VISUAL REHABILITATION AND REORGANIZATION:

CASE STUDIES OF CORTICAL PLASTICITY IN PATIENTS WITH

AGE-RELATED MACULAR DEGENERATION

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VISUAL REHABILITATION AND REORGANIZATION:

CASE STUDIES OF CORTICAL PLASTICITY IN PATIENTS WITH

AGE-RELATED MACULAR DEGENERATION

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To my mother and father, who’ve made all this possible.

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LIST OF SYMBOLS AND ABBREVIATIONS

AMD	Age-Related Macular Degeneration
BCEA	Bivariate Contour Ellipse Area
BCVA	Best Corrected Visual Acuity
cd/m^2	Candela per Square Meter
CNV	Choroidal Neovascularization
cpd	Cycles per Degree
ETDRS	Early Treatment Diabetic Retinopathy Study
EV	Eccentric Viewing
JMD	Juvenile Macular Degeneration
LPZ	Lesion Projection Zone
LV	Low Vision
LVR	Low Vision Rehabilitation
MAR	Minimum Angle of Resolution
MD	Macular Degeneration
OT	Occupational Therapy
REP	Retinal Pigment Epithelium
TMS	Transcranial Magnetic Stimulation
V1	Primary Visual Cortex

SUMMARY

The extent to which cortical maps may reorganize in adult humans is a significant and topical debate in visual neuroscience. Though there are conflicting findings, evidence from humans and animals indicates that the topography of the visual cortex may change after retinal deafferentation. Remarkably, this reorganization seems to be possible in adults, whose brains are less amenable to plastic change. If adult visual reorganization is legitimate, an understanding of its causes and consequences could be profound considering the millions suffering from age-related visual disorders.

This dissertation explores whether visual training may yield a reorganization of sensory maps in the adult visual cortex. It describes research in which patients, diagnosed with age-related macular degeneration (AMD), underwent visual rehabilitation therapy. Functional brain scans and behavioral tests were conducted pre and post training. These interventions generated valuable knowledge regarding whether "reorganized" activity is a true rewiring of feed forward cortical processes or an artifact of attentional feedback.

The rehabilitation training produced demonstrable differences in activation patterns along the primary visual cortex (V1), but sparse improvement in the behavioral tests. In contrast, there was significant improvement in fixation tests which assessed oculomotor control. These results suggest that the nature of reorganized activity has more to do with attentional mechanisms than feed forward reorganization. Future investigations could benefit from examining the brain sites that govern visual attention in the frontal and parietal cortices. These areas may have more to do with visual adaptation in AMD patients than V1.

CHAPTER 1: INTRODUCTION

The late Paul Bach-y-Rita, a pioneer of rehabilitative medicine, once described neuroplasticity as follows: “If you are driving from here to Milwaukee and the main bridge goes out, first you are paralyzed. Then you take old secondary roads through the farmland. Then you use these roads more; you find shorter paths to use to get where you want to go, and you start to get there faster” (Doidge, 2007).

Getting there and getting there more efficiently is the essence of brain adaptation. The destination is some former functionality, a behavioral or cognitive ability lost due to traumatic or acquired injury. The route is a detour through the neocortex, a roundabout way of reestablishing neural communication and initiating the patterned activity that underlies all our perceptions, thoughts and actions. The end result of this adjustment is often a shadow of the former ability and sometimes only achieved through coaxing, but however imperfect, the very fact our brains are capable of rewiring holds tremendous theoretical and clinical importance.

Neuroplasticity is arguably the most influential paradigm in the psychological and brain sciences today. It is the basis for burgeoning models of cognition (McIntosh, 2000) and consciousness (Hurley & Noë, 2003), as well as the theoretical foundation behind a slue of new clinical perspectives aimed at understanding everything from brain injury (Weiloch & Nikolich, 2006) to addiction (Everitt & Robbins, 2005) to dementia (Whalley, Deary, Appleton, & Starr, 2004). Perhaps most amazing, the idea of adult plasticity, that the mature brain is capable of change, was scientific heterodoxy less than half a century ago.

For much of the twentieth century neuroplasticity was considered a phenomenon of critical periods, distinct moments in early development in which the brain is amenable to change and recovery (Finger & Wolf, 1988; Kennard, 1938). The past thirty years, however, has witnessed a paradigm shift in the neurosciences. The brain, juvenile and adult alike, is now regarded as a dynamic structure, one in continual adaptation to both endogenous and exogenous demands (Stiles, 2000). Cortical maps, once thought to be immutable representations with fixed boundaries, are now known to be capable of extensive change (Buonomano & Merzenich, 1998; Cheung & Legge, 2005; Das, 1997; Kaas, 1991). Even more profound, the discovery of adult neurogenesis (Gage, 2000; Gould, Reeves, Graziano, & Gross, 1999) has upset one of the most entrenched dogmas of neuroscience, that the mature brain cannot generate new neurons (Gross, 2000; but see Rakic, 2002). Such discoveries have not only advanced our knowledge in the lab, they have opened possibilities in clinic as well.

The implications of adult neuroplasticity are far reaching for rehabilitative medicine (for an excellent treatise see Stein, Brailowsky, & Will, 1995). Knowledge of the conditions and limitations of cortical adaptation could help establish effective treatments and training programs for those suffering from damage to the central and peripheral nervous systems (Duffau, 2006; Elbert & Rockstroth, 2004; Stein & Hoffman, 2003). For example, an understanding of the cellular and extra-cellular mechanisms that are enacted when the brain is injured could yield pharmacological agents that enhance the brain's own natural protective properties and effectively halt secondary injury (Green et al., 1992; Roof, Duvdevani, & Stein, 1994; Rosenblum, Nelson, Bei, Brandt, & Chan, 1996). Knowledge of neural regeneration, such as the factors that elicit neurogenesis

(Ming & Song, 2005) and axonal sprouting (Doherty, Williams, & Williams, 2000; Pasterkamp & Verhaagen, 2001) may augment our ability to chemically repair the injuries themselves. Without question, the incorporation of stem cells could dramatically enhance these forms of therapy (Taupin, 2006).

Behavioral interventions have also been effective in inducing brain reorganization, particularly in the domain of motor function (Blanton, Wilsey, & Wolf, 2008; Taub, 2004). Investigations have demonstrated dramatic improvements in the range of motion by forcing the use of a cortically disabled appendage, (Friel, Heddings, & Nudo, 2000; Kunkel et al., 1999; Liepert, Bauder, Miltner, Taub, & Weiller, 2000). The effectiveness of such treatments may be augmented by the application of new technologies in brain stimulation. Transcranial magnetic stimulation (TMS)[1] shows promise not only as a scientific methodology used to link brain and behavior, but also as a therapeutic technique (Rossi & Rossini, 2004). TMS has been effectively employed to alleviate varieties of negative plasticity such as chronic pain and epilepsy (Lefaucheur, Drouot, Keravel, & Nguyen, 2001; Tamura et al., 2004; Tassinari, Cincotta, Zaccara, & Michelucci, 2003).

What is good about these approaches (biochemical, behavioral, brain stimulation) are that they are evolving quickly and in parallel. What is bad is this hardly allows time for the scientific community to catch its breath and gain some perspective. Some have proffered that a series of organizing principles is needed to understand the potentials and pitfalls of neuroplasticity in the adult brain (Kliem & Jones, 2008). Such a framework

[1] By delivering magnetic pulses through the skull, TMS induces artificial, electrical currents in superficial cortex, thereby exciting or inhibiting neuronal ensembles. For an introduction, see Barker (2002).

would ideally be grounded in basic science but also relevant to the needs of the physician and rehabilitation specialist. Ultimately, any useful theory of plasticity needs to address how we define and identify different manifestations of plasticity (e.g. neurogenesis, reorganization, diaschisis, and vicariance), under what conditions do these processes occur, and how may they be prompted and directed by medical interventions.

Such an integration is easier said than done. To begin with, the convenience of evoking the word "plasticity" to explain the range of human psychological experience actually masks a multitude of definitions, investigative domains, and theoretical standings. The scientists that occupy these niches don't always seek translational experience or even see eye-to-eye. An even thornier issue is getting the practitioners of basic science and clinical investigation to collaborate. As researchers, they often have different respective goals: uncovering principles of nature or improving patient health and well-being. These aims are not incompatible, but often require thought and patience for their mutual satisfaction.

However complicated, it is important that PhDs and MDs make these inroads, both within their own communities and between fields. The relevance of neuroplasticity is clear. Stroke, dementia, and other neurological disorders are becoming more commonplace as the citizens of industrialized nations live longer. Another, more immediate motivation is the human toll of military conflict. The United States' involvement in Iraq and Afghanistan has seen a dramatic increase in the number of servicemen and women suffering from traumatic brain injury (TBI). While body armor saves lives, sensory and cognitive impairment are all too often the result of enemy IEDs (improvised explosive devices).

In fact, one of the most vulnerable areas on a soldier's body is the eyes, and the percentage of wounded veterans with eye damage (13% of all serious casualties) is now greater than any major conflict since WWI (Zoroya, 2007). The plight of the partially blinded soldier raises some interesting questions as to plasticity's potential role as a practical and theoretical guide in patient rehabilitation. To what extent, if at all, does the adult visual system reorganize in response to the loss of sensory input? What components of physiology are involved? Is this change functional, structural or both?

Vision is the most complex of the Aristotelian senses. Seventy percent of our perceptual experience is visual and the majority of the brain's neocortex is devoted to visual processing (Felleman & Van Essen, 1991). Its scientific literature is appropriately rich and, within, the study of plasticity holds an integral place. The developmental effects of sensory deprivation on young animals comprise some of the most lauded work in vision science (Hubel & Wiesel, 1998) and theorists have long pondered the cortical mechanisms responsible for visual learning (Sasaki, Nanez, & Watanabe, 2009) and adaptation (Clifford et al., 2007).

Only in recent years, however, have investigations begun to address the possibility of large-scale, visual plasticity in the adult brain (Baker, Peli, Knouf, & Kanwisher, 2005; Masuda, Dumoulin, Nakadomari, & Wandell, 2008; Schumacher et al., 2008). Engaging this question may prove to be an important chapter in plasticity's scientific advancement as well as its growing relevance to the rehabilitation medicine, but there is no foregone conclusion. The brain is plastic, but it is also stable. Researchers have observed constancy in the ocular dominance columns of adult humans (Adams, Sincich, & Horton, 2007) and documented the presence of molecular mechanisms that

maintain existing neural pathways (Grados-Munro & Fournier, 2003; Kastin & Pan, 2005; Syken, Grandpre, Kanold, & Shatz, 2006). There is still much to resolve regarding the limitations visual plasticity (for a review, see Wandell & Smirnakis, 2009).

To the extent that the visual cortex is plastic, a working knowledge of its flexibility would impact more than the care of wounded veterans. Many are born and struggle their entire lives with hereditary eye diseases. Longevity has also brought with it a host of age-related visual disorders. Vision scientists, physicians, and rehabilitation specialists are making concerted efforts to treat these conditions through the development new medications and behavioral interventions. Knowing the parameters of visual plasticity would undoubtedly aid in these endeavors, but this means an honest appraisal of what the adult brain can and cannot do. This frontier is one of the most exciting in contemporary vision science, but most agree there is still a long way to go.

This dissertation seeks to make a contribution toward an understanding of adult, visual plasticity. Its focus is on a specific form, the reorganization of the primary visual cortex after partial loss of retinal input. I describe here a clinical investigation conducted on patients with the degenerative eye disease, age-related macular degeneration (AMD). The purpose was to see if standard forms of visual rehabilitation therapy, as well as more novel measures, could alter maps on the primary visual cortex. The findings could address a potential link between visual plasticity and the adaptations instilled by oculomotor training. This knowledge could potentially inform the development of new rehabilitation programs and enhance the quality of life of AMD patients. The hope of this research, then, is to add a piece to the growing conversation regarding visual plasticity and ultimately contribute to the well-being of those afflicted with visual disorders.

CHAPTER 2: MACULAR DEGENERATION

According to the Center on an Aging Society, visual pathologies affect about 8% of the US population (roughly 20 million people) and are one of the leading factors that prevent the elderly from living independently (2002). Most of these individuals are afflicted with *low vision*, meaning they are not completely blind but suffer from conditions that obfuscate or distort large parts of their visual field. Perhaps the most common low vision disorder is macular degeneration (MD), a type of progressive retinopathy characterized by the loss of central vision. Over the course of months to years, MD robs those afflicted of the most essential part of their vision, the central visual field, leaving only a blurred or darkened mass in its place. Figure 1 depicts the functional deficit associated with MD.

A. 

B. 

Figure 1. Visual Deficit Associated with MD. A. Normal vision. B. The visual field affected by MD. The grey mass obscuring the faces is called a scotoma. It is now widely acknowledged that scotomata do not simply manifest as a darkened mass. Due to perceptual filling-in, many patients are unaware of the extent of their deficit. The figures in this document depict opaque scotomata for illustrative purposes. This figure was adapted from the National Eye Institutes website: www.nei.nih.gov.

The prevalence of MD is growing, spurred primarily by a worldwide demographic shift. Older adults are more likely to acquire MD and the number of people over sixty will triple from 606 million to over 2 billion by 2050 (The United Nations, 2000). The growth of senior populations across the globe spells the arrival of MD as a serious and pervasive health concern. Indeed, it is already the most common cause of legal blindness in the industrialized world (Chopdar, Chakravarthy, & Verma, 2003).

Unfortunately, there is no cure for macular degeneration. At present the standard treatment is to stave off progression with available medication and help patients adapt to their new condition. Research on MD is far from static though. Ongoing investigations hold promise to produce more effective drug therapies (Schachat, 2005; Virgili, Do, Bressler, & Menchini, 2007) as well as surgical implants (Gorfinkel, 2006). Even if such endeavors do not yield a cure, the knowledge they produce could aid in the development of therapeutic tools for patient care and rehabilitation.

This chapter will explore the pathophysiology and functional consequences of MD, but it will also focus on the patient capabilities. Interestingly, MD patients tend to adopt a secondary area of the retina for focus and fixation in the absence of central vision. I will explore the use of this preferred retinal location (PRL) and how it figures prominently into the behavioral treatments designed to help MD patients adapt to their condition.

2.1 MD Classification

First described as a "choroido-retinal disease occurring in senile persons" (Hutchinson & Tay, 1874), macular degeneration results in the deterioration of the central or macular area of the retina. As a classification, MD is not specific to one disease but is actually an umbrella term for a spectrum of conditions affecting retinal vasculature and metabolism.

Macular degeneration can afflict both young and old. Juvenile macular degeneration (JMD) comprises of a set of hereditary conditions that include Stargardt's disease, Best's disease, juvenile retinoschisis and a variety of other macular dystrophies. The symptoms of these disorders sometimes manifest by the second to third decade of life, but the disease itself is present at birth, as many variants of JMD are linked to autosomal dominant or recessive genes, X-linked mutations, and other genetic abnormalities. Though potentially debilitating, juvenile macular degeneration is exceedingly rare, with an estimated prevalence of only 1 out of every 10,000 people (Duetman, 2003).

By far, the most common form of MD is age-related macular degeneration (AMD), which arises in seniors between 60 to 80 years. This late-onset variant afflicts 1.75 million people in the U.S. with a prevalence of 12% after the age of eighty (Friedman, O'Colmain, & Munoz, 2004). Though AMD and JMD share similar functional consequences, the etiology of AMD is multi-factorial, involving the interaction of genetic, environmental and dietary factors as well as the physiological changes of normal aging (Ambati, Ambati, Yoo, Anchulev, & Adamis, 2003). The study described

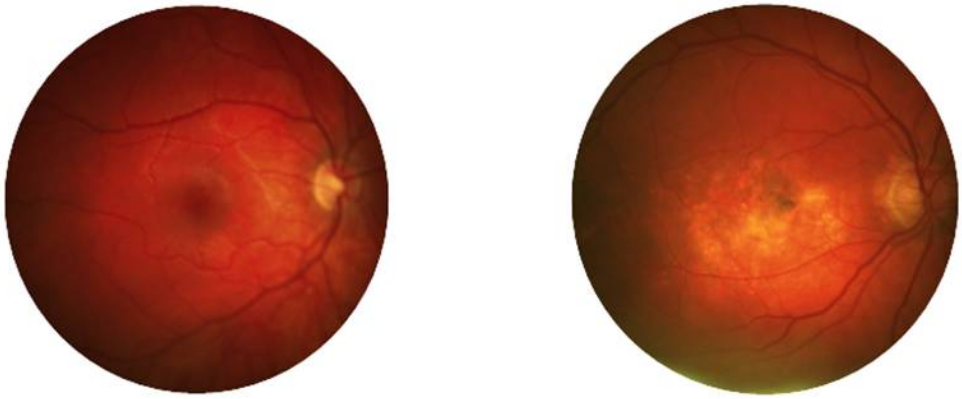
herein focused exclusively on patients with age-related macular degeneration, so further exposition of disease pathology will be limited to AMD. However, many of the following theoretical discussions of perceptual adaptation and attentional abilities could be applicable to those with JMD as well as other low vision conditions.

2.2 Pathophysiology

For over a hundred years AMD's diagnosis was based upon the identification of drusen via ophthalmoscope. Drusen is an extracellular material, often crystalline in appearance, which builds up between the retinal pigment epithelium (RPE) and the choriocapillaris of the eye (Lengyel et al., 2004). It is still unclear where exactly drusen comes from (Abdelsalam, Del Priore, & Zarbin, 1999) and whether it alone causes MD in the absence of other retinal abnormalities (Crabb et al., 2002; Sarks, Arnold, Killingsworth, & Sarks, 1999). What is known is that the accumulation of drusen prevents the RPE from providing nutrients to overlying photoreceptors. Lacking necessary metabolites, these photoreceptors eventually degrade and die, creating confined areas of retinal insensitivity (Figure 2).

AMD can manifest in two forms: wet and dry (de Jong, 2006). Dry AMD is characterized by geographic atrophy or localized pockets of cell death on the RPE due to the build up drusen. In contrast, wet or exudative AMD results from a process called choroidal neovascularization (CNV), the aberrant growth and leakage of blood vessels in the choroid. Of the two, wet AMD is more serious. The abrupt hemorrhage of a vessel can result in permanent vision loss in a matter of weeks while the functional deficits of

dry AMD arise gradually over the span of months to years. Despite these pathophysiological distinctions, it's important to understand that wet and dry AMD are, to a great extent, comorbid. The presence drusen often presages the eventual onset of wet AMD in addition to dry.



A. B.

Figure 2. Presence of Scarring on the Retina. A. A healthy retina. B. A retina scarred by macular degeneration. The dark area in the center of B is the scar proper. The lighter, yellowish area on the periphery is the pigment change that characterizes the presence of drusen.

2.3 Functional Deficits

2.3.1 The Central Scotoma

Both forms of AMD affect the macula, the area of the retina which corresponds to the central 15 – 20° of the visual field. This region contains the fovea and has the highest density of cones, the photoreceptors responsible for spatial resolution and color vision. The key pathophysiological outcome of AMD is the degradation and death of these macular photoreceptors. Many AMD patients, however, retain a significant degree of

visual function in the undamaged, peripheral areas of their retina. As AMD progresses and as the central field deficit grows larger and more absolute, patients may gradually become more reliant on use of the periphery to perform acuity-demanding tasks.

The perceptual consequence of AMD's progression is called a scotoma (plural: scotomata). Scotomata appear as dark or blurry areas in the central visual field. They can be a solid mass or spotted as well as take on a variety of shapes (Figure 3): ring, horseshoe, irregular (Fletcher, Schuchard, & Watson, 1999). In addition, many scotomata form in both eyes (Schuchard, Naseer, & de Castro, 1999). These bilateral scotomata constitute a particularly hampering condition since one eye cannot compensate for the other's deficit.

On average scotomata obscure between 10-20º of the visual field (c.f. Déruaz, Whatham, Mermoud, & Safran, 2002; Guez, Legargasson, Rigaudiere, & Oregan, 1993; Hassan, Lovie-Kitchin, & Woods, 2002; Schuchard et al., 1999), over twice the size of the physiological blind spot (Armaly, 1969), but they also grow with the progression of AMD. A longitudinal study by Sunness et al. (1999) showed that over a period of three years the approximate diameter of scotomata increased by a median of 5.69°. An important element in AMD diagnosis and monitoring are measurements of the size and opacity of scotomata.

A.

B.

C.

Figure 3. Types of Scotoma. A. A classic central scotoma. B. A ring scotoma in which a small, central area of the macula is spared. C. The spotting and distortion associated with the onset of MD.

2.3.2 Scotoma Measurement

Traditionally, measurements of scotomata have been conducted by conventional perimetry or "scotometry" exams (Anderson, 2003). In standard, automated perimetry a patient is seated in front of concave dome on which an array of light stimuli is either embedded or projected (often 2 - 6º apart, spanning 10 - 30º in the visual field). The patient holds a button-box and responds whenever he sees a light. A computer controls the location and intensity of the stimuli and maintains a record of patient responses. A scotoma is evidenced by the inability of a patient to detect contiguous stimuli within a specified area of the visual field. Though standard perimetry is still widely used, accurate results require patients to maintain stable, central fixation during testing (Westcott, Garway-Heath, Fitzke, Kamal, & Hitchings, 2002). This is often a difficult precondition for AMD patients to realize. Their tendency to fixate with their peripheral retina can bias the outcome of the test (Markowitz & Muller, 2004).

Later developments in perimetry saw the advent of the scanning laser ophthalmoscope (SLO). The SLO offers a greater degree of accuracy in the conduction of perimetric exams by combining high quality retinal images with precision stimulus presentation (for reviews, see Sharp & Manivannan, 1997; Sharp, Manivannan, Xu, & Forrester, 2004). SLO exams employ a low-power laser to scan the retina in a raster fashion, creating a real-time image. Another laser then selectively stimulates specific retinal locales eliciting a detect/no detect report from the patient. Importantly, the retinal scan and stimulus presentation features are married and continuously updated. This allows the operator to accurately present stimuli despite eye movements. Now discontinued, the SLO saw as much use by vision scientists as clinicians. Refinements of

its technology and techniques have yielded invaluable contributions toward understanding AMD's progression as well as the oculomotor adaptations of patients.

A new generation of perimeters has incorporated many of the features of the SLO into more compact and versatile systems. The MP-1 microperimeter (Nidek Technologies) combines automatic perimetry with color, fundus photography (Rohrschneider, Bültmann, & Springer, 2008; Rohrschneider, Springer, Bültmann, & Volcker, 2005). Like the SLO, the MP-1 uses automatic retinal tracking to provide accurate assessments of visual capability in patients that have trouble fixating. It does this through an on-line, video analysis of biological landmarks. This technology allows the operator to localize functional and damaged areas on the retina with high precision. In addition, the MP-1 hosts numerous in-device testing algorithms (static, kinetic perimetry) as well as procedures for training peripheral areas of the retina (Figure 4).

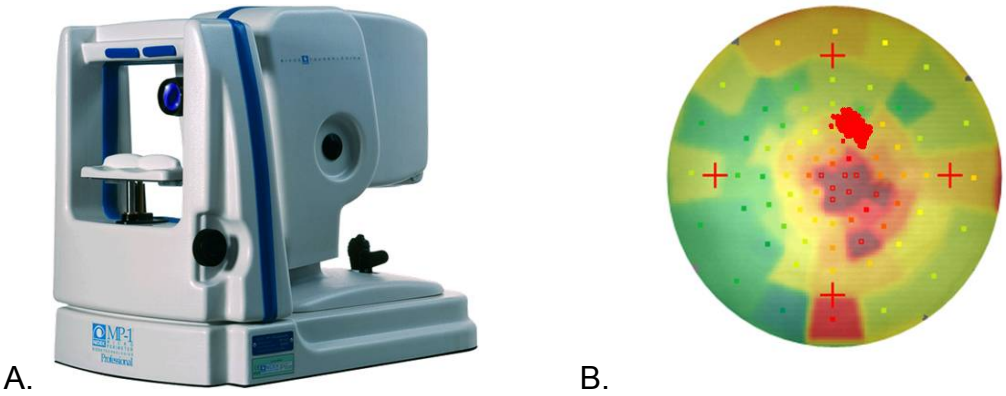


Figure 4. The MP-1 and its Output. A. The MP-1 microperimeter, developed by Nidek Inc. The patient sits in front of the lens (left). The operator sits behind the instrument (right) and administers tests through PC based controls (not shown). B. An example of the output provided by the MP-1. The colors represent the health of retinal areas as determined by threshold perimetry (green: healthy, brown: scotomatous). The red, circular markings are fixation points indicating how the patient positions his eye to view a target.

2.3.3 Behavioral Consequences

The onset and progression of AMD often significantly constrains the quality of one's life. The central scotoma severely impairs the ability of AMD patients to perform high acuity tasks like reading, driving, and computer use (DeCarlo, Scilley, Wells, & Owsley, 2003; Fletcher et al., 1999; Jacko, Vitense, & Scott, 2003). In many cases the ability to recognize faces may be hampered (Bullimore, Bailey, & Wacker, 1991; Tejeria, Harper, Artes, & Dickinson, 2002) as well as basic mobility (Elliott et al., 1995; Hassan et al., 2002). In lieu of a cure, studying the specific impairments of AMD is critical because such knowledge may render adaptive strategies that help patients cope with their remaining eyesight.

Reading is significantly impaired by the progression of MD, hampering patients' ability to understand instructions, write checks, and use computers. The presence of a central scotoma also seems to diminish reading beyond that of other low vision conditions. A study by Legge et al. (1985) found that the fastest reading speed in a group of MD patients was 70 words per minute (wpm). The same measure in other low vision patients was at least 90 wpm. A more recent study by Fletcher et al. (1999) echoed this finding, demonstrating that patients with MD read 2 times slower than those with other vision impairments.

Age-related MD, in particular, seems to retard reading performance. Legge et al. (1992) examined the reading abilities of 97 patients with central field loss (AMD: 41, JMD: 11, Other Conditions: 45). The AMD group showed a significant decrease in reading speed compared to acuity-matched JMD patients. This difference between AMD and JMD groups does not seem to be the direct result of age-related cognitive decline.

Comparative studies have found that reading performance is similar between the young and old when emergent visual conditions are effectively screened in the older participant group (Akutsu, Legge, Ross, & Schuebel, 1991; Lott et al., 2001). It may be that patients with JMD have better reading ability because they have had longer to adapt to their condition, coupled with greater motivational factors, such as the desire to perform in school and pursue a professional life.

Depression too is often an indirect result of AMD. Many studies have found that quality of life is substantially reduced with its onset (for a review, see Mitchell & Bradley, 2006). Patients can no longer engage in leisure activities and lose their independence due to the inability to drive (Mitchell, Bradley, Anderson, Ffytche, & Bradley, 2002; Mitchell et al., 2005). These circumstances often lead to emotional distress and feelings that they are a burden on their friends and family.

A cross-sectional study of 86 AMD patients by Williams et al. (1998) revealed that roughly a third reported greater emotional distress than those of the same age group with healthy vision. The rate of depressive disorder (American Psychiatric Association, 1994) in a sample of AMD patients was twice that of the general elderly population (Brody et al., 2001). There also is evidence that the emergence of depression is not tied to just the onset of AMD, but specifically an inability to adapt to the condition (Tolman, Hill, Kleinschmidt, & Gregg, 2005), a scenario that can instill frustration, hopelessness, and sadly, suicide (Waern et al., 2002).

2.4 Patient Adaptation

2.4.1 The Preferred Retinal Locus

The growth of scotomata results in the gradual loss of vision over months to years. This slow decline leads AMD patients to change their visual behavior as they attempt to accommodate preserved retina. Once the spatial resolution of the fovea can no longer be used to analyze images, patients often fixate with a preferred retinal locus (PRL) in their peripheral retina. This phenomenon, called *eccentric viewing*, is one of the most effective ways AMD patients can learn to continue to perform near vision activities (Timberlake, Peli, Essock, & Augliere, 1987). The mechanism driving the location of the PRL is unknown, but may be related to the cognitive and cortical adaptations that occur with disease progression (Cheung & Legge, 2005).

The preferred retinal locus has come under increasing investigation in the past twenty years in an effort to understand its origin and capabilities, mostly with an eye toward devising training regimes that would allow it to substitute for the damaged fovea. The most common measure used to probe the PRL is fixation stability.

However, fixation with the retinal periphery seems to be functionally different from the natural fovea. The PRL is not as stable as the fovea. In the normally sighted, foveal fixation can be described as a circular area between 0.2 to 0.5° in diameter (Crossland & Rubin, 2002). Fixation at the PRL is typically 2 to 15 times larger than that of the true fovea. In a study of 1339 eyes with various forms of low vision, the fixation stability of the PRL was found to be between 1 and 9° (Fletcher & Schuchard, 1997). In a group of 225 AMD patients it was between 1 and 8° (Schuchard et al., 1999). In addition,

the size of the fixation area for the PRL seems to be positively correlated with the size of the scotoma (Whittaker, Budd, & Cummings, 1988).

These findings indicate that the decrease of fixation stability for the PRL is a direct result of its location on the peripheral retina. It is known that fixation is naturally poorer in the retinal periphery. A study by Sansbury et al. (1973) demonstrated that at 10° fixation stability is 3 to 4 times worse than at the fovea. In addition, the ratio of retinal-to-ganglion cell connections and a corresponding reduction in cortical circuitry substantially reduces visual acuity for the peripheral retina (Anstis, 1998).

Despite this, some recent investigations indicate that the visual abilities of the PRL may improve with extended use. A study by Casco et al. (2003) showed that long-term engagement of a PRL may result in hyper-visual abilities beyond that of the normal retinal periphery. Altpeter et al. (2000) suggest that PRL development and performance may be dependent on the sustained allocation of visual attention. If peripheral visual performance does improve in AMD patients, the neural mechanisms that render this change are still unsubstantiated.

2.4.2 Multiple PRLs and Binocular Vision

There is evidence that the progression of AMD may actually yield multiple PRLs. The nature of these PRLs, how they develop and are subsequently used, is still a matter of investigation. In an examination of 35 AMD patients, Sunness et al. (1996) observed that five participants used one PRL for simple fixation while employing another for reading words or identifying letters. Two of these five used a left-field PRL for fixation and a lower-field PRL for words. Two others relied on a combination of left and right PRLs for

reading and the last used an upper-field PRL for fixation and a left PRL for letter identification.

It is hard to establish an observable trend with so few patients. Yet these results may be indicative of a tendency for patients to use lower-field PRLs for attention-demanding tasks while employing upper-field (either to the left or right) PRLs for less demanding tasks. Such an interpretation is consistent with findings that attentional resolution is greater in the lower than upper visual field (He, Cavanagh, & Intriligator, 1996, 1997).

There is also evidence that the location of the PRL is influenced by luminance levels. Lei and Schuchard (1997) found that at high luminance levels patients either used the fovea when they had a relative scotoma or a PRL on the very border of the scotoma. At low luminance, however, patients opted to use a PRL in a part of the retina with the best retinal sensitivity.

In addition to using different PRLs in the same eye, AMD patients may also combine the use of PRLs between their eyes. There is evidence that idiosyncrasies in the progression of AMD and the relative strength of PRLs may actually impair binocular vision. Normally, the summation of information between the left and right eyes aids visual performance. However, investigations of contrast sensitivity in AMD patients reveal that binocular viewing is often worse then monocular vision at low and medium spatial frequencies, a condition called binocular inhibition (Faubert & Overbury, 2000; Valberg & Fosse, 2002).

In a fascinating case study, Quillen (2001) documented the changing artistic abilities of a 68 year old AMD patient with bilateral scotomata. When painting solely

with her right eye (20/20) her finished canvas displayed fine detail, careful use of color and depth. Paintings completed with the left eye (6/200), however, were amorphous and pallid. Using both eyes the results were in-between, suggesting that the severity of her left eye affected the acuity and color sensitivity of her right.

2.4.3 Theories of PRL Development

A still unresolved issue is the manner in which PRLs develop. Related to this, vision scientists question whether the natural origination of a PRL is ideal or whether it should be trained into existence at a retinal location best suited to the patient. Hypotheses regarding the development of PRLs are broadly categorized as function-driven, performance-driven or retinotopy-driven (Cheung & Legge, 2005).

The function-driven hypothesis suggests that PRL formation is predominately guided by the necessity of action. In order to adapt to his or her diminishing sight, the AMD patient must employ spared areas of the visual field. Function-driven PRL formation is rooted in the idea that certain parts of the visual-field are better suited for particular tasks, and AMD patients adopt these areas as PRLs before others. For example, a lower-field PRL may be better suited for walking because it allows one to scan his or her path for obstacles (Turano et al., 2004). In contrast, a right-field PRL may be ideal for reading (specifically from left to right) because it places the scotoma to the left of un-scanned text (Fletcher et al., 1999; Legge et al., 1985).

An immediate problem for the function-driven explanation is that PRLs do not, in fact, seem to develop with regard to their utility, at least not in respect to reading. Some of the largest studies of AMD patients indicate that PRLs are often localized to the left or

lower pericentral retina (Fletcher & Schuchard, 1997; Fletcher et al., 1994). Such findings are at odds with the function-driven explanation as left-field PRLs hamper reading by allowing the scotoma to obscure upcoming text.

There is evidence that lower-field PRLs are better suited for reading (Nilsson, Frennesson, & Nilsson, 1998, 2003), but this may be only after training and not an inherent quality of the location itself. In fact, an investigation by Fletcher et al. (1999) found no difference in the reading speeds for lower-field PRLs and those at other locations. It seems then that the data regarding the function-driven hypothesis are at best inconsistent. It may be that other demands, such as mobility, drive PRL formation above that of reading, but to date no study has produced evidence to this end.

A second explanation for the local development of PRLs is natural variations in acuity that characterize the normal visual field. These gradations are called anisotropies and affect both the vertical and horizontal meridians. They were first documented by the 19th century psychophysicist Wertheim (Wertheim & Dunsky, 1980). Using his own eye as subject matter, Wertheim found that within the first 15°, acuity was much better in the upper visual field than the lower field. Beyond 15° there is better visual acuity in the temporal field than the nasal field. He also showed that the horizontal meridian had better acuity than the vertical meridian. These findings have been confirmed by more recent investigations (Carrasco, Talgar, & Cameron, 2001; Fahle & Schmid, 1988).

The performance-driven hypothesis suggests that these natural variations determine the formation of PRLs. If this is true, we may expect to see more PRLs along the horizontal meridian of the visual field than the vertical meridian. We also may expect to see more PRLs in the upper visual field than the lower. These scenarios are hit and

miss with the actual data. Although many patients develop a left field PRL, many also develop a lower field PRL. It seems then the upper/lower field is not born out, but a horizontal/vertical distinction may be accurate. Yet many scotomata are longer horizontally than vertically, perhaps wide enough to negate any horizontal advantage.

A final hypothesis regarding the formation of PRLs is that the process is primarily retinotopic. This idea suggests that a reorganization of cortical connections around the lesion projection zone results in a preference for particular retinal areas above others. Evidence that PRL formation is driven by retinotopy comes from the typical location of PRLs. A study by Fletcher and Schuchard found that 88.7% of PRLs in their sample were within 2.5° of the scotoma (1997). Similarly, Sunness sampled 27 AMD patients and found that the PRLs were always within 2° of the scotoma (1996). The two degree rule is true in JMD patients as well, with 90% of their PRLs located in the lower visual field. These findings suggest that PRLs may form when surrounding neural collaterals invade the deafferented cortex and established new or strengthened connections with cortical areas just beyond the LPZ[2]. If PRLs do form in this way, there is still much to learn regarding the mechanisms that dictate this change.

2.5 Low Vision Rehabilitation

Many people with AMD endeavor to treat their condition by taking nutritional supplements and antioxidants (Age-Related Eye Disease Study Research Group, 2001) or seeking interventions such as photodynamic therapy and intraocular injections (Rosenfeld

[2] The lesion projection zone (LPZ) is an area of the visual cortex deafferented or cut off from retinal input.

et al., 2006). These measures can help prevent the continued degradation of the retina, but often still leave patients with less than adequate sight. In lieu of a cure, those with AMD have benefited from other types of care. Low vision rehabilitation programs (LVR), for example, encompass a range of behavioral interventions aimed at teaching coping strategies and the optimal use of residual vision. These programs use diagnostic techniques to identify areas of functional sight then implement education and training regimes that teach patients to use their preserved vision for mobility, reading, driving, and a host of other daily-living activities.

Low vision rehabilitation draws on knowledge from medicine, occupational therapy and sociology to enact effective strategies for managing chronic vision conditions (Markowitz, 2006). The key elements of any LVR treatment program is an initial assessment of overall visual and cognitive skills, then a more specific identification of residual visual function and preferred retinal loci (González, Tarita-Nistor, Markowitz, & Steinbach, 2007; González, Teichman, Lillakas, Markowitz, & Steinbach, 2006) and finally the implementation of a tailored treatment program geared towards oculomotor training and the appropriate use of optical devices (Markowitz, 2006). Low vision rehabilitation has had success in helping patients re-engage aspects of daily living such as reading newspapers, watching television, paying bills, grooming, and participating in social activities (Walter, Althouse, Humble, Smith, & Odom, 2007).

The LVR approach sounds simple enough, but the dizzying combination of training practices, assistive technologies and patient idiosyncrasies often puts physicians and rehabilitation specialists at a loss. Recent evaluations may make low vision rehabilitation more effective in conveying necessary skills (Hooper, Jutai, Strong, &

Russell-Minda, 2008), but undoubtedly there is still much to learn. A lingering problem is that there does not seem to be a standard for the implementation of some types of therapy. Eccentric viewing (EV) training, for example, has been a hallmark of LVR since is inception in the 1970's (Holcomb & Goodrich, 1976). However, a study by Stelmack et al. (2004) found wide variation in the methods practitioners use to implement EV therapy.

There is a continuing need then to assess the merits of different approaches to LVR and operationalize those strategies that work best. This evaluation must occur on multiple levels (physical, psychological, social), but at its core LVR involves training one to use his or her eyes in novel ways. So a firm understanding of the processes, both ocular and neurological, that occur as patients begin utilize peripheral areas of the retina is critical.

This document will make the case that eccentric viewing and LVR as a whole can benefit from a theoretical grounding in the burgeoning science of neural plasticity. At the moment, there is no consensus regarding why eccentric viewing may improve sight. Is this change simply functional or is it accompanied by the neural substrates that characterize visual learning and adaptation? The next chapters will explore this idea, reviewing the domain of sensory plasticity, an established literature in its own right.

CHAPTER 3: CORTICAL REORGANIZATION

A seminal attribute of the nervous system is its changing structure. The brain's capability to alter neural configurations allows organisms to adapt in ways not programmed by their genomes (Kolb & Whishaw, 1996). Brain plasticity has become the focus of many recent endeavors in neuroscience. A growing body of research points to the cortex's ability to change in functionally meaningful ways, even in adulthood. Much of this research has focused on the state sensory maps (Buonomano & Merzenich, 1998; Kaas, 1991). This narrative increasingly supports a dynamic view of the neocortex in which the functional topography of cortical maps is altered in response to input change. The following chapter reviews the growing examples of sensory plasticity in both humans and animals with particular attention paid to the visual system.

3.1 Mechanisms of Adult Plasticity

To understand how neural representations vary with behavior and experience it is necessary to examine plasticity as the major factor dictating adaptability of the mammalian brain. Neural plasticity describes the brain's ability to physically and functionally adapt to both endogenous and exogenous contingencies. Historically, it has referred to the brain's ability to regain cognitive and motor capacity after brain injury. However, in recent years, plasticity has been invoked explain a wide variety of findings, from chemical changes at the level of the synapse, to alterations of connectivity patterns and overt behavior.

In this new paradigm, plasticity is part and parcel of normal brain function, an attribute which allows organisms to negotiate an ever-changing world. Plasticity then must be a *dynamic process* where organic elements (in this case neural tissue) yield changes in behavior or cognitive processes. It is also *adaptive,* in that it is a reaction to endogenous or environmental elements. Finally plasticity is *systematic*, it exists as an organized interaction between environmental and neural states (Stiles, 2000). This review will consider two conceptualizations of plasticity: plasticity at the level of the synapse and plasticity within a larger network of connections or map.

3.1.1 Synaptic Plasticity

Synaptic plasticity refers to changes in neuro-chemical states at the level of the synapse which influence the firing and communication of neurons (Stevens & Sullivan, 1998). Theorized by Hebb, the process of synaptic strengthening is now regarded as the primary way in which plasticity is expressed neuron-to-neuron (Hebb, 1949).

