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Residual function, spontaneous reorganisation and treatment plasticity in homonymous visual field defects

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Abstract

This thesis will focus on the residual function and visual and attentional deficits in human patients, which accompany damage to the visual cortex or its thalamic afferents, and plastic changes, which follow it. In particular, I will focus on homonymous visual field defects, which comprise a broad set of central disorders of vision. I will present experimental evidence that when the primary visual pathway is completely damaged, the only signal that can be implicitly processed via subcortical visual networks is fear. I will also present data showing that in a patient with relative deafferentation of visual cortex, changes in the spatial tuning and response gain of the contralesional and ipsilesional cortex are observed, which are accompanied by changes in functional connectivity with regions belonging to the dorsal attentional network and the default mode network. I will also discuss how cortical plasticity might be harnessed to improve recovery through novel treatments. Moreover, I will show how treatment interventions aimed at recruiting spared subcortical pathway supporting multisensory orienting can drive network level change.

Chapter 1: General introduction

Homonymous visual field defects: description and aetiology

Homonymous visual field defects (HVFD) result from damage to portions of the visual system posterior to the optic chiasm (i.e. post-chiasmatic), which can include the lateral geniculate nucleus, the optic radiations and visual cortex. HVFD are therefore distinguished from conditions stemming from pre-chiasmatic disorders affecting the eye, such as glaucoma and macular degeneration – which result in damage to the retina – or the optic nerve – such as optic neuritis, which result in damage to myelinated ganglion cells axons. HVFD can follow a number of pathological processes including, ischemia, arteriovenous malformation (AVM), trauma, haemorrhage, tumor, abscess, anoxia, or demyelination. These pathologies can affect the visual pathway from the optic tract to visual cortex. Most patients with HVFD have evidence of parenchymal damage directly involving the occipital lobes (45 – 51% of cases) or the optic radiations (29 – 32% of cases; Fujino et al., 1986; Zhang et al., 2006a), while cases arising from damage to the optic tract or the lateral geniculate body are significantly less common. Ischemic pathologies are generally associated with infarction of the posterior cerebral artery, whose branches supply the optic tract, the inferomedial temporal lobe and the majority of the occipital lobe. Middle cerebral artery stroke can also result in HVFD, when the area of brain ischemia includes the posterior parietal or temporal lobe (Meyer's Loop). Trauma and brain tumours can also result in HVFD. Indeed, much of the initial evidence regarding the retinotopic organization of visual cortex come from observation of visual perimetric deficits in soldiers who had fallen victim to bullet wounds to the head, after the introduction of high velocity projectiles (Holmes, 1918). Much more rarely, multiple sclerosis, and the associate demyelination of the optic radiation, or posterior cortical atrophy,

a variant of Alzheimer's disease (Formaglio et al., 2009; de Haan et al. 2014) can also result in homonymous visual field deficit.

Characteristics of visual field loss with post-chiasmatic lesions

Unilateral damage posterior to the optic chiasm will cause an homonymous (i.e. affecting the representation of the same side of the visual field from both eyes) visual loss on the side contralateral to the damage. The anatomical site and extension of the lesion typically determines the severity of the visual field deficit. Damage to the primary visual cortex (V1) produces a retinotopic loss in the contralateral visual field. HVFD can range from isolated scotomas, i.e. homonymous scotomatous hemianopia, affecting islands within otherwise preserved visual fields, to complete visual field loss (homonymous hemianopia). However, damage to V1 will often result in retained foveal vision, leading to so-called "macular sparring". One possible explanation for this phenomenon is that the representation of the fovea in visual cortex is bilateral. Alternatively, the most posterior regions of visual cortex, which contain a representation of the fovea, may belong to a territory supplied by branches of the middle cerebral artery, whereas more anterior regions, where representations of the visual periphery is contained, are supplied by branches of the posterior cerebral artery. Homonymous hemianopia is also caused by exhaustive damage to the optic radiation bundle. This leads to visual cortex being disconnected from its main thalamic input. If damage to the optic radiation is localised to its upper, parietal division, vision loss is mainly found to the inferior portion of the contralateral visual field (inferior quadrantonopsia or "pie in the floor defects"). Often visual field loss is also found in the upper quadrant and contralateral visual hemifield. Damage to the lower division, passing through the temporal lobe, results in contralateral superior visual field loss (superior quadrantopia or "pie in the sky defect").

Superior quadrantopia is less common than lower quandrantonopia, given the optic radiations' lower division being less susceptible to damage (Jacobson, 1997). Lesion site also determines the congruity of the homonymous visual field loss. For example, damage to the optic tract and partial lesions will cause partly incongruent visual loss in the two eyes. Lesion affecting visual cortex will result in a highly congruent visual loss in the two eyes (Luco et al., 1992). In some cases associated with diffuse cortical injury following anoxic-ischemic injury, widespread neural loss within the striate cortex causes multiple homonymous scotomic areas (Caine & Watson, 2000).

Epidemiology of HVFD: Prevalence and Incidence

Sample selection biases and inconsistencies between diagnostic criteria used in different studies complicate a precise tabulation of the prevalence of HVFD from the extant literature (de Haan et al., 2014). In an early study, Feigenson, McDowell et al. (1977) reported that 30% of all patients admitted to a stroke rehabilitation unit over a 16-month period showed evidence of homonymous hemianopia. Feigenson, McCarthy et al. (1977) similarly reported that 31% of all patients admitted to a stroke unit over a 33-months period (but who had been medically, neurologically and socially screened at preadmission to optimise treatment outcome) tested positive for hemianopia. A later study by Rossi et al. (1990) reported that 30% of patients receiving treatment at an inpatient rehabilitation centre tested positive for either hemianopia or visuo-spatial neglect. Heinsius et al. (1998) screened the Lausanne Stroke Registry for cases of infarction to at least two subterritories of the middle cerebral artery and found hemianopia to be present in 73% of cases, compared to 15% in a control group of patients with limited infarction to middle cerebral artery regions. Ng et al. (2005) report that visual field defects were present in 54% of a relatively small sample (n=89) of

patients with posterior cerebral artery stroke, observed at an urban rehabilitation hospital over an eight-year period. Zihl (2011) estimates that 89% of post-chiasmatic brain injury cases result in HVFD. In a review of 326 patients diagnosed with head trauma at a University-based clinic over an eight-year period, Van Stavern et al. (2001) reported that 14% of cases exhibited HVFD. In a large scale population screening study, Gilhotra et al. (2002) administered an automated visual field test to a sample of 3654 participants aged 49 or older, drawn from an urban population. 25 individuals showed evidence of HVFD, constituting 0.8% of the total sample. 13 of them had a known history of stroke, accounting for 8.3% of 156 individuals with a similar history of brain ischemia. The remaining 12 individuals were asymptomatic and had no known neurological history. In the most recent and diagnostically sensitive prevalence study, Zhang et al. (2006b) reviewed 904 HVFD cases observed at a treatment clinic over a 15-year period, and classified 38% as homonymous hemianopia, 29% as quadrantopia, 13% as homonymous scotomatous, 13% as partial homonymous hemianopia and 7% of cases as homonymous hemianopia with macular sparing. Thus in summary, HVFD appears to affect between 8% and 31% of individuals who experience stroke, with higher prevalence amongst vascular cases requiring inpatient rehabilitation services.

Impairments and disability in HVFD

HVFD is known to impact measures of quality of life and activities of daily living (Papageorgiou et al., 2007; Passamonti et al., 2009; Gall et al., 2010; Wagenbreth et al., 2010). Patients often report difficulties avoiding obstacles, reading, driving, carrying out errands and household chores, managing personal finances and engaging in recreational activities, such as watching television (de Hann et al., 2014). Much of the disability

experienced by patients with HVFD reflects impairments in two core abilities – mobility and reading.

Additional neuropsychological impairments and oculomotor deficits can play a key role in lasting maladaptation to the reduced visual field. For example it is well known that patients with complete loss of vision, following bilateral strokes of posterior brain regions, can deny their deficits, and appear unaware of their blindness, a condition common enough to merit its own eponym, i.e., Anton's syndrome. Warrington (1962) suggested that diminished awareness of one's own visual deficit may be a pervasive feature of visual loss in patients with hemianopia. She also reported that the severity of the anosognosia is strongly associated with the degree of mobility impairment. In a classic study using incomplete figures, patients with less awareness of their scotoma were more likely to report incomplete figures as complete. Warrington described this tendency as "imaginative completion", and suggested that it could lead to incorrect appraisal of the layout of the environment and hence difficulties in navigation. Gassel and Williams (1963) later reported that the degree of insight concerning the nature and extent of the visual loss correlated with the patient's navigational abilities (de Haan et a, 2014). Other studies examined the relation between neuropsychological scores and driving ability. Two studies (Wood et al., 2009; Elgin et al., 2010) reported that driving ability correlated with neuropsychological measures of visual search speed, processing and psycho-motor speed (Trail Making Task A). Interestingly, Elgin et al. (2010) reported that performance on Trail B of the battery, which draws more heavily on executive function, did not correlate with driving performance amongst the HVFD group, suggesting that impairment in visual search and basic processing speed are more relevant to problematic driving.

Passamonti et al. (2009) suggested that an oculomotor scanning deficit underscores many of the complaints and disability shared by HVFD patients. Oculomotor scanning behaviour of sixty hemianopic patients was assessed by Zihl (1995), who reported that only 40% of the patients scored within the normal range. The majority of patients showed significantly increased search times, as a consequence of a poorly organized saccadic strategy, characterized by longer scanpaths, increased frequency of refixations, longer fixations and shorter saccades relative to a control group of sixteen, age matched healthy controls. Furthermore, scanning abnormalities were observed in both the affected and unaffected visual field, suggesting a non-lateralised oculomotor impairment.

This latter observation was confirmed by number of later studies, which also demonstrated that the degree of scanning impairment is significantly greater in the affected visual field compared to the unaffected field. Principle deficits include a greater magnitude of fixations and hypometric saccades in the affected field (Ishiai et al., 1987; Kerkhoff, 1999; Zangemeister and Oechsner, 1996; Zihl, 2000; Tant et al., 2002). Reading appears to show distinctive abnormalities amongst HVFD patients, contingent on the laterality of the visual loss (Eber et al., 1987; Meienberg, 1988; Ciuffreda, 1994; Schoepf & Zangemeister, 1993; Passamonti et al., 2009). Scotomas in the left visual field compromises search for the beginning of new lines of text, while scotomas in the right visual field are generally associated with worse reading impairment because of abnormally prolonged fixations, hypometric saccades and saccadic regressions. The greater severity of reading impairments following right visual field loss is likely to reflect the loss of the ability to accurately localize targets on the text line for subsequent saccades (Zihl, 1995; De Luca et al., 1996; Trauzettel-Klosinski & Rheinard, 1998; Leff et al., 2001; Wang, 2003; Passamonti et al., 2009).

Residual function

The visual system has traditionally been viewed as a parallel and hierarchical network, in which signals originating in the retina are passed through a series of image filters which extract low level descriptors of the image along various dimensions, such as orientation, colour, motion direction and stereo disparity, which are then combined by filters of ever increasing complexity. These operations culminate in a set of neural responses that code for both low level features of the input image, as well as global semantic descriptors of the object contained with the image. However, this serial model has been refuted by evidence that the primate visual system exhibits both bottom up as well as top down effects. The primary visual channel, where damage is likely to cause a HVFD, is the retino-geniculo-striate pathway. This pathway is characterized early by an anatomical and functional parcellation between parvocellular and magnocellular streams, which are in turn characterized by different response properties in the spatio, temporal and chromatic domain. Signals from temporal hemiretinas (carrying information from the medial contralateral visual field) then travel along the ipsliateral optic tract, while signals from the nasal hemiretinas (carrying information from the lateral ipsilateral visual field) travel to the contralateral optic tract via the optic chiasm. The primary visual channel then proceeds via the optic tract to the lateral geniculate nucleus of the dorsal thalamus (LGN), where 90% of retinal fibres terminate and form a retinotopic representation of the contralateral visual field. The LGN contains six layers of neuronal cells: dorsal layers (1 - 4) receive projections from the parvocellular retinal cells, while ventral layers (5 - 6) from magnocelluar retinal cells. Axons from LGN form the optic radiations which carry signal to the striate cortex via two divisions – the upper division, carrying input from the lower quadrant of the contralateral visual field, terminates in the

dorsal bank of the calcarine sulcus, while the lower division, carrying input from the upper contralateral quadrant, terminates in the ventral bank of calcarine sulcus.

However, in addition to LGN, retinal ganglion cells' axons in the optic tracts also project to three subcortical structures. These include 1) the suprachiasmatic nucleus of the hypothalamus, controlling circadian rhythms; 2) the pretectum, controlling pupillary reflex and 3) the superior colliculus (SC), a dorsal midbrain structure which plays a major role in orienting toward objects of interest via body, head, and most importantly from the perspective of this thesis, eye movements. In cases of HVFD caused by retrochiasmatic lesions, the above mentioned alternative subcortical pathways are generally unaffected and can potentially provide a neural mechanism to support residual visual function. I will now review the documented residual function observed in HVFD patients in more detail.

Early reports at the beginning of the twentieth century described patients with occipital lesions who could detect flickering and moving stimuli (Riddoch, 1917; Holmes, 1918) suggesting that otherwise blind patients could access visual signals through other means than through signals generated in occipital visual cortex. Several reflexive responses may also endure in cases of cortical blindness. For example the pupil has been observed to still react to changes in the levels of ambient illumination (Magoun & Ranson, 1935; Bender & Krieger, 1951; Brindley et al., 1969). Clinically blind patients also show a preserved blink reflex in the presence of light flashes (Hackley & Johnson, 1996) and optokinetic nystagmus to large, moving visual stimuli (Pizzamiglio et al., 1984; Heide et al., 1990).

Pöppel et al. (1973) also observed that occipital lesion patients were capable of making saccadic eye movements towards light flashes presented at various positions of their blind field. Perenin and Jeannerod (1975) later expanded the repertoire of preserved residual ability to manual pointing, demonstrating that patients with visual field defects could accurately localise stimuli presented to their blind field with a manual point, even in the absence of any conscious awareness of the stimulus' presence. Further, the authors implicated projections to the extrastriate visual cortex in this preserved pointing ability, by demonstrating that patients with post-geniculate lesions could perform the task, while patients with lesions anterior to the optic chiasm, i.e., ablating all signals to both the superior colliculus and to the geniculate nucleus of the thalamus, could not. The ability was therefore attributed to signals projected to the extrastriate cortex, either via the spared retino-colliculo pathway, or via spared portions of the retino-geniculate pathway.

Direct assessment

A large body of studies have also investigated a specific residual visual phenomenon with HVFD, whereby a range of responses and judgements can be made about a stimulus presented to the blind field, despite patients not being consciously aware of its presence. This phenomenon, termed 'blindsight', was first described by Sanders et al. (1974), in a study of a patient who reported as blind in a specific region of their visual field on perimetric testing, consequent to lateralised retrochiasmatic lesion. However, when forced to chose, this patient could nonetheless make considerably accurate localisations of visual stimuli presented in the blind field, and, further, discriminate the orientation or spatial distribution of visual stimuli above the chance level, when forced to make a choice in a two-alternative choice task. This is an example of the direct assessment method of blindsight, i.e., paradigms where a patient is

required to make a conscious judgement about the nature or presence of a stimulus presented in their blind field, usually involving a forced choice between a small number of alternative responses (one always being the correct one). Blindsight patients are identified in such tasks by above-chance performances. For example, in the commonly applied two-alternative forced choice paradigm, response accuracy statistically above 50% would indicate above-chance performance, and the presence of blindsight.

Perenin and Rossetti (1996) used such an approach to offer further insight in to the substrate of preserved visuo-motor function in HVFD. In this study, a patient with HVFD performed a number of tasks aimed at probing different response modalities – a task which required verbalising the size and orientation of a stimulus presented in the blind field, a task which required manually matching the size or orientation of a stimulus in the blind field (with a modelling hand gesture) and a task which required a manual motor action on the stimulus (posting a card through a slot or grasping a shape with a pincer grip). The patient performed at chance level on the first two tasks, but could perform the third task (requiring a motor action) above the chance level. Authors concluded that the task-specific performance reflected the availability of specific neural networks spared following the patient's damage to primary visual areas (V1); the first two tasks required greater recruitment of the ventral 'what' pathway, which draws heavily on inputs from V1, while the dorsal 'where' pathway, which receives comparatively less input from V1, mediated the demands of the motor task. Another study by Magnussen and Mathiesen (1989) again showed a task-specific performance with patient BN, whose entire striate and extrastriate cortices were removed. BN could not detect high-contrast grating stimuli presented to her blind field, when the gratings were static. However when the bands of the gratings harmoniously moved in either horizontal direction, her detection was above chance. The absence of both striate and extrastriate

cortical areas prompted authors to attribute this task-specific performance to activity within the superior colliculus, which is preferentially activated by moving stimuli (Goldberg & Wurz, 1972).

A handful of studies have also demonstrated that patients with HVFD can not only detect but also discriminate the direction of motion. Blythe et al. (1986) presented a report of two patients with visual field defects consequent to damage to the striate cortex who could discriminate the displacement when two visual targets were presented sequentially at differing locations of their blind field. These patients were not able to discriminate the size or spatial pattern of stimuli, supporting the idea that their blind field performance relied on projections to extra striate regions contributing to the 'where' pathway. Perenin (1991) later demonstrated preserved motion discrimination ability in patients with cortical lesions performing a forced choice task where stimuli moving in opposing directions were presented in their blind field. Further, this ability was not preserved in a separate group of patients who had undergone hemispherectomy, i.e., complete removal of cortical structures on one side of the brain. The authors therefore attributed the preserved motion discrimination to cortical regions, involving the homologue of MT in the monkey (V5). This interpretation was further supported by Barbur et al. (1993) who performed a positron emission tomography (PET) on a hemianopic patient GY, who had a lesion to are V1 of his striate cortex, but could nonetheless consciously report the direction of stimuli presented in his blind field. The PET showed activations in area V5 of the extrastriate cortex, without parallel activations of area V1, while GY verbally reported the direction of stimuli, furthering the idea that in some patients, signals can bypass V1 and reach critical areas of extrastriate cortex for motion determination.

Signal detection paradigms have also been employed to probe the ability of patients to reliably report that a stimulus had been presented in their blind fields, without conscious experience of the stimuli. In these tasks, patients typically observe an auditory prompt, after which trials can either present a stimulus (i.e., a short light flash), or present nothing (catch trial). Patients are required to guess after each trial whether a stimulus had been presented. A d' value can then be computed, indexing the patient's ability to reliably detect the signal (Stoerig et al., 1985). Stoerig et al. (1985) administered such a paradigm to a patient with a post-geniculate lesion and demonstrated above chance signal detection. Stoerig and Poppel (1986) later demonstrated that more peripheral targets were more reliably detected. In this study, five HVFD patients with postgeniculate lesions were tested with a signal detection paradigm, at both a relatively central and more eccentric position. Four of the five patients demonstrated above chance signal detection, and, further, only with stimuli presented at the more peripheral location, perhaps due to the larger receptive fields of retinal ganglion cells receiving signals from peripheral vision. It is worth noting that in both of the above mentioned studies, the authors controlled for the confounding effect of light-scatter (i.e., a flash in the blind field being strong enough to be registered by the intact field) by running a control condition where stimuli were presented in the blind spot of the intact visual field. By demonstrating that signal detection was null at this location, the light-scatter from stimuli can be considered not strong enough to cross over from the bind field to the intact field, and thus inferences from these studies are reasonably insulated from the light-scatter confound.

In addition to signal detection and motion, some patients have also demonstrated the ability to perform higher order visual discriminations with stimuli presented in their blind fields. For

example, in the above cited study by Weiskrantz et al. (1974), their case patient DB was administered a battery of tests probing various forms of visual functioning. These tests suggested that DB could discriminate various blind field stimuli above chance (X's and O's, vertical and horizontal lines). In a later study, Perenin (1978) observed above chance discrimination in two out of six tested patients with HVFD, on a task discriminating triangles from circles. However the ability to discriminate form could be down to processes involving orientation. In a follow up study to Weiskrantz et al. (1974), Weiskrantz (1987) assessed patient DB's ability to discriminate between simple visual forms. The author first replicated DB's form discrimination using the blind-spot control condition described above to rule out the light-scatter confound. Further testing then demonstrated that as the orientation component of cues diminished, so to did DB's form discrimination performance. For example, DB could discriminate excellently between diamonds and squares (where orientation was the only differential cue), however his ability to distinguish squares from rectangles, or X's from Triangles, was at chance level. Further, his performance deteriorated when discriminating rounded triangles from sharp contoured triangles.

Finally, colour discrimination is another higher order function that can be preserved in the blind field following a retrochiasmatic lesion. For example, colour discrimination was demonstrated in an experiment by Stoerig and Cowey (1992), in which a sample of three patients with HVFD all discriminated colour above chance level. A later study by Brent et al. (1994) reported that patient GY also exhibited normal spectral response characteristics in his blind field using a two-colour incremental threshold assessment, and further noted that the patient could discriminate large colour stimuli above chance in a forced choice verbal identification paradigm. Both of these experiments controlled for discrimination being based on the brightness of stimuli, instead of their colour; Stoerig and Cowey (1992) tuned stimulus

luminance to individualised thresholds, while Brent et al. (1994) administered control conditions where stimuli could appear with random luminance levels and observed the same results.

Indirect assessment

The literature reviewed so far has detailed a range of abilities spared in patients with HVFD, ranging from simple reflexes, to motor actions, signal detection and discrimination of higher order features such as motion, colour or orientation of stimuli in the blind field. These data on such residual functioning were all acquired by direct assessment, which I described above as paradigms where patients are forced to make a judgement about the presence of a stimulus presented to their blind field, or forced to discriminate a certain characteristic in a forced-choice scenario. However such a paradigmatic approach could introduce bias. Recall that blindsight requires some manner of discrimination judgement about a characteristic of a stimulus, without any conscious awareness that a stimulus was present. Campion et al. (1983) argue that the criterion of 'awareness' may be a crucial confound. For example, if patients use a criterion of 'awareness' whereby stimuli in the blind field must be seen and recognised with the same precision and resolution as stimuli presented in their intact visual field, they may be under-reporting their 'awareness' of blind field stimuli; i.e., they may perceive something in the blind field, just not the same as what they perceive in their intact field. Thus, how 'awareness' is specifically defined (by both the patient and by the experimenter) could introduce a crucial bias. Further, as Cowey (2010) points out, a participant in a study who wants to do well, may begin noticing things that they initially regarded as irrelevant at the beginning of testing. Thus, studies that screen for conscious awareness and then administer the forced-choice paradigm, in that order, could be consequently confounded. Data are also

available to support the importance of the awareness criterion. Stoerig et al. (2002) demonstrated that on a trial-by-trial basis, patients' discrimination of square-waved gratings correlated with their awareness that something had appeared.

Other possible areas of bias include possible eye-movements into the bindfield, which many studies do not control, and light-scatter (Campion et al., 1983); though many studies have controlled for light scatter confounds as described above. Further, a two-alternative forced choice paradigm is not a clinical., but a psychophysical measure of vision, i.e., forced-choice judgement is a compound of both sensitivity to the target, and also, a tendency to select one response over the other, independent of the sensitivity (response bias; Cowey, 2010). For example, a patient with a more cautious approach to responding 'yes' will automatically yield a predominant 'no' response, independent of how sensitive they were to the signal. Stoerig et al. (1985) further demonstrated that signal detection in the blind field was affected by manipulating the ratio of target-to-blank trials. Finally, it is also important to note the potential for stress and discomfort to be bestowed upon patient participants, in settings where they are persistently asked to make judgements on visual stimuli they deny seeing (Cowey, 2010).

For these reasons, an alternative approach, 'indirect assessment', could provide a more reliable, bias-free assay into the implicit processing of unseen stimuli (Marzi et al., 2004). In such tasks, the effect of a stimulus presented to the blind field is measured on responses to a stimulus presented in the intact field. Blind and intact field stimuli can either be presented simultaneously or in sequence. With the appropriate experimental design such an approach can be insulated from the possible biases with the direct method, listed above.

An early indirect assessment of blind field stimuli on oculomotor responses was described by Rafal et al. (1990). In this experiment, patients fixated centrally, with an instruction to saccade toward a target in their intact field, following a cue (the cue in this case was the target box flashing). On half of the trials, distracter signals were presented in the blind field either preceding or proceeding the cue to saccade toward the target. Saccades were inhibited on trials with the preceding distracter signal., and further, only when the distracter signal was placed in the temporal half of the visual field. The authors attributed the inhibited saccade effect to the oculomotor system being primed by the preceding distracter stimuli, possibly via spared retino-colliculo projections.

Pöppel (1986) also describes a study using an indirect paradigm to assess the influence of implicit colour processing in the blind field. Typically, if a subject fixates on a white background surrounded by a ring of colour, an after-image effect ensues, whereby the surrounding colour appears to be its compliment (e.g., red would appear green) while the white central background would appear the colour of the surround. Interestingly, Pöppel (1986) demonstrated that when the surround colour was placed in the blind field of a patient with HVFD, the perceived hue nonetheless changed in accordance with the after-image effect.

The above two studies respectively used saccade inhibition and the colour after-effects as their dependent measures. Implicit processing of unseen stimuli is also commonly assessed using the redundant target paradigm (Todd, 1912), which uses response times as the

dependent measure. This paradigm draws on the phenomenon that when healthy subjects are presented with two identical (i.e., congruous) stimuli, response times are facilitated, in comparison to when incongruous or single stimuli are presented (the redundant target effect; (RTE); Todd, 1912; Raab, 1962; Mordkoff et al., 1996). For example Marzi et al. (1986) demonstrated that normal subjects react more quickly to two identical bilaterally presented visual stimuli, i.e., presented across the vertical meridian, than to a unilateral single stimulus. Further, the effect is also observed when the two identical stimuli are placed in the same hemifield. This effect is attributed to spatial summation, and has also been tested with patients with HVFD (Marzi et al., 1986; Corbetta et al., 1990). Marzi et al. (1986) tested twenty patients with retrochiasmatic lesions and demonstrated a group level RTE when the simultaneous stimuli were both presented in their intact visual fields (ruling out general perceptual impairment). However when the stimuli were presented across the vertical meridian, only one patient consistently demonstrated an RTE, with three other patients demonstrating the effect in at least one testing session. Similar results were observed in Corbetta et al. (1990), where all patients again showed the RTE with simultaneous unilateral stimuli, but only two out of four demonstrating RTE when simultaneous stimuli were presented across the meridian. Interestingly, two out of four patients with hemispherectomy demonstrated RTEs to bilateral simultaneous stimuli (Tomaiuolo et al., 1997), suggesting that the spatial summation can operate in some patients purely within subcortical networks involving the superior colliculus.

Indirect procedures have also been employed to assess higher order function. Marcel (1998) conducted a series of experiments with two HVFD patients (one of whom, GY, is listed above as a participant in many direct assessment studies). Interestingly, neither patient could consistently discriminate letters or words presented in their blind field above chance,

however when a word was presented in the blind field to prime a subsequently presented ambiguous target word in the intact field, both patients were semantically biased toward the priming word – for example the ambiguous target word CALF could be interpreted as a baby cow or the muscle on the lower part of the leg – the preceding blind field primes in this case could be COW or LEG, and depending on which prime was used, the patients would be consistently semantically biased when defining CALF. These experiments therefore suggest that not only are indirect measures insulated from certain biases (listed above), but they may also prove more sensitive to certain higher order residual function.

In summary, the findings from both the direct and indirect assessment of residual function demonstrate that a range of visual functions are possible without geniculate inputs to primary visual cortex. These functions range from simple signal detection, to higher order functions like colour and semantic processing. This research strongly suggests that either alternative pathways are mediating the implicit signals to higher order areas. In Chapter 1 I will present data from an a specific residual function, implicit emotional signal processing (which I will introduce in more detail in the introduction to Chapter 1), and demonstrate that when patients are screened of blindsight functioning with forced-choice procedures, the only signals that can be implicitly processed are fear signals, via the spared retino-colicullo-pulvinar pathway to the amygdala.

The blindsight literature also demonstrate that not all patients with the same lesion profile demonstrate the same residual visual function, suggesting that spontaneous plastic reorganisation appears to be possible following a retrochiasmatic lesion. However, the precise nature of cortical reorganisation following retrochiasmatic stroke has only been

investigated in a small number of studies. To that end, in Chapter 2, I aim to shed light on this phenomenon by presenting data from a case study of a patient whose visual cortex has been disconnected from its thalamic input by a lesion to the optic radiations. I will present data on the spatial selectivity of both the ipsilesional and contralesional cortices using a functional magnetic resonance imaging paradigm (fMRI) and further document the functional connectivity at rest in both hemispheres. In addition, I will present data of the patient's concentrations of excitatory and inhibitory neurotransmitters at rest, using magnetic resonance spectroscopy (MRS). The rationale for this study will be presented in more detail in the introduction to Chapter 2. To continue with this general introduction, I will now turn my attention to the multisensory nature of structures within subcortical visual networks, and how they offer an interesting and emergingly effective avenue for rehabilitation for HVFD patients.

Subcortical multisensory structures spared following retrochiasmatic lesion

As described above, a lesion to cortical sites posterior to the optic chiasm will generally spare subcortical networks involving the superior colliculus and pulvinar. In particular, the superior colliculus contains inputs from the visual., auditory and tactile domains. The primate superior colliculus can be parsed into superficial layers and deeper layers. Neurons within the superficial layer respond solely to visual stimuli, while 37% of neurons in deeper layers respond to visual stimuli, 18% to auditory stimuli and 18% to somatosensation. The remaining neurons within the deeper layers of the superior colliculus (28%) respond to more than one sensory modality, i.e. multisensory (Wallace et al., 1996). Further, the receptive fields of multisensory superior colliculus neurons overlap spatially for each contributing modality, resulting in increased firing from these neurons when the components of a

multisensory stimulus (e.g., the sound and the visual stimulus in an audiovisual stimulus) are presented in the same region of space. In contrast, multisensory neurons are inhibited when the component stimuli are separated spatially, and the neurons' firing is consequently diminished; this concept is referred to as the spatial rule (Meredith & Stein, 1986; Stein and Meredith, 1993).

Another factor governing the firing rate of multisensory neurons in the superior colliculus is temporal congruency. As the unisensory components of a multisensory stimulus are spaced farther apart in time, the overlap of their respective peak discharge periods reduces. This results in response depression. Conversely, components that are presented in temporal unison will have higher overlap of their respective peak discharge periods and a consequent response enhancement; this concept is referred to as the temporal rule (Meredith et al., 1987; Stein and Meredith, 1993).

Integrating information from different senses is an adaptive process that allows for a clearer sensory percept (Stein & Meredith, 1993; Stein et al., 1993). When signals from more than one modality are integrated in a multisensory perception, the consequent increase in neural activation underscores a number of behavioural advantages, such as enhanced visual detection, auditory processing, speech recognition and response times (Reisberg, 1987; MacLeod & Summerfield, 1990; Molholm et al., 2002; Bolognini et al., 2005; Bolognini, Frassinetti et al., 2005). Leo et al. (2011) also demonstrated that visual orientation sensitivity can also be enhanced with concurrent presentation of spatially and temporally congruent sounds, extending its effect to higher order visual processing.

Importantly for the clinical context, the facilitation from a multisensory percept mediated by the superior colliculus appears to have an inverse relationship with the strength of the composite unisensory inputs. Multisensory neurons in the superior colliculus fire at a gradient depending on the relative strength of unisensory signals. Responses within multisensory neurons are enhanced when weak unisensory components of a multisensory stimulus are combined, and diminished in the presence of strongly effective unisensory stimuli; the inverse effectiveness rule (Stein and Meredith, 1993). Thus, when a unisensory process is not strong enough to induce a behavioural response, concatenating the unisensory input with a spatially and temporally congruent input from an additional modality may therefore drive enhanced firing within multisensory channels and consequently augment responses in the weak sensory system (Làdavas et al., 2012). In the case of patients with HVFD, the unisensory visual signal disrupted by the lesion to primary visual areas may be facilitated by coincidently aligning visual stimuli with a spatially congruent auditory stimulus, in order to boost responses within multisensory neurons in the superior colliculus and accordingly augment visual perception (Làdavas, 2008; Làdavas et al., 2012).

Online multisensory facilitation

The above hypothesis has been tested with HVFD patients, first in an online context (Frassinetti et al., 2005). The term 'online' refers to multisensory systems enhancing unisensory responses in patients in an immediate manner, i.e., during behavioural paradigms. Online facilitation was first observed in HVFD by Frassinetti et al. (2005) in an experiment where a sample of HVFD patients performed a visual detection task where they fixated at the centre of a display, and were instructed to only respond to any light stimulus that could

appear at varying eccentricities on either side. Three stimulus conditions were presented - a unisensory auditory catch trial., to screen for false positives, a unisensory visual stimulus and a multisensory trial where the light stimulus was accompanied by a burst of white noise, which could be either spatially congruent, or displaced temporally or nasally. Patients could detect a significantly higher number of multisensory trials with spatial alignment, relative to both the unisensory visual condition and spatially misaligned multisensory conditions. The better performance on aligned trials relative to misaligned trials confirms that this effect was a multisensory facilitation, and not merely a consequence of higher overall attentional salience of the combined light and sound stimulus.

Online multisensory facilitation has also been demonstrated to work in the opposing direction, i.e., visual stimuli guiding impaired auditory localisation. Bolognini, Frassinetti et al. (2005) presented the case of a patient with right hemispheric lesion, who had no symptoms of neglect, but a consequent deficit in auditory localisation, which affected the entire field of space (i.e., bilateral). The patient completed an auditory localisation task under a unisensory (i.e., only auditory stimuli) and multisensory condition, using the same apparatus as Frassinetti et al. (2005). In a similar pattern of results, facilitation was observed on trials where a spatially and temporally congruent visual cue was presented with auditory stimuli, again demonstrating the utility of the multisensory mechanism in augmenting disrupted unisensory signals.

In addition, conscious awareness does not appear to be necessary to stimulate multisensory facilitation. In a study by Leo, Bolognini et al. (2008), patients with HVFD localised auditory stimuli in both their blind and intact visual fields. As with the two previously described

studies, trials could be unisensory (auditory), multisensory (auditory and visual) or multisensory with a spatial misalignment. In an expansion of previous studies, this experiment also introduced levels of temporal misalignment, to probe the importance of the temporal rule. A field-specific difference was observed; in the intact field, a bias was observed for spatially misaligned stimuli, regardless of temporal alignment, resulting in reduced localisation accuracy. In contrast, multisensory stimuli in the blind field only biased performance when the auditory and visual components were temporally and spatially aligned, and in a manner that increased localisation accuracy. The authors attributed this differing pattern of results between the two hemifields to the recruitment of field-specific visual networks - the cortical retino-geniculate pathway allowing for a finer analysis of all trials appearing in the intact field, and thus underscoring a deleterious bias when spatially incongruent multisensory components were presented. Meanwhile, the subcortical retino-colliculo pathway could only boost signals in a facilitating manner for spatially and temporally aligned stimuli presented in the blind field.

Just as with healthy subjects (Leo et al., 2011), the online effects of multisensory faciliation in HVFD patients have also been demonstrated to extend to higher order visual functioning. A study by Cecere, Romei et al. (2014) presented a case study of a patient with a bilateral lesion to striate region V1, with islands of spared function within the striate cortex. The ensuing diffusivity of the visual field loss allowed the researchers to present visual stimuli in regions of the visual field that were either completely blind, or fostered relatively preserved visual functioning. The patient discriminated the orientation of a straight line, while spatially and temporally coincident looming, receding and stationary sounds were presented. These data demonstrate that early visual areas are crucial in mediating orientation sensitivity enhancement by looming sounds. The second finding of this study, that only looming sounds

(and not stationary or receding sounds) underscored orientation facilitation, again implicated the spared retino-colliculo-extrastriate pathway; superior colliculus has been demonstrated to be preferentially stimulated by looming auditory signals.

Offline multisensory facilitation

The above studies demonstrate first that a lesion to primary visual areas does not appear to disrupt the integration of auditory and visual stimuli in subcortical structures, and further, that this integration has a facilatory effect in orientation and localisation of stimuli in the blind field. This prompted researchers to probe the offline effects of multisensory facilitation for patients with HVFD. The term 'offline', in this context, refers to multisensory systems being systematically stimulated in a training interval., in order to drive an enhancement of sensory responses tested after the training, either over short or long-term periods of time.

For example offline effects of multisensory facilitation were observed in a short-term context by Passamonti, Frissen and Làdavas (2009). In this experiment, patients with either HVFD or hemispatial neglect underwent a training interval of approximately four minutes of multisensory audio-visual stimulation of both sides of visual space. These training intervals were either spatially disparate (i.e., sound always at the centre, and the light always at a temporal shift of 7.5 degrees into either visual field, to train a temporal ventriloquism bias) or spatially coincident (i.e., light and sound always falling at the same location; in other words adhering to the spatial rule described above). Before and after training, patients performed a unisensory auditory localisation task. Results showed a deficit-specific effect of the spatially disparate training for auditory localisation; in their normal visual fields, all patients,

regardless of deficit, showed a temporal bias, i.e. a bias toward the visual cue from the training. However in the affected field, this temporal shift was still evident in neglect patients, but not evident in the patients with a HVFD. In contrast, auditory localisation was significantly improved for both patient groups, in both fields, following spatially coincident training. These results again support the roles of two-visual pathways – HVFD patients only saw a disparate training bias at the location of visual space where they could still recruit the retino-geniculo-striate pathway, while their spared retino-collico-striate pathway could drive coincident training bias in either field. The neglect patients, in contrast, could access both the retino-geniculo-striate pathway and the retino-collilculo-striate pathway in both fields of space and accordingly biases were observed for both training protocols in both fields of space.

Emerging evidence suggests that offline facilitation is also observed in a long-term clinical context, with multisensory stimulation treatment for HVFD, developed by Bolognini et al. (2005). This treatment harnesses offline multisensory facilitation within the compensatory framework for HFVD. Thus, before describing the treatment itself, I will first provide a brief general background on the aims and efficacy of compensatory treatment for HVFD.

Compensatory treatment for HVFD (unisensory)

Compensatory approaches for HVFD are based on developing oculomotor strategies, to facilitate saccadic eye movements. These strategies do not aim to reduce the size of the blind field, but rather to expand the field of view, which is defined as the part of the visual scene that can inspected by scanning eye movements. Typically, this is accomplished by training

patients to voluntarily explore visual arrays displayed on a computer screen (Zihl, 1995, 1999) or in far vision (Nelles et al., 2001). The rationale is that encouraging patients to explore location in their blind hemifield during training, produces a lasting spatial bias during visual search (Zihl, 1995). During treatment, patients are trained to make saccades into the affected blind field and systematically scan the visual scene in order to compensate for the visual loss (Gassel & Williams, 1963; Ishiai et al., 1987). For example, if the vision loss is on the right, patients are taught to move their eyes more frequently to the right so that they may see objects more easily with their intact, left visual field sector.

The total training duration for treatment is typically around one month, requiring daily one-hour sessions. After about five to six weeks, patients generally report improvements in scanning accuracy, exploration times and activities of daily life (Kerkhoff et al., 1992, 1994; Zihl, 1995; 2000, Nelles et al., 2001; Pambakian et al., 2004; Verlohr & Dannheim 2007). Notwithstanding these improvements, some concerns have been raised regarding the treatment's efficacy. For example, the unchanging visual field (scotoma) size means that scanning more often into the hemianopic side (say, to the right) results in the visual space of the intact visual field sector on the other side (left) moving temporarily out of view. In other words, there may be a tradeoff between increased field of view on the hemianopic side and diminished field of view on the unaffected side. Furthermore, increasing the volume of eye scanning may also increase the demands posed by the need to integrate visual information across saccades.

