Blindsight: neural substrates and plasticity following hemispherectomy

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Submitted: August 2019

A thesis submitted to McGill University in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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Acknowledgements

While it was clear from a young age that my academic interests were in biology, after taking an advanced placement biology course in my last year in high school and being exposed to neuroscience I knew that I would spend the remainder of my academic career pursuing the study of the brain. I enrolled in a BSc in biology with a specialization in physiology alongside a BA in psychology at the University of Ottawa which afforded me the largest exposure to a wide variety of neuroscience-related courses that have allowed me a unique opportunity to gain an appreciation for the brain from an interdisciplinary perspective. In second year, I reached out to several professors in different departments and started volunteering in two labs: an electrophysiology lab using electric fish models (Dr. John Lewis), and a cognitive neuroscience lab using brain imaging in humans (Dr. Andra Smith).

While attending a lecture given by Dr. Smith, she presented a documentary on blindsight, and I was completely in awe. I was fascinated by the brain's incredible ability for plasticity and adaptation, and immediately gained a profound appreciation for the study of the brain following injury and just how much we can learn about brain circuits and connectivity when one area, in this case, an entire hemisphere, is removed. It was therefore no surprise that when it came time to apply for graduate positions, I chose wholeheartedly to work in the lab of Dr. Alain Ptito, a pioneer in the field of blindsight research and whose patient, as it turns out, was the very same subject of the documentary I had seen years before in Dr. Smith's talk. I will be forever thankful to my high school biology teacher, Ms. Meulenbroek for fostering my interest in the brain, and to Dr. Smith for allowing me the opportunity to gain hands-on experience in human brain imaging and for exposing me to blindsight for the first time.

I am incredibly grateful to Dr. Ptito for taking me on as a master's student (later PhD), for his infallible guidance, for creating an environment of total scientific freedom, and for entrusting me with his precious patients. His support (financial and moral), advice, and continuous encouragement have been crucial through the ups and downs of my graduate career. His work and reputation in the scientific community at large have been pivotal in opening so many doors for international collaborations which have allowed me the opportunity to create global connections with other blindsight labs and experts in the field of visual research and brain plasticity. I am thankful to Dr. Marco Tamietto who reached out in the early stages of my master's degree and established a collaboration between our lab at the Montreal Neurological Institute and his group in Italy and in the Netherlands. Through this collaboration and in the years that followed I was fortunate enough to travel to Maastricht University to test our subjects using state-of-the-art technology and ultra-high-resolution in vivo MRI scanners, as well as to receive training in all aspects of brain imaging and visual research. I would like to thank Dr. Bert Jans for his dedication, patience, and the long hours he spent on Skype teaching me all things retinotopic mapping. I am grateful for Dr. Ptito for encouraging and funding my travels to Maastricht University to receive one-on-one training, and to various international conferences where I have made connections with organizations dealing with hemispherectomy patients that has been pivotal in our efforts to recruit new patients.

While my international collaborations have played a big role in my research over the past few years, I cannot neglect my local associations here at the Montreal Neurological Institute. I want to thank my friend and colleague Dr. Francois Chouinard-Decorte for arranging a collaboration with members of Dr. Alan Evans' lab, particularly Dr. John. D. Lewis and Dr. Gelb Bezgin. I am grateful for the many hours spent discussing blindsight and cortical thickness with

Dr. Lewis, as well as his dedication and unwavering support through all the challenging aspects of this research.

Having been a graduate student for as long as 7 years, I have seen many lab members comes and go, and I will always be appreciative for the support I have received over the years from staff and the comradery from students at the Cognitive Neuroscience Unit at the Montreal Neurological Institute, particularly Annie Le Bire, our fantastic administrative coordinator who has always been on top of things so we didn't have to be, to Dr. Jen-Kai Chen for his support in all things lab related, and to my lab mates here and abroad: Nicolas Sheppard-Jones, Avinash Vaidya, Scott Holmes, Guido Guberman, Alessia Celeghin, and Matteo Diano.

I would like to extend a grateful thank you to all the members of my advisory committee. To Dr. Tamietto for the endless hours spent on Skype, for his support and advice, as well as his direct intellectual contribution to my work through our collaborations. I'd like to thank Dr. Maurice Ptito for making the time to be present during my meetings despite his various international commitments, I have tremendously valued his input and advice and the perspective he offers on blindsight as an animal model researcher. I am grateful for Dr. Christopher Pack who joined my committee in recent years and has provided an additional source of encouragement and advice, as well as an internal perspective on my work as a faculty member at McGill University. I'd also like to thank Dr. Louis Collins for his appointed role as my mentor and committee chair. I am very fortunate to have had a strong team of mentors and educators that have guided me through my graduate career, and without whom my work would not have reached its current caliber.

Finally, I would like to thank my parents, Renee and Amir Georgy, and my sister, Verina Georgy. I'd like to thank my mom for always picking up the phone, I could not have accomplished what I have today without her support and encouragement to push through the tough times. I want to thank my dad for believing that I can do anything I put my mind to and teaching me to trust my gut. I hope I've been able to set a good example for my younger sister, and I have no doubt that she will reach higher and accomplish great things in her life and career. Thank you to all the friends I've made in all stages of my life who have celebrated my success and offered me support at times when I felt unsure, particularly Adal Farrah, Jaimee Gardner, and Basil Kadoura. I would also like to thank my partner, Kevin, for his continued interest in my research and his patience and support during the stressful times.

Statement of originality

This thesis document is presented in a manuscript-based format for a Doctoral Thesis following the 'Thesis Preparation Guidelines' outlined by the Department of Graduate and Postgraduate Studies at McGill University. The studies reported within were performed in the lab and under the supervision of Dr. Alain Ptito at the Montreal Neurological Institute and were discussed in a yearly meeting with my advisory committee members (Dr. Marco Tamietto, Dr. Maurice Ptito, Dr. Christopher Pack). The thesis contains six chapters: Chapter 1 offers a brief introduction, Chapter 2 is a review of the existing literature relevant to this body of work, Chapters 3-5 contain reports on original findings concerning the neural substrates of human blindsight following hemispherectomy, and Chapter 6 provides a summary and discussion of findings, future directions, and concluding remarks. Experiments outlined in Chapter 3 and Chapter 4 have been published in peer-reviewed scientific journals: *Cortex* 2016 and *Neuropsychologia* 2019 respectively. All results have been presented in part at the Scientific Symposium on Neurorehabilitation after Hemispherectomy (Anaheim; 2014), the Vision Health Research Network (VHRN) 22nd Annual Meeting (Montréal, 2016) which was awarded the Excellence in Poster Presentation, Category: PhD students award sponsored by the Fonds de la Recherche en Santé du Québec (FRSQ), and the Organization for Human Brain Mapping Conference (Singapore; 2018). The study outlined in Chapter 5 is in preparation for submission, and was presented at the Organization for Human Brain Mapping Conference in Rome, 2019.

Contribution of authors

Chapter 1 & 2: Loraine Georgy wrote the Introduction and Background chapters under the supervision of Dr. Alain Ptito.

Chapter 3: Loraine Georgy is a co-first author on the article presented in this chapter titled *"The superior colliculus is sensitive to gestalt-like stimulus configuration in hemispherectomy patients"* published in *Cortex* in 2016. The original experimental paradigm was implemented from Dr. Carlo Marzi (University of Verona) and Dr. Alessia Celeghin's (Turin University) previous work. Essential changes to the stimulus and presentation were adapted by Loraine Georgy and Dr. Marco Tamietto (Turin University). The subjects were recruited by Dr. Alain Ptito and accompanied to Maastricht University for testing by Loraine Georgy where the study was conducted as a collaborative effort with Dr. Marco Tamietto. Dr. Alessia Celeghin and Loraine Georgy collaborated on the data analysis and figure preparation. Loraine Georgy and Dr. Alain Ptito wrote the manuscript with input from Dr. Marco Tamietto, Dr. Alessia Celeghin, and Dr. Carlo Marzi.