The biochemical mechanisms that yield synaptic plasticity are long-term potentiation (LTP) and long-term depression (LTD). In these processes postsynaptic receptors known as NMDA sites respond to the binding of neurotransmitters (often glutamate) with a flood of calcium into the postsynaptic cell. This influx makes the cell either more or less likely to fire. Crucially, NMDA receptors only respond when glutamate molecules are at the synaptic cleft, making them sensitive to the constellation of molecular events associated with repeated pre-synaptic firing and, consequently, the behavioral or environmental events that trigger this firing. This quality makes NMDA

receptors excellent coincidence detectors. In addition, their capacity to alter inputs between neurons influences larger patterns of neural communication.

Synaptic plasticity may also induce macroscopic alterations of the cortex. Long term potentiation (LTP) has been implicated in the formation of dendritic spines on post-synaptic neurons (Ivanco, Racine, & Kolb, 2000). The development of new spines increases synaptic contact between dendrites and axon terminals (Horner, 1993; Luscher, Nicoll, Malenka, & Muller, 2000; Toni, Buchs, Nikonenko, Bron, & Muller, 1999) creating a dense web of branches which, in effect, generates more neural tissue.

These changes are evident in enriched environment studies (Rosenzweig & Bennett, 1996). These investigations house animals in developmentally "rich" (the presence of stimulating toys, exercise equipment, and other animals) or deprived (standard laboratory conditions) environments then examines physical aspects of their brains at maturity. Animals raised in the enriched environments often show a greater brain weight, cortical thickness (Diamond, Krech, & Rosenzweig, 1964) and increased dendritic branching (Greenough & Volkmar, 1973).

3.1.2 Map Plasticity

If gross qualities of the brain such as weight and cortical thickness are influenced by environment conditions, then same may be true on a more local level regarding specific cortical areas. This type of plasticity involves the expansion or contraction of an interconnected network of neurons that represents a specific sensory afferent or motor output. Because motor and sensory representations are topographically mapped onto the

cortex, the plastic modifications that occur within these networks are referred to as map plasticity.

Map plasticity begins with a change of inputs in some way. This could come from a disruption in peripheral receptors or through sustained experience. Recent research suggests that cortical representations form a kind of perceptual or motor memory trace that can expand or contract based on passive changes in input or active training (Buonomano & Merzenich, 1998; Das, 1997; Kaas, 1991). Whatever the situation, when the balance dictating the relationship of cortical maps is altered, either an expansion or contraction of cortical representation can occur. Both synaptic and structural mechanisms likely mediate this process.

It is likely that these gross, plastic changes in cortical representations result from the above-described LTP/LTD mechanisms (Kolb & Gibb, 2002). In this way, map plasticity is the macroscopic expression of synaptic forms of plasticity. It is also clear that these changes in cortical area effect the processing of sensory information and the execution of motor skills, providing the critical link between neural plasticity and behavior. The remainder of this review will focus on map plasticity and the functional changes it yields in cortical representations.

3.2 Reorganization from Deafferentation

Deafferentation involves damage or disruption of afferents, fibers that transmit sensory information to the brain. Previous developmental research on the effects of deafferentation has demonstrated large scale reorganization of cortical maps. Such dramatic change is usually not present in adults, but deafferentation of the mature brain

does result in expansion of neighboring cortical areas, even to the point that they overtake and occupy the deafferented cortex.

Such reorganization often takes the form of an expansion of receptive fields for neurons surrounding the lesion projection zone (LPZ), the area of cortex deafferented by damage to sensory receptors. Activity eventually resumes in the LPZ, but it is elicited by stimulation outside the area's normal receptive fields. In essence, the surrounding cortex functionally invades and incorporates the deafferented area into its sensory map. The following section reviews examples of this finding in humans and animals.

3.2.1 The Somatosensory and Auditory Cortices

The first forays into research on cortical reorganization involved somatotopic representations in animals (for a review see Kaas, 1991). Early studies using microelectrode recordings showed that the regular organization of the somatosensory cortex is easily disrupted by manipulation of peripheral sensory receptors. Kalaska and Pomeranz (1979) observed alterations in the forelimb representations of cats by denervating their paws. Other research demonstrated that the amputation of digits in raccoons and monkeys results in the neural expansion of the remaining digits into the former's cortical space (Merzenich et al., 1984; Rasmusson, 1982). Similar results have been obtained using nerve transection procedures (Merzenich et al., 1983), the transplantation of skin sections (Merzenich, 1988) and yoking afferent signals by suturing fingers together (Clark, 1988).

A remarkable quality of this reorganization is that it is reversible as long as the manipulation is reversible. For example, reorganization has been demonstrated when

deafferentation is attained by a specialized nerve crush procedure. Nerve crush allows axons to gradually regenerate and when they eventually do, there is a re-instantiation of the pre-surgical, cortical map (Sabel, 1999).

While the above research indicates that the somatosensory cortex is capable of reorganizing, much of it observes ectopic[3] responding within 1 to 2 mm of the deafferented zone. This may mean that potential of reorganization is limited by the projection of thalamocortical afferents. Pons et al. (1991), however, exhibited a more dramatic case of reorganization by amputating the upper limbs of monkeys and using microelectrodes to record from corresponding somatosensory areas. The deafferented areas soon became responsive to stimulation of the chin and lower jaw, whose cortical representation abuts that of the upper limb.

Critically, they found that this ectopic activation stretched the length of the deafferented zone, an area some 10 to 14 mm in length. However, it took ten years for this reorganized activity to pervade the entire LPZ. These results suggests that reorganization is not necessarily restricted by thalamocortical afferents, although the extent to which it is purely cortico-cortical (Majewska & Sur, 2006) or dictated in some manner by subcortical structures (Krupa, Ghazanfar, & Nicolelis, 1999) is not fully resolved. It also suggests that reorganization may be dramatic, even in adults, although it may take several years for the final mapping to resolve itself.

Reorganization has also been observed in the auditory cortex of laboratory animals. Robertson and Irvine (1989) administered lesions to the cochleae of guinea pigs,

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[3] Ectopic activity refers to neural firing triggered by stimulation outside the neurons' normal receptive field. LPZ activation (whether a single cell or groups) is an example.

producing an area of deafferentation on the primary auditory cortex (A1). The auditory cortex is organized tonotopically so that cortical, isofrequency bands respond selectively to certain tones. The authors noted that activity to the deafferented area was depressed when animals were presented with its natural, corresponding tone. However, after a month the deafferented area began to respond to tones that normally activate adjacent areas of A1. Again, it seems that deafferentation resulted in the functional expansion of cortical fields and the incorporation of formerly unresponsive areas.

3.2.2 Amputation and Phantom Limbs

Some of the most prominent examples of cortical reorganization have been observed in humans after amputation of a limb or other extremity. Loss of a limb sometimes causes the curious condition of phantom limb, where the amputee may actually continue to sense the presence of his or her former limb after it's gone (Woodhouse, 2005). These sensations sometimes even manifest as chronic pain (Hill, 1999).

In a series of papers Ramachandran et al. examined the perceptual experiences of post-operative amputees (1993; 1992). Using behavioral and magnetoencephalographic measures, the authors plotted the reference fields of phantom sensations when they stimulated the face of amputees. They found a systematic relationship between the stimulation of specific areas on the face and the perception of phantom limb phenomena for different parts of an amputated hand, arm or finger. For example, when a patient's cheek was touched he felt the sensation on both the cheek and phantom thumb. When his chin was touched, he reported the sensation on the chin and as well as the fifth digit of

the amputated hand (Ramachandran, 1993). Remarkably, these phantom sensations were found to be modality specific; i.e. warm water applied to the face afforded the same perception in the phantom limb (Ramachandran et al., 1992).

The relationships discovered by Ramachandran et al. are consistent with previous examples of cortical reorganization. The face and arms lie adjacent to one another on the cortical homunculus (Penfield & Boldrey, 1937). Phantom limb then seems to be another example of cortical expansion, where cortex that once corresponded to the arm or hand is marshaled to process input to the closest topographic location, in this case, the remaining part of arm or the face. The degree of this reorganization also seems to be associated with the occurrence of phantom pain (Flor et al., 1995). In some cases, however, reorganization may not be complete. As discovered in animals, if the deafferentation is extensive enough, parts of the cortex will never regain responsiveness to either normal or ectopic stimulation (Wall, Xu, & Wang, 2002).

3.3 Reorganization from Training

In their early studies of the motor cortex Penfield and Boldrey (1937) noticed that the representation of the racket hand for skilled badminton players was organized differently from their other hand, as well as the hands of unskilled players. Over fifty years of subsequent research leaves little doubt that experience plays a prominent role in cortical plasticity. Much of these investigations involved training animals to perform tasks while recording spike trains from particular sensory and motor areas. More recently, however, methodologies in cognitive neuroscience have been used to explore the brain

structure and activation patterns of skilled performers, such as musicians, as well as those trained in experimentally designed tasks.

3.3.1 Sensory Discrimination in Animals

Auditory discrimination training using a classical conditioning paradigm yields changes in the response properties of neurons in as few as five conditioning trials (Edeline, Pham, & Weinberger, 1993). The authors trained guinea-pigs to distinguish between a non-critical tone and one that preceded an electric shock to the foot. They observed a shift in the tuning curves of auditory neurons toward the tone that signaled the shock. These findings indicate a flexibility of neuronal response properties. Though, they do not display a change in receptive field size, a hallmark of reorganization.

Recanzone, Schreiner and Merzenich (1993), however, demonstrated that auditory receptive fields do respond to training. They used microelectrode arrays to map the tonotopic organization in the monkey auditory cortex after training the animals to perform a frequency discrimination task. The cortical representation of the trained frequency range expanded with practice and was correlated with increased auditory acuity. While response properties are modifiable almost immediately, moderate amounts of training (80 daily sessions in the above case) are capable producing alterations in sensory maps.

The relationship between training and cortical expansion has also been explored in the somatosensory cortex. Recanzone et al. conducted a series of experiments where they trained monkeys to distinguish between vibrations applied to a glaborous area of a digit (1992a, 1992b, 1992c). When training was complete, they recorded the response

properties of neurons for “trained” and “untrained” cortex. Behavioral measures revealed that discriminative ability improved with continuous training but did not transfer to other digits (Recanzone, 1992a). Further studies revealed that the somatotopic representation of the trained area expanded (Recanzone, 1992b, 1992c) and the response properties of trained neurons demonstrated larger amplitudes (Recanzone, Merzenich, & Schreiner, 1992). Interestingly, attention seems to be a critical determinant for the cortical expansion. Animals trained the same way but distracted by another task (auditory discrimination) did not show the same effect (Recanzone, 1992b).

3.3.2 The Musician’s Brain

Perhaps the best studied example of the human brain’s response to training lies with musicians. Professional musicians undergo years of training to master their instruments and may be ideal subjects to explore the potential of neural-plastic change in regard to skill learning. Playing a musical instrument requires the coordination of auditory perception and motor execution on several dimensions. For this reason, music differs from the simple discriminations employed in animal studies and may therefore be more instructive toward understanding plasticity in reference to complex skills.

The first indication of cortical change in musicians was submitted by Elbert et al. (1994). They showed the modification of magnetic source dipoles associated with the left hands of violinists. The amplitudes of the dipoles for the second and fifth fingers (those that continually manipulate the strings of the violin) were larger in musicians than non-musician controls. The dipole moment is an indictor of gross neural activity and

consequently, a larger dipole is a potential sign of the active contribution of a larger neural network.

The neural expansion of sensorimotor representations associated with musical ability has also become evident in the investigation of focal dystonia, a disorder that affects 1% of professional musicians. Focal dystonia is a debilitating condition that is characterized by the degradation of fine-motor abilities in heavily used appendages, namely the hands (Kleim et al., 2004). MEG and fMRI studies show that the underlying cause of focal dystonia is the over-expansion of cortical representations that direct the movement of individual fingers (Elbert et al., 1998; Pujol et al., 2000). This maladaptive expansion results in the merger of cortical areas and the inability to specify the separate movement of individual fingers (Pascual-Leone, 2001).

It is clear that both training and deafferentation have a profound effect on the mature brain. Up to now this review has concentrated solely on the changes apparent in somatosensory and auditory cortex. The case for similar cases of reorganization in the visual cortex is more complicated. The extent to which the visual cortex is plastic or stable in adult humans and animals is a question that has yielded conflicting results. The next chapters will review this evidence and discuss its relevance to those with suffering from maculopathies such as MD.

3.4 Visual Reorganization

3.4.1 The Visual Cortex

The modern understanding of the visual cortex and its influence on perceptual ability is the confluence of a century of research in psychology, neurophysiology, and developmental science. One of the first perceptual processors discovered in the human brain (Glickstein, 1988), the primary visual cortex (V1) is located in occipital lobe and runs the length of the calcarine sulcus from its tip at the occipital pole[4] to a junction with the parietooccipital fissure (McFadzean, 2002). Research in neuropsychology (Holmes, 1945), non-human primates (Tootell, Switkes, Silverman, & Hamilton, 1988) and, more recently, neuroimaging (Horton & Hoyt, 1991) all show a specific ordering of the primate V1, a topographic mapping where proportionally more cortex is devoted to the macula than the peripheral retina (Figure 5).

In humans the posterior half of the calcarine receives afferents exclusively from the first 10º of the retina while the other 30º are routed to the anterior calcarine (Dougherty, 2003). More visual cortex is devoted to the central retina because of its role in detailed analysis of the visual field. This uneven distribution, referred to as cortical magnification, underscores the functional importance of central vision in humans (Azzopardi & Cowey, 1993). It also raises several interesting questions: What happens to the majority of visual cortical neurons when the macula is lesioned? If deafferented, is the posterior calcarine rendered permanently inactive or does it regain functionality? The next sections will explore these possibilities and their potential mechanisms.

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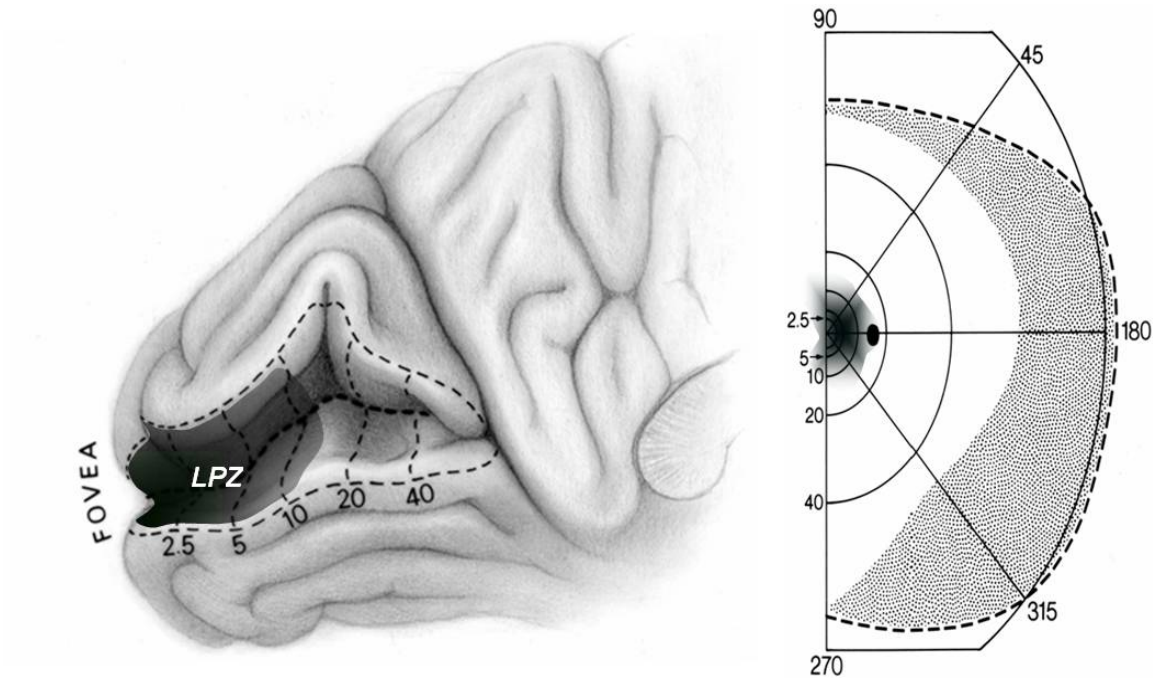
[4] The occipital pole or foveal confluence is the most posterior part of the calcarine sulcus.



A. B.

Figure 5. The Calcarine Sulcus and Visual Field. A. The left visual cortex. The representation here is according the Horton and Hoyt's revision of the Holmes map. Most of the primary visual cortex lies inside the fold of the calcarine sulcus. It is depicted as open with the isoeccentricity contours of the right visual field marked by dotted lines from 2.5° to 40°. The dark, perpendicular dotted line indicates the deepest part of the calcarine, representative of the visual field's horizontal median. The fovea is represented by the most posterior cortex, but the macula (15 – 20°) covers as much as half the calcarine's surface. The darkened area labeled LPZ depicts the area of the calcarine deafferented by a 10° retinal lesion. B. The right visual field. The area is defined by eccentric contours (2.5 - 40°) and radians (90 - 270°). The amorphous black area is a central retinal lesion. The black oval is the blind spot. Both representations are adapted with permission from Horton & Hoyt. The representation of the visual field in the human striate cortex: a revision of the classic Holmes map. *Archives of Ophthalmology*. 1991; 109: 816-824.

3.4.2 Animal Models

Sensory deprivation studies in cats and monkeys constitute some of the earliest examples that the visual cortex is modifiable through experience (Hubel & Wiesel, 1970; Hubel, Wiesel, & Levay, 1977). These findings were groundbreaking at the time, but only addressed plasticity when early development periods were manipulated.

More recent endeavors have looked for large-scale remappings of V1 in adult animals. Using single cell recording, these investigations have plumbed for examples of ectopic activation within surgically deafferented areas of cortex. Kaas (1990), for example, partially lesioned one eye in cats while completely enucleating the other. Monitoring the LPZ, he found that after 2-6 months deafferented neurons became responsive to stimulation of retinal areas bordering the lesion. This is perhaps the first compelling evidence that the topography of the adult visual cortex may actually change in response to an alteration of sensory inputs. Other research has produced similar findings by creating bilateral lesions on the retinas of monkeys (Heinen & Skavenski, 1991) and severing part of the optic chiasm in cats (Milleret & Buser, 1984).

Visual reorganization has also been observed in extra-striate areas. Krubitzer and Kaas (1989) partially lesioned area 17 in owl monkeys, effectively deafferenting MT, an extra-striate area involved in motion perception. Single cell recordings revealed that MT was largely unresponsive to stimulation unless intact parts of area 17 were involved, in which case the resultant activity expanded to all of MT.[5]

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[5] This result suggests that MT is primarily served by afferents direct from V1, but this may not be the complete case. Evidence suggests afferents to MT may travel through V2 (Sincich & Horton, 2003) or arrive from the lateral geniculate nucleus (LGN), bypassing V1 altogether (Sincich, Park, Wohlgemuth, & Horton, 2004).

In an effort to explore the electrochemical properties of such activity, Calford et al. (2000) lesioned the retinas of cats and recorded from the LPZ. After 24 weeks they observed ectopic activity from stimulation of the intact retina. Though the firing rate of these deafferented neurons was weaker, the size of their discharge fields was the same as other cells, indicating that the characteristics of reorganized activity may be similar to that of other cortex, just inconsistent with the normal retinotopic map.

In contrast to the above studies, other research has found no evidence of visual reorganization or has advanced different mechanisms. Murakami et al. (1997), for example, did not observe reorganized receptive fields after lesioning the macaque eye. They also argued that the presence of perceptual recovery is likely due to a "filling in" process, similar to that which masks the ocular blind spot. Horton and Hocking (1998) adopted the lesion procedure in monkeys but monitored levels cytochrome oxidase as an indicator of cellular metabolism. They found a significant increase in LPZ activity after five months, but argue that such perceived "reorganization" is actually a consequence of retinal healing.

Finally, some have argued that single cell recording methods may bias results by cherry picking active LPZ neurons. To avoid this problem Smirnakis et al. (2005) lesioned the eyes of adult macaques and used fMRI to examined the BOLD (Blood Oxygen Level Dependency) response within the LPZ. They found no evidence of reorganization, even 7 months after surgery. Because fMRI evaluates neural ensembles rather than single cells, this finding suggests that the overall pattern of neural connections within V1 do not reorganize.

In many ways the confluence of the above evidence is unclear. While the firing pattern of single cells is undisputed, it is hard to ascribe this activity solely to reorganization without accounting for the contribution of additional mechanisms (filling-in, retinal healing, etc.) as well as the behavior of other neurons. If reorganization does occur, it is likely elicited by a complex interplay of biological, behavioral, and temporal factors. It is probable then that different experimental scenarios would afford a wide variety of results. So while visual reorganization may be a real phenomenon, its mechanisms as well as the conditions under which it occurs are still largely undefined. The next section will review some possible scenarios for this process.

3.4.3 The Process of Reorganization

The locus of plasticity in the adult human visual system is likely the primary visual cortex. In the visual pathway, RFs are their smallest at V1 and get progressively larger for subsequent cortical sites. Numerous behavioral studies show that the fine discrimination abilities garnered from visual training are specific to task and retinal location (Crist, 1996; Fahle & Morgan, 1996; Schoups, Vogels, & Orban, 1995). The sizes of RFs in extra-striate areas lack the precision to accommodate this behavioral performance.

The only subcortical intermediary between the eye and V1 is the lateral geniculate nucleus (LGN). Psychophysical and physiological studies demonstrate that V1 RFs are much smaller than predicted by the LGN's anatomy (Gilbert, 1992a). In addition, studies examining reorganization in animals have shown that deafferented visual cortex begins to respond to stimulation outside of its receptive field, yet activity in the LGN remains silent

even after cortical recovery (Darian-Smith, 1995; Gilbert, 1992b). These findings make a strong case that if visual reorganization does occur it happens at the level of V1 and not at subcortical or extra-striate processors.

The structure and responsiveness of the primary visual cortex also suggest it is the main site of reorganization. Mappings specific to color, orientation, and directionality characterize the surface of V1 (Blasdel, 1986; Ts'o, 1990). Visual neurons or pyramidal cells are arranged in cortical columns with extensive horizontal connections (Martin, 1984; Rockland, 1982). This plexus of connections is achieved through the collateral branching of axons, extending up to 6 mm into the surrounding cortex (Gilbert, 1992a).

Though highly connected, V1 neurons are segregated according to RF properties (Gilbert & Wiesel, 1989; Livingstone & Hubel, 1984). Pyramidal cells sensitive to color, for example, connect to other color cells in adjacent columns. These interconnections are both excitatory and inhibitory, yielding an overall sub-threshold effect (Hirsch & Gilbert, 1991; Ts'o, Gilbert, & Wiesel, 1986; Weliky, 1995). The primary visual cortex, then, has the physical capacity of selectively altering the size and shape of its receptive fields via a dense web of subsidiary connections. These interactions could function as the neural substrate underlying cortical reorganization.

In response to retinal deafferentation, processes of reorganization may employ established cortical connections to reanimate neurons within the LPZ. Any such firing is ectopic in that it is associated with stimulation outside a neuron’s normal receptive field. As in the somatosensory and motor cortices, visual reorganization may manifest as the expansion of receptive fields along the perimeter of the LPZ, then a reactivation of all

deafferented cortex. However, if a lesion is made large enough, inactive areas may remain at the center of the LPZ (Heinen & Skavenski, 1991).

The resumption of LPZ activity also may occur in stages: a short term phase characterized by an immediate expansion of the receptive fields then long term phase involving the redirection of axons and formation of new connections (Pettet & Gilbert, 1992). Short term reorganization could involve the unmasking of existing horizontal connections. Research employing retinal ablation, manipulation of the optic disk and artificial scotomata has evidenced changes in receptive field size within minutes of deafferentation (Gilbert, 1992b; Pettet & Gilbert, 1992; Schmid, Rosa, & Calford, 1995; Schmid, Rosa, Calford, & Ambler, 1996).

In contrast, the neural substrates associated with long term reorganization may take months, even years, to develop. This process could involve the arborization of axons and dendrites, leading to the development new horizontal connections. Studies using the antegrade label biotcytin have demonstrated that in a matter of months suprathreshold activity in lateral connections leads to new axonal sprouting (Darian-Smith, 1995; Gilbert, 1992b). Synaptogenesis among these horizontal connections is also evidenced by the presence of neurotrophins and insulin growth factors (Obata, Obata, Das, & Gilbert, 1999). These biochemicals encourage cellular growth and differentiation, indicating that deafferented neurons are establishing new synapses with surrounding columns.

3.4.4 Blindness and Retinal Lesions

Loss of vision, whether congenital or acquired during the course of postnatal development, comprises a major challenge to the adaptability of the brain. Blind

individuals are laden with a significant area of deafferented cortex. The primary visual cortex and numerous, higher-order association areas no longer receive information from the eye. The brain compensates for this lack of input by increasing the amount and/or quality of information garnered from other senses, particularly touch and hearing. In light of these conditions, many researchers have wondered to what extent blindness modifies functional activity in the visual cortex or whether it emerges at all in the case of those blind from birth.

To a certain extent, this question has been answered through a striking discovery: blindness is capable of inducing cross-modal plasticity in the visual cortex. In this scenario, visual areas such as primary and extra-striate cortex become functionally active to input stemming form other sensory receptors. In most cases tactile information seems to predominate, likely due to the influence of Braille reading.

This cross-modal plasticity was first demonstrated by Sadato et al. (2002) using positron emission tomography (PET). Regional cerebral blood flow (rCBF) was observed in blind and sighted subjects as they performed tactile discrimination tasks. Discrimination of Braille and embossed English letters resulted in activation of the medial occipital lobe and primary visual cortex of blind subjects. In contrast, the sighted subjects showed a reduction of activity in the primary visual cortex to tactile discrimination. Neither group showed occipital activation to passive touch, implicating the ectopic activity as a part of higher-level, haptic processing.

Research with TMS has substantiated this finding, showing that transient pulses of stimulation actually disrupts the identification of Braille letters when administered to the occipital cortex of the blind (Cohen et al., 1997). Interestingly, this result seems

limited to the congenital or early-blind. Subjects who went blind after age fourteen (late-blind) do not show a disruption of Braille reading under TMS (Cohen, 1999), nor do they demonstrate activation in the primary visual cortex to tactile discrimination (Sadato et al., 2002). Cross-modal plasticity then may be bound by critical periods inherent to the maturation of the visual cortex.

On the whole these findings indicate a remarkable connection between the visual cortex and tactile abilities in the blind. Though the interplay of factors here is still under investigation, two prominent conditions seem to be at work: deafferentation of the visual cortex and mastery of tactile skills such as Braille reading. The analysis of these findings is similar to that of animal research. The lack of activity in one area of cortex diminishes lateral inhibition of adjacent areas, allowing their expansion. Unused cortex becomes bound to a new set of receptors and additional circuit space is organized toward the enhancement of residual perception. The notable difference with the congenitally blind is that plasticity crosses the cortical boundaries of sensory modalities.

While cross-modal plasticity is a dramatic example of sensory reorganization, it seems to be heavily modulated by development and perceptual experience. Other, more common forms of deafferentation are less severe than blindness. Imaging technology is now being used to address whether reorganization occurs in response to human maculopathies that diminish vision, but do not destroy it.

CHAPTER 4: MD AND REORGANIZATION

In a recent review, Cheung and Legge (2005) discussed the possibility of visual reorganization as an adaptation to partial vision loss. Drawing on investigations of retinotopic mapping in the animal and neuropsychology literatures, as well as research on eccentric viewing in AMD patients, they proposed that the technical and theoretical footings are now available for a decided exploration of human visual reorganization.

The crux of Cheung and Legge's argument is that the physical and behavioral characteristics of AMD patients comprise a set of conditions that may be favorable to cortical change. The absence of input to the occipital pole could spur new connections among horizontal collaterals and re-animate the firing of LPZ neurons. Adaptive visual behavior, like eccentric viewing, may impel this process, marrying attentional feedback to PRL-use and marshalling deafferented cortex to more effectively process peripheral targets.

Because understanding such a process would have a lasting clinical significance, it is crucial to explore to what extent and under what conditions visual reorganization may occur in those with AMD. Functional MRI will likely play an important role in this endeavor due to its focus on large-scale neural ensembles and application to alert, performing humans. This chapter will cover recent developments in the use of fMRI to assess cortical reorganization in patients with retinal disease. It will also discuss the limitations of this technology and how careful experimental design may be able to overcome ambiguous findings.

The first endeavor to image the low vision population focused on those with a specific genetic anomaly. Baseler et al. (2002) assessed activation patterns on the visual cortex of rod monochromats, individuals born with nonfunctional cone photoreceptors. Because the central retina is comprised almost entirely of cones, these individuals effectively possess a small scotoma on the fovea. Baseler et al. found that the occipital pole in their monochromats were responsive to stimulation from peripheral parts of the retina, prima facie evidence that the visual cortex has reorganized to compensate for the retinal defect. Subsequent research from the same group (Morland, Baseler, Hoffmann, Sharpe, & Wandell, 2001) evidenced cortical reorganization in response to other visual abnormalities such as lesions of the white matter and abnormal decussation of the optic chiasm.

These results convincingly suggest that long-standing retinal defects and abnormalities of the visual pathway can alter V1 activation patterns. However, their application to other maculopathies and specifically AMD is less clear. The onset of AMD is in late adulthood when plasticity is less dramatic. Simply the presence of a lesion may be a necessary but insufficient condition to induce reorganization.

The first retinotopic mapping of an AMD patient was conducted by Sunness, et al. (2004). The authors recruited a 60-year-old woman with bilateral, dry AMD. The participant had horseshoe-shaped scotomata, allowing her to fixate steadily with a small, central PRL. During scanning she viewed a contrast-reversing checkerboard pattern that expanded from the central to peripheral visual field. Stimulation produced a map with activation in the anterior part of the calcarine, but not in the deafferented posterior, the area representative of the scotoma.

Sunness et al.'s results demonstrate the feasibility and potential utility of visual neuroimaging of AMD patients but do not evidence retinotopic remapping. An N of 1, however, rarely settles a case and there could be a number of reasons for the lack of LPZ activation in this particular patient. If the retinotopic explanation of PRL formation is correct, then reorganization likely involves a functional and/or structural give-and-take between the cortical representations of the PRL and the scotoma. This means the capacity for reorganization may be dependent on the quality of the PRL and the topography of retinal damage. The fact that Sunness et al. used a patient with a horseshoe-shaped scotoma, where the PRL is a small, spared portion of the macula, could explain the negative result. If the macula still conveyed visual input, perhaps there was no cause for reorganization of horizontal connections in V1.

Shortly after, Baker et al. (2005) conducted a neuroimaging study in which two patients with JMD viewed pictures (faces, objects, and scenes) and text while being scanned. Both participants had large scotomata (> 10°) and identifiable PRLs. During scanning the patients performed a simple one-back task where they indicated consecutive presentations of the same stimulus. Baker et al. found pronounced activity in the lesion projection zones of both participants. They argued that this ectopic activation represents a large-scale reorganization of the visual cortex that extends beyond the normal reach of horizontal collaterals (6-8 mm).

These results present a dramatic departure from initial findings of Sunness et al. Reasons for the discrepancy may be the above-mentioned foveal sparing in the Sunness et al. participant. In addition, Baker et al. employed participants with longstanding cases of MD (20 years or greater) while the Sunness et al. participant had only been diagnosed

three years previous. It could take considerable time, months to years perhaps, for horizontal connections in the visual cortex to reform in functionally meaningful ways. Whether time or severity, Baker et al. admit in their paper that they do not know the parameters or mechanisms behind the observed activation, but suggest that a polysynaptic chain of connections or attentional feedback could be responsible.

In an effort to better understand the nature of ectopic activation, Schumacher et al. (2008) compared activation elicited from PRL stimulation to that from other areas of the retina. They imaged 6 MD patients (5 AMD and 1 JMD) while viewing contrast – reversing checkerboard patterns presented to different parts of the visual field. The authors were interested in the activation elicited by two areas in particular: the PRL and a select area dubbed the nonPRL. Critically, PRL and nonPRL areas were matched for retinal sensitivity and eccentricity, but the nonPRL differed in that it lacked the functional significance of the PRL. Patients did not use it to focus and fixate like the PRL.

Averaging across patients, PRL stimulation produced significantly more activation in the LPZ than that of the nonPRL. These findings suggest that reorganized activity in MD patients may be highly dependent on conditional aspects of the lesion and the PRL. Visual reorganization may be modulated by how attentional feedback is deployed onto the primary visual cortex, with select areas being more likely to utilize the deafferented circuitry because of attentional demand and behavioral precedent. At face value, this interpretation seems congruent with behavioral findings which suggest the PRL has a functional role apart from the rest of the retinal periphery.

Other investigations, however, have not found PRL activation to be unique and have actually questioned the functional nature of ectopic activation itself. Dilks et al.

(2009), for example, followed the PRL/nonPRL paradigm while scanning two patients with longstanding MD (20 and 26 years after onset). They did not find a significant difference between the two areas. Stimulation of both elicited ectopic activation of an equal magnitude in the LPZ. The authors argue this finding supports the existence of a passive, use-independent mechanism underlying reorganization.

In contrast, Masuda et al. (2008) found no evidence of reorganization in JMD patients under passive stimulation, but a prominent effect with a one-back task, suggesting that observed reorganization may be task specific. The authors go as far to argue that such ectopic activation is not truly "reorganized" in nature, but simply unconstrained, attentional feedback spreading into the LPZ (Figure 6). This interpretation highlights the fact that aberrant activation alone is not proof positive of functional reorganization. Its presence may simply be the artifact of normal attentional processes. Still, a mechanism modulated by attention is not necessarily functionally irrelevant. The widely accepted role of attentional feedback is the enhancement and filtering of V1 processing (Ahissar & Hochstein, 2004; Bashinski & Bacharach, 1980; Kastner & Ungerleider, 2000; Moran & Desimone, 1985; Motter, 1993; Posner, 1980). Reorganized activity then may be brokered by attentional demands, but it could still represent a working annexation of cortical space, if only under specific conditions.

The contradictory nature of the above findings hint that LPZ activation, reorganized or not, is a more complicated phenomenon than expected and may be only understood through a nuanced perspective. Recent papers have attempted to place the ectopic activation associated with MD on a stronger theoretical footing and have called for greater scrutiny of opposing findings. In a recent review, Baseler et al. (2009) argued

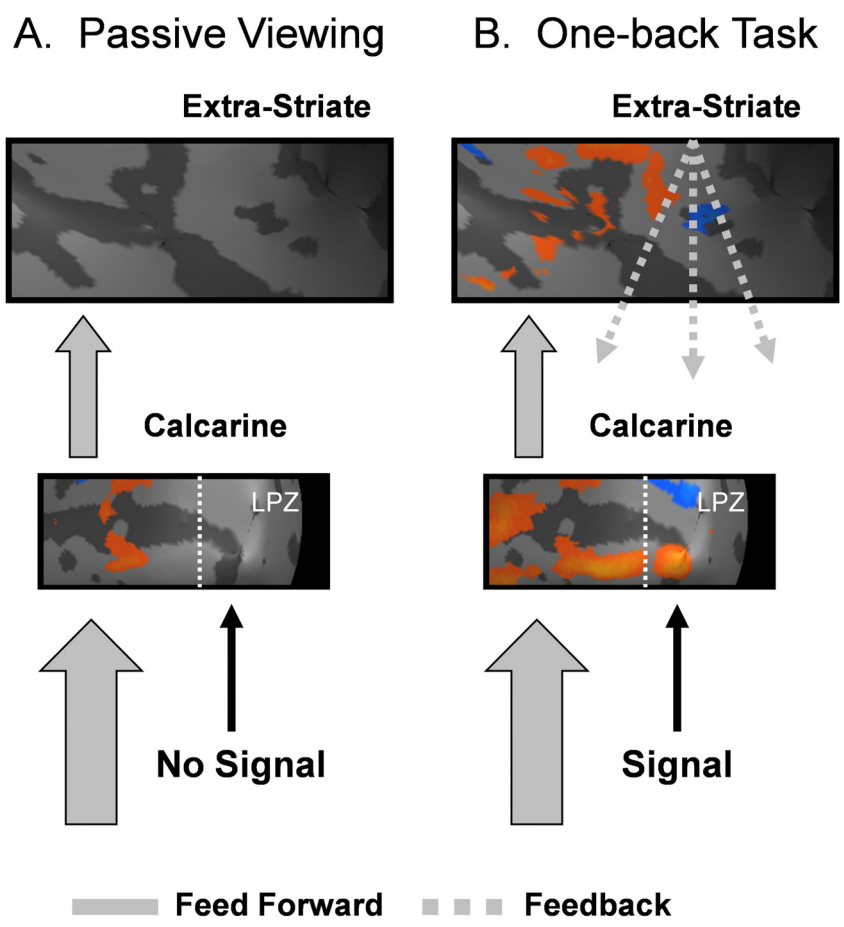

Figure 6. The Attentional Feedback Theory of Cortical "Reorganization". A. In passive viewing, feed forward signals in the retinogeniculate path travel through the primary visual cortex, eliciting activation in areas of the calcarine that correspond to the site of retinal stimulation. Because relatively little attention is required for passive viewing, there is no activation of extra-striate sites and no feedback into the primary visual cortex. Consequently, there is no activation within the LPZ. B. In a one-back task, which demands that a participant make a mental comparison between consecutive images, both calcarine and extra-striate areas are activated. The necessity of focal attention results in feedback from higher visual areas. Feedback activity spreads into the LPZ but does not represent a functional allocation of the deafferented cortex. This figure is adapted from Masuda et al. V1 Projection zone signals in human macular degeneration depend on task, not stimulus. *Cerebral Cortex.* 2008: 18: 2483-2493.

that there is a difference between the types of "reorganization" observed in AMD patients and those born with retinal defects. Reorganized maps in the former are not necessarily contiguous, while patients with congenital conditions exhibit an unbroken encroachment of peripheral activation into the LPZ. The reason for this discrepancy is unclear, but Baseler et al. caution that it means the clinical relevance of observed reorganization needs to be weighed with respect to patient etiology. The types of structural and/or functional changes that occur in patients with JMD, rod monochromacy, and other inborn conditions may not be the same as those affecting the AMD population.

In a comprehensive review of plasticity in the visual system, Wandell and Smirnakis (2009) also raise questions regarding the nature of ectopic activation. They argue that current inconsistencies in the neuroimaging data cloud our judgments about whether reorganization occurs and, if so, what parameters affect it. Limitations inherent in fMRI itself hamper our ability to plumb the mechanisms behind potential cases of reorganization. Functional MRI cannot evaluate the extent to which retinal pathology may change over time, nor can it determine whether cortical circuits have changed structurally or are simply conveying an altered pattern of neural signals. Finally, previous fMRI analyses have only probed activation along the primary and extra-striate visual cortices, ignoring the role that subcortical structures and frontal, attention networks could play in the process.

The above research calls attention to a number of critical questions now emerging in regard to the presence and nature of "reorganized" activity on the visual cortex. The main of which is whether this activity represents a true, functional remapping of V1

connections. Future efforts to address this question will involve exploring the factors that elicit reorganized activity on a number of different levels.

One of these fronts is the difference, if any, between passive and attention-related reorganization. If reorganized activity[6] is manifested through passive stimulation (i.e. contrast-reversing patterns) then it may result from a change in feed-forward processing streams and the expansion of receptive fields. If it is only present during attention demanding tasks, however, then a top-down explanation in which nonfunctional, attention-related activity encroaches into the LPZ may be more appropriate. Of course, current findings support both interpretations, depending on the patient; so individual differences may factor prominently into this dichotomy. Moreover, both passive and attention tasks could reflect a true functional change in cortical dynamics, just through different mechanisms.

An additional unknown is the extent to which eccentric viewing and top-down feedback interact to produce or influence reorganized activity. Is there any difference between the stimulation of the PRL and other preserved retinal areas bordering the scotoma? It may be that development of a PRL and consequent reorganization has much to do with experience in allocating attention to the peripheral visual field. This may make the PRL cortically unique and render greater LPZ activity than other preserved, retinal areas, as evidenced by Schumacher et al. (2008).

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[6] From here on out I will use the phrase "reorganized activity" to refer to ectopic activation that violates the normal, functional organization of the visual cortex, but will save the term "reorganization" for a theoretical scenario in which structural and/or functional changes in feed-forward visual processing induce such a change.

Finally, both feed-forward and feedback models may be influenced by the severity of the scotoma. In a follow-up to their 2005 paper, Baker et al. (2008) showed that large-scale reorganization is noticeably absent when there is foveal sparing and may be limited only to cases of an absolute scotoma. It may be that disease-related (scotoma size, opacity, etc) and individual factors (motivation, experience with a PRL) modulate the degree of reorganization. This means a definitive answer to the question of human, visual reorganization may have to await longitudinal research with larger subject pools and the ability to account for random effects.