Comparing the efficacy of different compensatory training protocols is further complicated by the lack of standardized outcome measures. Zihl (1995) introduced a simple sampling

task, i.e. dot counting, to differentiate between good and bad scanning performers. Higher performing hemianopic patients showed performance comparable to healthy controls, suggesting that factors beyond visual loss accounted for decrements in visual performance in some of the hemianopic patients. In a study by Nelles et al. (2001) compensatory treatment was performed on a three-metre wide training board placed at a distance of 1.5m from the observers. Training was conducted while head movements were restricted, and resulted in improved detection rate and reaction time to visual stimuli presented on the training board. The efficacy of this treatment protocol was compared to the a training procedure where participant performed the same detection task but eye movements were restricted. The latter procedure did not result in detection improvement suggesting that the ability to perform eye movements is crucial to the effectiveness of the training procedure.

The current emphasis is on training protocols with varying processing demands, presented on realistic, large field stimulus displays and allowing unrestricted head movements. Papageorgiou et al. (2012) recently observed efficient compensatory gaze patterns in patients with hemianopic visual field defects performing a more complex real life task (dynamic collision avoidance); these patterns showed increased exploratory eye and head movements towards the blind side. In some studies additional training was included to implement strategies learned in compensatory treatment in everyday life situations, such as crossing the street or finding objects (Kerkhoff et al. 1992, 1994; Pambakian et al. 2004). In summary, compensatory treatment techniques offer a relatively short intervention, with changes in scanning behavior that may generalize to everyday activities. However, the techniques vary considerably between laboratories, and standardized outcome measures would be desirable to evaluate the efficacy of various treatments.

Multisensory stimulation treatment for HVFD

Multisensory stimulation treatment for HVFD (MsST) is a recent development in the field of compensatory interventions for visual field defects. In contrast to the previous interventions, such as compensatory treatment, which are based on unisensory, visual stimulation, MsST is a multisensory procedure. One advantage of MsST over compensatory treatment, therefore, is that it capitalizes on the availability of multiple sensory channels, thus replicating naturalistic conditions. Further, perception frequently involves at least some element of multisensory integration (Frassinetti et al., 2005).

Subcortical networks have also been implicated in the plastic change associated with orienting response deficits associated with retrochiasmatic damage. Sprague (1966) was the first to report that a unilateral lesion to the striate and extra striate visual cortex abolishes orienting responses to stimuli presented in the contralesional visual field in cats. He further observed that ablation of the contralesional superior colliculus, or severance of the intertectal commissure (connecting the left and right superior colliculus), restored orienting responses to contralateral visual stimuli. This remarkable effect, namely restoration of orienting responses in hemianopia following ablation of the contralateral superior colliculus – the so called "Sprague effect" - has been replicated by several laboratories (Sherman, 1977; Wallace et al., 1990; Rosenquist et al., 1996; Ciaramitaro et al., 1997; Lomber et al., 2002, see also Sprague, 1996 for a review) and is not a controversial finding.

Others have demonstrated that ablation of the contralateral superior colliculus is not

necessary to restore orienting responses. For example, Lomber & Payne (1996) first cooled the feline homologue of the parietal cortex, producing contralateral neglect. They were able to remediate the contralateral deficits by cooling either the contralateral superior colliculus, or the contralateral parietal cortex. Chiaramitaro et al. (1997) were able to restore orienting responses toward locations with the visual field rendered hemianopic by unilateral visual cortex lesions, by injecting a GABA antagonist in the ipsilesional superior colliculus. This latter study demonstrates that the loss of orienting responses is likely mediated by an increased inhibitory drive on the ipsilesional colliculus, possibly originating in contralateral sites. Other studies have suggested that subcortical structures such as the substantia nigra pars reticulata and the pedunculopontine tegmental nucleus may also be sources of inhibitory inputs to the superior colliculus and in fact orienting responses are restored if these sites or their projections via the intertectal commissure are ablated (Wallace et al., 1989; 1990; Durmer & Rosenquist, 2001). Involvement of these particular midbrain structures rules out the original explanation of the Sprague effect, namely that ablation of the contralateral superior colliculus releases the normal flow of visual information from the superficial layers of the ipsilesional superior colliculus to the cortex, via the pulvinar (Diamond & Hall, 1969; Trojanowski & Jacobson, 1975; Robson & Hall, 1977). Rather, the effect is much more likely to be mediated by inhibitory projections into the intermediate and deeper layers of the superior colliculus, where orienting responses are coded (Krauzlis et al., 2013).

In one of the few studies investigating correlates of this effect in humans, Weddell (2004) reported the case of a patient in whom a tumour in right frontal cortex caused left sided neglect. Seven months later, the neglect abruptly resolved, and a CT scan showed an additional lesion in the brain stem, possibly involving the left superior colliculus, suggesting that the Spargue effect generalizes to humans.

Thus, guided by the Sprague literature and also by the above literature on the online and offline effects observed in the multisensory facilitation literature, Frassinetti et al., (2005) examined whether systematic stimulation with audio-visual stimuli would lead to lasting amelioration of patients' orienting responses to unisensory, visual stimuli and improved detection. Patients sat in front of the concave face of an elliptically shaped screen placed in a dimly lit, sound-proof room. Eight piezoelectric loudspeakers were positioned at eye level at eccentric positions right and left of the participant. In addition, eight red LED were placed in front of the loudspeakers. During the training blocks the patients were required to first fixate upon the central point of the display and then explore the display by moving their eyes. In each block, the patients were instructed to search for stimuli presented either visually or visually and auditorly. Auditory stimuli were presented alone in catch trials. Participants were instructed that the sound might sometimes predict the location and presence of the luminance target. To boost oculomotor exploration of the hemianopic visual field, a greater proportion of stimuli were presented in the blind visual field so that the patients learned to orient more frequently to that side over time. Training duration was approximately two weeks at a rate of 4 hrs / day, five days a week. Training was considered complete when the hit-rate for unisensory visual targets presented in the blind field exceeded 50% in at least one training session. After the treatment, patients showed increased visual sensitivity, improved visual search and reading abilities and a reduced disability in activities of daily living (ADL). The improvements were stable at the 1-month follow-up (Bolognini et al., 2005). In addition, a follow-up study conducted by Passamonti et al. (2009) revealed that the same treatment lead to improved ocolomotor scanning, indexed by eye-tracking in a separate sample of patients. Oculomotor improvements were characterized by fewer fixations and re-fixations, faster and larger saccades, and a reduced scanpath length, leading to a shorter search time for visual

stimuli in visual search tasks. Similarly, oculomotor behaviour in reading were affected by the training, with a reduction in both progressive and regressive saccades. Further, improvements were maintained at the one-year follow-up assessment.

However, it is worth noting that the improvements were seen only in tasks where eye movements could be used to compensate for the visual field loss, with no improvement apparent when patients instructed to maintain fixation. This finding suggests that the improvement in performance following the training is not due to an enlargement of the visual field, but rather to efficient oculomotor strategies learnt during training. Interestingly, the improvement appeared to be critically dependent on the use of multisensory targets during training, since no improvement was noted when only unisensory, visual and auditory targets were used in a control condition (Passamonti et al., 2009). It could also be argued that having stimuli that tap two independent sensory modalities, rather than just one, increases the overall salience of the targets and therefore evoke an orienting response more reliably. Auditory augmentation of visual stimuli presented in the hemianopic field may potentiate spatially tuned orienting mechanisms, directing gaze and attention to locations in the hemianopic field. This effect is likely driven by recruitment of the spared retino-colliculo-extrastriate pathway. Indeed, recent findings strongly support a superior colliculus involvement in multisensory spatial integration (Sylvester et al., 2007, Leo et al., 2007; Bertini et al., 2008). In addition, extrastriate visual areas, which receive collicular projections, may also be liable to the effects of multisensory stimulation in humans (Calvert, 2001; Bertini et al., 2010). Intensive multisensory stimulation during training could have enhanced the activity in those portions of the network subserving orienting responses to locations in the hemianopic and sensory analysis of corresponding locations in extra-striate visual regions (Barbas and Mesulam, 1981).

In summary, initial evidence suggests that training using multisensory stimulation could represent an effective methodology to ameliorate the functional impairment associated with visual field defects. However, the basis of the changes underpinning the effects of MsST remain unclear. In Chapter 3, I will therefore present data from an EEG study, where I index the plastic electrophysiological change driven by a typical course of multisensory stimulation treatment. I will employ a simple visual detection paradigm, presenting simple visual stimuli to both fields of space and recording the electrophysiological response – both the stimulus locked event related potentials (ERPs) and also the preparatory oscillatory signals which emerge during the foreperiod of stimulus onset. How these components are affected by treatment will give further insight into the nature of functional defects in HVFD and the substrate underscoring the plastic change driven by multisensory treatment.

Chapter 2: Implicit emotional processing in right and left HVFD patients with no cortical contribution

Direct and indirect studies demonstrate that a range of residual visual function can be spared following a retrochiasmatic lesion. In addition to the body of research presented in the introduction chapter, more recent literature has further demonstrated that emotional signals can also be processed in the absence of conscious vision. In this first experimental chapter, I will demonstrate that when the geniculo-striate pathway is damaged by a retrochiasmatic lesion, and the damage is such that no blindsight performance is observable for visual function on forced-choice tasks, the only emotional signal that can be implicitly processed is fear and further, this effect is observed in patients with a left hemisphere lesion. In the discussion, I will present a rationale for this preserved signal being processed via a spared sub-cortical network, from the superior-colliculus via the pulvinar into the amygdala. First, I will review the extant literature on implicit emotional processing in patients with retrochiasmatic lesion.

Experiment 1: Implicit emotional processing in right and left HVFD patients with no cortical contribution

Blindsight, as described in the introduction to this thesis, is the phenomenon where patients can discriminate certain features of a stimulus above the chance level while not being consciously aware of the stimulus' presence (Weisenkrantz et al, 1974). Such feature discrimination has been observed with signal processing, colour, motion, orientation and even

gender. However in a landmark study by deGelder and colleagues (1999), blindsight patient GY displayed above chance discrimination of the emotion of static face stimuli presented to his blind field. In five out of eight experimental blocks, the patient performed above chance in a two-alternative forced-choice (2AFc) design, between fearful faces and happy faces, angry faces and fearful faces and angry faces and sad faces. In a second experiment in the same study adding a dynamic component, GY was also able to discriminate the emotional expression on the face of a woman in a video presented in his blind field. Four emotional conditions were employed, whereby the woman either had a fearful, angry, sad or happy expression on her face while reading a passage of text, without any change in the vocal tone. Interestingly, in both the static and dynamic experiments, GY could better recognise happiness and sadness, than he could anger and fear. The authors described this above chance discrimination of emotional signals as 'affective blindsight'.

In a follow-up study by deGelder et al (2001), GY's implicit emotional processing was further demonstrated in a series of indirect tasks. Recall from the general introduction that indirect measures are preserved from both response bias and confounds in determining the criterion for 'awareness'. Further, in some cases, indirect measures have been demonstrated as more sensitive to residual visual processing than direct means (e.g., Marcel, 1998). deGelder et al (2001) presented two experiments. In experiment 1, a half-face in the intact could be matched in the blind field by a congruent (both halves displaying the same emotion) type I incongruent (half-faces had different emotional expressions, e.g., happy/fear) or type II incongruent (one face had an emotional expression, the other neutral) half-face in the opposing hemifield. In experiment 2, a full face was presented in the intact field, and either a congruent, incongruent or no face was presented in the blind field. In both experiments, a response cost to incongruent faces was observed, demonstrated by slower reaction times

judging the emotional expression of stimuli in the intact field. The authors interpreted this as evidence of subcortical pathways processing emotional stimuli presented in the blind field, leading to attention capture in the case of incongruity and consequent impoverished response to the stimuli in the intact field, and spatial summation in the case of congruency and consequent facilitation of responses.

In an attempt to isolate the substrate underscoring implicit emotional processing, deGelder et al (2002) used a paradigm where emotional visual cues preceded auditory emotional words. Patients GY and DB attended to a central fixation and performed a trivial judgement discriminating the gender of a voice reading out a single word stimulus. Words were read out in either a happy or fearful tone of voice. The auditory stimulus was preceded by either an emotional face, or an image of an emotional scene, in either the patient's intact or blind hemifield. The auditory evoked N1 component was significantly increased for congruent face and scene cues preceding the stimulus in the intact field, however for trials where the cue was presented to the blind field, only face cues drove increased N1 amplitudes. The authors argued that the naturalistic pairing of a face with an emotional voice could be mediated by a non-striate circuit, while the semantic pairing of a scene to a word required feed forward cortico-cortical activation from fusiform or other higher order areas of the cortex not available in the lesioned hemisphere. Thus in support of the implicit processing being mediated by a non-striate, subcortical pathway, a cueing effect on the N1 was only observed for face cue stimuli in the blind field.

Affective blindsight has also been observed in another patient (TN; Pegna et al, 2005) who was left cortically blind following bilateral destruction of primary occipital cortex following

two consecutive strokes. However despite being blind in his entire visual field, TN was significantly above chance level discriminating the emotional content of static faces presented in his blind field. TN was able to discriminate angry from happy, sad from happy and fearful from happy, in separate forced choice testing blocks. In further experimental blocks, TN was observed to be at chance level when discriminating the gender of emotionally neutral stimuli, or discriminating authentic faces from scrambled images. Interestingly, TN was also unable to discriminate whether animals were in a threatening or non-threatening body posture, or whether the emotional valence of a scene was positive or negative. Thus, TN appears to have an exclusively preserved ability to discriminate the emotional component of face stimuli.

However very few studies aside from those described above have demonstrated affective blindsight. Further, studies demonstrating affective blindsight have largely drawn from the same small pool of patients (GY, DB and TN). Further still, two of these patients (GY and DB) have been extensively studied in the blindsight literature (reviewed in the general introduction) where they have demonstrated a host of residual functioning (relating to orientation, colour, movement and gender). Accordingly, studies using larger groups of patients have recorded conflicting results. In a study by Bertini et al (2012), a group of eight patients with retrochiasmatic lesions were administered the same redundant stimulus paradigm as deGelder et al (2001). In contrast to the congruency effect observed by the previous group, these patients demonstrated response facilitation only when unseen fearful stimuli were presented coincidently with happy faces in the intact field – a fear/incongruency effect (Bertini et al, 2012). Importantly, the sample of patients had been screened using a series of forced choice paradigms; all patients were at chance when discriminating the presence of a signal, geometric forms, gender or the emotional content of faces, thus, not

demonstrating any blindsight. In addition, unseen fearful stimuli were observed to facilitate responses even when the emotional component of the face was task irrelevant. In a task discriminating the gender of neutral faces in the intact field, a specific response facilitation was observed when fearful faces were presented in the blind field. Results from these experiments prompted authors to draw a distinction between 'blindsight patients', who demonstrate above-chance emotional discrimination and congruency-dependent facilitation effects with redundant target paradigms, and 'hemianopes', who demonstrate chance-level emotional discrimination and a fear-specific facilitation on redundant target paradigms. A similar pattern of results was observed in an electrophysiology study conducted by Cecere et al (2014) where a sample of hemianopes (confirmed by prior forced-choice screening) again showed a fear-specific effect, this time illustrated by enhanced amplitudes of a face-encoding component (N170); further, this effect was only observed for patients with a left lesion.

The distinguishing feature between hemianopes and blindsight patients could lie cortical contribution, specifically, blindsight patients' access to spared or reorganised geniculo-striate and or geniculo-extrastriate connections which is not available in hemianopes. In a study by Cecere et al (2013), a redundant target paradigm was presented to normal subjects, where backwardly masked emotional faces (masked in order to prevent conscious perception) were presented in the right hemifield, while unmasked stimuli appeared concurrently in the left. Under these conditions, an emotion congruency effect was observed, similar to the performance of blindsight patients, demonstrated by faster reaction times to pairs of emotionally congruent stimuli, regardless of the emotion (fearful/fearful or happy/happy). However when transcranial direct current stimulation was used to inhibit activity in the left occipital cortex, the congruency effect was no longer observed; in contrast, a facilitation in reaction times was now only observed when a happy face was presented in the unaffected

hemifield (i.e., the left field, ipsilateral to the stimulation) and a fearful face concurrently placed in the affected hemifield contralateral to stimulation. Thus, early studies with blindsight patients suggested that emotional signals can be processed in the absence of conscious awareness, with authors arguing that this phenomenon is mediated by a subcortical pathway involving the superior colliculus, pulvinar and amygdala (de Gelder et al, 1999; de Gelder et al, 2001; de Gelder et al, 2002; Pegna et al, 2005). However more recent findings suggest the behavioural profile of blindsight patients might reflect a peculiar and uncommon functional and anatomical reorganisation involving primary visual areas. When retino-geniculate signals to the striate cortex are disrupted to the extent that no blindsight performance can be observed in forced-choice tasks, or disrupted artificially via inhibitory stimulation, the only emotional signal that can be implicitly processed via subcortical visual pathways appears to be fear (Bertini et al, 2012; Cecere et al, 2013; Cecere et al, 2014).

A core medial temporal lobe structure for the perception and evaluation of fearful information is the amygdala. Widely considered a central substrate of the emotional network, studies have demonstrated that the amygdala is heavily involved with the evaluation and response to emotional stimuli (Dolan, 2002; Zald, 2003; Phelps & LeDoux, 2005), in addition to playing a crucial role in Pavlovian fear conditioning (Wilensky et al., 2006). The amygdala also appears to respond preferentially to fearful stimuli (Whalen, 1998; Davis & Whalen, 2001; Zald, 2003; Öhman, 2005), in particular fearful facial expressions (Adolphs et al., 1995; Broks et al., 1998; Sprengelmeyer et al., 1999; Anderson & Phelps, 2000; Hariri et al., 2002; Graham et al., 2007; Loughead et al., 2008). Fearful signals are also known to elicit activation in the amygdala, concurrent with activation in areas associated with action representation in motor areas (deGelder et al, 2004). The implicit visual processing of fearful

signals via subcortical networks could therefore facilitate responses via a subcortical 'fight or flight' response network involving the amygdala.

However potentially contradicting the fear-specificity of implicit emotional processing in HVFD patients is a trend observed in the studies with hemianopes, whereby no facilitation was observed on trials where fearful stimuli were presented in both the blind and intact hemifields. In Bertini et al (2012), no facilitation of response times were observed in conditions where unseen fearful stimuli were presented concurrent with seen fearful stimuli (i.e., fear/congruent). In a similar vein, no enhancement of N170 components was observed for the fear/congruent condition in Cecere et al (2014). Also, normal subjects with inhibited left occipital cortex again only displayed a facilitation in fear/incongruent trials Cecere et al (2013). Thus, if fear is indeed the sole signal being implicitly processed in the blind field, it doesn't appear to facilitate responses to consciously presented fearful stimuli. This could be explained by inhibitory modulation (Cecere et al, 2013). Functional connectivity analyses suggest that during conscious attention to fear signals, negative co-variation is observed between the right and left amygdala, and the thalamic LGN and striate cortex, suggesting that these latter sites are negatively neuromodulating the subcortical visual pathway (Williams et al, 2006). In contrast, fear signals that are presented below psychophysical thresholds drive positive correlations between the right amygdala, superior colliculus and thalamic pulvinar, with no functional connectivity observed between the striate cortex and amygdala, suggesting that subconscious fear stimuli are processed via the subcortical colliculo-pulvinar pathway to the amygdala, free from negative neuromodulation from striate cortex (Williams et al, 2006).

On the other hand, the facilitatory effect observed in these studies could be a function of the amygdala being preferentially activated by the ambiguity that arose between the fearful face in the blind field and the happy face in the intact field (Cecere et al, 2013). In this context, ambiguity is defined as the degree to which the consequences of a forthcoming event cannot be predicted, requiring continued monitoring of the environment (Whalen et al, 1998; Hsu et al, 2005). In the studies with hemianopes, the combination of a consciously perceived happy face with an unseen fearful face could therefore be facilitating responses in an effort to resolve the ambiguity of the stimulus pair. Herry et al (2007) demonstrated that in both mice and humans, unpredictability is sufficient to elicit anxiety-like behaviour in the amygdala even in the absence of aversive events. Using an emotionally neutral auditory paradigm, sequences of tones could be presented in a predictable (rhythmic pulses), or unpredictable (random inter-stimulus intervals) fashion. When presented to mice, the unpredictable sequence increased both anxiety and avoidance like behaviours, together with increased single cell recordings in the lateral and basal nuclei of the amygdala. In humans, the unpredictable tones again increased anxiety-like behaviours (indexed by faster response time in a dot-probe task toward angry faces), in addition to sustained neural activity in the amygdala, demonstrated by fMRI.

In order to therefore dissociate an implicit fear facilitation from an implicit ambiguity facilitation, I conducted two experiments measuring residual visual function in a large group of patients with retrochiasmatic lesion and consequent visual field defects. In the first experiment, I administered a series of two-alternative forced choice tasks, in order to screen for blindsight. Patients were only recruited for the second experiment if their performance on the forced-choice tasks was at the chance level. The second experiment was a redundant target paradigm, in which emotional faces were presented in the blind field, while patients

performed a go/no-go gabor orientation discrimination in their intact field. If response facilitation is indeed mediated by the fear component of face stimuli, responses should be facilitated for target gabor detection only when fearful faces are presented concurrently in the intact field. On the other hand, no fear-specific facilitation would support the hypothesis that previously observed implicit fear facilitation was mediated by the ambiguity between the two simultaneously presented emotional stimuli.

In addition, the sample in the present study is of sufficient size to perform a comparative analysis between implicit processing of unseen emotional signals between left and right lesion patients. The side of the lesion could be important in mediating an implicit emotional signal, given the apparent right lateralisation of emotional processing (Gainotti, 1972; Gainotti et al, 1993). Recent studies have further demonstrated that right hemisphere processing is also associated with withdrawal behaviours, i.e., reflexive behaviours that distance the organism from an aversive and potentially harmful event (Davidson et al, 2000). The right hemisphere has also been demonstrated to be preferentially activated in the perception of unconsciously perceived faces (Morris et al, 1999; Pegna et al, 2005; Williams et al, 2006). If indeed the right hemisphere does play a critical role in mediating the unseen fear signal into a response, the patients with left lesions might exhibit a greater response facilitation when unseen fearful faces are presented in their blind field.

Materials and methods

Participants

Sixteen right-handed patients with chronic visual field defects

(4 females; mean age: 47.8 years; sd: 13.4) took part in Experiments 1a and 1b. All patients presented with chronic visual field defects, consequent to post-chiasmatic lesions causing either deafferentation or destruction of the visual cortex. Eight patients (3 females; mean age: 48.25; sd:13.7) presented with right lateralized lesions and subsequent left visual field defect, and eight patients reported left lateralized lesions and subsequent right visual field defect (1 female; mean age: 47.4; range: 14.1). All patients had normal or correct-to-normal visual acuity, and no additional unresolved neurological or psychiatric impairment. All patients provided informed written consent prior to participation and all procedures were approved by the Departmental Ethics committee at the University of Bologna and conducted in accordance with the Declaration of Helsinki.

Apparatus

Both experiments were conducted in a dimly lit room with sound attenuation. Stimuli were presented on a 17" PC monitor with a refresh rate of 60Hz, using Presentation software (V0.60, www.neurobs.com). Participants were seated 57cm from the screen and instructed to maintain fixation on a white central fixation cross, subtending 2° of visual angle, presented on a black background. Eye-fixation was monitored using a Pan/Tilt optic eye-tracker (Eye-Track ASL-6000), with a sampling rate of 60Hz. Participants who had difficulty maintaining a constant head position were assisted with a chin rest. Three patients (P2, P3 & P12) presented with quadrantopic visual field deficit. Accordingly, the fixation cross was positioned in the central point of the upper (in the case of lower quadrantopia) or lower (in the case of upper quadrantopia) edge of the computer monitor, to ensure that redundant stimuli were presented in their scotoma. All other patients fixated on a cross positioned at the

centre of the screen. Stimuli were presented either 10° to the left or right of the fixation cross.

Stimuli and trial structure

Experiment 1a – a two-alternative forced choice (2afc) experiment was conducted to ensure that patients displayed no residual visual abilities as assessed by a direct investigation method. Patients performed direct 1afc discrimination judgments on stimuli, which were presented in their blind field, with no concurrent stimulus presented in the intact field. Patients performed three different discriminations, in three separate blocks – in the emotional discrimination block, patients discriminated if a facial expression (from a sample of 12 greyscale photographs of six different identities (three female), taken from Ekman and Friesen, 1976) was happy or fearful; in the gender discrimination block, patients discriminated if the gender of an emotionally neutral face (from a sample of 12 greyscale photographs of six different identities (three female), taken from Ekman and Friesen, 1976) was male or female; in the simple visual detection block, patients discriminated the presence (absent/present) of a white dot. For the emotional discrimination and gender discrimination blocks, picture stimuli subtended 7.5° x 11° of visual angle, while in the simple visual detection block, the diameter of the white dot stimulus subtended 2° of visual angle. Each trial commenced with a fixation cross (500ms), followed by the presentation of the stimuli (1500ms), followed by a blank interval of 250ms. An auditory beep would sound at the end of stimulus presentation, after which patients provided a verbal response, which was recorded manually by an examiner. The examiner started each proceeding trial manually, once patients were fixating centrally (as read by the eye tracker). In each of the three experimental blocks, patients performed 180 trials (90 trials for each choice – fear/happy; male/female;

present/absent), totaling 540 experimental trials. Mean percentage of correct discriminations was computed separately for each block, and compared to the 50% chance level using a binomial test.

Experiment 1b – A go/no go experiment was conducted to test whether redundant emotional face stimuli (fear, happy, neutral) presented in patients' blind fields could influence the detection of target gabor patches (vertical or horizontal) presented concurrently in patients' intact field. Patients performed a total of six experimental blocks, three of which where the go target in the intact field was a horizontal gabor patch, and three of which where the go target was a vertical gabor patch. Emotional face stimuli presented in the blind field were taken from the same pool as Experiment 1a. Gabor patch stimuli presented in the intact field had a frequency of eight cycles per visual degree and subtended two degrees (of visual angle). Patients were instructed to maintain central fixation, attend specifically to the intact visual field and respond via button press when the go target appeared. Trials with eye movements were discarded from the analysis. The response button was the space button on the computer keyboard. Each trial commenced with a fixation cross (500ms), followed by the presentation of the stimuli (200ms), followed by a blank interval of 1000ms for a response. If no response was recorded during this 1000ms window, the response was coded as a 'no go'. Following the response window, a random gap, ranging in length 500 to 800 ms served as the inter trial interval, before the next trial, which commenced automatically. Patients performed blocks of vertical and horizontal go target conditions in alternate order, with series order counterbalanced across participants (i.e., ABABAB or BABABA). Patients performed a total of six blocks, three where the go response was vertical and three where the go response was horizontal. Each block contained 60 trials, 30 go, and 30 no-go, 10 trials per condition go-happy, go-fear, go-neutral, no go-happy, no go-fear, no go-neutral. Mean response times were

computed separately for each of the three redundant stimulus conditions for correct responses to go trials, collapsed across the two go conditions, for each participant. To control for the influence of outliers, trials where the response time exceeded 1.5 standard deviations above or below a participants' mean response time for that condition were excluded from the analyses.

Results

Results from 1afc direct assessment – experiment 1a.

Experiment 1a used a direct method to test if patients were able to detect or discriminate the nature of stimuli directly presented to their blind fields. Accordingly, patients were first asked to discriminate the emotional expression of a face stimulus (which alternated in gender), after which they were asked to discriminate the gender of a neutral face stimulus, after which they were finally asked to discriminate whether a white dot had been presented or not.

For each participant, and for each condition, the percentage of correct discriminations was compared to the chance level of 50%, using a binomial test; this addressed their ability to directly discriminate or detect stimuli presented in their blind field. Results confirmed that patients were not able to detect the presence nor determine the nature of stimuli presented in their blind field. Patients were at chance level discriminating the emotion (all p-values > 0.123) and gender (all p-values > 0.266) of face stimuli, and were also at chance level detecting the presence of the white dot all (all p-values > 0.215).

Indirect assessment – Experiment 1b

Experiment 2b used an indirect method to determine whether an emotional face presented to a hemianopia patient's blind field could affect responses to target go conditions in a gabor orientation go/no go task presented to their intact field. Response times were analysed with a 2x3 repeated measures ANOVA, using the factors, orientation of the go stimulus gabor (horizontal, vertical) and emotion of the face stimulus concurrently presented in the blind field (fear, happy, neutral). This ANOVA reported no significant main effects or interactions (all p-values above 0.237). To assess whether the emotional stimuli presented in the blind field might differentially affect patients with a lesion to different hemispheres, response times were further analysed with a 2x2x3 mixed ANOVA with between group factor lesion side (left, right) and within group factors gabor orientation (horizontal, vertical) and blind field stimulus emotion (fear, happy, neutral). This ANOVA returned a marginally significant interaction between group and the emotion of the stimulus presented in the blind field ($f(2,28) = 3.20$; $p=0.056$). A Newman-Keuls post hoc test reported that this interaction was driven by response times to go trials in the intact field, summarise below in figure 2.1, when a fearful face was concurrently presented in the blind field (577ms), were significantly faster than go trials with a concurrent happy (594ms; $p = 0.036$) and neutral faces (597ms; $p = 0.043$), for patients with a lesion to the left hemisphere. In contrast, response times to go trials in the intact field, when a fearful face was concurrently presented in the blind field (622ms), were not significantly faster than go trials with a concurrent happy (612ms; $p = 0.216$) nor neutral faces (622ms; $p = 0.956$), for patients with a lesion to the right hemisphere. No other post-hoc comparisons were significant, suggesting that the blindsight facilitation was unique to left lesion patients for fearful stimuli.

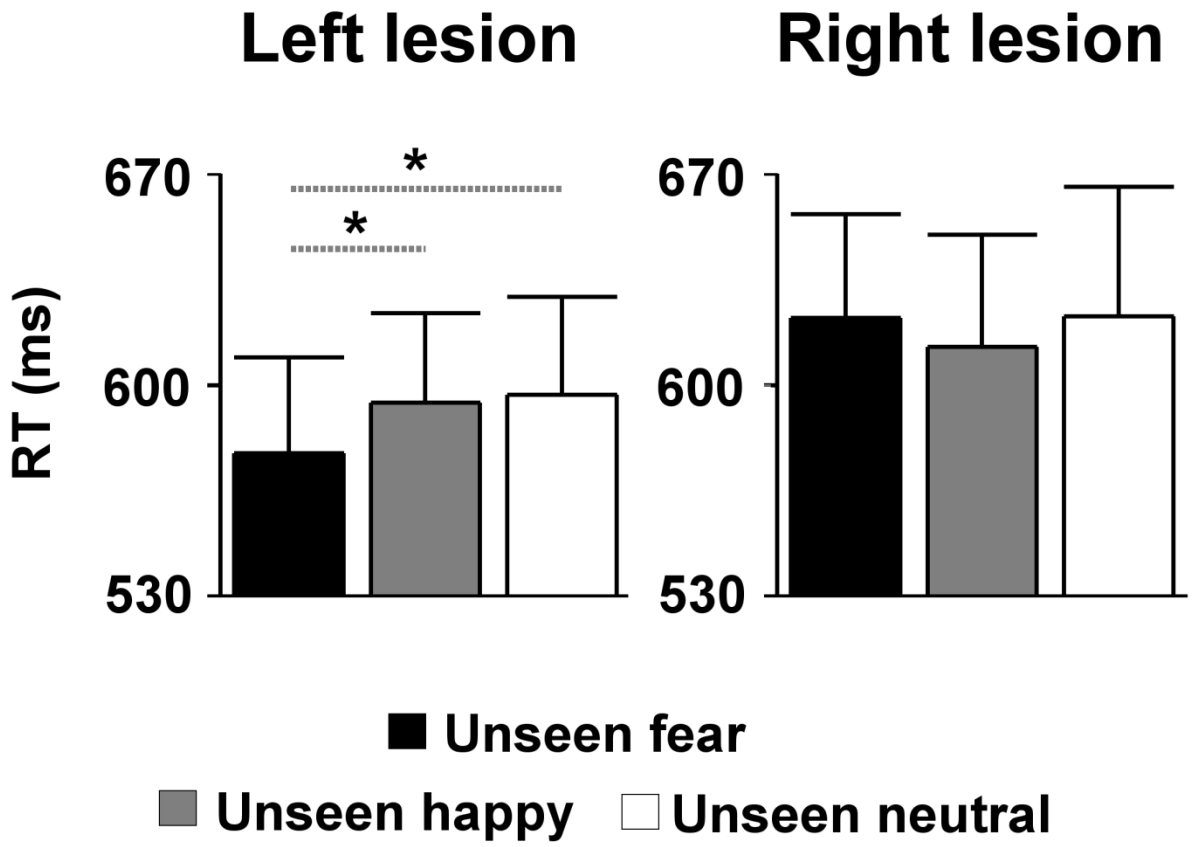


Figure 2.1. - Mean RTs of go/no go gabor orientation task, from Experiment 1b, separately for patients with left (left panel) and right (right panel) lesions for each redundant target condition (unseen fearful face, unseen neutral face, unseen happy face). Error bars represent the standard error of the mean. Data demonstrate that reaction times were significantly faster for the left lesion group, only when a fearful face appeared in their blind field, relative to conditions of an unseen neutral or happy face. No such facilitation was observed in patients with right lesions.

Discussion

The aim of this study was to probe the functionality of implicit emotional processing in a sample of patients with visual field defect who demonstrated no blindsight ability, suggesting they could not draw on abnormal cortical reorganisation when processing unseen emotional signals. Results confirmed that the bottom-up saliency of fearful faces presented in the blind field of such patients with right visual field defect facilitated their responses to target orientations of gabor patches simultaneously presented in their intact visual field. The facilitation of gabor discrimination was not observed when neutral or happy faces were presented to the blind field. Gabor patches are both inanimate and emotionally neutral, thus sharing no critical feature aspects with the stimuli presented to the blind field and minimising any ambiguity that may arise in simultaneously processing both stimuli. This first main finding therefore contributes to resolving the first experimental hypothesis set out in the introduction, namely that response facilitation from unseen stimuli is a fear-specific effect, and not attributable to the emotional ambiguity between stimuli. The second main finding from this experiment was that the effect was only observed in left lesion patients, further supporting the crucial role of the right hemisphere in mediating implicit fear signals. I will now comment on both of these main findings in more detail.

Only fear can take the low road

Detecting threat in the environment offers organisms a distinct adaptive advantage. As described in the introduction to this chapter, the amygdala is a core medial temporal lobe structure that mediates the perception and evaluation of fearful information. Drawing upon evidence from animal studies, lesion studies in humans and neuroimaging studies in humans, LeDoux (1996) argues that the amygdala receives visual inputs from two parallel pathways; a

so-called 'high-road', communicating high-resolution, low-latency information originating in the lateral geniculate nucleus of the thalamus, projecting into the amygdala via the striate cortex; and a so-called 'low-road', communicating low-resolution, high-latency information, originating in the superior-colliculus, projecting into the amygdala via the pulvinar. The trade off between latency and resolution can be interpreted functionally; inputs to the amygdala via the 'high road', draw upon contributions from multiple cortical areas in order to provide a detailed analysis of visual stimuli. Such a fine-grained analysis would afford a clear recognition and conscious perception of the stimuli, in order to guide a contextually appropriate behaviour response. However the cost of such an analysis would be the additional processing requirements and consequent high response latency. In contrast, inputs to the amygdala via the 'low road' would be coarsely evaluated in subcortical regions, thus precluding the stimuli reaching the level of conscious perception, but granting a higher latency relaying the information to the appropriate motor response.

Support for the dual pathway comes first from animal studies. Linke et al (1999) used anterograde tracers in rats and charted direct colliculo-thalamic and thalamo-amygdaloid connections. Shi & Davis (2001) later reported that fear conditioning in rats was subserved by two separate pathways to the amygdala; a thalamo-cortical-amygdala and a thalamo-cortical pathway. A coliculo-pulvinar-amygdala tract has also been documented in a both the shrew and in monkeys (Jones & Burton, 1976; Romanski et al., 1997; Chomsung et al., 2008; Day-Brown et al., 2010). In humans, fMRI studies have reported activity within the SC, pulvinar and the amygdala, when participants observed backward-masked fear stimuli, with increased functional connectivity between these regions suggesting that this network underscores the processing of subliminal (implicit) fearful information (Morris et al., 1999; Liddell et al., 2005; Williams et al., 2006). Another study by Vuilleumier et al (2003)

presented both high and low spatial frequency face stimuli to healthy subjects. Regardless of the emotional expression of the face, higher spatial frequency stimuli elicited greater activation in the fusiform cortex. Amygdala responses were greatest for fearful faces, with activation in the SC and pulvinar driven specifically by low contrast fearful faces. Computational evidence also appears to support the dual-path hypothesis; Garrido et al (2012) used Bayesian modelling on MEG data elicited by tones presented in the context of fearful stimuli. Two models were compared; one which comprised of a parallel cortical and subcortical pathway, and the other only a cortical pathway. The model comparison suggested that salient stimuli were better explained by the parallel model, with the subcortical pathway appearing to be recruited more in the early stages of visual processing.

The present data suggest that when the cortical 'high road' is damaged to the extent that patients cannot perform visual discriminations of gender, emotion or forms above chance level, the only signal that can be implicitly processed via the spared subcortical 'low road' is fear. The existing literature had offered good evidence that this might be so, however the absence of response modulation in fear-congruent conditions in all of the recent studies with hemianopes had left a possible alternative interpretation that the 'low road' may instead process the ambiguity of emotionally incongruent stimulus pairs. The present data refute the ambiguity hypothesis by demonstrating response facilitation on a task where the characteristics of the stimulus in the intact field could not drive any conflict with an emotional face. It is therefore likely that the absence of fear-congruent effects in previous studies were indeed a consequence of inhibitory neuromodulation of the 'low road' by regions of the geniculo-striate network (Williams et al, 2006). Indeed, re-entrant feedback to striate cortex is thought to underscore the conscious perception of visual stimuli (Lamme & Roelfsema, 2000). In a case where parallel inputs are available to the amygdala, such as in

the case of attention to a fearful signal, downregulation of the parallel inputs would allow stimuli to be elaborated exclusively by the 'high road' network, i.e. a network that can draw on the processing of both the amygdala and higher-order association visual areas (Williams et al, 2006) driving a more perceptually informed response. Thus, in previous studies, the trials where a fearful face was observed in the intact field, the intact field stimulus would dominate in terms of saliency, driving inhibition of the 'low road'. This would accordingly prohibit any emotion-specific response facilitation from stimuli presented in the blind field, which could only be processed via the now inhibited 'low road'.