It is the policy of McGill University that in the case where a thesis contains an article which has been published with co-first authors, that only one student can use the article in a manuscript-based thesis, and that a written agreement is provided from the other co-first author student. While Dr. Alessia Celeghin has used some preliminary data from this study as part of her thesis submission, the article in whole as submitted to *Cortex* has only been used by Loraine Georgy in this thesis. The following is a statement from Dr. Alessia Celeghin, *"I, Alessia Celeghin, post-doc at University of Turin and co-author of the paper entitled* "The Superior Colliculus is sensitive to gestalt-like stimulus configuration in hemispherectomy patients" *published on* Cortex *in 2016, declare that the data used in the paper was included in my PhD*

thesis in a preliminary form, although the manuscript as published in Cortex *is original and was not included in the aforementioned dissertation."*

Chapter 4: Loraine Georgy is the first author of the article and took a lead role in the preparation of the study presented in this chapter titled *"Functional reorganization of population receptive fields in a hemispherectomy patient with blindsight"* published online in *Neuropsychologia in* 2019. Dr. Marco Tamietto was involved in conceiving the experiment with Dr. Alain Ptito and Loraine Georgy while Dr. Jans Bert (Maastricht University) provided specialized expertise on retinotopic mapping. The subject was recruited by Dr. Alain Ptito and tested in the Montreal Neurological Institute by Loraine Georgy. Dr. Jans Bert and Loraine Georgy collaborated on the data analysis, and Dr. Marco Tamietto contributed to the preparation of the figures. Loraine Georgy and Dr. Alain Ptito wrote the manuscript with input from Dr. Jans Bert and Dr. Marco Tamietto. Loraine Georgy is the corresponding author on this publication.

Chapter 5: Loraine Georgy is the first author of the article and took a lead role in the preparation of the study presented in this chapter titled *"Changes in peri-calcarine cortical thickness in blindsight"* currently in preparation for submission. Dr. Marco Tamietto was involved in conceiving the experiment with Dr. Alain Ptito and Loraine Georgy. Dr. John D. Lewis (McGill University) provided specialized expertise on cortical thickness analysis. Two of the subjects were recruited by Dr. Alain Ptito and one subject was recruited by Dr. Marco Tamietto. Dr. Alessia Celeghin and Dr. Matteo Diano assisted Loraine Georgy in data collection through a collaborative effort. Dr. Gleb Bezgin acquired the control data from the NKI database and helped with data preprocessing while Loraine Georgy performed quality control measures. Loraine Georgy and Dr. John D. Lewis collaborated on the data analysis and interpretation of results. Loraine Georgy prepared the manuscript with Dr. Alain Ptito and Dr. John D. Lewis with input

from Dr. Gleb Bezgin, Dr. Marco Tamietto, Dr. Alan Evans, Dr. Alessia Celeghin and Dr. Matteo Diano.

Chapter 6: Loraine Georgy wrote the Conclusions chapter under the supervision of Dr. Alain Ptito.

Ethics, Funding & Support

Loraine Georgy obtained ethics approval from the MUHC (McGill University Health Centre) Research Ethics Board (NEU-11-026) for studies conducted in the Montreal Neurological Institute. This work was supported by a Natural Sciences and Engineering Research Council of Canada grant awarded to Dr. Alain Ptito (NSERC: 37354-2011) as well as a Canadian Institutes of Health Research doctoral research fund (CIHR: 380343-2017) and a Don Baxter Collaborative Fund (2015) awarded to Loraine Georgy. Other funding support for collaborators is indicated within each respective project under 'Acknowledgements'.

Abstract

"Blindsight" is a phenomenon whereby cortically blind patients following primary visual cortex damage maintain visuo-motor processing in their blind visual field, contralateral to the injury, but remain unaware of such perception. Research has uncovered many of the plastic changes that occur in the brain to allow for such functions and with the advent of neuroimaging it became possible to investigate the neural substrates that underlie this paradoxical behavior. However, blindsight has received much criticism for the possibility that spared islands of visual cortex surrounding the lesion may have sustained some forms of degraded vision. In this body of work, hemispherectomy patients are used as a model for blindsight because their lack of cortical mantle in one hemisphere ensures that there are no surviving retino-recipient structures apart from the superior colliculus in that damaged hemisphere. These patients provide a unique opportunity for the study of plasticity within the visual system following damage to the primary visual cortex and for the investigation of the underlying neuronal mechanisms while excluding the possibility that the source of reorganization is due to residual inputs from spared islands near the margin of the lesion.

Previous research into the neural substrates of blindsight implicated the superior colliculus as a key player in the blindsight pathway, responsible for relaying the information about the visual stimulus from the blind visual field to the extrastriate visual cortices in the intact hemisphere. In this thesis, I used a modified spatial summation paradigm to test the redundant target effect in two hemispherectomy patients which first served to validate the existence of blindsight in these subjects, but more importantly to demonstrate that the superior colliculus is in fact sensitive to higher-order perceptual organization, which it was previously thought incapable of encoding. The results showed that there was facilitation in the form of a faster reaction time to

multiple dots presented simultaneously in the blind and seeing visual fields that were spatially organized in a coherent shape, and that this summation effect was more pronounced than for singular dots or multiple stimuli that were arranged randomly. I utilized a new retinotopic mapping technique, population receptive field mapping, in order to investigate the functional reorganization within the intact visual cortex of a hemispherectomy patient and found that while the retinotopic organization remained largely undisturbed, there were blurred boundaries in the dorsal compartments which upon further investigation showed a significant increase in the receptive field sizes. Finally, using cortical thickness analysis on two hemispherectomy patients and one localized V1 lesion patient I was able to demonstrate that there are morphological differences in the intact visual cortex which present as an increase in the grey matter thickness in these regions, a finding persistent across all subjects with documented blindsight despite their varying clinical history, but notably absent in healthy controls. Taken together, these results serve to further implicate the superior colliculus and the intact visual cortex in their role in the blindsight pathway and provide evidence for structural and functional plasticity that allows this persistent residual vision in the blind visual field following primary visual field damage.

Résumé

La « vision aveugle » est un phénomène dans lequel des patients aveugles après une lésion du cortex visuel primaire maintiennent un traitement visuo-moteur dans le champ visuel aveugle, controlatéral à la lésion, sans toutefois en être conscients. La recherche a mis au jour une plasticité cérébrale qui permet une telle fonction ; avec l'avènement de la neuro-imagerie, il est devenu possible d'étudier les substrats neuronaux à l'origine de ce comportement paradoxal. Cependant, la vision aveugle a fait l'objet de nombreuses critiques dont la possibilité que des îlots de cortex visuel épargnés et entourant la lésion aient pu sous-tendre certaines formes de vision dégradée. Dans le présent travail, des patients porteurs d'une hémisphérectomie sont utilisés comme modèle pour la vision aveugle car l'ablation ou la déconnection d'un hémisphère cérébral garantit l'absence de structures rétino-corticales sauf celles aboutissant au colliculus supérieur de l'hémisphère enlevé. Ces patients offrent une occasion unique d'étudier la plasticité du système visuel après une lésion du cortex visuel primaire et d'étudier les mécanismes neuronaux sous-jacents tout en excluant la possibilité que la source de la réorganisation soit due aux entrées résiduelles d'îlots épargnées avoisinants la lésion.

Des recherches antérieures sur les substrats neuronaux de la vision aveugle avaient impliqué le colliculus supérieur en tant que structure-clé dans la vision aveugle, étant chargé de relayer les informations émanant du champ visuel aveugle au cortex visuel extra-strié dans l'hémisphère intact. Dans cette thèse, j'ai utilisé un paradigme de sommation spatiale modifié chez deux patients porteurs d'hémisphérectomie pour d'abord valider l'existence d'une vision aveugle chez ces sujets, mais surtout pour démontrer que le colliculus supérieur est en fait sensible à une organisation perceptuelle d'ordre supérieure alors qu'on le pensait incapable d'une telle capacité. Les résultats ont montré qu'il y avait une facilitation sous la forme d'un temps de

réaction plus rapide à de multiples points organisées sous une forme cohérente présentés simultanément dans les champs visuels aveugles et intacts comparé à des points singuliers ou des stimuli multiples disposés de manière aléatoire. J'ai utilisé une nouvelle technique de cartographie rétinotopique des champs récepteurs dans le but d'étudier la réorganisation fonctionnelle au sein du cortex visuel intact d'un patient hémisphérectomisé. J'ai constaté que, bien que l'organisation rétinotopique soit restée pratiquement inchangée, des frontières moins bien définies dans les régions dorsales montraient une augmentation significative de la taille des champs récepteurs. Enfin, en utilisant la technique d'analyse de l'épaisseur corticale de deux patients hémisphérectomisés et d'un patient atteint d'une lésion de V1 localisée, j'ai pu démontrer qu'il existait des différences morphologiques dans le cortex visuel intact qui se traduisent par une augmentation de l'épaisseur de la matière grise dans ces régions, un résultat noté dans l'ensemble des sujets ayant une vision aveugle documentée malgré leurs antécédents cliniques variés, mais pas chez les sujets témoins sains. Pris ensemble, ces résultats servent à impliquer davantage le colliculus supérieur et le cortex visuel intact dans la vision aveugle et à fournir des preuves de la plasticité structurelle et fonctionnelle qui permet à cette vision résiduelle de persister dans le champ visuel aveugle après une lésion du champ visuel primaire.

