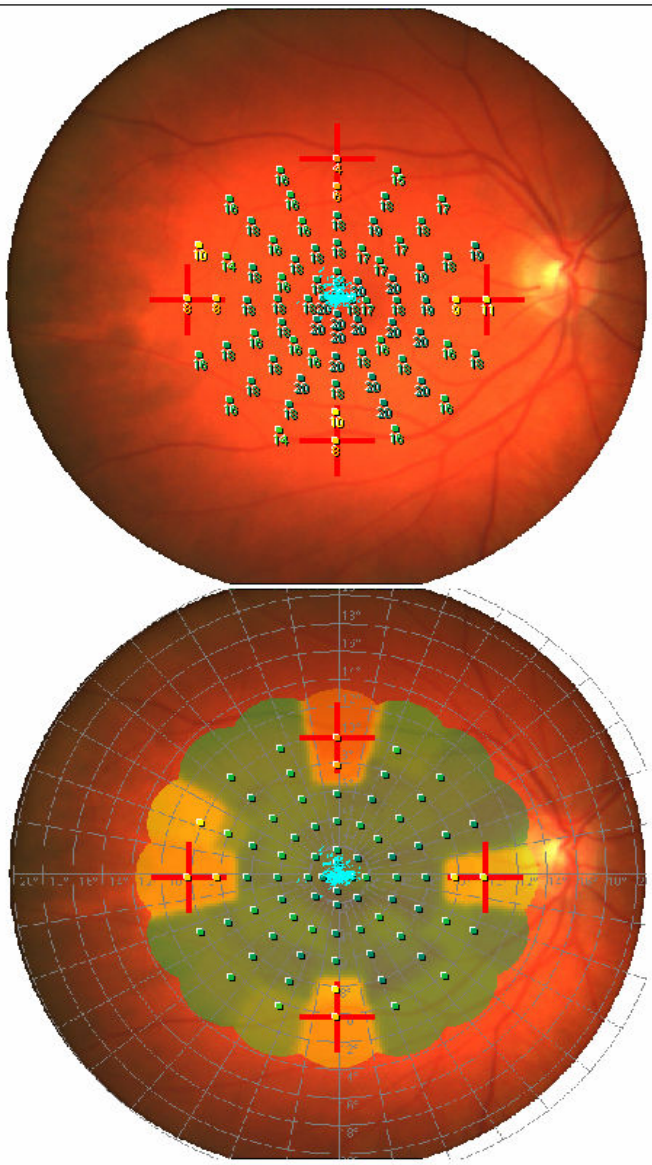

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Attenuation scale (dB) : 0 2 4 6 8 10 12 14 16 18 20

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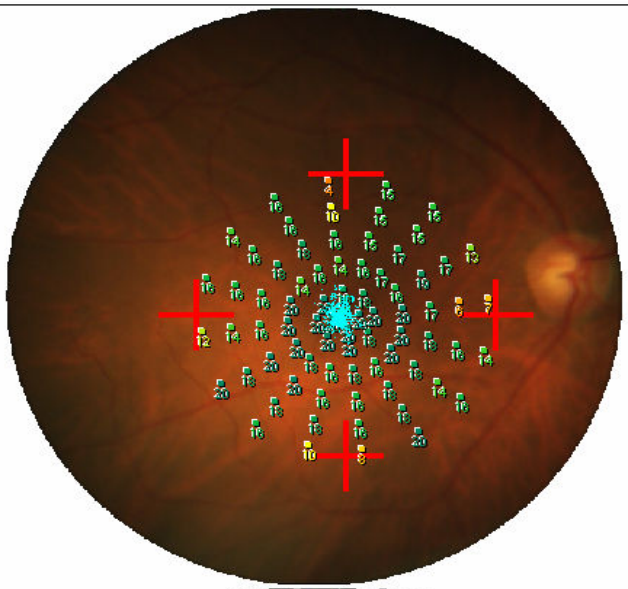

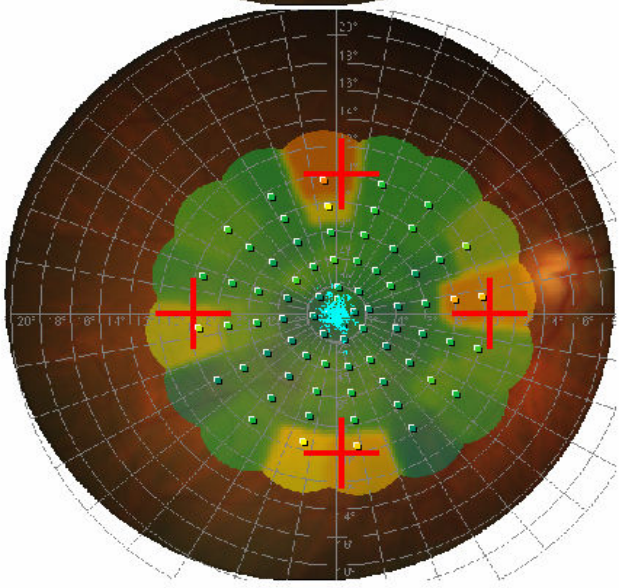

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Attenuation scale (dB) : 0 2 4 6 8 10 12 14 16 18 20

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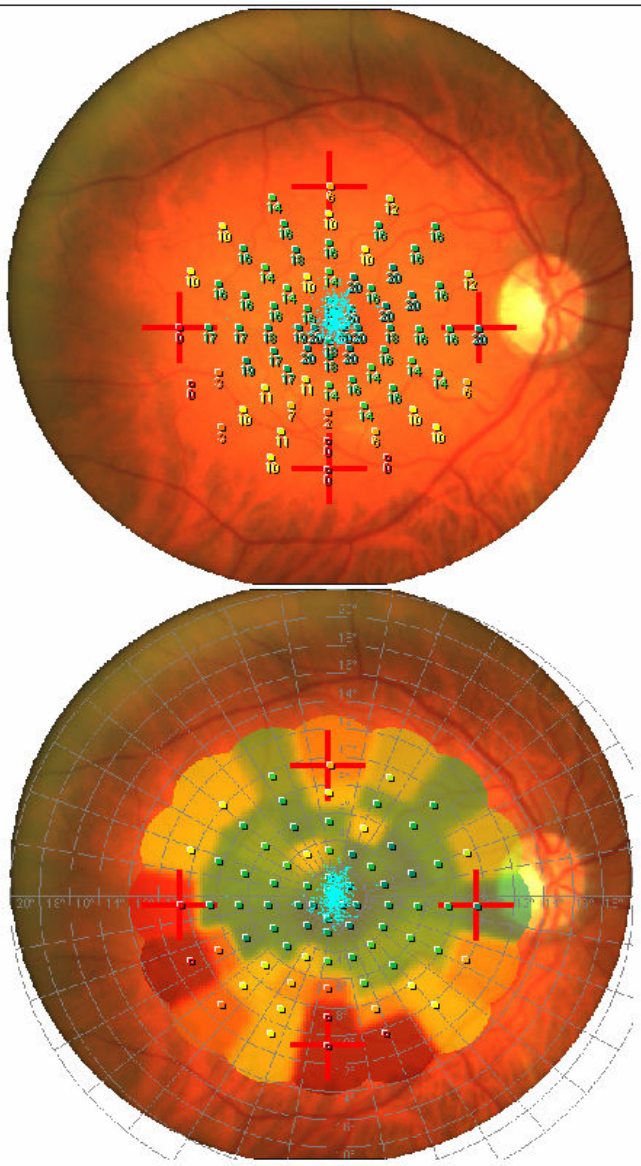

Test	Background	Fixation target	Reliability test	Pattern	Thresh. strategy	Stimulus
AMD	White	4 crosses, 1° (20°)	Not Available	macula 20° 0dB (76	4-2	Goldmann III