Role of the right hemisphere

Responses to target gabor patches were only facilitated by unseen fearful faces in patients who had lesions in the left hemisphere. Notably, this cannot be attributed to damage within subcortical structures contributing to the 'low road', as all patients presented with retrochiasmatic lesions focal to the cerebrum. Thus, it would appear that implicit fear signals can only facilitate responses to targets that are processed by the right hemisphere. As mentioned in the introduction, emotional processing in humans appears to be lateralised to the right hemisphere (e.g., Gainotti, 1972; Làdavas et al., 1993). Further, in normal subjects who perceive backward masked negative emotional stimuli, significant neural responses can be observed in the right amygdala, in contrast to when emotional stimuli are not masked (Morris et al, 1998). Studies with patients with visual field loss have further demonstrated that when fearful faces are presented in the blind field of patients with striate lesions, higher activation is observed in the right amygdala (Morris et al, 2001; de Gelder et al., 2005; Pegna et al., 2005). deGelder et al (2005) observed a fear specific activation of the right amygdala when fearful faces were presented to the blind field of patient GY, confirming previous

results observed by Morris et al (2001). Pegna et al (2005) further observed significant responses in the lateral part of the right amygdala when patient TN (a bilateral lesion patient with complete cortical blindness) was presented with emotional faces, specifically fear, suggesting the role of the right amygdala in implicit fear processing is not a consequence of the hemisphere of the lesion.

The paradigm employed in this study is not sensitive enough to isolate the specific anatomical connections that mediate implicit fear signals facilitating responses. However the above imaging studies suggest that the right amygdala is preferentially activated by fearful stimuli, regardless of the site of the lesion. This 'lesion independent' role of the right amygdala might implicate reciprocal anatomical connections between the left and right hemispheres (possibly via the anterior commisure – Demeter et al, 1990; Brown et al, 1999; Cecere et al, 2014) in response to unseen fear. Furthermore, and as mentioned in the introduction to this chapter, the amygdala plays a crucial role in a network mediating 'fight or flight' responses to fearful stimuli (deGelder et al, 2004), characterised by fearful stimuli concurrently activating both the amygdala and action representation networks in motor areas. The right hemisphere also appears to play a crucial role in a number of other behaviours typically exhibited in response to aversive stimuli. For example, Angrilli et al (1996) presented a case study of a patient with a benign tumour on the right amygdala. In contrast to controls, the patient did not exhibit startle blink potentiation in the presence of an aversive stimulus. Other studies have further demonstrated that the right hemisphere plays a dominant role in the withdrawal response – an adaptive response characterised by withdrawing an organism away from a potentially harmful event (Davidson, 1993; Davidson et al, 2000). It therefore seems likely that the specific effect observed in left lesion patients in this study, is a

consequence of having an intact right-hemisphere, to mediate the implicit fear signal into a faster motor response.

Concluding remarks

The present data take an empirical step toward confirming that only fearful signals can be processed via the subcortical retino-colliculo-pulvinar pathway to the amygdala, following damage or disconnection of striate cortex. That fearful signals appear to inhibit this pathway via downregulation when the geniculot-striate pathway is intact, presents an interesting question for future research, as to what specific circumstances and contexts might downregulation be mediated outside of clinical cases of retrochiasmatic lesions. Another point worth noting is that the performance of blindsight patients (e.g., GY, DB, TN) is idiosyncratic and reflects rare plastic reorganisation of the visual system following a retrochiasmatic lesion. A clearer understanding of this reorganisation would be an important step toward understanding the potential for residual function in HVFD patients and the possible development of treatment interventions.

Chapter 3: Visual reorganisation in HVFD

In the previous chapter I focused on the residual ability of visual functioning, spared in patients with post-chiasmatic lesions. Specifically, I demonstrated that fearful stimuli facilitate behavioural responses to visual targets presented in the intact field of patients with visual field defects. I interpreted this result as evidence for a spared subcortical retino-colliculo-pulvinar-amygdala pathway, i.e., the 'low road' (LeDoux, 1996), which processes visual and emotional signals. The underlying assumption is that existing networks can be recruited after a lesion to the central nervous system (CNS) to support lost functionality. However, a number of studies have indicated that the brain continues to display the capacity to adapt to changes in the external and internal milieus throughout adulthood, past the closure of critical periods (Espinoza & Stryker, 2012). Harnessing the capacity of the brain to adapt could very likely benefit patients' rehabilitation. A crucial point is then to understand the nature and limitation of neural plasticity in the adult brain.

Experiment 2: A case imaging a spectroscopy study of visual reorganisation in a patient with HVFD

Most of functional imaging studies carried out in human patients with lesions of the CNS have concentrated on either cortical or subcortical strokes affecting the motor system (Chollet, DiPiero, Wise, Brooks, Dolan, & Frackowiak, 1991; Fridman, Hanakawa, Chung, Hummel, Leiguarda, & Cohen, 2004; Carter, Astafiev, Lang, Connor, Rengachary, Strube, & Corbetta, 2010; Rehme, Eickhoff, Rottschy, Fink, & Grefkes, 2012). Few studies also examined the effects of strokes involving other functional networks, such as language

(Rosen, Petersen, Linenweber, Snyder, White, Chapman, & Corbetta, 2000) or attention (He, Snyder, Vincent, Epstein, Shulman, & Corbetta, 2007; Corbetta, Kincade, Lewis, Snyder, & Sapir 2005). In the proceeding chapter, I aim to characterize the functional and neurochemical correlates of reorganization of the visual system following strokes along the white-matter tracts connecting the thalamus to visual cortex, in a patient with parietal lesions. The reason I decided to examine neural reorganization in this patient is that the nature of the lesion allowed me to compare visually evoked and spontaneous activity in homologous retinotopic regions of the unaffected and lesioned hemisphere. I expected that post-lesional neural plasticity in the deafferented visual cortex of the ipsilesional hemisphere would lead to prominent changes in visually evoked responses recorded therein and its resting state functional connectivity, compared to homologous regions of the contra-lesional hemisphere because of the loss of thalamic input and network level reorganization. Previous studies indeed demonstrated that visual cortex in blind individuals can take on entirely new functionalities, for example responding to linguistic stimuli, e.g. Braille script presented in the tactile modality (Sadato, Pascual-Leone, Grafman, Ibañez, Deiber, Dold, & Hallett &1996). This suggests that even the sensory modality to which a piece of cortex is responsive can be altered in ways that are probably functionally advantageous. However, the degree of plasticity exhibited by blind individuals depends on the age when a person experienced visual loss, suggesting that cross-modal plasticity in visual cortex also displays a critical period. Whether central, rather than peripheral lesions resulting in partial visual loss can also lead to significant reorganization of cortical functionality is not well established in the adult literature. Further, previous studies carried out in non-human primates, examining the effects of retinal lesions on receptive fields of neurons in primary visual cortex have led to conflicting results. Initial reports suggested that units with receptive fields corresponding to the location of the retinal lesion become responsive to visual stimuli presented at perilesional

locations in the days and months following the lesions (Gilbert & Li, 2012). Others have found minimal evidence of reorganization in primary visual cortex of adult animals but possibly some reorganization in extrastriate visual regions (Smirnakis, Brewer, Schmid, Tolias, Schüz, Augath, & Logothetis, 2005). A more thorough literature review of plasticity within and outside the visual system follows.

The discovery that experience dependent plasticity of ocular preference in neurons of primary visual cortex is mainly limited to early periods of postnatal life (Hubel & Wiesel, 1963; Hubel & Wiesel, 1970) brought many to assume that the functional architecture of visual cortex can no longer be modified in the adult brain. Indeed, the loss of plasticity has been suggested to be beneficial in the face of continuously changing environmental conditions. The idea that the connectivity in the adult brain of humans is largely stable has been further confirmed by studies which have failed to find evidence of plasticity in the primary visual cortex of adult animals, following retinal lesions, (Horton & Hocking, 1998; Smirnakis et al., 2005) or adult patients with macular degeneration (Sunness, Liu, & Yantis, 2004), notwithstanding earlier reports to the contrary. However, these findings have been challenged by evidence indicating that after removal of visual input (Gilbert & Li, 2012) or direct damage to visual cortex (Reitsma et al., 2013), visual cortex can undergo functional reorganization in adult primates. Therefore, whether visual cortex can undergo reorganization in the adult brain remains contentious.

Much of what we know about adult brain plasticity in humans stems from studies on stroke patients using neuroimaging, mainly functional magnetic resonance (fMRI) and Positron Emission Tomography (PET). These studies, which have mostly concentrated on motor

strokes affecting function in the upper limb, have revealed several patterns of neural reorganization. Reorganization can occur in areas of the ipsi-lesional hemisphere, homologous cortex of the contralesional hemisphere and in regions that are not part of the functional network(s) involved by the stroke (Grefkes & Ward, 2013).

A number of investigators have documented that perilesional cortex can take over functions previously carried out by the infarcted tissue. A meta-analytical study, which included 225 patients, found evidence for increased activity in ipsilesional primary motor (M1) and medial-premotor cortices of chronic stroke patients attempting to move their paretic limb. Moreover, the same study did find that the degree of activation positively correlated with the degree of motor recovery (Favre et al., 2014), suggesting that regions in ipsilesional motor regions can take over functions previously lost. The functional relevance of perilesional activity to motor recovery has been assessed also using Trans-cranial Magnetic Stimulation protocols (TMS). TMS of M1 (Lotze et al., 2006) and premotor cortex (PM) (Fridman et al., 2004) of the ipsilesional hemisphere was found to interfere with movement of the paretic limb, further supporting the inference that activity in perilesional cortex is important for controlling movements in the affected limb of recovered stroke patients.

A second form of brain plasticity is the emergence of movement related BOLD responses in motor regions of contra-lesional cortex. A metal-analysis has confirmed the generality of these findings and specifically that movement of the hemiparetic limb leads to activation of M1, PM cortex and Supplementary Motor Area (SMA) of both hemispheres in stroke patients, while healthy subjects demonstrate strictly contralateral activations (Rehme, Eickhoff, Rottschy, Fink, & Grefkes, 2012), suggesting that contralesional cortex may

become competent for limb movements on both sides. Indeed TMS applied to contralesional dorsal PM cortex was found to cause greater interference with motor function of the hemiparetic limb in more severely impaired patients (Johansen-Berg et al., 2002), whereas TMS to ipsilesional dorsal PM was more disruptive in less severely impaired patients (Fridman et al., 2004). A conclusive interpretation of these findings awaits replication, which suggest that the role of ipsilesional and contralesional cortex plasticity may depend on the severity of the impairment and/or the extent of the anatomical lesion. Interestingly, in two studies carried out by the same group of investigators in patients with strokes of the visual system, visually evoked responses in retinotopic cortex of the contralesional hemisphere were found following stimuli presented in both the contralateral visual field and ipsilateral, hemianopic field (Nelles et al., 2007; Nelles et al., 2002a), suggesting that visual cortex of the contralesional hemisphere may acquire novel spatial selectivity following a lesion affecting homologous regions of the opposite hemisphere. BOLD responses evoked by ipsilateral visual stimuli have also been documented in the visual cortex of the contralesional hemisphere by other group of investigators, but only in about 10% of patients with various pathologies affecting post-chiasmatic visual pathways (Reitsma, Mathis, Ulmer, Mueller, Maciejewski, & DeYoe, 2013).

Despite the apparent generality of contralesional activations as a mechanism of neural recovery, a number of authors have indicated that contralesional hemisphere activity might actually be deleterious to performance. The underlying idea is that activation of the contralesional hemisphere reflects release from inhibition rather than a compensatory phenomenon (Grefkes et al., 2008a). Double pulse TMS in patients with chronic subcortical stroke (Murase, Duque, Mazzocchio, & Cohen, 2004) have indicated that the inhibitory drive from contralesional motor cortex onto ipsilesional motor cortex is transiently increased just

preceding movement of the paretic hand, contrary to healthy controls who show a facilitation when the hemisphere on the same side of the moving hand is stimulated. This result was interpreted to indicate that disruption of mutual inhibitory influences between left and right motor cortex, in the presence of a subcortical lesion, results in diminished phasic activity in the motor cortex of the lesioned hemisphere and contributes to the severity of the lateralized motor deficits.

An additional and potentially maladaptive consequence of stroke is its remote effects on metabolic activity in distant regions, a phenomenon known as diaschisis (Feeney and Baron, 1986). For example, lesions to the right Temporo-Parietal Junction (TPJ), and ventral frontal lobe, in patients with left spatial neglect, are associated with abnormal pattern of task related activations in the dorsal fronto-parietal regions, which show a strong hemispheric asymmetry in affected individuals compared to healthy controls (Corbetta et al, 2004). The greater activation in dorsal regions of the left than right hemisphere has been interpreted as reflecting diaschisis of right hemisphere regions and provide the physiological underpinning for the attentional biases exhibited by neglect patients (Carter et al., 2010; He et al., 2007).

Another mechanism of recovery worth mentioning is cross-modal plasticity which occurs when cortex takes over novel functions following its anatomical or functional deafferentation. For example, it has been shown that tactile signals can activate the visual cortex in blind adults (Voss, 2013). Cross-model plasticity leads to recruitment of deafferented regions by other sensory modalities and may play an important role in patients with lesions to thalamo-cortical connections.

The cellular mechanisms, which may underpin plasticity in the adult brain probably include synaptic plasticity associated with either long-term potentiation (LTP) or long term depression (LTD). LTP is the long-lasting enhancement of synaptic transmission, through increased excitatory synaptic drive, and is thought to reflect Hebbian mechanisms (Feldman, 2009). Enhanced LTP has been found in areas adjacent to experimentally induced strokes (Hagemann, Redecker, Neumann-Haefelin, Freund, & Witte, 1998), suggesting that reorganization of peri-lesional circuits may depend on glutammatergically mediated plasticity. However, there is good evidence that the induction of LTP also requires other neurotransmitters, and that the remodelling of glutammatergic synaptic strength alone is insufficient to account for the range of synaptic plasticity encountered in animal models. Among the neurotransmitters thought to play a major role in plasticity is GABA, which is the major inhibitory neurotransmitter used in cortical circuits. For example, it has been shown that reducing GABA levels in M1 facilitate the induction of LTP-like plasticity (Castro-Alamancos, Donoghue, & Connors, 1995), while the application GABA receptor agonists to cortex can prevent LTP-like plasticity process (Trepel & Racine, 2000). GABA seems to play also an important role in plasticity found in the primary visual cortex. For example, local infusion of GABA antagonist, to reduce intra-cortical inhibition, can reopen a critical period-like window for ocular dominance plasticity in adult animals (Espinosa & Stryker, 2012)).

Using MRI spectroscopy, a few studies have examined the relation between cortical GABA concentration and cortical plasticity in human sensorimotor cortex. Stagg (2013) found that inactivating peripheral nerves (via reversible ischemic arm block) is associated with reduced GABA level in contralateral sensorimotor area, but not in V1 (Levy, Ziemann, Chen, &

Cohen, 2002), suggesting that changes in GABA concentrations can follow functional deafferentation of sensory cortex. Phasic decreases in GABA levels within motor cortex were observed also during a sequence-learning task but not in control subjects (Floyer-Lea, Wylezinska, Kincses, & Matthews, 2006) performing a motor task of similar complexity but devoid of a learnable sequential structure. These findings have led to the suggestion that GABA reduction might be important to unmask synaptic connections within cortical circuits and promote synaptic plasticity. In a recent study, stroke patients who had shown greater motor improvement after rehabilitation were found to have experienced greater decrements in GABA concentrations (measured before and after the therapy) in the hand area of motor cortex than patients who had shown less improvement (Blicher et al 2013).

In this study, I aim to investigate the physiological mechanisms underlying visual reorganization following a brain lesion affecting the optic radiation. Such investigation was expected to provide some if preliminary answers to the following questions: 1) Do the visual cortices in the affected and unaffected hemisphere acquire novel patterns of spatial selectivity? 2) Are there changes in the excitatory-inhibitory balance in the visual cortex of the affected vs. the unaffected hemisphere? 3) Do the visual cortices display novel patterns of functional connectivity with the rest of the brain? I compared the functional and neurochemical markers of residual neuronal activity in the visual cortices in a young patient (N.P.), who suffered a parietal lesion with involvement of the superior optic radiation (sOR). The lesion spared both LGN and primary and extrastriate visual cortices, thus providing an opportunity to examine the residual functionality of retinotopic cortex after its main thalamic input has been damaged.

Materials and methods

Case History

At the time of testing, the patient was a 31 years old, right handed woman, who was independent in her activities of daily living and pursuing a higher degree. She was reporting that she would occasionally bump into obstacles placed in her left lower visual field but denied otherwise having any cognitive difficulties. About 13 years previous to the studies described here, she sought medical attention following a witnessed seizure. She was found to have suffered an intra-cerebral hemorrhage and later to harbor an arterio-venous malformation (AVM) in occipito-parietal junction of the right hemisphere. About seven years prior to testing she had undergone endovascular embolization of the AVM and suffered a second seizure shortly after the procedure. She has been seizure free since, and had discontinued antiepileptic drugs two years prior to testing. The patient has a lower greater than upper left quadrantanopsia and mild left neglect.

Visual Testing

The patient was tested to determine the extent of her perimetric visual loss. The testing procedure was controlled by a custom coded script running on an Apple Mac Pro 1.1. Accurate timing of the visual stimuli was achieved by using a set of freely available routines (Brainard, 1997; Pelli, 1997) for Matlab® (Mathworks, 2008a, Natick, MA). Stimuli were presented on the screen of a LaCie Electron 22blue CRT monitor, set a refresh rate of 60Hz. The monitor was placed at a distance of 70cm from the participant. The participant's head position was restrained by a chin and forehead rest. The stimuli were presented at forty-eight separate locations, placed at eccentricities of 3.2°, 6.4°, 9.6° and 12.9° respectively, and spaced 30° apart in the radial direction. The stimuli were single, bright, circular dots 0.42° in

diameter, presented on a dark background. The stimulus was shown for 300ms. Each stimulus was preceded by a warning sound which indicated the start of a new trial. The stimulus appeared following a non-aging fore-period lasting between 0.5 and 2.5s. On about 10% of the trials no stimulus was presented. The participant was instructed to maintain fixation on a centrally located cross and report the stimulus as soon as she saw it, but to avoid pressing the response key unless she was certain the stimulus had appeared. The participant performed the task under monocular condition: the left and right eyes were covered by an eye patch on alternating testing blocks. The patient completed 960 trials with each eye condition.

Imaging Paradigms

Three fMRI studies were carried out. First, a blocked design was used to localize the cortical representation of the vertical and horizontal meridian and thus highlight borders between retinotopic visual areas. Second, an event related design was used to examine the BOLD responses to visual stimuli presented in each of the four visual quadrants. Finally, a resting-state paradigm was used to obtain data for a seed based functional connectivity analysis. Additionally, Magnetic Resonance Spectroscopy measures of GABA and glutamate concentrations in contralesional and ipsilesional visual cortices were also carried out. The imaging protocols were approved by the local NHS Trust Ethics committee and the institutional review board of Bangor University. The patient gave written consent prior to each of the scanning sessions.

The boundaries between retinotopic regions were functionally localized using a display containing red, green and blue dots moving over a grey background radially. The display dots density was, on average, 0.25/deg^2. The dots' diameter was 0.6° and the peak speed was

3.5°/s. The dots' lifetime was limited to ten frames or to the frame when they reached the wedges' boundaries. The dots were then replotted at random locations. Every 2.5s the direction of motion of all dots reversed from centripetal to centrifugal and vice-versa. The dots were contained within two triangular wedges whose vertex was at the central fixation point. Each wedge subtended an angle of 36° in the image plane and extended from an eccentricity of 1.5° to an eccentricity of 14°. The orientation of the wedges' main axis changed every 12.5s from vertical to horizontal and vice-versa. The participant was instructed to maintain central fixation in each scan on a central dot. Two scans were acquired, each lasting 352.5s.

Resting-State FMRI

During a resting state scan the patient was instructed to maintain fixation on a centrally presented red fixation dot, 0.6 in diameter presented over a dark background. Four 352.5s long scans were acquired.

Quadrant Visual Hemi on a central field Stimulation

Stimuli were single wedges containing coloured dots moving at a speed of 3.5deg/s. Each stimulus lasted 12.5s and was followed by an interstimulus interval whose duration was jittered randomly between 2.5, 5, 7.5 or 10s. The wedges' vertex was at the fixation point and subtended 50° in the image plane. The main axis was aligned with the four oblique axes. The patient maintained fixation while passively viewing the wedges. Four scans were acquired, each lasting 352.5s.

MRI Spectroscopy

MRS spectroscopy measurements of GABA and Glutamate concentrations were obtained separately in left and right visual cortex. The measurements were carried out using a single voxel aligned against the voxel's largest dimension with the orientation of the calcarine sulcus, obtained from a sagittally acquired anatomical localizer. Care was taken to avoid venous sinuses, bone and gliosis tissue. The approximate position of the voxels is shown in panel A of Figure 3.1. Each MRS scan was acquired for 12 minutes while the participant maintained quiet wakefulness.

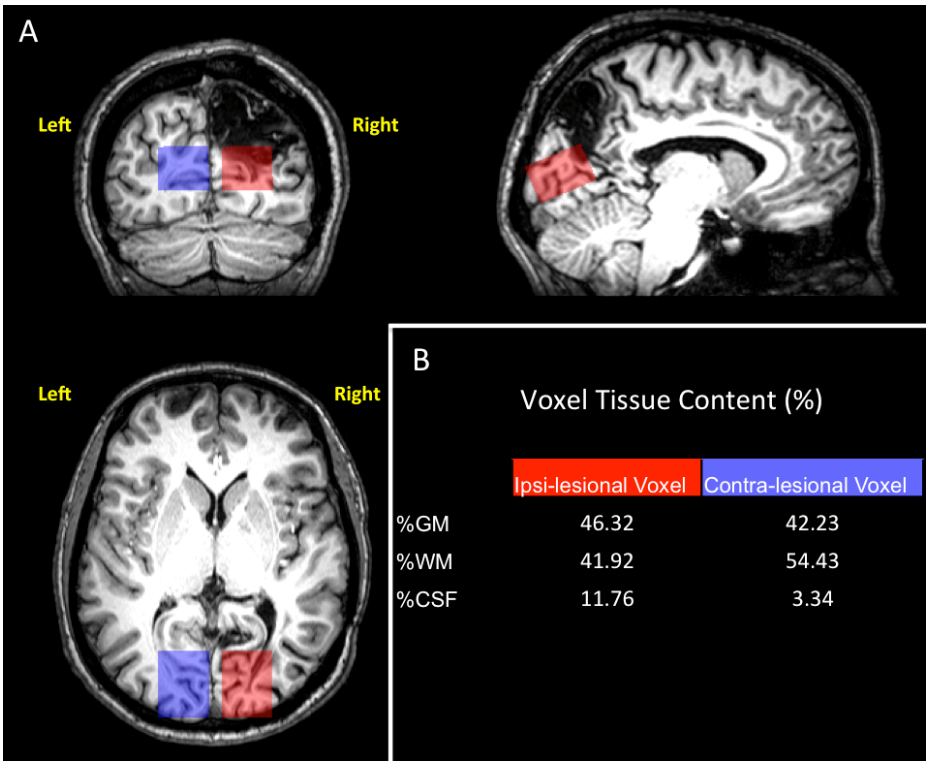


Figure 3.1 - Positioning the MRS voxels and the brain tissue contents in each voxel. The ipsilesional (red) and the contralesional (purple) voxels (A) both located mainly in the dorsal visual cortices, were carefully prescribed to avoid contamination from venous sinuses and scalp. The percentages of GM,

WM and CSF in each voxels (B), were estimated using a tissue segmentation process in SPM (8). Note that the ipsilesional voxel contains parts from the lesion, resulting in a higher CSF content, which is taken into account during MRS analysis.

MRI Data Acquisition and Pre-processing

Data were acquired on a Philips Achieva 3-T MRI system (Philips Healthcare, Best, Netherlands) located at the Bangor Imaging Unit. A 32-channel head RF signal receiver coil was used. Visual stimuli were generated using a customized MATLAB (The MathWorks Inc. Natick, Massachusetts) program and were displayed on a 24 inch, MR compatible screen (Cambridge Research System Ltd., Rochester UK). The resolution of the screen was set to 1920 x 1200 pixels and the refresh rate to 60Hz. The screen was placed 95cm behind the rear-viewing mirror placed above the head coil.

3D, axial T1 weighted structural scans, with an isotropic voxel size of 0.69mm, were acquired using a spoiled-gradient, multiple-echoes sequence (TR=23 ms, TE_s=[5,10,15,20 ms], FA=8^0). A 3D-T1 image was obtained by averaging the four echoes data sets.

An axial $T2^*$-gradient-echo pulse sequence with fat suppression was used (TR= 2500 ms, TE= 35 ms, FA= 90^0) for all the fMRI BOLD scans. In each scan, 165 volumes were acquired, consisting of 35 contiguous 3.5 mm tick axial slices with no gap, and providing full brain coverage. Images were reconstructed using a 3.0 mm isotropic resolution. The onset of

the stimulation paradigms was synchronized with the onset of the acquisition by a scanner generated TTL pulse in both visual experiment studies.

The subject's representative anatomical image was obtained by averaging data from two scans, obtained in separate sessions. The image was normalized to Talairach space and corrected for non uniformity of the magnetic field using a cubic field and was used to generate the representation of the white grey matter boundary and thus allow the reconstruction and flattening of brain surfaces using Surefit/CARET version 5.65 software packages (Van Essen, Drury, Joshi, & Miller, 1998; Van Essen et al., 2001).

The functional data were pre-processed using a set of custom coded routines and included the following steps: 1) Compensation for slice acquisition time differences by synch interpolation. 2) Correction for signal intensity differences between odd and even slices, caused by interpolated acquisition. 3) Data within and across runs were realigned using a linear affine transformation with six degrees of freedom, to correct for rigid body motion. The volume of reference was the middle one for within scans realignment and the first one for between scans realignment. 4) Functional data were transformed into Talairach atlas space (Talairach & Tournoux, 1988) using a series 12 degrees of freedom affine transformations. The functional data were resampled in Talairach space by combining multiple affine transformations in one step starting with the images in native scanner space.

MRS Data Acquisition and Analysis

H^1-spectroscopy data were acquired using a voxel with an anterior-to-posterior size of 30mm, right-to-left size of 25mm, and superior-to-inferior size of 20 mm and a MEGA-PRESS pulse sequence (Mescher, Merkle, Kirsch, Garwood, & Gruetter, 1998). In the MEGA basing 15ms long, dual-banded Gaussian inversion pulses were applied. One pulse was used for water suppression and was directed to the frequency band at 4.7ppm, the other was used for spectral editing and alternated between 1.98 ppm (edit-on) and 7.8 ppm (edit-off), in an interleaved manner. Twenty-four blocks were collected resulting in three hundred and eighty four separate spectral averages. Finally, an un-suppressed water PRESS-spectroscopy data set (TR=3400 ms, TE=80 ms, NSA=1) was acquired from the same voxels of interest, to be used as a reference for calculating the concentration of major metabolites.

All blocks were pre-processed and analysed using TARQUIN 4.3.4 software (Wilson et al 2011). The pre-processing included the following steps. First, residual water signal was removed from the spectroscopy tail by modelling the signal up to a 45Hz cut off. To adjust for frequency shifts and phase instability, a pair-wise frequency and phase correction was applied across the entire acquisitions, using the Creatine (Cre) signal as a reference. The data were then averaged, resulting in a sum edited difference spectrum which was used for estimating GABA concentration. The same pre-processing steps were applied for estimating the other metabolites signals, including Glutamate, except that the non-edited PRESS spectroscopy data were used instead.

fMRI data analysis

Visually evoked BOLD responses were estimated using a general linear model (GLM). For each scan, the four regressors of interest were obtained by convolving a boxcar function with an assumed hemodynamic response function (Boynton, Engel, Glover, & Heeger, 1996). Additional regressors included 1) a constant term modelling the baseline BOLD signal magnitude, 2) linear trend modelling slow drifts of the BOLD signal, and 3) three sine and cosine functions of low frequency harmonics of the BOLD signal (< 0.009 Hz). The estimated BOLD signal changes were normalized by the constant term averaged over scans and smoothed using a 6-mm FWHM 3D Gaussian kernel. BOLD signal changes were assessed voxel-wise using t-test statistics. For display purposes, z-transformed, multiple comparison corrected maps were used. BOLD responses evoked by quadrantic stimuli were estimated within regions of interest by modelling the BOLD response frame by frame, using four sets of twelve delta functions, one set for each of the quadrantic stimuli. The timecourse of the BOLD responses were estimated by averaging voxel-wise estimates over the entire ROIs.

The borders between retinotopic areas were localized by comparing the response evoked by vertical and horizontally oriented stimuli. Following published conventions, the ventral and dorsal borders between the visual regions (i.e. the primary [V1], secondary [V2], tertiary [V3] and quaternary [V3A, V4v]) in each hemisphere were identified. These boarders were localized based on both the locations of the vertical and horizontal meridians representations, and major anatomical landmarks such as the calcarine sulcus, see 3.2A. Sixteen ROIs were drawn over flat representations of participant's brain, as shown in Figure 3.2B. These include

four dorsal regions (V1d, V2d, V3d and V3A) and four ventral regions (V1v, V2v, V3v and V4v) in each hemisphere.

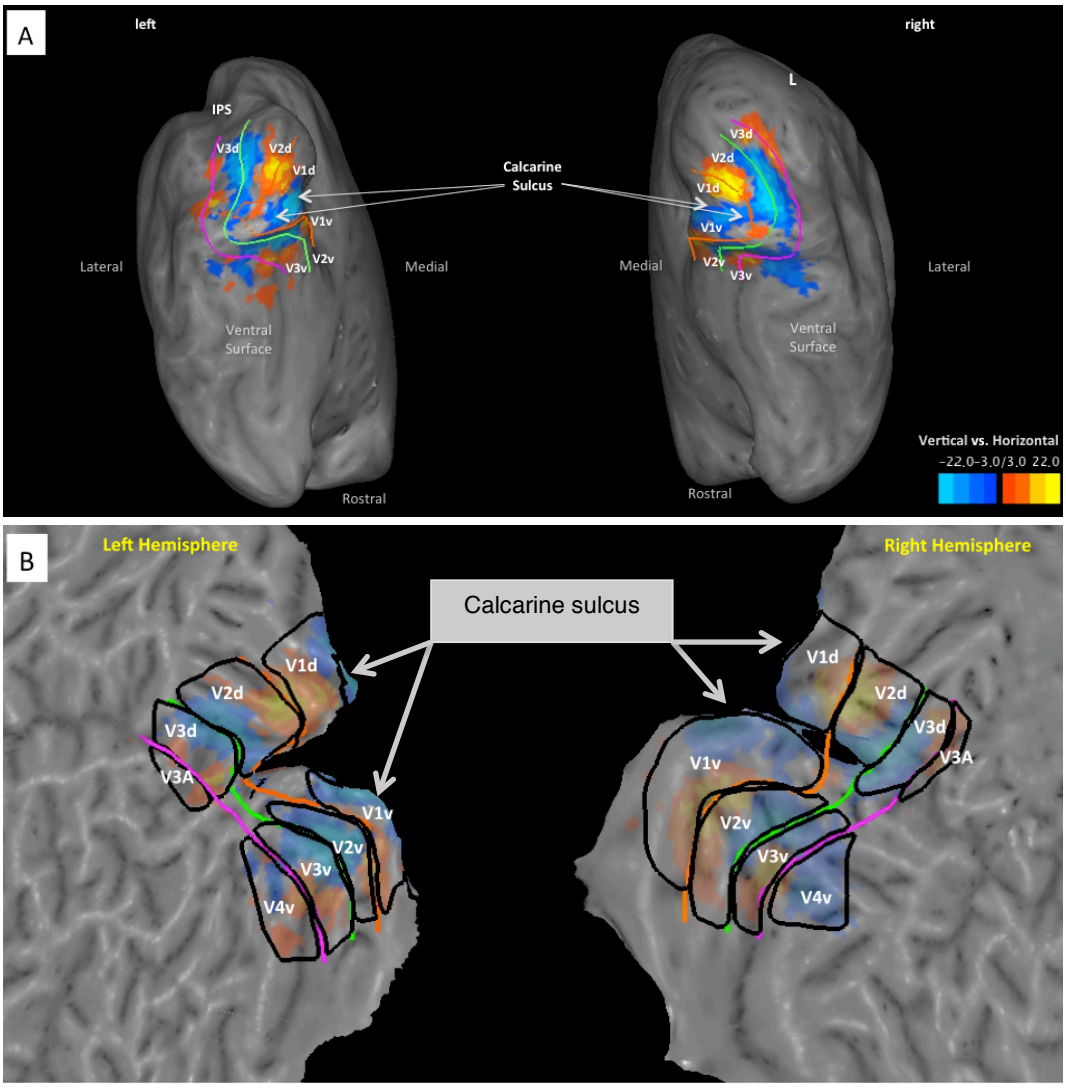


Figure 3.2. The retinotopic boarders projected onto the participant's inflated (A) and flattened (B) brain surfaces. Both panels illustrate the BOLD responses evoked by stimulus presented along the vertical or horizontal meridians. (A) Multiple retinotopic representations of the vertical and horizontal meridian were highlighted and used as functional markers to demark boundaries between visual areas. The orange, green and pink lines highlight these boundaries. (B) Left and right flat surfaces focused to the dorsal and ventral visual cortices revealing the sixteen regions of interest ROIs. L=lesion; IPS=Intra-parietal Sulcus.

Functional Connectivity Analysis

Functional connectivity maps were computed for each of the sixteen ROIs using a GLM based analysis. For each ROI, the timecourse of the BOLD signal in the resting state scans was used as the regressor of interest. Nuisance regressors included the BOLD signal averaged over the whole brain and the frame-by-frame estimates of the head position generated during the realignment procedure. Prior to running the GLM, BOLD time courses were normalized and band-pass filtered between 0.008 Hz and 0.1Hz. Voxel-wise, t-tests were performed to assess statistical significance. The resulting contrast images were z-transformed for display purposes.

Principal Component Analysis of Resting Stare signals in visual ROIs

A Principal Component Analysis (PCA) was used to examine the functional connectivity between regions of the visual network identified by the retinotopic scans. The principal components were estimated from the eigenvectors of the covariance matrix computed between the normalized, zero mean timecourses of the regional BOLD signals. The eigenvectors were then used to compute the timecourses of the principal component (PC) of the resting state signals in the visual ROIs. The first three PCs were used as regressors in whole-brain GLM analysis to examine their functional connectivity, using the same procedure described in the earlier section, 'Functional Connectivity'. For this study, the first three components were used and these accounted for approximately 91% of the variance across all BOLD time courses, PC1:61%, PC2:20% and PC3:10%.

MRS Analysis

Using TARQUIN software, the pre-processed edit-GABA was used for estimating GABA concentration, and the non-edited-PRESS data were used for measuring Glu level. GABA and Glu analyses were performed separately. Briefly, TARQUIN used the MRS parameters (specified in the header of the supplied MRS file) to generate a simulated PRESS bases set spectra in the time domain. The simulation process is based on the chemical shift and J-coupling values specified previously in Govindaraju, Young, & Maudsley, 2000). The linear combination of all simulated bases set spectra (N=25) which contain metabolites, lipids and macromolecules, was used to model the experimental data in the time domain. Figure 3.3 illustrates GABA analysis which shows the acquired edit-GABA spectrum, the estimated model, as well as the residuals. A non-negative least-squares analysis was then applied to estimate the metabolites' amplitudes.

The quality of MRS data and the quantifications analysis were assessed by, 1) visually inspecting raw data and 2) reading the standard deviations of the residuals of the fitted metabolite peaks which are reported in CRLB (Cramer-Rao lower bound). No noticeable artefacts or baseline drifts were observed. All fitted metabolites have a CRLB < 20%, a limit that is conventionally considered reliable for a metabolite's peak to be further analysed.

The relative concentrations of metabolites (measured in mill mole [mM]) were calculated by scaling their fitted peaks by the amplitude of water signal. Using the acquired un-suppressed water signal, TARQUIN algorithms used a supposed prior knowledge of water concentration (55550 mM) and attenuation of (1) in brain tissues to calculate the absolute water concentration. Based on the resulting water concentration, the water-scaled GABA and Glu concentrations were then estimated and reported in mM unit.

In a separate analysis, GABA and Glu concentrations in the brain tissues (grey matter [GM]+ white matter [WM]) were estimated, excluding CSF fraction, by a method described in Geramita et al. (2011). To do this, partial volume segmentation using costumed software was performed which used the 3D-T1 anatomical data for segmentation as well as for localization of the voxel of interest. The 3D-T1 data were segmented into GM, WM and CSF using SPM8. Based on the percentages of (GM+WM) in the spectroscopy voxel, see Figure 3.1 (B), GABA and Glu signal were corrected for partial volume effect and then transferred into absolute concentration measured in mM per tissue unit.

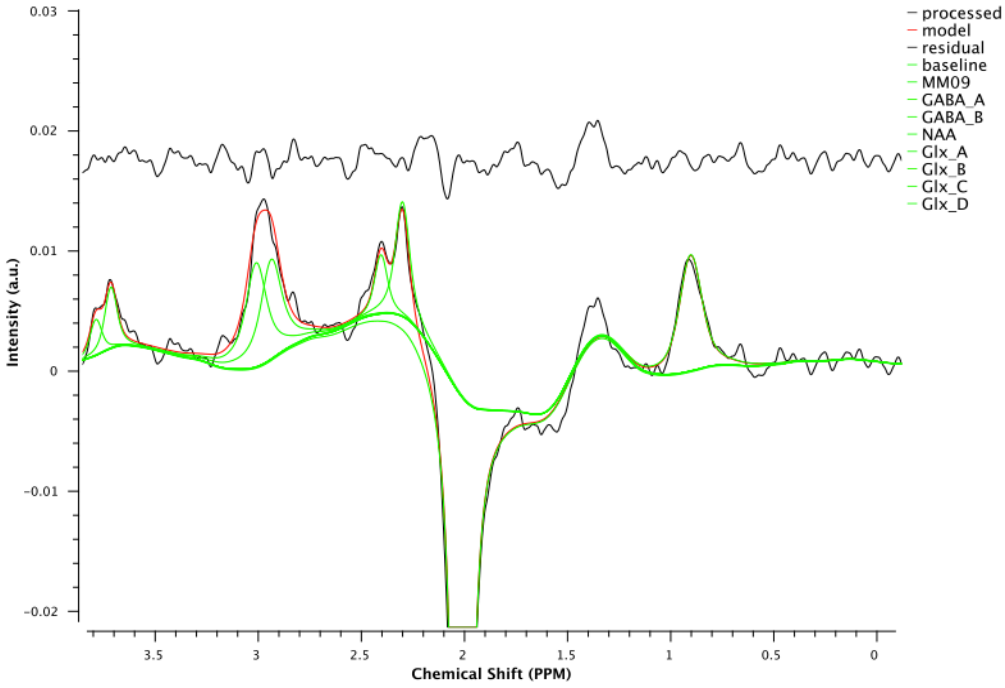


Figure 3.3. Sample MEGA-PRESS spectroscopy analysis. The data acquired from the ipsilesional visual cortex. The graph shows the bases set functions (green) that were linearly combined by TARQUIN to construct a model spectroscopy (red). The model was fitted into the pre-processed acquired data (processed [black]). The top row is the fit residuals, which is visually inspected to assess the fitting quality. Representative GABA peaks can be seen at 3 ppm.