"Arguably the most important breakthrough in neuroscience since scientists first sketched out the brain's basic anatomy, this revolutionary discovery called neuroplasticity promises to overthrow the centuries-old notion that the brain is fixed and unchanging. The brain is not, as was thought, like a machine, or 'hardwired' like a computer. Neuroplasticity not only gives hope to those with mental limitations, or what was thought to be incurable brain damage, but expands our understanding of the healthy brain and the resilience of human nature."

— Norman Doidge, *The Brain That Changes Itself: Stories of Personal Triumph from the Frontiers of Brain Science*

Chapter 1: Introduction

In neuroscience, one is often faced time and time again with the word “deficit”, a term that describes an impairment in neurological function. For centuries, the adult brain was regarded as a rather unchanging object, one that if injured is not capable of self-repair unlike many of human’s other organs. However, the term “neuroplasticity” is now becoming a recurring concept, one which denotes not only the brain’s lifelong ability to maintain and change itself in response to learning and experience, but also its remarkable capacity to adapt, rewire, and compensate following damage, an idea that was once thought impossible outside the short epochs in early development.

While brain injury and disease often have a severe impact on the patient and their family, they provide a unique opportunity to study the brain and determine its response to the trauma, a perspective lost when studying healthy subjects. By examining patients with brain lesions (localized or widespread), it becomes possible to determine the role *and* the necessity of the implicated structures in neurological functions which can be revealed by studying the ensuing deficits.

In this thesis, I focus on one such deficit: cortical blindness following damage to the primary visual cortex. According to Holmes in 1918, damage to the primary visual cortex abolishes all visual abilities in the corresponding visual field. This was widely accepted until research over the past 50 years showed a varied range of unconscious residual visual functions in the presumed blind field. These unconscious residual visual functions have been termed ‘blindsight’ by Weiskrantz and colleagues in 1974. In their paper, blindsight is described as the ability of the subject to exhibit above-chance performance in stimulus localization within the presumably blind visual field despite lacking knowledge of a visual percept.

By examining this phenomenon and the patients exhibiting them we can determine which structures were affected, which connections remain, and how the brain might utilize these remaining structures and the connections surrounding them to compensate for the visual deficit. From a scientific point of view, the study of the residual visual functions and underlying neural basis of blindsight provides a means for a better understanding of the function of the various brain structures involved in vision, the extent of their contribution to awareness, and, by exclusion, their contribution to normal brain function and conscious visual processing. Clinically, this work has a potentially large impact on the patients as we continue to search for answers to questions surrounding neuroplasticity and how to promote it in order to capitalize on the brain's innate capacity for dynamic change and compensation.

Chapter 2 of this thesis provides a review of the existing literature on blindsight and discusses the current evidence for this phenomenon, its main criticisms, as well as its underlying mechanism as we understand it thus far. This is followed by three novel studies that represent original findings concerning the neural substrates and neuroplasticity involved in blindsight. In Chapter 3, I present a behavioural study that aimed to determine whether the nonconscious vision in the blind hemifield can be sensitive to higher-order perceptual organization, and which structure underlies such processing independently of the primary visual cortex. Chapter 4 concerns the contribution of the intact occipital cortex to visual processing without awareness, and the nature of plastic and functional compensatory changes in the retinotopic organization and response properties in these remaining visual areas. Chapter 5 focuses on anatomical differences as measured by cortical thickness in the intact visual cortex that might be related to the functional reorganization seen in blindsight. The results are summarized in Chapter 6 along with concluding statements, implications of this body of work, and avenues for further research.

Chapter 2: Background

2.1 The beginning of blindsight

In a letter to Nature, Pöppel *et al.* (1973) documented the first cases of blindsight in humans. They reported on four patients that had scotomas within their visual fields owing to lesions within their occipital cortex. In their experiment, they asked the patients to fixate a central point which was followed by a light flashed in their blind visual field and the patients were asked to move their eyes to the position of the flash. Since the patients were not able to consciously 'see' the visual stimulus to which they were required to respond, a secondary auditory stimulus played simultaneously in order to solicit a response. They observed an increase in the amplitude of saccadic eye movements for more eccentric targets presented within the cortically blind areas of the patients' visual fields. It was hypothesized that this residual visual processing was making use of direct connections between the retina and the midbrain that allowed detection of the stimuli without conscious awareness from the striatum (Ingle, 1967; Schneider, 1969).

The next step was to study subjects with restricted primary visual cortex injury that spared the posterior association cortex which would receive projections from the superior colliculus via the posterior thalamus. Weiskrantz and colleagues (1974) used one such patient, DB, who suffered from an arteriovenous malformation in the right occipital pole. The malformation caused severe migraines preceded by flashing lights that evolved into a scotoma, and in some instances, sensory disturbances down the left side of his body. Due to the severe threat these headaches posed to DB's employment and social life, the malformation was removed, extending anteriorly into the occipital pole including a major portion of the calcarine cortex on the medial surface of the hemisphere. Since the operation, DB has had a persistent homonymous hemianopia as measured by conventional perimetry. However, a series of studies

using large stimuli showed that DB could locate them in the frontal plane by reaching with considerable accuracy (Figure 2.1) and that he was able to differentiate line orientation and at least one pair of shapes (an ‘O’ and an ‘X’). When questioned about his vision in the left hemifield, his most common response was that he saw nothing at all. When pressed, he expressed that perhaps he had a ‘feeling’ that stimuli were pointing one way or another, but repeatedly stressed that he saw nothing in the sense of ‘seeing’ and insisted that he was merely guessing. In order to capture this dissociation between perception and performance, the phenomenon was termed ‘blindsight’, and the statement Weiskrantz poses in his conclusion questions whether DB’s blindsight is merely degraded normal vision or whether it represents a qualitatively distinct visual capacity.

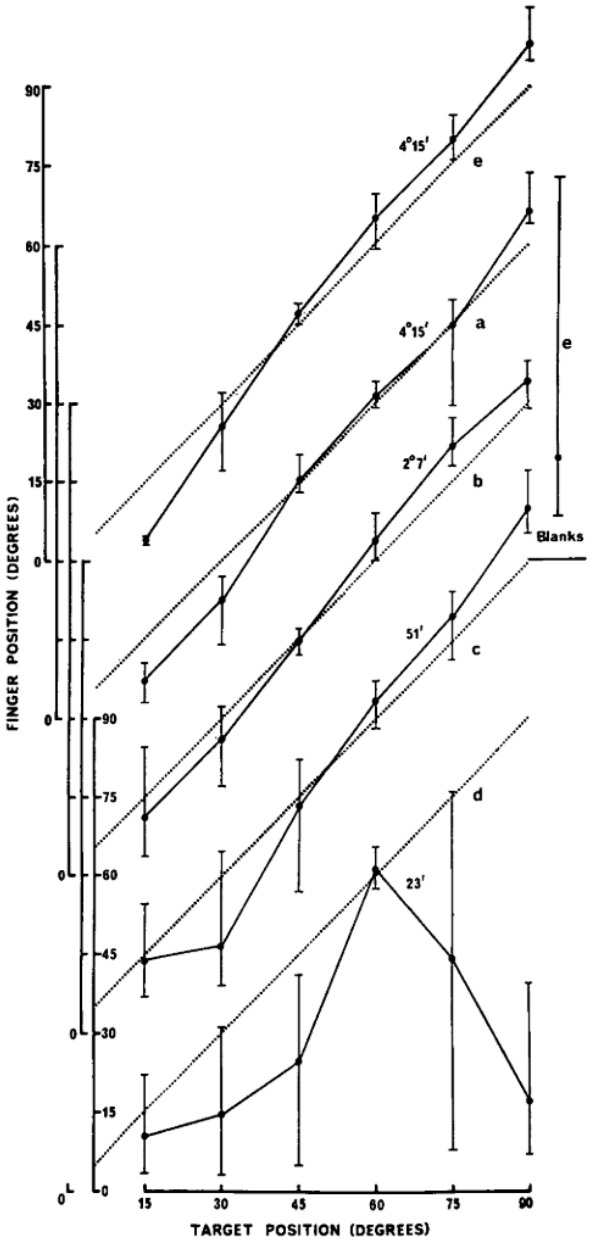


FIGURE 2.1: Target Localization by Finger Pointing

Mean finger reaching responses for targets of given eccentricity. Series was conducted in order a through e. Vertical bars refer to ranges of obtained values. For each point in a to d, n = 6; in e, n = 3. In condition e blank trials (n = 18) were randomly interspersed between stimulus trials, and mean response positions and range for blanks are shown to right of experimental results. Figure from Weiskrantz *et al.* (1974).