In the meantime, careful consideration of task, visual behavior and disease conditions may yield some additional insights into the nature of reorganization. Perhaps the ideal way to go about this is to explore reorganized activity's relationship to visual performance. All previous neuroimaging studies of MD patients have observed V1 activity at a fixed point in time. It would be interesting then to monitor whether reorganized activity changes with the acquisition of new visual skills. If activity patterns are altered by the application of clinical interventions aimed at enhancing residual vision, then it is probable that reorganized activity has a real, functional relation to visual ability and is not simply artifactual.

CHAPTER 5: CURRENT STUDY

5.1 Design

The goal of the present study was to acquire more definitive information about the nature of reorganized activity in AMD patients by assessing its relationship to visual performance. AMD patients underwent a training regime specially designed to develop eccentric viewing skills. The PRL of each patient was identified and trained over the course of four weeks via occupational therapy and biofeedback tasks. Paper and computer-based behavioral testing evaluated the patients' peripheral vision before and after the training. In addition, pre and post-test fMRI scans measured any changes in patterned activation along the visual cortex. This design affords leverage on some key theoretical questions regarding cortical reorganization. It also addresses a clinical need to understand the relationship, if any, between PRL development and reorganized activity.

The main question sought in this experiment is whether behavioral performance is linked in any way to reorganized activity. If reorganization reflects a functional change in visual processing, then it is hypothesized that alterations in V1 activation should be concomitant with gains in peripheral vision. This relationship may manifest as an increase in the area and/or magnitude of post-test activity, especially within the bounds of the lesion projection zone. In contrast, if activation patterns are unaffected by training, such a result would support an alternative view, one in which reorganized activity is not functional but rather the artifact of normal visual processes.

To the experimenter's knowledge, this study represents the first time that standard forms of low vision rehabilitation have been assessed in conjunction with brain activation

routines. The within-subject, pre/post-test design of the experiment allows for a sensitive assessment of visual abilities and cortical activation patterns. This strategy is crucial given that the individual history of PRL use and development in AMD patients is often unknown. Moreover, it is likely that any group of AMD patients will have a varied set of visual abilities as well as different success rates in response to low vision rehabilitation. Disease severity, motivation, experience, and a host of other factors could contribute to visual performance as well as the presence or absence of reorganized activity. The present study does not assume it can control these inter-individual factors, but attempted to reduce the associated error through a within-subject administration of treatments and a case-by-case analysis of results.

5.2 Behavioral Hypotheses

Tasks and stimuli will be elaborated on in Chapter 6. Here, hypotheses and basic design elements of the study's behavioral component are addressed. The experiment employed three separate assessments of visual behavior: computer-based vision tests administered before and after LVR therapy, fixation tests conducted at the start of each LVR session, and finally, the expert evaluation of the rehabilitation specialist expressed through paper-based reading tests.

Performance on the computer-based tests was hypothesized to yield significant post-test improvements in recognition acuity and contrast sensitivity. Threshold stimuli were found for each patient and their performance assessed in frequency-based identification and orientation tasks. Patients were expected to yield higher accuracy scores in the post-test as a benefit of the visual rehabilitation training.

The MP-1 Microperimeter, a computerized instrument for retinal diagnostic, gathered fixation data. A biofeedback task was administered at the start of each LVR session. The MP-1 measured fixation stability as patients attempted to view a target with a pre-specified retinal area (PRL). A series of tones guided them toward accurate fixation. Statistical analysis of this data was expected to show a trend across sessions towards more stable fixation, indicating an improvement in eccentric viewing.

Reports from the occupational therapist were also critical in assessing individual progress during the training. Some of this information was qualitative in nature, comprising the therapist's professional assessment of a patient's performance session-to-session. A quantitative measure, the Pepper Visual Skills for Reading Test (VSRT), assessed reading ability before and after training. The VSRT was expected to reveal demonstrable improvements in visual performance post-treatment.

5.3 Neuroimaging Hypotheses

Neuroimaging analysis was expected to reveal demonstrable changes in the activation patterns between pre and post fMRI scans. It was hypothesized that visual stimulation of the trained PRL would yield more activity (in terms of intensity and area compared to baseline firing) in its corresponding cortical projection zone as well as that of the scotoma (LPZ).

The use of different visual tasks during scanning was thought to yield further insights into the nature of reorganization. Even if LVR is effective in producing reorganization, questions remain whether that reorganization is attentional in nature or possible under passive viewing conditions. For example, finding reorganized activity

under attention demanding conditions but not passive viewing would indicate that the allocation of attention is necessary and reorganized activity represents top-down feedback from higher visual processors. In contrast, LPZ activity even under passive stimulation would support a feed-forward account.

Comparison of PRL stimulation to a healthy but untrained location of the retina may also be meaningful. Such an area, dubbed the nonPRL, may allow a method to compare claims of true reorganization to top-down feedback. If stimulation of the nonPRL lacks LPZ activity or does not demonstrate the same trend (increases in activity with attentional demand) then it seems unlikely that aberrant activity is merely the result of top-down feedback. Such activation differences could indicate a unique process is occurring at the PRL. This may involve a rewiring of lateral connections in concert with attentional feedback or passively, either scenario comprises a reorganization of visual receptive fields.

Finally, neuroimaging analysis sought to examine how inherent characteristics of PRL formation may modulate the degree of reorganized activity. It was hypothesized that better functioning PRLs, in terms of fixation stability, would demonstrate more reorganized activity due to their status as established attentional loci. It is difficult to establish unequivocally whether this is the case in the small sample size of the current study. However, to the extent there is a demonstrable trend among patients, such a finding would indicate the degree that individual differences play in reorganization.

CHAPTER 6: METHOD

6.1 Patients

Institutional review board approval was obtained at both Emory University and the Georgia Institute of Technology. Participants consisted of 7 patients (6 experimental; 1 control) diagnosed with age-related macular degeneration within the last eight years. The age range was between 63 to 87 years. Visual health and other pertinent characteristics are shown in Table 1.

All participants were recruited from the patient pool of the Emory Eye Center and gave informed consent. The participants had either atrophic (dry) or medically stabilized exudative (wet) AMD. Diagnoses were based on physical characteristics such as the coloration of the retina, the presence of drusen and choroidal neovascularization within 3,000 μm radius of the fovea. Patients also demonstrated profound deficits in visual acuity associated with central retina degradation.

Certain ineligibility criteria were applied to participant selection through an analysis of medical files, interviews, and in-office visual testing. A logMAR (logarithm of the minimal angle of resolution) visual acuity of 1.3 (20/400) or better was necessary for the test eye. Participants were free of significant media opacities such as cataract, glaucoma, and corneal scarring. None of the patients had undergone visual rehabilitation therapy prior to the study, though some did have experience with handheld and closed-circuit television magnifiers. Finally, all patients had to pass an fMRI contraindications interview that excluded those with ferrous metal implants, claustrophobia, and a history of neurological disorder.

Table 1. *Patient Characteristics*

Patient	Condition	Age/Sex	Test Eye	Time since Onset	BCVA	Contrast Sensitivity
BE	Test	80/M	OD	4 years	20/400	1.025
HN	Test	87/M	OD	8 years	20/200	1.025
JM	Test	72/M	OD	1 year	20/100	1.175
MK	Test	81/F	OD	2 years	20/160	0.65
PC	Test	79/F	OS	3 years	20/160	1.225
VH	Test	80/F	OD	3 years	20/125	0.95
YS	Control	63/M	OS	3 years	20/63	0.7

Patients are designated by their initials. YS is the only control. OD = Ocula dexter (right eye). OS = Ocula sinister (left eye). BCVA = Best corrected visual acuity, determined by ETDRS (Early Treatment for Diabetic Retinopathy Study) charts. Contrast sensitivity was measured with Pelli-Robson charts.

6.2 Apparatus

6.2.1 Behavioral Testing

Behavioral testing involved computer-controlled stimulus presentation and data collection. A custom program, written in E-Prime 2.0 (Psychology Software Tools, Inc.), executed the experiment and recorded patient responses (Schnieder, Eschman, & Zuccolotto, 2002). Stimuli appeared on a LCD monitor (12″ x 15″, 1280 x 1024 pixels). The display was calibrated for uniform luminance using a colorimeter (Pantone, SpyderPRO). Participants made all their responses verbally. The experimenter relayed the responses to the program via a QWERTY keyboard.

6.2.2 MP-1 Evaluation/Training

The MP-1 Microperimeter (Nidek Corporation, Ltd) was used to locate scotomatous and preserved parts of the retina, identify areas of preferred fixation (PRLs), and conduct biofeedback training during the rehabilitation sessions. The MP-1 combines computerized perimetry with full-field fundus photography to allow a visual and quantitative assessment of retinal health (for a review, see Rohrschneider et al., 2008). It uses standard and radial perimetric exams to delineate scotomata and preferred fixation tests to indicate the location of PRLs. All testing with the MP-1 begins with an infrared photograph of the retina. Stimuli are then projected onto the retina in reference to the biological landmarks (retinal vasculature) depicted in this image. After testing, the registration of exam results with a high quality retinal photograph provides a data-rich and diagnostic depiction of the retina.

The MP-1 employs automatic, fixation-tracking technology to provide an accurate assessment of visual capability despite eye movements. An infrared retinal photograph is digitally registered to a live video feed of the eye allowing for an online analysis of blood vessel location. The stimulus array is repositioned in accordance with any detected eye movement. The MP-1 performs this check automatically, 40 times a second (25 Hz), allowing for reliable perimetry data even in patient populations that have trouble fixating (Rohrschneider et al., 2008).

In addition to perimetry and fixation analysis, the MP-1 also functions as a training tool. The auditory biofeedback feature aids visual rehabilitation by allowing patients to exert control over eye movements, normally an involuntary process. The MP-1 accomplishes this by tracking fixation in relation to a predetermined area of the retina and generating a pulse-variant series of tones that guide the position of the eye for optimal fixation. Clinical research with the MP-1 has shown the biofeedback feature is effective in improving the oculomotor control of MD patients (Vingolo, Cavarretta, Domanico, Parisi, & Malagola, 2007).

6.2.3 Functional Neuroimaging

A 3T functional MRI (Siemens Magnetom Trio) was used to acquire BOLD signals in relation to visual tasks for all patients. The scanner, operated by the Biomedical Imaging Technology Center (BITC) at Emory University Hospital, is a research dedicated whole body system. An eight channel array radio frequency (RF) head coil was used in all scans. An echoplanar sequence (TR = 2000 ms, TE = 30 ms, flip angle = 90°)

acquired data sensitive to the blood oxygen level dependent signal. All scans were acquired in an ascending, interleaved sequence.

Participants completed 2 scanning sessions separated by roughly 6 weeks. Each session consisted eight functional fMRI runs (33 axial slices of 3.4 mm isotropic voxels) and a high-resolution, 3D MPRAGE (TI = 1100 ms, flip angle = 8°, 1 mm isotropic voxels) structural scan collected at the end of the session. The functional runs consisted of two passive conditions: checkerboard and Gabor patch stimulation; and two active conditions: single-task and conjunction decision. There were two runs per condition. Checkerboard runs lasted 5:24 min/sec (162 volumes/run). Passive Gabor, single-task and conjunction runs all lasted 4:52 min/sec (146 volumes/run). The structural scan lasted 8:08 min/sec (192 volumes/run).

6.3 General Procedure

Data collection was carried out over the course of a year and consisted of visual assessment and rehabilitation phases. Onset of participation depended on when a patient was recruited. There were pre and post-test components to visual assessment phase, occurring before and after rehabilitation. Pre-assessment employed behavioral measures (computer-based testing and MP-1 evaluation) to evaluate the utility of possible PRLs and fMRI to assess the brain activation associated with their use. Visual rehabilitation then required each patient to attend weekly training sessions for four weeks.[7] Each

[7] Due to scheduling conflicts not all patients were trained in 4 consecutive weeks. However, all patients did receive four weeks of training total and no gap in the training regime of any patient lasted longer than a month. When unavailable to meet patients were encouraged to supplement in-office training with home visual exercises.

rehabilitation session involved biofeedback training to establish PRL stability and standard occupational therapy to improve oculomotor control and reading performance.[8] At the end of the rehabilitation, post-assessment behavioral and fMRI measures (the same as the pre-test) identified any training specific improvements in PRL use and consequent changes in brain activation patterns.

6.3.1 Initial Evaluation

All patients underwent an initial visual evaluation before experimental testing. Best corrected visual acuity (BCVA) was determined for both eyes via EDTRS charts. The eye with the better BCVA became the test eye. The Pelli-Robson chart (Pelli, Robson, & Wilkins, 1988) assessed the contrast sensitivity for this eye. Patients then underwent perimetry and fixation tests to identify scotomatous areas as well as PRL positions.

Microperimetry

Patients completed a perimetry exam of the test eye administered with the MP-1. Visual perimetry involves the systematic measurement of the retina's light sensitivity by presenting intensity-variant stimuli to different parts of the visual field and determining the threshold necessary for their detection. In the case of AMD patients, retinal scarring prevents the detection of stimuli at normal intensity levels or not at all. A high sensitivity

[8] Due to gross involuntary eye movements and issues with cooperation, patients BE and MK were unable to participate in the MP-1 feedback training. They did, however, complete four weeks of visual training with the occupational therapist.

threshold then indicates the presence of a scotomatous region while lower values mark preserved parts of the retina.

Stimuli

The perimetry exam consisted of the serial presentation of several stimuli over the black background of an LCD screen (Figure 7). All stimuli were Goldman III in design (white, circular, 0.47° diameter) and presented randomly to a predetermined array of visual field locations. This array covered 40° of the visual field and consisted of the 76 individual testing points. The test locations were radially arranged with 2° of linear spacing between them and decreasing density at more peripheral positions.

Procedure

Each perimetry exam began with the patient looking into the lens of the MP-1 with the test eye, the other patched. A photo of the retina was taken and vascular landmarks identified to allow fixation tracking. Patients were instructed to keep scotomatous regions of the visual field within the bounds of four pericentral fixation crosses (1° in extension, lateral and vertical spread was dependent on scotoma size). To maintain this eye position, patients were asked to imagine the extension of the lateral and vertical lines so that they meet in the center of the screen. This particular fixation strategy minimized eye movements and gave patients a non-central reference.

Testing proper consisted of the random presentation of Goldman III stimuli to different points on the stimulus array. All stimuli were presented individually for durations of 200 ms. Patients responded to a stimulus by pressing a button on a hand-held

joystick. An audible ding informed them of a correct response. Patient fixation was tracked during the entire exam. If a deviant eye movement, head shake or blink prevented the valid presentation of a stimulus, testing was automatically suspended and resumed when the eye was successfully repositioned.

The location and intensity of the stimuli changed with patient responses. Stimulus intensity (highest level: 0 dB, 127 cd/m^2; lowest level: 20 dB, 1.27 cd/m^2)[9] varied according to a 4-2 staircase method where subsequent stimuli increased in intensity by 4 decibels (dB) with a hit and decreased 2 dB with a miss (Figure 7). This process resulted in an intensity threshold value for each location in the stimulus array. The perimetry threshold is defined here as the inverse of the detectable stimulus intensity, measured in dB, according to the formula

$$\mathrm{dB} = 10\log_{10}(L_{max}/L_{min}) \quad (1)$$

where L_{max} is the maximum stimulus luminance of the instrument and L_{stim} is the luminance of the presented stimulus.

Stimulus presentation stopped for a specific location when the threshold value was reached. Patients continued with the exam until all thresholds were obtained or they wished to discontinue. Test time varied depending on the stability of a patient's eyes. Some exams took less than 20 minutes, others as long as an hour. Patients were allowed frequent breaks in tests over 15 minutes. After the exam was complete, registration of data with a retinal photo produced light sensitivity maps illustrative of healthy and scarred retinal regions.

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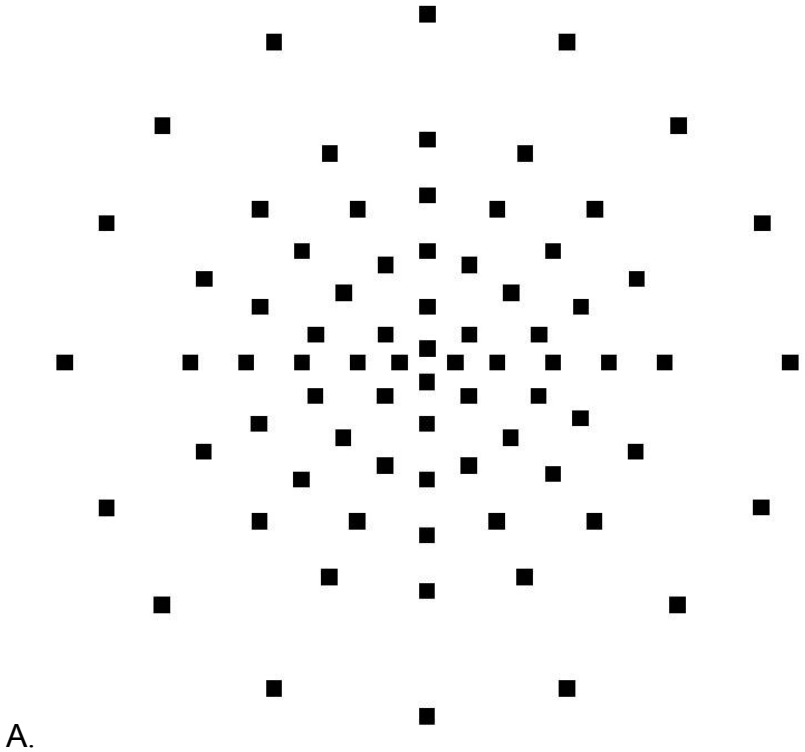
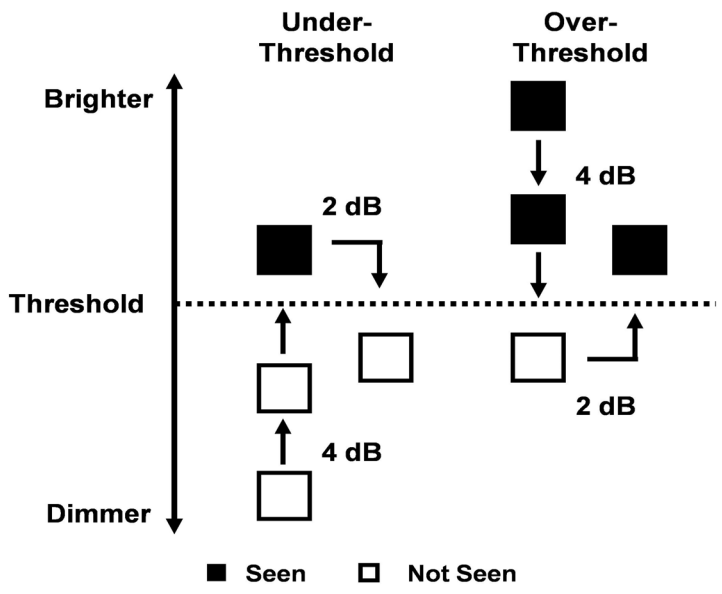
[9] cd/m^2 = candela per square meter. This is a SI unit of luminance (L_v) sometimes called a nit.



A.



B.

Figure 7. Perimetry Exam Stimuli. A. A representation of the MP-1 stimulus array. Each square is a test point. The array covered 40° of the visual field horizontally and vertically. B. The 4-2 test procedure with examples of the initial stimulus under-threshold and over threshold.

Fixation Tests

Fixation analysis identified the presence of preferred retinal loci in the patients. As with perimetry, the MP-1 captured an image of the test eye's retina with the other eye patched. Selection of vascular landmarks allowed online tracking of eye position. Fixation analysis began with the presentation of a white cross, 2° of visual angle in diameter, in the center of the MP-1 display. Patients were instructed to orient their eye so that they could stably focus on the cross. This act engages the part of the retina that patients naturally use to fixate in the absence of a functional macula, namely the PRL. The MP-1 recorded the retinal position patients used to fixate the cross, stopping and starting tracking as necessary to exclude gross eye movements. Each test lasted 30 seconds (excluding unsuccessful tracking) and yielded ~750 fixation points. Repetition insured the first instance was not coincidental.

6.3.2 Behavioral Assessment

The behavioral tests involved an evaluation of residual visual abilities, specifically the functionality of PRL and nonPRL areas. Peripheral vision, like central vision, depends on the brain's ability to integrate inputs from different visual channels, particularly those of high and low resolution (Peli, 2001). Visual acuity, for example, may be conceptualized as a process in which information is first processed for contrast, then resolved into separate elements, and finally recognized as a definable object. One way to evaluate the neurological resolution of part of the visual field is to assess its performance through hierarchal testing of these channels (Markowitz, 2006).

Drawing on this theoretical understanding, behavioral testing identified recognition acuity and contrast sensitivity as two independent avenues to address the performance of PRL and nonPRL areas of the test eye. Because performance in both recognition and contrast tests have been linked to cortical magnification (Cowey & Rolls, 1974; Duncan & Boynton, 2003; Rovamo, Virsu, & Nasanen, 1978; Virsu & Rovamo, 1979), these tests indirectly address the computational power of the brain in processing visual information. All behavioral tests were computer-controlled, consisted of presentation to the PRL and nonPRL and administered solely to the test eye.

Recognition Acuity

Recognition acuity refers to the ability to resolve detail and interpret form. Tests of recognition, such as Snellen and ETDRS charts, present patients with visually standardized symbols called optotypes which decrease in size from the top of the chart to bottom. Acuity is scored by recording the final position (either row-by-row or letter-by-letter) at which a patient can successfully read or identify stimuli.

Since their advent in the 1860's, acuity charts have undergone a continual evolution and refinement. The current standard for low vision assessment is the Early Treatment for Diabetic Retinopathy Study (ETDRS) or logMAR chart (Ferris, Kassoff, Bresnick, & Bailey, 1982; National Research Council, 1980). The ETDRS chart employs optotypes in 20 logarithmically defined sizes with a standardized spacing. The design permits letter-by-letter scoring, testing at most viewing distances, and also holds high test/re-test reliability (Arditi & Cagenello, 1993).

The ETDRS chart has proven indispensible in low vision evaluation. However, non-visual variables also affect acuity scores. Because low vision primarily afflicts the elderly, issues of literacy, inattention, and cognitive decline undercut the accuracy of any acuity measure. In efforts to mitigate such intervening variables, researchers have developed acuity tests with simplified response criteria (Harris, Robins, Dieter, Fine, & Guyton, 1985; Regan, Giaschi, Kraft, & Kothe, 1992) and have forgone charts for computer-based testing which improves the efficiency and accuracy of data collection (González et al., 2007).

Following these advancements, this study's recognition testing employed tumbling E stimuli in a computer-based, four-alternative forced-choice (4-AFC) task. Tumbling E stimuli differ only in their orientation and were originally used to assess acuity in illiterate populations (Taylor, 1978). In addition to their simplicity, the grating-like form allows superior recognition ability compared to other optotypes (Alexander, Xie, & Derlacki, 1994).

During recognition testing, E's were presented to PRL and nonPRL areas of the retina. Their orientation changed randomly from trial to trial. Patients responded to the orientation by voicing the direction of the E's prongs. Testing consisted of preliminary and main procedures. The preliminary test used an adaptive staircase to manipulate the size of the stimuli in reference to patient responses (Hairston & Maldjian, 2009). In this test the optotype size varied throughout the trials, with stimuli drawn from a pre-programmed range based on logMAR values. The main recognition test used the same stimulus size for all trials. This value was calculated from the results of the staircase

procedure. Together the procedures took a total of 40 minutes. Recognition tests were run before and after visual rehabilitation and preceded neuroimaging.

Stimuli

Recognition stimuli consisted of Snellen E optotypes (Sloan, 1959) presented individually in white over a black background (Figure 8). The optotypes had a luminance of 127 cd/m^2, the background a luminance of 1.27 cd/m^2, yielding a Michelson contrast $[(L_{max} - L_{min})/(L_{max} + L_{min})]$ of 98%. The orientation of stimuli varied among the cardinal directions (up, down, left, right).

The size of the stimuli varied between participants. This is because individualized retinal damage placed PRL/nonPRL locations at different eccentricities. The distribution of retinal ganglion cells and the allocation of circuit space in visual cortex are biased toward the central retina (McFadzean, 2002). Optotype size then must necessarily increase for identification at increasingly peripheral parts of the visual field (Anstis, 1974, 1998). To adjust for this effect of eccentricity, all stimuli were *M*-scaled in reference to the human cortical magnification factor using the following formula:

$$M = 7.99(1 + .33E + [.00007E^3])^{-1} \quad (2)$$

where *M* is the cortical magnification factor and *E* is the eccentricity of the stimulus in degrees of visual angle (Virsu & Rovamo, 1979).

M-scaling effectively controls for the loss of resolution at peripheral locations in the visual field by equating the size of stimuli's cortical projections (Goolkasian, 1994, 1997). Consequently, patients with PRL and nonPRL areas at greater eccentricities were presented with larger stimuli during the recognition tests. There was, however, no

difference between the size of PRL and nonPRL stimuli within a patient, as all nonPRL areas were selected to match the PRL in eccentricity.

Figure 8. Recognition Acuity Stimuli. Snellen E's with prongs to the four cardinal directions: right, up, left, down (left to right).

Procedure

Both preliminary and main tests followed the same general procedure (Figure 9). Patients were seated 40 cm from the computer monitor. Their heads were secured by a chin rest. The monitor was adjusted to eye-level. Patients focused monocularly on the center of the screen by placing their scotoma within the bounds of four white fixation crosses (i.e. the four cross method). PRL and nonPRL trials were presented in separate blocks, their order randomly determined.

The experimenter initiated each trial. A delay (1000 ms) followed in which only the fixation crosses were present. Depending on the block, a Snellen E then appeared at either the PRL or nonPRL location of the monitor. The orientation of the stimulus was random. It remained on-screen until the patient responded: "left", "right", "up", or "down". The experimenter recorded the response by hitting directional keys on the keyboard, which automatically coded accuracy, reaction time, and advanced the program. The experimenter offered periodic encouragement, but no formal feedback was given.

In the preliminary test, stimulus selection and response accuracy were yoked so that a patient's previous response determined the size of the subsequent stimulus. A 1-2 algorithm (for a full explanation, see Hairston & Maldjian, 2009) increased stimulus size by two steps if the previous response was incorrect and decreased it by one step if correct. The program tallied the number of reversals (i.e. switches from larger to smaller stimuli or vice versa) and terminated at a pre-set value (16 reversals).

After the program ended, the experimenter averaged the stimulus size values of the last five correct responses. This test value, calculated separately for each patient, was then used in the main recognition testing. The purpose of this method was to avoid ceiling and floor effects by selecting a stimulus size of moderate difficulty. If the value for the PRL and nonPRL differed, the lower of the two was used for both areas.

The main recognition test consisted of 180 trials, divided evenly between PRL and nonPRL presentations. The size of the stimuli was set to the value obtained in the preliminary, adaptive staircase procedure. During the testing, if the patient had difficulty determining the orientation of a stimulus, they were encouraged to guess. If they were unable guess, the trial was recorded as a miss.

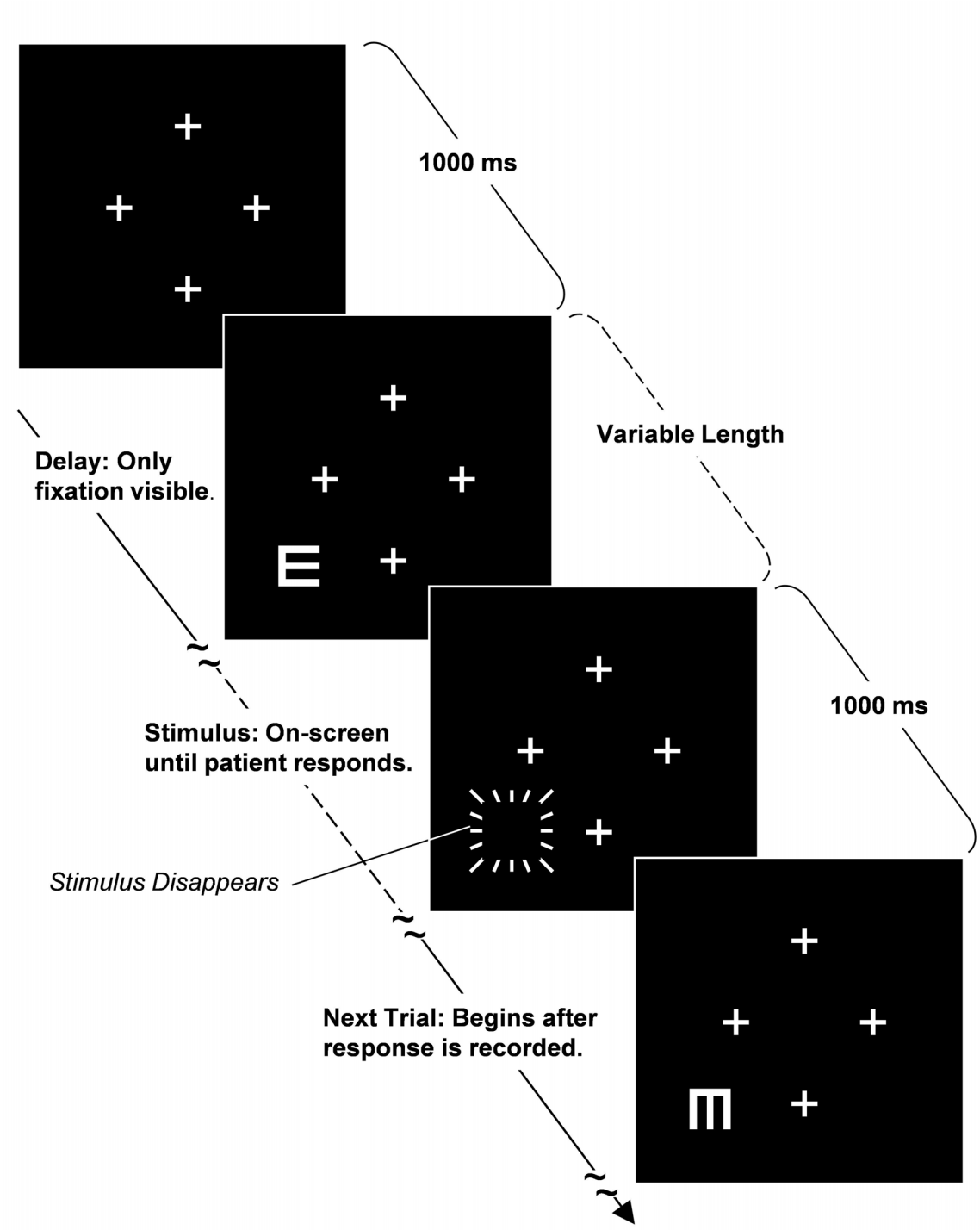


Figure 9. Recognition Testing Presentation.

Contrast Sensitivity

Contrast sensitivity refers to the ability to detect a target against its background. A critical measure in LV assessment, contrast sensitivity thresholds are determined by manipulating dimensions of spatial resolution and contrast detection (Ginsburg, Evans, Sekuler, & Harp, 1982). Most contrast sensitivity tests alter the contrast of sinusoidal gratings until patients are unable to spatially differentiate their luminance bands. These tests produce a characteristic curve in which high frequency gratings with low contrast are more difficult to detect than low frequency gratings with high contrast (Kelly, 1977). In most people optimal contrast sensitivity ranges between 2 and 5 cycles per degree or cpd (Figure 10). Although aging can affect this range, decreasing the detectable cpd at high spatial frequencies but preserving it at the lower frequencies (Arundale, 1978; Ross, Clarke, & Bron, 1985).

Assessment of contrast sensitivity in the AMD patients involved presentations of Gabor patches to PRL and nonPRL areas in a computer-based, three-alternative forced-choice (3-AFC) task. Stimulus orientation varied trial-to-trial, and patients had to determine whether a Gabor was vertical, rotated to the left or rotated to the right. A preliminary test using the adaptive staircase methodology assessed the best contrast ratio to discern a grating's orientation at three different spatial frequencies. This procedure was conducted for the PRL and nonPRL locations yielding a total of 6 cpd/contrast pairings (3 for the PRL, 3 for the nonPRL). Patients then performed the main test in which all Gabors were set to the optimal contrast ratio for each cpd condition in the PRL and nonPRL. Contrast sensitivity testing took approximately 40 minutes. It was conducted before and after visual rehabilitation and preceded neuroimaging.

Stimuli

The contrast test stimuli were based on those from F.A.C.T (Functional Acuity Contrast Test), a chart-based vision test that evaluates the clinically relevant range of human contrast sensitivity (Ginsberg, 1996). Stimuli were Gabors, sinusoidal gratings with a Gaussian window. They were constructed in MATLAB then converted to bitmaps for presentation in E-Prime 2.0 (Figure 10). All Gabors were temporally constant with the following luminance profile:

$$L(x, y, t) = L_0 \{1 + m \cdot \exp\left[\frac{-2.77(x - x_0)^2}{W_x^2}\right] \exp\left[\frac{-2.77(y - y_0)^2}{W_y^2}\right] \cdot \cos\left[2\pi f_s (x - x_0) + \theta_s\right]\} \quad (3)$$

where x_0 and y_0 are the center positions for the x and y-axes respectively, W_x^2 is the width of the Gabor at half height, W_y^2 is the full width, f_s is the frequency of the sinusoid, θ_s is the phase of the sinusoid, and m is the overall amplitude.

Each Gabor was circular in form and composed of alternating black and white luminance bands that blended into a gray background (28 cd/m^2). The number of bands within a degree of visual angle determined the cycles/degree (cpd) of the patch. Cycles/degree values were restricted to lower frequencies (0.5, 1.5, 3, or 6 cpd) in order to accommodate the vision of older adults.

The contrast ratio of the stimuli varied between 0.7–48 cd/m^2, with each cpd having a set of 12 applicable contrast ratios (Table 2). For each trial, stimuli were presented either vertically (90°), rotated to the left (105°) or to the right (75°). Table 2 depicts the cycles-per-degree and paired contrast ratios for all potential stimuli.

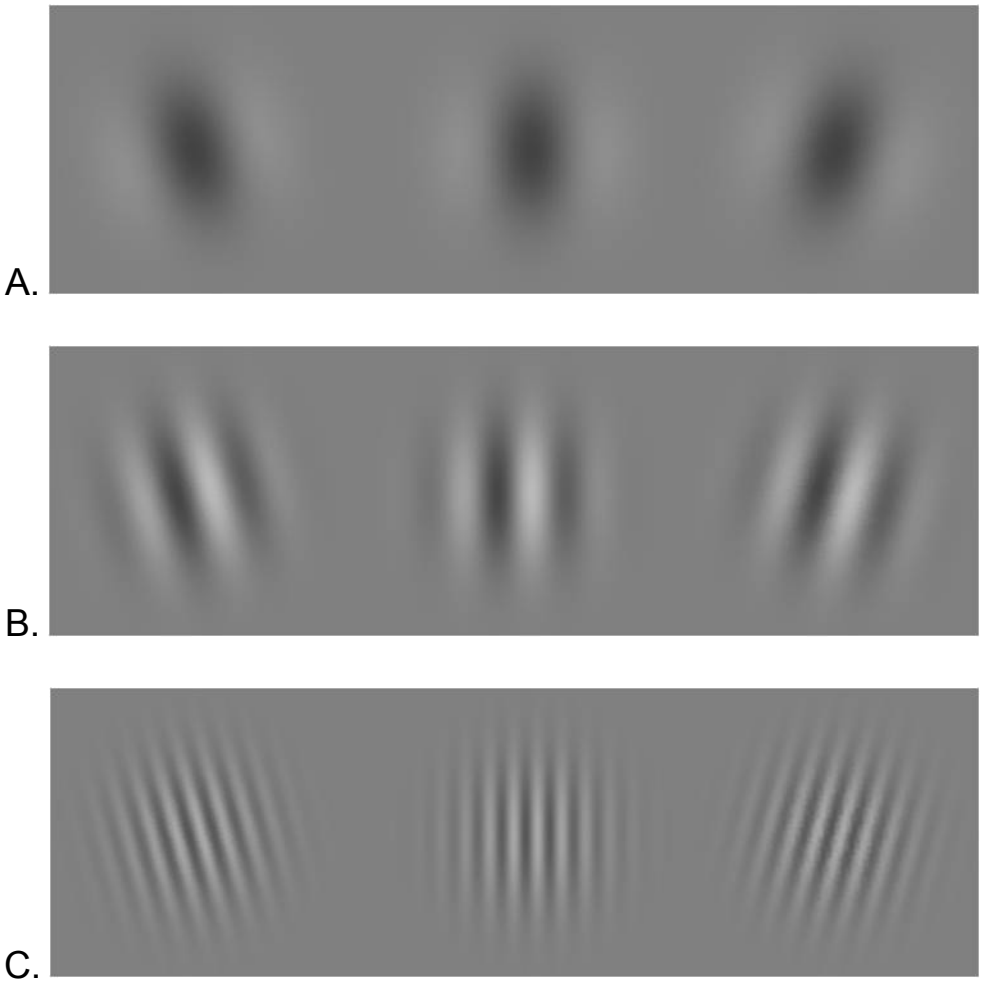


Figure 10. Contrast Sensitivity Stimuli. A. 0.5 cpd (cycles per degree) Gabors at 105, 90, and 75° orientation, left to right. B. 1.5 cpd Gabors. C. 3 cpd Gabors. A cycle per degree is a measure of angular resolution which equals the number of cycles (one dark and one light band in a grating or Gabor) that is perceptible within the area that subtends one degree of visual angle on the eye.

Table 2. *Contrast Sensitivity Values*

Cycles-per-Degree (cpd)	Contrast Ratio (cd/m^2)											
0.5 cpd	1	1.5	2	3	4	6	8	12	16	24	32	48
1.5 cpd	1	1.5	2	3	4	6	8	12	16	24	32	48
3 cpd	0.7	1.4	1	2	2.8	4	5.6	8	11.2	16	22.4	32
6 cpd	0.7	1.4	1	2	2.8	4	5.6	8	11.2	16	22.4	32

The table shows all possible contrast ratios paired to the spatial resolution (cpd) of the Gabors. The contrast ratio is calculated by the following formula: L1 + 0.05) / (L2 + 0.05), where L1 is the luminosity of the lightest pixels, and L2 is the luminosity of the darkest pixels. The constant 0.5 is a control for ambient light. Larger contrast ratios represent more clearly defined stimuli that stand out better against the gray background.

Procedure

The trial-by-trial procedure was the same for both preliminary and main tests (Figure 11). Patients were seated 57 cm from the monitor at eye-level. A chin rest reduced head movements. Patients focused monocularly using the four cross method. The experimenter controlled the pace of the experiment by initiating the trials.

Each trial began with a 1000 ms delay in which only the fixation crosses were visible. Gabor patches then appeared at either PRL or nonPRL locations of the screen. PRL and nonPRL presentations were blocked, their order randomly determined. The Gabors remained on-screen until the patient made a verbal response to their orientation: "Left", "Right", or "Straight." The experimenter recorded the responses, which were tagged for accuracy and reaction time and advanced the program.

In the preliminary test, the contrast ratio of the stimuli changed from trial-to-trial. Each of the 6 cpd conditions began with a mid-range cd/m^2 value that became lower or higher with correct or incorrect responses, respectively. The algorithm for stimulus presentation and the calculation of the test cd/m^2 value were the same as those described for the recognition testing. Accordingly, the number trials in the preliminary test varied between conditions and patients.

The main test had a total of 180 trials, divided evenly between PRL and nonPRL presentations. Each of the six cpd conditions was allotted 30 trials. Presentation was blocked according to cpd condition. Their order was random. The contrast ratios used in the main test were the same values obtained from the preliminary procedure and did not change within a cpd block. During testing patients were encouraged to guess even if they were unsure of the orientation. Failure to respond was recorded as a miss.