Results

Lesion anatomy

Anatomical imaging showed a 37-cm^3 CSF-filled cavity surrounded by gliotic tissue. Figure 3.4 illustrates the extend of the parenchymal lesion across four coronal slices placed posterior to the splenium of the corpus callosum. The lesion extends anteriorly from white matter structures located just lateral to the trigon of the right lateral ventricle, as shown in slice 1 of Figure 3.4, to posteriorly the posterior parietal lobe, as shown in slice 4 of Figure 3.4. The lesion involves portion of the precuneus (see slice 3 in 3.4), the superior parietal lobule and the parieto-occipital sulcus (POS) (slice 2 and 3 in Figure 3.4). The lesion most likely involves part of the superior optic radiation (sOR), while sparing primary and adjacent, extrastriate visual areas. Specifically, the anatomy of the optic radiations has been described in detail in previous sectional anatomical (Chen et al., 2009; Parraga, Ribas, Welling, Alves, & de Oliveira, 2012) and in Diffusion Tensor Imaging studies (Sherbondy, Dougherty, Napel, & Wandell, 2008). These studies have indicated that the sOR emerges from the LGN and courses posteriorly, forming the superior wall of the temporal horn, and the lateral wall of the trigon. It then enters the occipital lobe forming the roof of the occipital horn before reaching the cortex along the upper lip of the calcarine sulcus. Since the lesion involves white matters structures along much of the superio-lateral wall of the trigon, as shown in slice 1 (see 3.4) and the roof of the occipital horn, known to include the sOR, the patient is likely to have suffered damage to the sOR.

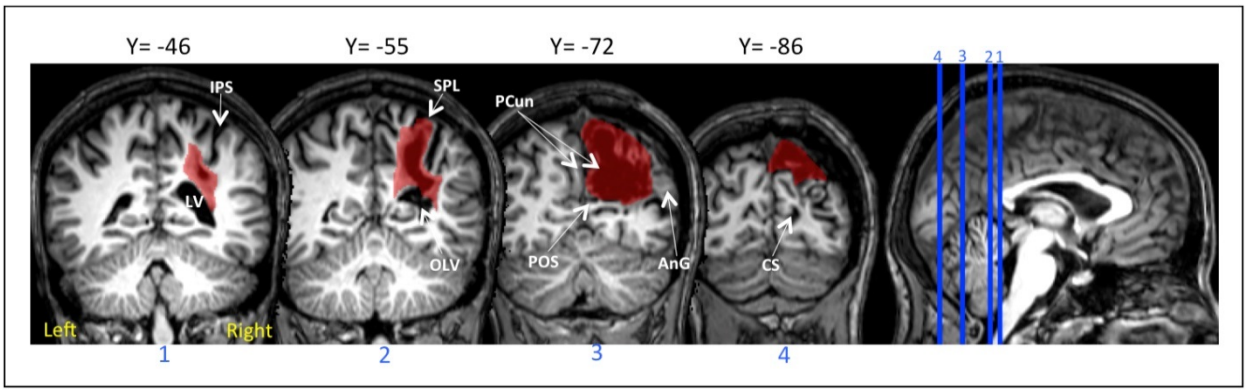


Figure 3.4. Selected coronal T1 images revealing the right parietal lesion. The affected regions (highlighted in transparent red) are plotted onto the subject's normalized brain using MRIcron software (Roden & Brett, 2000). The number above each image is the corresponding Y coordinate in the Talairach space, and the level and orientation of each image are indicated by a blue line in the sagittal T1 image (far right). The primary cortex and most of the extrastriate cortex are spared. IPS = intraparietal; LV = lateral ventricle; SPL = superior parietal lobule; Sulcus; OLV = occipital horn of the lateral ventricle; PCun = precuneus; AnG = angular gyrus; POC = parietal occipital sulcus; and CS = calcraine sulcus.

Visual Perimetry

Figure 3.5 shows detection rates obtained in a simple target detection task, at forty-eight separate locations, when the participant viewed the display with the left and right eye. In the left lower quadrant, detection probability was lower than at locations of corresponding eccentricity in the other three quadrants. This difference was particularly noticeable for location close to the fovea. This pattern of diminished detection sensitivity was consistent in both eyes, consistent with a homonymous visual defect due to a retrogeniculate lesion, in accordance with the anatomical data.

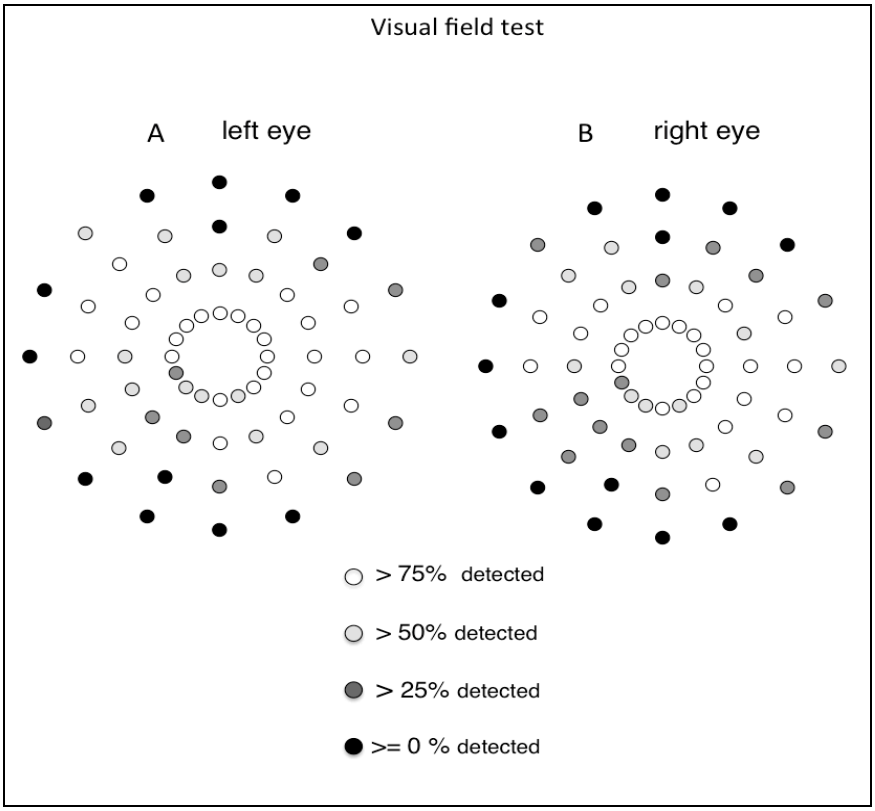


Figure 3.5. Monocular visual perimetry under viewing. The percentage of detected targets at each location in the visual field is shown using a grey scale, with white circles corresponding to location where targets were detected more than 75% of the times and black circles to locations where the target was detected less than 25% of the times. Targets appeared at eccentricities of 3.2°, 6.4°, 9.6° and 12.9°. The detection rates showed a similar spatial distribution when the display was viewed with the left eye (A) and the right eye (B).

BOLD Responses evoked by Quadrantic Stimuli

BOLD responses in primary and quaternary retinotopic cortices evoked by the quadrantic stimuli are shown below. These regions include dorsal and ventral primary visual cortex (V1d and V1v), V3A and V4 of the left and right hemisphere. Figure 3.6 shows the activation maps

and outline of primary visual cortex overlayed on flattened representations of the posterior cortical surface of the patient's left and right hemisphere. Moreover, the timecourses of BOLD responses evoked by 12.5s long quadrantic stimuli are shown below. The activations maps show, in dorsal

V1 of the left hemisphere, a significant response to visual stimuli presented in the right lower quadrant, as expected, but also to stimuli in the left lower quadrant. Stimuli presented in the upper quadrants did not lead to a significant activation. On the other hand, in dorsal V1 of the right hemisphere, there was a significant BOLD response only when the stimulus appeared in the left lower quadrants but not following stimuli appearing in any of the other three quadrants. The BOLD response to contralateral, lower quadrant stimuli were typical in both hemispheres, showing a latency of about 2.0s and a sustained timecourse up to 2.0s following the offset of the visual stimulus (see figure 3.6B). On the other hand, the BOLD response evoked by the ipsilateral lower quadrant stimulus in left dorsal V1 was not typical, both its onset and offset having a long latency.

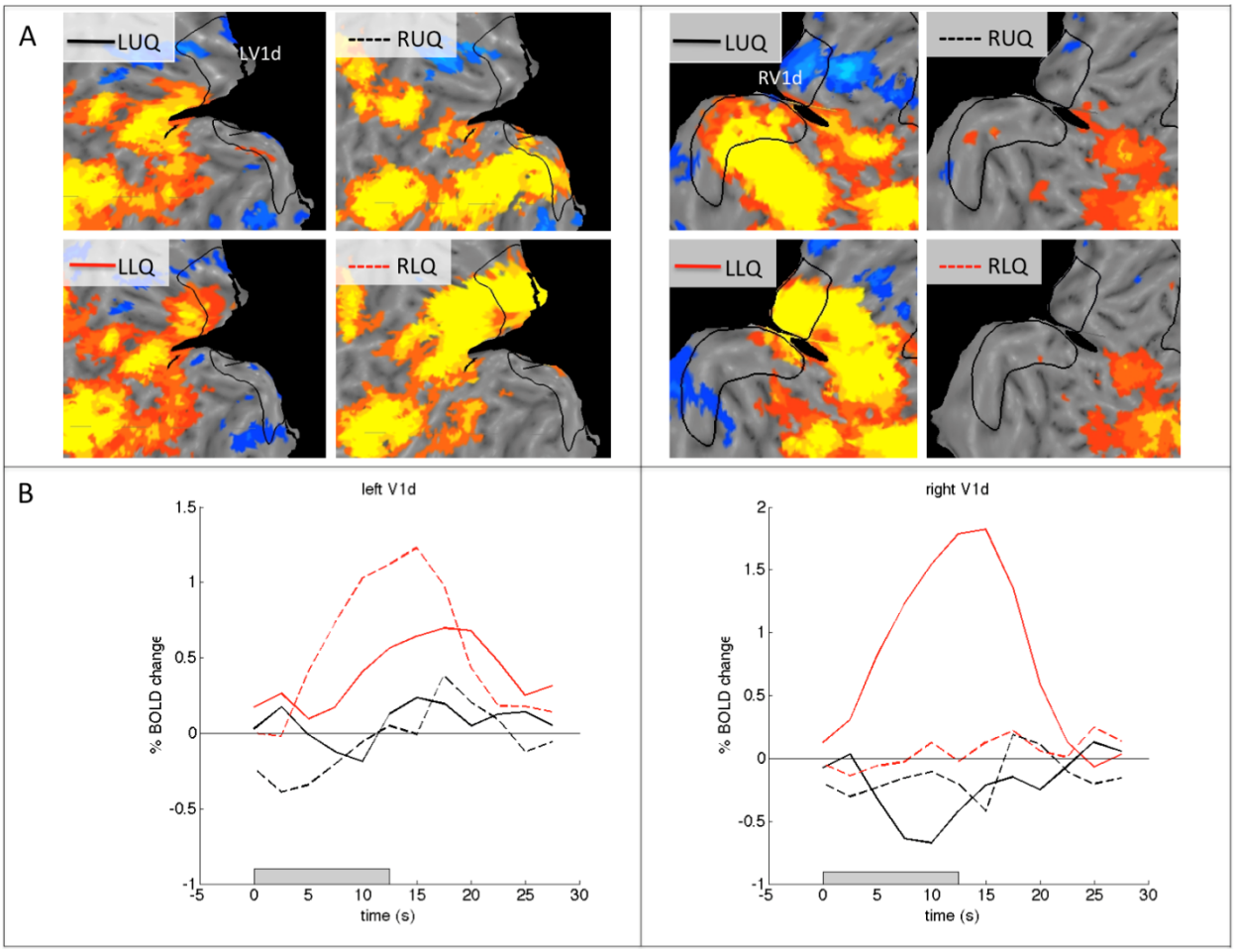


Figure 3.6. Visually evoked BOLD responses in left and right dorsal primary visual cortices. (A) Z-transformed, t-stat maps of the four quadrantic visual responses are overlaid on the flat representations of the left, on the left, and right visual cortex on the right. The maps show voxels of significant activation compared to the baseline (corrected $p < .05$) following LUQ, LLQ, RUQ and RLQ stimulation. The threshold was ± 2. The black outlines show the boundaries of left V1d and right V1d respectively. In left V1d, significant activations were evoked by the RLQ and LLQ stimuli but not with LUQ or RUQ stimuli. Right V1d exhibited a positive activation with LLQ stimulation and a negative activation with LUQ but not with other quadrant stimuli. (B) The time courses of these activations evoked in the left V1d and right V1d by each of the four quadrantic stimuli are shown. The onset and offset times of the quadrantic stimuli which lasted 12.5s, are highlighted by the grey bar placed along the abscissa.

Figure 3.7 shows visually evoked BOLD response in ventral V1 of the left and right hemisphere. In left V1v, there was a significant BOLD response only to stimuli presented in the right upper quadrant. The timecourse of the response to the right upper quadrant stimulus was typical if somewhat more phasic than in dorsal regions. The homologous region of the right hemisphere showed also a significant and response with a typical timecourse to stimuli presented in the contralateral, upper visual space quadrant and, interestingly, a highly atypical response to the stimulus presented in the left lower quadrant. This response was very delayed and it matched poorly the shape of the assumed response used in the GLM analysis, from which the activation maps were computed. Moreover, while a limited positive response was found posteriorly along the calcarine sulcus (which corresponds to the narrow angle elbow along the cut through the calcarine sulcus) corresponding to foveal representations, a negative BOLD response was found in voxels placed more anteriorly and therefore representing more eccentric locations. Examining the timecourse of the BOLD response in foveal and eccentric voxels separately found that foveal voxels showed a response whose timecourse replicated the one showed in figure 3.7, indicating that the atypical timecourse of the BOLD response evoked by the left lower quadrants stimulus did not reflect averaging of timecourses from voxels with different spatial selectivities (data not shown).

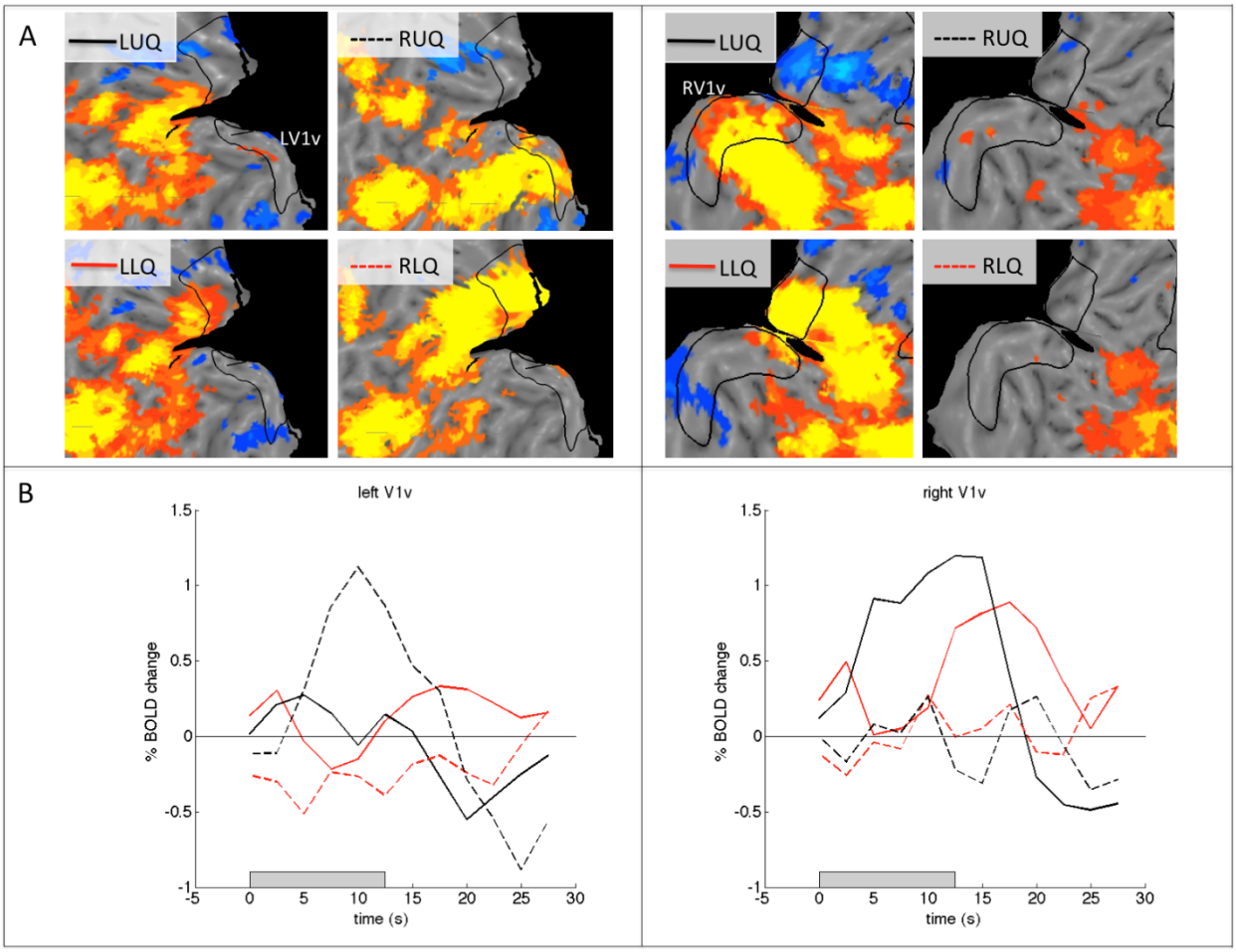


Figure 3.7. Visually evoked BOLD responses in left and right ventral primary visual cortices. (A) Z-transformed, t-statistic maps of the BOLD responses evoked by each of four quadrantic stimuli are overlaid on the flat representations of left (on the left) and right visual cortex (on the right). Left V1v shows significant activations evoked by RUQ stimuli, but no response to other quadrants stimuli. Right V1v shows a significant activation following contralateral stimuli (LUQ and LLQ). (B) The time courses of the activations evoked in LV1v (left graph) and RV1v (right graph) by each of the four quadrantic stimuli.

Figure 3.8 shows the activation maps and time courses of visually evoked BOLD responses in left and right V3A. Left V3A responded to stimuli presented in all quadrants. The latency, time to peak and amplitude of BOLD responses evoked by stimuli in the four quadrants was

similar. In contrast, right V3A mainly responded to stimuli presented in the left lower quadrant. Almost the entire surface of the V3A was significantly activated by stimuli presented in the left lower quadrant, the average BOLD timecourse showing a typical profile. The most ventral voxels of V3A, however, showed significant if less pronounced activations following stimuli appearing in the three other quadrants. These voxels were of a large cluster of activations located outside RV3A.

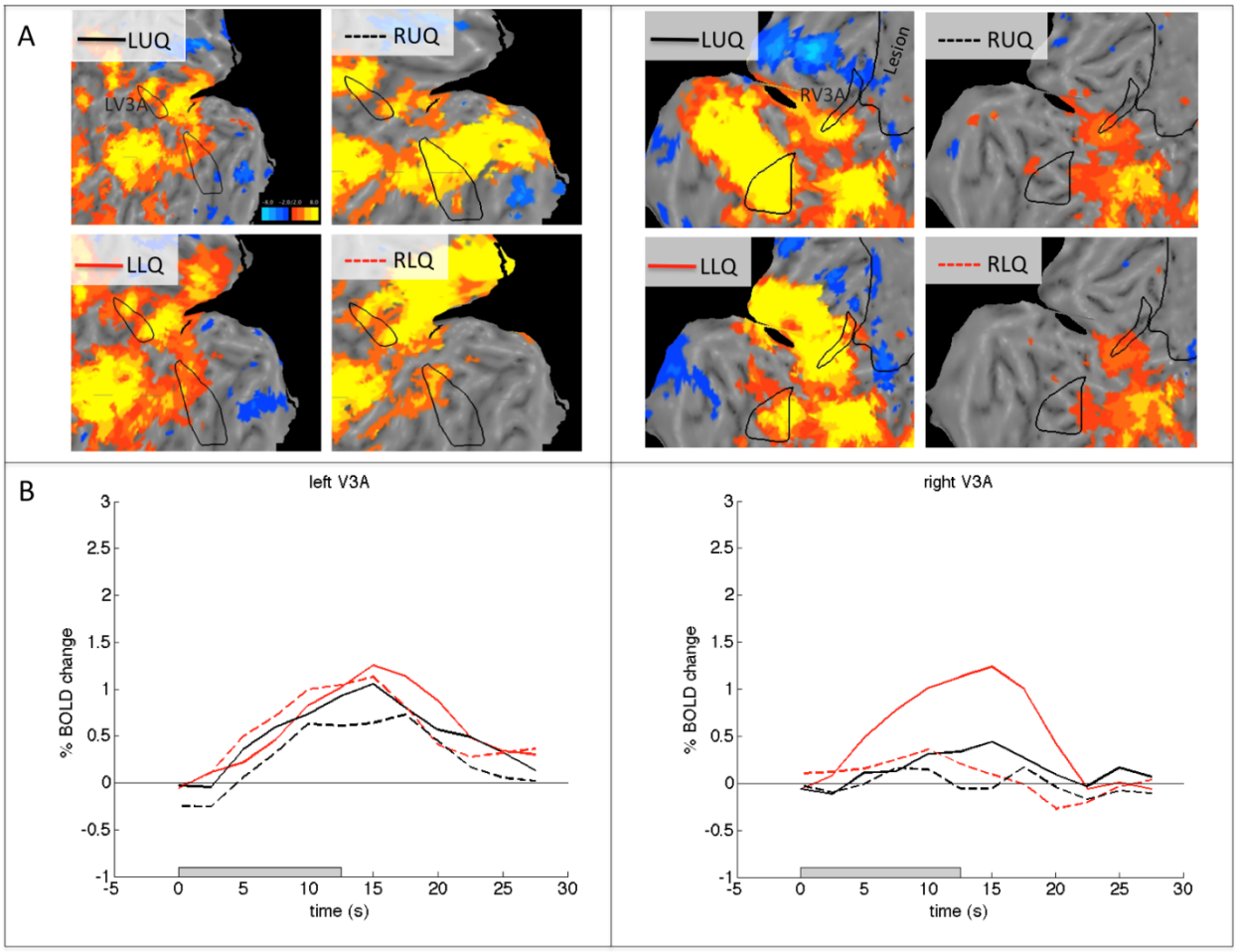
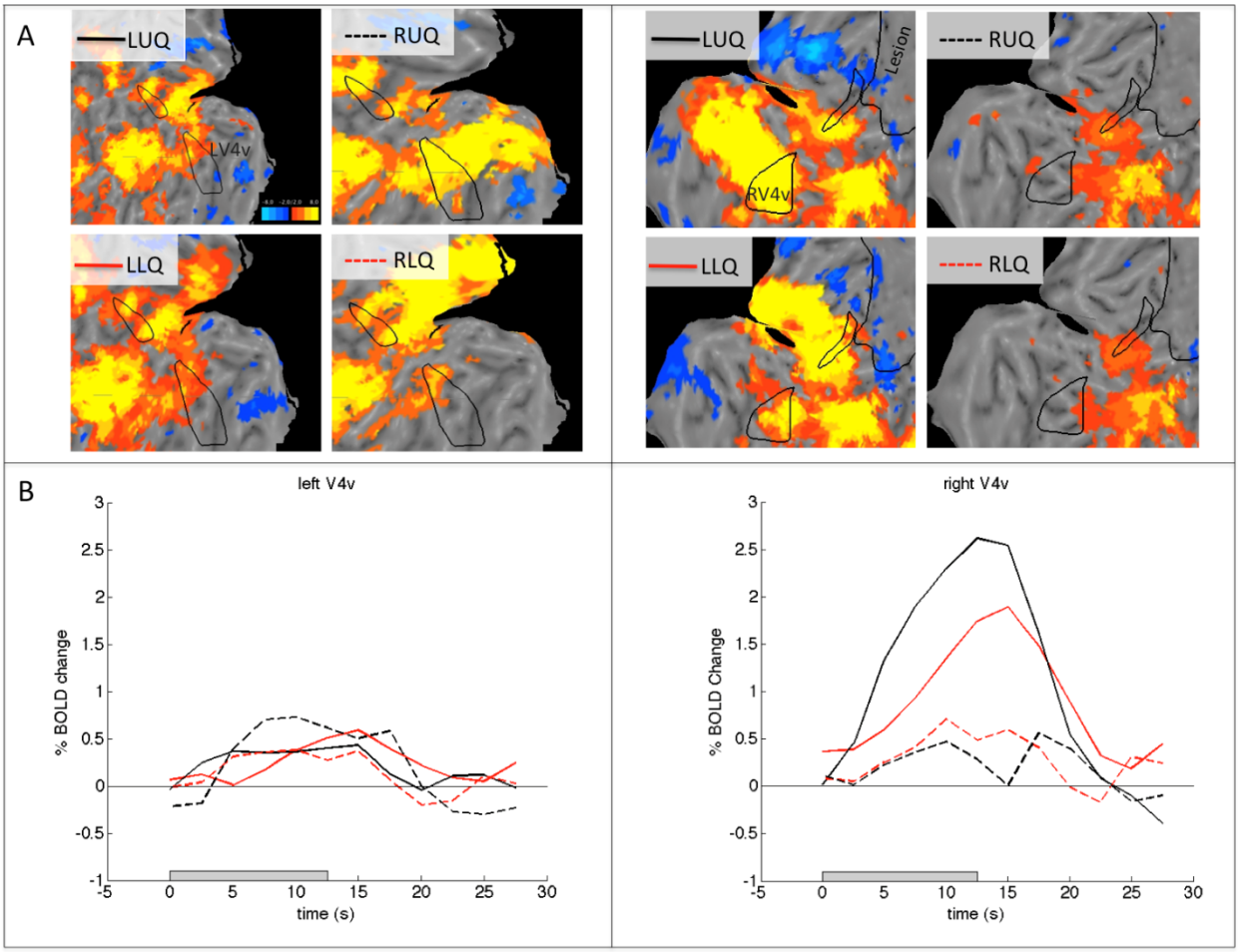


Figure 3.8. Visually evoked BOLD responses in left and right V3A regions. (A) Z-transformed, t-stat maps of the four quadrantic visual responses overlaid on the flattened left visual cortex (left figures) and right visual cortex (right figures). The maps showing voxels of significant activation compared to baseline condition (corrected p<.000) following the LUQ, LLQ, RUQ and RLQ stimuli. A threshold (Min ±2 < Z-value > Max ±8) was applied to the

significant voxels. Almost the entire region within LV3A was significantly responded to all quadrant stimuli. RV3A, however, respond only to LLQ. The most ventral portion of the RV3A contains significantly active voxels with LUQ, RUQ and RLQ stimulation. (B) The time courses of these activation evoked in LV3A (left graph) and RV3A (right graph) by each of the four quadrantic stimuli.

Figure 3.9 shows the activations and time courses of BOLD responses in the left and right V4v. In left V4v, there was a significant BOLD response to all stimuli, regardless of their location. The activation maps shows that almost the entire region responded to stimulus in the right upper quadrants, while only its most dorsal voxels were significantly activated following stimuli presented in the other three quadrants, suggesting that the foveal representation showed most degree of bilateral responses. However, the amplitude and latency of BOLD responses evoked was similar regardless the location of the visual stimuli. In the V4v of the right hemisphere, there was a significant activation following stimuli presented either in the left upper and lower quadrants but not following stimuli in the right upper quadrants. The timecourse of the BOLD response was notable because its amplitude was three to four larger than that of responses evoked in area V4 of the opposite hemisphere. While one needs to interpret cautiously interregional amplitude differences, the degree of difference does certainly suggest a difference in the gain of visual response in area V4 of the left and right hemisphere



baseline condition (corrected p<.000) following the LUQ, LLQ, RUQ and RLQ stimuli. A threshold (Min

Figure 3.9. Visually evoked BOLD responses in left and right V4v regions. (A) Z-transformed, t-stat maps of the four quadrantic visual responses are overlaid on the flattened left visual cortex (left figures) and right visual cortex (right figures). The maps show voxels of significant activation compared to the ±2 < Z-value > Max ±8) was applied to the significant voxels. Within LV4v, there is a spatially large significant activation following RUQ stimulation. Also, its dorsal portion region showed significant responses to LUQ, LLQ and RLQ stimuli. In RV4v, almost the entire region was activated when stimuli appeared in LUQ or in the LLQ. (B) The time courses of these activation evoked in LV4v (left graph) and RV4v

(right graph) by each of the four quadrantic stimuli. Note, the large responses evoked in the RV4v compared to the significant responses in the LV4v.

Table 1 reports the significance of the difference of the BOLD response amplitude evoked by contralateral and ipsilateral visual stimuli in homologous retinotopic regions of left and right hemisphere. Ipsilateral visual responses were of greater magnitude in dorsal regions of the left hemisphere than homologous regions of the right hemisphere, suggesting that especially higher tier regions of the left hemisphere, like V3 and V3A, became responsive to ipsilateral visual stimuli. On the other hand, no such difference was found for ventral regions. This is because the magnitude of the BOLD response evoked by ipsilateral visual stimuli was similar in these regions, even though V4 in the left hemisphere showed no obvious spatial selectivity, whereas V4 in the right hemisphere did. Contralateral visual responses were instead much greater in the right V4 than the left V4, with no other region showing a hemispheric difference, suggesting that in V4 of the affected hemisphere there was an increase in response gain to contralateral visual stimuli.

Table 1 – Comparison of contralateral and ipsilateral response magnitudes in left and right hemisphere

	Contralateral response (left - right hemisphere)		Ipsilateral response (right - left hemisphere)	
	Z-Score	p-value (two-tailed)	Z-Score	p-value (two-tailed)
Dorsal				
V1	0.29	*0.77*	0.31	*0.76*

V2	0.25	*0.8*	0.74	*0.44*
V3	0.19	*0.85*	**2.12**	*0.03*
V3A	1.02	*0.31*	**3.88**	*<0.01*
Ventral				
V1	-0.82	*0.41*	-0.18	*0.86*
V2	-0.99	*0.32*	-0.18	*0.86*
V3	-0.94	*0.35*	0.66	*0.51*
V4	**-2.82**	*<0.01*	0.63	*0.53*

Functional Connectivity of Retinotopic Regions

The present study also examined patterns of functional connectivity of homologous retinotopic regions of the left and right hemisphere. Figure 3.10 shows the brain regions with significant functional connectivity with the ventral and dorsal aspects of V1 of the left and right hemisphere. Dorsal primary visual cortices of both hemispheres showed significant correlations with visual cortices, thalamus and SMA. They also showed negative correlations with Medio-PreFrontal Cortex (MPFC), a component of the default mode network. However, LV1d showed greater negative correlations with MPFC than RV1d, and greater positive correlations with the frontal eye fields (FEF) of left and right hemispheres compared to RV1d, as revealed in difference FC map (3rd column from left).

As for ventral V1 (LV1v and RV1v), it exhibited significant functional connectivity with visual cortices of both hemispheres, superior parietal lobule (SPL), thalamus, bilateral

sensory-motor cortices (SM) and SMA. These regions also showed significant anticorrelations with the MPFC. However, LV1v exhibited greater functional connectivity with left MT+ and FEFs of both hemispheres compared to RV1v, while RV1v showed greater FC with retinotopic regions along the medial surface of the occipital lobe, as shown by the difference map in Figure 3.10.

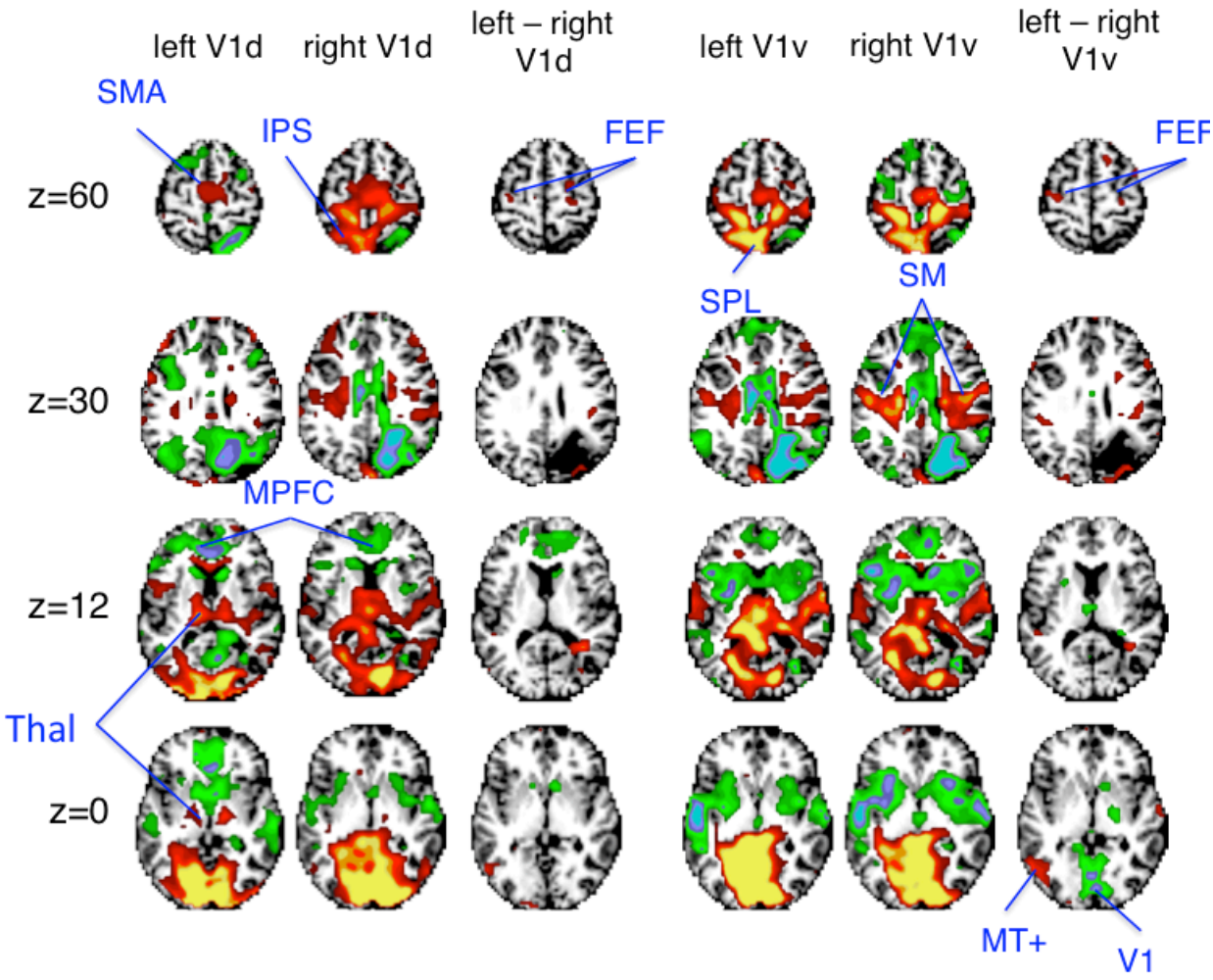


Figure 3.10. Functional connectivity of dorsal and ventral primary visual cortices. The z-transformed, t-stat maps of significant positive correlation (orange to yellow) or negative correlation (green to blue) with the corresponding seed regions, indicated above each FC

map, is shown into selected patient's axial slices. The numbers to the left of the images is the corresponding Z coordinates in the Talairach space. The slices presented based on the neurological convention. SMA: Supplementary Motor Area; IPS:Intra-parietal lobule; MPFC:Medio-Pre-Frontal Cortex; Thal:Thalamus; FEF:Frontal Eye Field; SPL: Superior-parietal Sulcus; SM:Sensory Motor area; MT+:Medial Temporal Cortex.

Figure 3.11 shows the functional connectivity maps for V3A and V4v. The FC maps of the left and right V3A seed regions were largely similar. Both regions showed positive correlations with visual cortices of both hemispheres, including lateral occipital complex (LOC) and MT+. Additional they showed significant correlations with left SPL and FEFs of both hemispheres. They were anticorrelated with posterior Insula in both hemispheres (structure not labelled in Figure 3.11) and MPFC. However, the left V3A showed greater functional connectivity with the left LOC, left IPS and bilateral FEF, than right V3A.

V4 of both hemispheres exhibited significant functional connectivity with extra-striate visual cortices, bilateral primary auditory cortex, left SPL, SMA and bilateral FEF. However, left V4 showed greater functional connectivity with lateral extra-striate visual cortex, including LOC and MT+, and FEFs of both hemispheres than right V4. On the other hand, right V4v showed greater FC with the MPFC compared to left V4v.

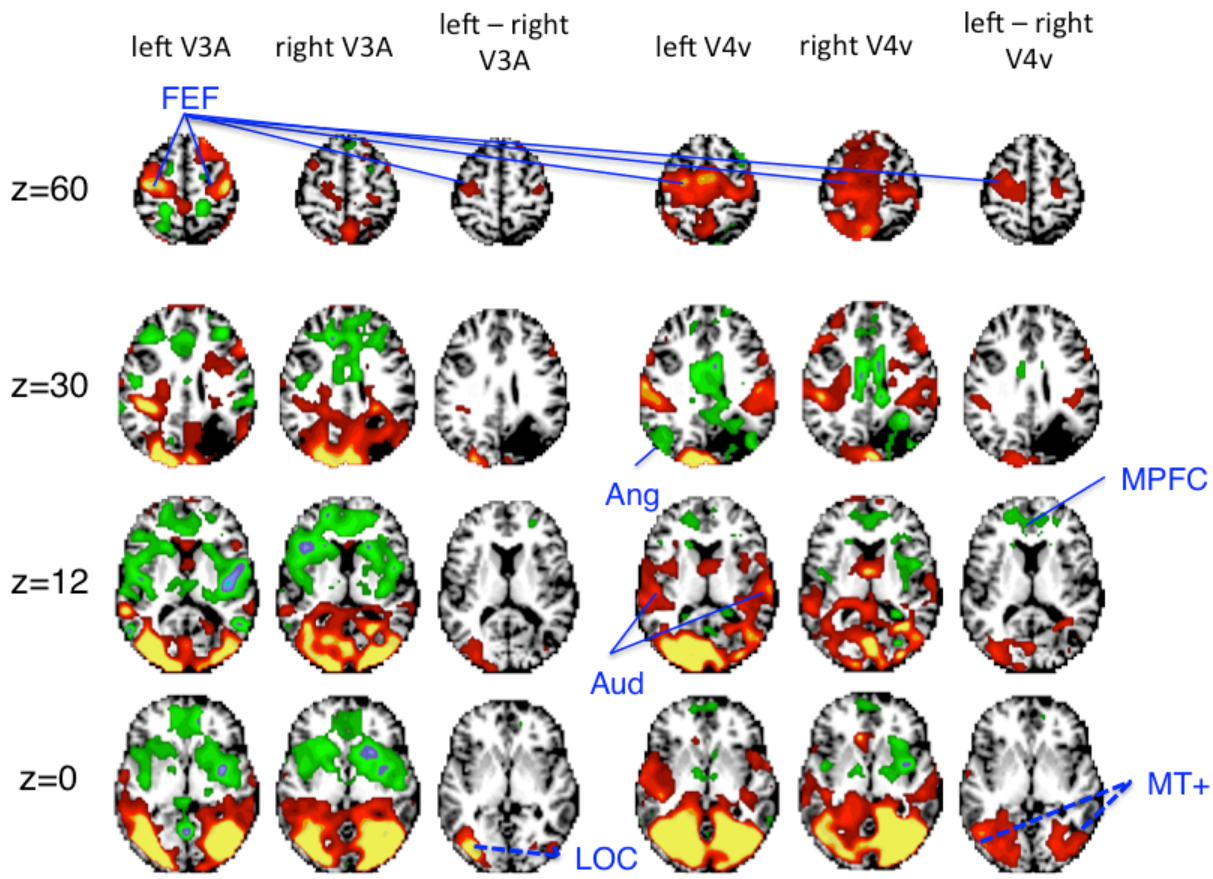


Figure 3.11. Functional connectivity dorsal and ventral quaternary visual cortices (V3A and V4v). The z-transformed, t-stat maps of significant positive correlation (orange to yellow) or negative correlation (green to blue) with the corresponding seed regions, indicated above each FC map, is shown into selected patient's axial slices. The numbers to the left of the images is the corresponding Z coordinates in the Talairach space. The slices are presented based on the neurological convention. Ang:Angular gyrus; Aud: Auditory cortex; LOC:Lateral Occipital Cortex

In summary, regional functional connectiivty showed consistent differences between homologous retinotopic regions of the left and right hemisphere, since retinotopic regions in

the left, contralesional hemisphere showed greater functional connectivity with FEFs, left SPL, left IPS and bilateral extrastriate visual cortex compared to homologous regions in the ipsilesional, right hemisphere. Moreover, regions of the left hemisphere showed greater anticorrelations with the MPFC. These hemispheric difference appeared to be greater in higher tier region (V3A and V4V) than primary visual cortex.