2.2 Anatomy of the human visual system

"We see with our brains, not with our eyes," ― Norman Doidge, *The Brain That Changes Itself: Stories of Personal Triumph from the Frontiers of Brain Science*

In 1886, Ferrier wrote that 'it is manifestly absurd to establish an antithesis between "cortical" and any other form of blindness', implying that the pathways from the eye that remain anatomically intact following primary visual cortex damage are no longer useful for transmitting visual information. This notion was widely accepted by clinical neuroscientists for a century, and neurological investigations were unanimous in showing that severe lesions of the visual cortex cause complete blindness in the corresponding areas of the visual field with patients firmly denying any perception of stimuli presented in those areas (Holmes, 1918).

In virtually all textbooks, the visual pathway denotes projections that travel from the retina through the optic nerve, chiasm, and tract to different targets in the brain via several parallel pathways, the largest of which is to the lateral geniculate nucleus of the thalamus and onward via the optic radiations to the striate cortex (cortical area V1), hence: the geniculo-striate pathway. When this route is damaged, there are apparent devastating effects that were established early on in vision research, and the conclusions were clear: the occipital lobes are indispensable for vision in humans. But while the majority of the 1 million fibers in each optic nerve is ultimately destined for V1, there remains about 150,000 fibers from the retina of each eye that travel elsewhere in the brain. In addition, the lateral geniculate nucleus was thought to project only to the striate cortex, but a series of papers showed that a few thousand of these neurons projected to the extrastriate visual cortex (Benevento & Yoshida, 1981; Bullier & Kennedy, 1983; Fries, 1981; Yoshida & Benevento, 1981; Yukie & Iwai, 1981). Thus, information from the retina can either reach extrastriate visual areas directly from retino-

recipient subcortical nuclei such as the lateral geniculate nucleus (Cowey & Stoerig, 1989; Yukie & Iwai, 1981) and the inferior pulvinar (Grieve *et al.*, 2000), or indirectly via other structures such as the accessory optic nuclei (Maioli *et al.*, 1989) (Figure 2.2). It therefore became clear that in primates these parallel pathways could mediate some aspects of vision in the total absence of the striate cortex (Weiskrantz, 1986).

In 1992, Goodale and Milner suggested that the differences in the required computations of visual perception and visual control of action led to the emergence of separate visual pathways in the primate cerebral cortex: a ventral visual stream that projects from the early visual areas to the inferotemporal cortex and mediates our perception of the world, and a dorsal visual stream that projects to the posterior parietal cortex and mediates the visual control of action.

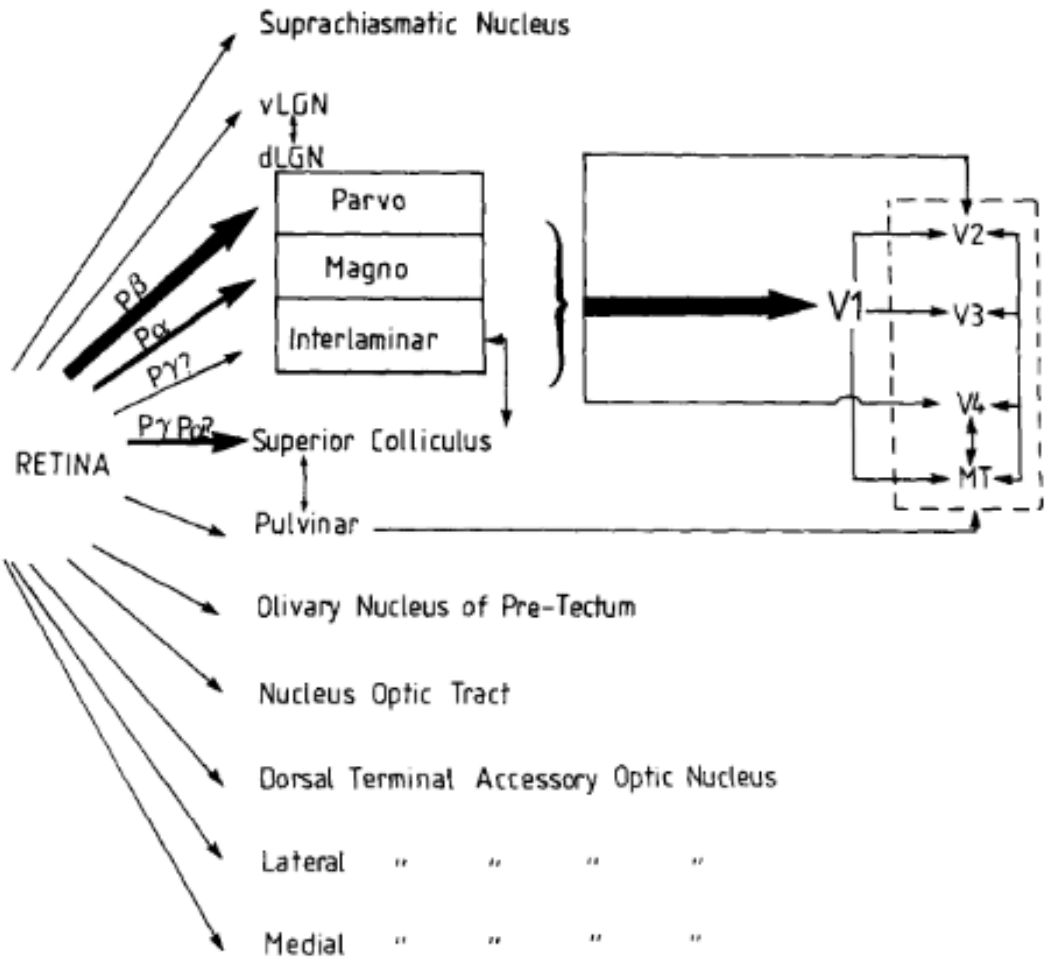


FIGURE 2.2: The Visual Pathways, Then

The known pathways from the eye into the brain, together with the initial cortical projections. The scheme excludes the extensive further connections between the initial cortical visual areas and the many further visual areas. The thicker arrows indicate the heaviest and most studied projections. The classes of retinal ganglion cells projecting to most of the brainstem targets are unknown. Figure from Cowey & Stoerig (1991).

2.3 Behavioral evidence for blindsight

The years that followed the classification of blindsight by Weiskrantz saw a host of new studies designed to test the blind visual fields of patients with scotomas due to V1 damage. There already existed a plethora of evidence of blindsight reported in nonhuman primates following ablation of the primary visual cortex (Keating, 1975; Keating, 1979; Keating, 1980; Pasik & Pasik, 1971; Weiskrantz & Cowey, 1970; Weiskrantz, 1972). Pasik and Pasik conducted a series of experiments on monkeys with striate ablations and demonstrated their capacity to discriminate luminous flux (Pasik *et al.*, 1969), brightness (Schilder *et al.*, 1971), shape and color (Schilder *et al.*, 1972), the presence of light (Pasik & Pasik, 1973), spatial frequency in the form of gratings (Miller *et al.*, 1980), as well as successfully demonstrating reaching behavior (Feinberg *et al.*, 1978) and accurate spatial localization (Solomon *et al.*, 1981). Cowey & Stoerig (1995) offered their hemianopic monkeys the option to respond 'no target' to blind field stimuli, and showed that the monkeys would choose this option consistently on target trials even though they were able to localize the targets perfectly when they were not presented this option, showing that like humans the monkeys behaved as if they could not perceive the stimuli despite being able to respond to them.