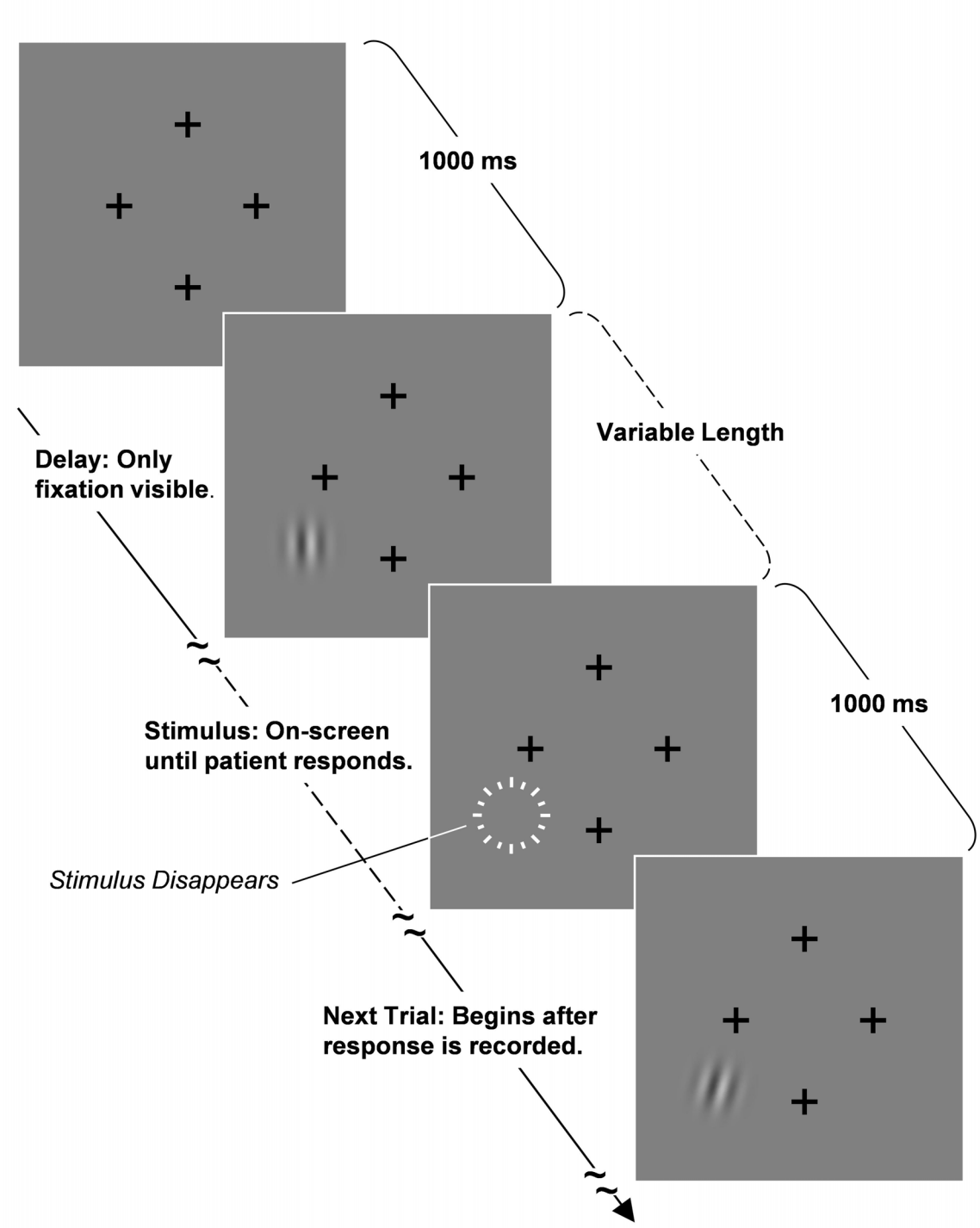


Figure 11. Contrast Sensitivity Testing Presentation.

6.3.3 Neuroimaging Assessment

Functional neuroimaging evaluated brain activation along the calcarine sulcus before and after the rehabilitation sessions. During scanning patients engaged in checkerboard and attention tasks. The attention tasks were divided into passive, single-task and conjunction runs. Patients repeated each run type twice for a total of 8 runs per session. All tasks were programmed and presented in E-Prime 2.0. Each run took approximately 5 minutes. The entire scanning session, including prep time, took an hour an a half.

Checkerboard Task

The checkerboard runs involved the presentation of contrast reversing checkerboard stimuli. These animated patterns have been successful in revealing retinotopically specific activation along the calcarine sulcus (Engel, Glover, & Wandell, 1997; Engel et al., 1994). In a departure form previous work, the checkerboard tasks for this study were designed to elicit activation in particular parts of V1, PRL and nonPRL locations, not map the entire visual cortex (c.f. Schumacher et al., 2008).

Stimuli

Checkerboard stimuli consisted of a 4 x 4 block of square checks that alternated between a black and white fill at 8 Hz. The stimuli were presented over a uniform gray background, adjacent to four black peri-central fixation crosses. Both the checkerboards and fixation crosses were scaled individually to patients according to the human cortical magnification factor.

Procedure

The experimenter coached the patients outside the scanner on how to perform the tasks as well as what to expect during functional runs (noises, vibrations, etc). Specific instructions conveyed how to fixate on the screen; that scotomatous areas should be situated within the bounds of the peri-central fixation crosses (i.e. the four cross method).

Once in the magnet bore, patients adjusted the viewing mirror so that they could see examples of both PRL and nonPRL stimuli. The experimenter fine-tuned the position of the fixation crosses with patient feedback. The head coil and surrounding padding restricted head movement. Patients wore head phones that muffled scanner noise and allowed communication with the experimenter.

Checkerboard runs were event-related in design (Figure 12). The fixation crosses remained on-screen during the entire run. Stimulus presentation was yoked to the onset of functional volumes. Stimuli appeared at either PRL or nonPRL locations for the length of a single volume (2000 ms). Subsequent inter-stimulus intervals (ISI) lasted 2000, 4000, or 8000 ms. Fifty percent of the ISIs were 2000 ms, while 4000 and 8000 ms durations were each 25% of the total. Stimulus location and ISI length varied randomly. A full run consisted of 162 volumes and contained 16 stimulus presentations, 8 PRL, 8 nonPRL. Similar variable-ISI designs have proved successful in extracting signal from event-related presentations (Ollinger, Shulman, & Corbetta, 2001a, 2001b).

The passive tasks only required patients to view the stimuli monocularly with the test eye. In lieu of eye-tracking, patients were repeatedly encouraged before and during scanning to maintain fixation and make sure the stimuli were in their field of view.

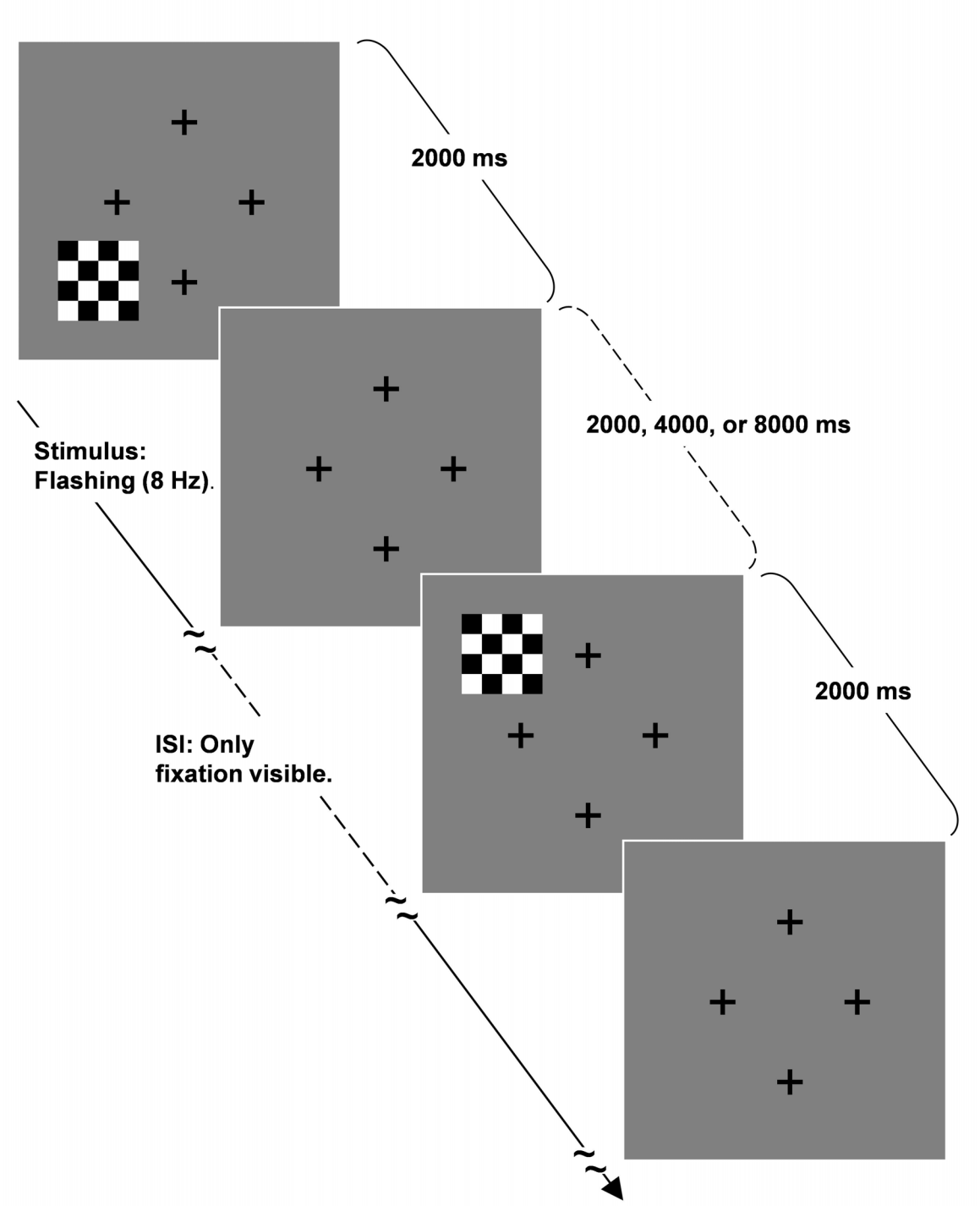


Figure 12. fMRI Checkerboard Task Presentation.

Attention Tasks

The attention runs tasked patients to respond to one or more dimensions of the Gabor stimuli. Attentional load is known to modulate activity in the primary and extra-striate visual cortices, increasing the magnitude of activation maps for an attended stimuli (Gandhi, Heeger, & Boynton, 1999; Hopfinger, Buonocore, & Mangun, 2000; Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999; Munneke, Heslenfeld, & Theeuwes, 2008) while at the same time decreasing the activation of corresponding, unattended stimuli (Bahrami, Lavie, & Rees, 2007; O'Connor, Fukui, Pinsk, & Kastner, 2002; Pinsk, Doniger, & Kastner, 2004; Schwartz et al., 2005). The attention tasks here were designed to elicit a stepped increase in V1 activation in reference to an increase in attentional load.

Stimuli

The stimuli in the attention runs were circular Gabor patches composed of alternating black and white luminance bands at spatial frequencies of 1 or 2 cpd. Gabors were either vertical or horizontal in orientation. All were 3° of visual angle in diameter and had a high contrast ratio, 48 cd/m^2. The Gabors were presented over a gray background, adjacent to four peri-central fixation crosses.

Procedure

The attention runs followed the same scanner prep as the passive runs. Patients were familiarized with the tasks outside the scanner. Adjustments within the magnet assured both the stimuli and fixation crosses were visible.

The attention runs were blocked (Figure 13). Block onset was yoked to the progression of volumes. Individual blocks presented stimuli to either the PRL or nonPRL. The fixation crosses were present throughout. Each block was 16 sec in length and consisted of 8 stimulus presentations of 1800 ms. A 200 ms ISI separated the presentations. An 8 sec baseline period followed every block. During this time only the fixation crosses were visible. The order of PRL and nonPRL blocks was random. Each run had 146 volumes, consisted of 12 stimulus blocks (6 PRL, 6 nonPRL), and 12 baseline periods.

Attention tasks consisted of passive, single-task, and conjunction runs. Passive Gabor runs only required patients to look at the stimuli. For the single task runs patients had to respond to a specific dimension of the stimuli: orientation or cycles/degree. Before scanning the experimenter conveyed to patients their target. Patients were consulted beforehand regarding which dimension (orientation or cpd) they were more comfortable discerning and targets were designated accordingly.

For the conjunction runs, patients responded to the same stimulus set as the single-task runs, the only difference was the task. The conjunction runs required patients to respond to two specific pairings of stimulus dimensions: all vertical stimuli at 2 cpd and all horizontal stimuli at 1 cpd. At the same time patients refrained from responding to horizontal stimuli at 2 cpd and vertical stimuli at 1 cpd.

Patients responded to targets via an optical button box placed in their right hand. There were a total of 48 stimuli (24 targets and 24 non-targets) in every run. Failure to respond to a target within 1800 ms was recorded as a miss, as well as responses to non-targets. The experimenter monitored patient performance during scanning.

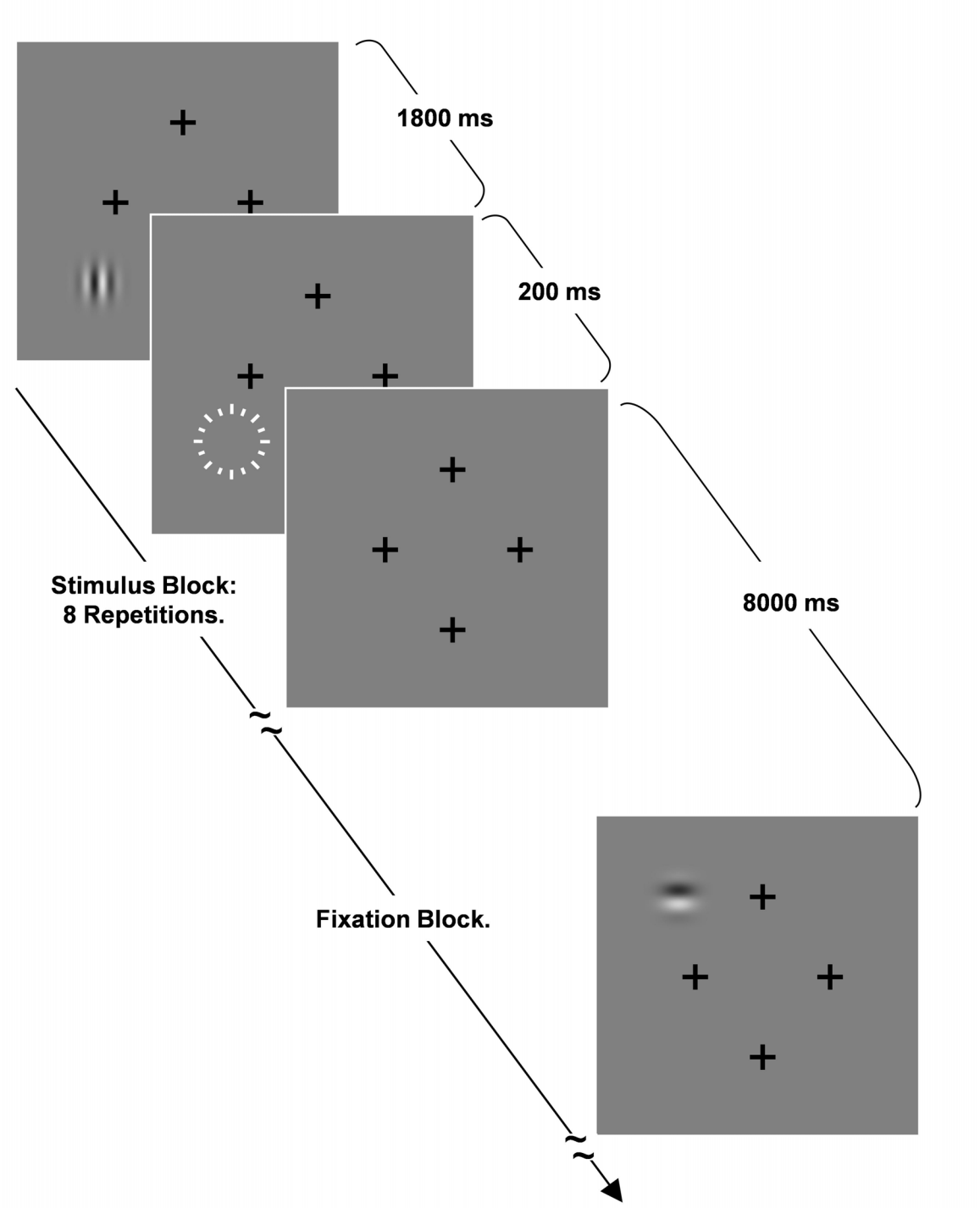


Figure 13. fMRI Attention Task (Passive, Single-Task, Conjunction) Presentation.

6.3.4 Visual Rehabilitation

The largest part of the study was the rehabilitation phase which entailed training patients to effectively use their PRLs. This goal was accomplished in two ways: 1) an in-device training regime employing the MP-1's biofeedback feature and 2) traditional occupational therapy focused on oculomotor control and reading proficiency. This two-fold strategy attempted to improve the effectiveness of rehabilitation by priming PRL awareness with biofeedback then reinforcing this association with intensive, person-centered training. To the experimenter's knowledge this was the first time biofeedback training has been utilized in conjunction with traditional occupational therapy to train MD patients in PRL use.

Biofeedback Training

Each therapy session began with biofeedback training conducted using the MP-1 Microperimeter (Figure 14). Biofeedback allows the patients to bring a formerly non-voluntary parameter, such as fixation behavior, under voluntary control. The procedure involved the use of audible cues to direct the patient's eye to a desired position. Biofeedback training has been shown to significantly improve fixation stability and retinal sensitivity in AMD patients (Vingolo et al., 2007). Moreover, the ability to successfully train a PRL and thereby enhance attention to a specific part of the visual field is theorized to be a critical element in eliciting the reorganization of cortical neurons (Safran & Landis, 1996).

Each biofeedback session lasted approximately 15 minutes. Patients gazed monocularly into the lens of the MP-1. The experimenter identified PRLs via their

surrounding vasculature and registered them with the device. Training began with the appearance of a fixation cross (2.5 diameter) in the center of the MP-1's LCD. The experimenter instructed patients to fixate on the cross with their PRL. As patients attempted this, the MP-1 generated a pulse-variant series of tones active in guiding the position of the eye for optimal fixation. As patients' eyes became more efficient and stable in engaging information with the PRL, the tones became more frequent, signaling them that they were accurately fixating with the desired part of the retina. Less frequent tones signaled a deviation from the PRL. Holding fixation precisely at the PRL elicited an uninterrupted tone.

When patients were able to reach the goal of an uninterrupted tone the experimenter encouraged them to practice holding this position during training. Each training period lasted a minute. Patients were allowed 3 min breaks in between these periods to reduce eye strain. There were 3-4 training periods in a session.

A.  B. 

Figure 14. MP-1 Biofeedback. A. The MP-1 operator keeps the lens positioned on the retina while the test runs. B. The difference between foveal (cross) and eccentric (circle) fixation. The blue dots represent retinal fixation progressing toward the area of eccentric fixation over the course of testing.

Occupational Therapy

The occupational therapy (OT) used in this study was specifically designed to enhance reading abilities. It supplemented the training provided by the MP-1, allowing patients to utilize formative PRLs in meaningful tasks. Patients underwent occupational therapy for 1 to 2 hours a week. They were also assigned between 3 to 4 hours of homework a week.

Initial sessions began with tasks to elicit PRL awareness. While all patients displayed fixation toward a specific area of the retina, as indicated by MP-1, they were often unaware of this preference and did not know how to effectively employ it. The first OT session acquainted patients with the location of their PRLs. Later sessions then revolved around instructing patients to fixate eccentrically and keep attention trained on the PRL using a steady eye strategy. A more detailed explanation of the visual rehabilitation procedures can be found in Appendix C.

Scotoma Awareness

Initial OT sessions involved helping patients realize the location of their scotomata. Material effective toward this aim are simple pictures on card stock. An example is a picture of a clock face (Figure 15). The therapist held this picture in front of patients and asked them to focus on the center to the best of their ability. She then asked a series of questions designed to help each patient realize how their visual field is occluded by the scotoma: “What numbers are blurry, faded, or distorted? What areas are missing entirely?” Inspection of the clock face presented patients with unique spatial identifiers (the numbers) enabling them to more easily realize the boundaries of their scotoma.

PRL Awareness

After the scotomatous areas of the visual field were located, the therapist helped patients discover the location of their PRLs using additional picture and phrase cards. The procedure involved asking the patient to move his or her eye so that they were best able to view a target. The position that yielded the most improvement in vision was considered to engage the PRL. The results of this exercise were double checked with the PRL location obtained from the MP-1. The PRL awareness task is ideal if patients keep their heads still and only move their eyes, but for some individuals with larger scotomata, head movement was unavoidable. Afterwards the therapist explained the significance of the PRL to the patient, where it is located in their visual field and how it can be used to focus in lieu of a functional macula.

PRL Training

Once the PRL was located, the therapist engaged patients in a number of monocular tasks designed to build PRL effectiveness and reliance. The locating task involved presenting patient targets (a letter or picture on card stock) at various positions at eye level. The patient's task was to move their PRL to each location and fixate on the target. The tracking task involved slowly moving target cards from one side of the patient's face to the other while they followed their course with the PRL. The therapist stopped movement if patients lost the target, allowing them to re-establish fixation. In gaze shifting exercises the therapist presented two targets to the patients. They were required to shift gaze, using the PRL, from one target to another. The therapist tested this

ability along the horizontal, vertical, and diagonal axes. The final step of PRL training involved using the Warren Pre-Reading exercises to prepare the patient for reading text (Warren, 1996). In Warren's exercises the patient was simply asked to read aloud columns of letters using their PRL. The task was repeated for improvement in time and error rates. Magnification was sometimes used to aid performance.

Pepper VSRT.

Once patients could orient and maintain fixation with their PRL they were given the Pepper Visual Skills for Reading Test (VSRT) to evaluate its reading effectiveness (Figure 15). The VSRT is a set of materials and procedures designed to monitor reading skills in low vision patients (Watson, Baldesare, & Whittaker, 1990). The therapist used the VSRT to evaluate PRL performance on such tasks as word recognition, reading rate, and movement control. It was conducted before and after training.

A.  B. 

Figure 15. Occupational Therapy. A. Administration of the Pepper VRST. B. A representation of the clock face stimulus and how a scotoma can occlude or distort specific parts of it.

CHAPTER 7: DATA ANALYSIS

7.1 Behavioral Analysis

Prior to analysis, trials with RT outliers (± 2.5 *SE* of the mean) were removed from the behavioral (contrast and recognition) and fMRI behavioral (single-task and conjunction) data. An upper bound of 10 seconds was set for the recognition and contrast data. All trials with RTs over this value were considered compromised by distraction and removed. Trials in which the patient was unable or refused to guess were removed. Finally, all incorrect trials were removed from the RT data on the grounds that an incorrect response indicates a disruption of information processing.

Due to the influence of autocorrelation, standard statistical analyses (i.e. *t*-test and ANOVA) are inappropriate for single-subject designs. Patient behavioral data were analyzed instead with randomization tests which compared the conditions (pre-test vs. post-test) for PRL and nonPRL locations (Edgington, 1969; Manly, 1991). Each randomization test involved the comparison of the pre and post-test conditions by randomly selecting and interchanging their data values without replacement then conducting a *t*-test on the resulting samples. This process was repeated 1000 times in a bootstrapping procedure, producing a distribution that was centered on zero and estimated the sampling distribution when H_0 is true. Significant differences were determined by finding the proportion of significant *t* values within the distribution and squaring the number to approximate a two-tailed *p*-value.

7.2 Fixation Analysis

All fixation data (four cross, single cross, feedback) were analyzed using the bootstrapping procedure described above and by calculating the bivariate contour ellipse area (BCEA) of the distributions. BCEA is a two-dimensional measure of normally distributed data plotted in Cartesian space. Analogous to a bivariate form of the standard deviation, BCEA produces an elliptical contour line that encloses 68.2% of plotted fixation points. The area of this contour, expressed in minutes of arc squared, reflects the location where fixation is most likely to occur. BCEA is calculated as follows:

$$BCEA = 2.28\ \pi\ \sigma_H\ \sigma_V (1 - \rho^2)^{1/2} \quad (4)$$

Here σ_H is the standard deviation of fixation points along the horizontal meridian, σ_V, the vertical meridian, and ρ their product moment correlation.

7.3 fMRI Analysis

BrainVoyager QX 1.8 (Brain Innovation, Maastricht, The Netherlands) was used to process and analyze functional MRI data (Goebel, Esposito, & Formisano, 2006). BrainVoyager QX allows for the presentation of functional and structural MRI data through optimized 2D and 3D visualization routines. It is also capable of in-program statistical tests using whole-brain and region-of-interest models.

Preprocessing of the functional data constituted 3D motion correction, slice timing, and temporal filtering. Motion correction was performed in reference to the last functional run. Slice timing employed a trilinear/sinc interpolation based on the TR (2000 ms) and the order of slices (ascending, interleaved). Temporal filtering consisted of linear trend removal and a high-pass filter which removed low frequency drifts of 3 cycles

(0.0092 Hz) or less. Both measures were applied to the temporal filtering of the blocked data, while only linear trend removal was used on the event-related runs. The high-pass filter was avoided in this case because its benefits are questionable with variable ISI designs (Della-Maggiore, Chan, Peres-Neto, & McIntosh, 2002)

A rigid body transformation centered the structural images along the AC-PC plane and a trilinear interpolation warped them to Talairach space (Talairach & Tournoux, 1988). Additional processing segmented the gray matter from each structural image, digitized the fiducial, and inflated it to produce a 3D surface with delineated sulci. The functional data from each patient (pre and post-test) were coregistered to the structural image attained from their pre-test session. Mapping both pre and post-test data onto the same structural space allowed in-program analysis of the conditions as well as a more faithful depiction of activation differences along the calcarine sulcus.

The functional data from each condition were analyzed using the general linear model (GLM). Target location (PRL and nonPRL) and task (checkerboard, passive, single, and conjunction) were the covariates. Significant activation ($q(FDR) < .05$) was displayed on the inflated brains in reference to baseline. In order to alleviate the number of multiple comparisons, a calcarine mask restricted analyses to the primary visual cortex. Regions of interest (ROIs) were created by selecting and integrating significant areas of activation (30 voxels and larger) for each condition—for example, all pre-test, PRL activation in the left calcarine. The activation of these pre and post-test ROIs were then compared through contrast analyses.

CHAPTER 8: RESULTS

8.1 Evaluation Results

Initial evaluations were conducted to provide basic information regarding the health of the patients' retinas. The results below record overall retinal health, as assessed by microperimetry, as well as the locations of PRLs, established through fixation tests.

8.1.1 Microperimetry

Microperimetry data were processed by interpolating between the thresholds of tested retinal locations to produce a topographic, sensitivity map for each patient. Visual inspection of these maps revealed large scotomata in the test eyes of all patients. These scotomatous regions encompassed the macula and in many cases extended into the peri-central retina. The size of the scotomata varied between 22 and 116 mm^2 and were largely consistent with the locations of visible scarring observed on the retinographs (Figure 16).

The mean sensitivity of the test eyes ranged between 0.5 and 8.5 dB (Table 3). The sensitivity of scotomatous areas was considerably less (0.5-6.7 dB). The maps also showed the presence of an absolute scotoma in every patient, defined here as retinal areas where the patient was unable to detect a stimulus at the highest deliverable luminance level (0 dB). In addition to such serious damage, many patients demonstrated areas of moderately impaired retina (sensitivity thresholds between 6 and 12 dB) surrounding or adjacent to the absolute scotoma. In some patients healthy retinal areas were also observed. These locations elicited responses at the lowest luminance levels (16-20 dB).

A prerequisite for diagnosing retinal field defects is a definition of the normal range of light sensitivity. Midena and Cavarzeran (2006) constructed an age-related, normative database of light sensitivity values using the MP-1. Their analysis revealed that the average dB for stimulus detection ranges from 18.8 dB at 20 years of age to 16.9 dB at 70 and over. The patients in this study demonstrated scotoma sensitivity thresholds well below (> 2 *SD*) the healthy standard of their age group. The microperimetry data then indicate locations of real functional deficits as well as areas of relative preservation on the retinas of the patients. Figure 17 depicts the interpolated, color-coded maps derived from raw threshold values.

Table 3. *Scotoma Size and Retinal Sensitivity*

Patient	Scotoma Size (mm^2)	Mean Sensitivity (dB)	
		Entire Retina	Scotoma
BE	116.19	2.2	1.4
HN	106.85	3.3	1.9
JM	22.72	8.5	6.7
MK	113.81	0.5	0.2
PC	51.39	1.8	0.9
VH	109.75	1.2	0.5
YS	23.31	4.8	0.6

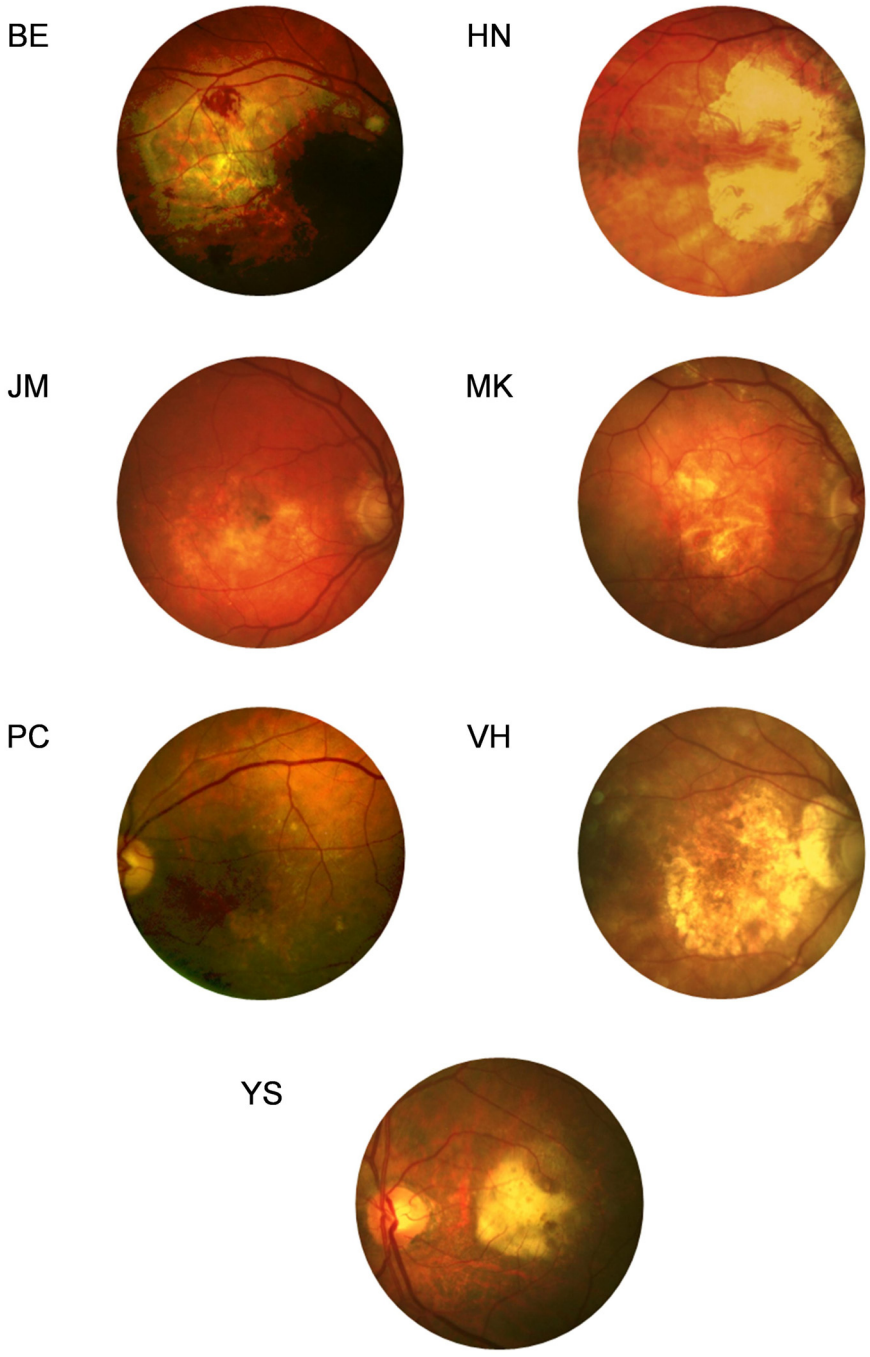


Figure 16. Patient Retinographs.

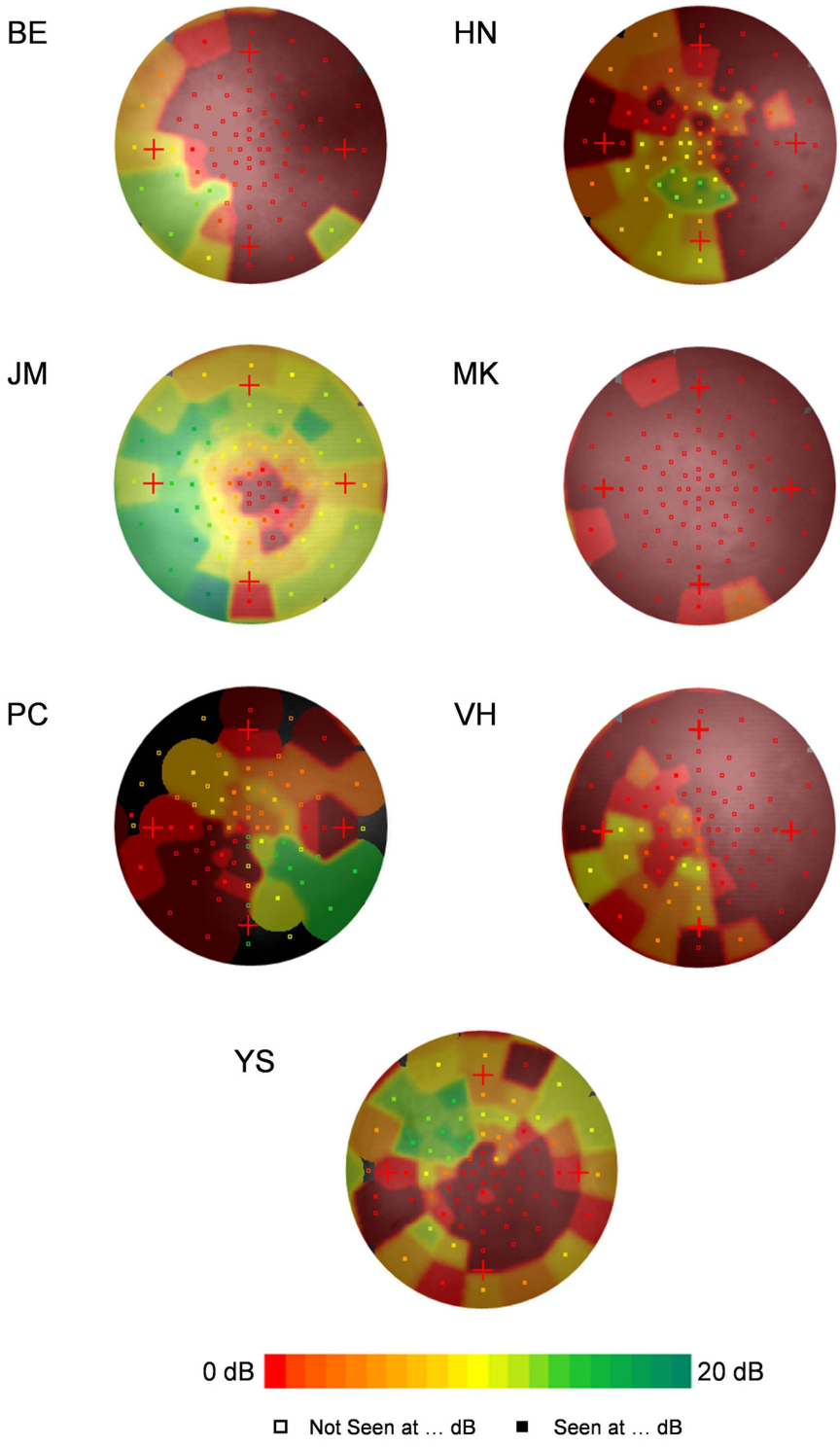


Figure 17. Patient Sensitivity: Interpolated Maps.

8.1.2 Fixation Analysis

Fixation analysis involved assessment of the scattergrams from 1-cross and 4-cross fixation. Analysis of the 4-cross data revealed unstable fixation; 6 to 47% of fixation points were within 2° of the fovea. BCEA values ranged between $6.03°^2$ and $44.49°^2$ (Table 4). Though unstable by normal standards, 4-cross fixation does indicate that the patients have the ability to keep their eye centered and largely free from saccades to the PRL. Analysis of 1-cross data demonstrated that many patients preferred using areas immediately to the right or upper-right of their scotomata to fixate the cross, a finding consistent with many studies of PRL location. Typical of AMD patients, fixation at most of these locations was unstable; 29 to 56% of fixation points were within 2° of center. BCEA values ranged between $5.04°^2$ and $13.34°^2$ (Table 4). Figure 18 depicts scattergrams from the 4-cross and 1-cross fixation procedures.

Table 4. *Patient Fixation: Percents and BCEA Values.*

Patient	4-cross (% in 2°)	4-cross (BCEA)	1-cross (% in 2°)	1-cross (BCEA)
BE	14%	$20.23°^2$	40%	$6.19°^2$
HN	6%	$44.49°^2$	29%	$13.05°^2$
JM	46%	$6.03°^2$	56%	$5.04°^2$
MK	47%	$6.27°^2$	29%	$8.09°^2$
PC	22%	$16.82°^2$	36%	$13.34°^2$
VH	12%	$19.06°^2$	48%	$8.79°^2$
YS	12%	$29.20°^2$	35%	$11.27°^2$

The notation "% in 2°" refers to the proportion of fixations within 2 degrees of the fovea.

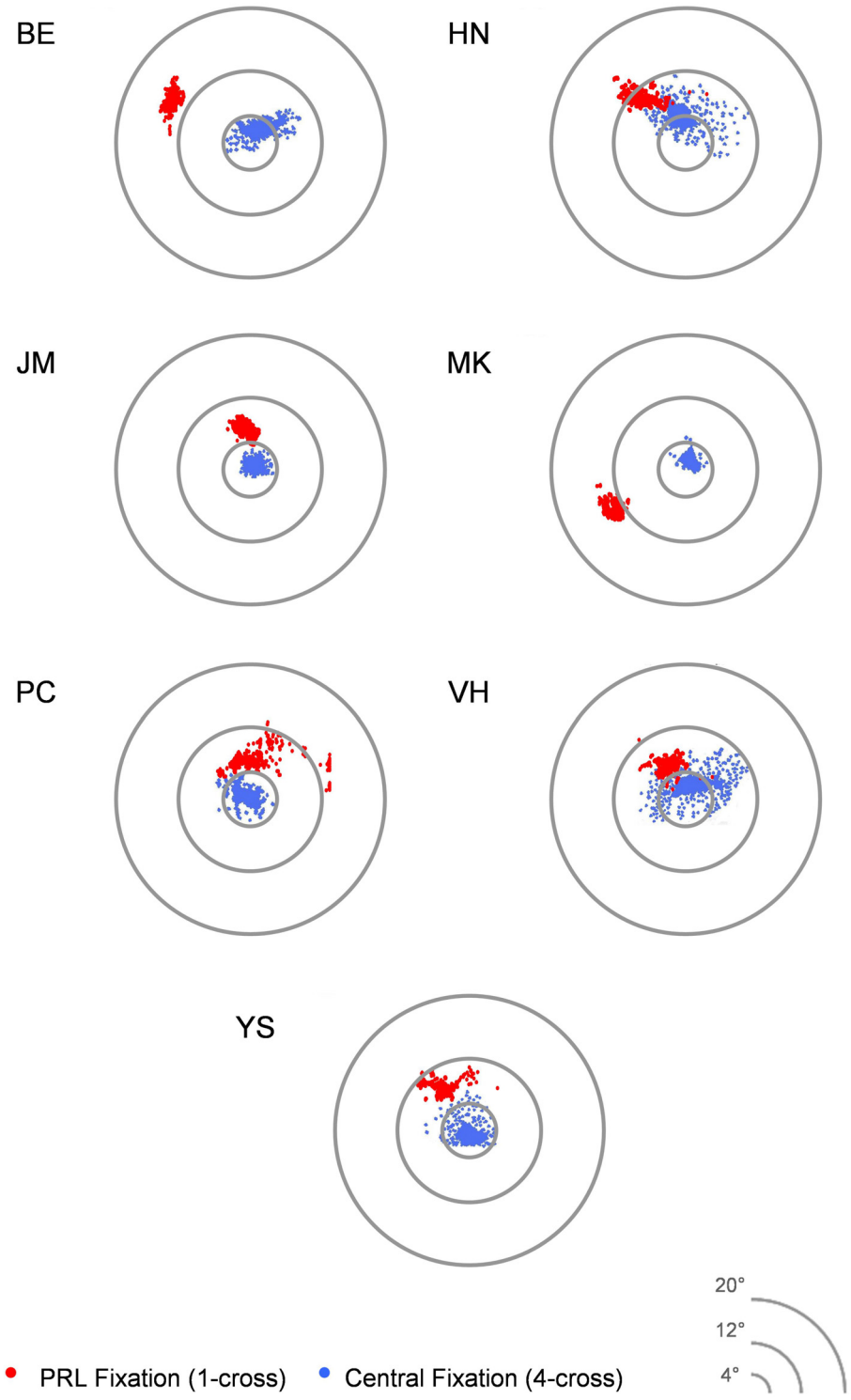


Figure 18. Patient Fixation: Scattergrams.