Legenda: □ Not seen at ... dB ■ Seen at ... dB △ Not projected

Attenuation scale (dB): 0 2 4 6 8 10 12 14 16 18 20

NIDEK - MP1 MICROPERIMETER

		Date of print:	7/13/2006
PARTICIPANT: BR (CONTROL)		Date of birth:	8/1/1927
Examination:	MICROPERIMETRY	Eye:	OD
Date:	7/13/2006 11:30:06 AM	Duration:	19m 13s
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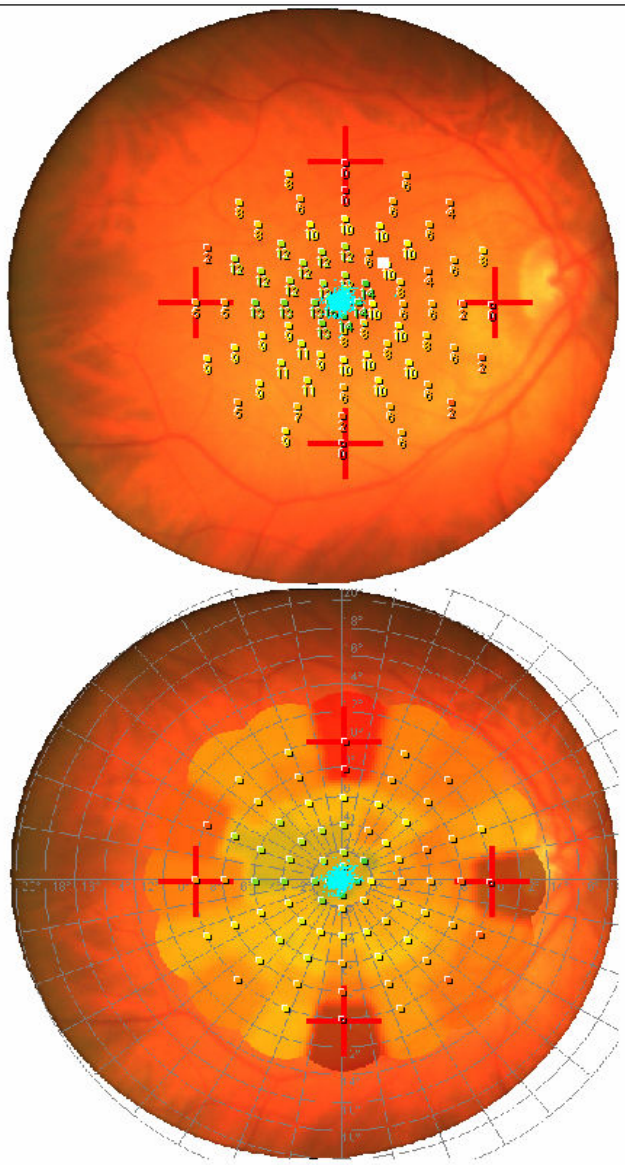


Test	Background	Fixation target	Reliability test	Pattern	Thresh. strategy	Stimulus
AMD	White	4 crosses, 1° (20°)	Not Available	macula 20° 0dB (76	4-2	Goldmann III

Legenda: □ Not seen at ... dB ■ Seen at ... dB △ Not projected

Attenuation scale (dB) : 0 2 4 6 8 10 12 14 16 18 20

NIDEK - MP1 MICROPERIMETER

Date of print: **6/30/2006**

PARTICIPANT: EJ (CONTROL)

Date of birth: **11/24/1923**

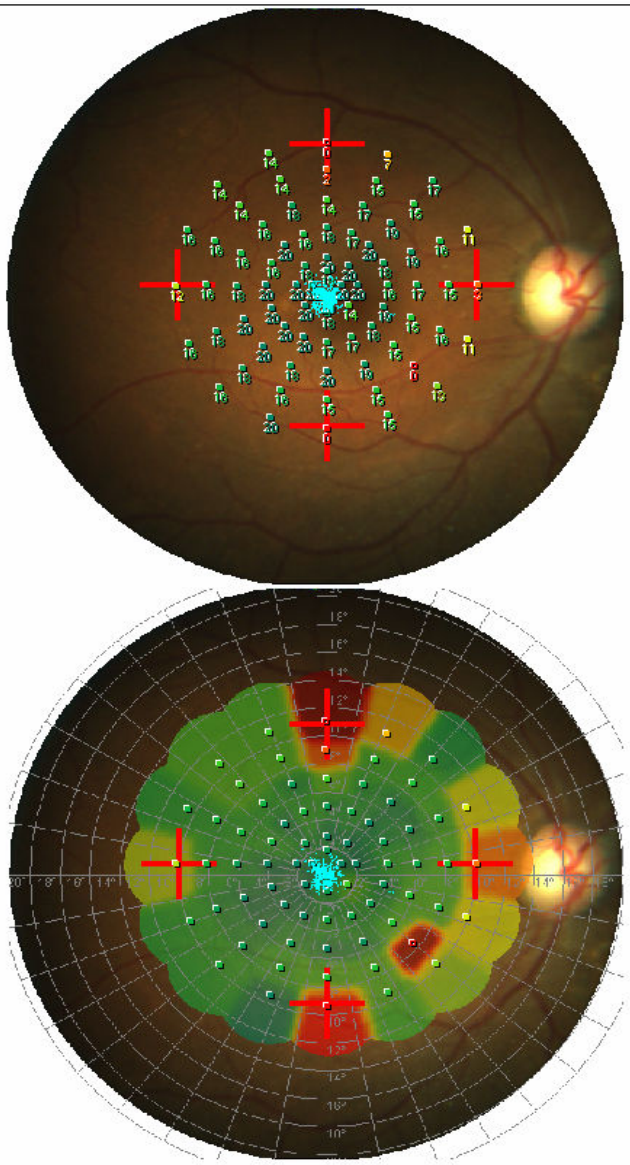
Examination: **MICROPERIMETRY**

Eye: **OD**

Date: **6/30/2006 1:11:53 PM**

Duration: **13m 38s**

Note:



Test	Background	Fixation target	Reliability test	Pattern	Thresh. strategy	Stimulus
AMD	**White**	**4 crosses, 1° (20°)**	**Not Available**	**macula 20° 0dB (76**	**4-2**	**Goldmann III** ○

Legenda: □ Not seen at ... dB ■ Seen at ... dB △ Not projected

Attenuation scale (dB) : 0 2 4 6 8 10 12 14 16 18 20

NIDEK - MP1 MICROPERIMETER

		Date of print:	7/10/2006
PARTICIPANT: JT (CONTROL)		Date of birth:	11/6/1942
Examination:	MICROPERIMETRY	Eye:	OS
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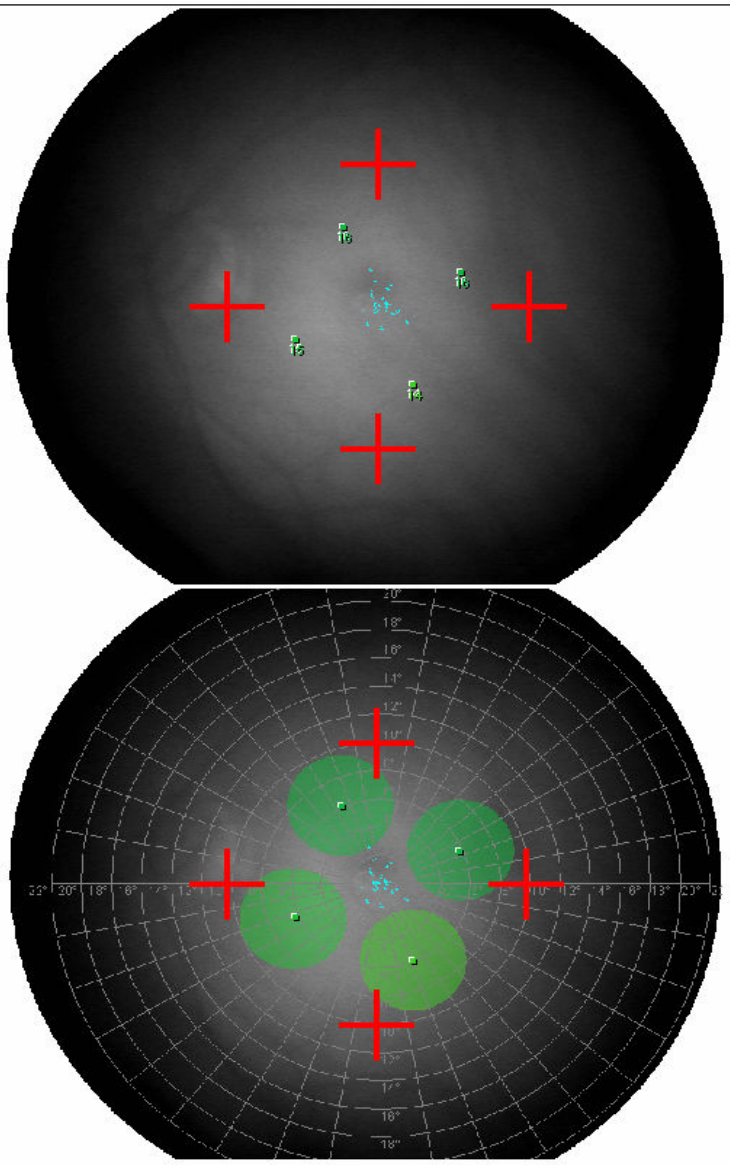

Test	Background	Fixation target	Reliability test	Pattern	Thresh. strategy	Stimulus
AMD	White	4 crosses, 1° (20°)	Not Available	macula 20° 0dB (76	4-2	Goldmann III