In addition to Pöppel and Weiskrantz's seminal papers on blindsight in humans, a variety of experiments showcased that these functions manifested through the detection and localization of stationary and moving stimuli (Blythe *et al.*, 1987; Pöppel *et al.*, 1973; Stoerig *et al.*, 1985; Weiskrantz *et al.*, 1974; Zihl & von Cramon, 1980) and through stimulus discrimination based on motion (Barbur *et al.*, 1993; Blythe *et al.*, 1986; Hervais-Adelman *et al.*, 2015; Magnussen & Mathiesen, 1989; Morland *et al.*, 1999), line orientation (Weiskrantz *et al.*, 1974), colour (Danckert *et al.*, 1998; Morland *et al.*, 1999), form (Danckert *et al.*, 1998; Marcel, 1998),

wavelength (Kentridge *et al.*, 2007; Stoerig, 1987; Stoerig & Cowey, 1989; Stoerig & Cowey, 1992), frequency (Magnussen & Mathiesen, 1989), categories (Van den Stock *et al.*, 2014), as well as the ability to maintain circadian entrainment (Czeisler *et al.*, 1995), exhibit visuo-motor transformation (Celeghin *et al.*, 2017), semantic priming (Marcel, 1998), emotional processing (Burra *et al.*, 2017; de Gelder *et al.*, 1999; Pegna *et al.*, 2005; Van den Stock *et al.*, 2011), spectral sensitivity (Stoerig & Cowey, 1991), and navigational skills (de Gelder *et al.*, 2008). In addition, Zihl (1980) showed that responses to light stimulation within blind visual field areas improved with repetition and Barbur *et al.* (1980) reported that subject GY could detect a dark shadow when transient lights were shown in his blind field. Additional research also uncovered evidence of an interaction between stimuli presented simultaneously to the blind and intact hemifields (Corbetta *et al.*, 1990; Marzi *et al.*, 1986; Pizzamiglio *et al.*, 1984; Rafal *et al.*, 1990; Singer *et al.*, 1977; Torjussen, 1976; Torjussen, 1978).

With time, it became apparent that residual visual abilities varied between patients (Corbetta *et al.*, 1990), which led to the classification of blindsight into 'Type I' and 'Type II' subcategories. Patients with Type I blindsight showed unconscious visual abilities that were associated with the retino-tectal pathway (Sahraie *et al.*, 1997) and included neuroendocrine responses (Czeisler *et al.*, 1995) as well as interhemispheric facilitation (Marzi *et al.*, 1986; Torjussen, 1978). In contrast, patients with Type II blindsight described some awareness of stimuli presented in their blind field, and demonstrated the ability to detect targets and localize them using saccadic eye movements (Pöppel *et al.*, 1973; Weiskrantz *et al.*, 1974) and manual pointing (Weiskrantz *et al.*, 1974), to discriminate movement direction, relative velocity (Barbur *et al.*, 1980; Blythe *et al.*, 1986; Blythe *et al.*, 1987; Weiskrantz *et al.*, 1995) and stimulus

orientation (Weiskrantz, 1987), as well as indicate a sensitivity to semantic priming from words presented in the blind field (Marcel, 1998).

2.4 Controversy: criticisms, responses, and further evidence

Naturally the existence of blindsight, this puzzling ability of cortically blind patients to see without any conscious awareness of their vision, has been put into question. Scientists challenged the evidence and presented alternative explanations for this phenomenon, motivating the search for blindsight under a new light.

2.4.1 Experimental artifacts

Some researchers argued that residual vision within the scotomas, whether conscious or unconscious, was due to methodological inadequacies such as eccentric fixation, inadvertent eye movements, or intra- and extra ocular light scatter. (Campion *et al.*, 1983; Fendrich *et al.*, 1992). In response, Faubert and colleagues (1999) presented a model that could explain the scatter properties of the eye on the visual sensitivities obtained in blindsight patients while Wessinger *et al.* (1996b) used a double Purkinjie eye tracker to stabilize the stimulus display on the retina and eliminate artifacts due to eye motion. They then tested stimulus detection and discrimination in the blind visual field and showed that patients with blindsight distinguished with above chance performance the stimuli within the areas of residual vision and that they were able to verbally identify simple shapes demonstrating that blindsight is not an artifact of light scatter, eccentric fixation, or inadvertent eye movement.

2.4.2 Behavioral paradigms

Another criticism of blindsight research was the prominent use of forced-choice paradigms which depended not only on the patients' sensitivity to the different stimuli but was also affected by the response criteria bias which manifested as a tendency to consistently select

one of the stimuli in favor of another independently of sensitivity (Azzopardi & Cowey, 1997; Cowey, 2004). Additionally, this method sometimes proved tricky with subjects who denied any vision within their blind field and dismissed these experiments as nonsensical, with some even stubbornly declining to play 'such a game' or accusing the experimenter of forcing them to lie. In a Ferrier lecture, Weiskrantz (1990) tells of subject CM who flatly refused to participate in a forced-choice experiment, and staunchly replied 'no' to every stimulus presentation even though she was told that a grating would be present in 50% of the trials. Once she relaxed and showed willingness to participate, she guessed correctly with high significance even though she continued to deny seeing any stimulus. Weiskrantz warns that had they given up at the first attempt, their subject would have been documented as a negative case. He also urges the experimenters to keep an open mind, and not show the same reluctance as their subjects if they have pre-formed expectations of the outcome. Therefore, while this method of assessment in blindsight research is valuable and its outcome is the most consistent and impressive in subjects that are well-practiced and who are willing to participate, it is not always the optimal choice for assessing blindsight in reluctant patients, infants, and animals.

Therefore, alternative, reliable, indirect experimental paradigms that allowed researchers to draw an unambiguous inference implicitly without forcing the subjects to guess at a stimulus they claim they cannot see were in high demand. Two general implicit approaches gained popularity for use in blindsight research, one which relied on reflex responses of the subject to the stimuli presented in their blind visual field, and another which exploited the bilateral interaction effects between the intact visual field and the blind visual field. Concerning the former, measuring untrained reflex responses such as the galvanic skin response (Zihl *et al.*, 1980) and the pupillary reflex (Weiskrantz *et al.*, 1998) were straightforward approaches that

were used to implicitly test blindsight, and have proven especially useful as tools when conducting experiments on animal models and in human infants. With regards to the latter, the first person to exploit this approach to bilateral interaction was Torjussen (1976; 1978) whose method was later used by several researchers (Marcel, 1998; Perenin, 1978; Perenin & Jeannerod, 1978). This approach relies on the phenomenon of 'completion' whereby stimuli that are presented symmetrically in the intact and blind hemifields are both seen, even though the subject reports nothing if the stimulus is only presented in the blind field.

Another successful approach that relies on bilateral interaction is a *spatial* summation phenomenon known as the 'redundant-target effect' (Marzi *et al.*, 1996; Miller, 1982; Mordkoff *et al.*, 1996; Raab, 1962) whereby healthy controls show a faster reaction time to simultaneous presentation of two or more stimuli across the vertical meridian than to a single stimulus presentation. Marzi *et al*. (1986) were able to successfully use this paradigm on blindsight subjects where the seeing visual field was stimulated either alone (using a single or double flash) or in conjunction with the blind visual field. These patients showed that even though under bilateral stimulation conditions half of the stimulus fell within their blind visual field, and they claimed to have only seen the flash in their seeing visual field, their reaction time was significantly faster when compared to a stimulus presented in their sighted visual field alone (Figure 2.3). Stoerig (1993b) used this spatial summation effect to demonstrate the sensitivity of blindsight to wavelength and intensity information, and a more recent study used the reaction time paradigm to demonstrate blindsight in patients with chronic hemianopic field loss and provided preliminary behavioural evidence for the role of the intact hemisphere in motor responses to unconscious visual stimuli (Celeghin *et al.*, 2015a).

A related *temporal* interaction effect known as the 'psychological refractory period' has also been demonstrated in healthy subjects whereby presenting two successive stimuli with a brief interval in between will cause the reaction time to the second stimulus to become slower or inhibited altogether (Welford, 1952). This paradigm was successfully used by Corbetta *et al.* (1990) in blindsight subjects where they presented the first stimulus within the blind visual field followed rapidly by a second stimulus in the seeing visual field. They found the same effect in these subjects as reported by Welford in that the reaction time to the second stimulus was much slower despite the subjects having no conscious awareness of the first stimulus. Further evidence regarding the integration of visual inputs separated in time and presented entirely or partially within the blind field of blindsight subjects was reported by Singer *et al.* (1977) who showed that visual stimulation of a point in the blind field could reset the visual detection threshold of a previously adapted symmetric point in the seeing visual field. In this vein, Blythe *et al.* (1986) showed that blindsight subjects were capable of discriminating the direction of displacement of two lights sequentially flashed within the blind visual field with an 800ms interstimulus interval.