8.1.3 PRL/nonPRL Determination

MP-1 evaluation identified scotomatous regions of the retina and areas of preferred fixation. Based on the fixation analysis, a PRL from the test eye was chosen for future training. In addition, a nonPRL area was selected from the same eye, defined as an area of retina that is similar in sensitivity to the PRL but lacks functional significance (i.e. fixation tests indicate a preference for the PRL rather than the nonPRL).

These nonPRLs served as comparators to the PRLs. To insure their validity in this regard, nonPRLs were chosen from the same retinal eccentricity as the PRLs (Table 5), so variations in visual receptor distribution and cortical magnification would be similar. To make sure PRL/nonPRL use was not conflated during the behavioral tasks, nonPRLs were selected from the opposing visual hemifield when possible (Figure 19).

Table 5. *Patient PRL and nonPRL Locations*

Patient	PRL (ecc deg)	PRL (radial deg)	nonPRL (ecc. deg)	nonPRL (radial deg)
BE	12°	150°	12°	210°
HN	6°	135°	6°	225°
JM	6°	90°	6°	270°
MK	13°	195°	13°	270°
PC	6°	0°	6°	90°
VH	6°	0°	6°	90°
YS	8°	120°	8°	300°

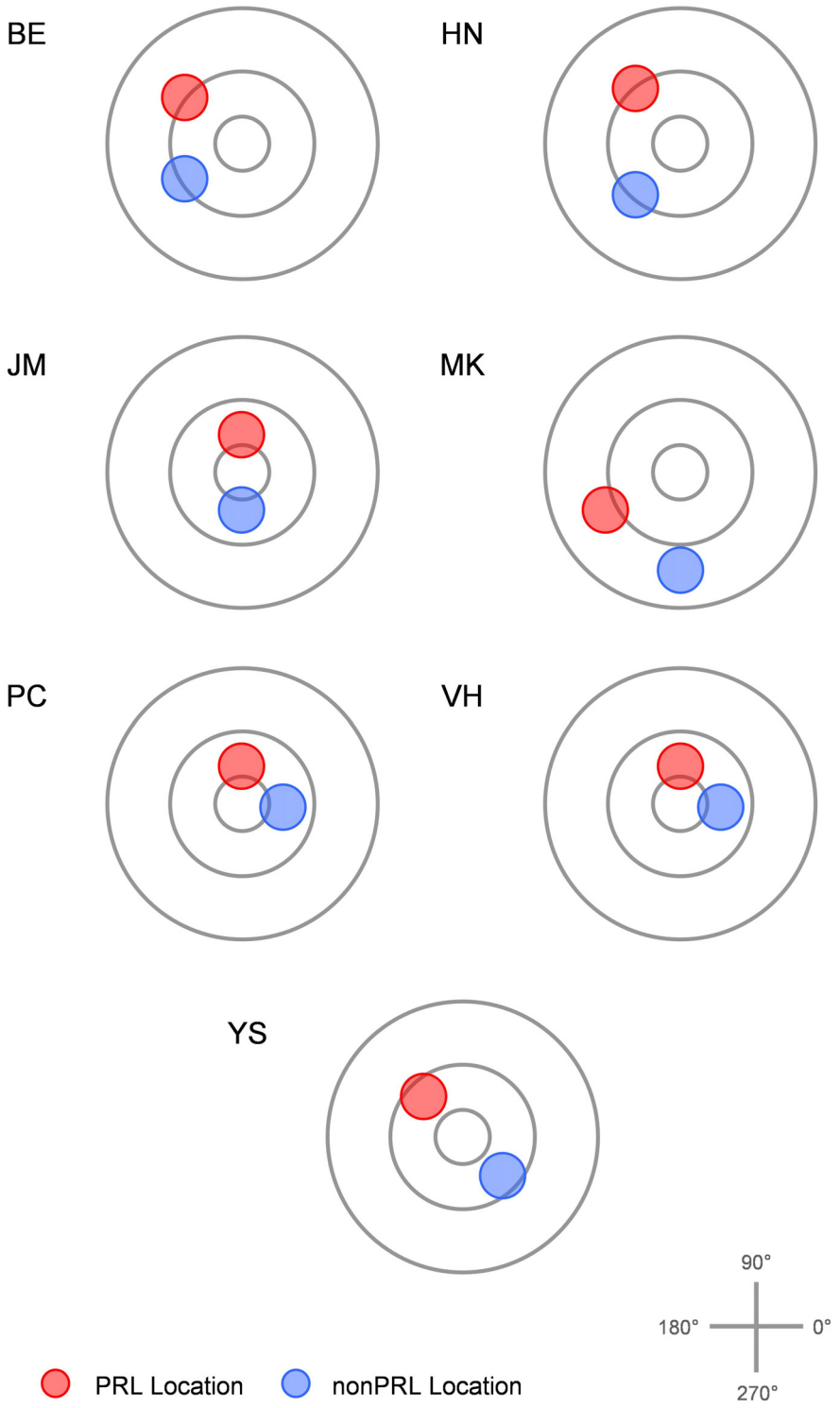


Figure 19. Patient PRL and nonPRL Locations.

8.2 Rehabilitation Results

8.2.1 Occupational Therapy

Occupational therapy yielded improvement in patient fixation and reading ability. Because each patient was different, the benefits of visual rehabilitation were addressed individually. In addition to qualitative observations, the Pepper VRST demonstrated post-test improvements in reading accuracy and rate for many patients (Table 6). Patients BE, JM, and VH all showed improvements in accuracy after the training, though BE exhibited a slower reading rate. Patient MK did not reveal demonstrable improvements in accuracy or rate. Patient PC actually showed a decrease in reading accuracy for the post-test, perhaps the consequence of fatigue. Finally, HN was unable to finish both pre and post-tests. His data are not included.

Table 6. *Pepper VRST Pre and Post Test Results*

Patient	Reading Accuracy (%)		Reading Rate (wpm)	
	Pre-test	Post-test	Pre-test	Post-test
BE	89.33	96.20	24.69	23.55
HN	--	--	--	--
JM	96.56	100	14.93	30.99
MK	88.08	87.40	15.24	11.93
PC	90.10	74.63	19.12	19.46
VH	86.14	91.85	6.46	12.98

WPM = words per minute.

8.2.2 Biofeedback

Biofeedback training yielded demonstrable changes in eccentric fixation for patients HN, JM, PC, and VH.[10] Fixation eccentricity, measured in degrees from the PRL, significantly decreased between sessions 1 and 4 for all patients, $p < .01$ (Table 8). In addition to eccentricity, BCEA values were reduced across the test sessions, indicating that fixation points concentrated around the PRL with training (Table 7).

Though all tested showed a significant reduction in fixation eccentricity, there was wide variation between patients (Figure 20). For example, patient HN saw a relatively minor improvement between the first and last sessions, a difference of .86°. In contrast, patient VH showed a more prominent decrease of 2.84°. Most patients saw an improvement in eccentricity session-to-session, but VH and PC actually showed a small increase between sessions 1 and 2.

The reduction of BCEA values also showed some inconsistency. Most patients showed a decrease of 1 to 2 BCEA between sessions. However, patient PC saw dramatic reductions after sessions 1 and 2 (4.16 and 2.84 BCEA, respectively). Some patients actually showed isolated increases in BCEA. Latter values were slightly larger for patient VH between sessions 1 and 2 and HN between sessions 2 and 3.

The above increases were minor, though, and may simply represent error. In contrast, all patients showed prominent reductions between the first and fourth sessions for both BCEA and fixation eccentricity.

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[10] Patients BE and MK exhibited prominent head movements and erratic fixation that overwhelmed MP-1 recording abilities. For this reason they were excluded from the biofeedback training and only participated in occupational therapy.

Table 7. *BCEA Values across Biofeedback Sessions*

Patient	Session 1	Session 2	Session 3	Session 4
HN	$2.13°^2$	$1.97°^2$	$2.05°^2$	$1.27°^2$
JM	$3.10°^2$	$2.87°^2$	$1.50°^2$	$1.22°^2$
PC	$7.46°^2$	$3.30°^2$	$0.46°^2$	$0.17°^2$
VH	$6.42°^2$	$7.74°^2$	$3.62°^2$	$0.51°^2$

The bivariate contour ellipse is expressed in minutes of arc squared and describes a two dimensional area. The measure assumes that the eye positions generate a bivariate normal distribution.

Table 8. *Mean Eccentricity Values across Biofeedback Sessions*

Patient	Session 1	Session 2	Session 3	Session 4
HN	1.94°	1.79°	1.69°	1.54°
JM	2.88°	1.19°	0.82°	0.75°
PC	2.14°	3.12°	0.90°	0.64°
VH	3.92°	4.87°	3.67°	1.08°

Mean eccentricity here describes the average distance of eye positions (in degrees of visual angle) from the location of the PRL.

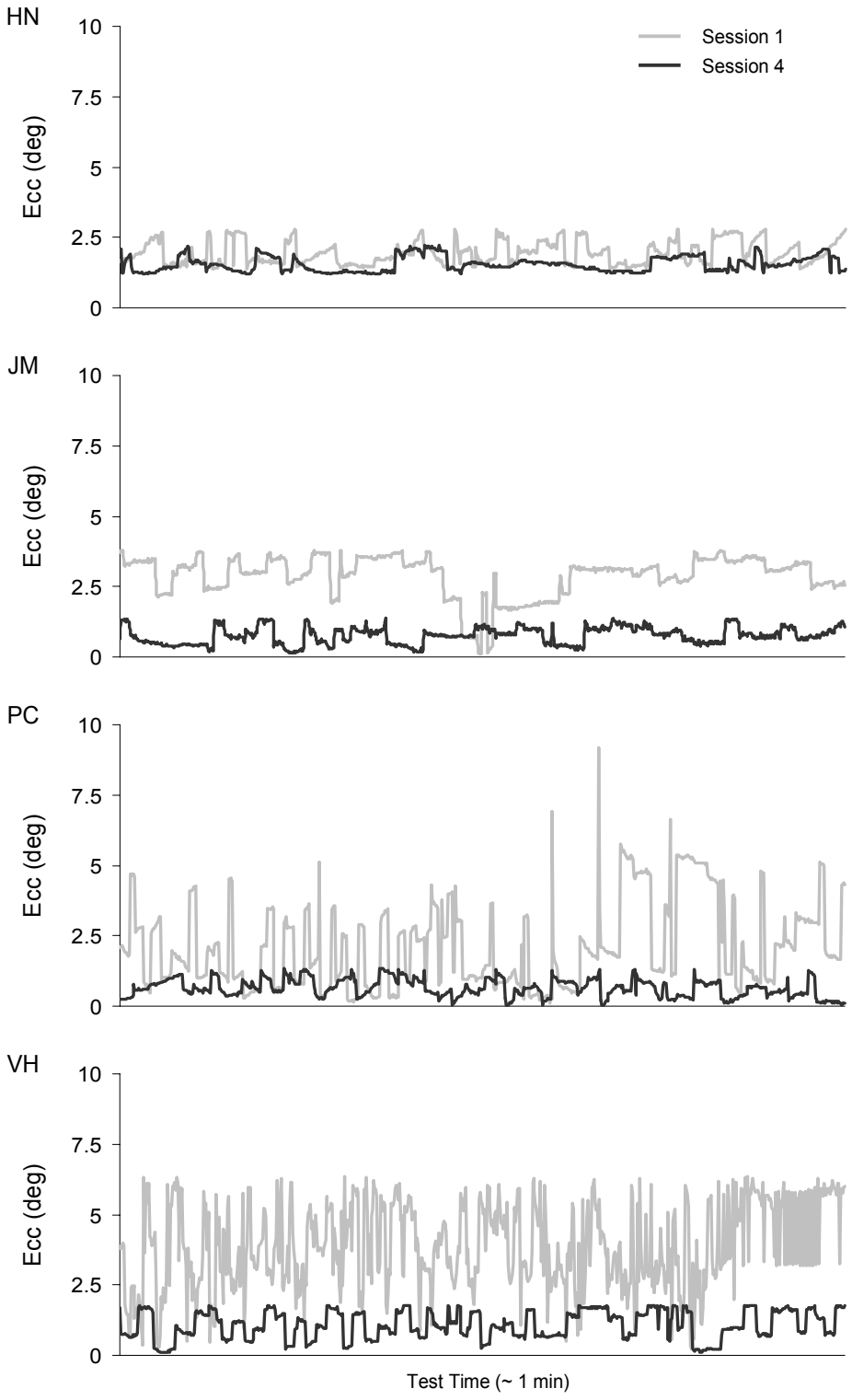

Figure 20. Fixation Eccentricity for Feedback Sessions 1 and 4.

8.3 Assessment Results

8.3.1 Behavioral Tests

Before formal recognition and contrast sensitivity testing, pre-tests determined the stimulus size and contrast ratios (cd/m^2) necessary for optimal performance (Table 9). For the recognition tests, a set of 3 stimulus sizes, defined by their minimum angle of resolution[11], were chosen for each patient based around the threshold value (mean) obtained through the staircase procedure. Patients BE and MK demonstrated large increases and/or decreases in accuracy bounding their thresholds. For this reason, only the threshold values were used for these patients.

Pre-tests of the contrast sensitivity procedure found that Gabor patches of 0.5, 1.5, and 3 cpd were best suited for patient performance. These values were used in all contrast tests, expect for JM, whose vision was good enough to warrant values of 1.5, 3, and 6 cpd. Pre-testing also determined the contrast ratio applicable for each cpd. For example, pre-testing of patient BE yielded contrast ratios of 4 cd/m^2 for 0.5 cpd, 6 cd/m^2 for 1.5 cpd and 2.8 cd/m^2 for 3 cpd. These thresholds represent the lowest contrasts at which stimulus discrimination is possible. They were determined independently for each cpd value and subsequently used in the contrast sensitivity tests proper. All of the following graphs of behavioral data (Figures 21, 22, 23 and 24) depict mean values with error bars indicating the standard error of the mean (SEM).

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[11] The minimum angle of resolution (MAR) describes the angle, in minutes of arc, that the smallest stroke of a character subtends an individual's retina. This angle, often given in log10 form (logMAR), has a linear relationship with Snellen notation, so that better Snellen fractions yield smaller MAR values: 20/100 = 5.0, 20/80 = 4.0, 20/60 = 3.2, etc.

Table 9. *Recognition and Contrast Test Values for all Patients*

Patient	Recognition Stimulus (MAR)			Contrast Ratio (cd/m^2)		
BE	--	6.3	--	12	8	8
HN	6.3	5.0	4.0	24	12	32
JM	8.0	5.0	3.2	8	4	2.8
MK	--	12	--	48	16	32
PC	10	8.0	6.3	48	16	11.2
VH	6.3	5.0	4.0	12	12	22.4
YS	6.3	5.0	4.0	48	8	5.6

The middle numbers for the recognition stimuli are the threshold values obtained through the staircase procedure. Values to the left and right are stepped increases and decreases, respectively, in stimulus size chosen by the experimenter. The contrast ratio values were determined separately for each cpd condition via the staircase. From left to right, they correspond to the 0.5, 1.5, and 3 cpd conditions; 1.5, 3 and 6 cpd for patient JM.

Recognition Acuity

The recognition acuity data showed isolated differences between the pre and post-test sessions in patients HN, MK, PC, and YS.[12] Patients BE and VH showed no differences in either accuracy or reaction time. Only patient JM demonstrated a consistent difference in reaction time across all test conditions. Every one of JM's stimulus conditions (8.0, 5.0, and 3.2 MAR), for both PRL and nonPRL presentations, showed an increase in RT for the post-test session, $p < .05$ & .01 (Figure 21). In contrast, most of JM's accuracy scores did not differ between pre and post-test sessions. Only condition 3.2 MAR/nonPRL demonstrated greater accuracy in the pre-test, $p < .01$ (Figure 21).

In other patients significant results were less consistent. Patient HN demonstrated a significant decrease in the post-test RT for 6.3 MAR/nonPRL, $p < .05$ (Figure 21). Patient MK showed an increase in RT for 12 MAR/PRL, $p < .05$ (Figure 21). Patient PC demonstrated a decrease in accuracy for 6.3 MAR/PRL, $p < .01$, but showed an improvement in the same condition for the nonPRL, $p < .01$ (Figure 22). Patient YS showed an improvement in accuracy for 5.0 MAR/PRL and 5.0 MAR/nonPRL, $p < .05$. Finally, YS also showed a decrease in RT for the 5.0 MAR/PRL, $p < .05$ (Figure 22).

[12] As described the in the Chapter 7, a bootstrapping procedure was used to analyze all behavioral data. This statistical test produces a distribution of *t*-values based on resampling from the data sets in question. Because there are literally 1000 *t*-values associated with each test, only *p*-values are given here. Information on bootstrapping can be found in (Edgington, 1969) and (Manly, 1991).

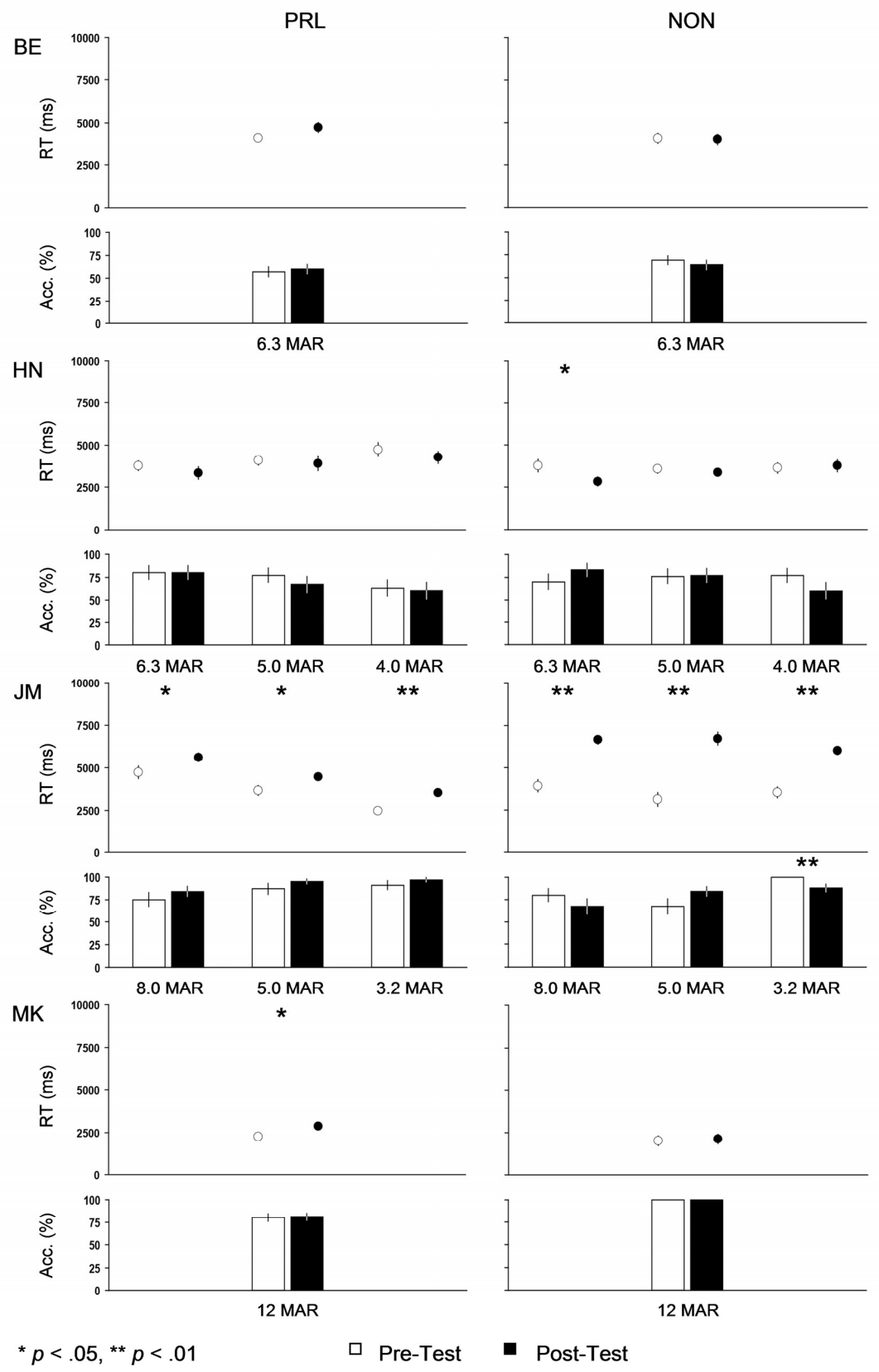

Figure 21. Recognition Task Data (BE - MK).

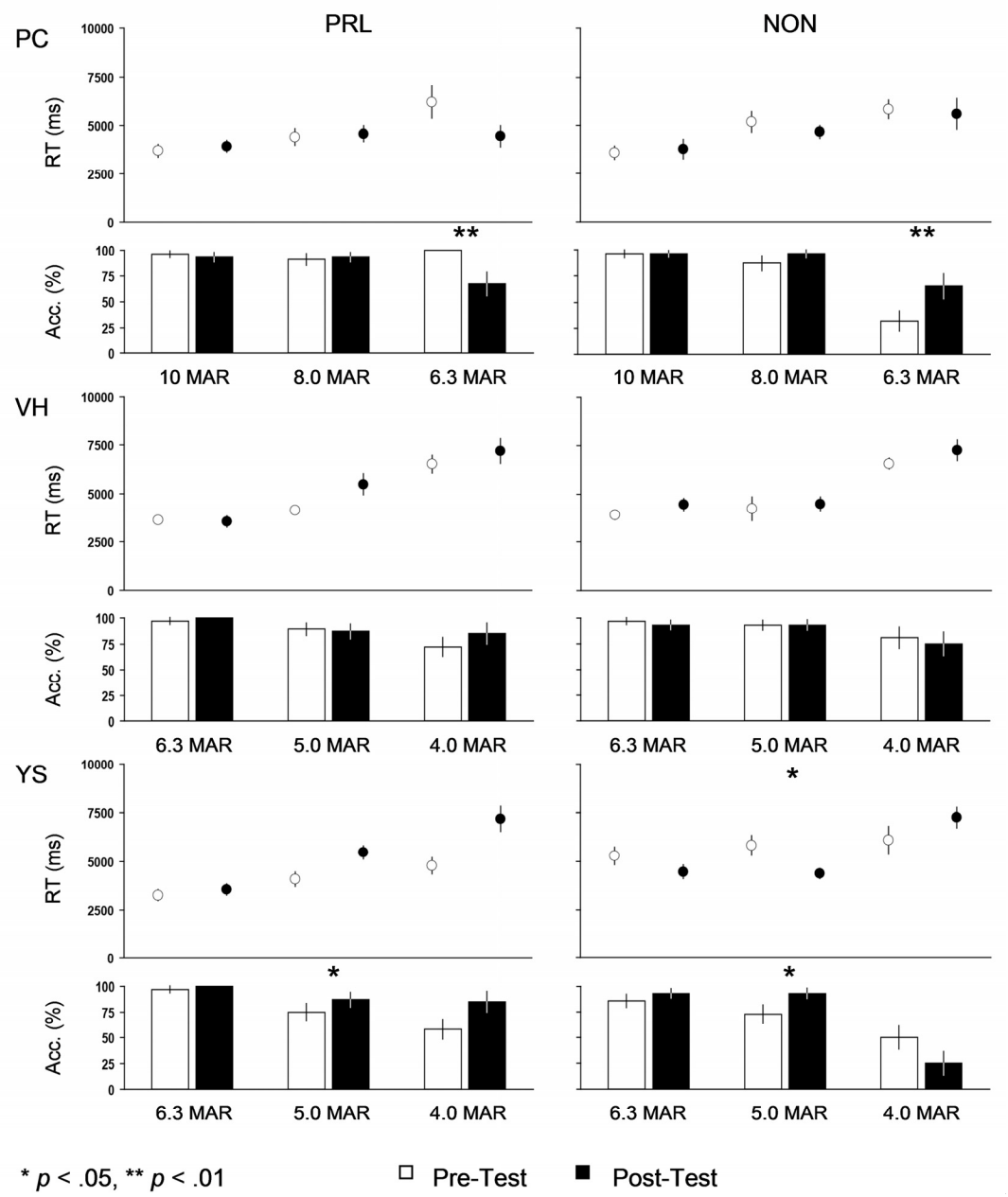

Figure 22. Recognition Task Data (PC - YS).

Contrast Sensitivity

The contrast sensitivity data showed variable differences between the pre and post-test sessions across patients (Figure 23, 24). Only patient BE demonstrated a consistent difference between pre and post measurements. The nonPRL presentation for BE showed a significant increases in accuracy as well as decreases in reaction time for all the cpd conditions, $p < .05$ (Figure 23).

Other patients showed isolated differences between pre and post-test sessions. Patient HN showed an increase in accuracy for 3 cpd/nonPRL, $p < .05$ (Figure 23). Patient JM demonstrated an RT increase for 1.5 and 6 cpd, PRL and nonPRL, $p < .05$. JM also showed a significant increase in accuracy for 6 cpd, PRL and nonPRL, 3 cpd/nonPRL, and a decrease in accuracy for 1.5 cpd/PRL, $p < .05$ (Figure 23).

Patient MK showed no differences between the pre and post-test sessions (Figure 23). Patient PC saw a decrease in accuracy for 0.5cpd/nonPRL and an increase in RT for the 3 cpd/nonPRL, $p < .05$ (Figure 24). Patient VH demonstrated an increase in RT for 1.5 and 3 cpd/PRL, as well as 0.5 and 3 cpd/nonPRL, $p < .05$ (Figure 24). Patient YS showed an improvement in accuracy at 1.5 cpd/PRL and 0.5 cpd/nonPRL, $p < .05$. Finally, YS also showed a decrease in accuracy at 1.5 cpd/nonPRL, $p < .05$ (Figure 24).

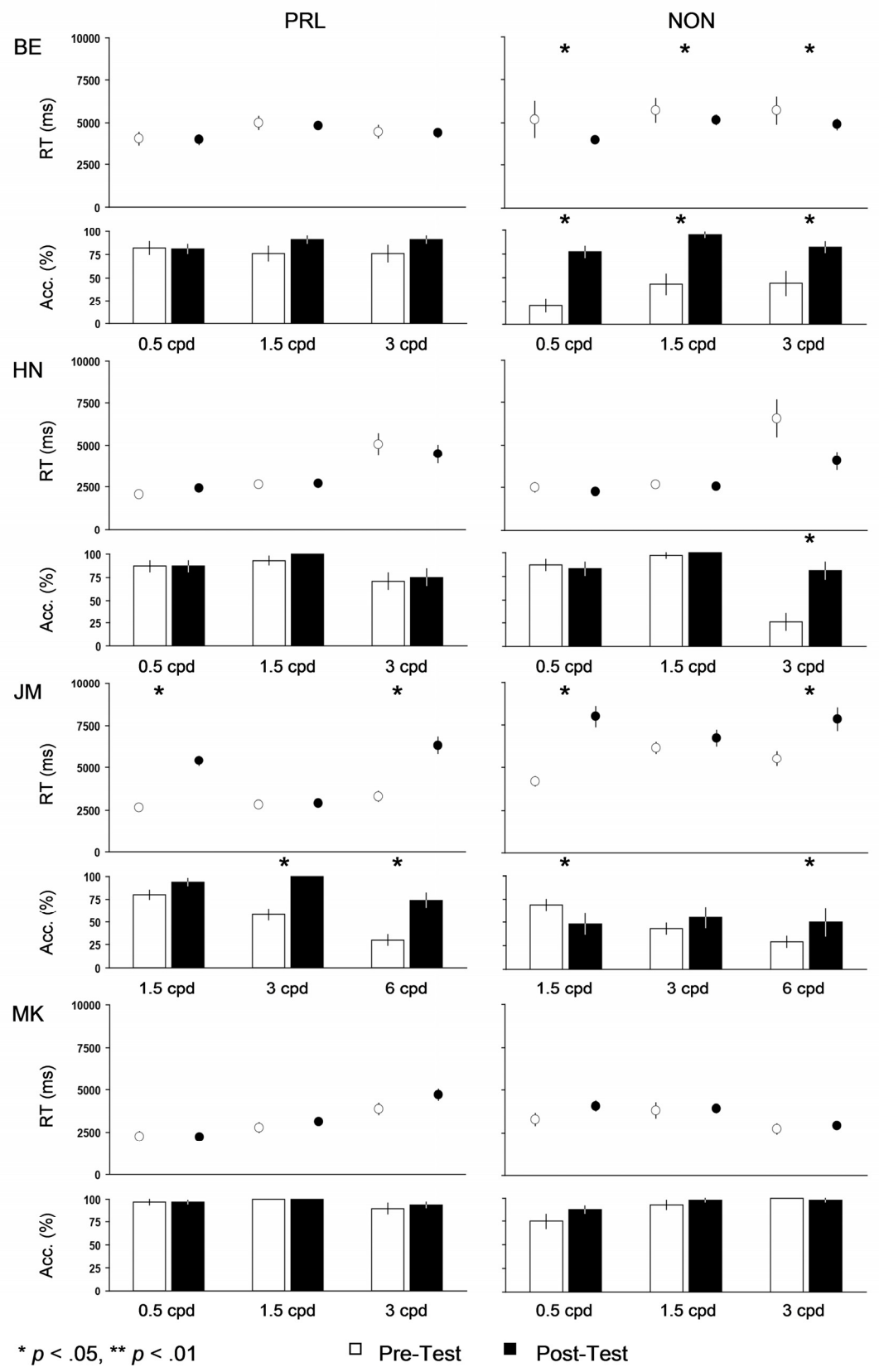

Figure 23. Contrast Task Data (BE - MK).

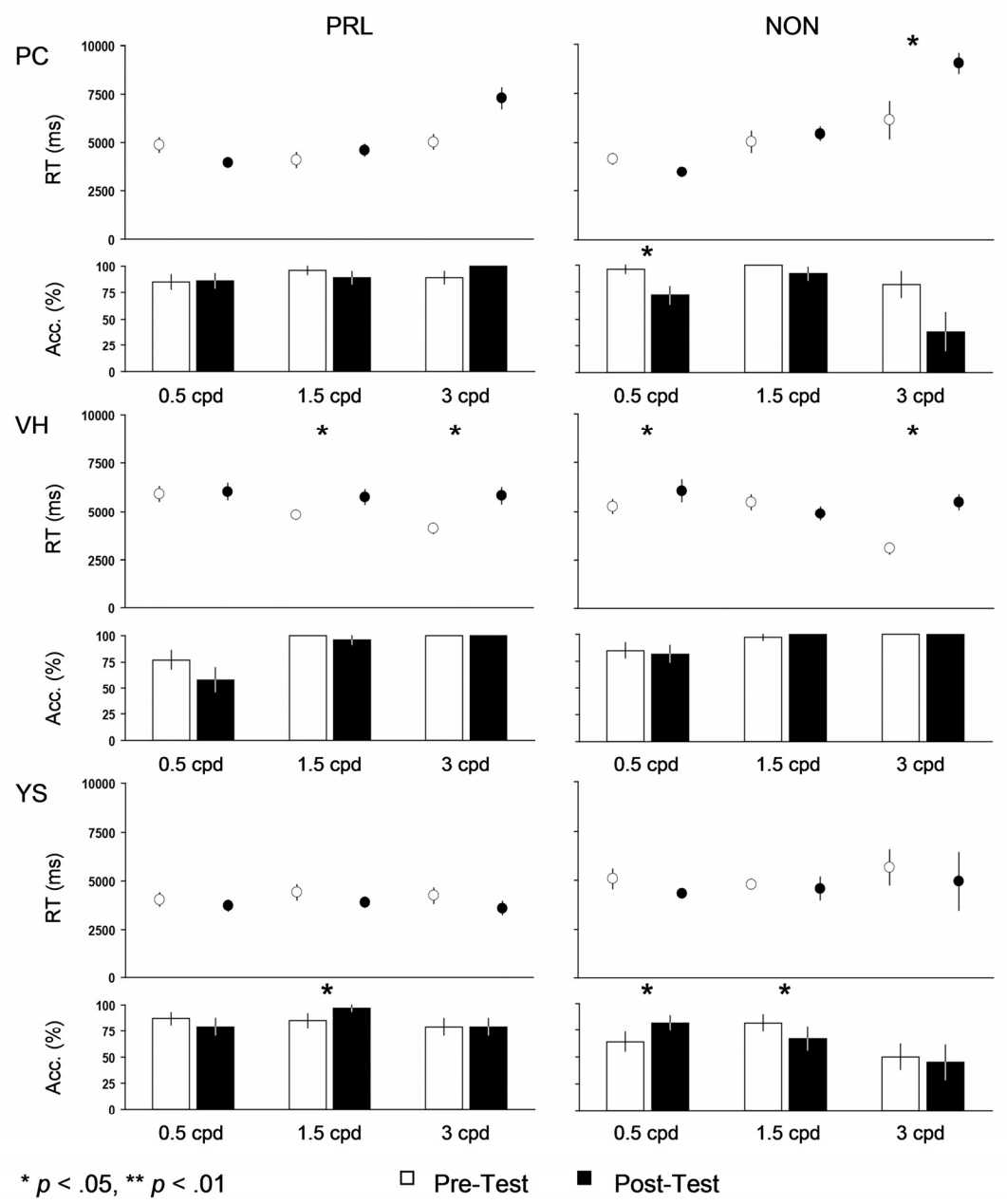

Figure 24. Contrast Task Data (PC - YS).

8.3.2 Functional Neuroimaging

Behavioral Results

The behavioral results from the fMRI scans showed a significant shift in the reaction times between pre and post-test sessions (Figure 25, 26). Some patients like HN, PC, and VH showed a significant increase in RT for post-test conditions, $p < .05$ & $.01$. Others like JM, MK, and YS showed decreases, $p < .01$. Patient BE demonstrated no change. This pre/post-test difference (whether positive or negative) was present in most or all of the conditions for some patients (HN, MK, and VH) while only in certain conditions for others (JM, PC, and YS). Among those with irregular differences, patient JM showed a reduction in RT for only the nonPRL, conjunction run, $p < .01$. YS showed the same but for the single-task run, $p < .01$. Patient PC showed an increase in the single-task RT for both the PRL and nonPRL, $p < .01$.

The post-test sessions also demonstrated greater accuracy (Figure 25, 26). Though this finding was always positive, it was also more sporadic. That is, no patient demonstrated a consistent increase in accuracy across conditions, but all patients showed isolated examples of post-test improvement. Patient BE, for example, demonstrated greater accuracy for both single-task and conjunction runs in the nonPRL condition, $p < .01$. Patients PC and MK showed greater accuracy for single-task and conjunction runs, PRL and nonPRL respectively, $p < .01$. Finally, patient YS showed greater accuracy in the conjunction run for the nonPRL condition, $p < .05$. The following graphs (Figures 25 and 26) show mean values with error bars depicting the SEM.

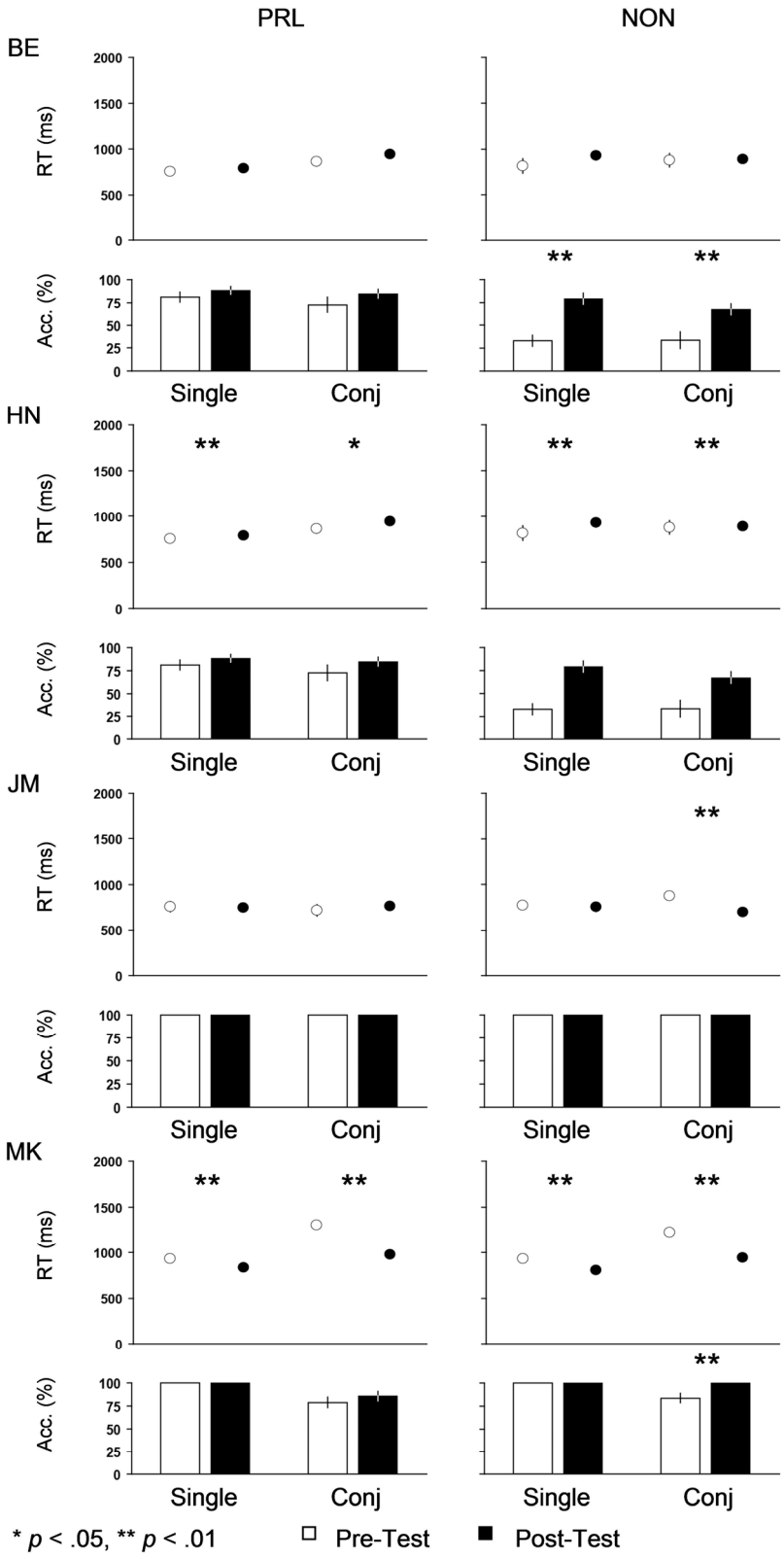

Figure 25. fMRI Behavioral Data (BE - MK).