Legenda: □ Not seen at ... dB ■ Seen at ... dB △ Not projected

Attenuation scale (dB) : 0 2 4 6 8 10 12 14 16 18 20

NIDEK - MP1 MICROPERIMETER

		Date of print:	7/11/2006
PARTICIPANT: RP (CONTROL)		Date of birth:	4/26/1925
Examination:	MICROPERIMETRY	Eye:	OS
Date:	7/11/2006 3:21:30 PM	Duration:	18m 33s
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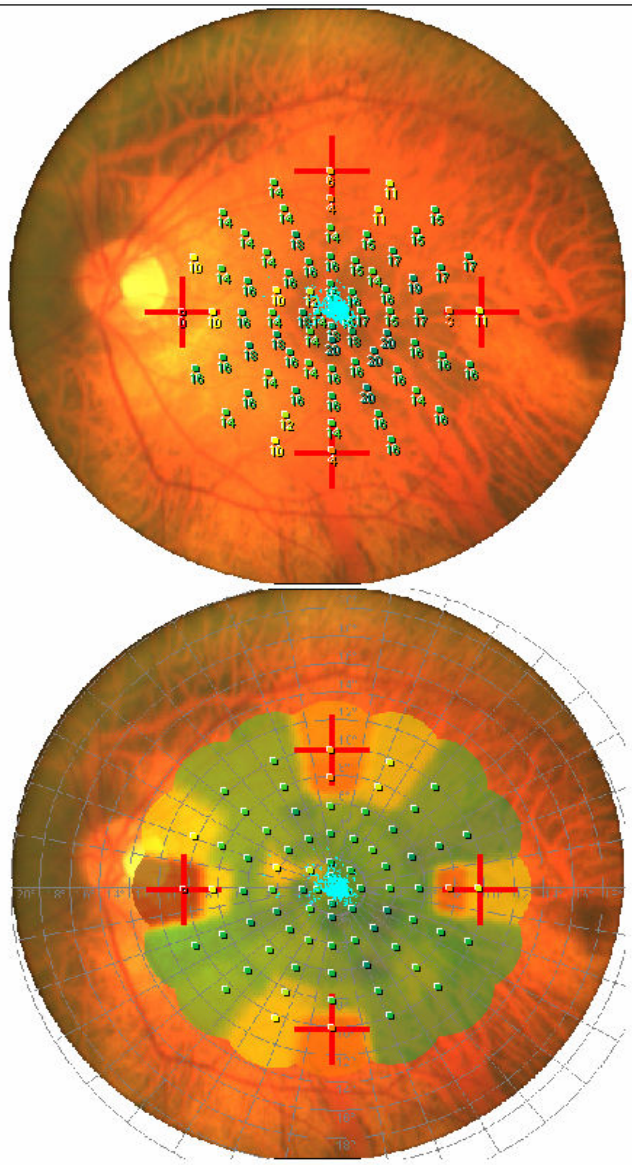


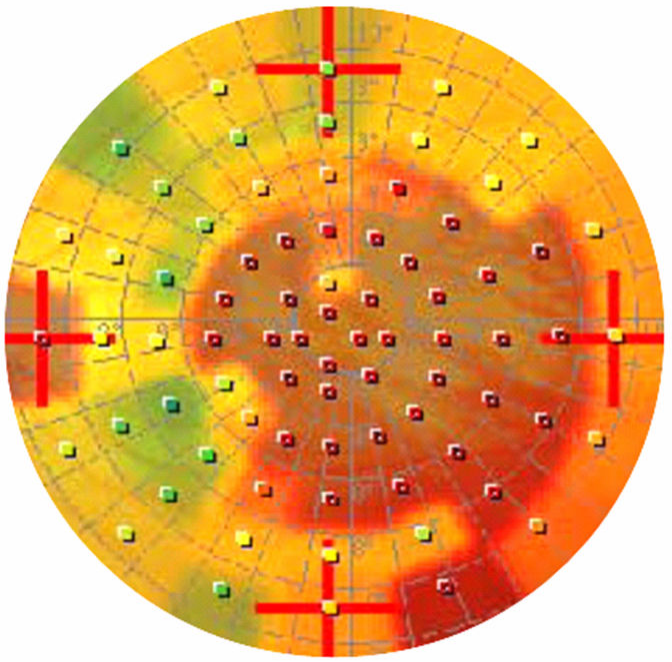
Test	Background	Fixation target	Reliability test	Pattern	Thresh. strategy	Stimulus
AMD	White	4 crosses, 1° (20°)	Not Available	macula 20° 0dB (76	4-2	Goldmann III

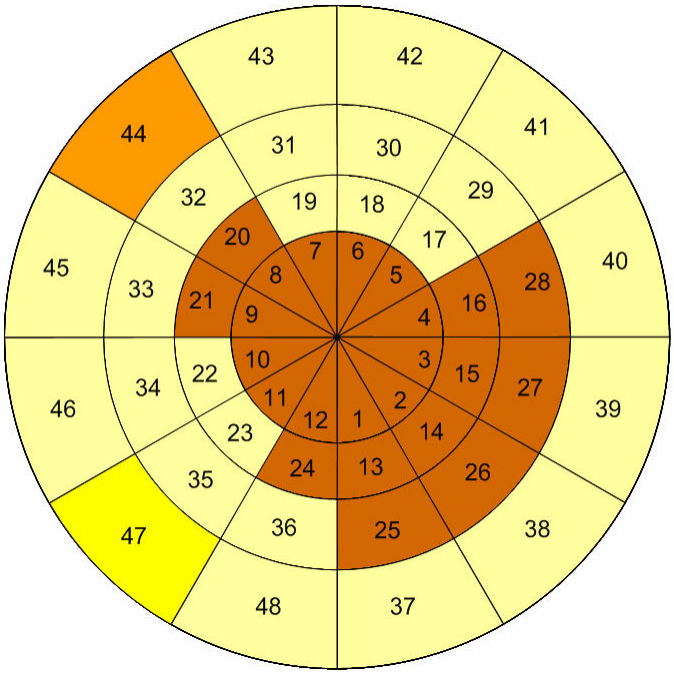
Legenda:
- □ Not seen at ... dB
- ■ Seen at ... dB
- △ Not projected