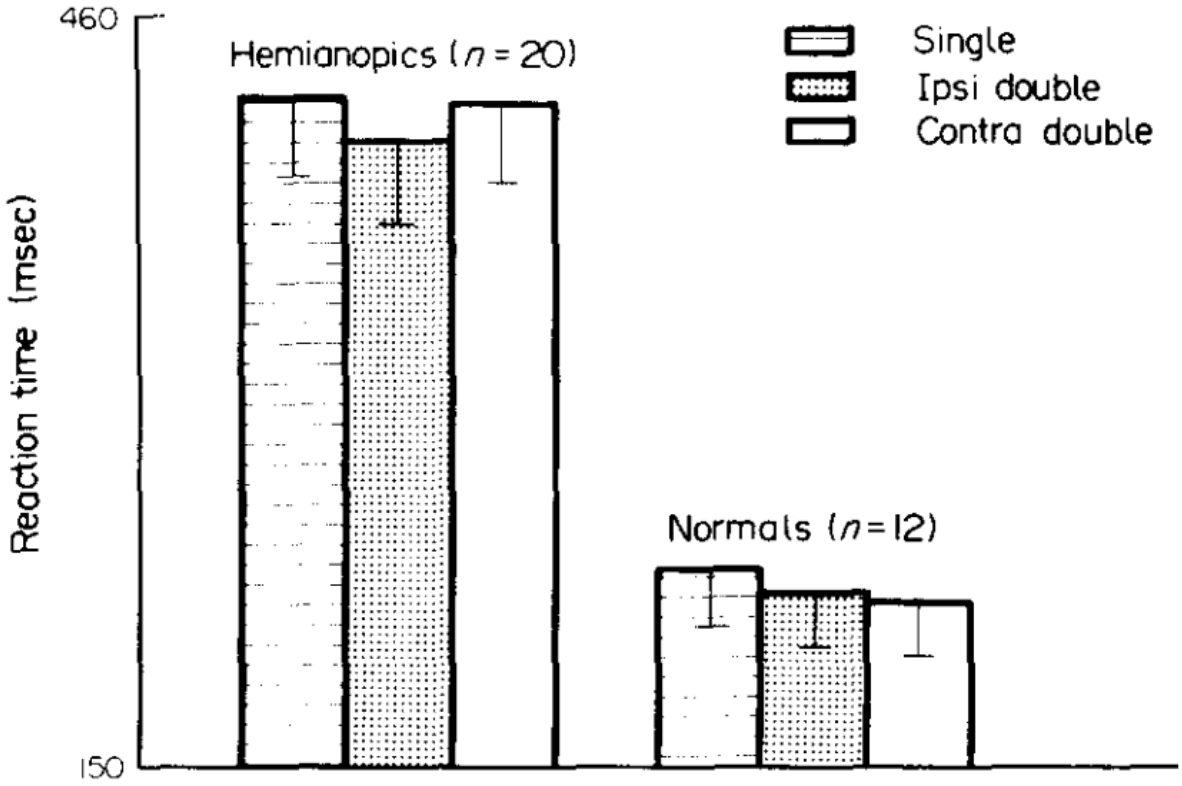


FIGURE 2.3: Spatial Summation in Hemianopics

Mean reaction time and half the standard deviation in msec for patients (left-hand side) and controls (right-hand side) in the three conditions of stimulus presentation. Figure from (Marzi *et al.*, 1986).

2.4.3 Patient models

Among the most prevalent criticisms is the fact that blindsight studies at the time were predominantly performed in patients with localized V1 lesions in whom fragments of islands of intact functional striate cortex could be responsible for the residual visual functions, rather than extrastriate pathways, or that perhaps cortical plasticity or reorganization occurred in the tissue surrounding the lesion. (Campion *et al.*, 1983). Fendrich (1992) demonstrated in one patient significant evidence of detection and discrimination only if the stimuli were presented at a particular position in the blind field, and not in a number of other positions, and therefore concluded that this island of residual vision was due to a corresponding spared island of functioning cortex within the patient's lesion. However, other lesion patients do not show such a pattern of blindsight confined to spatially isolated islands (Kentridge *et al.*, 1997; Stoerig & Pöppel, 1986; Stoerig, 1993a) and neuroimaging failed to reveal evidence for activation within the lesioned primary visual cortex (Barbur *et al.*, 1993; Goebel *et al.*, 2001).

In order to further address this concern, researchers turned to 'hemispherectomy' patients who had undergone complete removal or deafferentiation of an entire cerebral hemisphere (Figure 2.4) (de Almeida & Marino, 2005; De Almeida *et al.*, 2006; Fountas *et al.*, 2006; Perenin, 1978; Perenin & Jeannerod, 1978). This is a radical surgical technique that is considered in patients with severe intractable seizure disorders originating from one side of the brain, such as Rasmussen's encephalitis or porencephalic cysts. These patients represent an excellent model for the study of blindsight because with the entire striate cortex ablated or disconnected, the possibility that residual visual abilities in these patients are due to spared islands within the striate cortex is not tenable. Ptito *et al.* (1987) tested hemispherectomy subjects using a forced-choice paradigm and found that some of the subject exhibited blindsight characterized by an

ability to accurately discriminate three-dimensional stimuli presented simultaneously in both their blind and sighted fields, thus demonstrating that some complex visual abilities persisted in these patients, and that the blind visual field has some access to the intact hemisphere. In follow-up studies, some of these subjects were shown to be able to detect and localize stationary, flashing, and moving targets, and to react to the presence of a grating and its movement when presented in their blind visual field (Ptito *et al.*, 1991a).

More blindsight responses were reported in 1992 (Braddick *et al.*) where two hemispherectomized infants were able to fixate targets presented in their blind hemifield, and again by Wessinger *et al.* (1996a) where fixation instabilities were controlled by retinal stabilization and two adult subjects with functional hemispherectomy were able to achieve simple shape discrimination with awareness to stimuli presented within the zones of residual vision in the blind field (Figure 2.5). The capacity for simple pattern differentiation (Perenin, 1978) as well as velocity and movement detection (Ptito *et al.*, 1991a) in the hemianopic field lent further support to the idea of blindsight following hemispherectomy. Additionally, Tomaiuolo *et al.* (1997) were able to demonstrate blindsight in two hemispherectomy patients by invoking spatial summation across the vertical meridian, an effect that was not present in two other hemispherectomy patients with no previously documented blindsight (Figure 2.6). The possibility of light diffusion accounting for these results was excluded by the control condition that allowed presentation of the second stimulus in the blind spot of healthy controls, none of whom subsequently showed a spatial summation effect.