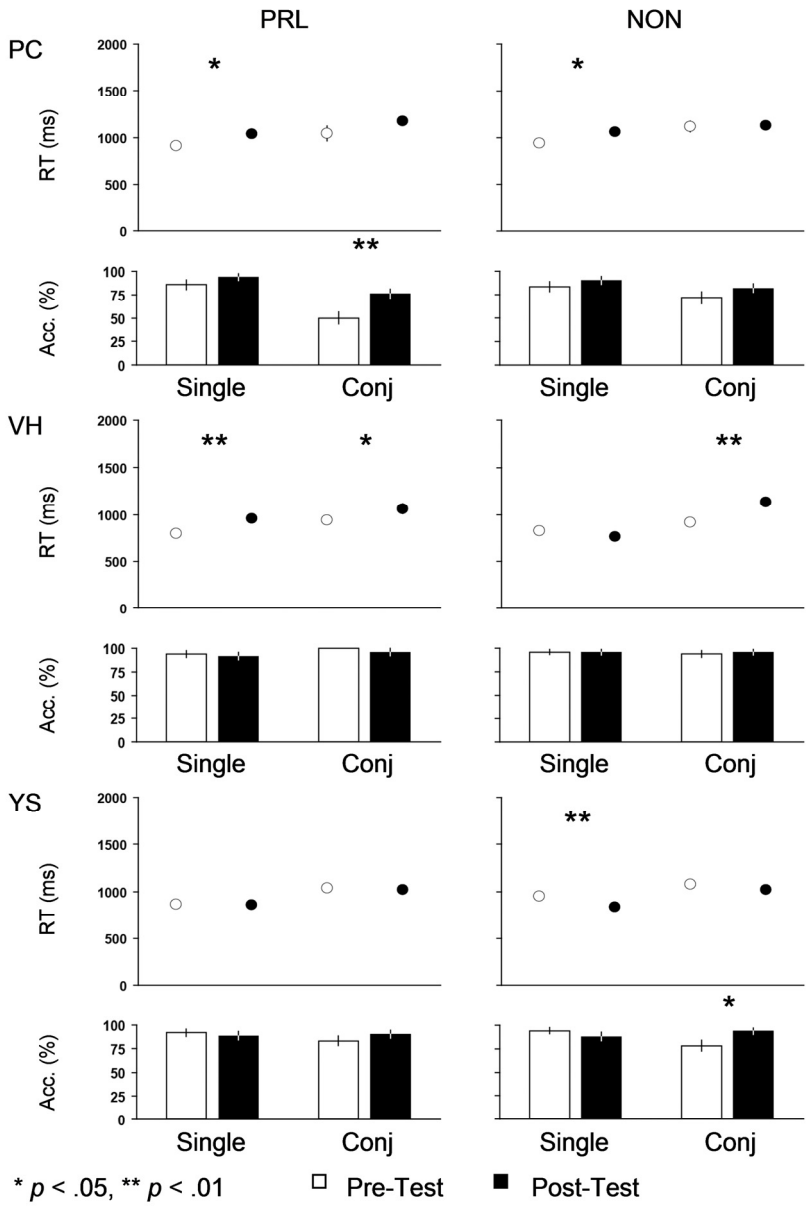

Figure 26. fMRI Behavioral Data (PC - YS).

PRL Activation

The PRL runs exhibited a variety of activation patterns depending on the patient and condition. Some patients showed little to no activation in passive conditions (BE, HN, VH) while others demonstrated activity throughout the runs (JM, MK, PC, YS). A noticeable trend was that the attention demanding conditions (single-task and conjunction) exhibited the most activation in terms of area. The passive Gabor runs elicited the least amount of activation. The greatest magnitude of activity was elicited by the checkerboard runs.

Another interesting trend was a reduction in the extent of cortical activation and/or magnitude in the post-test sessions. All patients exhibited this phenomenon for at least one condition, often in the attention-demanding single-task or conjunction run. In addition to positive activation, some patients also exhibited strong negative activity along the calcarine sulcus and at the occipital pole.[13] Sometimes this negative activity was concomitant with positive activity, other times, such as with BE, calcarine activation was exclusively negative.

Patient BE

Patient BE largely showed negative activation in pre and post-test runs (Figure 27). There was no activity in the checkerboard pre-test, but significant positive and negative activation in the post-test. The pre-test run for the passive task showed negative activation at the occipital pole. The post-test run, however, exhibited a marked reduction

[13] From here on modifiers such as "greater", "less than", etc., will refer to the absolute value of negative betas. For example, a β value of -10.18 is greater than a β value of 5.08.

in the area this activity as well as a shift to the anterior calcarine. Patient BE's single-task runs showed positive activation at the occipital pole for the pre-test but negative activation for the post-test. There was limited negative activation in the conjunction task's pre-test run. Significantly more negative activation at a greater magnitude was observed in the post-test (Table 10).

Patient HN

Patient HN showed limited activation in the PRL runs with much of it located in the posterior calcarine (Figure 28). Pre and post-test checkerboard runs showed positive activation at the occipital pole. There was no activity in the passive task's pre-test run. However, the post-test exhibited negative activation in the posterior calcarine. Both pre and post-test single-task runs demonstrated positive activation at the occipital pole. The post-test also showed substantial negative activation in the anterior calcarine. Finally, the conjunction task's pre-test run exhibited positive activation at the occipital pole as well the anterior calcarine, but no significant activation was observed in the post-test.

Patient JM

Patient JM exhibited prominent changes in the area and magnitude of activity between pre and post-test runs (Figure 29). For the checkerboard, the pre and post-test runs showed positive activation in posterior calcarine and at the occipital pole. Though there was little activation in the passive runs overall, the magnitude of negative activation was greater in the post-test. For the single-task runs, the area of positive activation was

greater in the post-test. The conjunction runs demonstrated greater area and magnitude of positive activation in the pre-test (Table 10).

Patient MK

Patient MK showed significant positive activity in the posterior calcarine for most of the pre-tests runs. In many cases these areas were markedly reduced in the post-test runs (Figure 30). There was significant pre-test activation at the occipital pole for the checkerboard task, but this was largely absent in the post-test. The passive Gabor runs showed both negative and positive activation, but, again, areas of positive activation were reduced in the post-test. The single-task showed only negative activity and little difference between runs. The conjunction runs, however, exhibited significant positive activation in the pre-test which was reduced in magnitude and relegated to the anterior calcarine in the post-test (Table 10).

Patient PC

Patient PC demonstrated an overall reduction in activity between pre and post-test runs (Figure 31). There was no difference in the area or magnitude of activation between the checkerboard runs. In contrast, the passive and single-task runs showed significant positive activation at the occipital pole for the pre-test, but no activation anywhere along the calcarine for the post-test. The pre-test conjunction run showed negative activation in the posterior calcarine. The post-test run showed the same, but also a small area of positive activity at occipital pole.

Patient VH

For patient VH, there was little difference between pre and post-test activation for all tasks except conjunction (Figure 32). The checkerboard run showed an area of positive activation in the pre-test while only negative activity was observed in the post-test. No activation was observed in either of the passive runs. The single-task showed only negative activity, with no difference between sessions. In contrast, the conjunction task did show a significant difference in the magnitude and area of activation between pre and post-test runs. Positive activation had a larger area and stronger magnitude in the post-test (Table 10). The opposite effect was observed for negative activation, the area and magnitude were greater in the pre-test (Table 10).

Patient YS

Patient YS exhibited significant positive activation in all pre and post-tests runs (Figure 33). Single-task and conjunction runs also showed areas of negative activation in the anterior calcarine. Positive checkerboard activation did not differ between sessions. For the passive runs, positive activation had greater magnitude and area in the pre-test (Table 10). Single-task and conjunction runs did not exhibit a pre/post-test difference for positive activation, but the magnitude and area of negative activation decreased for both in the post-test (Table 10).

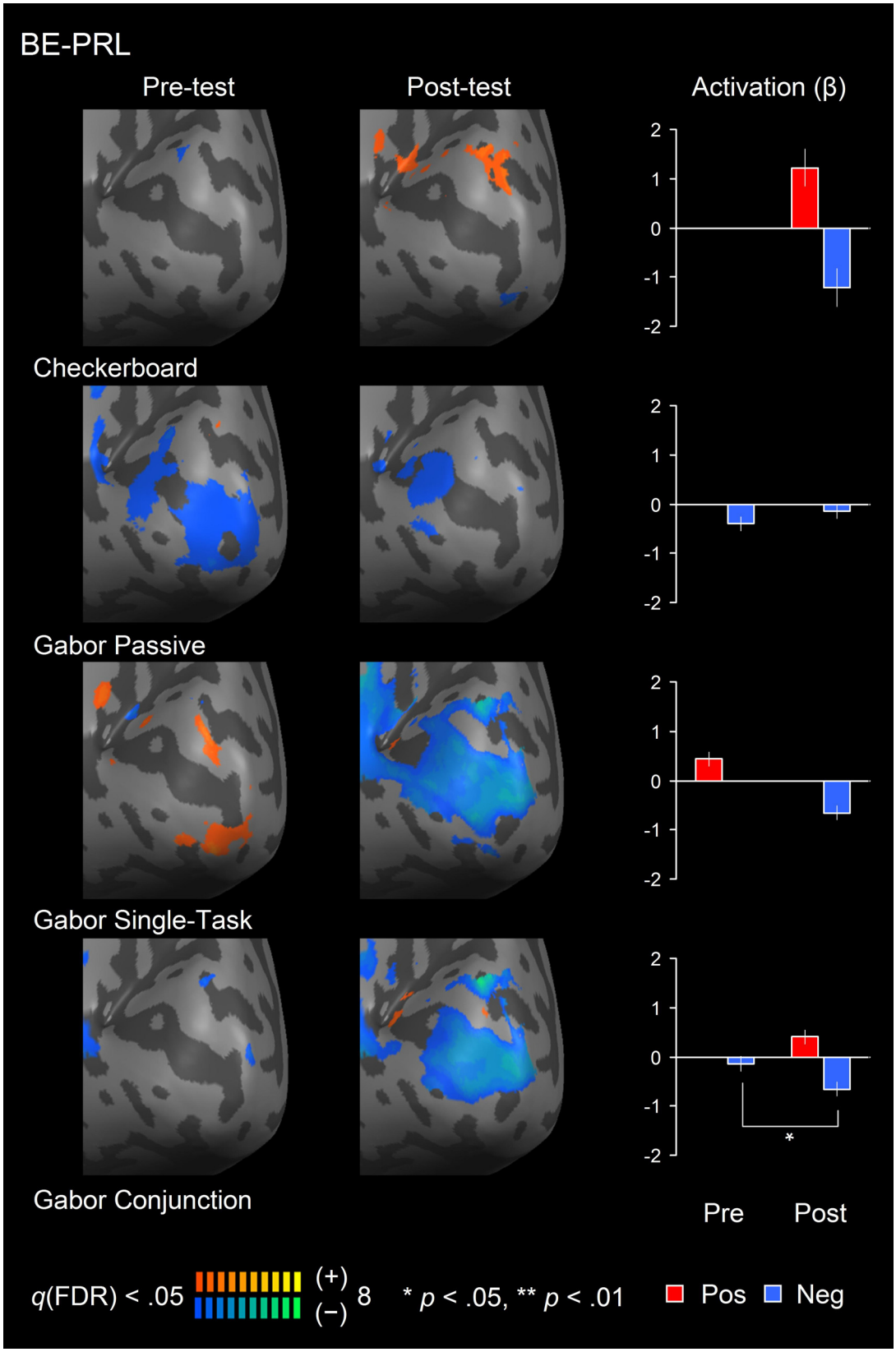

Figure 27. Patient BE PRL Activation.

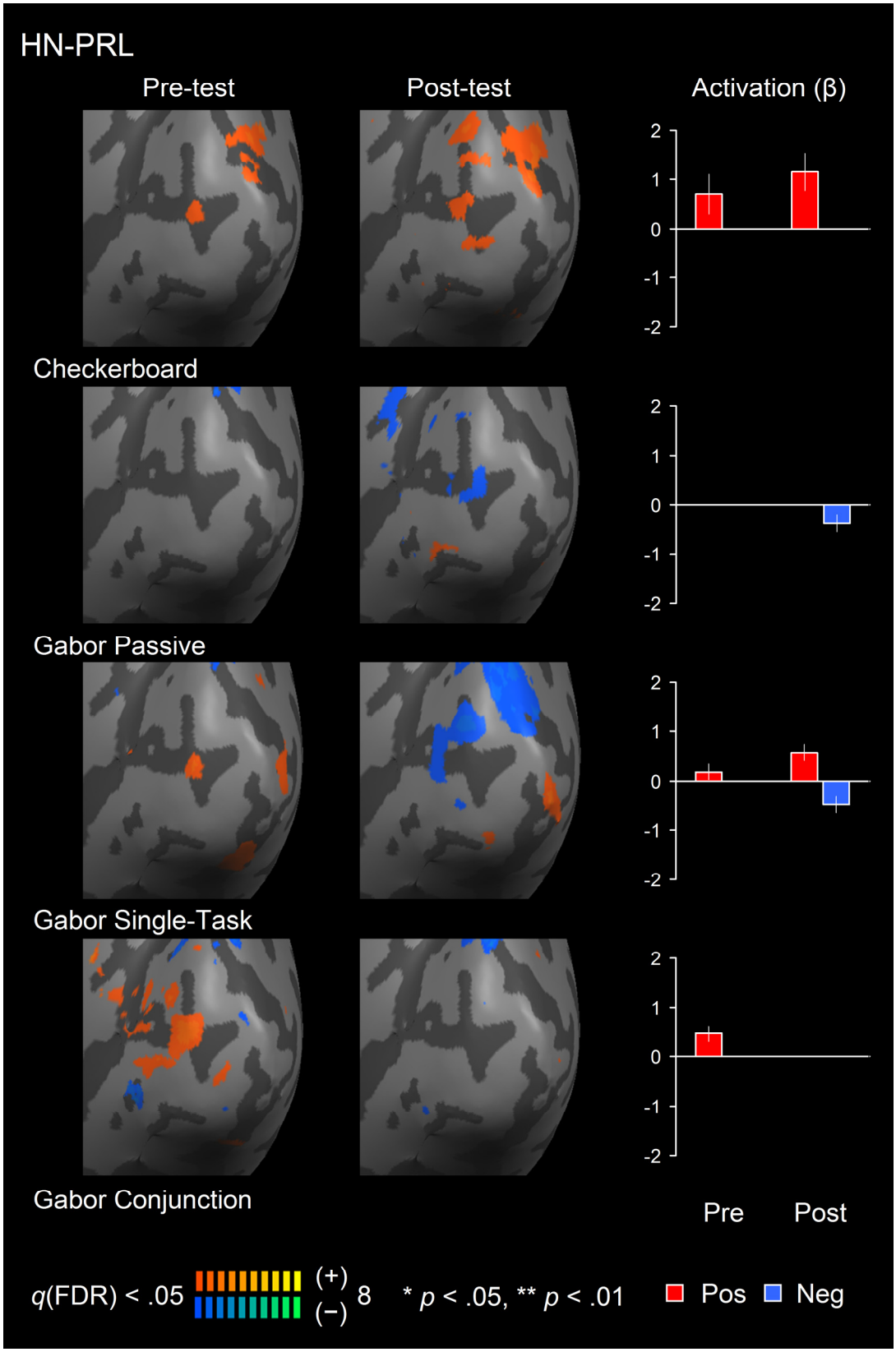

Figure 28. Patient HN PRL Activation.

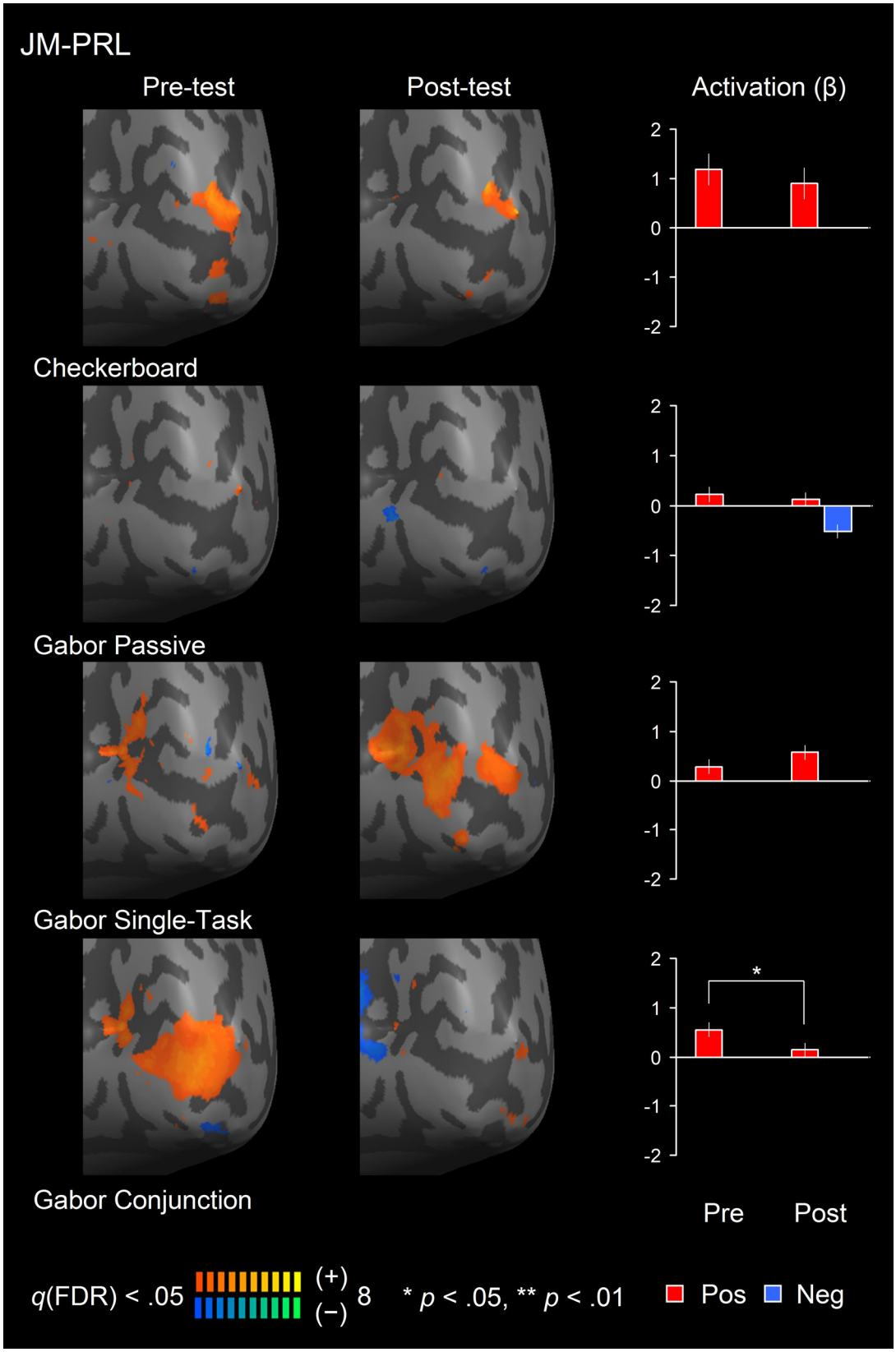

Figure 29. Patient JM PRL Activation.

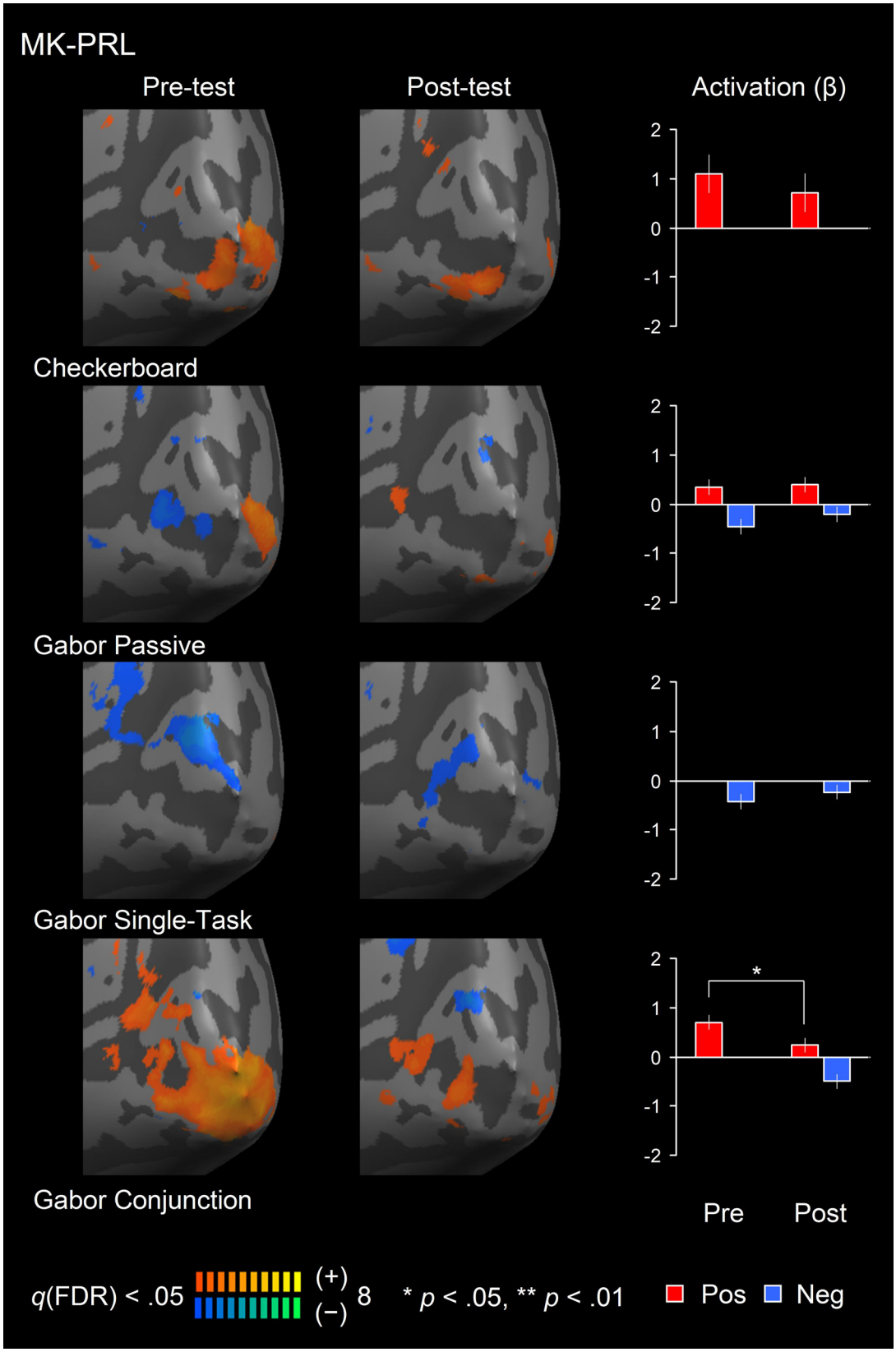

Figure 30. Patient MK PRL Activation.

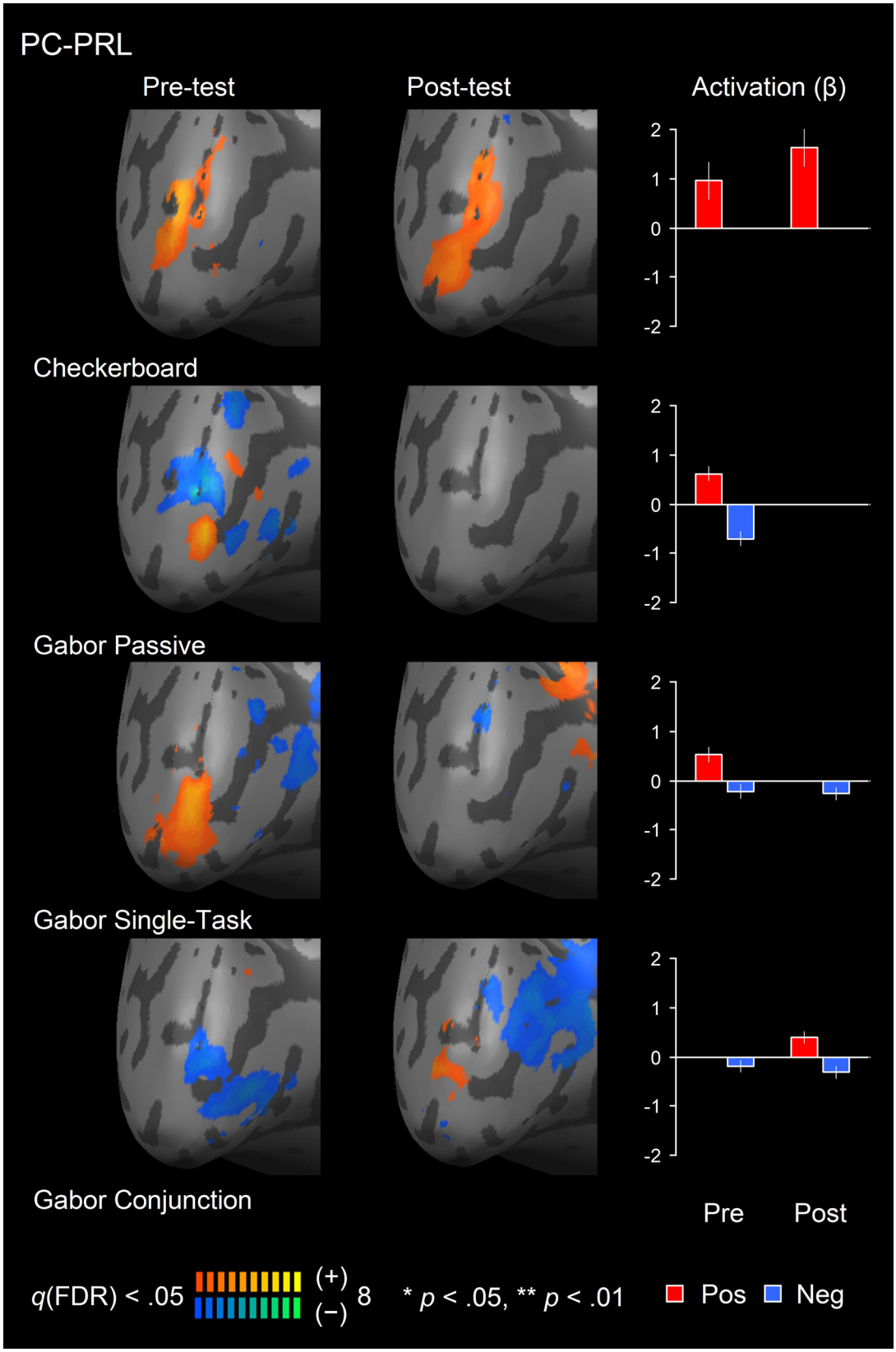

Figure 31. Patient PC PRL Activation.

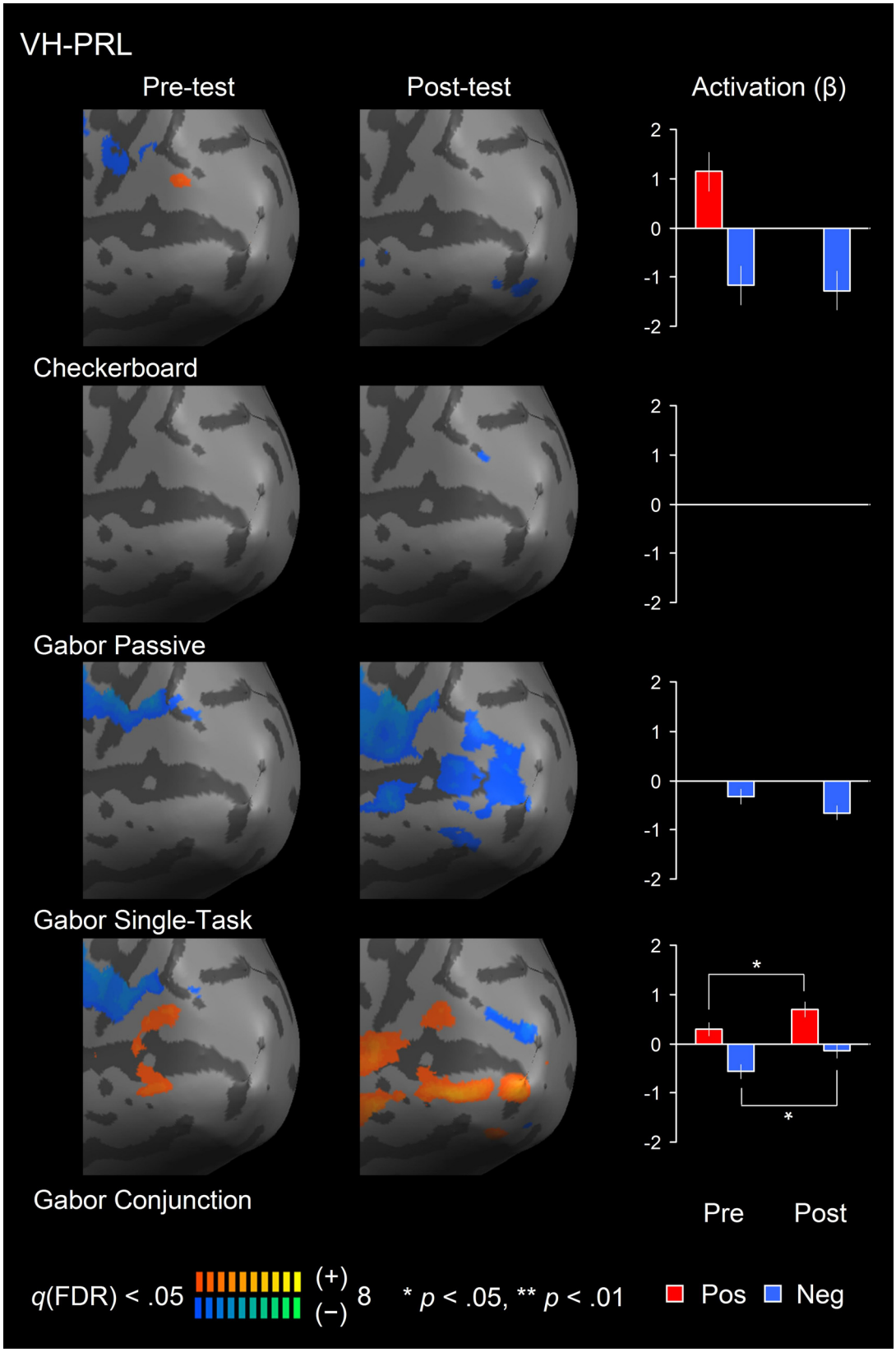

Figure 32. Patient VH PRL Activation.

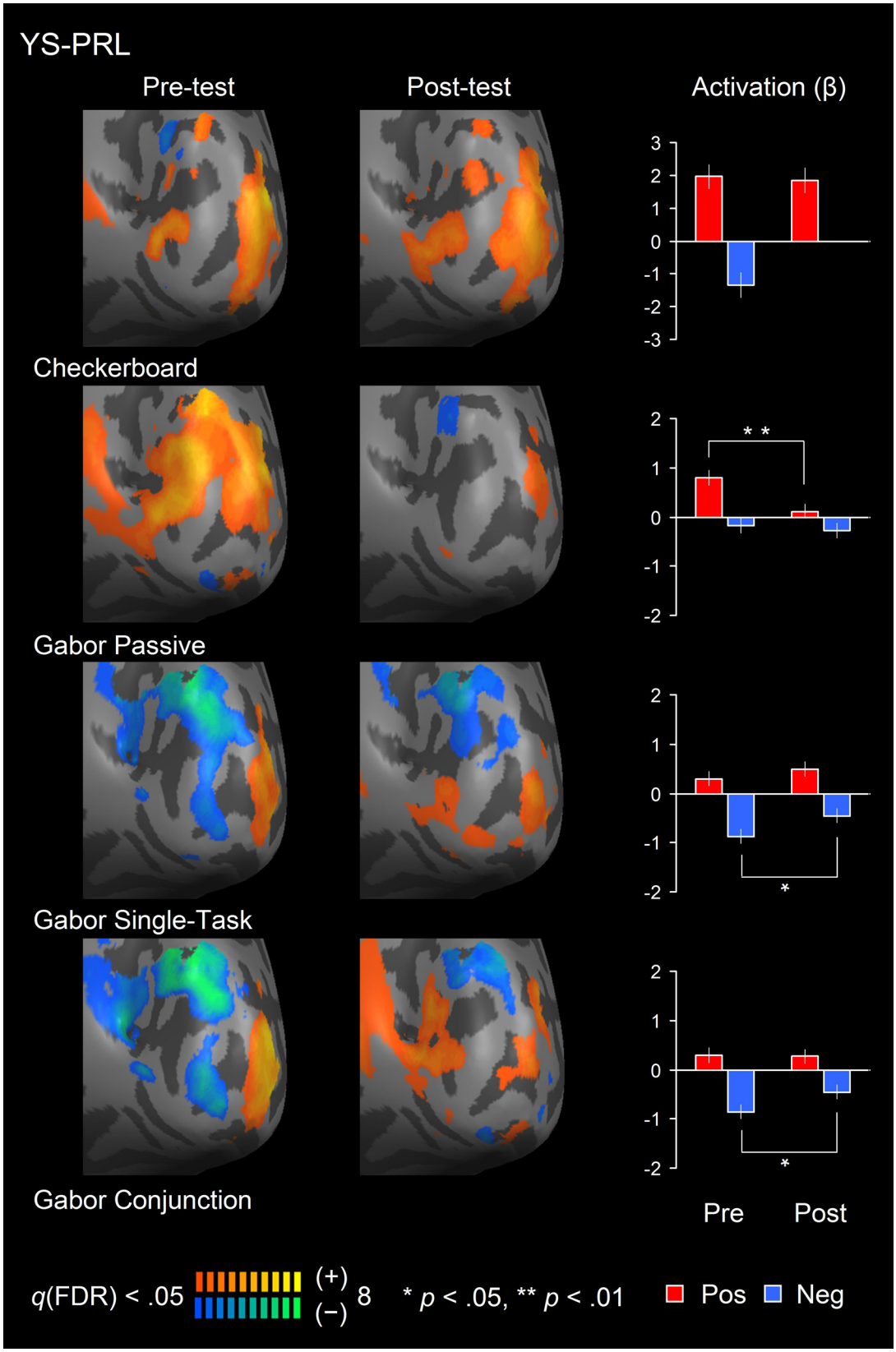

Figure 33. Patient YS PRL Activation.

Table 10. *fMRI Voxels, Betas, and t Values—PRL.*

Patient	fMRI Conditions											
	Checkerboard			Passive			Single-Task			Conjunction		
	Voxels	β	*t*	Voxels	β	*t*	Voxels	β	*t*	Voxels	β	*t*
BE	--/ 670	--/ 1.221	--	--/--	--	--	1393/ --	.438/ --	--	--/ 29	--/ 408	--
	--/ 146	--/ -1.213	--	3790/ 1342	-.398/ -.150	-1.199	--/ 5942	--/ -.654	--	203/ 4225	-.143/ -.568	**2.53****
HN	715/ 1642	.694/ 1.14	0.418	--/--	--/--	--	743/ 750	.186/ .574	-1.717	1190/ --	.462/ --	--
	--/--	--/--	--	--/ 173	--/ -.379	--	--/ 2381	--/ -.487	--	--/--	--/--	--
JM	839/ 376	1.190/ .896	0.661	172/ 71	.222/ .127	0.483	179/ 4091	.283/ .570	-1.463	3169/ 240	.549/ .354	**2.089***
	--/--	--/--	--	--/ 358	--/ -.523	--	--/--	--/--	--	--/--	--/--	--
MK	1628/ 538	1.096/ .714	0.690	957/ 441	.346/ .394	-0.232	--/--	--/--	--	6752/ 1341	.698/ .236	**2.272***
	--/--	--/--	--	406/ 81	-.460/ -.210	1.271	2153/ 813	-.426/ -.238	-0.920	--/ 527	--/ -.606	--
PC	1178/ 2174	.955/ 1.624	-1.239	540/ --	.618/ --	--	1852/ --	.532/ --	--	--/ 447	--	--
	--/--	--/--	--	2596/ --	-.705/ --	--	993/ 224	-.220/ -.265	0.235	2254/ 3156	-.194/ -.317	0.729
VH	146/ --	1.143/ --	--	--/--	--/--	--	--/--	--/--	--	1300/ 2389	.293/ .659	**-1.994***
	314/ 505	-1.167/ -1.273	0.105	--/--	--/--	--	1568/ 6732	-.327/ -.654	1.635	1448/ 312	-.567/ -.144	**-2.087***
YS	3674/ 4658	1.962/ 1.850	0.215	8513/ 1025	.794/ .115	**3.286***	1735/ 1842	.299/ .491	-0.928	2096/ 2526	.500/ .386	0.551
	562/ --	-1.345/ --	-2.438	296/ 845	-.174/ -.279	0.500	5316/ 3008	-.876/ -.453	**-2.091***	4275/ 1731	-1.180/ -0.256	**-4.290***

The white rows contain values for positive activation, the gray rows, negative activation. Pre and post-test values are depicted using the notation Pre / Post, with pre-test values above and post-test values below. Significant *t* values are in bold. * = $p < .05$, ** = $p < .01$.

nonPRL Activation

Activation in the nonPRL runs was more variable than the PRL. Many post-test conditions exhibited a dramatic expansion of activity which covered the occipital pole, a retraction to the anterior calcarine, or simply no activity at all. Like the PRL runs, attention demanding conditions exhibited the largest areas of activation while the passive Gabor runs showed the least. The greatest magnitude was found in checkerboard runs.

Patient BE

Patient BE showed almost entirely negative activation in nonPRL runs (Figure 34). The passive runs (checkerboard and passive Gabor) demonstrated a larger area of negative activation in the post-test. This expansion extended into the occipital pole for checkerboard, but not for the passive Gabor. Both single-task and conjunction runs had significant negative activation across the entire calcarine and the occipital pole for the pre-test session. This activation retracted slightly in the post-test, exposing the occipital pole.

Patient HN

Patient HN exhibited little activation overall for nonPRL runs (Figure 35). The checkerboard pre-test showed spotty positive activation in the upper calcarine, but nothing in the post-test. The passive run demonstrated negative activation only in the post-test. For the single-task, minor pre-test activation at the occipital pole expanded into a large positive ROI in the post-test (Table 11). The conjunction task showed no activation in either session.

Patient JM

Like the PRL, patient JM demonstrated extensive activation along the calcarine sulcus and at the occipital pole for nonPRL runs (Figure 36). Checkerboard and passive runs showed limited positive activation in the pre-test. The area and magnitude of this activation was greater in the post-test runs (Table 11). Single task and conjunction pre-test runs showed large areas of positive activation that encompassed the occipital pole. The post-test had similar activation of the same magnitude, but it did not cover the occipital pole.

Patient MK

Patient MK showed positive activation at the occipital pole for all the pre-test runs (Figure 37). Passive, single-task, and conjunction runs also exhibited negative activation in the anterior calcarine. The area of this activation was reduced in the post-tests runs. For checkerboard and conjunction runs this reduction involved a shift of positive activation to the anterior calcarine. Passive and single-task post-test runs showed very little activation. The passive run showed only negative activation. The single task had a small positive ROI in the anterior calcarine, significantly less in magnitude (Table 11).

Patient PC

There was little difference between the activation of pre and post-test checkerboard runs (Figure 38). Both showed positive activation along the calcarine

extending into the occipital pole. Passive and single-task pre-test runs demonstrated positive activity at the occipital pole. The magnitude of this activity was significantly reduced in the post-test (Table 11). There was also a difference in the expanse of activity, the pre-test runs having larger areas of activation (Table 11). In contrast, the pre-test conjunction run showed no activity, while the post test demonstrated a large area of activation at the occipital pole.

Patient VH

Patient VH showed mostly negative activity in the nonPRL runs (Figure 39). Checkerboard runs saw negative activation in the pre-test but nothing in the post-test. Passive and single tasks did show differences in the expanse and magnitude of activation. Each demonstrated minor areas of positive activation in the pre-test that were absent in the post-test. The passive run showed more activation at a greater magnitude in the pre-test. The single-task showed the same effect for the post-test (Table 11). For the conjunction runs, there was positive activity in the pre-test, which was absent in the post-test and more negative activation in the post-test (Table 11).

Patient YS

Patient YS showed positive activation at the occipital pole in all pre-test runs as well as some negative activation in the anterior calcarine (Figure 40). Positive activation in the checkerboard, single-task and conjunction post-test runs had the same area and magnitude as the pre-test. In contrast, the passive post-test run showed only negative activation with nothing at the occipital pole.