Attenuation scale (dB): 0 2 4 6 8 10 12 14 16 18 20

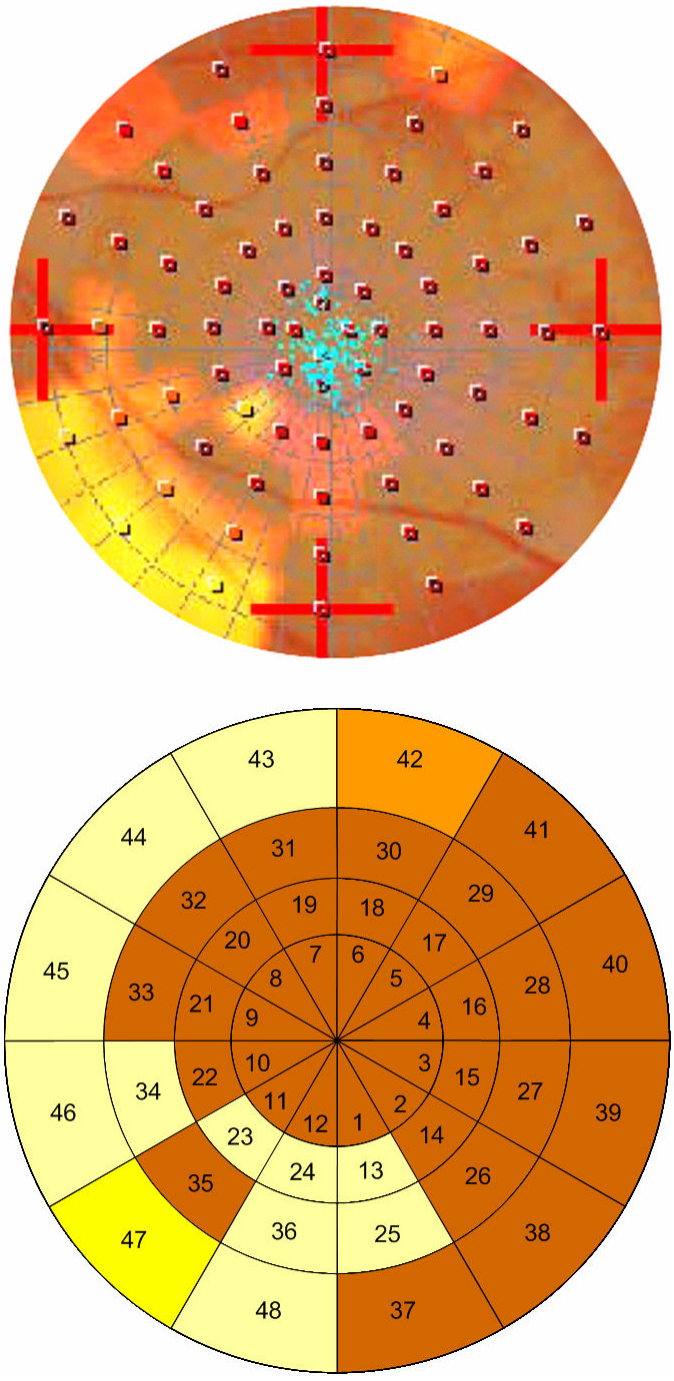
APPENDIX C

MP-1 OUPUT AND COLOR CODED SECTIONS

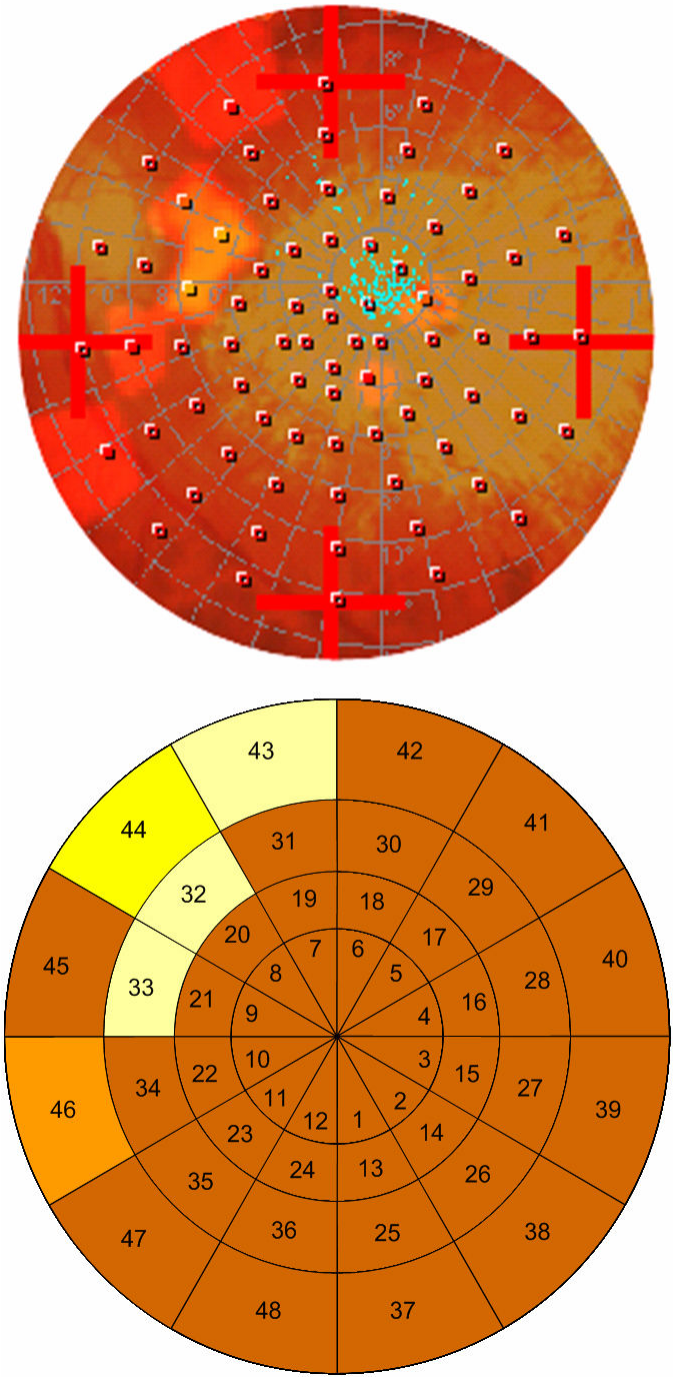




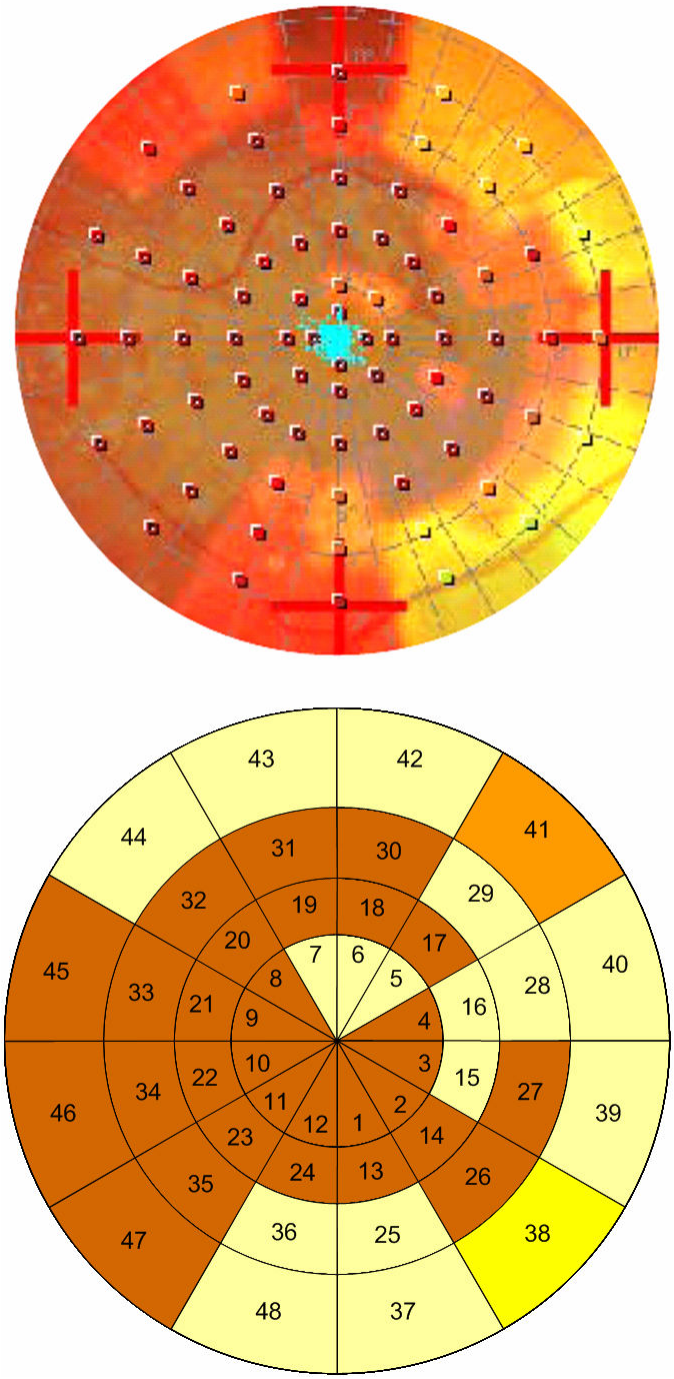
PARTICIPANT CO



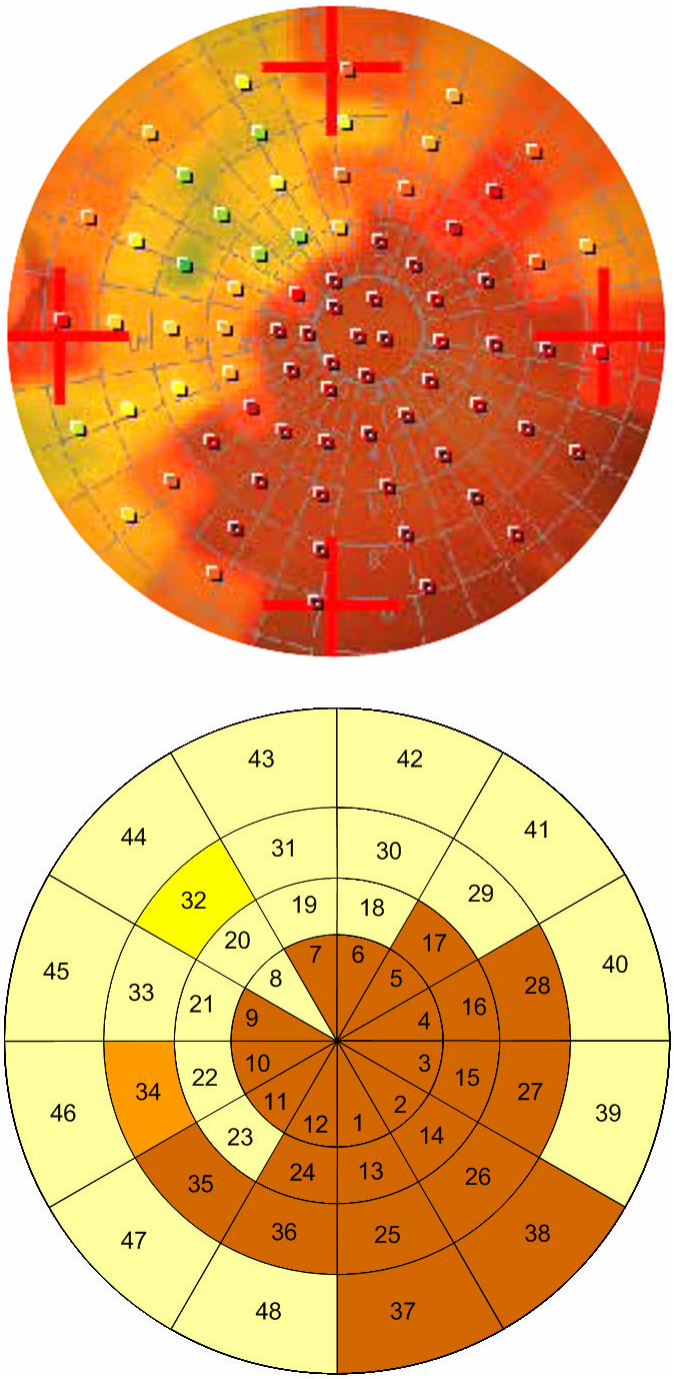
PARTICIPANT HG



PARTICIPANT JJ



PARTICIPANT JR



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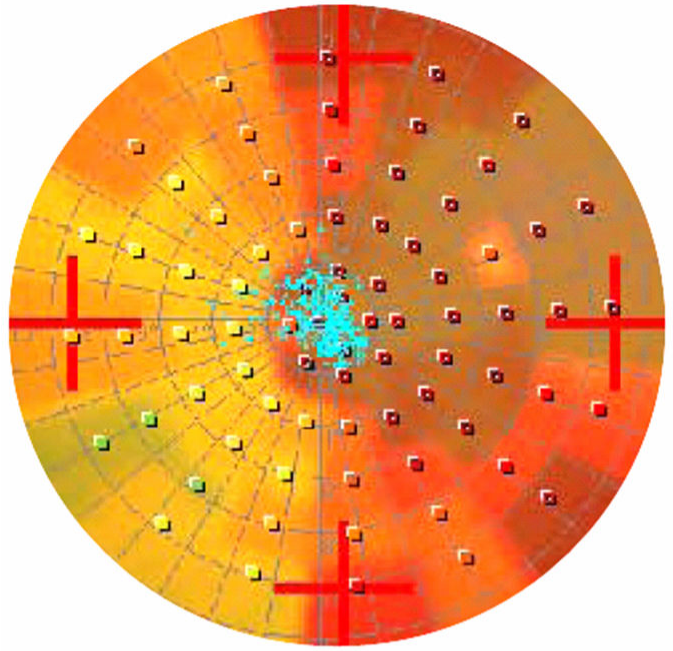

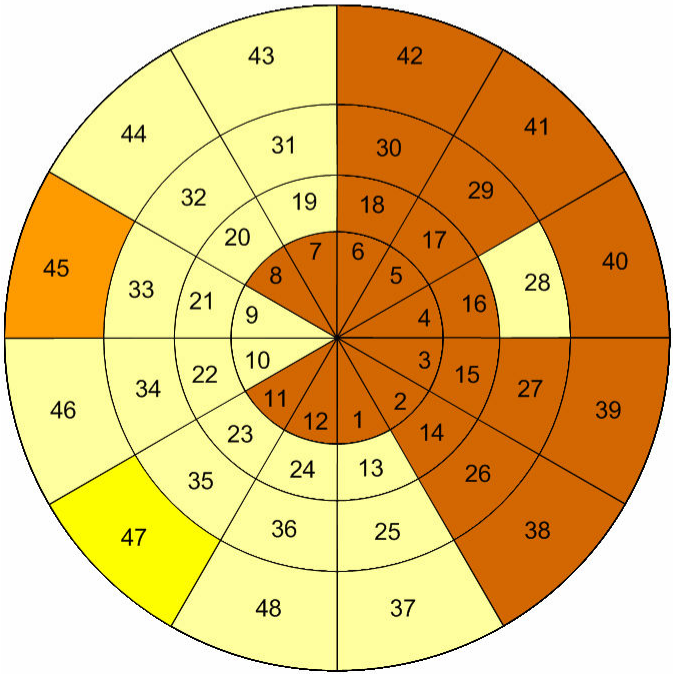

PARTICIPANT SL

REFERENCES

Altpeter, E., Mackeben, M., & Trauzettel-Klosinski, S. (2000). The importance of sustained attention for patients with maculopathies. *Vision Research, 40*(10-12), 1539-1547.

Ambati, J., Ambati, B. K., Yoo, S. H., Anchulev, S., & Adamis, A. P. (2003). Age-related macular degeneration: Etiology, pathogenesis, and therapeutic strategies. *Survey of Ophthalmology, 48,* 257–293.

Anderson, D. R. (2003). Standard perimetry. *Ophthalmology Clinics of North America, 16,* 205–212.

Azzopardi, P. & Cowey, A. (1993). Preferential representation of the fovea in the primary visual cortex. *Nature, 361,* 719–721.

Baker, C. I., Peli, E., Knouf, N., & Kanwisher, N. G. (2005). Reorganization of visual processing in macular degeneration. *Journal of Neuroscience, 25*(3), 614-618.

Bandettini, P. A., Jesmanowicz, A., Wong, E. C., & Hyde, J. S. (1993). Processing strategies for time-course data sets in functional MRI of the human brain. *Magnetic Resonance Medicine, 30,* 161–173.

Baseler, H. A., Brewer, A. A., Sharpe, L. T., Morland, A. B., Jagle, H., & Wandell, B. A. (2002). Reorganization of human cortical maps caused by inherited photoreceptor abnormalities. *Nature Neuroscience, 5*(4), 364-370.

Baseler, H.A., Sutter, E.E., Klein, S.A., & Carney, T. (1994). The topography of visual evoked response properties across the visual field. *Electroencephlography & Clinical Neurophysiology, 90*, 65-81.

Bauer, J. A., & Held, R. (1975). Comparison of visually-guided reaching in normal and deprived infant monkeys. *Journal of Experimental Psychology: Animal Behavior Processes, 1,* 298-308.

Blasdel, G. G. & Salama, G. (1986). Voltage-sensitive dyes reveal a modular organization in monkey striate cortex. *Nature, 321,* 579–85