Functional Connectivity of Retinotopic Regions Principal Components

In a second functional connectivity analysis, timecourses obtained by computing the principal component of resting state BOLD fluctuations obtained from each of the sixteen retinotopic regions of interest were used as seeds. The first three components, which accounted for over 90% of the overall data variance were used (PC1, PC2 and PC3). PC1 is a component that is roughly the average timecourses across all visual regions. The brain regions that showed a significant FC with this component are the left and right visual cortices and SM. The MPFC and bilateral anterior insular cortex showed anticorrelation with this component (the first column in Figure 3.12). The PC2 is a component that separates medial and lateral visual regions and was positively correlated with activity in medial visual cortices, thalamus, and bilateral posterior insula, but negatively correlated with activity in extrastriate visual cortices and FEFs (second column in Figure 3.12). The PC3, which basically captures spontaneous fluctuations that are anticorrelated between left and right visual regions, was positively correlated with activity in right visual cortex, mainly its ventral extension, and a set of regions comprising the default mode network (Raichle, MacLeod, Snyder, Powers, Gusnard & Shulman, 2001; Greicius, Krasnow, Reiss & Menon, 2003). These regions included bilateral RetroSplenial Cortex (RSC), Angular Gyri and MPFC. Interestingly, areas of the Medial Temporal Gyrus (MTG), corresponding to the likely location of secondary auditory cortex (Burton, Diamond, & McDermott, 2003) but also potentially comprising regions

corresponding to poorly characterized foci of the DMN (Buckner, Andrews-Hanna & Schacter, 2008)were functionally connected with right, but anticorrelated with left visual cortex, possibly suggesting some degree of cross-modal plasticity in right visual cortex.

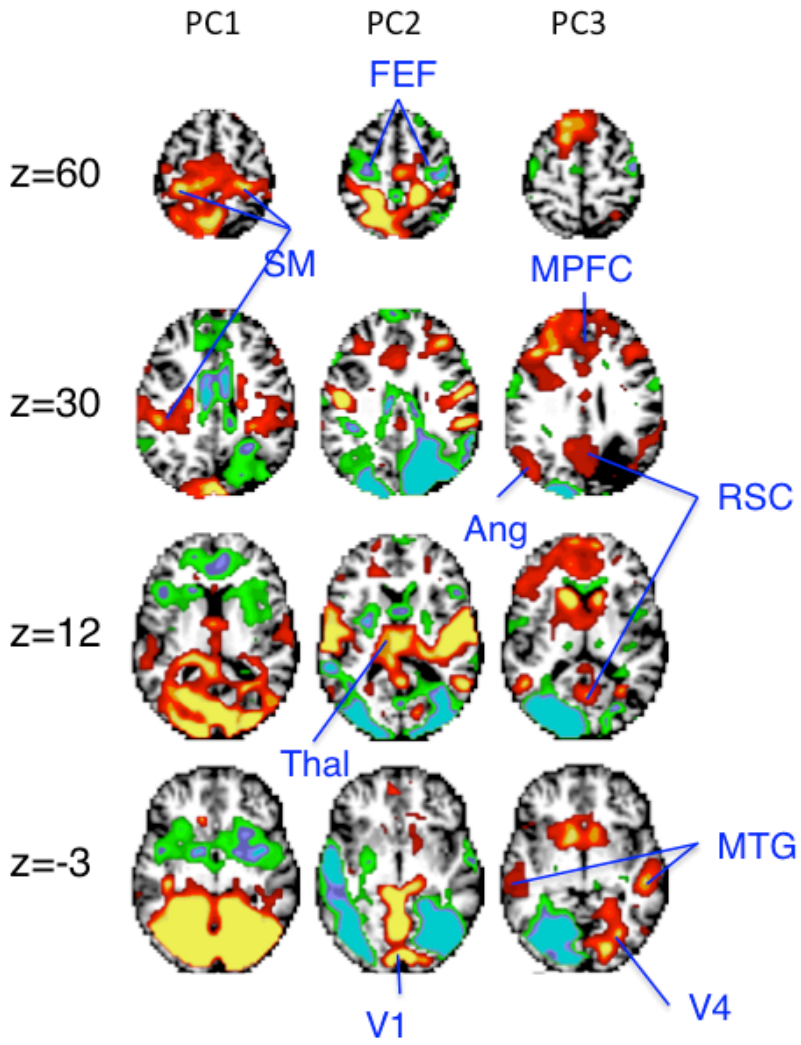


Figure 3.12. Functional connectivity maps based on principal components. The z-transformed, t-stat maps of significant positive correlation (orange to yellow) or negative correlation (green to blue) with the corresponding seed principal component, indicated above each FC map, is shown into selected patient's axial slices. The numbers to the left of the images is the corresponding Z coordinates in the Talairach space. The slices are presented based on the neurological convention. The 3rd PC specially

demonstrates positive functional connectivity between right ventral visual regions (V4v) and default mode network (MPFC, RSC, Ang). MTG: medial temporal gyrus; Ang: angular gyrus; RSC: retrosplenial cortex; and Thal: thalamus.

Glutamate and GABA concentration in visual cortices

Table 2 reports the GABA and Glutamate concentrations estimated before and after correction for partial volume effect, due to volume occupied by CSF. Partial volume corrected estimates, reported under the 'Parenchymal Concentration' column in the table, indicated that GABA concentrations were higher in ipsilesional visual cortex than contralesional cortex. Conversely, Glutamate concentration was higher in the contralesional area compared to ipsilesional visual cortex.

Table 2: MRS-GABA and Glutamate measurements

Voxel	GABA			Glu		
	Mean (mM)	SD (mM)	Parenchymal Concentration (mM)	Mean (mM)	SD (mM)	Parenchymal Concentration (mM)
Right VC	2.97	0.37	1.65	4.33	0.36	2.39
Left VC	2.47	0.28	1.18	13.5	2.2	6.27
Notes.	mM: mill mole.					

The NAA concentration was similar in both cortices. The GABA to NAA ratio was greater in the ipsilesional (0.22) than contralesional cortex (0.16), while the Glutamate to NAA ratio was lower in the ipsilesional (0.31) than contralesional cortex (0.83).

Discussion

The present study investigated the functional correlates of visual reorganization in an adult patient with a left lower visual quadrant defect, due to a lesion affecting the right optic radiation. Results suggest that the visual cortex of the contralesional hemisphere exhibited BOLD responses to stimuli presented in both the ipsilateral and contralateral visual field. This effect was more evident in higher tiers of visual cortex than primary visual cortex. Moreover, comparison of the functional connectivity maps obtained from homologous retinotopic regions of the left and right hemisphere, indicated that regions of the left, contralesional hemisphere exhibited greater functional connectivity with the FEFs of both hemispheres than homologous regions of the right hemisphere. In contrast, visual cortex of the right, ipsilesional hemisphere exhibited larger BOLD responses to contralateral visual stimuli compared to the contralesional cortex. Ipsilesional visual cortex, especially its ventral division, showed positive FC with the DMN, while contralesional visual cortex showed the opposite effects. Finally, ipsilesional visual cortex showed higher GABA and lower glutamate concentrations compared to the contralesional visual cortex. The MRS and the above findings are discussed below in detail.

Spatial Tuning in Contralesional Visual Cortex

This study found that visual stimuli appearing in the left visual field, and especially the lower quadrant, elicited BOLD responses in retinotopic regions of the visual cortex of the left,

contralesional hemisphere. Moreover, responses evoked by ipsilateral visual stimuli appeared to be delayed and smaller in amplitude in primary visual cortex (see Figure 3.6), compared to responses evoked by contralateral stimuli. However the time of onset and amplitude of responses evoked by ipsilateral and contralateral visual stimuli were indistinguishable in higher tier regions of the cortical hierarchy (see figures 8 and 9). Moreover this effect was not found in homologous retinotopic regions of the right, ipsilesional hemisphere, which instead showed a degree of spatial selectivity consistent with that commonly found in retinotopic regions of healthy controls (Tootell, Mendola, Hadjikhani, Liu, & Dale, 1998), with no or slightly negative response to visual stimuli presented in the ipsilateral visual field. The activation found in the contralesional cortex is consistent with the considerable amount of literature concerning brain reorganization, including findings in patients with motor strokes, who show ipsilateral cortical activation when trying to move their paretic limb (e.g. Chollet, DiPiero, Wise, Brooks, Dolan, & Frackowiak, 1991; Cramer, Nelles, Benson, Kaplan, Parker, Kwong, & Rosen, 1997; Grefkes & Ward, 2013), and aphasic patients with large left hemispheric lesions who can show activations in regions of the right hemisphere during the performance of language tasks (Cao, Vikingstad, George, Johnson, & Welch, 1999; Fernandez et al., 2004; Rosen, Petersen, Linenweber, Snyder, White, Chapman, & Corbetta, 2000) and patients with strokes of the visual system (Nelles et al., 2002; Nelles et al., 2007), suggesting that recruitment of homologous regions of the contralesional hemisphere may be a ubiquitous mechanism of brain recovery. It should be noted that it is not yet entirely clear whether the contralesional activations that are found in stroke patients are adaptive or whether they might actually have a deleterious effect on performance. It has been suggested that in motor stroke patients, there is increased cross-hemispheric inhibition from contralesional onto ipsilesional M1, using both effective connectivity (Grefkes et al., 2008b) and TMS measures (Murase et al., 2004). Similarly, functional imaging studies have found

that the amplitude of BOLD signal associated with a language tasks correlated with task performance in perilesional regions of the left hemisphere but not in contralesional regions homologous to those affected by the stroke (Rosen et al, 2000). In patients with unilateral neglect, Kinsbourne (1976) suggested that the main reason for the presence of lateralized attentional deficits was an hemispheric imbalance brought about by unihemispheric lesion. This suggestion has found preliminary confirmation in longitudinal functional studies, which have provided evidence for increased activity in parietal regions of the left hemisphere of neglect patients which normalizes upon recovery (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005) and TMS studies, which have suggested increased excitability in parietal regions of the left hemisphere (Koch, Oliveri, Cheeran, Ruge, Gerfo, Salerno, & Caltagirone, 2008) as well as improved performance when left hemisphere function is disrupted (Fierro, Brighina, & Bisiach, 2006). Therefore, it is possible that contralesional activations evoked by ipsilateral visual stimuli may reflect loss of cross-hemispheric inhibitory signals in this patient that normally suppress contra-lesional visual cortex activity. However, it should be noted that visual cortex in the ipsilesional hemisphere was not directly affected by the stroke and therefore its connection with the contralateral visual cortex were most likely spared as well. However, it is plausible that diaschisis of the ipsilesional visual cortex may have resulted in diminished activity therein (Corbetta et al, 2005), and hence diminished inhibitory drive onto the contralesional hemisphere. On the other hand, the spatial selectivity and retinotopic organization of visual cortex is specified very early in development, prior to first visual experiences and reflects the orderly connectivity of retinal afferents on visual thalamus and thalamic afferents onto visual cortex (Espinosa & Stryker, 2012). This suggests that cross-hemispheric inhibition may not play a major role in determining the spatial selectivity of visual cortex and that there are other reasons why visual cortex of the contralesional visual cortex starts responding to stimuli presented in the ipsilateral visual field, contrary to what

had been previously suggested (Reitsma et al., 2013). Ultimately, determining the nature of contralesional activations will require establishing their functional role.

The Top-down Attentional Effect on Ipsilateral Activation

An alternative explanation for the ipsilateral activations observed in contralesional visual cortex is that top-down attentional effect may modulate the spatial profile of receptive fields in visual cortex (Reynolds & Heeger, 2009). In this patient, the remapping of visual responses observed in the contralesional visual cortex was more pronounced in higher tiers than in lower tiers of the retinotopic cortex which may reflect the fact that these regions contain units with larger receptive fields than primary visual cortex and therefore more amenable to undergo a spatial shift as a result of top-down, attentional biases. Interestingly, V3A and V4 regions of the left hemisphere also showed greater functional connectivity with the dorsal attentional network regions (bilateral FEF, left SPL and left IPS) than homologous regions of the right hemisphere, replicating, but more pronouncedly, a pattern of inter-hemispheric connectivity differences exhibited by primary visual cortex as well. One interpretation of this interhemispheric difference in functional connectivity between left and right visual cortex, is that attentional regions, and especially the FEFs, may reconfigure the spatial properties of receptive fields in retinotopic regions, especially in retinotopic regions of the right, lesioned hemisphere, through top-down modulations. This proposal is broadly consistent with a large body of literature concerning the anatomical distribution and nature of attentional effects in visual cortex. For example, animal studies have showed that micro-stimulation of the FEF can modulate visually evoked neural ingle unit responses in V4 in a spatially selective manner (Moore & Armstrong, 2003) and that attention can displace receptive fields in extrastriate visual areas toward the attended location (Womelsdorf, Anton-Erxleben, Pieper, & Treue, 2006). fMRI studies have also documented the presence of

increasing attentional effects along the retinotopic hierarchy for a wide range of tasks, associated with deployment of either feature (Chawla, Rees, & Friston, 1999) or spatial attention (Noesselt et al., 2002).

Response Gain Increases in Ipsilesional Visual Cortex and DMN

Ventral retinotopic regions of the ipsilesional hemisphere showed greater BOLD responses to contralateral visual stimuli than homologous regions of the contralesional hemisphere (see Figure 3.9) but no evidence of a change in spatial selectivity that is characteristic of these regions in healthy controls. These findings suggest that ipsilesional visual cortex, at least along its ventral extension, can recalibrate its gain to accommodate a decrement in sensory inputs from the thalamus. An interesting question is how recalibration may take place. The functional connectivity analysis indicated that ventral region of visual cortex in the ipsilesional hemisphere synchronized their resting state activity with regions belonging to the DMN (see Figure 3.12), as indexed a by positive correlation between spontaneous BOLD fluctuations recorded in these regions. On the other hand, contralesional visual cortex showed anticorrelated activity with the DMN, suggesting that synchronized activity with the DMN was specific to ipsilesional visual cortex. One may therefore put forth a highly speculative suggestion, namely that the increased response gain to visual stimuli observed in these same regions may depend on their increased connectivity with the DMN, which follows recovery. The implication of this proposal is that the DMN may act as a backup system for failing brain functions. This is motivated by the literature on normal aging (Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Hafkemeijer, van der Grond, & Rombouts, 2012), which has indicated that the DMN showed less deactivation in older adults than younger adults. The role of the DMN in neural reorganization following a stroke has been documented in a study carried out in a large group of neglect patients. Increased correlations

between regions of the ipsilesional hemisphere and DMN (Baldassarre, Ramsey, Hacker, Callejas, Astafiev, Metcalf, & Corbetta, 2014) was reported and interpreted as demonstrating a loss of networks segregation within the lesioned hemisphere, rather than a reconfiguration of functional connectivity for adaptive purposes. Additionally, ipsilesional visual cortex was functionally connected to regions in the MTG of both hemispheres, corresponding to the location of secondary auditory cortex. This finding suggests that visual cortex in the ipsilesional hemisphere may undergo some degree of crossmodal plasticity, similarly to the visual cortex of blind individuals (Sadato et al, 1996; Burton et al, 2003). Whether it responds or not to auditory stimuli was not assessed in this study.

MRS-Assessed GABA and Glutamate Levels

Ipsilesional visual cortex showed higher GABA and lower glutamate concentrations than contralesional visual cortex. Based on published values for Glutamate concentrations in visual cortex (Baker, Dilks, Peli, & Kanwisher, 2008; Wilson et al., 2011) ipsilesional visual cortex exhibits decrements in Glutamate levels, consistent with the fact that it receives a diminished excitatory sensory input because of the damage to the optic radiation. While the attribution of changes in glutamate concentrations to diminishes excitatory input is speculative, it is supported by the finding that MRS measures of Glutamate concentration are closely correlated with measures of local neuronal excitability (Stagg et al., 2011). The decrement of Glutamate found in ipsilesional cortex may have implications for the interpretation of the increased excitability observed there, since it suggests that plastic changes in visual response gain found in the ipsilesional visual cortex may be mediated by homeostatic mechanisms, which aim to maintain constant levels of activity, rather than LTP-like mechanisms (Espinoza & Stryker, 2012).

It is not entirely clear whether and in which hemisphere changes in GABA concentrations are found in our patient compared to healthy controls, given the lack of published normative values for GABA concentrations in the visual cortex of age matched individuals. Nevertheless, the data suggest that GABA and Glutamate concentrations did not covary. In fact, while Glutamate concentrations were increased in the contralesional hemisphere, GABA concentrations were actually lower in the contralesional than ipsilesional hemisphere. This finding appears at variance with previous studies showing a reduction in GABAergic inhibition in perilesional tissue after a stroke, which have also suggested that GABA decrements may be important in fostering recovery of function (e.g. Castro-Alamancos et al., 1995; Trepel & Racine, 2000). However, a recent MRS study reported that in a group of chronic, hemiparetic patients undergoing a two weeks long treatment with constraint induced therapy, there was no overall change in GABA levels between a pretreatment baseline scan and a post-treatment follow-up scan in ipsilesional motor cortex. However, the degree of motor improvement following treatment correlated with the degree of GABA concentration decrements observed following treatment (Blicher et al., 2013), suggesting that patients who had decrements in cortical GABA concentrations were more likely to improve with treatment because of enhanced neural plasticity in motor cortex. One possibility is that lower GABA concentrations in contralesional visual cortex may reflect a reduction in GABAergic tone following recovery, and be somehow related to the changes in spatial tuning observed there. GABA concentration decrements in regions distal to the lesion have been shown in previous MRS studies conducted in patients with stroke (Głodzik-Sobańska et al., 2004). Perhaps even more interestingly, decrements in $GABA_A$ receptor availability, especially in the contralesional hemisphere, have been documented recently in patients with motor stroke (Kim, Yang, Cho, Lim, & Paik, 2014), suggesting that changes in inhibitor tone following stroke may have both pre and postsynaptic components. A study carried in animal models of

stroke has indicated that extrasynaptic GABAergic activity may be increased in perilesional cortex, due to failure of GABA reuptake, and that administering a selective antagonist for extra-synaptic $GABA_A$ receptors enhances of motor function recovery (Clarkson, Huang, MacIsaac, Mody, & Carmichael, 2010), suggesting that changes in GABA concentrations may have physiological effects on both synaptic and extrasynaptic sites. Whether changes in GABA concentration observed in this patient reflect changes in reuptake efficiency, as suggested by the study above, or rather decreases synthesis, as suggested by studies in patients with epilepsy (Stagg et al., 2010), remains unknown.

Limitations

The main limitation of this study is that there was no record of eye position during the fMRI experiments. The observed remapping of special selectivity in the left contralesional visual cortex assumes that the patient was compliant with the instruction to maintain central fixation throughout the scans. The fact that the remapping showed a gradient, being more robust and appearing earlier in higher cortical tiers, gives us some reassurance that an eye movement confound is not majorly implied in determining this result. One possibility to control for such an issue in the scanner would be to employing very brief visual stimuli (150ms long), to prevent visually evoked saccades to interfere with visually evoked BOLD signals.

Additionally, the absence of control data in healthy participants require that the conclusions of this study are mainly based on the comparison of patterns of BOLD activity, either evoked or ongoing, recorded in homologous regions of the ipsi and contralesional hemisphere. This issue is also being currently addressed by collecting data, with the same paradigm, in age-matched, gender-matched controls.

Concluding remarks

The patient examined exhibited BOLD response differences between ipsilesional and contralesional visual cortex. These changes included remapping of ipsilateral visual stimuli on contralesional visual cortex and increase BOLD response gain in the ipsilesional compared to the contralesional hemisphere. The interpretation of these findings is clearly preliminary and speculative. Outstanding questions that future data will need to address include the following: 1) are ipsilateral activations in contralesional visual cortex functionally relevant and do they reflect attentional biases? This point is crucial to determine whether ipsilesional activations are beneficial or not to recovery and whether they reflect crosshemispheric interactions or are there top-down effects? 2) Are there differences in the amplitude of the BOLD response of ipsi and contralesional visual cortex to stimuli of varying contrast? BOLD responses in ipsilesional visual cortex should be greater than contralesional visual cortex only when high contrast, but not low contrast stimuli are presented. This is because visual thresholds should be elevated in the affected visual field, despite the increased response gain in the contralateral, ipsilesional visual cortex. This would provide evidence that difference in response gain reflect neural rather than hemodynamic factors. Additionally ERP recordings could be used to provide additional evidence for a neural origin of the response gain effects. 3) Finally, do auditory stimuli evoke a BOLD response in contralesional and ipsilesional visual cortex? If indeed contralesional visual cortex undergoes some degree of cross-modal plasticity by synchronizing its resting state BOLD fluctuations with areas of auditory cortex, is that reflected in increased responsiveness to auditory stimuli compared to homologous regions of the opposite hemisphere?

Chapter 4: Treatment driven plasticity in HVFD

In the previous chapter I presented evidence from a case imaging study on how the brain adapts to changes in how it receives visual signals, namely, the disconnection of the visual cortex from its thalamic input. The data demonstrated spontaneous plastic change involving the spatial selectivity of the unaffected hemisphere, response gains in the lesioned hemisphere and differing patterns of functional connectivity and baseline metabolic activity between the two hemispheres at rest. However in addition to spontaneous reorganisation following lesion, structures and networks within the human visual system can also reorganise through practice and training. Understanding the neural correlates of treatment effects in visual rehabilitation is a crucial line of investigation for advancing both the efficacy of treatment and the selection of appropriate treatment protocols for the appropriate patient group. Further, analysing the nature of plastic change, in conjunction with behavioural correlates of improvement, can give further insight into the biases driven by the lesion, or ensuing neurological condition. In this chapter, I will therefore present results from two experiments using electrophysiological indices of the plastic change driven by multi-sensory stimulation treatment (Bolognini et al., 2005; Passamonti et al., 2009; Làdavas, 2008).

4.1 Experiment 3: Effects of Multisensory stimulation treatment on stimulus-evoked ERP components of spatial attention

A lateralised lesion to the human cortex can disrupt inhibitory interhemispheric fibres assumed to keep interhemispheric competition in a state of equilibrium (Cazzoli et al., 2009;

Kinsbourne, 2003; Sprague, 1966), resulting in hyperactivation of the contralesional hemisphere and hypoactivation of the lesioned hemisphere. Converging evidence implicates such interhemispheric disturbance in the neuropsychological condition hemispatial neglect, in which the hyperactivation of the intact hemisphere drives attention toward the ipsilesional visual field, with a resulting lack of attentional allocation to the contralesional field (Brighina et al., 2003; Koch et al., 2012).

Interhemispheric competition might extend to homonymous visual field defects on the grounds that he continuous asymmetric visual input experienced by hemianopic patients could cause imbalanced attention processing and a consequent functional hemispheric asymmetry (Tant et al., 2002). This hypothesis has been tested using the greyscales task (Mattingley et al, 1994; Tant et al, 2002; Mattingley et al, 2004) a task where two left to right mirror reversed color gradients are aligned vertically in front of the subject (see figure 4.1).

Figure 4.1: Example stimulus in the greyscales task, adapted from Mattingley et al, (2004)

The task requires that participants judge whether the top or bottom gradient appears darker, overall. Despite both gradients being of equal brightness, patients with unilateral visual field defects tend to show a bias toward selecting the gradient with the darker colour ipsilateral to their lesion, that is, right lesion patients exhibit a bias toward selecting the gradient with the darker wedge to the right, and left lesion patients exhibiting a bias toward selecting gradients with the darker wedge to the left (Tant et al, 2002). The authors argue that this bias suggests hyperactivation of the intact hemisphere, due to the unilateral sensory field loss.

However, evidence from studies using another form of assessment – line bisection - suggests that hemianopia could be underscored by a contralateral bias. In the line bisection task, which is often used as part of the assessment of hemispatial neglect, subjects are asked to bisect the midpoint of a series of horizontal lines, presented in a sinuous vertical alignment. Neglect patients will place their response in the hemispace ipsilateral to their lesion (Barton & Black, 1998), demonstrating an iplsilateral attentional bias. However in contrast, Barton and Black (1998; results in figure 4.2 below) demonstrated that patients with homonymous visual field defects have a bias contralateral to their lesion, that is, patients with a right lesion consistently reported the midpoint in the region of hemispace to the left of veridical centre, while left lesion patients reported the centre consistently to the right.

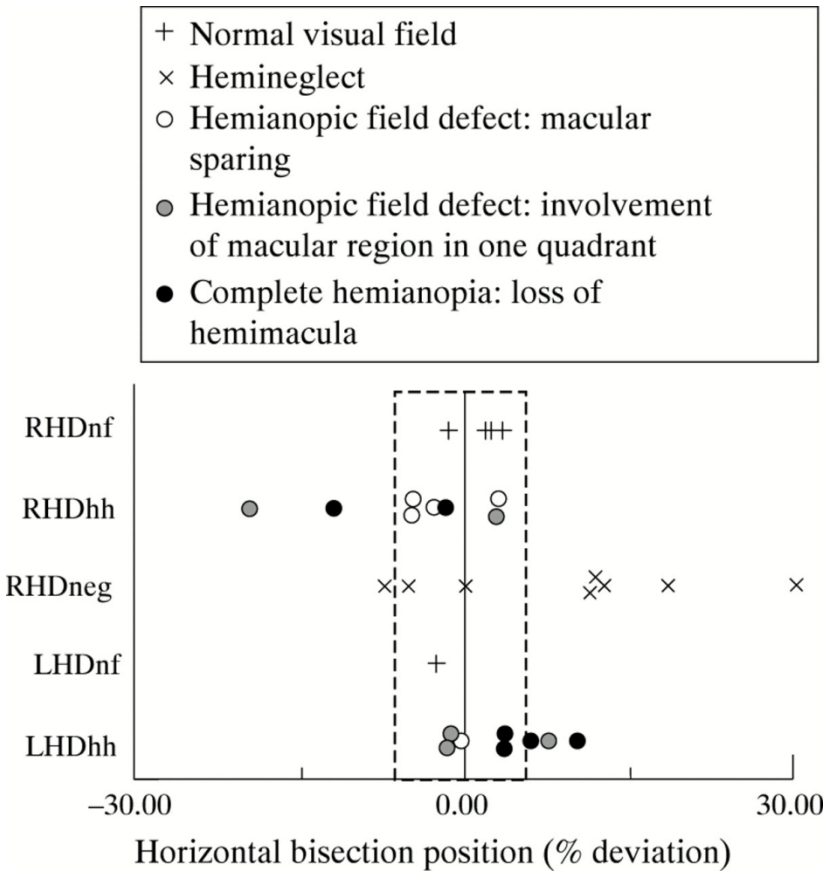


Figure 4.2 - Results from Barton and Black (1998) Patient groups from top to bottom: Right hemisphere lesion with normal visual and attentional functioning (RHDnf); Right hemisphere lesion with homonymous hemianopia (RHDhh); Right hemisphere lesion with hemispatial neglect (RHDneg); Left hemisphere lesion with normal visual and attentional functioning (LHFnf); Left hemisphere lesion with homonymous hemianopia. Negative deviations reflect responses to the left of veridical centre.

As highlighted in the introduction to this thesis, insight into the presence of a lesion is an important component of recovery and such insight could drive a bias toward the scotoma itself in an adaptive manner (Barton & Black, 1998). However a later replication by Baier et

al (2010) observed the contralateral line bisection error effect in acute patients, suggesting that the bias can emerge immediately.

Available evidence therefore suggests that at least two conflicting attentional biases can be observed in patients with homonymous visual field defect, depending on the behavioural task employed. Testing the degree to which treatment affects attentional biases could therefore offer important insight into the nature of both the impact of post-chiasmatic lesions and treatment effects. To that end, I will probe both the behavioural effects and the electrophysiological plastic change driven by multi-sensory stimulation treatment for hemianopia (Bolognini et al., 2005). As described in the general introduction to the thesis, this particular model of compensatory treatment has been shown to improve oculomotor efficiency stimulating the spared retino-colliculo-extrastriate network, with generalisation to dynamic visual detection, reading and activities in daily living. However to date, no studied have assessed the precise mechanism underscoring the treatment's effects.

Passamonti et al (2009) administered a two-week course of multisensory stimulation treatment to a group of eleven patients with HVFD. In their study, treatment effects were indexed by a host of clinical measures, including visual detection, visual search and reading tasks, while patients' eye movements were recorded using 60Hz optic eye-tracker. By demonstrating that the treatment improved oculomotor parameters (such as reduced fixation-refixation rates and shortened scanpath) the authors speculated that the treatment affected higher order cognitive correlates of visual exploration, such as spatial attention and strategic oculomotor planning; indeed, a likely substrate of multisensory stimulation treatment, the

superior colliculus, projects directly to the frontal eye fields, a key substrate in planning and execution of saccades (Liversedge & Findlay, 2000; Hanes and Wurtz, 2001).

One way to index the effect of treatment on spatial attention is to use event-related potentials (ERPs) elicited by simple visual stimulation of patients' intact visual fields. Simple visual stimulation typically evokes an N1, P1, and P3 component. Illustrated in the example figure below (Figure 4.3 - adapted from Vogel et al, 1998), stimuli appearing in a region of space where covert attention is directed will evoke higher P1, N1, P2, N2 and P3 responses in comparison to stimuli appearing at unattended locations (Neville & Lawson, 1987; Mangun et al, 1993; Luck et al., 1994).

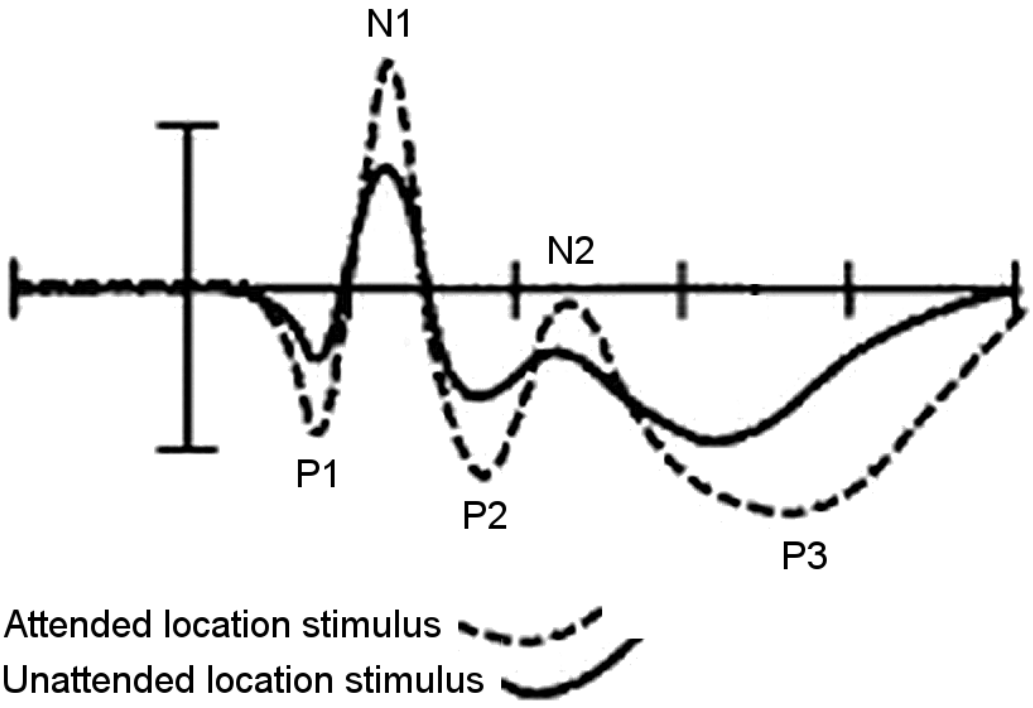


Figure 4.3 - An example event-related-potential waveform adapted from Vogel et al, 1998, depicting the relationship of spatial attention on ERP components. X-axis subtends the temporal window -100ms to 500ms post-stimulus, vertical ticks reflect time-windows of 100ms and time 0 (intersection of x and y axes) reflects the onset of the stimulus. Note that this diagram also contains a P2 and N2 which will only be elicited under certain paradigm conditions.

This pattern of results suggests that covertly directed spatial attention can influence the electrophysiological response to visual stimuli as early as 70 to 100ms post stimulus. Further, earlier components, such as P1 and N1, do not appear to be influenced by the relevance of the stimulus, i.e., whether the stimulus is a target requiring response. In contrast, later components such as the P3 are considered to reflect post-perceptual processes driving resources toward the response (Heinze et al, 1990; Luck et al., 1993). The component has been interpreted as indexing resource allocation of attention (Isreal et al., 1980; Wickens et al., 1983) specifically within a late stage of cortical visual processing, involving endogenous attention (Hopfinger & West, 2006).

In experiment 3, I will present the results from a study that administered a simple visual detection EEG paradigm, that afforded the analysis of stimulus evoked responses to stimulation of the intact visual field of a group of hemianopia patients before and after a typical course of multisensory stimulation treatment. In addition to the EEG paradigm, a clinical battery was also administered to patients before and after treatment, to probe the behavioural effects of treatment that co-occurred with any plastic change. If, as speculated by Passamonti et al (2009), multisensory stimulation treatment does indeed affect spatial

attention, treatment effects should be observable on components of the waveform elicited by simple visual stimulation. In addition, the nature of the treatment effects on these components could provide further insight in to the biases underscoring hemianopia; a post-treatment increase in amplitudes of ERP components would indicate greater attention being deployed to the intact field, while a decrease in amplitudes would suggest less attention to the intact field, likely a function of more attention being directed toward the blind field.

Materials and methods

Participants

Eight patients (1 female, mean age = 47.4 years, sd=16.7) with chronic visual field deficits were recruited (Table 4.1). The average time from lesion was 13.8 months (sd=17.4). Selection was contingent on reported visual field defects, the availability of a full visual perimetry (Figure 4.4) and CT/MRI scans of the lesion (Figure 4.5). All patients showed normal hearing and normal or corrected to normal visual acuity. Right lesioned patients were screened using the Behavioural Inattention Test neglect assessment (Wilson et al., 1987), to ensure performance was in the normal range. All patients presented deafferentation or destruction of the occipital cortex, consequent to postchiasmatic lesions, as documented by CT and MRI scans.

ID	Sex	Age	Education	Onset	Lesion Site	Aetiology
P1	M	41	11	9	Right Temporo-Occipital	AVM
P2	F	38	13	12	Right Temporo-Parietal-Occipital	Ischaemic

P3	M	47	13	3	Right Temporo-Parietal-Occipital	Ischaemic
P4	M	69	8	3	Right Temporo-Occipital	Ischaemic
P5	M	70	8	9	Right Fronto-Parietal-Occipital	Ischaemic
P6	M	24	13	56	Left Temporal	Traumatic
P7	M	57	13	7	Left Occipital	Ischaemic
P8	M	33	13	11	Left Temporal	Ischaemic

Table 4.1 - Demographic and clinical data of patients: M=Male; F=Female; Age in years; Educationin years; Onset of lesion prior to treatment in months; AVM = Arteriovenous malformation.

Informed consent was acquired from participants and all experimental procedures were administered in accordance with the Declaration of Helsinki and the Ethical Committee of the University of Bologna.

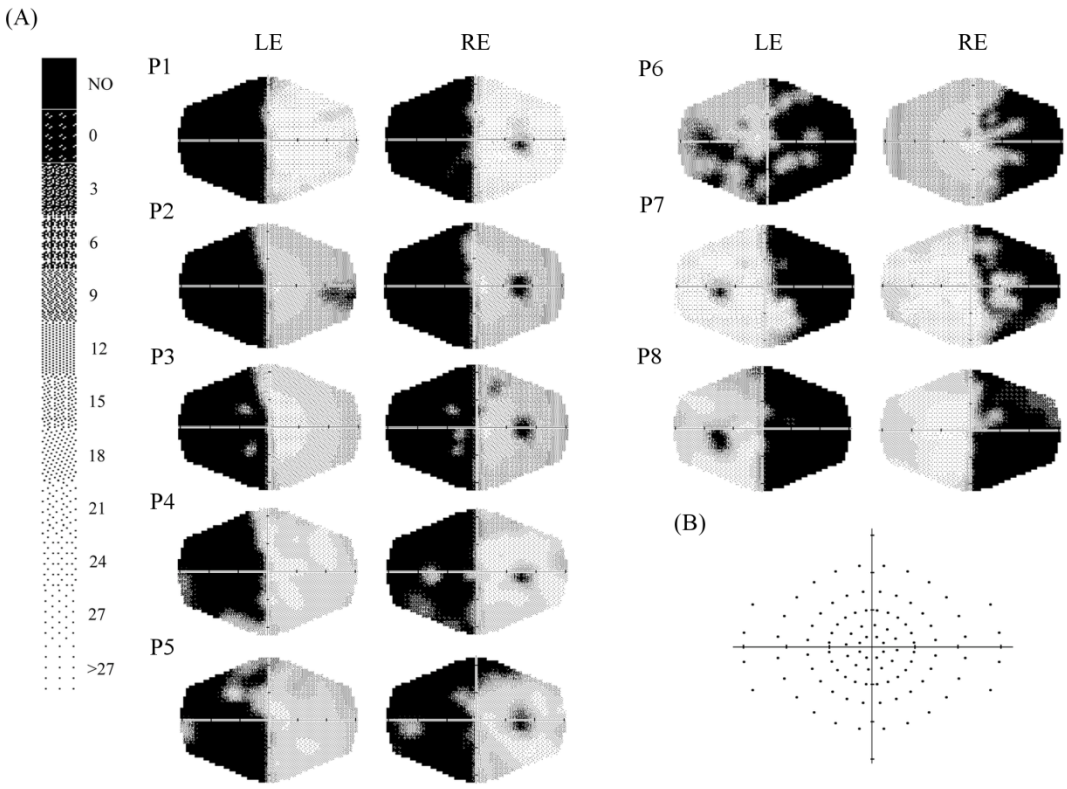


Figure 4.4 - Computerised automated visual perimetry (Medmont M700 automated perimetry apparatus, Melbourne, Australia). Panel in bottom right (B) describes a schematic view of the visual field maps, i.e., locations of visual stimulation. Axial hash marks denote ten visual degree increments. Colourmap reports decibel values corresponding to each point in the grey scale; LE=Left Eye; RE= Right Eye.