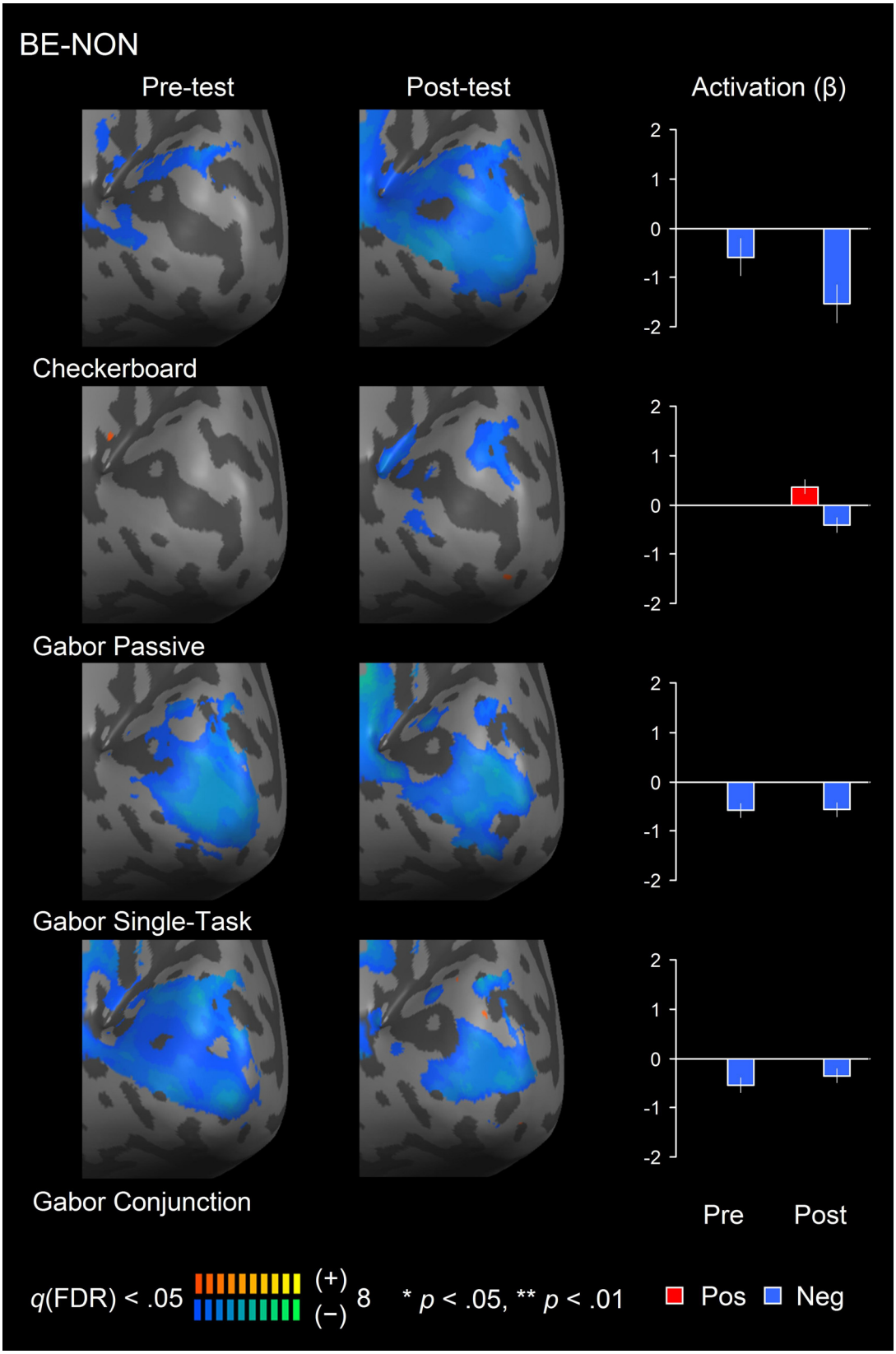

Figure 34. Patient BE nonPRL Activation.

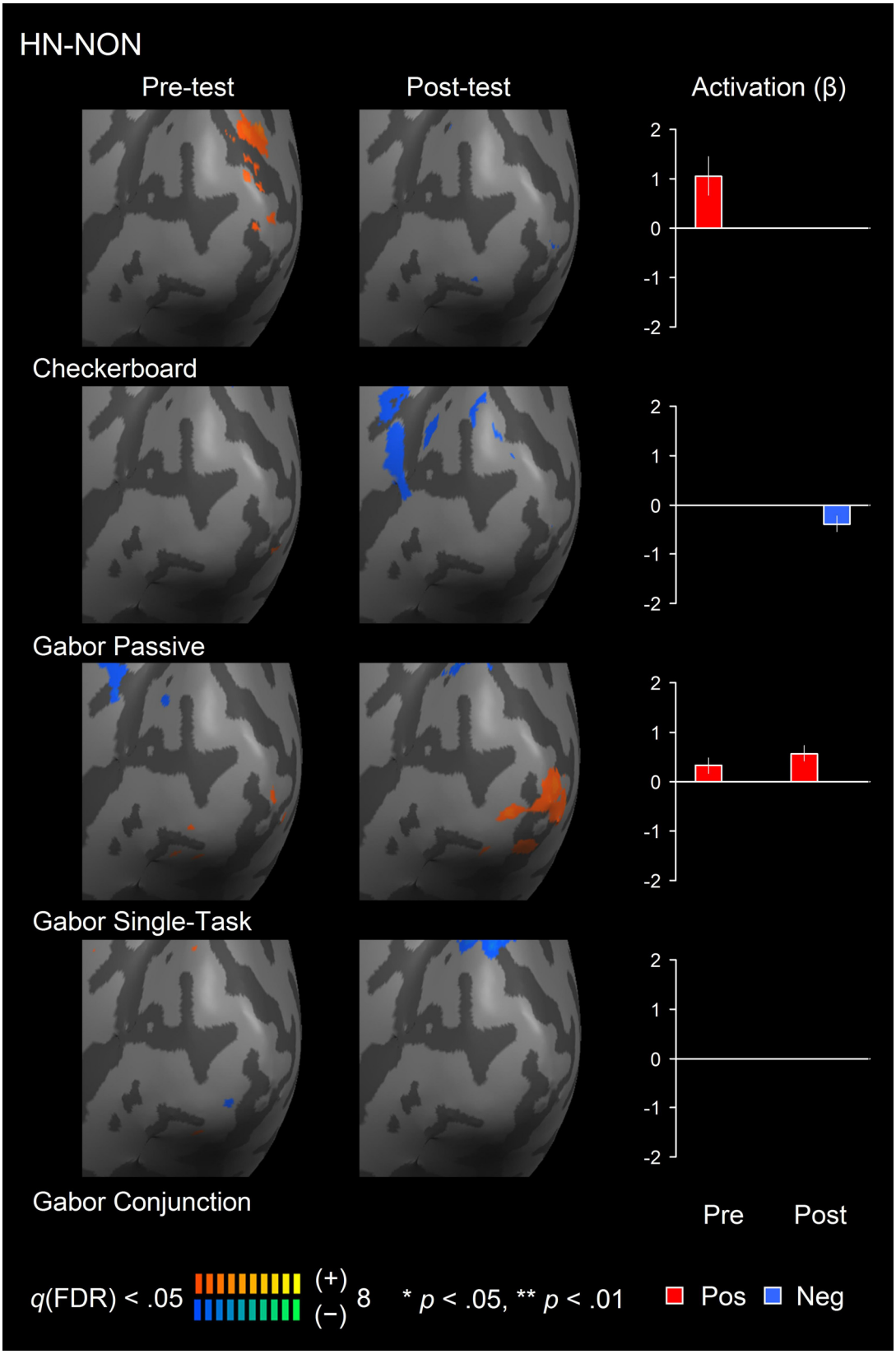

Figure 35. Patient HN nonPRL Activation.

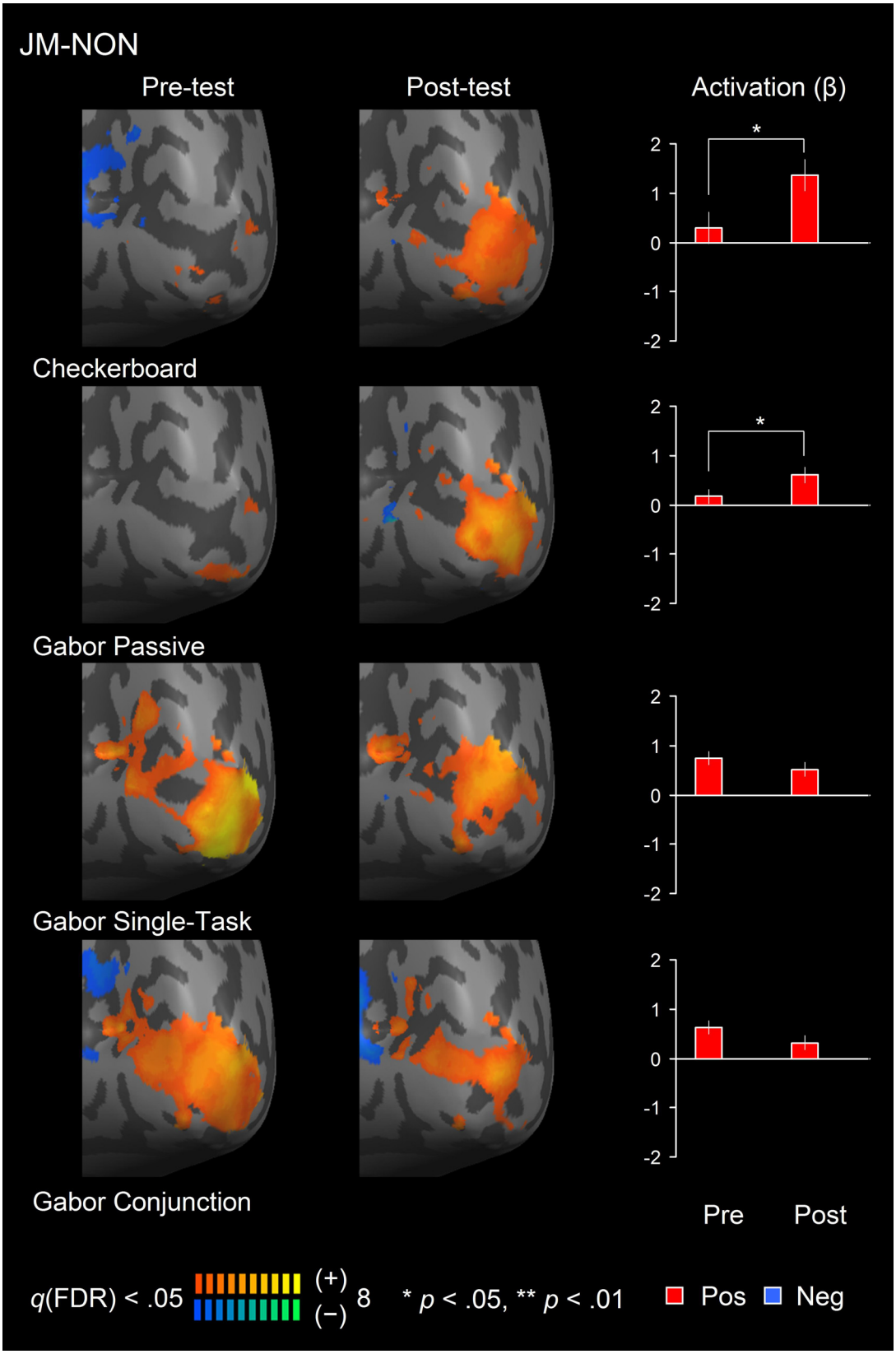

Figure 36. Patient JM nonPRL Activation.

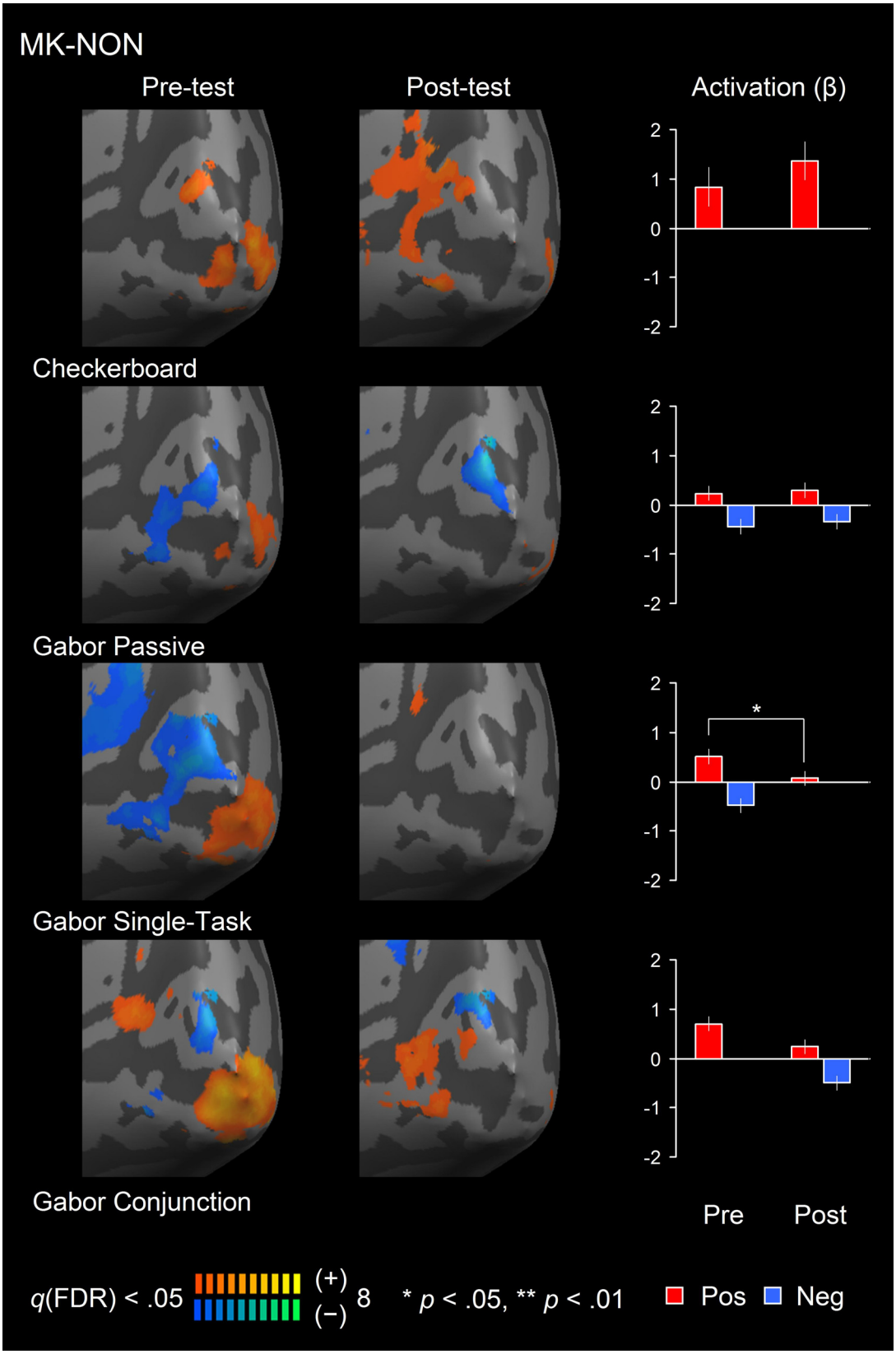

Figure 37. Patient MK nonPRL Activation.

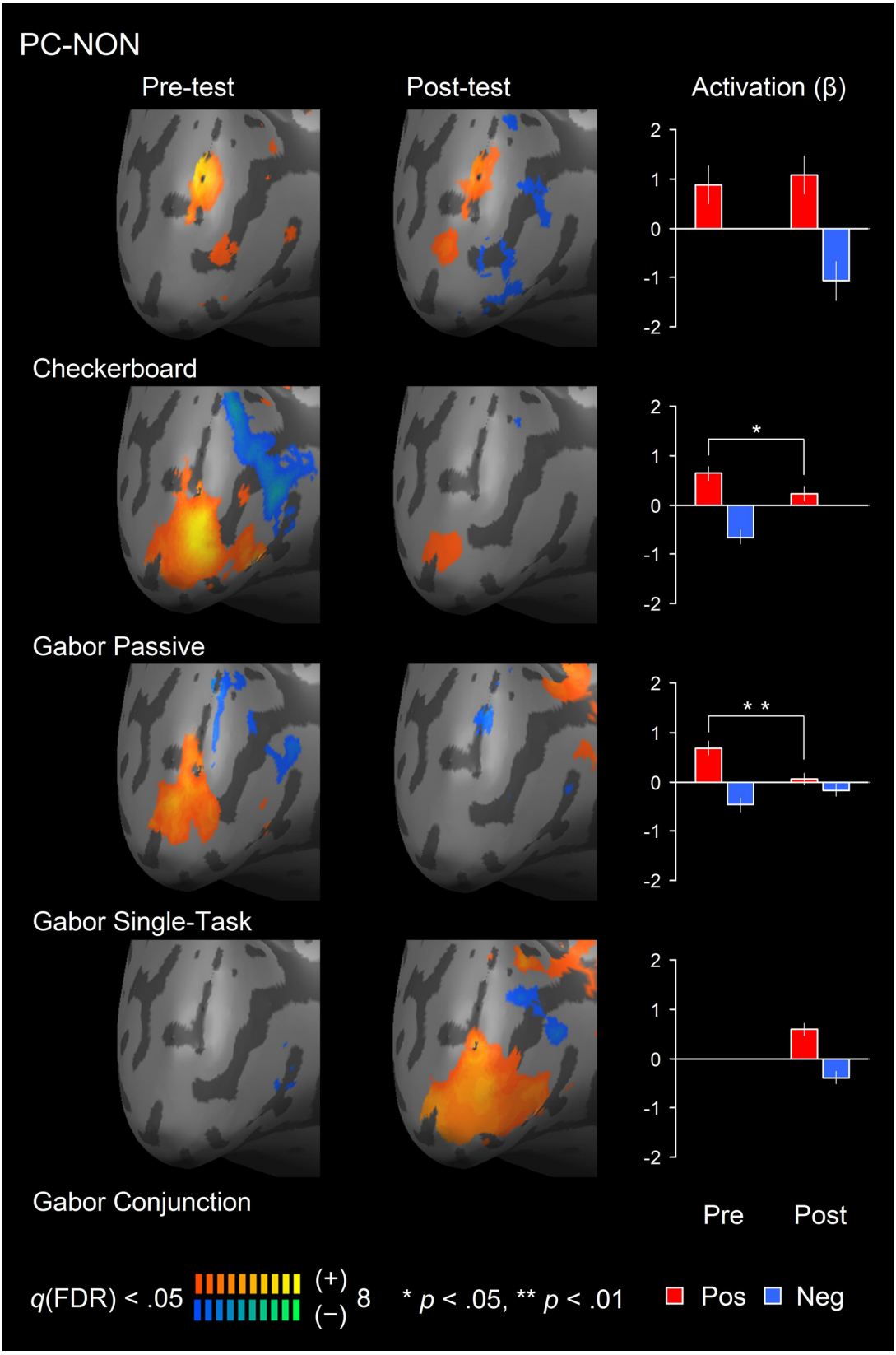

Figure 38. Patient PC nonPRL Activation.

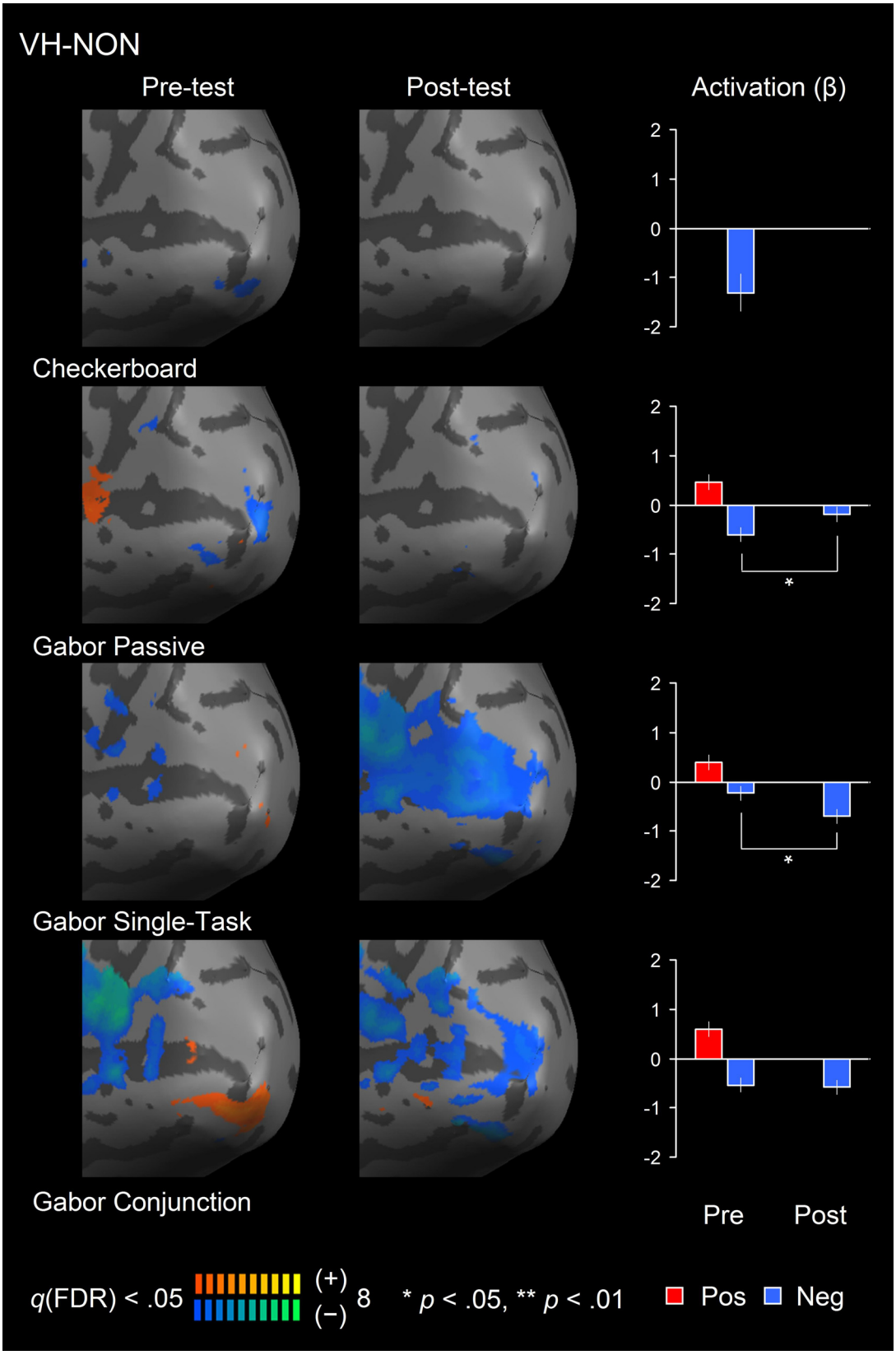

Figure 39. Patient VH nonPRL Activation

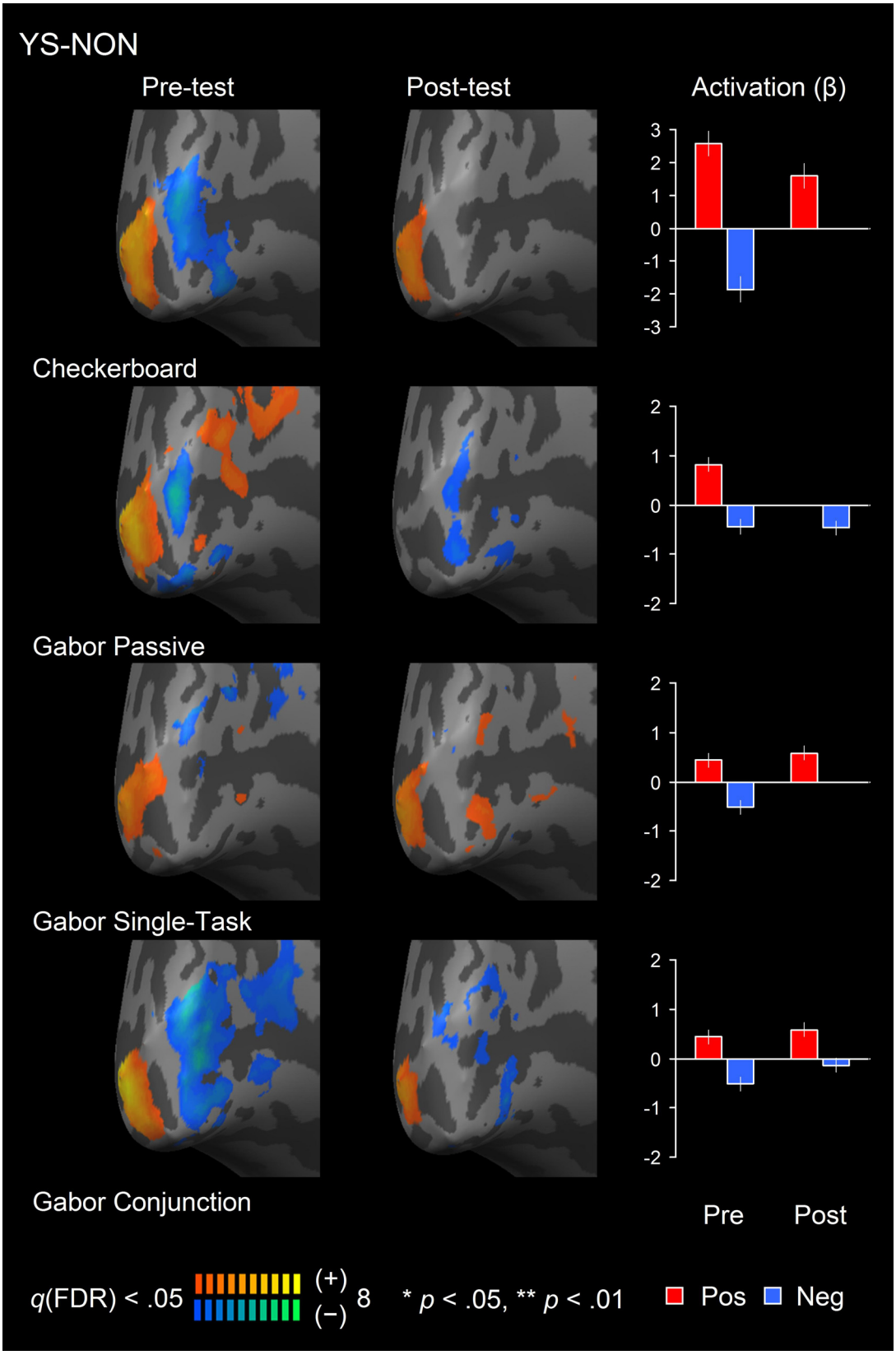

Figure 40. Patient YS nonPRL Activation

Table 11. *fMRI Voxels, Betas, and t Values—nonPRL.*

Patient	Checkerboard			fMRI Conditions: Passive			Single-Task			Conjunction		
	Voxels	β	*t*	Voxels	β	*t*	Voxels	β	*t*	Voxels	β	*t*
BE	--/--	--/--	--	--/ 38	--/ .366	--	--/--	--/--	--	--/--	--/--	--
	2956/ 11035	-.592/ -1.528	1.744	--/ 1519	--/ -.412	--	6041/ 6203	-.582/ -.569	-0.064	6954/ 3753	-.539/ -.461	-0.899
HN	1029/ --	1.057/ --	--	--/--	--/--	--	118/ 1338	.327/ .573	-1.099	--/--	--/--	--
	--/--	--/--	--	--/ 958	--/ -.385	--	--/--	--/--	--	--/--	--/--	--
JM	178/ 2920	.297/ 1.396	**-2.395****	524/ 2488	.171/ .604	**-2.090***	5634/ 4056	.741/ .518	1.152	5683/ 3223	.627/ .317	1.575
	--/--	--/--	--	--/--	--/--	--	--/--	--/--	--	--/--	--/--	--
MK	2060/ 2604	.832/ 1.370	-0.981	873/ 429	.255/ .438	-0.289	2484/ --	.508/ --	--	3790/ 1966	.543/ .334	0.986
	--/--	--/--	--	1936/ 1111	-.447/ -.342	-0.507	4647/ --	-.484/ --	--	892/ 652	-.418/ -.375	-0.211
PC	798/ 820	1.259/ 1.372	-0.376	3693/ 481	.636/ .229	**1.973***	1769/ 619	.685/ .062	**3.267****	--/ 4623	--/ 587	--
	--/ 1041	--/ -1.064	--	2037/ --	-.653/ --	--	871/ 178	-.466/ -.169	-1.555	--/ 442	--/ -.386	--
VH	461/ --	1.228/ --	--	501/ --	.456/ --	--	371/ --	.388/ --	--	1440/ --	.593/ --	--
	1218/ --	-1.306/ --	--	782/ 22	-.605/ -.125	**-1.988***	959/ 8050	-.231/ -.691	**2.273***	4283/ 6286	-.540/ -.585	0.222
YS	2016/ 1670	2.577/ 1.601	1.824	3013/ --	.818/ --	--	1696/ 2217	.439/ .401	-0.689	1852/ 1002	.439/ .582	-0.698
	3419/ --	-1.306/ --	--	1880/ 1367	-.443/ -.465	0.106	602/ --	-.515/ --	--	6851/ 1047	-.515/ -.138	-1.843

The white rows contain values for positive activation, the gray rows, negative activation. Pre and post-test values are depicted using the notation Pre / Post, with pre-test values above and post-test values below. Significant *t* values are in bold. * = $p < .05$, ** = $p < .01$.

CHAPTER 9: DISCUSSION

9.1 Summary of Results

The juxtaposition of behavioral and neuroimaging results from the current study may have critical implications for our understanding of adult visual plasticity. Any valid interpretation, however, needs to account for the relationships and/or inconsistency between the data sets. On one hand, rehabilitation efforts seemed to have, at best, erratic effects on visual performance as assessed by the behavioral testing. However, there were demonstrable improvements in patient fixation over the course of MP-1 feedback sessions. In addition, the neuroimaging data showed examples of reorganized activity, but in many areas this activation was reduced, in some cases dramatically, for the post-test fMRI sessions.

These findings seem disparate in some ways and it is hard to conclude anything definitive from case studies. However, I will argue here that the present results, in light of previous findings and known parameters of the visual system, actually present a meaningful contribution to the topical conversation regarding visual plasticity. The following section will recount these results and characterize overall patterns in the data.

9.1.1 Behavioral Outcomes

The most reliable behavioral result was an increase in RT after the training. Most patients demonstrated this effect, though not all examples were significant. In addition, in many cases, RT increases were irregular, affecting certain conditions but not others. Accuracy scores often demonstrated the same. The only patients to show a consistent

change in accuracy or RT were JM for the recognition data (PRL and nonPRL) and BE for the contrast data (nonPRL).

In light of these findings, it is appropriate to consider what data pattern would represent a recovery or enhancement of visual ability. A definitive improvement would be characterized by a post-test increase in accuracy scores and a reduction in reaction time for threshold stimuli across the conditions. Only patient BE, for nonPRL contrast sensitivity, demonstrated this pattern of results. Patient JM showed a consistent improvement in accuracy but a concomitant increase in RTs. A speed/accuracy tradeoff, in which the patient sacrifices response speed for an improvement in accuracy could account for this finding. In such a case, better accuracy may be an artifact of increased RT, not a genuine improvement in visual acuity. Other patients showed isolated improvements in accuracy often coupled with increased RT. Some showed a reduction in accuracy for certain conditions.

As a whole, the behavioral results do not demonstrate the criteria expected if rehabilitation training truly augmented basic visual abilities. Measures of recognition acuity and contrast sensitivity reflect the amount of cortex devoted to visual processing. Enhanced spatial resolution and contrast sensitivity are the consequence of larger allocations of cortical space (Duncan & Boynton, 2003; Virsu, Nasanen, & Osmoviita, 1987; Virsu & Rovamo, 1979). It follows then, if the visual cortex of AMD patients reorganizes by delegating deafferented cortex to the peripheral visual field, the PRL in particular, then visual performance of patients should improve across conditions for the post-test session. The current data do not bear out this interpretation.

The case of BE is interesting however. While his contrast sensitivity data showed a clear improvement, it was at the nonPRL. While this could be a manifestation of reorganization, no other conditions for BE, recognition or contrast, PRL or nonPRL, demonstrated the same pattern. It is unclear why V1 would exhibit this selectivity, or why it would be for the nonPRL rather than the PRL. It could be, even though visual rehabilitation targets the PRL, the process elicits awareness to other areas of residual vision. Behavioral testing may have also inadvertently prodded the use of the nonPRL through repeated presentation of stimuli. Performance then may dramatically improve for the nonPRL relative to its utility before training, but this is probably due to consciousness of the area and better attentional control than true cortical reorganization. This concept will be explored further in later sections of the discussion.

9.1.2 Fixation Outcomes

Unlike the behavioral measures, the fixation tests did show differences between conditions. These tests were conducted during every training session with the MP-1 and all patients tested demonstrated a decrease in fixation eccentricity (distance from the PRL) and area (BCEA) between sessions 1 and 4. This decrease was not always apparent session-to-session. On some occasions, performance was no better or slightly worse than that of the previous session. Some patients, showed a gradual decrease in eccentricity and BCEA across sessions. For others improvement was more abrupt. This assortment of results may be the interaction of individual differences with the efficacy of training. However, the final outcome of the feedback sessions for all patients tested was greater precision and accuracy in use of the PRL as alternate area of fixation.

These findings are similar to those of other rehabilitation studies that employed biofeedback. Vingolo et al. (2007) showed that 10 weekly sessions of biofeedback training with the MP-1 (10 minutes a session) produced significant improvements in fixation, visual acuity, and reading speed. Other investigations using different biofeedback systems have reported benefits in visual acuity, contrast sensitivity, color vision, and flash VEP (Contestabile et al., 2002; Giorgi, Contestabile, Pacella, & Gabrieli, 2005).

A recent investigation by Tarita-Nistor et al. (2009) assessed the potential of auditory biofeedback to direct fixation away from the original PRL to a retinal area more suitable for reading. The authors trained six AMD patients with the MP-1 over the course of five, hour-long, sessions. Fixation results demonstrated patients were able to relocate their PRLs and lower their corresponding BCEA scores. Reading speed and acuity also improved.

The reputed cause of the above findings is a newfound precision in the peripheral and central nervous system pathways that levy control over the eye. Biofeedback effectively trains eye movements toward a specified area of the visual field. More accurate and stable fixation is the result. However, an improved ability to engage targets could also yield dividends in global measures of visual acuity, contrast sensitivity, and other perceptual skills.

The likely cause of these improvements is enhanced oculomotor control, the neural substrates of which are separate and distinct from V1 (Corbetta et al., 1998; Corbetta & Shulman, 2002). Gains in visual fixation then may be a result of brain

plasticity, but cannot be ascribed definitively to changes in the primary visual cortex. The networks that direct eye movements and spatial attention may be more probable sources.

9.1.3 Neuroimaging Outcomes

Comparison of pre and post-test fMRI sessions reveal two prominent neuroimaging results. Patients either showed a notable reduction in the area of significant activation or an expansion of this activity along the calcarine sulcus. Both effects were localized to the posterior calcarine, often influencing the presence of activity at the occipital pole. Changes in area were sometimes accompanied by an increase or decrease in magnitude. In addition, activation size and magnitude were also affected by conditional factors such as retinal presentation (PRL or nonPRL) and attentional demand (i.e., passive, single-task, conjunction). Finally, many patients exhibited both positive and negative activation within in the same maps. Some displayed exclusively negative activity depending on the condition.

For the PRL presentations, five of the seven patients (BE, HN, JM, MK, and PC) demonstrated a marked reduction in positive activity at the posterior calcarine for at least one of the conditions. These patients showed reorganized activation within the LPZ for the pre-test, but in the post-test, calcarine activation was either completely absent or relegated to middle or anterior areas of the sulcus. All conditions demonstrated an example of this change, but it was more prominent in those that require attention.

In contrast to the above findings, patient VH showed little activation in the majority of pre and post-test conditions. However, VH did show an expansion of positive activity into the LPZ for the post-test, conjunction run. This finding runs contrary to that

of the other patients since activation expanded, rather than contracted, after training. Data from YS, the control, also departed from the norm. Patient YS showed little difference between the pre and post-test conditions. Both displayed LPZ activation. As YS received no training, this finding is an indication that changes in calcarine activity among the other patients is a result of the rehabilitation. The reasons why these changes may manifest as either an expansion or reduction in different patients or for specific conditions is unclear.

Taken as a whole, these results are surprising. It was hypothesized that rehabilitation would expand activation along the calcarine, a response to training's potential to reorganize unused cortex. Instead there is an obvious reduction. This finding cannot be explained through performance as patients' accuracy scores were largely the same between pre and post-test sessions.[14]

The present results also show clear departures from neuroimaging data collected by other researchers. Preliminary data from Tony Morland's group failed to demonstrate evidence of reorganized activity in AMD and JMD patients using passive, checkerboard stimulation (Baseler et al., 2009). Similarly, Masuda et al. (2008) only found LPZ activation for attention demanding tasks. In contrast, the current data show clear examples in LPZ activity in response to flashing checkerboard patterns and passively viewed Gabors (HN, JM, MK, PC, YS).

The nonPRL activation maps were more varied than those for the PRL. Some patients demonstrated an increase in the area of positive activity for the post-test session (HN and JM). Others showed a decrease (MK and VH). A third finding was both

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[14] Like the recognition data, BE's behavioral fMRI data showed significantly better accuracy for the nonPRL in the post-test. As explained above, this result may have more to do with nonPRL awareness than augmented performance.

expansion and contraction of activation in PC's maps depending on condition. The passive and single-task runs showed a reduction in activity after training while the conjunction run saw an expansion. Finally, nonPRL activation in YS was similar to that of the PRL. Both pre and post-test sessions displayed LPZ activation. Although an exception was the passive run which saw little activation in the post-test.

In an examination of two JMD patients, Dilks et al. (2009) found no difference between the PRL and nonPRL in terms of the area and magnitude of activation within the LPZ. The findings here are in clear contrast with these results. The current patients showed prominent differences in the quantity and nature of activation depending on whether the PRL or nonPRL was stimulated. There was no clear pattern to these distinctions. Sometimes the PRL demonstrated more LPZ activity than the nonPRL, other times this effect was reversed. Sometimes the quality of activation (i.e., negative or positive) differed. Condition and session also seemed to play a role, enhancing or minimizing differences after training or within specific conditions. Though the reasons for these deviations are unclear, the present findings do not support an account of parity between PRL and nonPRL activation.

9.2 Feed Forward or Feedback Reorganization

What do the current findings imply about the nature of ectopic, calcarine activation in MD patients? At present, theoretical considerations are drawn toward two conclusions: reorganized activity represents a feed forward change in the cortical pathways that process visual information, or the activity is the manifestation of feedback signals that re-enter V1 to enhance initial processing.

The distinction between these claims is important. If LPZ activation stems from the re-entrant signals of higher visual areas, then it could be simply the artifact of miss-localized firings rather than the representation of true visual processing (Masuda et al., 2008). In essence, it is not really reorganization. In contrast, if LPZ activation is feed forward, representing V1's response to deafferentation without influence from oculomotor or attentional feedback, then the activity is genuinely reorganized and reflects a use-independent process (Dilks et al., 2009). The truth of either hypothesis holds significance for how we treat those with MD.

The present findings are more in line with the feedback interpretation of reorganized activity. The behavioral data demonstrate little improvement in measures of recognition acuity and contrast sensitivity. Yet the fMRI maps show striking fluctuations in the area of activation within and outside the LPZ. Visual performance is not diminished when fMRI reveals a substantial decrease in LPZ activation. Conversely, performance is not enhanced when maps expand.

It is known that certain perceptual abilities like acuity and contrast sensitivity are largely determined by how cortical space is apportioned (Virsu et al., 1987; Virsu & Rovamo, 1979). If reorganized activity represents the functional recruitment of unused cortex and the establishment of a new norm in V1 organization, then these areas of activation should not vary so readily. The disconnection between the behavioral data and the activation maps suggests that factors other than V1 dynamics affect the area and magnitude of activation.

The influence of attention may be the best explanation for this investigation's findings. Attentional feedback is a known effector of V1 activation. Return signals from

the parietal and frontal cortices assist initial processing by increasing the synchrony of neural responses, filtering unattended input, and enhancing baseline neural firing (Ahissar & Hochstein, 2004; Kastner & Ungerleider, 2000; Moran & Desimone, 1985; Motter, 1993).[15] Feedback is also highly retinotopic, so that attention to specific parts of the visual field yields greater activation in corresponding areas of the visual cortex (Datta & DeYoe, 2009; Tootell et al., 1998).

Evidence that attention may play a role in the current observations lies in the fact that MP-1 tested patients improved their fixation ability over the course of training. As explained above, fixation is neurologically distinct from other visual abilities, and a growing body of research suggests that the cortical sites which dictate oculomotor control also direct attentional feedback (for a review, see Awh et al., 2006). The changes observed in V1 activation for the current patients could be the result of how oculomotor training circumscribes feedback to specific parts of the calcarine.