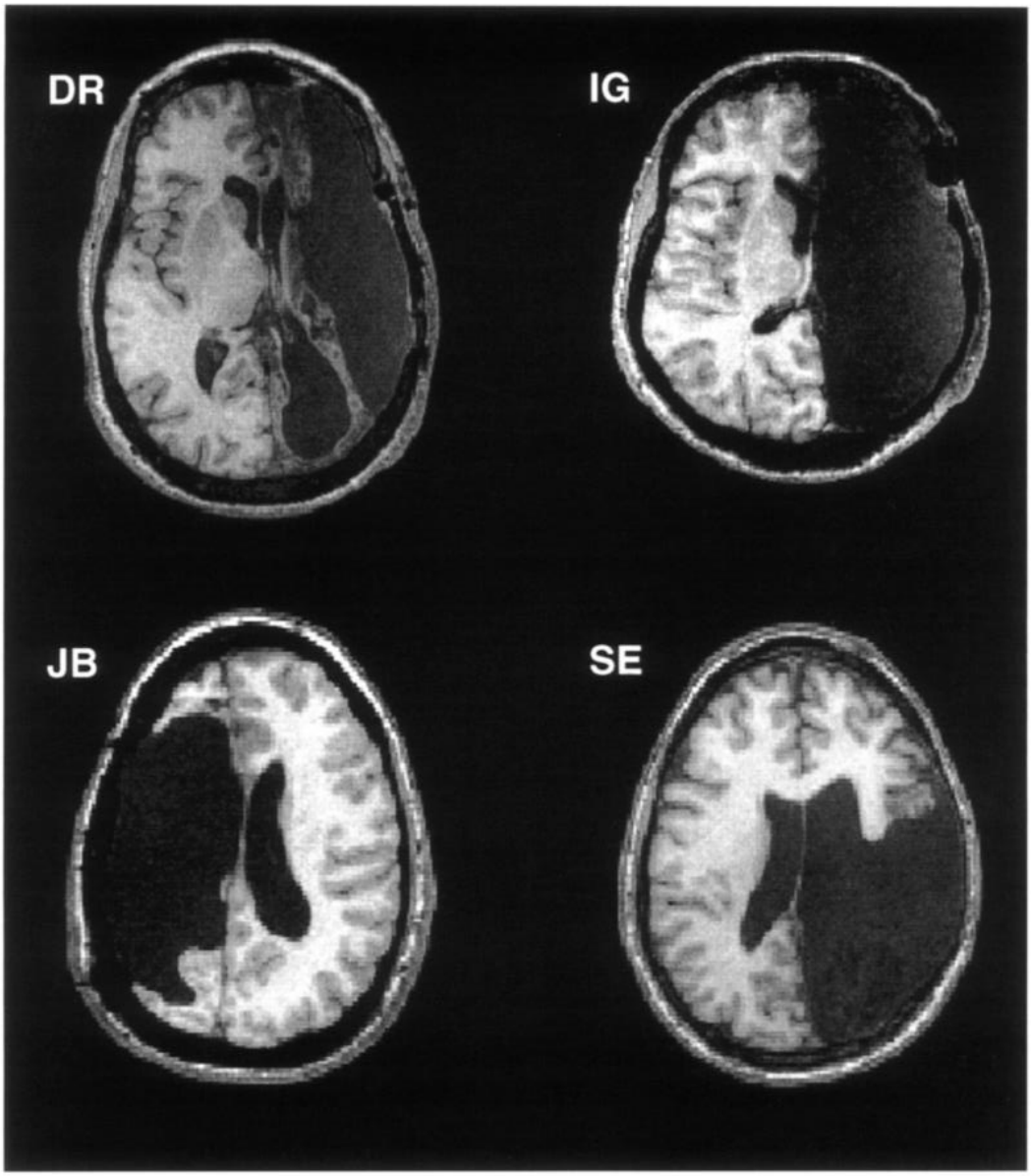


FIGURE 2.4: Hemispherectomy Subjects

Magnetic resonance axial images … showing the surgical ablation. Figure from Ptito *et al.* (2001).

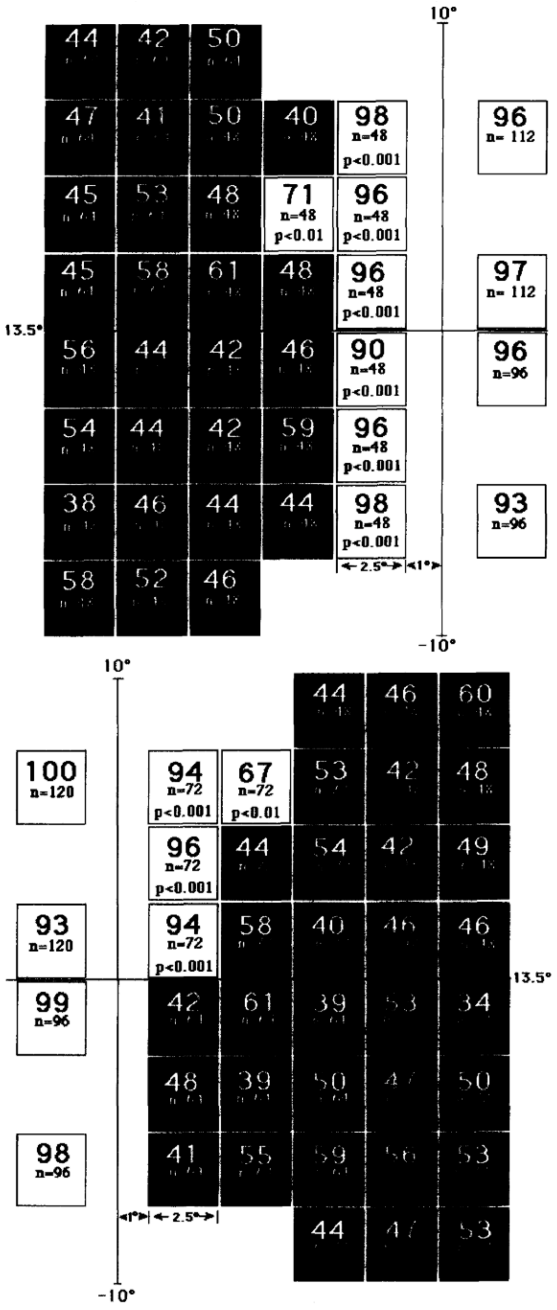


FIGURE 2.5: Blind Visual Field Detection in Hemispherectomy

Schematic representations of stabilized visual field detection results for SE (top) and JB (bottom). Open squares represent above chance performance, filled squares indicate chance performance. Values presented at each location are percent of correct detections… Figure from (Wessinger *et al.*, 1996a).

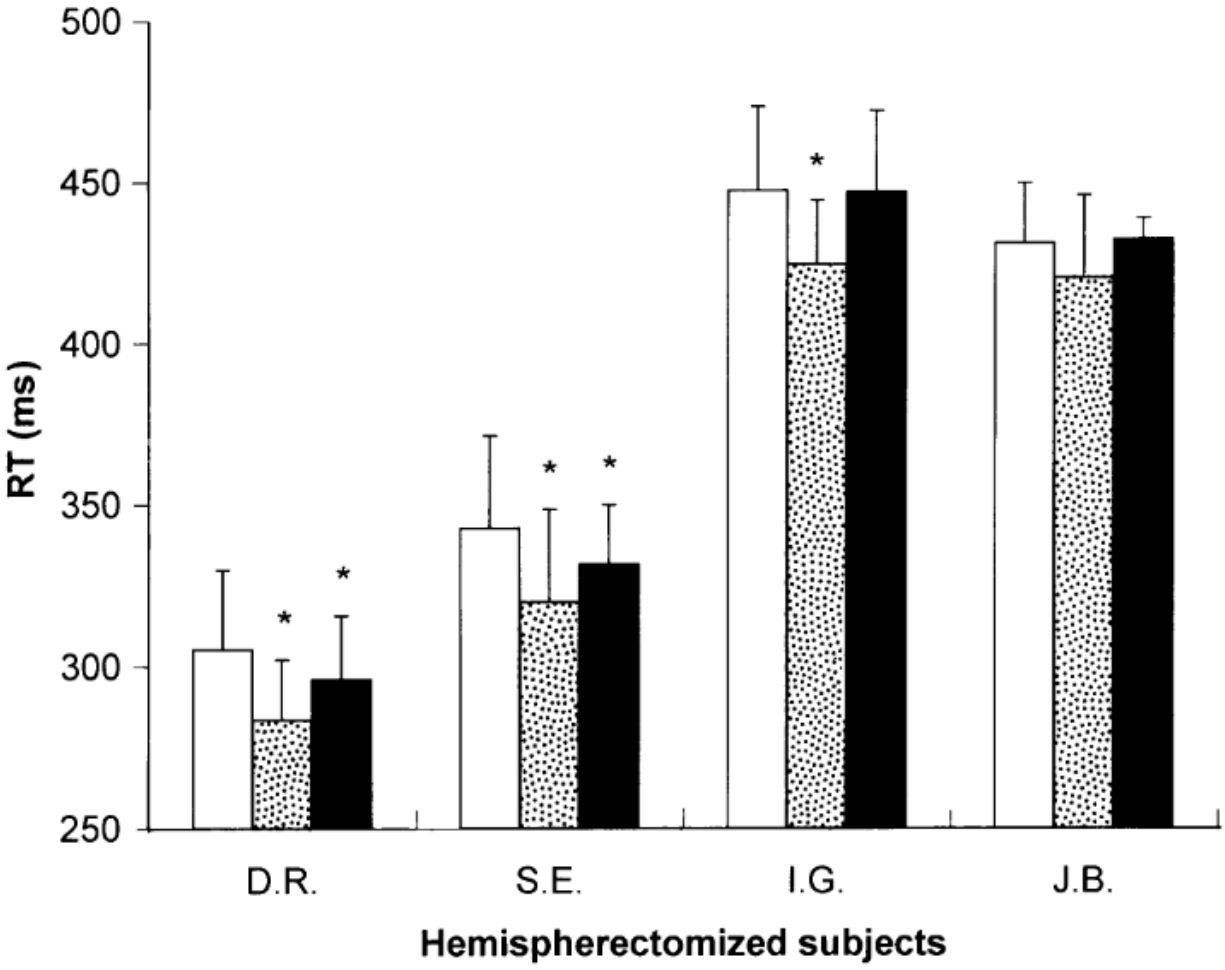


FIGURE 2.6: Spatial Summation in Hemispherectomy

Mean reaction times (RT) for the four hemispherectomized patients in the three conditions of stimulus presentation. Open, shaded and filled bars show results from single, double unilateral flash, and double bilateral double flash experiments, respectively. Asterisks mark a statistically significant difference in the crucial comparison between double bilateral flash presentations and single flash presentations in the sighted hemifield. Such a difference is significant in D.R and S.E but not in I.G. and J.B. … Figure from Tomaiuolo *et al.* (1997).