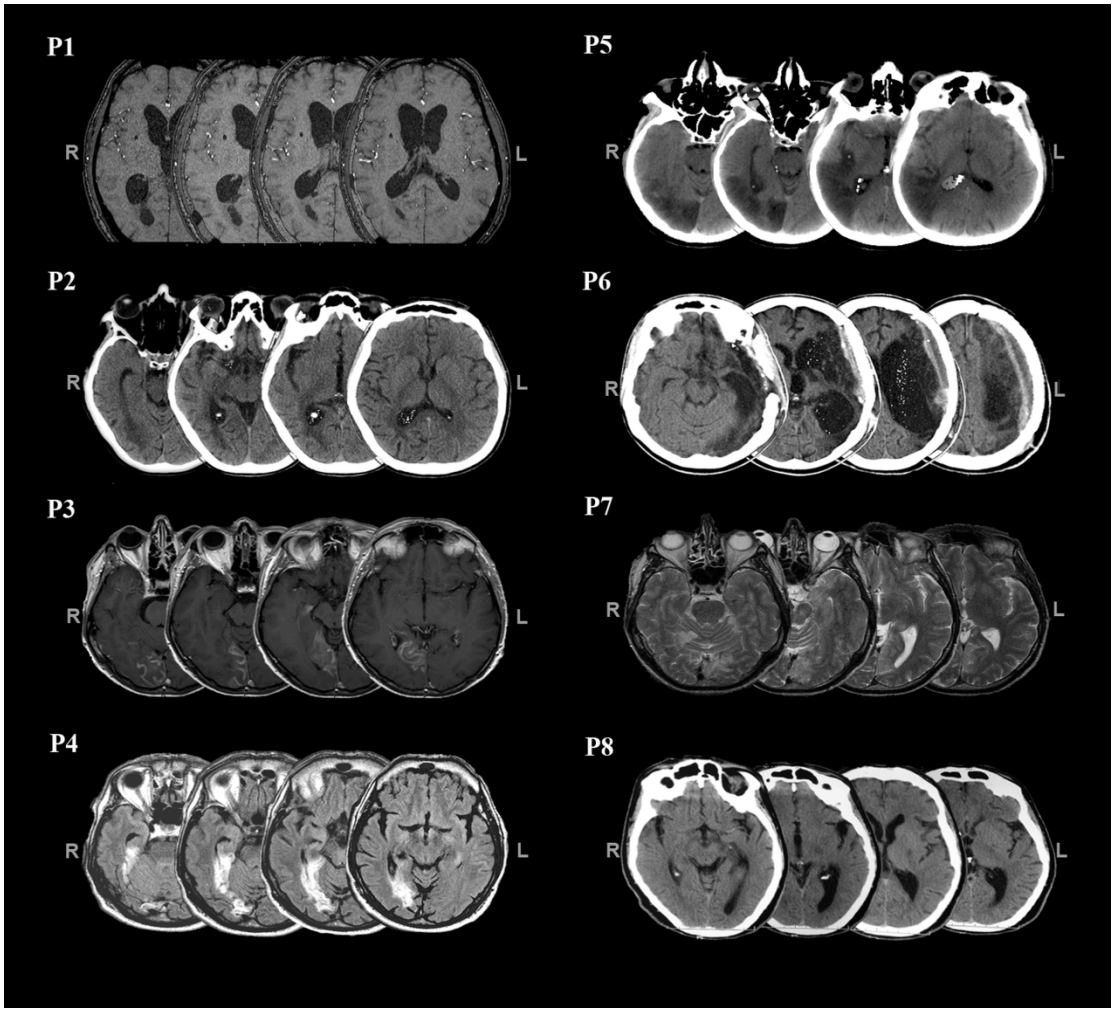


Figure 4.5 - CT scan or MRI scannings of patients. All scans are presented in axial views. R: right; L: left.

Experimental design

The present study used a within-subjects design. Participants completed both a clinical assessment and an EEG paradigm at three time intervals – baseline 1, i.e., before treatment

(B1), control baseline 2, i.e., two weeks after B1 immediately before treatment (B2 – control for practice effects) and finally after treatment (P).

Clinical assessment

Participants completed a neuropsychological examination (Bolognini et al., 2005; Passamonti et al., 2009) to measure visual detection, visual scanning and self-perceived disability in daily activities.

Visual Detection - Unisensory visual test (Bolognini et al., 2005) –Using the treatment apparatus (Figure 4.6), patients detected the presence of a light stimulus appearing at one of eight eccentricities (56°, 40°, 24° and 8° bilaterally), by pressing a button. Participants could move their eyes, while the head remained fixed. An experimenter monitored when eyes were centred and administered the light stimulus (100 ms). Participants performed three blocks of 120 trials (12 trials at each eccentricity and 24 catch trials, i.e. no light stimulus). The percentage of correctly detected targets (accuracy) at each position constituted the outcome metric.

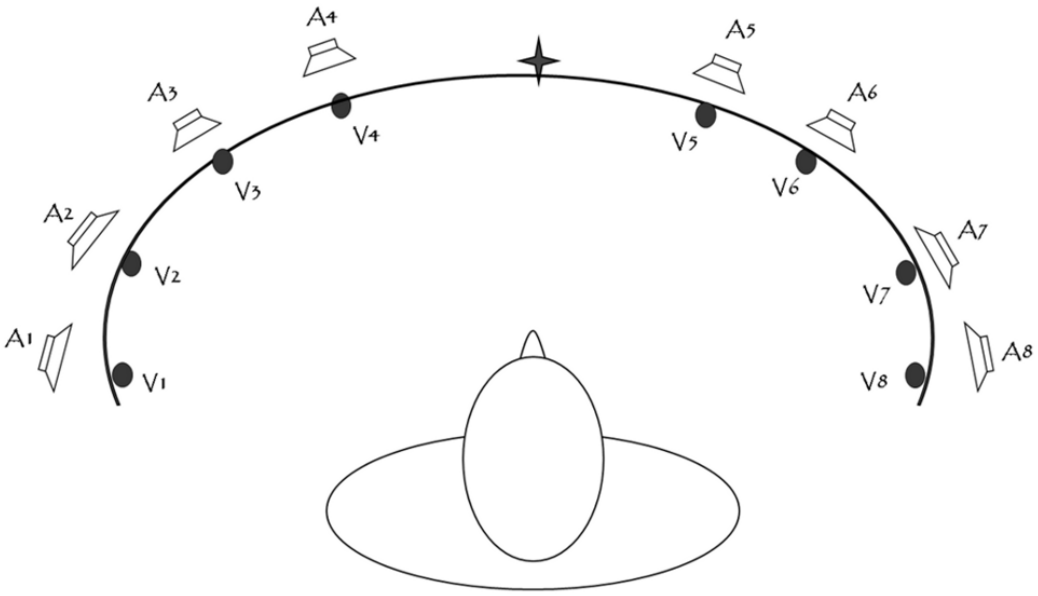


Figure 4.6 - Training apparatus. A schematic bird's eye view of the apparatus used both for the training and for the unisensory visual test. In each case, Participants are positioned at the centre of a concave ellipse, 200cm in width by 30 cm in height. A piezoelectric loudspeaker and red LED light are located at eight positions along the median line, at 8, 24, 40 and 56 degrees of eccentricity to the right and left of centre. For the unisensory visual test, only the LEDs are used as stimuli.

Visual Search – E-F test (modified from Zihl, 2000; Bolognini et al., 2005; Figure 4.7) – One target stimulus (green capital F) and 20 distractors (green capital E) were displayed randomly within a 52°x45° array on a black background (stimuli 2°x2°). Participants (distance 120cm) fixated centrally before each array and responded as quickly as possible if the target was present or not, with two different key-buttons. Participants performed one block of 20 trials - 16 target-present and 4 target-absent (i.e., catch trials). Response time and accuracy were

recorded. Inverse efficiency indices (IE = response time divided by the percentage of accurate detections) constituted the outcome metric.

Visual Search – Triangles test (modified from Zihl, 2000; Bolognini et al., 2005; Figure 4.7) – uses the same procedure as above, except targets (yellow triangles, amongst distractors of yellow squares) were to be counted. Response time, defined as time taken to indicate the number of targets in the array, was recorded via button press. Inverse efficiency scores constituted the outcome metric.

Visual Search – Numbers test (modified from Zihl, 2000; Bolognini et al., 2005; Figure 4.7) – Eight stimulus arrays were presented depicting the numbers one to fifteen (printed in red), in random positions. Participants identified each number, in ascending order, using a laser pointer. Response time (time taken to complete this array at verbal declaration of the number 15, error free), constituted the outcome metric.

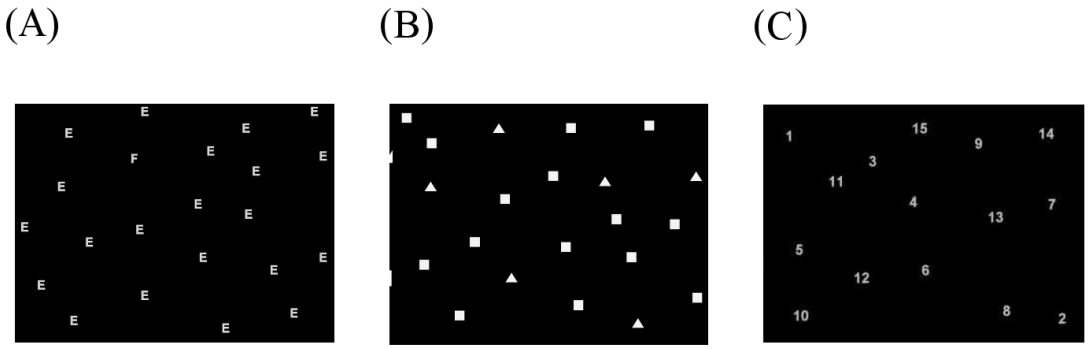


Figure 4.7 – example stimuli from the (A) E-F Letters, (B) Triangles and (C) Numbers visual search tests

Self-report - Activities of Daily Living Inventory (ADL; modified from Kerkhoff et al., 1994; Bolognini et al., 2005). A ten-item, five-point Likert scale questionnaire exploring the dimension of visual impairments in daily life. Raw mean scores constituted the outcome metric.

EEG experiment

EEG data were recorded at B1, B2 and P while participants performed a simple visual detection task. A target stimulus (white 1° diameter circle) appeared at one of six locations (upper, midline, lower, 15° right or left of central fixation cross). Each trial (Figure 4.8) consisted of a central fixation cross (1000ms), followed by a gap (800ms to 1200ms), a target (100ms) and a response window (1000ms). Participants were instructed to maintain central eye-fixation throughout the entire trial and press a response button as quickly as possible if they detected a stimulus anywhere on the screen. To control for false-positives, 14.3% of trials were catch trials, i.e., fixation cross, gap, but no stimulus. Participants performed 27 blocks of 30 trials (an average of 115 trials at each visual location and 115 catch trials).

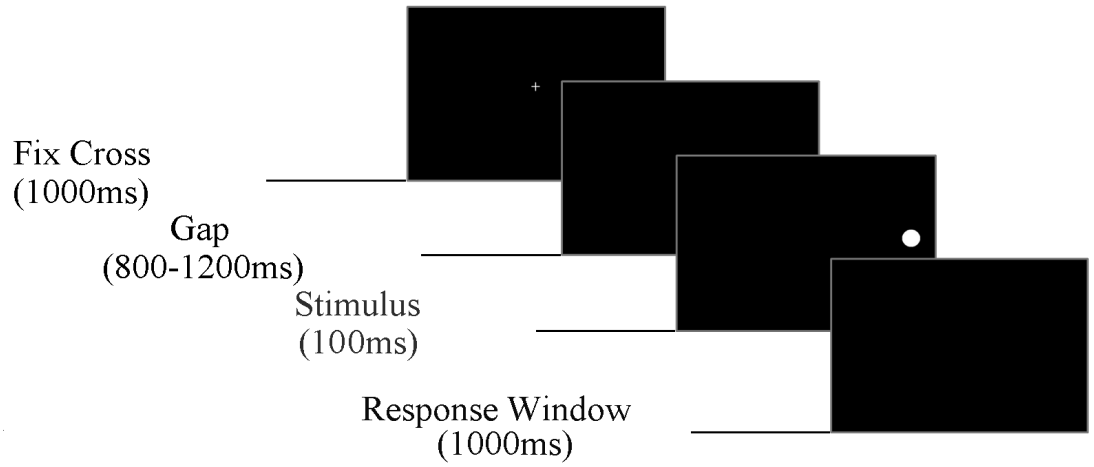


Figure 4.8 - Graphical representation of trial structure in the EEG behavioral task, used to measure both preparatory oscillatory activity and ERPs. Fixation cross (1000ms) was followed by a gap between 800 and 1200 ms in length. A stimulus was then presented for 100ms at one of six locations - upper, median or lower, 15 degrees to the right or left visual field. A window of 1000ms then followed, for responses (space-bar press) indicating detection of stimuli to be recorded.

EEG data were recorded with Ag/AgCl electrodes (Fast'n Easy-Electrodes, Easycap, Herrsching, Germany) from 27 electrode sites (Fp1, F3, F7, FC1, FC5, C3, T7, CP1, CP5, P3, P7, O1, Fz, Cz, Pz, Fp2, F4, F8, FC2, FC6, C4, T8, CP2, CP6, P4, P8, O2) and the right mastoid. The left mastoid was used as reference, while the ground electrode was positioned on the right cheek. Vertical and horizontal electrooculogram (EOG) were recorded from above and below the left eye, and from the outer canthus of both eyes. Data were recorded with a band-pass filter of 0.01-100 Hz and amplified by a BrainAmp DC amplifier (Brain Products, Gilching, Germany). The amplified signals were digitized at a sampling rate of 500 Hz, and off-line filtered with a 40 Hz low-pass filter, and then analysed using custom routines in MatLab 7.0.4 (The Mathworks, Natic, MA, USA) running EEGLAB 5.03 (Delorme & Makeig 2004). Data from all electrodes were re-referenced, off-line, to the average of both mastoids. Stimulus triggers were located within the continuous EEG waveform and used to anchor the epochs (-200ms to 900ms; baseline window -100ms to 0 ms pre-stimulus). Epochs containing artefacts were excluded using methods from EEGLAB toolbox (Delorme et al., 2007). Epochs with large EOG peaks (> an individually adjusted threshold, mean 126 μV)

and with improbable data (joint probability of a trial > 5*sd) were also excluded (mean: 25 epochs per participant per session). Remaining EOG artifacts (vertical and horizontal) were corrected using a regression approach (Gratton et al., 1983).

Event related potentials (ERPs)

Epochs contributing to the stimulus evoked ERP dataset were discarded if horizontal saccadic movements (>30μV on horizontal EOG channels) were registered 0ms to 200ms post-stimulus onset, to control for eye-movements explaining stimulus detection (mean: 28 epochs per participant per session). In total, 8.5% of epochs were excluded. Remaining epochs were averaged, both for individuals and for the group (electrodes were swapped cross-hemispherically for participants with lesions to the left hemisphere, thus, de facto making the entire participant sample right-lesioned).

Effects of treatment were analysed on amplitudes of the P1, N1 and P3 ERP components, elicited by stimulation of the intact visual field. For the main statistical analysis, the electrode corresponding to the peak amplitude at B1 for each component during time windows specified below was selected for a component by time two-way ANOVA; O1 for the P1, P7 for the N1 and Pz for the P3. For additional statistical analyses, all electrodes that fell within the maximal amplitude contour were used for in separate one-way ANOVAs for the effect of treatment on each component, using a peak anchoring method of amplitude calculation (see results section below). Scalp topographies in the post-stimulus P3 time-window 345-385ms showed maximal positive amplitude inflection over electrodes CP1, P3 and Pz at all three testing sessions. Data from these electrodes were therefore used for statistical analysis. Scalp

topographies showed maximum negative inflection in the N1 time-window 160-200ms to be over electrodes CP5, P3 and P7. Finally, scalp topographies showed maximum positive inflection in the P1 time-window 120-140ms to be over electrode O1. Mean amplitudes of components within these time windows were extracted for statistical analysis.

Behavioural data were screened to exclude trials with deviant horizontal eye movements (>30μV on horizontal EOG channels 0 to 200ms post-stimulus), to control for false positive responses. On average, 9% of trials were excluded in this way. Accuracy scores, reaction times and d' values were recorded for each of the six target locations.

Training

The training protocol is described fully in previous studies (Bolognini et al., 2005; Passamonti et al., 2009; see Figure 4.6). In summary, during a full course of treatment (10 days; 4 hours of training per day), participants were presented with three different kinds of sensory stimulation: (i) unisensory visual (UV; 100ms red LED light), (ii) unisensory auditory (UA; 100ms 80dB white noise) and (iii) multisensory visual-auditory condition (MAV; UV and UA simultaneously at the same location). Participants fixated centrally and performed visual eye explorations, while the head remains stationary. Participants explored for stimuli and responded with a button-press when any visual stimulus (UV or MAV) was observed. Stimuli were disproportionately allocated to the hemianopic side, to encourage exploration of this field. Participants performed approximately 30 blocks per day, of 48 trials (12 UV; 12 UA and 24 MAV).

Results

Repeated measures ANOVAs were conducted to test treatment effects on behavioural and electrophysiological measures. To compensate for violations of sphericity, Greenhouse-Geisser corrections (Greenhouse & Geisser, 1959) were applied whenever appropriate; corrected p-values (but uncorrected degrees of freedom) are reported. Post-hoc comparisons were conducted using a Newman-Keuls test.

Results of treatment on clinical tests

Unisensory visual test - 2x3x4 Within Subjects ANOVA, using factors, visual field (hemianopic, intact), session (B1, B2, P) and location (56°, 40°, 24°, 8°) was performed on raw accuracy scores. The main effects of visual field ($F(1,7)=107.76$, $p<.001$;), session ($F(2, 14)=22.74$; $p<.001$) and location ($F(3,21)=8.14$, $p=.01$) were significant. Notably, the three-way interaction between visual field, session and location was also significant ($F(6,42)=2.56$; $p=.03$). Two separate ANOVAs were consequently run, for the hemianopic and intact visual field, respectively, with factors session (B1, B2, P) and location (56°, 40°, 24°, 8°). ANOVA on the hemianopic field revealed a significant effect of session ($F(2,14)=30.40$; $p<.001$): accuracy scores significantly increased from B1 (34%) and B2 (39%) to P (71%; both p-values <.001), while no change was observed between B1 and B2 ($p=.253$).

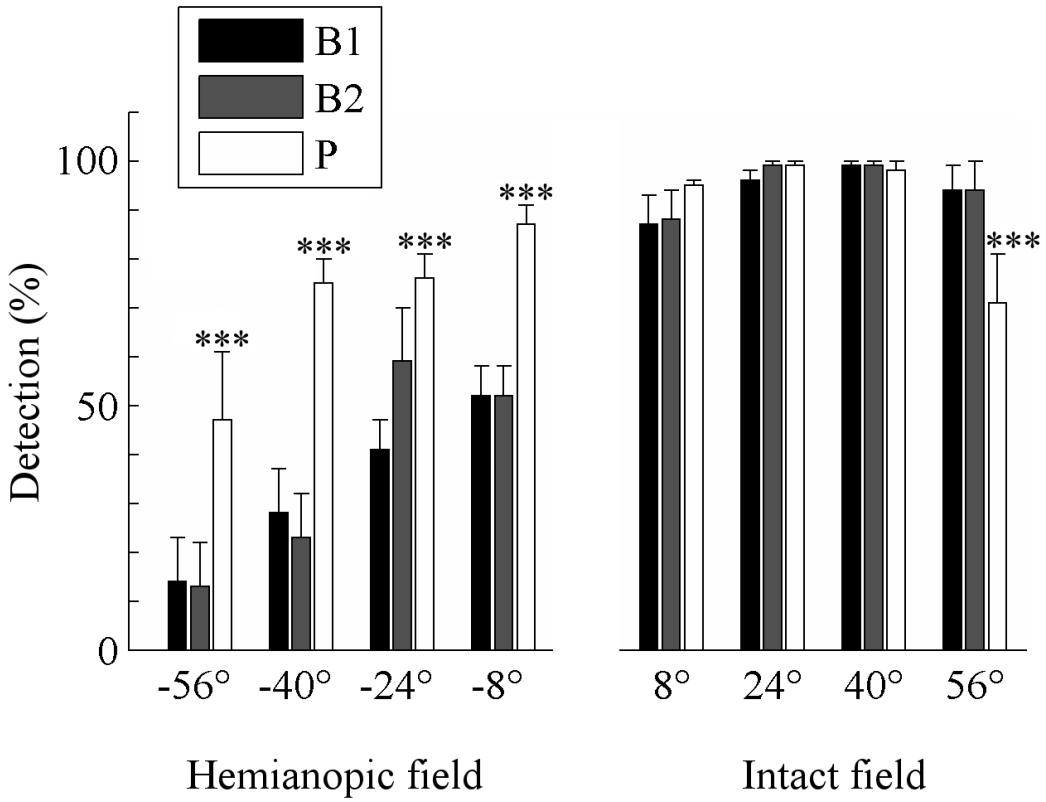


Figure 4.9 - Results of treatment effects on unisensory visual detection test. Accuracy (% correct stimulus detections; error bars report standard error of the mean) depicted as a function of stimulus eccentricity (8, 24, 40 and 56 degrees) and visual field (intact, hemianopic), at B1 (black bars), B2 (grey bars) and post (white bars) treatment.

The location effect was also significant ($F(3,21)=9.49$; $p=.01$): accuracy was significantly lower at 56° (24%), compared to 40° (42%; $p=.04$), 24° (58%; $p=.001$) and 8° (65%; $p<.001$); no other comparisons were statistically significant (all p-values >.231). ANOVA on the intact field, revealed a significant interaction between session and location ($F(6,42)=6.49$; $p=.01$). Accuracy significantly reduced at 56° at P (71%), compared to B1 (94%; $p<.001$) and B2 (94%; $p<.001$; Figure 4.9); no other comparisons were statistically significant (all p-values >.161). An ANOVA with main factor session (B1, B2, P) compared the percentage of

false alarms, revealing no significant differences between sessions (F(2,14)=2.52; p=.15; B1: 0%; B2: 6%; P: 1%).

Visual Search – E-F test: ANOVA with main factor session (B1, B2, P), comparing the effect of treatment on IE scores, revealed a significant main effect of session (F(2,14)=74.28, p=.04): IE scores at P (32) were significantly lower compared to B1 (37; p=.02) and B2 (39; p=.01; Figure 4.10), reflecting a post-treatment improvement in scanning efficiency, while no significant difference was observed between B1 and B2 (p=.468). The same ANOVA computed on the percentage of false alarms revealed no significant difference (F(2,14)=1.00, p=.39; B1: 3%; B2: 0%; P: 0%).

Visual Search – Triangles test: ANOVA with main factor session (B1, B2, P), comparing the effect of treatment on IE scores, revealed a significant main effect of session (F(2,14)=5.55, p=.049): IE scores at P(92) were significantly lower compared to B1 (124; p=.02) and B2 (127; p=.02; Figure 4.10), reflecting more efficient visual scanning post-treatment, while no significant difference was observed between B1 and B2 (p=.807). The same ANOVA computed on the percentage of false alarms revealed no significant difference (F(2,14)=1.00, p=.39; B1: 2%; baseline B2: 0%; P: 2%).

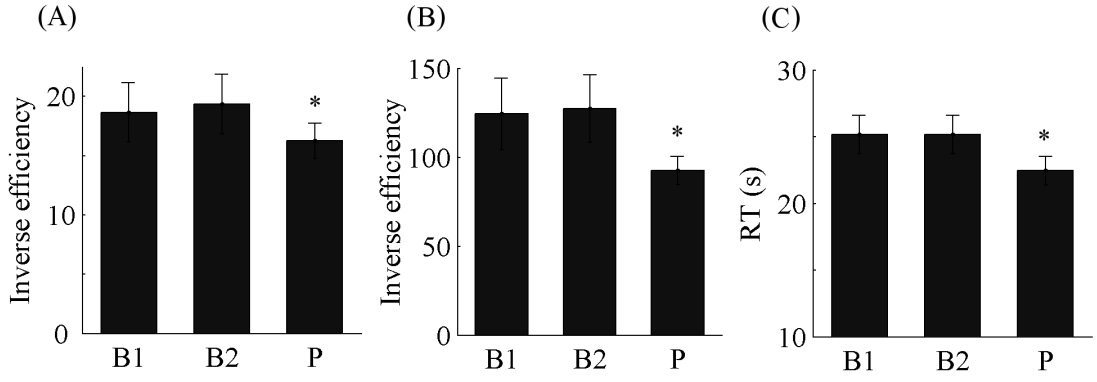


Figure 4.10 - Treatment effects on visual search. Inverse efficiency (% accuracy /

Reaction time) of visual search tests (A) E-F and (B) Shapes as a function of testing session (B1, B2, P). Panel C depicts reaction times from the Number test, as a function of treatment (B1, B2, P). On all panels, error bars report standard error of the mean.

Visual Search – Numbers test: ANOVA with main factor session (B1, B2, P) comparing the effect of treatment on RTs revealed a significant main effect of session ($F(2,14)=11.17$, $p=.01$): RTs were significantly lower at P (22.4 s) compared to B1 (25.1 s; $p=.003$) and B2 (25.1 s; $p=.001$; Figure 4.10), revealing a significant post-treatment improvement in visual exploration while no significant difference was observed between B1 and B2 ($p=.995$).

ADL - ANOVA with main factor session (B1, B2, P) revealed a significant main effect ($F(2,14)=11.77$, $p=.01$). ADL scores were significantly lower post treatment (7), compared to B1 (11; $p=.002$) and B2 (11; $p=.002$), showing a significant improvement in the quality of patients'daily living, post treatment while no significant difference was observed between B1 and B2 ($p=.709$).

Results of treatment on EEG paradigm behavioural data

Given the requirement of eye-fixation, patients expectedly detected a low number of stimuli in the hemianopic field (1% at B1, 1% at B2 and 2% at P). In the intact field, patients detected 99% of stimuli at B1, 99% at B2 and 99% at P. Due to the lack of responses in the hemianopic field, analysis on accuracy, response times and detection sensitivity (d' values) were restricted to the intact field and were analysed with 3x3 ANOVAs using session (B1, B2, P) and location (upper, middle, lower) as factors. Neither accuracy ($F(2,14)=.26$, $p=.78$), response time ($F(2,14)=1.75$, $p=.21$) nor detection sensitivity ($F(2, 14)=1.37$, $p=.29$) changed

across sessions, nor were there any significant interactions involving session and location (all p-values > .29).

Results of treatment on stimulus evoked ERPs

As shown in Figure 4.11, no worthwhile ERP was elicited by stimuli in the hemianopic field, in accordance with the low magnitude of stimuli detected by participants.

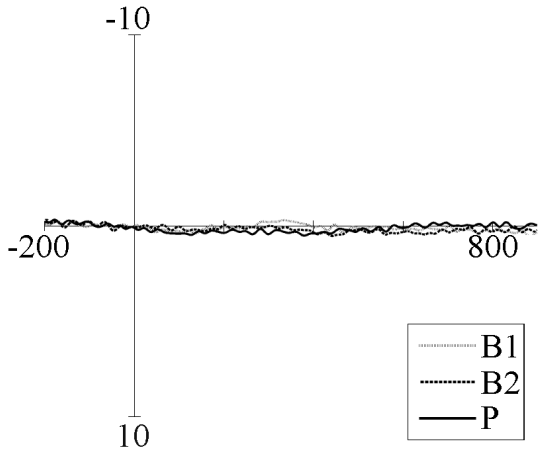


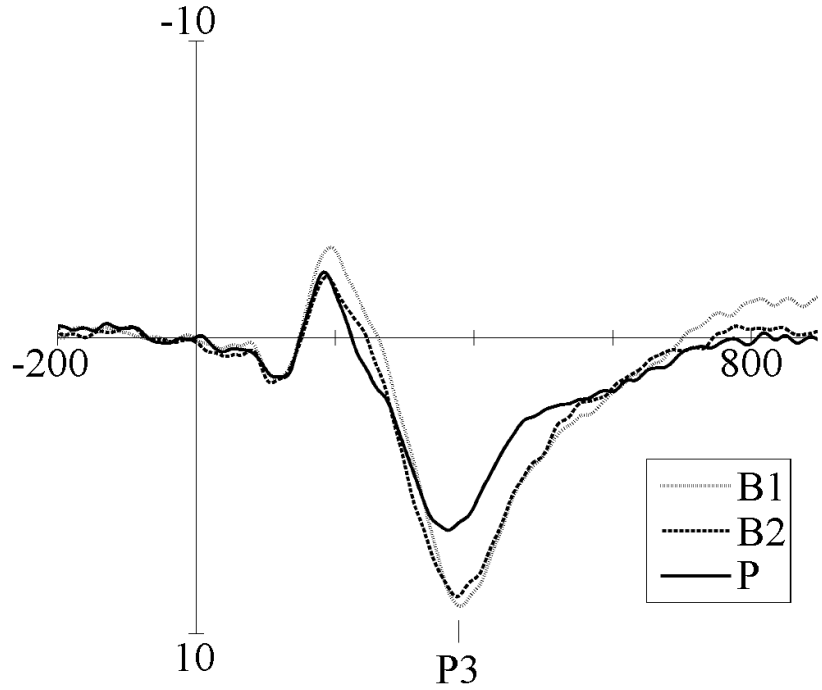
Figure 4.11 - Representative waveform from stimuli presented to hemianopic field, grand averaged across electrodes PZ, P3 and CP1.

Therefore, only ERPs elicited by stimuli presented in the intact field were analysed. The treatment effects on mean amplitudes of the P1, N1 and P3 components elicited by stimuli in the intact visual field were first compared using a 3x3 within-subjects ANOVA, with factors component (P1,N1,P3) and session (B1, B2, P). Mean amplitudes were extracted for each component in the time windows 120-140ms, 160-200ms and 345-385ms for the P1, N1 and

P3 components respectively. As described in the methods section, each component peaked over a different number of electrode sites (three sites for the N1 and P3, one site for the P1); for this analysis, only one electrode at the maximal peak location was therefore chosen to represent each component - O1 for the P1, P7 for the N1 and Pz for the P3, in order to keep the power at each level of the component factor equal. This ANOVA revealed a significant interaction between session and component ($F(4,28)=4.79$, $p=.005$), driven by P3 amplitude at P (6.03 μV) being significantly lower than B1 (8.46 μV, $p<.001$) and B2 (8.32 μV, $p<.001$), while no significant difference was observed between B1 and B2 ($p=.601$). In contrast, no significant differences were observed for the N1 component (B1 = -2.62 μV; B2 = -2.12 μV; P = -1.99 μV; all p-values >.41) or for the P1 component (B1 = 1.66 μV; B2 = 1.59 μV; P = 1.98μV; all p-values >.60). Treatment therefore appeared to attenuate amplitude for the P3 component, while not having any effect on the amplitudes of the P1 or N1 component.

As a control, component amplitudes were re-quantified using a peak-anchoring technique. This technique first localised the peak amplitude for each participant within extended time-windows: 100-150ms for the P1, 150-200ms for the N1 and 350 to 400 ms for the P3, to allow for variance amongst participants. The time of this peak amplitude was then used to anchor a relative sub-time-window of -10ms to +10ms. Components were quantified as the mean amplitude within this sub-time-window for each participant. This method controlled for latency variance of component onset, while preserving the mean amplitude measure's lower susceptibility to spurious peaks (Luck, 2005).

Separate within-subjects ANOVAs were also administered for each component, to allow for the factor of electrode to now be included. The effect of treatment on peak-anchored mean-amplitude values of the P1 component over electrode site O1 was tested using a one-way within subjects ANOVA with a single factor of session (B1, B2, P). No main effect was observed ($F(2, 14)=.63$, $p=.545$; Figure 4.14). The effect of treatment on peak-anchored mean-amplitude values of the N1 component elicited by intact field stimulation was tested using an electrode (CP5,P3,P7) by session (B1,B2,P) 3x3 within-subjects ANOVA. No main effect or interaction was observed (all p-values > .152; Figure 4.13). Finally, a 3x3 within subjects ANOVA, with factors electrode (Pz, P3, CP1) and session (B1, B2, P), was used to compare the effects of the treatment on the peak-anchored amplitude of the P3 component elicited by intact field stimuli. Only the main effect of session was significant ($F(2,14)=9.32$ $p=.003$; Figure 4.12): peak-anchored P3 amplitude at session P (7.57μV) was significantly lower than B1 (9.99μV; $p=.005$) and B2 (9.82μV; $p=.003$) while no significant difference was observed between B1 and B2 ($p=.684$). Thus, using a different quantification technique for component amplitude, which accounted for peak latency possibly confounding mean amplitudes, the treatment again only appeared to affect the P3. As a final test of integrity of the treatment effect on the P3 component, paired samples t-tests were conducted on the P3 amplitude difference between B1 and B2 (Diff1), and B2 and P (Diff2). Diff1 (-0.17) was significantly smaller than Diff2 (-2.24; $t(df=7)=3.03$, $p=.01$).


-10
-200
800
10
P3
B1
B2
P

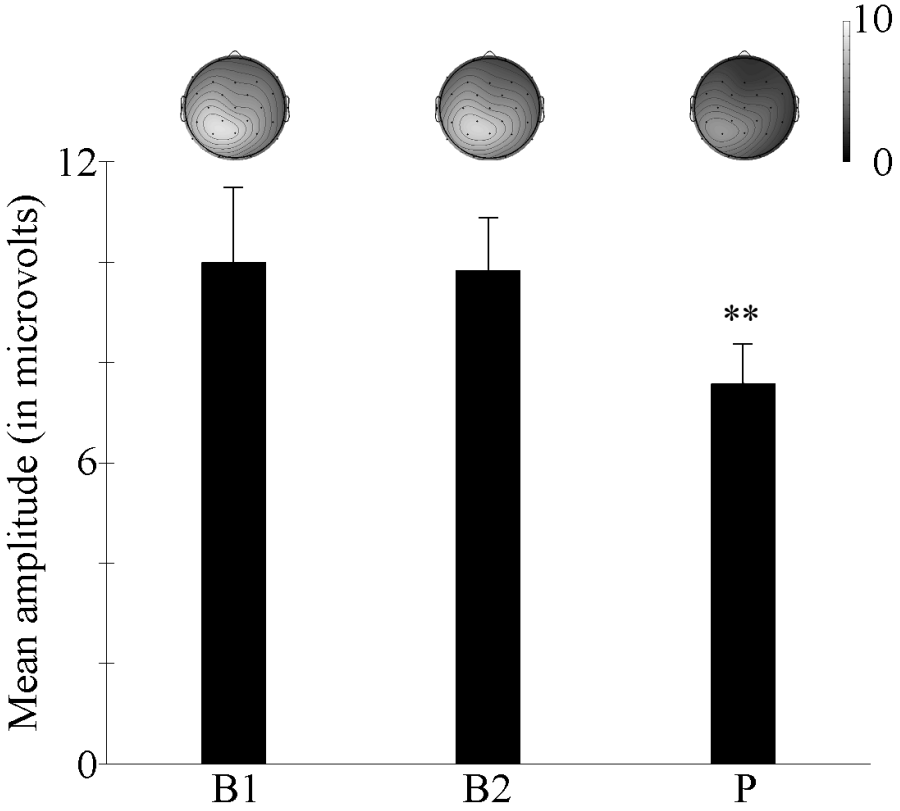

10
0
12
6
0
Mean amplitude (in microvolts)
**
B1
B2
P

Figure 4.12 - Treatment effects on P3 component. Upper panel depicts grand averaged ERPs averaged across electrodes PZ, P3 and CP1, elicited by stimuli presented to the intact visual field, as a function of session (B1,B2 and P). Lower panel depicts the mean amplitude of the waveform ±10ms of individual peak positive values within the P3 range, as a function of session, along with scalp topographies of the mean voltage in a time window of 345-385ms, which was used to guide electrode selection for analyses; Pz, P3 and CP1 all fall within the central contour denoting maximal positive amplitude inflection in the P3 range at these electrodes. Error bars reflect standard error of the mean.

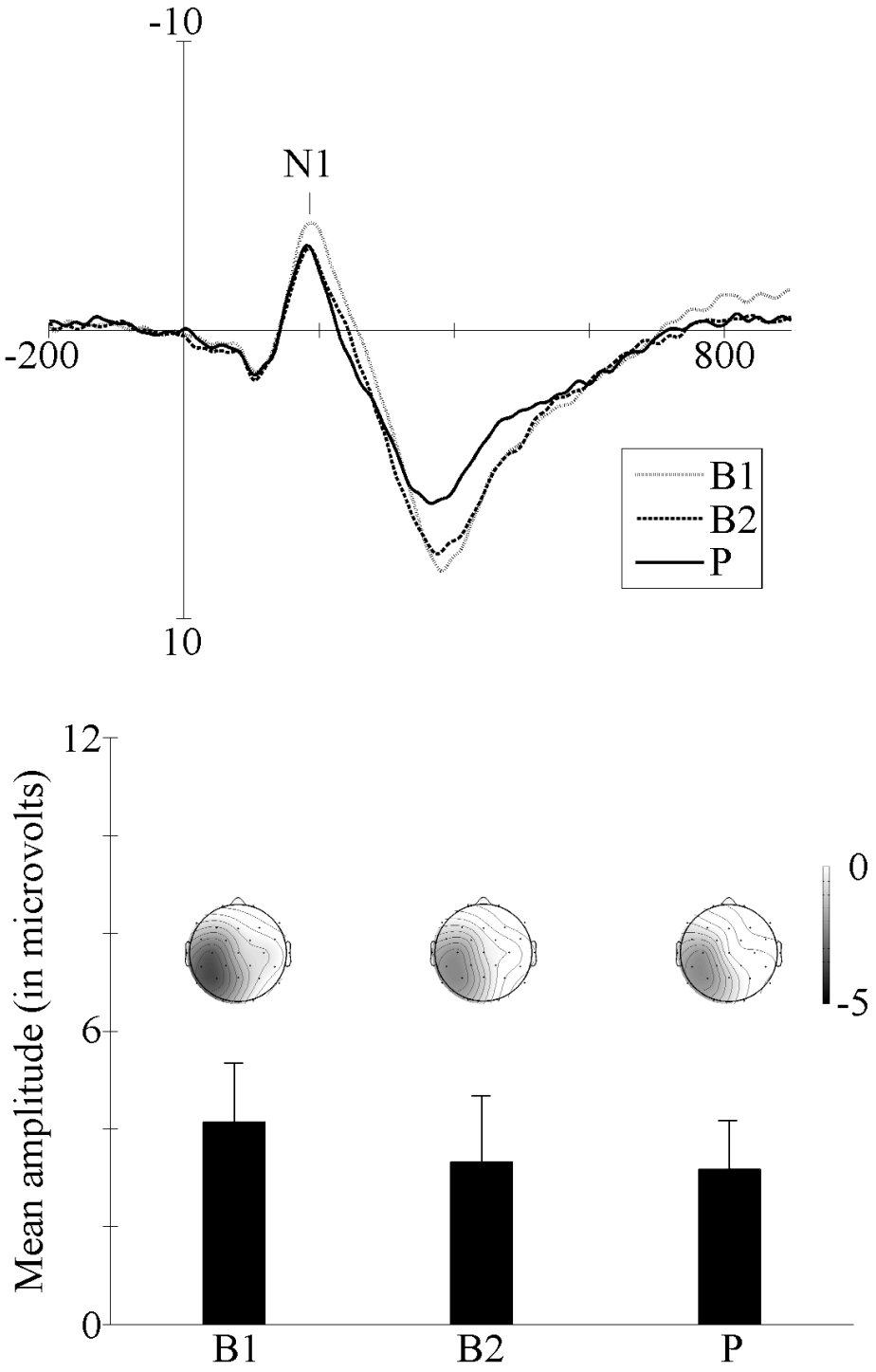


Figure 4.13 – Treatment effects on N1 component. Upper panel depicts grand averaged ERPs averaged across electrodes CP5, P3 and P7, elicited by stimuli presented to the intact visual field, as a function of session (B1, B2, P). Lower panel depicts mean amplitude ±10ms of individual peak negative values within the

N1 range, as a function of session, along with scalp topographies of the mean voltage in a time window of 160-200ms, which was used to guide electrode selection for analyses of the N1 component; electrodes CP5, P3 and P7 are all within the contours of maximal negative amplitude. Error bars are the standard error of the mean.