Before training, feedback activation is approximate and diffuse, spreading into the lesion projection zone. However, by exercising volition over ocular movements, feedback becomes more precise, restricting activation to only stimulated parts of the calcarine. The result is that PRL activation decreases dramatically after training, particularly within the LPZ.

This interpretation is consistent with Masuda et al.'s theory that reorganized activity is a manifestation of attentional feedback and not evidence of a functional

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[15] One of the more developed concepts of attentional feedback is Merav Ahissar's and Shaul Hochstein's reverse hierarchy theory (RHT) which argues that perceptual performance is directed by neural processors that enhance or limit information in a top-down fashion. Ahissar and Hochstein have used their model to explain a wide range of data, including perceptual learning, adaptation, and priming (Ahissar & Hochstein, 2004; Ahissar, Nahum, Nelken, & Hochstein, 2009).

reorganization. However, this circumstance may be subject to time and experience. Even if reorganized activity starts out as non-functional, its coincidence with normal, V1 firing over prolonged periods could yield a different scenario. The reorganization observed by Baker et al. (2005) and Dilks et al. (2009) involved JMD patients that had macular degeneration twenty years or over. Perhaps such periods are long enough to engender a true reorganization of cortical connections. The next sections will explore the factors that influenced activation in this data set and how they may effect reorganization in general.

9.3 PRL and nonPRL Activation

The neuroimaging data showed differences between the activation patterns of PRL and nonPRL maps. With the exception of VH, most of the patients showed a reduction in PRL activation after training. In contrast, nonPRL data showed both reductions and expansions, sometimes within the same patient. What are the reasons for this variability?

Schumacher et al. (2008) proposed that reorganized activity may manifest differently for PRL and nonPRL retinal areas. Their findings demonstrate a greater magnitude of LPZ activation for the PRL compared to the nonPRL, suggesting that ectopic activation is some how contingent on the development and/or use of a preferred retinal locus. The current data reveal a more complex picture. While some patients mirror the results of Schumacher et al., others do not. Patients such as MK and VH have nonPRL activation patterns, both pre and post, that are similar to the PRL. The reasons for this variability may have to do with an individual patient's visual behavior, attentional anisotropies, and the topography of retinal damage.

Since MD patients demonstrate multiple PRLs (Lei & Schuchard, 1997; Sunness et al., 1999), it is possible that the selection of a nonPRL, which is simply an experimental designation, is actually the inclusion of another PRL. While it is true that the patients did not fixate with their nonPRLs, this may be because visual conditions and the nature of the task favored the PRL. It does not mean, however, the nonPRL lacks utility. The nonPRL could be engaged at different luminance levels or in more attention demanding tasks, such as reading. The fact is, categorizing retinal areas as functional (PRL) or non-functional (nonPRL) has experimental utility but is likely an over-simplification of visual behavior. By happenstance, the selection of patients in this study could include those without nonPRLs, but actually more and less functional PRLs, in which case their activation patterns would be similar.

Other patients did show a difference between PRL and nonPRL activation. In these cases nonPRL stimulation showed little activation for the pre-test, but significantly more for the post-test. The pre-test status of these areas may be closer to what is meant by the term nonPRL, an area of preserved retina without functional significance. Many MD patients are perceptually unaware of these areas, perhaps because attention is trained to the macula for most of our lives. This is why rehabilitation specialists must prompt patients to recognize the existence of preserved retina. If reorganized activity is an attentional phenomenon, it makes sense that the pre-test nonPRL would yield little to no activation.

However, this interpretation raises another question: Functional or not, why does activation in reference to the nonPRL change along with the PRL? These areas were not selected for rehabilitation. A reason for this may be the global nature of oculomotor

training. No specific set of eye muscles corresponds to either the PRL or nonPRL. Honing ocular control to improve fixation at one area necessarily affects the other. Interesting evidence of this comes from Tarita-Nistor et al. (2009). The authors showed improved fixation ability for a newly trained PRL, but to a lesser degree these gains translated to the old PRL as well.

The effect of training on PRL and nonPRL activation may rest on the initial condition of the area. If the patient is cognizant of its location and uses it on occasion, then the retinal location may be primed and with training demonstrate the curtailed activity observed for many of the PRLs. If the patient is unaware of the area, then training, whether direct or indirect, could elevate its attentional status and enhance feedback activation.

9.4 Negative Activation and No Activation

Many patients demonstrated negative calcarine activation in addition to positive for the fMRI tasks. In fact, patient BE displayed only negative activation for most of his task conditions. The presence of negative activity is hard to interpret because scientists are currently debating its functional significance. Some argue its presence represents only vascular drainage to parts of the calcarine activated by retinal stimulation (Shmuel et al., 2002). Still others contend that negative activation holds a functional relationship to visual processing (Bressler, Spotswood, & Whitney, 2007; Smith, Williams, & Singh, 2004).

Functional or not, the presence of negative activity could reflect large-scale changes in cortical architecture, the result of aging and brain health. Older adults exhibit less activity in the visual cortex than young adults (Crossland, Morland, Feely, von dem

Hagen, & Rubin, 2008). This may be because the majority of visual processing is re-directed to extra-striate visual sites. Such changes may be efforts by older brains to more effectively utilize aging substrates (Whalley et al., 2004).

Patients with negative activity surrounding the deafferented cortex could exhibit a "blood stealing" effect where positive LPZ activation has a hemodynamic draw on the local blood supply. No activation could be the result of other visual sites taking over processing from V1, reducing its overall signal-to-noise ratio. These are speculations, but until better understood, negative activity may poise an inherent difficulty in interpreting fMRI data from older MD patients.

CHAPTER 10: CONCLUSIONS

The present research contributes to the growing evidence regarding visual activity in MD patients, leverages this data toward a theoretical position, and uncovers other potential dimensions of reorganized activity. To the author's knowledge, the above findings represent the first attempt to assess the effect of visual training on the status of reorganized cortical maps. The instability of LPZ activation suggests its presence is directed by attentional parameters rather than feed-forward reorganization. In addition, the degree to which attention affects V1 activity may be influenced by the utility of preserved retina. The functional standing of healthy retinal areas may be governed by factors such as time, sensitivity, and adaptations of ocular control. Consistent use of these areas may warrant the label PRL and, in time, sharpen attentional feedback exclusively to corresponding cortex.

What do these findings and their interpretation mean for endeavors to rehabilitate MD patients? The most important realization is that a more restrained view of cortical reorganization is necessary. It may be that after several years of consistent PRL use deafferented cortex begins to respond in functionally meaningful ways to visual stimulation. Initially, however, these "reorganized" maps are likely the byproduct of attention, not reorganization.

Though this interpretation may be sobering for the clinically minded, an attention-based view of cortical activation still presents a number of avenues to explore PRL development and holds promise to inform rehabilitation efforts. To begin with, LPZ activation could become an important metric for determining the maturity of PRLs. If

ideal patterns of activation can be reliably linked to behavioral measures, like BCEA scores, then such values could carry both neurological and behavioral import, ultimately setting standards for PRL fitness.

A broader area of inquiry could be how attentional networks change with the exercise of eccentric viewing. So far neuroimaging studies of AMD patients have only examined the calcarine sulcus and have advanced a retinotopic understanding of plasticity. However, the lack of topographic reorganization in V1 does not preclude changes in attentional networks. Techniques such as diffusion tensor imaging (DTI) and Granger causality could be instrumental in revealing adaptive communications among these attention sites. The finding that oculomotor exercises alone can improve reading speeds (Seiple, Szlyk, McMahon, Pulido, & Fishman, 2005) suggests that understanding the neurology of attention is crucial in treating AMD.

Finally, a full accounting of the cortical areas affected by eccentric viewing (striate, extra-striate, and attentional) could provide the basis for brain stimulation programs to aid established rehabilitation protocols. Technologies like TMS could be used to excite regions of deafferented cortex or those of oculomotor control, thereby augmenting efficacy of training. This approach is ambitious with many unknowns, but the growing interest in brain stimulation may bring it to action.

Of course, the above research programs assume the attention-based hypothesis advanced here is correct. More investigations of AMD patients are necessary to determine whether or not this is true. More importantly, though, additional studies are necessary to expand our general knowledge base regarding AMD's effect on visual neurology. Many recent neuroimaging papers have employed JMD patients to assess the

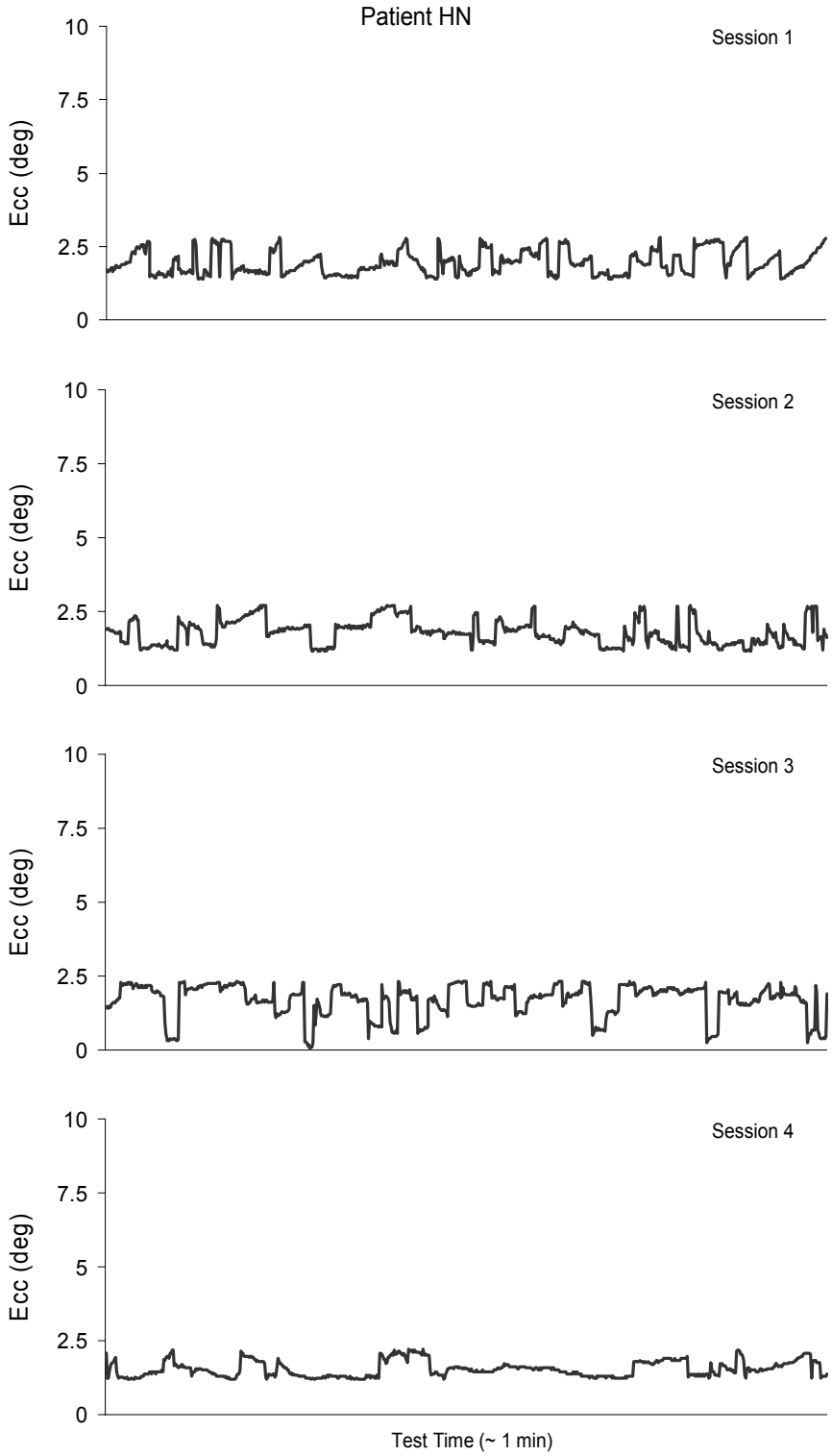
cortical response to MD. These patients offer a visually stable, neurologically healthy, and experienced (in terms of eccentric viewing) study population. However, they are not representative of the majority of the people with MD. Most people with MD have AMD, are older adults, and do not have twenty/plus years of experience with the disorder.

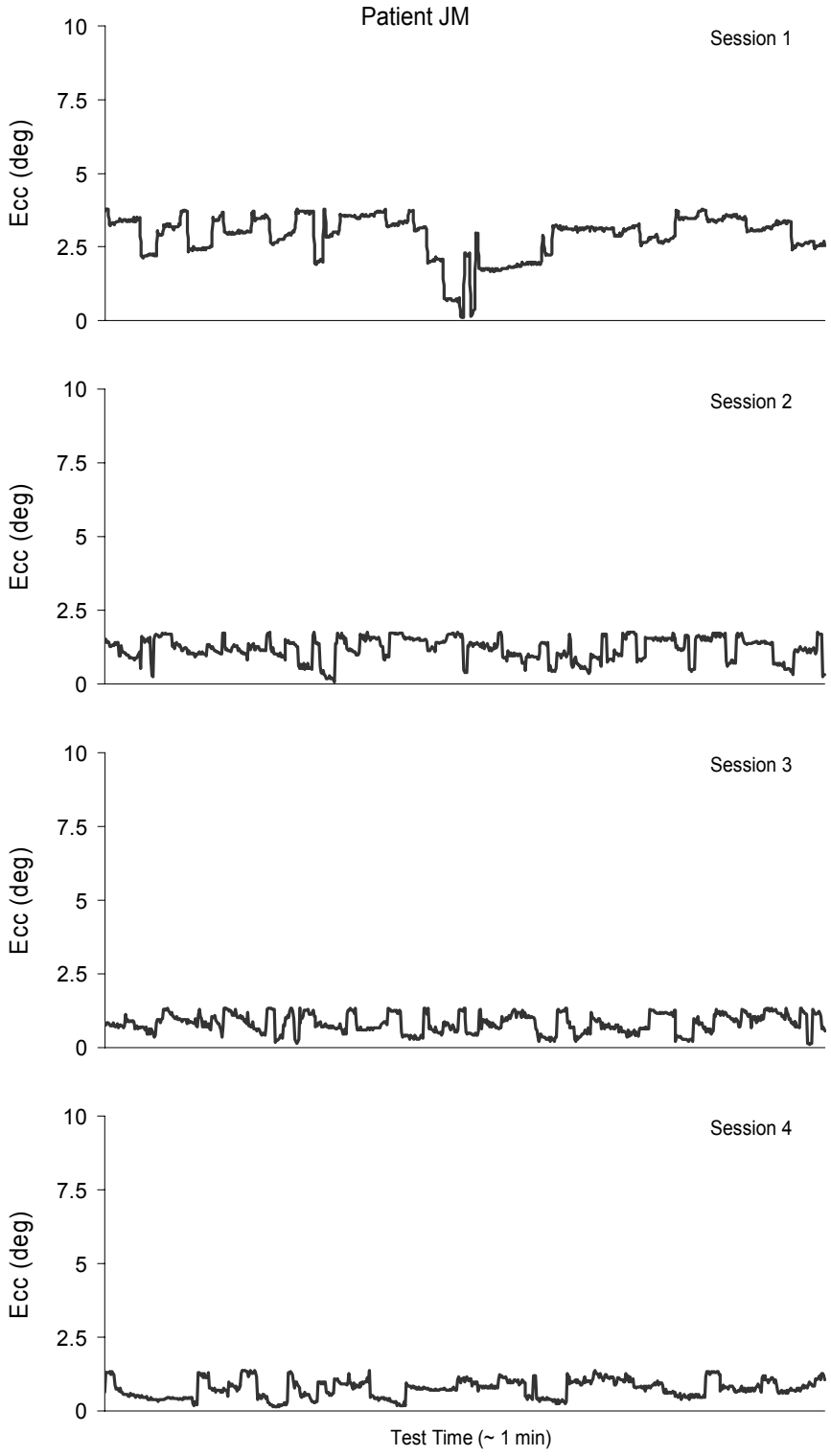
There is a necessity, then, to begin an earnest behavioral and neurological evaluation of AMD patients within the first three years of their diagnosis. Such an endeavor could provide additional evidence of a relationship between cortical activation and rehabilitation, perhaps identifying the most effective training techniques. It may render important discoveries, such as neural hallmarks of PRL formation or associations between disease topography and attentional skills. Most importantly, though, it would build a standard body of clinical and neurological data on which evaluate future rehabilitation efforts.

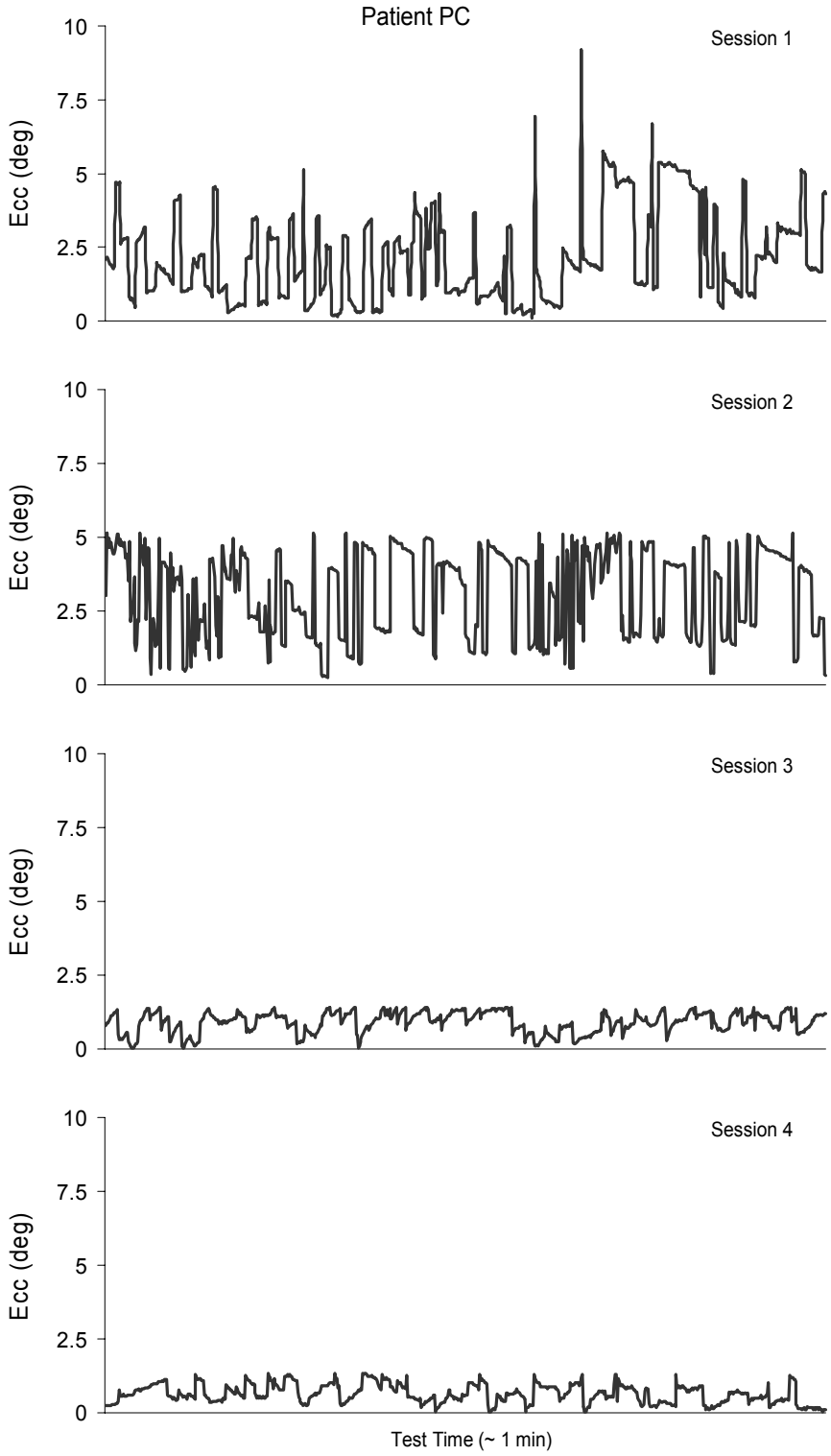
This dissertation began by recounting a sea change in neuroscience: how brain plasticity has come to dominate our thinking about the boundaries of human cognition. However, it also called attention to the necessity of addressing the bearings and limitations of this paradigm. While the findings of this study diminish the likelihood of one form of visual plasticity, they open consideration to others. The adaptive nature of the brain is multifaceted and to explore it means determining the level of action. It is my hope that this research helps point us in the right direction. The outcomes are not merely academic, but part of a larger undertaking. A new science is developing, one with the promise of elevating human psychology and medicine to a new province. Our best efforts are needed to press it into service.

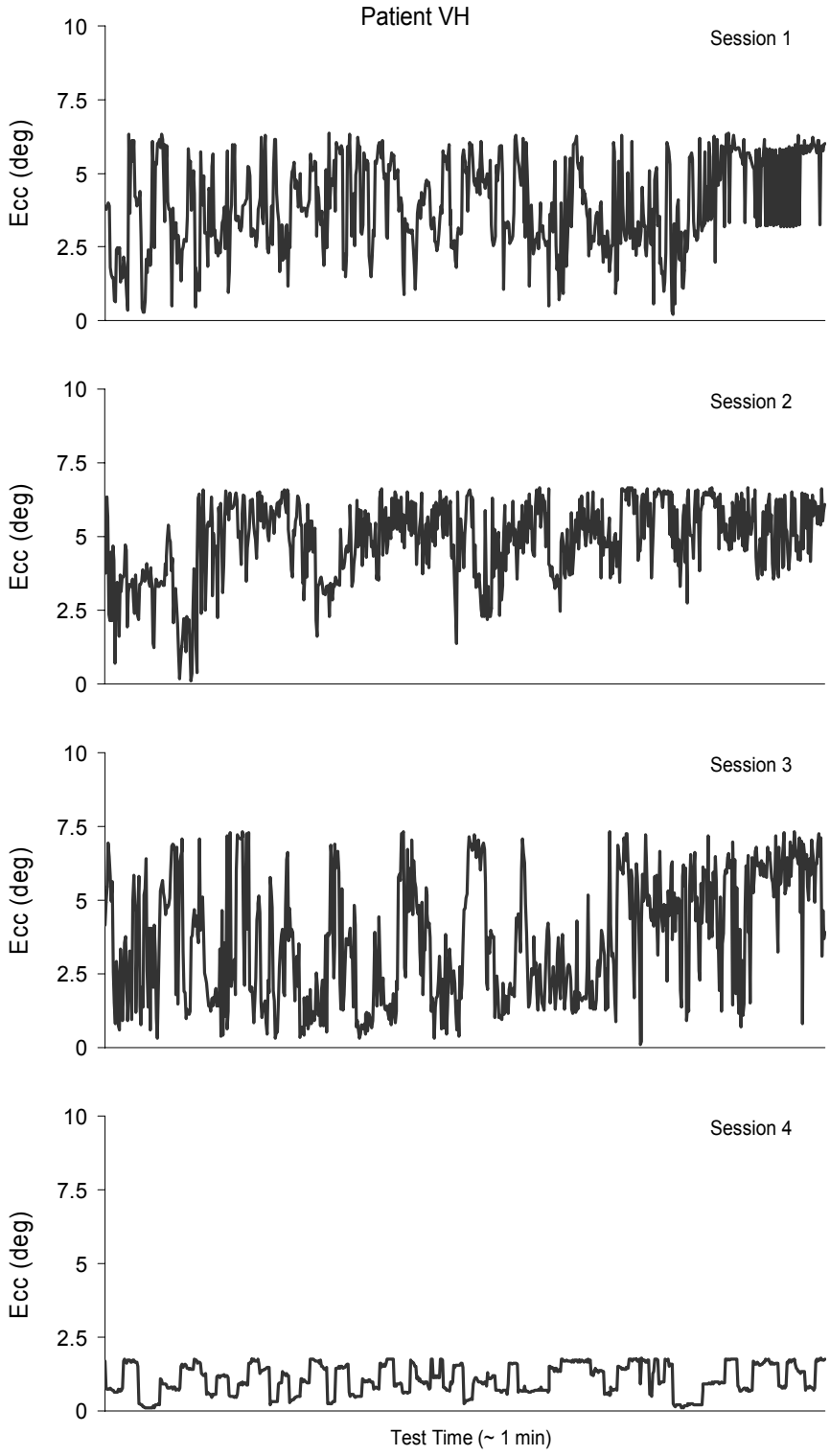
APPENDIX A

The following are graphs of fixation eccentricity across the four feedback sessions.




Patient JM
Session 1
Session 2
Session 3
Session 4
Ecc (deg)
10
7.5
5
2.5
0
Test Time (~ 1 min)


Patient PC
Session 1
Session 2
Session 3
Session 4
Ecc (deg)
10
7.5
5
2.5
0
Test Time (~ 1 min)


Patient VH
Session 1
Session 2
Session 3
Session 4
Ecc (deg)
10
7.5
5
2.5
0
Test Time (~ 1 min)

APPENDIX B

The following are recreations of Pepper VRST data sheets. They illustrate how reading performance was scored. Note, these are examples. They show the general format but not actual test items from the Pepper VRST. Patient BE's scores are depicted.

Pre-Test

Line		# correct / # item	percent correct
1	a k l o h b y m v o q f g t j	14 / 15	93.3%
2	f g k t x n c x a z y d w e r	15 / 15	100%
3	won do if nip k he four out j o hers q	10 / 12	dummy
4	but can l me did file q u all c at g as	13 / 13	100%
5	great boat water job kind stump did cool	8 / 8	100%
6	never captain jump rocks midnight paper	6 / 6	100%
7	strawberry grass touchstone token	4 / 4	100%
8	glue gold skinny elbow truth can f yes	7 / 8	dummy
9	slide fresh fellow grand orange crab	6 / 6	100%
10	mailbox railroad congress forfeit	4 / 4	100%
11	feet allow general somersault metaphor rebel	0 / 6	0%
12	fearless squirrel mushroom crane meteor diagonal	6 / 6	100%
13	compel f neither sugar grave help tag	7 / 7	dummy

- Total Number Correct (add lines 1-13) = *100*
- Mean Percent Correct (sum of percentages/10) = *89.33%*
- Total Test Time = *4* min *03* sec (Time in Minutes) = *4.05*
- Correct Reading Rate = Total # Correct/Total Time (in min) = *24.69*

- Error Codes -

Misidentification……..	substitution written above…….	e.g. rust
Repetition……..	wavy line below……..	e.g. blue
Spells Word……..	"sp" placed above…….	e.g. barn
Omission……..	circle for omission…….....	e.g. for
Insertion…….....	caret at insertion…….....	e.g. go it
Connects Words…….....	line underneath……..	e.g. home less
Separates Words……..	slash……..	e.g. cowboy
Changes Order……..	arrow to where item was read……...	e.g. a f t
Line Skip……..	arrow to skipped line	
Termination……..	1. 10 consecutive errors 2. skipped line twice	3. fatigue of reader 4. exceeded time limit

Post-Test

Line		# correct / # item	percent correct
1	h j u o k w q d j p n b x n t	13 / 15	87%
2	g c h i x j q u k v y m h r e	15 / 15	100%
3	can do for kill b no let hard n p fish z	12 / 12	dummy
4	cut go u beg we too h c did s (z) rat y ill	12 / 13	92%
5	rain champ fail wrap coin less take fix	8 / 8	100%
6	choose airplane yelp candle wrench cap	6 / 6	100%
7	muffin tamper investment wrangle	4 / 4	100%
8	tooth con (Kick) zipper neck label fur c van	8 / 8	dummy
9	slide kiss banker navel truck vulgar	5 / 6	83%
10	pamper jubilant rowdy arrangement	4 / 4	100%
11	chicken slump tuba hollow future cake	6 / 6	100%
12	check rampant bell unit starch indifferent	6 / 6	100%
13	tango i never supper jump goldfish eat	7 / 7	dummy

- Total Number Correct (add lines 1-13) = *106*
- Mean Percent Correct (sum of percentages/10) = *96.2%*
- Total Test Time = *4* min *30* sec (Time in Minutes) = *4.50*
- Correct Reading Rate = Total # Correct/Total Time (in min) = *23.55*

- Error Codes -

Misidentification……..	substitution written above……	e.g. rust (trust)
Repetition……	wavy line below……	e.g. blue
Spells Word……..	"sp" placed above……	e.g. burn (sp)
Omission……..	circle for omission…….....	e.g. (for)
Insertion……...	caret at insertion…….....	e.g. go it (for)
Connects Words……...	line underneath……..	e.g. home less
Separates Words……..	slash…….....	e.g. cowboy
Changes Order……	arrow to where item was read……...	e.g. a f t
Line Skip……..	arrow to skipped line	
Termination……..	1. 10 consecutive errors 2. skipped line twice	3. fatigue of reader 4. exceeded time limit

APPENDIX C

The following are guidelines used in the visual rehabilitation exercises. Treatment was individualized so not all techniques or tools were used. The text here is reproduced with permission from Mary Warren.

Scotoma Awareness and PRL Ability

Test Materials

Clock card, Go For It card, or the examiner's face. Letter targets.

Environment

Well-lighted room with the light source directed from behind the client onto the test targets; ensure that the light source is not shining directly into the client's eyes.

Scotoma Awareness

1) Use the clock card, the *Go For It* card or the examiner's face as targets.

2) Evaluate each eye separately beginning with the dominant eye and then together.

3) Show the target you have selected to the client and familiarize them with it. Make sure they can see the features of the target (such as the numbers on the clock or the words in the GFI phrase). Point out such details as the hands on the clock, the color of your eyes etc.

4) Center the target directly in front of the patient and close enough to the client for the details to be seen. Make sure the target is well illuminated.

5) Instruct the client to look at the center of the target and without moving his/her eye tell you if certain areas of the target look blurry, faded, distorted, or are missing. Be sure that the client does not move his/her eyes while viewing the target.

6) Note the location of the blurred or missing vision-this indicates the position of the scotoma.

Instructions to the Client

Your eye disease often creates holes or blind spots in a person's vision. You may have noticed that sometimes when you look at peoples faces, or a page of print, or the TV screen, parts of the object are blurry and won't come into focus or are bent out of shape or even missing. Those areas are caused by blind spots. I need to find out if you have blind spots in your vision and where they are located because it will affect how well you can use your vision to (supply example such as reading).

I am going to hold (insert selected target) in front you and ask you to look directly in the center of (the target). Then without moving your eyes, I want you to tell me whether parts of (the target) are missing, blurry or distorted. YOU MUST KEEP YOUR EYES LOCKED ON THE CENTER OF THE TARGET.

Location of PRL

Use the clock figure, face or the Go For It card as the target.

Test the eyes together; in doing this you will locate the PRL for the dominant eye. If no PRL can be found, test each eye separately.

1) Instruct the client to look at the center of the target and without moving his/her eyes locate the area of the figure not seen clearly because of the scotoma.

2) Then instruct the client to move his/her eye up so that he/she is fixating above the figure and tell you whether, if in making this eye movement, all parts of the figure come into clear view. Cue the client by holding your hand and wiggling your fingers in the direction you want to client to look. Encourage the client to only move the eyes but some clients with large scotomata may need to use a head movement to locate the PRL.

3) Repeat, instructing the client to move his/her eyes to fixate below the figure; then to the right of the figure; and then to the left of the figure.

4) Repeat steps 1 and 2 instructing the client to move h/her eye in the direction that provides the clearest view of the figure. Record the direction the client moves his/her eye-the client will move the eye in the direction of the PRL.

Instructions to the Client

Now I want to see if you can move the blind spot out of the way so you can see all of (the target) clearly. I am going to hold (the target) in front of you and I want to look directly at the center of the target. Then I want you move to your eyes (up, down, left, right) so you are looking (above, below, right or left sides) the target. I'll wiggle my fingers to show you the direction I want you to look. When you move your eyes that direction, tell me if (the target) becomes clearer and more complete.

5) When the PRL is located, explain to the client what a PRL is and how it will be used for reading.

Using the PRL to Locate a Target

Use a letter target made out of a black 1" or 2" stick on letter attached to a strip of poster board or a tongue depressor. Make several letter targets for variety. The client completes this task binocularly.

1) Hold the letter target in various positions in front of the client while the client focuses straight ahead on your face. Each time the letter is moved to a new location, instruct the client to quickly move his/her eyes towards the new location to fixate on the letter. Instruct the client to tell you when he/she has the target clearly in view. The client may move his/her head initially if he/she is having difficulty locating the target by just using eye movements. The client is instructed to look again at the examiners face before the target is moved to a new location.

2) Repeat several times using different letter targets to determine the client's ability to use the PRL to locate and fixate on a target. Keep placement of the target within the area immediately surrounding the client's face. (no higher than the forehead, lower than the Adam's apple, or wider than the shoulders).

Instructions to the Client

Now I want to see how quickly you can locate a target using your PRL. I am going to place this letter (show and identify the letter) in various locations and ask you to move your eyes to find it and to tell me when you are able to see it clearly. I want you to look back at my face after you have found (the target)

Begin by looking at my face (place the target) now look at (the target)

Look back at my face (move the target to a new location) now look at (target)

Using the PRL to Track a Target

Complete binocularly using the letter targets.

1) Hold the letter target up in front of the client and instruct the client to fixate on the target and to tell you when he/she clearly views the target. Slowly move the target horizontally to the edge of the face-first in one direction and then in the other. Instruct the client to track the target, keeping it in clear view at all times as it moves and to tell you if the target goes out of focus. If the client loses the target, reestablish fixation and then continue to move the target. Move the target vertically and diagonally, reestablishing fixation every time the client loses it. Do not move the target beyond the boundaries of the face.

2) Repeat several times using different letter targets to determine the client's ability to lock the PRL on the target and track it through horizontal, vertical and diagonal movements without losing fixation.

Instructions to the Client

Now we are going to see how well you can use your PRL to track a target. I am going to hold this (target) in front of you. I want you to look at it and tell me when you can see it

clearly. Now I want you to follow it with your eyes as I move it. Tell me if parts or all of the (target) disappear or become blurry or distorted.

Shifting PRL Gaze Between Targets

Complete binocularly using the letter targets.

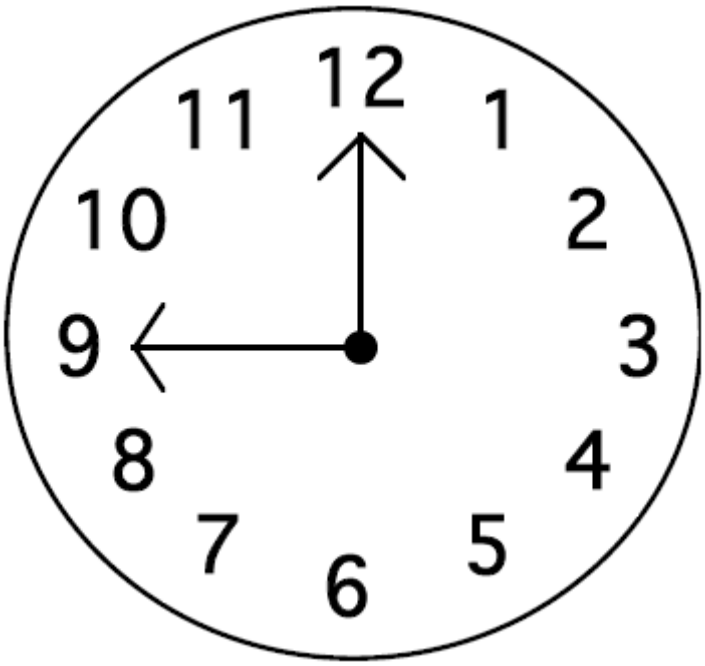
1) Hold up two letter targets about 12 inches apart along a horizontal line. Instruct the client to focus clearly on one target and then to shift h/her eyes quickly and focus clearly on the other target.

2) Repeat, holding the targets in a vertical line and then a diagonal line.

3) Repeat several times to determine the client's ability to quickly shift gaze using the PRL and consistently achieve a clear view of the target.

Instructions to the Client

Now we are going to see how well you can use your PRL to look from target to target. I am going to hold up these two letters. One is a ___ and the other is a ____. Look first at the ____ and tell me when you can see it clearly. Now look at the ____ and tell me when you can see it clearly.



GO FOR IT

Eccentric Viewing/PRL Training Exercises

Practice with these exercises precedes attempts to use the PRL to view through a magnifier and read words. The client should be proficient in completing these exercises before magnification is introduced.

Exercise 1 Awareness of Scotoma

1) Instruct the client to look at the center of a large figure (example: a clock face) and without moving his/her eyes tell you if certain areas of the figure look blurry, faded, distorted, or are missing. Be sure that the client does not move his/her eyes while viewing the figure.

2) Instruct the client to view the largest print on the Go For It card. Ask the client to tell you if certain letters of the phrase look blurry, faded, distorted or are missing. Be sure that the client does not move his/her eyes while viewing the card.

Exercise 2 Area of Clearest Viewing/PRL Location

Use the large figure and the Go For It card from the previous exercise.

1) Instruct the client to look at the center of the figure and without moving his/her eyes locate the area of the figure not seen clearly because of the scotoma.

2) Then instruct the client to move his/her eyes up so that he/she is fixating above the figure and to tell you, if in making this eye movement, all parts of the figure come into clear view. The client may need to move his/her head initially to achieve this position.

3) Repeat, instructing the client to move his/her eyes to fixate below the figure; then, to the right of the figure; and finally, to the left of the figure.

4) Repeat steps 1 and 2 instructing the client to move his/her eyes in the direction that provides the clearest view of the figure.

Exercise 3 Using the PRL to Locate a Target

Use a letter target made out of a black 1" or 2" stick on letter attached to a strip of poster board or a tongue depressor for this exercise. Make several letter targets for variety.

1) Hold the letter target in various positions in front of the client while the client focuses straight ahead. Each time the letter is moved to a new location, instruct the client to quickly move his/her eyes towards the new location to fixate on the letter. Instruct the client to tell you when he/she has the target clearly in view. The client may move his/her head initially if he/she is having difficulty locating the target by just using eye movements.

2) Repeat several times using different letter targets until client can quickly locate the target with the PRL in each location.

Exercise 4 Using the PRL to track a Target

Use the letter targets for this exercise.

1) Hold the letter target up in front of the client and instruct the client to fixate on the target and to tell you when he/she clearly views the target. Slowly move the target horizontally to the edge of the face—first in one direction and then in the other. Instruct the client to track the target keeping it in clear view at all times as it moves and to tell you if the target goes out of focus. If the client loses the target, reestablish fixation and then continue to move the target. Move the target vertically and diagonally, reestablishing fixation every time the client loses it. Do not move the target beyond the boundaries of the face.

2) Repeat several times using different letter targets until the client can lock the PRL on the target and track it through horizontal, vertical and diagonal movements without losing fixation.

Exercise 5 Shifting PRL Gaze Between Targets

1) Hold up two letter targets about 12 inches apart along a horizontal line. Instruct the client to focus clearly on one target and then to shift his/her eyes quickly and focus clearly on the other target.

2) Repeat, holding the targets in a vertical line and then a diagonal line.

3) Repeat until the client can quickly shift gaze using the PRL and achieve a clear view of the target consistently.

Exercise 6 Using the PRL for Letter/Number Recognition

1) Use letter jump and single letter underline exercises from the Warren Prereading and Writing Exercises.

2) Select a size of print that the client can see without magnification.

3) Instruct the client to read through the exercises out-loud while you time his/her performance.

4) Record time and error rate.

5) Repeat the exercise as a drill, encouraging the client to complete the exercise with increasing speed.

6) As the client perfects accuracy and speed on the exercise, reduce the size of the print until the client is practicing on a print size which he/she is just able to see accurately without magnification.

7) Progress to single letter alphabet and number searches and then to word searches. Continue to time the client's performance and to monitor his/her accuracy. When beginning a new exercise, use a larger print size and progress down to the smallest print size possible.

Exercise 7 Using the PRL with Magnification

1) Select the letter underline exercise from the Prereading and Writing Exercises. Begin with large print and a weak magnifier (2.5x - 4x). Assist the client to position the magnifier correctly and then instruct the client to read out the underlined letters using the magnifier.

2) As the client's speed and accuracy improve, gradually reduce the print size and increase the magnification until the client is reading 1M print using his/her prescribed magnification.

3) Progress to using the magnifier to spot read labels, and short instructions, etc.

4) Progress to short continuous text materials such as the "Dear Abby" column.

5) Gradually introduce longer continuous text materials as client's ability allows.

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