Boothe, R.G., Dobson, V., & Teller, D.Y. (1985). Postnatal development of vision in human and nonhuman primates. *Annual Review of Neuroscience, 8,* 495-545.

Bressler, N. M. et al (1994).Clinicopathological correlation of drusen and retinal pigment epithelial abnormalities in age-related macular degeneration. *Retina, 14,* 130-142.

Brindley, G. S. & Lewin, W. S. (1968). The sensations produced by electrical stimulation of the visual cortex. *Journal of Physiology, 196,* 479–493.

Brown, M. M., Brown, G.C., Sharma, S., Landy, J., & Bakal, J. (2002). Quality of life with visual acuity loss from diabetic retinopathy and age-related macular degeneration. *Archives of Ophthalmology, 120,* 481–484.

Buonomano, D. V., & Merzenich, M. M. (1998). Cortical plasticity: From synapses to maps. *Annual Review of Neuroscience, 21,* 149–186.

Calford, M. B., Wang, C., Taglianetti, V., Waleszczyk, W. J., Burke, W., & Dreher, B. (2000). Plasticity in adult cat visual cortex (area 17) following circumscribed monocular lesions of all retinal layers. *Journal of Physiology-London, 524*(2), 587-602.

Casco, C., Campana, G., Grieco, A., Musetti, S., & Perrone, S. (2003). Hyper-vision in a patient with central and paracentral vision loss reflects cortical reorganization. *Visual Neuroscience, 20*(5), 501-510.

Cheung, S. H., & Legge, G. E. (2005). Functional and cortical adaptations to central vision loss. *Visual Neuroscience, 22*(2), 187-201.

Chopdar, A., Chakravarthy, U., & Verma, D. (2003). Age related macular degeneration. *British Medical Journal, 326,* 485–488.

Clark, S. A., Allard, T., Jenkins, W. M. & Merzenich, M. M. (1988). Receptive fields in the body-surface map in adult cortex defined by temporally correlated inputs. *Nature, 332,* 444–445.

Cohen, L. G., Weeks, R. A., Sadato, N., Celnik, P., Ishii, K., & Hallett, M. (1999). Period of susceptibility for cross-modal plasticity in the blind. *Annals of Neurology, 45*(4), 451-460.

Crist, R. E., Kapadia, M. K., Westheimer, G. & Gilbert, C. D. (1996). Perceptual learning of spatial localization: specificity for position, orientation and context. *Society for Neuroscience Abstracts, 22,* 269.

Daniel, P. M. & Whitteridge, D. (1961). The representation of the visual field on the cerebral cortex in monkeys. *Journal of Physiology, 159,* 203–221.