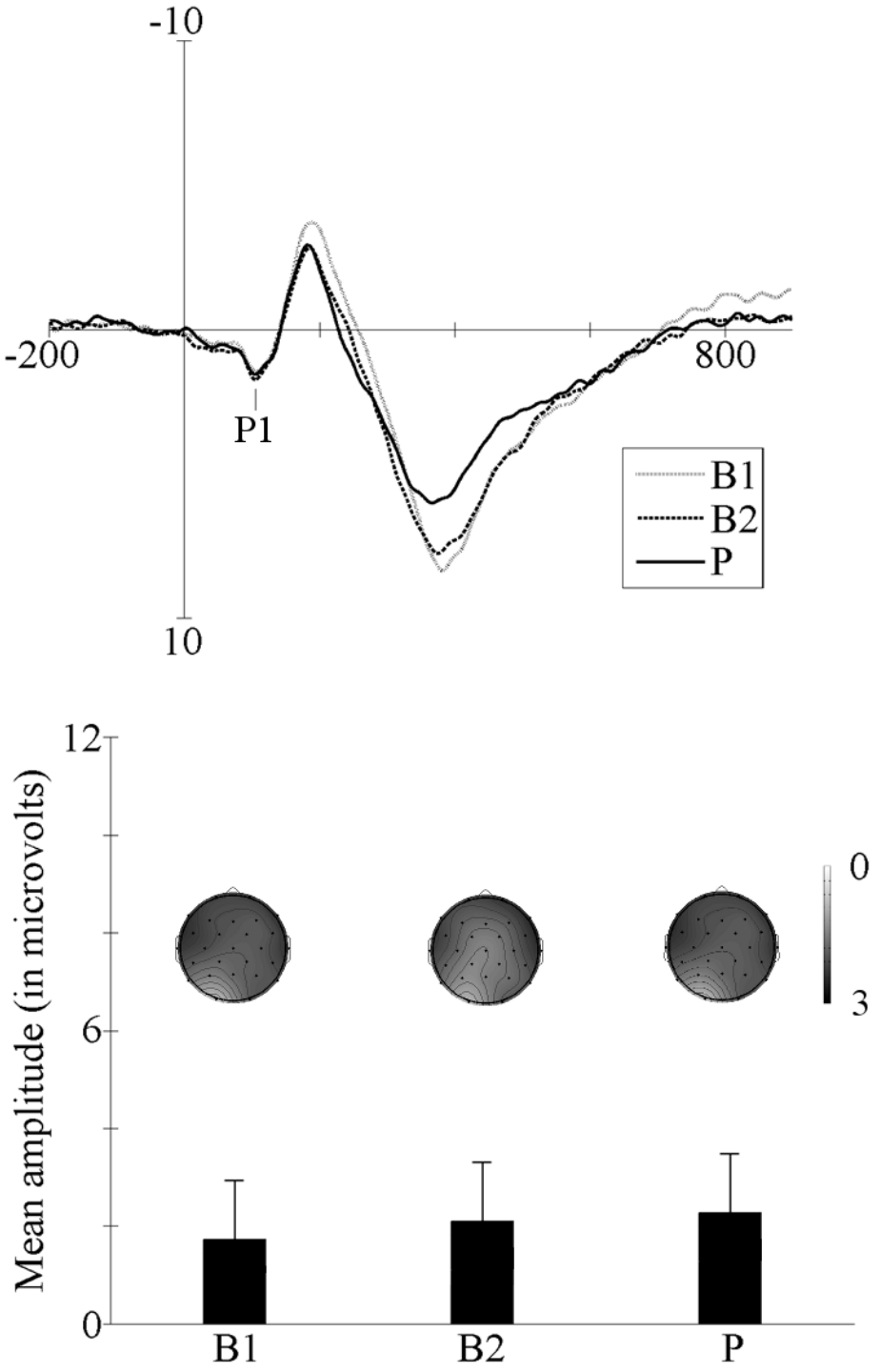


Figure 4.14 – Treatment effects on P1 component. Upper panel depicts grand averaged ERPs at electrode O1, elicited by stimuli presented to the intact visual field, as a function of session (B1, B2, P). Lower panel depicts mean amplitude ±10ms of individual peak positive values within the P1 range, as a function of

session, along with scalp topographies of the mean voltage in a time window of 120-140ms, which was used to guide selection of the O1electrode for analyses of the P1 component. Error bars are the standard error of the mean.

Discussion

The present study investigated the behavioural and electrophysiological correlates of treatment-driven neural reorganization in hemianopia patients following a course of multi-sensory stimulation treatment. In line with previous studies, behavioural correlates of oculomotor functioning demonstrated a treatment effect, indicating improved performance with visual search tasks and visual detection in the hemianopic field, post treatment. Analyses of stimulus-evoked ERPs further demonstrated that treatment did not affect early components of spatial attention, however the treatment did drive attenuation in post-perceptual P3 component. These findings will now be discussed in more detail.

Behavioural evidence of treatment-driven attention shift toward the scotoma

Results on the simple visual detection and visual search behavioural tasks confirm the findings from previous studies, namely that an intensive course of multi-sensory stimulation to the blind field of hemianopia patients improves oculomotor functioning, such as detecting stimuli presented in the blind field, finding targets in a bilateral array of distractors, and saccading sequentially through bilateral arrays of randomly presented number stimuli. Visual detection improvement was only observed on tasks where eyes could perform exploratory saccades; treatment did not affect trials where eyes were instructed to remain at fixation (i.e., the behavioural results from the EEG paradigm). Accordingly, the effects of the treatment

can be dissociated from any reduction in the size of the scotoma, i.e., the effects are driven by compensatory plasticity and not restorative re-engagement of residual visual areas (for a review of the restorative approach, see Sabel et al, 2011).

Interestingly, patients detected fewer stimuli, post-treatment, at the most peripheral sites of the intact visual field. This was observed on the unisensory visual detection test, on trials where stimuli appeared at 56 degrees of eccentricity into the blind field. No such attenuation in detection was observed for stimuli appearing at more medial positions of the intact field, and significant improvements were observed for stimuli presented at all positions in the blind field. A long held finding in the attention literature is that responses to stimuli at attended regions of the visual field are generally faster and more accurate than responses to stimuli that appear at unattended regions (Posner et al, 1978, 1980). Perhaps more pertinent to the present study, oriented attention plays a crucial mediatory role in eye-saccades, where saccades toward a covertly attended region of the visual field are faster and more accurate than saccades away from covertly attended locations - a concept known as the validity effect (Eckstein et al, 2006). The present pattern of behavioural results therefore suggests that the treatment orients attention away from the intact visual field, at least from the most peripheral eccentricities, and redeploys it toward the scotoma, thereby strengthening the adaptive bias toward the scotoma.

As described in the introduction to this thesis, the synchronised spatial and temporal alignment of the audio and visual stimuli administered during a course of multi-sensory stimulation treatment preferentially stimulate the superior colliculus (SC). Accordingly, since the likely neural substrate of the multisensory treatment effects is the spared retino-colliculo-

extrastriate network, SC might have mediated the observed effect, where attention appears to be oriented toward the intact field, post treatment. In animal studies, removal of lateralised visual cortex causes contralesional defects of visually guided behaviour, associated with a hypoactivation of the colliculus ipsilateral to the cortical lesion, probably due to inhibitory projections from the contralesional colliculus (Sprague, 1966). Interestingly, ablation of the contralesional colliculus, or splitting of the collicular commissure, restores function in the ipsilesional colliculus and, consequently, improves visually guided behaviour ('Sprague effect'; Sprague, 1966; Durmer & Rosenquist, 2001). Similar mechanisms could underscore the present treatment, where multisensory stimulation might have increased activation of the ipsilesional SC (Stein & Meredith, 1993), rebalancing attentional networks to improve orienting responses in the hemianopic field.

Stimulus-evoked electrophysiological treatment effects are focal to post-perceptual processes (P3)

Treatment drove an attenuation in P3 amplitude in response to stimuli presented to the intact visual field, with no such attenuation observed for the P1 or N1 stimulus evoked component. At first glance, the absence of an effect with the posterior sensory-evoked components (P1 & N1) appears to conflict with the above interpretation from the behavioural data, namely that treatment drives a redeployment of spatial attention from the intact field toward the blind field. These early components are specific to the visual modality (i.e., not evoked by auditory stimuli), and thought to be generated by processing in regions of the primary visual projection areas of extra-striate cortex (Clark & Hillyard, 1996), relaying the selectively attended visual signals from the visual cortex to regions in the ventral stream (Mishkin & Ungerleider, 1982; LaBerge, 1995; Desimone & Duncan, 1995; Eimer 2000). Accordingly,

stimuli presented to regions of the visual field where participants are covertly attending will elicit an increased P1 and N1 response over lateral posterior electrode sites, in comparison to stimuli presented to unattended regions (Eason, 1981; Harter et al, 1982; Mangun & Hillyard, 1987; Hillyard & Münte, 1984; Eimer, 2000). While no observed change in P1 and N1 amplitude, post treatment, initially suggest that patients are not attending any less to the intact field, this effect could be due treatment having an influence on one of two distinct attentional mechanisms. Hopefinger and West (2006) demonstrated that early and late stages of attention can have both distinct and overlapping effects on information processing. When the aims converge of early (exogenous) attention and late (endogenous) attention, the resulting electrophysiological activity gives the appearance of a serial network, i.e., network where early waveform activity feeds into later stages. Thus, a task where a stimulus appears at a covertly attended region will align both exogenous and endogenous attention processes, and accordingly influence both early and late stages of ERP waveforms. However Hopfinger and West (2006) demonstrated that under circumstances where the aims of exogenous and endogenous attention can be separated, early and late waveform activity can accordingly behave in distinct ways, suggesting that post-perceptual attention can be influenced without effects on early processes. The attenuation of only the P3 ERP in the present data suggests that the electrophysiologically indexed treatment effects are indeed focal to post-perceptual attentional processes. An early interpretation of the P3 component was that it indexed the degree of attentional resources allocated to tasks (Isreal et al., 1980; Wickens et al., 1983). In dual-task paradigms for example, P3 amplitudes to target tones are attenuated when participants perform a concurrent visual tracking task, relative to the single task condition (Isreal et al, 1980), suggesting that the P3 may index the amount of top-down attentional resources that have been allocated to performing tasks.

Experiment 4: Effects of Multisensory stimulation treatment on preparatory alpha oscillations

A further way of exploring how the brain establishes biases in perception is through the study of anticipatory mechanisms (Foxe and Snyder, 2011). This line of enquiry declines the traditional approach of concentrating on the processes, which are elicited following stimulus presentation, and instead focuses on activity preceding significant events. The logic which underscores the analysis of anticipatory attentional activity is that in order to optimally attend to a task, it is advantageous for the cognitive system to prepare for events, either by attending to a specific location, item, action or process, prior to the execution of the required action or the presentation of the relevant stimulus (Foxe and Snyder, 2011).

Accordingly, in the last two decades, a body of research has been published detailing the substrates controlling attentional biases in the anticipatory foreperiod of tasks (Foxe et al., 1998; Fu et al., 2001; Worden et al., 2000; Kelly et al., 2006; Snyder and Foxe, 2010). These studies have demonstrated that a crucial component of attentional biasing, whether to a specific location, perceptual modality, or stimulus feature, is the supression of task-irrelevant information. For example Foxe et al (1998) administered an intersensory attention paradigm, where participants were cued to attend to either the visual (discriminating the eccentricity of two dots) or auditory (discriminating the pitch of binaurally presented tones) portion of a compound audio-visual stimulus. In order to attend to the cued modality, participants needed to inhibit the uncued modality. Analyses of EEG oscillations in the foreperiod between the cue (detailing which modality to attend) and stimulus showed significantly larger activity in parieto-occipital alpha oscillations before trials in which auditory trials were to be attended.

The authors interpreted this effect as the gating of mechanisms in parieto-occipital regions involved with processing visual stimuli.

Bilateral diffuse distribution of preparatory alpha in the above study suggests that in order to drive attention selectively toward the auditory domain, the entire visual field was inhibited. However, alpha oscillations can also show much spatial selectivity in a unisensory domain. A later a study by Worden et al (2000) demonstrated that in a unisensory visual motion-judgement paradigm, where participants fixated centrally but oriented covertly toward the upper, lower, left or right visual field upon cue, sustained focal increases in alpha oscillations were observed in the pre-stimulus foreperiod ipsilateral to the side of the cued visual field. Further, alpha oscillations were retinotopically mapped to the upper or lower quadrant contingent on the cue direction. Thus, when participants were spatially attending, alpha oscillations increased over retinotopic occipital regions corresponding to regions of visual space that were to be inhibited. Alpha oscillations, therefore, appear to be a retinotopically selective index of where subjects are actively focusing visual attention, a finding that has been replicated and expanded in several subsequent studies (Sauseng et al., 2005; Yamagishi et al., 2005; Kelly et al., 2006; Thut et al., 2006; Rihs et al., 2009; Cosmelli et al., 2011).

By presenting a visual detection paradigm that does not cue regions of space (i.e., the same paradigm as Experiment 3, above), I propose to assay the bias driven voluntarily by patients to regions of space. Accordingly, if hemianopia patients deploy a visual attention bias toward a certain field, this may be observed in their preparatory alpha activity as they await a stimulus, which can appear with equal probability in any region of their visual field. For

example, a bias toward the blind field would be reflected by higher alpha power over electrode sites at the posterior part of the intact hemisphere (inhibiting the intact field), whereas a bias toward the intact visual field would be indicated by greater alpha power over posterior electrode sites on the lesioned hemisphere. To that effect, this experiment will first test the hypothesis that patients have an attention bias toward a particular visual field, indexed by increased alpha bias over relevant electrode sites during the foreperiod of uncued stimulus onset. I will then index the effects of a course of multisensory stimulation treatment on preparatory alpha oscillations, to test whether the treatment specifically addresses any observed bias. In addition, given that preparatory alpha signals can be extracted from the same paradigm administered in Experiment 3, I can also record stimulus-evoked components with a view to replicating the P3 attenuation with a larger group of patients.

Materials and methods

Participants

The eight participants from Experiment 3 participated in this study, along with an additionally recruited 11 patients (P9 – P19 in Table 4.2), bringing the total sample to 19. Details on this new sample are provided in Table 4.2. Selection of additional patients was again contingent on reported visual field defects, the availability of a full visual perimetry and CT/MRI scans of the lesion (not shown). The new sample of patients (n=19; 1 female, mean age = 46.3 years, sd=15.3) had chronic visual field deficits and an average time from lesion of 19 months (sd=16.2). All patients showed normal hearing and normal or corrected to normal visual acuity. Right lesioned patients were screened using the Behavioural Inattention Test neglect assessment (Wilson et al., 1987), to ensure performance was in the normal range. All patients presented deafferentation or destruction of the occipital cortex,

consequent to postchiasmatic lesions, as documented by CT and MRI scans (scans not shown).

ID	Sex	Age	Education	Onset	Lesion Site	Aetiology
P1	M	41	11	9	Right Temporo-Occipital	AVM
P2	F	38	13	12	Right Temporo-Parietal-Occipital	Ischaemic
P3	M	47	13	3	Right Temporo-Parietal-Occipital	Ischaemic
P4	M	69	8	3	Right Temporo-Occipital	Ischaemic
P5	M	70	8	9	Right Fronto-Parietal-Occipital	Ischaemic
P6	M	24	13	56	Left Temporal	Traumatic
P7	M	57	13	7	Left Occipital	Ischaemic
P8	M	33	13	11	Left Temporal	Ischaemic
P9	M	29	16	23	Bilateral Fronto-Prietal-Occipital	Trauma
P10	M	64	8	16	Left Occipital Cortical-Subcortical, Left Internal Capsule	Vascular
P11	M	26	13	22	Left thalamus	Trauma

P12	M	44	unkown	2	Left Occipital	Vascular
P13	M	63	9	33	Right Temporal-Parietal-Occipital	Vascular
P14	M	56	unkown	13	Vertebrobasilar Left, Occipital Left	Vascular
P15	M	51	13	27	Right Temporal-Parietal	Vascular
P16	M	32	13	17	Right Frontal-Temporal-Occipital	Vascular
P17	M	34	11	53	Left Parieto-Occipital	Trauma
P18	M	58	8	40	Left Occipital	Vascular
P19	M	39	13	7	Left Occipital, Left Thalamus	Vascular

Table 4.2 - Demographic and clinical data of patients: M=Male; F=Female; Age in years; Education in years; Onset of lesion prior to treatment in months; AVM = Arteriovenous malformation.

Procedures were again conducted in accordance with the Declaration of Helsinki and all participants provided informed written consent prior to participating.

Experimental design

This experiment again used a within-subjects design. Participants completed both a clinical assessment and an EEG paradigm. The same clinical battery was administered as in Experiment 3, however due to time constraints, patients did not perform the double baseline (i.e. only pre and post). However the battery demonstrated both in Experiment 3 and in previous studies indexing the effects of multisensory stimulation treatment (Bolognini et al., 2005; Passamonti et al., 2009) that the tasks are well insulated from practice effects. The EEG paradigm was administered, as in Experiment 3, at three time intervals – baseline 1, i.e., before treatment (B1), control baseline 2, i.e., two weeks after B1 immediately before treatment (B2 – control for practice effects) and finally after treatment (P).

EEG – event related potentials

ERP waveforms were filtered, referenced , screened for artifacts and epoched using the same procedures in Experiment 3. However instead of swapping electrode sites as previously done, the present experiment chose electrode sites specifically for patients with right and left lesions. This procedure was carried out by visual analysis of the location of peak maximal amplitudes within the relevant component time window for separate topography maps computed for right and left lesion patients (see figures 4.19 to 4.21 in the results section). For the P1 time-window (100-140ms post stimulus), P8 fell within the central contour denoting maximal positive amplitude for left lesion patients, while O1 was the maximal amplitude site for right lesion patients. For the N1 time-window (160-200ms post stimulus), C4 fell within the central contour denoting maximal positive amplitude for left lesion patients, while C3 was the maximal amplitude site for right lesion patients. For the P3 time-window (350-400ms post stimulus), Pz fell within the central contour denoting maximal

positive amplitude for both left and right lesion patients. Waveforms were extracted from the relevant electrode site for each component for each participant, depending on the site of their lesion, i.e. P1 component amplitudes were recorded at O1 for right lesion patients, but P8 for left lesion patients, and so on. Mean amplitudes were computed within the above time windows for the dependent variable for statistical analysis, given both the increased power in the larger sample to insulate from latency variation, and that Experiment 3 yielded similar results using mean and peak-anchored amplitude values.

EEG - Preparatory oscillations

Before extracting alpha band oscillatory activity, whole waveforms from concatenated testing blocks were referenced and screened for artifacts using the same procedures as the ERP waveforms. Epochs were then created for the time window -1300ms to 300ms post stimulus. Epochs were discarded if horizontal saccadic movements (>40μV on horizontal EOG channels) were registered during the window from -500ms pre-stimulus, to stimulus onset, to control for eye-movements explaining alpha power (mean: 45 epochs per participant per session; together with the above procedures, a total of 8% of epochs were excluded). Note that 30μV was used in the post-perceptual window in Experiment 3, however the longer screening window used here in Experiment 4 was resulting in a large number of epochs for some participants (2 patients >60%), and accordingly the threshold was increased. Alpha band oscillatory activity was then characterised in each trial using the temporal spectral evolution technique (TSE; Salmelin & Hari 1994), which has been previously employed to analyse preparatory alpha band activity (e.g., Worden et al, 2000). Once epochs had been offline referenced, lowpass filtered and screened for artifacts as described above, epochs were subjected to a further bandpass filter (Butterworth zero phase,

24dB/octave) tuned to the alpha frequency range (8-14Hz). Epochs were then full-wave rectified. To control for tonic alpha variation between participants, epochs were baseline normalised to the time-window -1000 to -900 pre-stimulus, i.e., immediately after the offset of the fixation cross. Waveforms were then averaged across all trials for each electrode. The TSE method allows alpha band oscillatory activity to be measured as a function of time, with higher positive values indicating higher alpha power. Given that preparatory (pre-stimulus) activity was the metric of interest, and that patients had no cue indicating where stimuli would appear, epochs were not sub divided into conditions relating to stimulus position.

For statistical analysis of the preparatory alpha oscillations at baseline, mean pre-stimulus alpha TSE values, in the window -500 to -200ms pre-stimulus, were computed for each participant from a montage of left and right posterior scalp electrodes. Previous studies have demonstrated that pre-stimulus alpha band activity has a focal distribution over posterior occipital sites (Worden et al, 2000). Accordingly, electrodes O1, P3 and CP1 were used to measure alpha band activity in the left hemisphere, while O2, P4 and CP2 were used for the right.

In order to perform a statistical analysis on the effects of treatment on preparatory oscillations, left and right electrode montages were re-classified as belonging to the lesioned or intact hemisphere, depending on the side of the lesion, for each participant. Preparatory alpha activity was computed at B2 and P using the same procedure as above for the baseline activity. TSE values were also computed for both the delta (0.5-4Hz) and theta (4-8Hz) frequency bands at sessions B1, B2 and P, using the same methods as above, to perform control analyses.

Results

Uncued alpha imbalance

Figure 4.15 illustrates the time course of electrophysiological activity preceding stimulus onset, for electrode montages on the left and right hemispheres, separately for the right lesion and left lesion group, at all three testing sessions, B1, B2 and P. In a similar fashion to when normal subjects are cued to attend to a specific lateral visual field, alpha values initially (in a window of approximately -1000 to -700ms pre-stimulus) behave similarly over both hemispheres. However, from approximately -700ms pre-stimulus, a sustained difference in alpha values can be observed at, which carries through to stimulus onset. This imbalance appears to be characterised by alpha power over electrode sites on the intact hemisphere being greater than alpha power over the lesioned hemisphere.

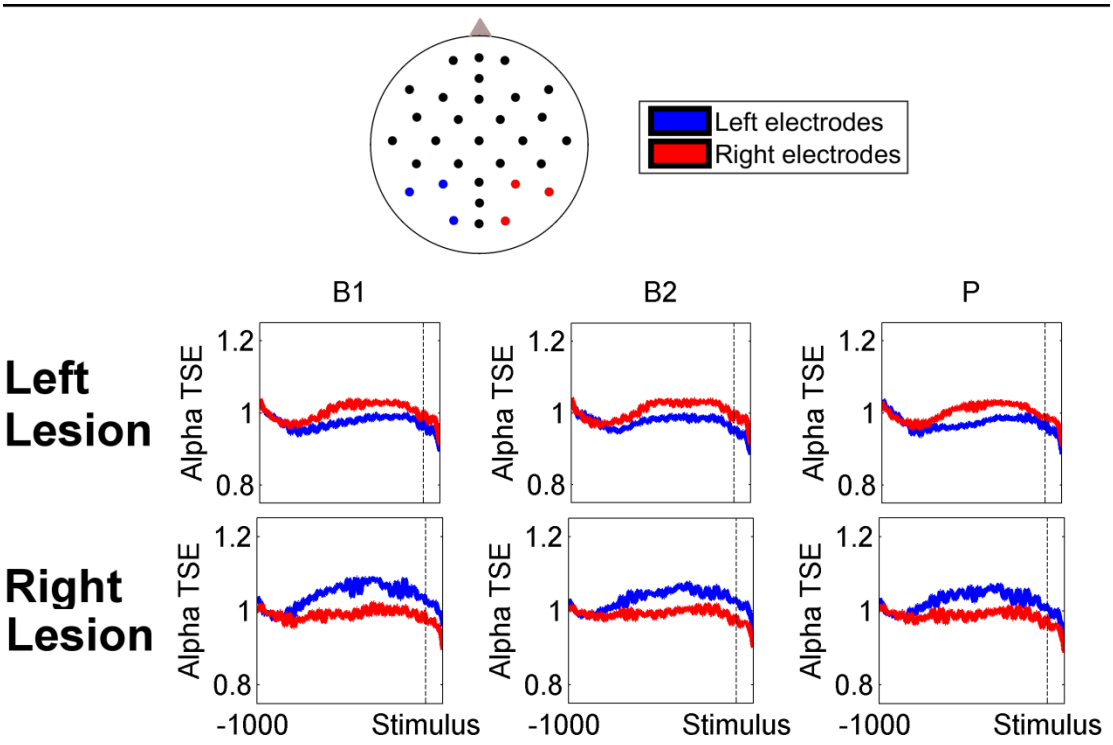


Figure 4.15 – Preparatory alpha waveforms. Preparatory oscillations in the foreperiod preceding stimulus onset for patients with left sided lesions (top row) and right sided lesions (bottom row) at testing sessions B1, B2 and P. The electrode map describes sites of electrode montages on the left (blue) and right (red)..

To test the significance of this imbalance, a paired t-test compared the mean pre-stimulus alpha TSE in the time window -500 to -200ms pre-stimulus, for data recorded at B1, i.e., the baseline alpha imbalance. To test the entire group in a single comparison, electrode sites were re-coded as either situated on the intact or lesioned hemisphere. The t-test confirmed that pre-stimulus alpha power on the intact hemisphere (mean = 1.04) was significantly higher than mean alpha power over electrode sites on the lesioned hemisphere (mean = 0.99) ($t=3.28$; $df=18$; $p=.015$), suggesting that patients were inhibiting their intact field.

Effects of treatment on preparatory alpha

Summarised below in Figure 4.16, a hemisphere (intact, lesion) by time (B1, B2, P) within subjects ANOVA was conducted to test the effect of treatment on preparatory alpha oscillations. The main effect of hemisphere was significant ($F(1,18)=20.86$; $p<.001$), driven by alpha power being significantly higher at electrode sites on the intact hemisphere (1.04) than on the lesioned hemisphere (.99) collapsed across all three testing sessions ($p<.001$). No other main effects or interactions were significant (all p-values > .43). Thus, in an uncued visual detection paradigm, participants were directing attention toward their blind field at all

three testing sessions, in a similar fashion to normal subjects' electrophysiological profile when cued to a specific hemifield.

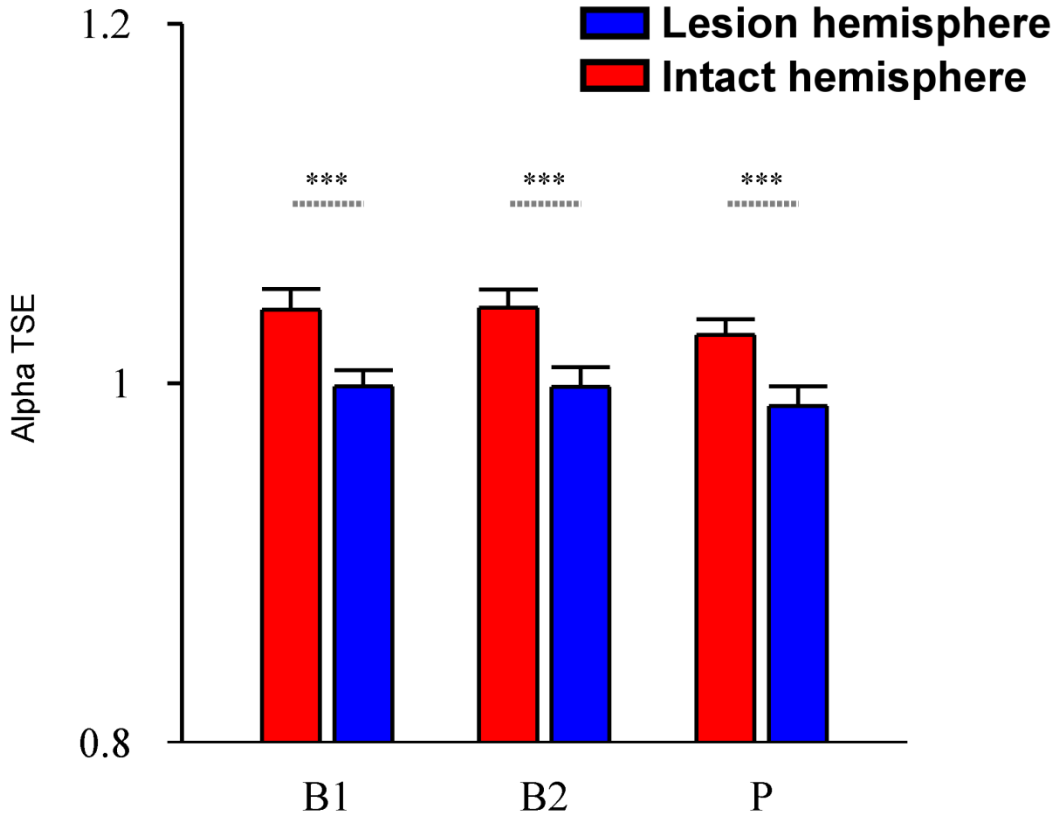


Figure 4.16 – Treatment effects on preparatory oscillations. Intact hemisphere electrode sites are depicted with red bars, lesioned hemisphere sites with blue bars. Y-axis values correspond to the mean TSE in the foreperiod -500 to -200ms preceding stimulus onset for the alpha (8-14Hz) frequency band, at testing session B1, B2 and P.

Control analyses on delta and theta bands

Anticipatory delta and theta band activity were extracted from the EEG data in the same manner as the anticipatory alpha and subjected to the same statistical analyses. Paired t-tests comparing data recorded over lesioned and intact hemisphere reported that no uncued imbalance was present before treatment for either the theta ($t(df=18)=.021$; $p=.984$) or the delta band ($t(df=18)=.443$; $p=.663$). The uncued imbalance appears therefore to be focal to the alpha band. A hemisphere (intact, lesion) by time (B1, B2, P) within subjects ANOVA further reported no significant main effects or interactions for anticipatory theta (all p-values >0.48) or delta (all p-values >0.34) signals.

Results of treatment on clinical tests

Unisensory visual test – Summarised below in Figure 4.17, a 2x2x4 Within Subjects ANOVA, using factors, visual field (hemianopic, intact), session (pre,post) and location (56°, 40°, 24°, 8°) was performed on raw accuracy scores. The main effects of visual field ($F(1,18)=404.22$, $p<.001$;), session ($F(1, 18)=41.59$; $p<.001$) and location ($F(3,54)=36.27$, $p<.001$) were significant. Notably, the three-way interaction between visual field, session and location was also significant ($F(3,54)=6.72$; $p<.001$). Two separate ANOVAs were consequently run, for the hemianopic and intact visual field, respectively, with factors session (pre,post) and location (56°, 40°, 24°, 8°). ANOVA on the hemianopic field revealed a significant effect of session ($F(1,18)=70.22$; $p<.001$): accuracy scores significantly increased from pre (33%) to post (62%; $p<.001$) across all locations.

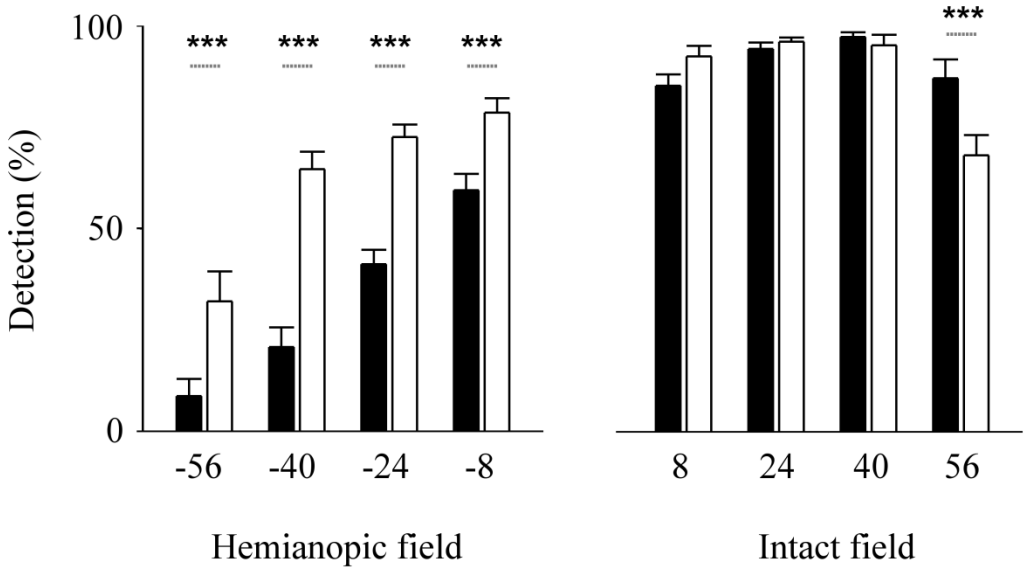


Figure 4.17 - Results of treatment effects on unisensory visual detection test. Accuracy (% correct stimulus detections; error bars report standard error of the mean) depicted as a function of stimulus eccentricity (8, 24, 40 and 56 degrees) and visual field (intact, hemianopic), at pre (black bars) and post (white bars) treatment.

The location effect was also significant ($F(3,54)=41.75$; $p<.001$): accuracy was different for all pairwise comparisons of the four stimulus locations, 56° (20%), 40° (43%), 24° (57%), 8° (69%) (all p-values <.01). ANOVA on the intact field, revealed a significant interaction between session and location ($F(3,54)=10.25$; $p<.001$). Accuracy significantly reduced at 56° at post (68%), compared to pre (87%; $p<.001$), while no other accuracy reduction was observed at any other location in the intact field (all p-values >.112). A paired t-test

compared the percentage of false alarms between pre and post, revealing no significant differences between sessions t(df=18) = -1.31, p=0.207 (pre: 0% post: 1%).

Visual Search – Summarised in figure 4.18, paired t-tests were used to compare IE scores on the E-F test, Shape test and Numbers test pre and post treatment. A significant reduction in IE scores was observed for both the E-F test (t=2.83;df=18;p=.011) and the Numbers test (t=4.27;df=18;p<.001), while the Shapes test trended toward a significant reduction (t=1.93;df=18;p=.069). Recall from Experiment 3 that reduced IE scores reflect an improvement in performance, i.e., more efficient visual search.

Activities of Daily Living (ADL) – A paired t-test compared scores on the ADL self-report instrument before treatment with scores recorded post treatment. This analysis suggested that scores after treatment (mean = 9.05) were significantly reduced, relative to before treatment (14.10; t=2.19;df=18;p=.042). Patients were therefore reporting less complications with daily living, post treatment.

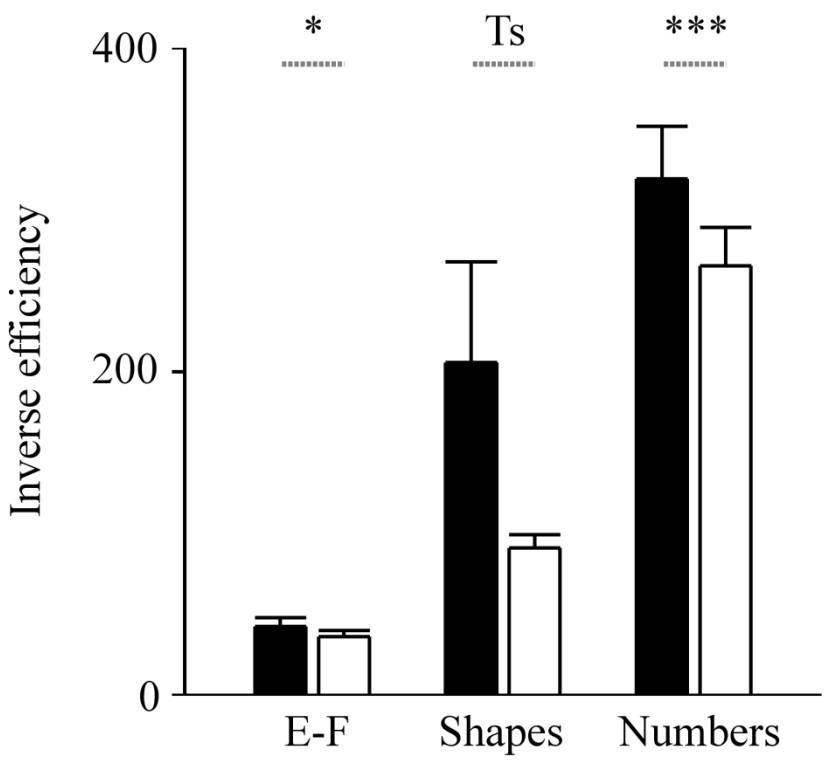


Figure 4.18 - Treatment effects on visual search. Inverse efficiency (% accuracy / Reaction time) of visual search tests E-F, Shapes and Numbers, as a function of testing session pre (black bars) and post (white bars). Note that the pre/post difference for the Shapes test was trending towards significance (Ts; p = .069).

Results of treatment on stimulus evoked ERPs

As with Experiment 3, only ERPs elicited by stimuli presented in the intact field were analysed (summarised in figures 4.19 – 4.21 below). The treatment effects on mean amplitudes of the P1, N1 and P3 components elicited by stimuli in the intact visual field were compared using a 3x3 winthin-subjects ANOVA, with factors component (P1,N1,P3)

and session (B1, B2, P). This ANOVA revealed a significant interaction between session and component ($F(4,72)=5.38$, $p<.001$), driven by P3 amplitude at P (5.96 μV) being significantly lower than B1 (7.97 μV, $p<.001$) and B2 (8.17 μV, $p<.001$), while no difference was observed between B1 and B2 ($p=.638$). In contrast, no significant differences were observed for the N1 component (B1 = -2.49 μV; B2 = -2.35 μV; P = -2.62 μV; all p-values >.740) or for the P1 component (B1 = 1.81 μV; B2 = 1.50 μV; P = 1.77μV; all p-values >.544). These data therefore replicate the effect observed in Experiment 3, namely that treatment attenuated the amplitude for the P3 component, while not having any effect on the amplitudes of the P1 or N1 component.

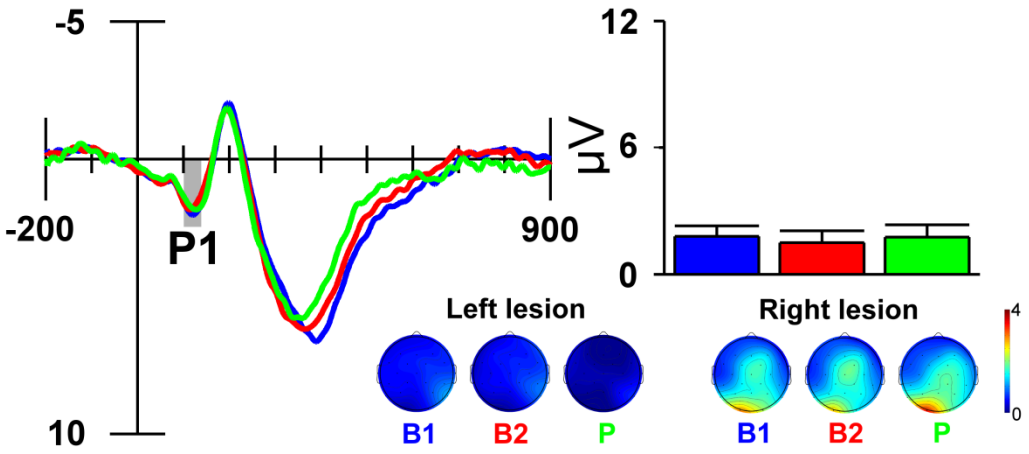


Figure 4.19 - Treatment effects on P1 component. Left panel depicts grand averaged ERPs elicited by stimuli presented to the intact visual field, as a function of session (B1,B2 and P). Waveform is depicts both left and right lesion groups, collapsing waveforms recorded at electrode P8 for the left lesion group, with waveforms recorded at electrode O1 for the right lesion group. Electrode selection for each group was guided by visual inspection of the separate scalp

topographies for the P1 time-window (100-140ms post stimulus), presented in lower right of figure. P8 and O1 both fall within the central contour denoting maximal positive amplitude respectively for left and right lesion patients. The bar-graph to the right of the panel depicts the mean amplitude of the waveform within the P1 range, as a function of session. Error bars reflect standard error of the mean.

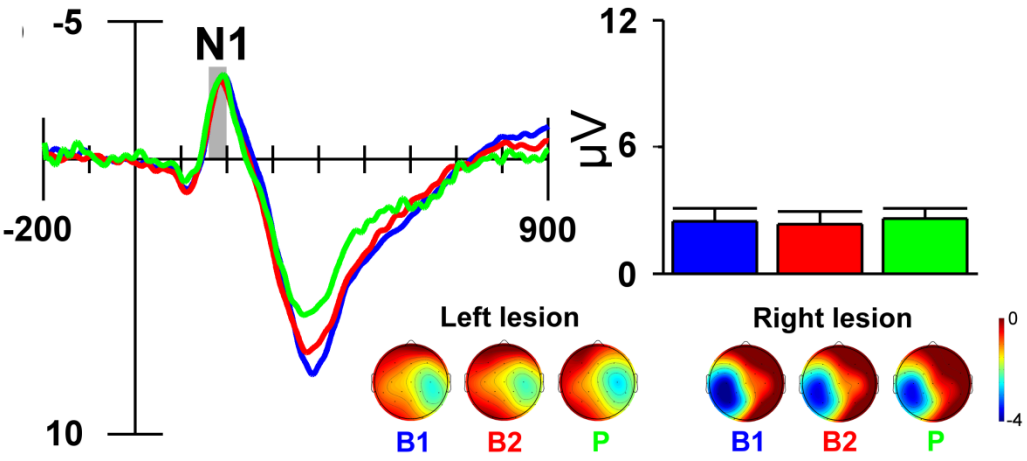


Figure 4.20 - Treatment effects on N1 component. Left panel depicts grand averaged ERPs elicited by stimuli presented to the intact visual field, as a function of session (B1,B2 and P). Waveform is depicts both left and right lesion groups, collapsing waveforms recorded at electrode C4 for the left lesion group, with waveforms recorded at electrode C3 for the right lesion group. Electrode selection for each group was guided by visual inspection of the separate scalp topographies for the N1 time-window (160-200ms post stimulus), presented in lower right of figure. C4 and C3 both fall within the central contour denoting maximal negative amplitude respectively for left and right lesion patients. The

bar-graph to the right of the panel depicts the mean amplitude of the waveform within the N1 range, as a function of session. Error bars reflect standard error of the mean.

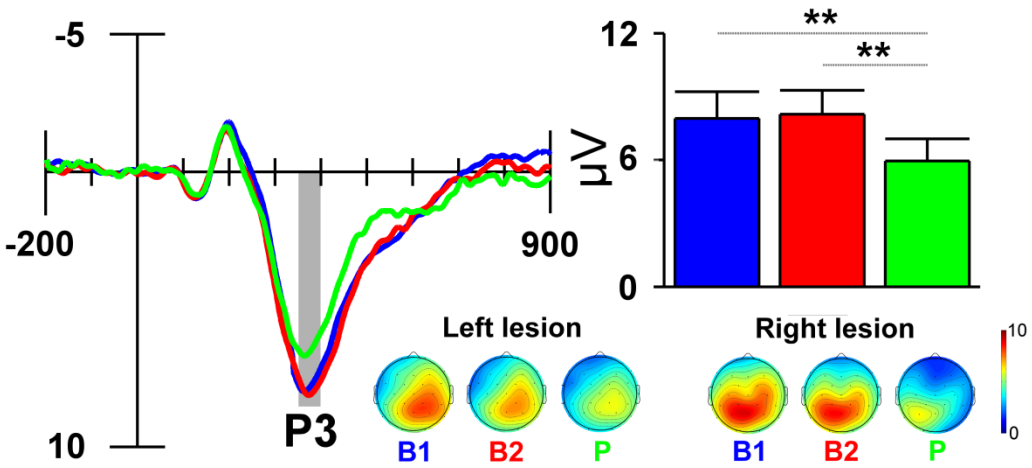


Figure 4.21 - Treatment effects on P3 component - large group. Left panel depicts grand averaged ERPs elicited by stimuli presented to the intact visual field, as a function of session (B1,B2 and P). Waveform is depicts both left and right lesion groups, collapsing waveforms recorded at electrode Pz both lesion groups. Electrode selection for each group was guided by visual inspection of the separate scalp topographies for the P3 time-window (350-400ms post stimulus), presented in lower right of figure. Pz falls within the central contour denoting maximal positive amplitude respectively for left and right lesion patients. The bar-graph to the right of the panel depicts the mean amplitude of the waveform within the P3 range, as a function of session. Error bars reflect standard error of the mean.

Discussion

The findings of the present experiment first demonstrate that HVFD patients appear to have a bias toward their blind field during the anticipatory window prior the onset of a stimulus. This was demonstrated in inhibitory alpha band activity being significantly higher over the intact hemisphere, than over the lesioned hemisphere. This imbalance was focal to the alpha band and onset approximately 700ms before stimulus onset, strongly suggesting a phasic preparatory process. In addition, findings from this experiment replicate findings of Experiment 3 in a larger group of hemianopia patients, confirming that a course of multisensory stimulation treatment improves various measures of visual search and dynamic visual detection while concurrently attenuating post-perceptual attention processes elicited by visual stimulation of the intact field. I will now discuss these findings in greater detail.

Hemianopia patients have an uncued bias of spatial attention toward their blind field

The first finding from the experiments in this chapter was that pre-stimulus alpha band activity is significantly higher in posterior electrode sites on a hemianopia patient's intact hemisphere (relative to the lesioned hemisphere), during the foreperiod of an uncued simple visual detection task. In previously published studies using spatial cues with healthy subjects (e.g. Worden et al, 2000), higher alpha power is observed over posterior electrode sites contralateral to the to-be-ignored region of space. Thus, the patients were therefore inhibiting their intact visual field when awaiting the appearance of an uncued stimulus, in a manner similar to how a normal subject would inhibit the to-be-ignored visual field during the foreperiod preceding a spatially cued stimulus. The hemianopia patients in this study

therefore appear to be voluntarily focusing visual attention toward their affected visual field, even when the likelihood of a stimulus appearing there is the same as the likelihood of it appearing in the opposite visual field, and further, even when the overwhelming majority of detected stimuli were appearing in the opposite visual field.

A control analysis observed no similar effect in theta or delta band activity, suggesting that this phenomenon is focal to the alpha band. In addition, similarly to normal subjects (e.g., Worden et al, 2000), visual inspection shows that the alpha band activity was symmetrical in the early pre-stimulus window, commencing at -1000ms, lasting until approximately -700ms pre-stimulus (i.e., 200ms after the baseline period used to normalise the waveforms). However, a phasic lesion-specific asymmetry emerged in the time-window from approximately 700ms pre-stimulus to stimulus onset. It is therefore unlikely that tonic alpha band activity (possibly attributable to the greater cortical volume in occipito-parietal regions of the contralesional hemisphere) is driving the observed effects.

These data support the idea that hemianopia patients drive attention toward their blind field. Barton and Black (1998) hypothesised that the bias demonstrated by hemianopia patients on line bisection tasks could be a function of strategic adaptivity. Under this model, patients with better insight into the presence of their lesion will place more salience on their blind field of space, which, over time, generates an attention (and possibly eye-movement) over-compensation (Baier et al, 2010). Initially supporting this idea were behavioural tasks which showed that hemianopia patients appear to overcompensate with both a higher number and longer duration of fixations into the contralesional side of a letter array when searching for targets in a visual search task, in contrast to normals, who distributed fixations evenly and,

further, neglect patients, who demonstrated an inpsilesional bias (Behrmann et al, 1997). The same gradient, i.e., a higher number of fixations at more peripheral sites in the blind field (Barton et al, 1997). A later study by Machner et al (2009) further supported the strategic hypothesis by demonstrating that acute hemianopia patients commit an ipsilateral line-bisection error, in contrast to patients in the chronic phase. (However Baier et al (2010), did observe a contralateral bias with one patient in the acute phase).

Can a treatment-driven shift in early spatial attention be ruled out?

Treatment did not appear to have any effect on the above described alpha imbalance. In addition, the findings in the present experiment mirror the findings with the smaller sample in Experiment 3, where treatment plasticity only affected post-perceptual electrophysiological markers of attention. Nonetheless, conflating the findings of Experiments 3 and 4 present a number of reasons why a treatment-driven shift in covert spatial attention from the intact field to the hemianopic field might still at least in part, or even entirely, underscore the treatment effects. Perhaps most tellingly, the behavioural data from the unisensory visual detection task present a strong argument that attention has been redeployed from the intact visual field into the scotoma.

In the discussion to the results from Experiment 3, I discussed how in light of the treatment only influencing P3 amplitude, and not earlier components of spatial attention (N1, P1), the treatment may have affected one component of a duel attention system, incorporating early and late processes. One interpretation I discussed was that less top-down attentional

resources are now being allocated to processing in the intact field. However it is also worth noting that data from Eimer (2000) demonstrate that under very specific conditions and task instructions, the amplitude of the P3 component can be influenced by spatial attention, without concurrent influence on earlier spatial attention ERPs like the P1 and N1. In their experiment, when participants attended to one of the visual field quadrants, validly spatially cued stimuli expectedly elicited larger P1, N1 and P3, compared to invalidly cued stimuli. However when participants attended to rings of space in the visual field subtending all four visual quadrants, cue-validity effects were only observed on the P3 component. While it appears unlikely that participants in the current paradigm are attending in a ring-like fashion, it nonetheless cannot be ruled out they are attending to regions of space in an idiosyncratic manner. For example, knowing that stimuli could appear at either side of the screen may have parsed attentional deployment into two columns at either side of hemispace, resulting in an attentional deployment similar to that required by the paradigm administered in Eimer (2000).

Finally, the nature of the multisensory treatment, and its likely recruitment of spared subcortical visual circuitry involving the superior colliculus, could be a further explanation why a spatial attention shift wasn't registered in the early sensory evoked components of the electrophysiology paradigm. As described above, the P1 and N1 are specific to the visual modality, reflecting processing within extra striate regions. The superior colliculus plays a crucial role in both overt orienting movements of the eyes and head, and in covert spatial attention, even in the absence of orienting movements (Krauzlis et al, 2013). Further, primate studies have demonstrated that the superior colliculus can alter spatial attention without altering the mechanisms of spatial attention in the visual cortex. For example, Lovejoy and Krauzlis (2010) demonstrated a behavioural impairment in spatial attending to

stimuli contralateral to a monkey's superior colliculus which had been reversibly inactivated. Interestingly, aspects of spatial attention within the visual cortex, such as neuronal firing rates, were not affected by the inactivation of the superior colliculus, despite the alteration on behavioural performance, suggesting that the superior colliculus has the capacity to alter spatial attention with no registered impact on the visual cortex (Lovejoy & Krauzilis, 2010; Krauzilis et al, 2013). Though it must be noted that this was observed in non-human primates, and to date no study has observed an anologuous finding in humans. Nonetheless, further studies are required to confirm whether spatial attention underscores the multi-sensory stimulation treatment effects, possible using alternative networks from subcortical regions. As Passamonti et al (2009) argue, the treatment likely capitalises on the strong connectivity between the superior colliculus and the frontal eye fields in dorsal parietal cortex to strengthen oculomotor function. Thus, long term plastic recruitment of multisensory networks bolstering unisensory and oculomotor function could be mediated via strengthened connectivity between visual signals mediated via the superior colliculus to directly to the frontal eye fields, bypassing striate and extra striate regions. In such a case, treatment effects would not be expected on more posterior networks of spatial attention (such as N1 and P1) put likely to be observed on down-stream processes (such as the P3), consistent with the findings in my experiments.

Study limitations

The present study (in addition to Experiment 3) used a within-group treatment effects design, in which patients served as their own control group.. In addition, performance on any of the measures was not compared to either a healthy control group, or a no-treatment hemianopia sample, or a no-treatment brain injury sample with no visual defect. The study

was also lacking a long-term control group, in order to test whether effects maintained over time. On this point, follow-up EEG sessions are being recorded with the original patient sample.

Concluding remarks

Conflating the evidence in the line-bisection and greyscale literature together with the findings from Experiments 3 and 4 allow for a speculative hypothesis to be drawn about the nature of attentional biases in hemianopia: hemianopia is affected by both lesion-driven and deficit-driven biases in spatial attention. The lesion-driven bias toward the healthy field can be observed in the acute phase using line bisection, where patients report centres of lines to be consistently biased toward their intact field, or in the chronic phase using the greyscale task where patients consistently report darker gradients on the same side as their intact field. In contrast, the adaptive deficit-driven bias is observed in the chronic phase on line-bisection task, where over the course of the chronic period, patients appear to develop a bias toward reporting the centre of the line consistently biased in the direction of their blind field. The deficit-driven bias can also be indexed using electrophysiological signals of preparatory attention signals, as suggested by the data in Experiment 4. The nature of the greyscale task may explain how it remains sensitive to the lesion-driven bias into the chronic phase (i.e., after the development of the deficit-driven bias) – i.e., that it forces a discrimination between two gradients, as opposed to prompting free localization of the midpoint of a line in two-dimensional space. Finally, overall, the treatment data suggest that impaired visual search in hemianopia patients might also be a function of the deficit-driven bias. This interpretation is drawn first from the behavioural data demonstrating a post-treatment shift in attention toward the blind field (observed in both Experiments 3 and 4), strengthening this adaptive

bias. Our main finding from the EEG paradigm also suggest that post-treatment attentional resources may be reduced toward the intact field, as the post-perceptual P3 component attenuated in response to intact field stimulation after treatment (again, observed in both Experiment 3 and replicated in Experiment 4). Though the precise role of early spatial attention mechanisms remains unclear, an exciting possibility from our data is that the attentional effects of treatment may be bypassing the visual cortex, and boosting orientation toward the scotoma, via subcortical networks.

Future studies should index plastic effects of multisensory stimulation treatment with hemianopia patients using paradigms sensitive to the lesion and deficit driven biases, to see which (or whether both) of the biases are affected. A number of behavioural and electrophysiological measures merit investigation - firstly, performance on the grayscale and line-bisection task should be compared, before and after treatment. Of particular interest would be an interaction between treatment and task, which would give further weight to the notion that two biases exist pre-treatment and which one is more affected by treatment at a behavioural level.

Chapter 5: General Discussion

The primary channel of the human visual system carries the majority of signals from the retina to the lateral geniculate nucleus of the dorsal thalamus (LGN) and onward via the optic radiations to the striate cortex for further processing (the retino-geniculo-striate pathway). Disruption to this pathway at any point posterior to the optic chiasm will likely result in a loss of conscious visual representation for a portion of lateralised space, a homonymous visual field defect. This dissertation sought to explore three phenomena in human patients who have suffered such a lesion and ensuing visual deficit - residual function, plastic reorganisation and treatment driven plasticity.

Over the past two million years, the human visual system has evolved to afford the species more informative and adaptive visual information, by way of providing an increasingly detailed analysis of the world around us (Kaas, 2013). In order to facilitate such functional evolution, the anatomy of the visual system appears to have evolved in an additive rather than substitutive manner, i.e., new anatomical networks have been appended to existing systems rather than replacing them entirely. In other words, the complex human visual system has preserved multiple parallel neural inputs, varying in terms of the detail they provide and how fast they relay their signals. Further, the brain can integrate signals from various sources in order to strengthen perception. In fact, scope for residual visual function following a retrochiasmatic lesion stems largely from the fact that there are ten known pathways into the brain from the eye, with each pathway involving different combinations of substrates and recruited by different perceptual demands (Stoerig and Cowey, 1997). Disruption to the

primary pathway to striate cortex could therefore leave a number of alternative networks intact and capable of relaying specific signals, even in the case of conscious vision loss.

In Chapter 1 I explored one such residual signal - implicit fear processing. Identifying danger in the immediate environment is pivotal to a species's survival. Accordingly, the functions of even the most primitive non-mammalian visual systems weight heavily on relaying signals of danger from the retina through structures involving rapid emotional processing and behavioural responses, such as the amygdala. In the human visual system, a pathway has been identified which can relay signals without contribution from the primary visual pathway; from the retina to the superior colliculus, onward to the pulvinar, and finally terminating in the amygdala (the retino-colliculo-pulvinar-amygdala pathway; LeDoux. 1996). This subcortical threat pathway, typically spared in patients with a lesion to the cerebrum, purportedly provides a fast, coarse detection of threat in order to initiate fight-or-flight responses (Öhman & Wiens, 2003). However since the late 1990s, the precise role of this pathway had been challenged by a number of studies demonstrating that a small selection of patients with retrochiasmatic lesions could perform remarkably well on tasks where they were forced to make a judgement about various emotional signals (fearful, happy, angry) presented in the regions of space where they were blind (deGelder et al, 1999;2001;2002; Pegna et al, 2005). This phenomenon was termed 'affective blindsight', and was further supported by data from indirect assessment, where the effect of an emotional signal in the blind field of space influenced responses to stimuli presented in the intact field, again for signals of varying valence, i.e. not just fear (deGelder et al, 2001;2002; Pegna et al, 2005). The overarching hypothesis purported in this literature was, that in the absence of a primary pathway to striate cortex, several emotional signals presented in these patients' blind fields

could be processed by the spared subcortical network, an interpretation that conflicts with its adaptive fear specificity.

However, data from Experiment 1 in Chapter 1 contribute a novel finding to the literature that supports the fear-specific nature of implicit affective processing in HVFD patients. A series of studies emerged in more recent years, that had already made a strong case that the patients recruited in the affective blindsight studies were representative of a minority amongst HVFD patients (Bertini et al, 2012; Cecere et al, 2013;2014). Indeed the degree to which these patients could discriminate a host of visual features (Weiskrantz et al, 1974; Weiskrantz, 1987; Brent et al, 1994), in addition to the manner in which their performance on indirect tasks mirrored that of healthy subjects prior to artificial inhibition of the healthy occipital cortex (Cecere et al, 2013), strongly suggested that these patients were benefiting from abnormal plastic reorganisation which had more than likely spared some degree of function within either geniculo-striate or geniculo-extrastriate regions. In Experiment 1 in this thesis, a sample of patients with retrochiasmatic lesions and consequent HVFD were therefore first screened using forced-choice tasks, to ensure that they displayed no residual capacity to discriminate visual stimuli in their blind field. In a subsequent go/no go gabor orientation task presented in their intact visual field, the patients responded faster to the target gabor when a fearful face was presented concurrently in their blind field. This response facilitation was not observed when a happy or neutral face was presented concurrently in the blind field, suggesting that when the primary visual pathway is damaged to the extent that no residual discrimination capacity is preserved, the only signal that can be implicitly processed via the subcortical pathway is fear. Interestingly, unseen fear only boosted responses in patients with lesions to their left hemisphere, suggesting that an intact right hemisphere is required for implicit fear signals to facilitate orientation discrimination. On the one hand, this finding is

consistent with the right hemisphere being dominant in emotional processing (e.g., Gainotti, 1972; Làdavas et al, 1993), fight-or-flight motor activation (deGelder et al, 2004) and adaptive responses such as the startle blink (Angrilli et al, 1996) and the withdrawal response (Davidson, 1993; Davidson et al, 2000). In addition, relative to the left, the right amygdala holds stronger functional connectivity with components of the subcortical visual pathway, such as the pulvinar and the superior colliculus (Morris et al., 1999) and also displays stronger activation in response to unseen fearful faces (Morris et al, 2001; deGelder et al., 2005; Pegna et al., 2005).

A recently published study used the same screening procedure prior to administering a go/no go task in the intact field for target emotions or genders (Bertini et al, 2012). Similar to the data in Experiment 1, patients were only faster on trials where fearful faces were presented concurrently in their blind fields, both when detecting target emotions and when detecting target gender. However in the emotion task, no facilitation was observed when an unseen fearful face accompanied a target fearful face in the intact field (i.e., no fear/congruency effect); the facilitation was only observed when an unseen fearful face accompanied a target happy face in the intact field (fear/incongruency effect). The findings presented in Experiment 1 in this thesis are therefore important, as they rule out an alternative hypothesis that the subcortical pathway requires emotional conflict or emotional ambiguity in order to facilitate behavioural responses. Indeed, the amygdala, as part of its role in monitoring the environment for potential threats to the organism, also responds preferentially to ambiguity, even when stimuli contain no emotional valence or indication of threat. However Experiment 1 has demonstrated that emotional ambiguity between two stimuli is not a requirement for signals to be processed via the subcortical visual pathway, by recording an unseen-fear-driven facilitation of responses in an emotionally neutral, inanimate task requiring orientation

discrimination. Thus, an intriguing implication of the absence of fear/congruency effects in Bertini et al (2012) is the prospect that consciously perceived fear can inhibit activation of the subcortical pathway, which would explain the absence of any facilitatory effect from subcortically mediated signals when fearful faces appeared in the intact field. In a survival situation where there is no conscious awareness of threat, it may benefit the organism to hedge its bets, and execute a motor response to any potential threat picked up in the environment by the coarse analysis of the subcortical visual pathway. Response to no threat is more adaptive than no response to a real threat. However in a situation where the threat is consciously perceived by the primary visual pathway, a finer analysis of the threat will allow for a more appropriate, informed response. However while this finer analysis is being processed, it would be maladaptive to have a potentially conflicting motor response reflexively activated in parallel by the subcortical pathway. An optimally harmonious, dual-pathway system would therefore require the interactive facility for the 'low road' to be deactivated when the primary visual pathway also picks up a threatening signal, and boosted when it alone registers the potential threat. Functional connectivity data support this exact interactive model, by demonstrating anticorrelations between LGN, striate cortex and the subcortical visual pathway in cases of consciously perceived fear, and positive correlations within the subcortical visual network in cases of fear presented below psychophysical thresholds (Williams et al, 2006).

Parallel inputs to the visual system is just one area where the human brain boasts shrewdly evolved architecture for interacting adaptively with the environment. The numerous inputs from the eye to the both cortical and subcortical areas that have developed over the evolution of the species first afford context specific processing of visual signals via different structures in a normal brain when required (e.g. the recruitment of the subcortical visual pathway in the

case of unseen threat signals), and further, spared pathways for residual function in the case of disruption to the primary channel. However, another fascinating manner in which the human brain offers the organism survival adaptation is its ability to spontaneously adapt, reorganise and compensate for the complete loss of function following disruption from a lesion. Findings from studies with patients who have experienced lateralised lesions have demonstrated that both local (e.g. perilesional) and distal (e.g. contralesional) regions can take over the function of the cortical regions lost in the lesion. A wealth of literature has demonstrated that such spontaneous plastic change can occur with motor function in limb movement (Chollet et al, 1991; Cramer et al 1997; Grefkes & Ward, 2013), language production (Cao et al, 1999; Rosen et al, 2000; Fernandez et al, 2004), and emergingly, visual function (Nelles et al, 2002; 2007). However the precise nature of how this occurs in the visual system has been scarcely studied; of specific interest would be what spontaneous organisation can take place, is it adaptive and what residual networks might be mediating the plastic change?

Experiment 2 in Chapter 2, therefore, presented a case study which used a number of imaging techniques to explore the physiological mechanisms that underscored the reorganisation of visual cortex following a brain lesion affecting a quadrantopic HVFD patient's right optic radiation, i.e., the ipsilesional visual cortex was anatomically spared, but functionally disconnected from its thalamic input. This lesion profile allowed BOLD signals derived from visual field stimulation in homologous regions of functional and dysfunctional visual cortex to be compared without the confound of visual cortex in one hemisphere having less anatomical volume. The first analysis in this case study focused on whether there would be patterns of spatial selectivity loss, which had been reported in a small number of previous studies (Nelles et al 2002; 2007). The occipital cortex in a normal brain can be spatiotopically

portioned into four regions, separated laterally by the great longitudinal fissure and dorsoventrally by the calcarine sulcus. In a healthy brain, these four quadrants are retinotopically selective. That is, they should primarily respond to visual stimulation in only one quadrant of the visual field; specifically, regions respond contralateral and elevationally inverted to the region of visual stimulation (Tootell et al, 2008). In line with previous studies, the patient examined in Experiment 2 displayed a loss of spatial selectivity in the visual cortex of her intact hemisphere. Specifically, stimuli presented to the left visual field were now eliciting a BOLD response in the left primary visual cortex. Experiment 2 further presented a novel finding to this literature by demonstrating a gradient of retinotopic remapping; in early visual cortex, the remapping was focal to homologous regions of visual cortex between the two hemispheres, i.e., BOLD signals were observed in left ventral V1 following stimulation of the right lower quadrant of the visual field (the expected response) and also the left lower quadrant (visual location that should only drive response in the region homologous to left ventral V1, i.e., right ventral V1). However in the higher visual areas V3a (dorsal) and V4 (ventral), stimulation of all four visual quadrants were now prompting BOLD responses, suggesting that these higher tiers of visual cortex had completely lost their spatial tuning to specific regions of space. In contrast, visual cortex in the lesioned hemisphere displayed no such loss of spatial tuning; instead, response gain was observed in BOLD signals in higher visual areas of the lesioned hemisphere, in response to stimulation of both the upper and lower left visual quadrant.

These findings were taken from a single case participant, in the absence of long term behavioural assessment, which complicates a direct inference about the adaptivity of the above pattern of reorganisation. However, one possible less benign interpretation is that the reduced spatial selectivity in the intact hemisphere is simply a release from cross callosal

inhibition. With less inhibitory signals being received via the corpus callosum, visual cortex of the intact hemisphere may simply be over-indulging in regions of visual space, in a wayward manner that could be deleterious to visual functioning. A number of studies have demonstrated that increased activity in the intact hemisphere can have harmful consequences on behaviour in unilateral lesion patients, to the extent that spontaneous normalisation of such over-excitation or intervention via inhibitory stimulation in neglect can underscore recovery (Corbetta et al, 2005; Koch et al, 2008). However arguing against the release from inhibition hypothesis is the fact that the reorganisation observed in the patient's intact hemisphere visual cortex is not so much related to the intensity of signals (i.e. a hyperactivation) but the spatial selectivity of responses. Further, the deleterious effects of intact field hyperactivation in neglect drives attention in an ipsilesional direction, while the spatial selectivity loss demonstrated by the patient, if anything, was driving attention in the opposite direction, i.e., left cortex now responding to signals in the left visual field suggests a contralesional shift. The MRS data collected in Experiment 2 also contribute to the discussion on the adaptivity of the patient's' neural reorganisation. Expectedly, concentrations of Glutamate were lower in the lesioned visual cortex, given the reduction in excitatory signals being projected to that area from the optic radiations. However the response gains observed in upper tiers in the lesioned visual cortex appear to conflict with the idea that neurons local to the lesioned visual cortex had become less excitable.

The nature of this reorganisation therefore appears to be more consistent with the idea that the visual system is using distal plastic change in an attempt to compensate for unilateral vision loss. The intact visual cortex in the patient now appears to be have doubled its workload, by way of attending to the entire region of visual space, while responses that get registered in higher visual areas of the lesioned hemisphere have significantly increased in

intensity. It would therefore appear that the intact hemisphere has undergone a functional reorganisation, while the lesioned hemisphere is being supported in some capacity. In order to probe what may be underscoring these plastic changes, a functional connectivity analysis was carried out on BOLD signals recorded while the patient was at rest. These analyses reported a novel finding that top-down attentional regulation appears to be modulating the spatial profile of receptive fields in the visual cortex. Strong, positive correlations were observed between regions of the visual cortex in the lesioned hemisphere and substrates of the dorsal attentional network, in particular the frontal eye fields. A further gradient was also observed, with this connectivity being stronger for higher tier visual areas than for primary areas. Thus, given that attention can influence a wide variety of processes in the visual cortex (Desimone and Duncan, 1995; Reynolds and Chelazzi, 2004), including the spatial profile of receptive fields (Reynolds & Heeger, 2009), it's likely that this network is underscoring the loss of spatial tuning in the intact hemisphere. A further analysis on the principle components of the BOLD signal, revealed a component with strong, positive correlations between regions of the default mode network and visual cortex on the lesioned hemisphere. These regions included bilateral retrosplenial cortex, angular gyri and medial prefrontal cortex. This would appear to suggest that the response gain observed in the lesioned hemisphere is a consequence of supportive functional connectivity with the default mode network, a network which has been demonstrated to serve as a backup system for failing brain functions.

Dorsal attentional network and the default mode network may therefore comprise two key networks that can guide spontaneous plastic change in the event of a retrochiasmatic lesion. Although follow up studies will need to confirm both the adaptivity of the spatial selectivity loss in the intact hemisphere and response gains in the lesioned hemisphere, an exciting implication of these data is that the visual system has the capacity to recognise when signals

are entering the brain asymmetrically, and recruit high-order attentional processes to try and restore an equilibrium. However the reorganisation could also simply be a function of the patient trying to compensate by actively directing attention in the direction of her blind field, a process which, over a sustained period of time, could recruit sites in the dorsal attention network in the intact hemisphere and default mode network in the lesioned hemisphere, resulting in an adaptive reorganisation in visual cortex.

Experiments 1 and 2, respectively, described the residual function and spontaneous plastic change following retrochiasmatic lesion, within a unisensory domain. Indeed, findings from Experiment 1 suggest that fear could be the only signal that can be mediated by subcortical networks when patients demonstrate no preserved ability to directly discriminate characteristics of stimuli on forced choice tasks (i.e., blindsight). However, in addition to preserving parallel pathways for processing unisensory signals such as fear, the perceptual system can also provide detailed analysis of the surrounding environment by integrating information from multiple sensory modalities. Converging evidence implicates another subcortical pathway in the integration of multisensory signals; a pathway from the retina to the superior colliculus, and from the multisensory neurons within the deeper layers of the superior colliculus to extrastriate regions (retino-colliculo-extrastriate pathway). In the general introduction to this thesis, I described the crucial role that the superior colliculus appears to play in integrating simultaneous auditory and visual signals, especially when one of these modalities is weak (Stein and Meredith, 1993). As with the fear pathway, this subcortical multisensory network is likewise usually spared in cases of a lesion focal to visual regions within the cerebrum, and evidence from both online (Frassinetti, Bolognini et al, 2005; Bolognini, Frassinetti et al, 2005;Leo, Bolognini et al, 2008; Leo et al, 2011; Cecere, Romei et al, 2014) and offline (Bolognini et al, 2005; Passamonti et al, 2009) studies have

demonstrated the short and long term potential for this site to be recruited via appropriately administered stimulation, in order to facilitate unisensory perception and contribute adaptively to visual functioning. These findings prompted the development of a clinical treatment for HVFD, which administers a sustained audio-visual stimulation of this network via patients' blind visual fields, usually over a two-week period, with published results thus far demonstrating significant improvements in oculomotor behaviour such as visual search and reading efficiency (Bolognini et al, 2005; Passamonti et al, 2009).

Multisensory stimulation treatment demonstrates that a further avenue of neural reorganisation is possible in a brain with a retrochiasmatic lesion, where an unaffected pathway from the eye to the brain is recruited by way of a treatment intervention, aimed at long-lasting functional reorganisation - treatment-driven plasticity. In addition to offering clinical benefits to patients in their everyday lives, treatment plasticity can also provide theoretical insights into the consequences of retrochiasmatic lesion before treatment. In Chapter 3, I conducted two EEG experiments to measure the effects of treatment on perceptually driven (Experiment 3) and anticipatory (Experiment 4) perceptual and attentional processes, in order to probe the substrate of treatment effects and further, to shed light on the attentional biases that appear to emerge after retrochiasmatic lesion. Behavioural studies with hemianopia patients have documented conflicting, task-specific biases in visual attention. When performing a greyscales task, which requires a judgement on which of two simultaneously presented horizontal black-to-white gradients are darker, patients demonstrate a bias toward their intact field, suggesting that the unilateral loss of visual inputs has resulted in an over activation of processes in the intact hemisphere (Tant et al, 2002). However, in contrast, a number of behavioural tasks have shown that hemianopia patients appear to be biased in the opposite direction, i.e., toward their blind field. Eye tracking studies have

demonstrated that patients overcompensate with both a higher number and longer duration of fixations into the contralesional side of both visual search (Behrmann et al, 1997) and line bisection (Barton et al, 1997) tasks, while performance by HVFD patients on line bisection tasks appears to be consistently biased toward their blind field (Barton and Black, 1998).

In Experiment 3, I observed a typical course of multisensory treatment to first improve a series of clinical measures of visual search and dynamic visual detection, replicating the treatment effects documented in previous studies (Bolognini et al, 2005; Passamonti et al, 2009). Concurrent with these improved effects, patients appeared to be shifting spatial attention away from their intact field, into their blind field, following treatment. On a clinical measure of dynamic visual detection (i.e., one where eyes-movements could explore the visual field), accuracy was significantly diminished at the most peripheral testing site in the intact visual field, while accuracy was significantly improved for all testing sites in the blind field. This behavioural pattern is consistent with patients' attention being more strongly allocated toward the blind field. In addition, patients' allocation of post-perceptual attention resources in their intact field appeared to attenuate, post-treatment. EEG waveforms elicited by a simple visual detection EEG paradigm were compared before and after treatment. These waveforms reported no change in early components of spatial attention (P1, N1), but a post-treatment attenuation in the P3, a post-perceptual posterior-parietal ERP component, interpreted as indexing resource allocation of attention from endogenous processes (Isreal et al., 1980; Wickens et al., 1983; Hopfinger & West, 2006). Given that this apparent shift toward the blind field co-occurred with overall improvements in oculomotor behaviour, it appears as though patients with HVFD may indeed have a bias toward their intact field (as argued by Tant et al, 2002), and further, that this bias is maladaptive.

To explore this matter further, I conducted Experiment 4, an EEG study with a larger group of patients, in which anticipatory electrophysiological signals were compared before and after treatment. Typically, when normal subjects direct attention toward a region of space, stronger alpha power is observed at posterior electrode sites, on the same hemisphere as the side of the attended region; these signals are thought to reflect the inhibition of the to-be-ignored region of space, contralateral to the increased alpha power (Worden et al, 2001). In Experiment 4, EEG activity elicited by the simple visual detection paradigm was once again compared before and after treatment; importantly this paradigm provides no cue as to which region of space to attend prior to the arrival of the stimulus. This allowed a measure of the degree to which patients were biasing their attention voluntarily toward either visual hemifield in anticipation of the onset of a stimulus. Results confirmed that, even before treatment, patients had an uncued bias. However this bias appeared to be directing covert attention toward the blind field. Despite receiving no cue to direct their spatial attention, patients' anticipatory alpha power was significantly higher over the intact hemisphere (suggesting an inhibition of the intact field) while they awaited the arrival of stimuli. In addition, this asymmetry was not affected by treatment, suggesting that the alpha signals remained unchanged by the course of multisensory stimulation.

Merging available evidence allows for a speculative interpretation, whereby a dual-bias may be observable in HVFD. Performance on the greyscale task suggests HVFD patients are biased toward their intact field. This is supported and characterised by the findings from Experiment 3 in this thesis, where a treatment which improves visual search also attenuates attention processing in the intact field. Further, this bias may be a consequence of a unilateral

lesion, not specific to HVFD, possibly indexing an over excitation of intact hemisphere cortex (Mattingley et al, 2004). Meanwhile, the line-bisection literature suggests that patients with HVFD can have an attention bias toward their blind field, a finding which is supported by the anticipatory alpha rhythm imbalance observed in Experiment 4. That this anticipatory bias is not affected by treatment suggests that it characterises a separate process. Studies have further demonstrated that the bias observed on the line bisection task reverses over time; patients in the acute phase demonstrate a bias toward their intact field, while patients in the chronic phase display a bias toward the blind field (Machner et al, 2009). It could therefore be the case that the bias toward the blind field is an adaptive strategy that is learned and that multisensory treatment augments this adaptive strategy by recruiting subcortical multisensory structures like the superior colliculus to strengthen attention signals toward the blind field and consequently facilitate oculomotor function. An interesting interpretation of these data is that such recruitment of subcortical multisensory networks can influence late electrophysiological components of attention (P3 attenuation), without influencing anticipatory biases or early stimulus evoked potentials (N1 or P1).

Concluding remarks

Patients who have suffered an acquired brain injury face an extremely challenging adjustment to a new reality. Critical avenues of research which must be explored , in order to support and guide this difficult transition, include understanding what abilities are spared after the lesion, how the spared brain networks have changed, what can be improved or restored with training, and how, exactly, treatment change is driven at a neural level. In so doing, we can mine a wealth of information about the nature and limits of the human brain, and most importantly, further the advancement of effective treatments. In this thesis, I have presented three experimental chapters, exploring residual visual functioning, spontaneous reorganisation and treatment-driven plastic change, in patients with retrochiasmatic lesions and consequent homonymous visual field disorders.

Taken together, the data suggest that a host of alternative networks are available to the human visual system following a lesion to retrochiasmatic sites. These networks may directly perform their original function, as was observed in Chapter 1 with implicit fear signals. They may themselves drive spontaneous re-organisation of visual cortex, as was observed with dorsal attentional networks and default mode networks in Chapter 2. Or they may be activated with a targeted intervention, to strengthen visual function, as was observed with multisensory networks in Chapter 3. In any event, a great deal of residual capacity appears possible within the human visual system and its affiliate substrates, which will hopefully ultimately guide effective rehabilitation for patients.

Future studies can be guided by the experimental chapters of this thesis. From Chapter 1, it would be interesting to see if implicit fear signals can boost performance on tasks in the intact field requiring left lateralised processes (such as language), and whether such performance may be focal to right lesion patients. From Chapter 2, it would be interesting to see if phosphenes could be generated in all regions of visual space, by artificially stimulating only the intact hemisphere of a HVFD patient displaying spatial selectivity loss in their intact hemisphere visual cortex. Further, correlating this reorganisation with behavioural measures to confirm its adaptivity is an important follow up. Finally, findings from Chapter 3 require that treatment effects of multisensory stimulation treatment should be indexed by line bisection and greyscale tasks, to identify precisely which bias is affected by recruitment of spared subcortical multisensory networks.

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