Darian-Smith, C., & Gilbert, C. D. (1994). Axonal sprouting accompanies functional reorganization in adult cat striate cortex. *Nature, 368*(6473), 737-740.

Darian-Smith, C. & Gilbert, C. D. (1995). Topographic reorganization in the striate cortex of the adult cat and monkey is cortically mediated. *Journal of Neuroscience, 15,* 1631–1647.

Das, A. (1997). Plasticity in the adult sensory cortex: A review. *Network: Computation in Neural Systems, 8,* 33-76.

DeCarlo, D. K., Scilley, K., Wells, J., & Owsley, C. (2003). Driving habits and health-related quality of life in patients with age-related maculopathy. *Optometry and Vision Science, 80,* 207–213.

DeYoe, E. A., Carman, G. J., Bandettini, P., Glickman, S., Wieser, J., Cox, R., Miller, D., & Neitz, J. (1996). Mapping striate and extra-striate visual areas in human cerebral cortex. *Proceedings of the National Academy of Sciences of the USA, 93,* 2382–2386.

Dilks, D.D**.**, Baker, C.I, Peli, E., & Kanwisher, N (2006, November). *Reorganization of Cortical visual processing: further evidence from individuals with macular degeneration.* Poster session presented at Society for Neuroscience, Atlanta, GA.

Dougherty, R. F., Koch, V. M., Brewer, A. A., Fischer, B., Modersitzki, J., Wandell, B. (2003). Visual field representations and locations of visual areas V1/2/3 in human visual cortex. *Journal of Vision, 3,* 586-598.

Dow, B. M., Vautin, R. G., & Bauer, R. (1985). The mapping of visual space onto foveal striate cortex in the macaque monkey. *Journal of Neuroscience, 5,* 890-902.

Duncan, R. O. & Boynton, G. M. (2003). Cortical magnification within human primary visual cortex correlates with acuity thresholds. *Neuron, 38,* 659–671.

Duvernoy, H. M. (2000). *The Human Brain: Surface, Blood Supply and Three-Dimensional Sectional Anatomy.* Wien, NY: Springer.

Engel, S. A., Glover, G. H., Wandell, B. A. (1997). Retinotopic organization in human visual cortex and the spatial precision of functional MRI. *Cerebral Cortex, 7,* 181–192.

Engel, S. A., Rumelhart, D. E., Wandell, B. A., Lee, A. T., Glover, G. H., Chichilnisky, E. J., & Shadlen, M. N. (1994). fMRI of human visual cortex. *Nature, 369,* 525.

Eye Disease Prevalence Research Group. (2004). Prevalence of age-related macular degeneration in the United States. *Archives of Ophthalmology, 122,* 564–572.

Fahle, M. & Morgan, M. (1996). No transfer of perceptual learning between similar stimuli in the same retinal position. *Current Biology, 6,* 292–297.

Farnsworth, D. (1943). The Farnsworth-Munsell 100-hue and dichotomous tests for color vision. *Journal of the Optical Society of America, 33,* 568-578.

Felleman, D. J. & van Essen, D. C. (1991). Distributed hierarchal processing in the primate cerebral cortex. *Cerebral Cortex, 1,* 1-47.

Ferris, F. L., Kassoff. A., Bresnick, G. H., Bailey, I. L. (1982). New visual acuity charts for clinical research. *American Journal of Ophthalmology, 94,* 91-96.

Fine, A. M. (1989). Earliest symptoms caused by neovascular membranes in the macular. *Archives of Ophthalmology, 104,* 513-514.

Fiorani, M., Rosa, M. G. P., Gattass, R., & Rocha-Miranda, C. E. (1992). Dynamic surrounds of receptive fields in primate striate cortex: A physiological basis for perceptual completion? *Proceedings from the National Academy of Sciences, 89,* 8547-8551.

Fletcher, D. C. & Schuchard, R. A. (1997). Preferred retinal loci relationship to macular scotomas in a low-vision population. *Ophthalmology, 104,* 632–638.

Fletcher, D.C., Schuchard, R.A., & Watson, G. (1999). Relative locations of macular scotomas near the PRL: Effect on low vision reading. *Journal of Rehabilitation Research and Development, 36,* 356–364.

Foundation for Fighting Blindness (2005). *Age-related Macular Degeneration Treatments.*

Fox, K. (1992). A critical period for experience-dependent synaptic plasticity in rat barrel cortex. *Journal of Neuroscience, 12,* 1826–38.

Fox, P. T., Miezin, F. M., Allman, J. M., Van Essen, D. C., & Raichle, M. E. (1987). Retinotopic organization of human visual cortex mapped with positron-emission tomography. *Journal of Neuroscience, 7,* 913–922.

Fox, P. T., Mintun, M. A., Raichle, M. E., & Herscovitch, P. A. (1984). A noninvasive approach to quantitative functional brain mapping with $H_2{}^{15}O$ and positron emission tomography. *Journal of Cerebral Blood Flow and Metabolism, 4,* 329–333.

Fox, P. T., & Raichle, M. E. (1986). Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proceedings of the National Academy of Sciences of the USA, 83,* 1140–1144.

Fox, P. T., Raichle, M. E., Mintun, M. A., & Dence, C. (1988). Nonoxidative glucose consumption during focal physiologic neural activity. *Science, 241,* 462–464.

Friston, K. J., Jezzard, P., & Turner, R. (1994). Analysis of functional MRI time-series. *Human Brain Mapping, 1,* 153–171.

Fuchs, W. (1938). Pseudo-fovea. In *A Source Book of Gestalt Psychology*, ed. & trans. Ellis, W. D., pp. 357–365. London: Kegan Paul.

Gazzaniga, M. S., Ivry, R. B., & Mangun, G. R. (2002). *Cognitive Neuroscience: The Biology of the Mind.* New York: Norton.

Gibson, E. J. (1967). *Principles of Perceptual Learning and Development.* New York: Appleton-Century-Crofts.

Gilbert, C. D. (1992). Horizontal integration and cortical dynamics. *Neuron, 9,* 1–13.

Gilbert, C. D. (1994). Early perceptual learning. *Proceedings of the National Academy of Sciences, 91,* 1195–1197.

Gilbert, C. D. & Wiesel, T. N. (1989). Columnar specificity of intrinsic horizontal and corticocortical connections in cat visual cortex. *Journal of Neuroscience, 9,* 2432–2442.

Gilbert C.D., & Weisel, T.N. (1992). Receptive field dynamics in adult primary visual cortex. *Nature, 356*, 150–152.

Glickstein, M. (1988). The discovery of the visual cortex. *Scientific American*, 188-127.

Greenough, W.T., & Chang, F. F. (1989). Plasticity of synapse structure and pattern in the cerebral cortex. *Cerebral Cortex, 7,* 391–440.

Heeger, D. J., Simoncelli, E. P., & Movshon, J. A. (1996). Computational models of cortical visual processing. *Proceedings of the National Academy Sciences, 93***,** 623–627.

He, S., Cavanagh, P., & Intriligator, J. (1996). Attentional resolution and the locus of awareness. *Nature, 383,* 334-338.

Hebb, D. O. (1949). *The Organization of Behavior: A Neuropsychological Theory.* New York: Wiley.

Hein, A., Held, R. & Gower, E.C. (1970). Development and segmentation of the visually-controlled movement by selective exposure during rearing. *Journal of Comparative and Physiological Psychology, 73,* 181-187.

Heinen, S. J., & Skavenski, A. A. (1991). Recovery of visual responses in foveal V1 neurons following bilateral foveal lesions in adult monkey. *Experimental Brain Research, 83*(3), 670-674.

Hirsch, J. A. & Gilbert, C. D. (1991). Synaptic physiology of horizontal connections in the cat's visual cortex *Journal of Neuroscience, 11,* 1800-1809.

Holmes, G. (1945). Ferrier Lecture: The Organization of the Visual Cortex in Man**.** *Proceedings of the Royal Society of London. Series B, Biological Sciences, 132* (869), 348-361

Holmes, G. & Lister, W. T. (1916). Disturbances of vision from cerebral lesions, with special reference to the cortical representation of the macula. *Brain, 39,* 34–73.

Horton, J. C. & Hocking, D. R. (1998). Monocular core zones and binocular border strips in primate striate cortex revealed by the contrasting effects of enucleation, eyelid suture, and retinal laser lesions on cytochrome oxidase activity. *Journal of Neuroscience, 18,* 5433-5455.

Horton, J.C. & Hoyt, W.F. (1991). The representation of the visual field in human striate cortex. A revision of the classic Holmes map. *Archives of Ophthalmology, 109*, 816-24

Hubel, D. H. & Wiesel, T. N. (1982). Exploration of the primary visual cortex, 1955-1978. *Nature, 299,* 515-524.

Hubel, D.H., Wiesel, T.N., & LeVay, S. (1977). Plasticity of ocular dominance columns in monkey striate cortex. *Philosophical Transactions of the Royal Society of London: Series B, Biological Sciences, 278,* 377-409.

Illing, R-B. (2004). Maturation and plasticity in the central auditory system. *Acta Oto-Laryngologica, 552,* 6-10.

Jacko, J. A., Vitense, H. S., & Scott, I. U. (2003). Perceptual impairments and computing technologies. In J. A. Jacko & A. Sears (Eds.), *Human-Computer Interaction Handbook: Fundamentals, Evolving Technologies and Emerging Applications*. Mahwah, NJ: Lawrence Erlbaum.

James, W. (1890). *Principles of Psychology*. NewYork: Henry Holt and Company.

Kaas, J. H. (1991). Plasticity of sensory and motor maps in adult mammals. *Annual Review of Neuroscience, 14,* 137–167.

Kaas, J. H., Krubitzer, L. A., Chino, Y. M., Langston, A. L., Polley, E. H., & Blair, N. (1990). Reorganization of retinotopic cortical maps in adult mammals after lesions of the retina. *Science, 248*(4952), 229-231.

Kandel E. R. (2000). Nerve cells and behavior. In Kandel, E. R., Schwartz, J. H., Jessell, T. M. (Eds.). *Principles of Neural Science* (4th ed.). New York: McGraw-Hill.

Kattah, J. C., Dennis, P., Kolsky, M. P., Schellinger, D., & Cohan S. L. (1981). Computed tomography in patients with homonymous visual field defects: A clinico-radiologic correlation. *Journal of Computer Assisted Tomography, 5,* 301-312.

Kelahan, A. M. & Doetsch, G. S. (1984). Time-dependent changes in the functional organization of somatosensory cerebral cortex following digit amputation in adult raccoons. *Somatosensory Research, 2,* 49–81.

Kennard, M. A. (1938). Reorganization of motor function in the cerebral cortex of monkeys deprived of motor and premotor areas in infancy. *Journal of Neurophysiology, 1,* 477–496.

Konorski, J. (1948). *Conditioned Reflexes and Neuron Organization.* New York: Cambridge University Press.

LeVay, S., Wiesel, T.N., & Hubel, D.H. (1980). The development of ocular dominance columns in normal and visually deprived monkeys. *The Journal of Comparative Neurology, 191,* 1-53.

Livingstone, M. S. & Hubel, D. H. (1984). Specificity of intrinsic connections in primate primary visual cortex. *Journal of Neuroscience, 4,* 2830–2835.

Martin, K. A. C. & Whitteridge, D. (1984). Form function and intracortical projections of spiny neurons in the striate visual cortex of the cat. *Journal of Physiology, 353,* 463–504.

Masuda, Y., Nakadomare, S., Asakawa, K., Dumoulin, S. O., Liu, J., Cheung, S., Ben Shachar, M., Kithara, K., & Wandell, B. (2006, November). *Lack of cortical reorganization in macular degeneration patients*. Poster session presented at Society for Neuroscience, Atlanta, GA.

McAuley, D. L. & Russell, R. W. R. (1979). Correlation of CAT scan and visual field defects in vascular lesions of the posterior visual pathway. *Journal of Neurology, Neurosurgery and Psychiatry, 42,* 298-311.

McFadzean, R., Brosnahan, D., Hadley, D., & Mutlukan, E. (1994). Representation of the visual field in the occipital striate cortex. *British Journal of Ophthalmology, 78,* 185-190.

McFadzean, R. M., Hadley, D. M., & Condon, B.C. (2002). The representation of the visual field in the occipital striate cortex. *Neuro-Ophthalmology, 27,* 55–78.

Merzenich, M. M. & Jenkins, W. M. (1995). Cortical plasticity, learning, and learning dysfunction. In B. Julesz & I. Kovacs (Eds.), *Maturational windows and adult cortical plasticity* (pp. 247–264). Reading, MA: Addison-Wesley.

Merzenich M M, Recanzone G, Jenkins W M Allard T T and Nudo R J 1988 Cortical representational plasticity. In P. Rakic & W. Singer (Eds), *Neurobiology of Neocortex*. New York: Wiley.

Morland, A. B., Baseler, H. A., Hoffmann, M. B., Sharpe, L. T., & Wandell, B. A. (2001). Abnormal retinotopic representations in human visual cortex revealed by fMRI. *Acta Psychologica, 107*(1-3), 229-247.

Movshon, A. J. & Sluyters, R. C. (1981). Visual neural development. *Annual Review of Psychology, 32,* 477-522.

Murakami, I., Komatsu, H. & Kinoshita, M. (1997). Perceptual filling-in at the artificial scotoma following a monocular retinal lesion in the monkey. *Visual Neuroscience, 14,* 89-101.

Nilsson, U. L., Frennesson, C., Nilsson, S. E. G. (1998). Location and stability of a newly established eccentric retinal locus suitable for reading, achieved through training of patients with a dense central scotoma. *Optometry and Vision Science, 75,* 873–878.

Nilsson, U. L., Frennesson, C., Nilsson, S. E. G. (2003). Patients with AMD and a large absolute central scotoma can be trained successfully to use eccentric viewing, as demonstrated in a scanning laser ophthalmoscope. *Vision Research, 43,* 1777–1787.

Obata, S., Obata, J., Das, A., & Gilbert, C. D. (1999). Molecular correlates of topographic reorganization in primary visual cortex following retinal lesions. *Cerebral Cortex, 9,* 238–248.

O'Leary, D. D. M, Ruff, N. L. & Dyck, R. H. (1994). Development critical period plasticity and adult reorganizations of mammalian somatosensory systems. *Current Opinion Neurobiology, 4,* 535- 544.

Ollinger, J. M., Shulman, G. L., Corbetta, M. (2001a). Separting processes within a trial in event-related functional fMRI I. The method. *NeruoImage, 13,* 210-217.

Ollinger, J. M., Shulman, G. L., Corbetta, M. (2001b). Separting processes within a trial in event-related functional fMRI II. The analysis. *NeruoImage, 13,* 218-229.

Orr, L. S., Schatz, N. J., Gonzalez, C. F., Savino, P. J., & Corbett, J. J. (1977). Computerized axial tomography in occipital lobe lesions. In. Smith J. L. Ed. *Neuro-ophthalmology Update*. New York: Masson, 351-367.

Pascual-Leone A. (1996). Reorganization of cortical motor outputs in the acquisition of new motor skills. In J. Kinura & H. Shibasaki (Eds.) *Recent Advances in Clinical Neurophysiology*, (pp. 304–308). Amsterdam: Elsevier Science.

Pascual-Leone, A., Amedi, A., Fregni, F., Merabet, F. B. (2005). The plastic human brain cortex. *Annual Review of Neuroscience, 28,* 377-401.

Pascual-Leone. A, Cohen. L. G., Brasil-Neto, J. P., Valls-Sole, J., Hallett, M. (1994). Differentiation of sensorimotor neuronal structures responsible for induction of motor evoked potentials, attenuation in detection of somatosensory stimuli, and induction of sensation of movement by mapping of optimal current directions. *Electroencephalography and Clinical Neurophysiology, 93,* 230–36.

Pelli, D. G., Robson, J. G., & Wilkins, A. J. (1988). The design of a new letter chart for measuring contrast sensitivity. *Clinical Vision Sciences, 2,* 187-199.

Pettet, M.W., & Gilbert, C.D. (1992). Dynamic changes in receptive-field size in the cat primary visual cortex. *Proceedings of the National Academy of Sciences, 89,* 8366-8370.

Ramachandran, V. S. (1993). Behavioral and magnetoencephalographic correlates of plasticity in the adult human brain. *Proceedings of the National Academy of Sciences, 90,* 10413–10420.

Ramachandran, V. S., Rogers-Ramachandran, D., & Stewart, M. (1992). Perceptual correlates of massive cortical reorganization. *Science, 258,* 1159–1160.

Ramachandran, V. S., Stewart, M., & Rogers-Ramachandran, D. (1992). Perceptual correlates of massive cortical reorganization. *NeuroReport, 3,* 583–586.

Rasmusson, D. D. (1982) Reorganization of raccoon somatosensory cortex following removal of the fifth digit. *Journal of Computational Neurology, 205,* 313–26.

Rasmusson, D. D. & Turnbull, B. G. (1983). Immediate effects of digit amputation on S-1 cortex in the raccoon unmasking of inhibitory fields. *Brain Research, 288,* 368–370.

Recanzone, G. H., Jenkins, W. M., Hradek, G. T., & Merzenich, M. M. (1992a). Progressive improvements in discriminative abilities in adult owl monkeys performing a tactile frequency discrimination task. *Journal Neurophysiology, 67,* 1015–1030.

Recanzone, G. H., Merzenich, M. M., Jenkins, W. M., Grajski, K. A. & Dinse, H. A. (1992b). Topographic reorganization of the hand representation in cortical area 3b of owl monkeys trained in a frequency discrimination task. *Journal of Neurophysiology, 67,* 1031–1056

Recanzone, G. H., Merzenich, M. M., & Jenkins, W. M. (1992c). Frequency discrimination training engaging a restricted skin surface results in an emergence of a cutaneous response zone in cortical area 3a. *Journal of Neurophysiology, 67,* 1057–1070.

Rockland, K. S. & Lund, J. S. (1982). Widespread periodic intrinsic connections in the tree shrew visual cortex. *Brain Research, 169,* 19–40.

Sadato, N., Okada, T., Honda, M., & Yonekura, Y. (2002). A critical period for cross modal plasticity in blind humans: A functional MRI study. *NeuroImage, 16,* 389-400.

Sansbury, R.V., Skavenski, A. A., Haddad, G.M., & Steinman, R.M. (1973). Normal fixation of eccentric targets. *Journal of the Optical Society of America, 63,* 612–614.

Saper, C. B., Iversen, S., & Frackowiak, R. (2000). Integration of sensory and motor function. In E. R. Kandel, J. H. Schwartz, & T. M. Jessell (Eds.) *Principles of Neural Science* (4th ed, pp 349-380). New York: McGraw-Hill.

Schmid, L. M., Rosa, M. G. P., & Calford, M. B. (1995). Retinal-detachment induces massive immediate reorganization in visual cortex. *NeuroReport, 6,* 1349-1353.

Schmid, L. M., Rosa, M. G. P., Calford, M. B., & Ambler, J. S. (1996). Visuotopic reorganization in the primary visual cortex of adult cats following monocular and binocular retinal lesions. *Cerebral Cortex, 6*, 388-405.

Schneider, W., Eschman, A., & Zuccolotto, A. (2002). *E-Prime User's Guide.* Pittsburgh: Psychology Software Tools, Inc.

Schoups, A. A., Vogels, R., & Orban, G. A. (1995). Human perceptual learning in identifying the oblique orientation: Retinotopy, orientation specificity and monocularity. *Journal of Physiology, 483*(3), 797–810

Schuchard, R. A. & Fletcher, D. C. (1994). Preferred retinal locus. A review with applications in low vision rehabilitation. *Low Vision and Vision Rehabilitation, 7,* 243–256.

Schuchard, R. A., Naseer, S., & de Castro, K. (1999). Characteristics of AMD patients with low vision receiving visual rehabilitation. *Journal of Rehabilitation Research and Development*, 36, 294–302.

Seddon, J.M. (2001). Epidemiology of age-related macular degeneration. In A. P. Schachat, S. Ryan (Eds.) *Retina* (3rd ed). St. Louis, MO: Mosby, 1039-1050.

Sereno, M. I. (2005). Plasticity and its limits. *Nature, 435,* 288-289.

Sereno, M. I., Dale, A. M., Reppas, J. B., Kwong, K. K., Belliveau, J. W., Brady, T. J., Rosen, B. R., Tootell, R. B. H. (1995). Borders of multiple visual areas in humans revealed by functional magnetic resonance imaging. *Science, 268,* 889–893.

Sharp P. F., Manivannan A., Xu, A., & Forrester J. V. (2004). The scanning laser ophthalmoscope–A review of its role in bioscience and medicine. *Physics in Medicine and Biology, 49,* 1085–1096.

Smirnakis, S. M., Brewer, A.A., Schmid, M. C., Tolias, A. S., Schuz, A., Augath, M., Inhoffen, W., Wandell, B. A., & Logothetis, N. K. (2005). Lack of long-term cortical reorganization after macaque retinal lesions. *Nature, 435*(7040), 300-307.

Spalding, J. M. D. (1952). Wounds of visual pathway II: The striate cortex. *Journal of Neurology, Neurosurgery and Psychiatry, 15,* 169-183.

Spector, R. H., Glaser, J. S., David, N. J., & Vining, D. Q. (1981). Occipital lobe infarctions: perimetry and computer tomography. *Neurology, 31,* 1098-1106.

Sunness, J. S., Applegate, C. A., Haselwood, D., & Rubin, G. S. (1996). Fixation patterns and reading rates in eyes with central scotomas from advanced atrophic age-related macular degeneration and Stargardt disease. *Ophthalmology, 103*(9), 1458-1466.

Sunness J. S., Gonzalez-Baron J., Applegate, C. A., Bressler, N.M., Tian, Y., Hawkins, B., Barron, Y., Bergman, A. (1999). Enlargement of atrophy and visual acuity loss in the geographic atrophy form of age-related macular degeneration. *Ophthalmology, 106,* 1768–1779.

Sunness, J.S., Liu, T., & Yantis, S. (2004). Retinotopic mapping of the visual cortex using functional magnetic resonance imaging in a patient with central scotomas from atrophic macular degeneration. *Ophthalmology, 111(8),*1595-1598.

Sur, M., Garraghty, P. E., & Roe, A. W. (1988). Experimentally induced visual projections into auditory thalamus and cortex. *Science, 242,* 1437–1441.

Stiles, J. (2000). Neural plasticity and cognitive development. *Developmental Neuropsychology*, *18*(2), 237–272.

Swindale, N. V. (1996). The development of topography in the visual cortex: A review of models. *Network: Computation in Neural Systems, 7,* 161-247.

Talairach, J. & Tournoux, P. (1988). *Co-Planar Stereotaxic Atlas of the Human Brain: Three-Dimensional Proportional System*. New York: Thieme Medical

Talbot S. A. & Marshall, W. A. (1941). Physiological studies on neural mechanisms of visual localization and discrimination. *American Journal of Ophthalmology, 24,* 1255-1264.

Timberlake, G. T., Peli, E., Essock, E. A., & Augliere, R. A. (1987). Reading with a macular scotoma retinal locus for scanning text. *Investigative Ophthalmology & Visual Science, 28*(8), 1268-1274.

Tootell, R. B. H., Switkes, E., Silverman, M. S., & Hamilton, S. L. (1988). Functional anatomy of macaque striate cortex II. Retinotopic organization. *Journal of Neuroscience, 8,* 1531–1568.

Tessier-Lavigne, M. (2000). Visual processing by the retina. In E. R. Kandel, J. H. Schwartz, & T. M. Jessell (Eds.) *Principles of Neural Science* (4th ed, pp 507-522). New York: McGraw-Hill.

Ts'o D. Y., Frostig, R. D., Lieke, E. E. & Grinvald (1990). A functional organization of primate visual cortex revealed by high resolution optical imaging. *Science, 249,* 417–420.

Van Essen, D. C., Newsome, W. T., & Maunsell, H. R. (1984). The visual field representation in striate cortex of the macaque monkey: anisotropies, and individual variability. *Vision Research, 24,* 429-448.

Vellringer, A. (2000). Physiological changes during brain activation. In P. A. Bandettini & C. T. W. Moonen (Eds.) *Functional MRI* (pp 3-13). Berlin: Springer.

Von Noorden, G., & Mackensen, G. (1962). Phenomenology of eccentric fixation. *American Journal of Ophthalmology, 53*, 642-659.

Wandell, B. A., Chial, S., Backus, B. T. (2000). Visualization and measurement of the cortical surface. *Journal of Cognitive Neuroscience, 12,* 739-752.

Webb, R. H., Hughes, G. W. & Pomerantzeff, O. (1980). Flying spot TV ophthalmoscope. *Applied Optics, 19,* 2991–2997.

Weinberger, N. M. (1995). Dynamic regulation of receptive fields and maps in the adult sensory cortex. *Annual Review of Neuroscience, 18***,** 129–58.

Weliky. M., Kandler, K., Fitzpatrick, D. & Katz, L. C. (1995). Patterns of excitation and inhibition evoked by horizontal connections in visual cortex share a common relationship to orientation columns. *Neuron, 15*, 541–52

Wertheimer, M. (1938). *Laws of Organization in Perceptual Forms.* New York: Harcourt Brace Jovanovitch.

Wiesel, T.N., & Hubel, D.H. (1965). Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens, *Journal of Neurophysiology, 28,* 1029-1040.

Worsley, K. J. & Friston, K. J. (1995). Analysis of fMRI Time-Series Revisited - Again, *NeuroImage, 2,* 173-181.

Wurtz, R. H. & Kandel, E. R. (2000). Central visual pathways. In E. R. Kandel, J. H. Schwartz, & T. M. Jessell (Eds.) *Principles of Neural Science* (4th ed, pp 523-546). New York: McGraw-Hill.

Zilles, K. & Clarke, S. (1997). Architecture, connectivity and transmitter receptors of human extrastriate visual cortex. Comparison with nonhuman primates. In K. S. Rockland, J. H. Kaas, & A. Peters (Eds.), *Cerebral Cortex* (pp 673-742). New York: Plenum Press.