2.5 Imaging and ablations: the underlying mechanism for blindsight

Once the abilities of blindsight patients passed criticism and were proven to exist as a genuine phenomenon, the search for the structures that mediate these residual visual functions was imperative. It was perhaps intuitive to assume that the visually guided responses elicited from stimulation of the blind fields in patients with cortical blindness would make use of all the pathways that survive the effects of a striate cortical lesion. Additionally, it has been shown that plasticity following brain damage may not only strengthen existing neural pathways, but also give rise to new connections (Pascual-Leone *et al.*, 2005). Yet the pathways hypothesized to underlie the residual visual abilities of blindsight appeared to be weak in the healthy visual system (Schmid *et al.*, 2010; Sincich *et al.*, 2004; Warner *et al.*, 2015), which made it initially a more difficult target for research. However, with the use of ablations and reversible inactivation in animal models, as well as the advent of functional magnetic resonance imaging (fMRI), it was possible to investigate the underlying neural components that might be involved or responsible for blindsight.

2.5.1 Extrastriate areas

The retino-recipient nuclei that have been investigated following striate cortex ablation show responses to stimuli presented in the cortically blind visual field which all project either directly, such as through the lateral geniculate nucleus and pulvinar, or indirectly, via the superior colliculus to extrastriate visual cortical areas, all differing in the extent to which they respond to the information presented in the blind field (Payne *et al.*, 1996). Physiological evidence in monkeys whose striate cortex was ablated or reversibly inactivated indicate that the extrastriate cortical areas that form the dorsal stream retain much more of their visual responsiveness (Bullier *et al.*, 1994) than the ventral stream. Visual responses have been recorded in the dorsal extrastriate areas of unilaterally destriated monkeys which accompanied a

host of residual visual functions that involved direct responses (Rodman *et al.*, 1989; Rodman *et al.*, 1990). In Pasik & Pasik (1971), the direct role of the extrastriate cortex in blindsight was addressed by comparing the residual visual functions in monkeys who had undergone either circumscribed V1 lesions alone, or extensive ablations of the extrastriate cortex in addition to lesions of V1. They showed that these monkeys were severely impaired, requiring twice as many trials to select which of two targets was larger in size, and failed to relearn the discrimination task after 10x as many trials as monkeys with more localised damage.

Barbur *et al.* (1993) were the first to demonstrate that extrastriate motion area MT+/V5 was activated in GY when moving stimuli were presented in his blind visual field. Bittar and colleagues (1999) were the first to use fMRI to visualize the cerebral regions involved in hemispherectomy patients with blindsight. They were able to demonstrate that stimulation of the blind field produced activation in the ipsilateral visual areas, while such stimulation failed to produce any statistically significant activation in those visual areas in hemispherectomy patients who do not exhibit blindsight. Another study performed retinotopic mapping on patient GY with a V1 lesion (Baseler *et al.*, 1999) and showed that while retinotopy was conventional during foveal presentation allowing for several visual areas to be identified using a typical angular and annular mapping stimulus, responses were found primarily in the dorsal extrastriate areas (Figure 2.7) and around the lower vertical meridian when stimuli were restricted to the blind portion of the visual field.

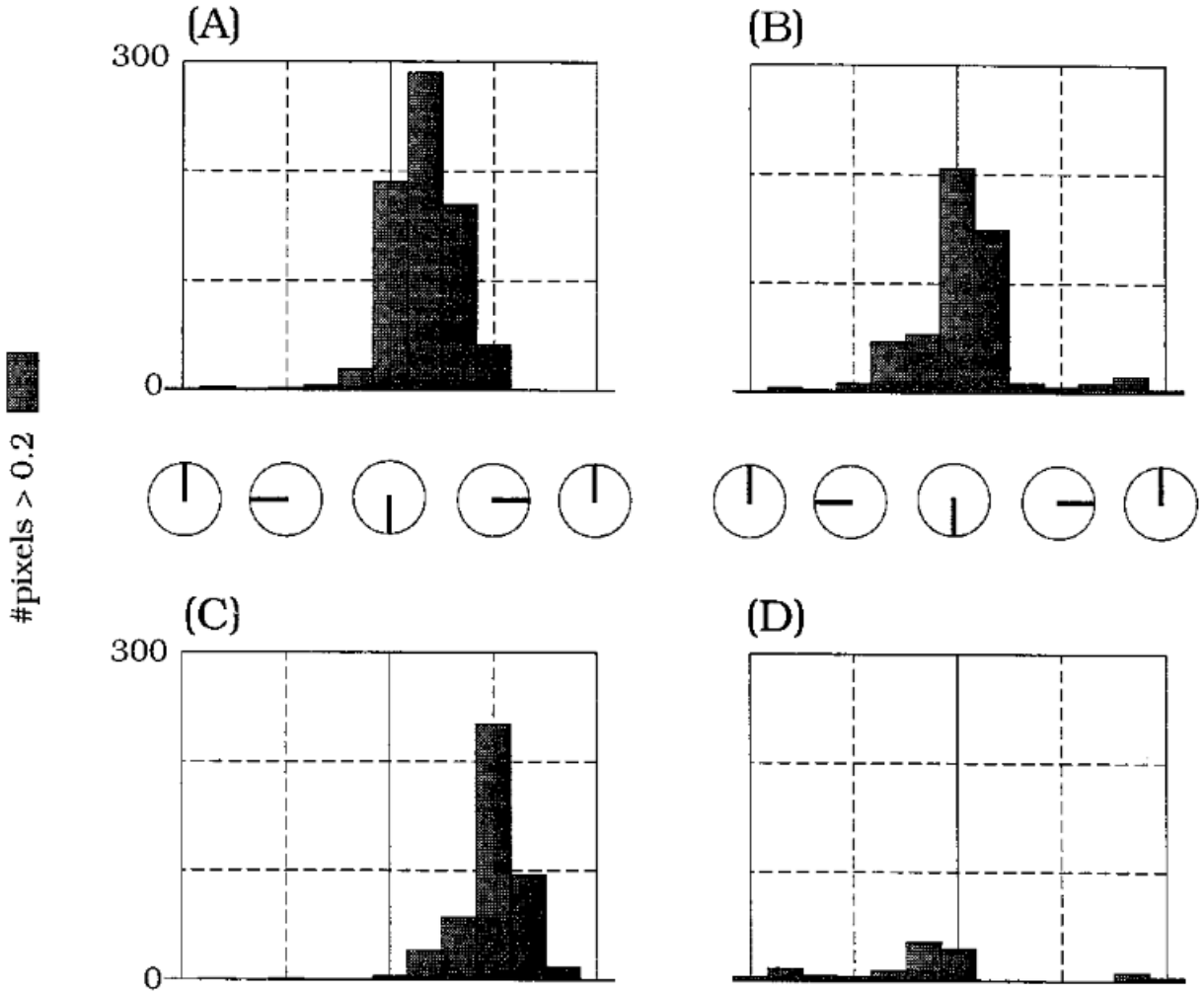


FIGURE 2.7: fMRI Responses of the Extrastriate Visual Cortex in Blindsight

Comparison of the fMRI responses within dorsal and ventral areas to the two types of rotating wedge stimulus in G.Y.'s left (lesioned) occipital lobe. Responses from areas V2 and V3 are combined in each histogram. (A) Dorsal responses, full wedge stimulus. (B) Dorsal responses, annular wedge stimulus. (C) Ventral responses, full wedge stimulus. (D) Ventral responses, annular wedge stimulus. Figure from Baseler *et al.* (1999).

2.5.2 Superior colliculus

While extrastriate cortices have been implicated in the processing mechanism of blindsight, subcortical structures such as the superior colliculus and the pulvinar have been suspected to act in conjunction with the remaining hemisphere to produce such a phenomenon (Cowey & Stoerig, 1991; Ptito *et al.*, 1991a; Ptito *et al.*, 1991b). The superior colliculus is a phylogenetically ancient structure that is involved in sensory coding and the generation of saccadic eye movements (Rafal *et al.*, 1990; Stoerig & Cowey, 1997). It has been established in primates that the visual field is mapped topographically onto the superficial layers of the superior colliculus (Goldberg & Wurtz, 1972; Schiller & Koerner, 1971), that it receives direct input from the retina (Schiller, 1972a; Schiller, 1972b), and that it might provide a potential channel to the extrastriate areas via the pulvinar (Cowey *et al.*, 1994). It was suggested that this retinal projection via the colliculus and pulvinar to the associative visual cortices might be sufficient to mediate residual vision in the blind field, and indeed, the residual detection abilities observed in monkeys with striate ablation disappear following destruction of the ipsilateral superior colliculus (Kato *et al.*, 2011; Mohler & Wurtz, 1977; Rodman *et al.*, 1990).

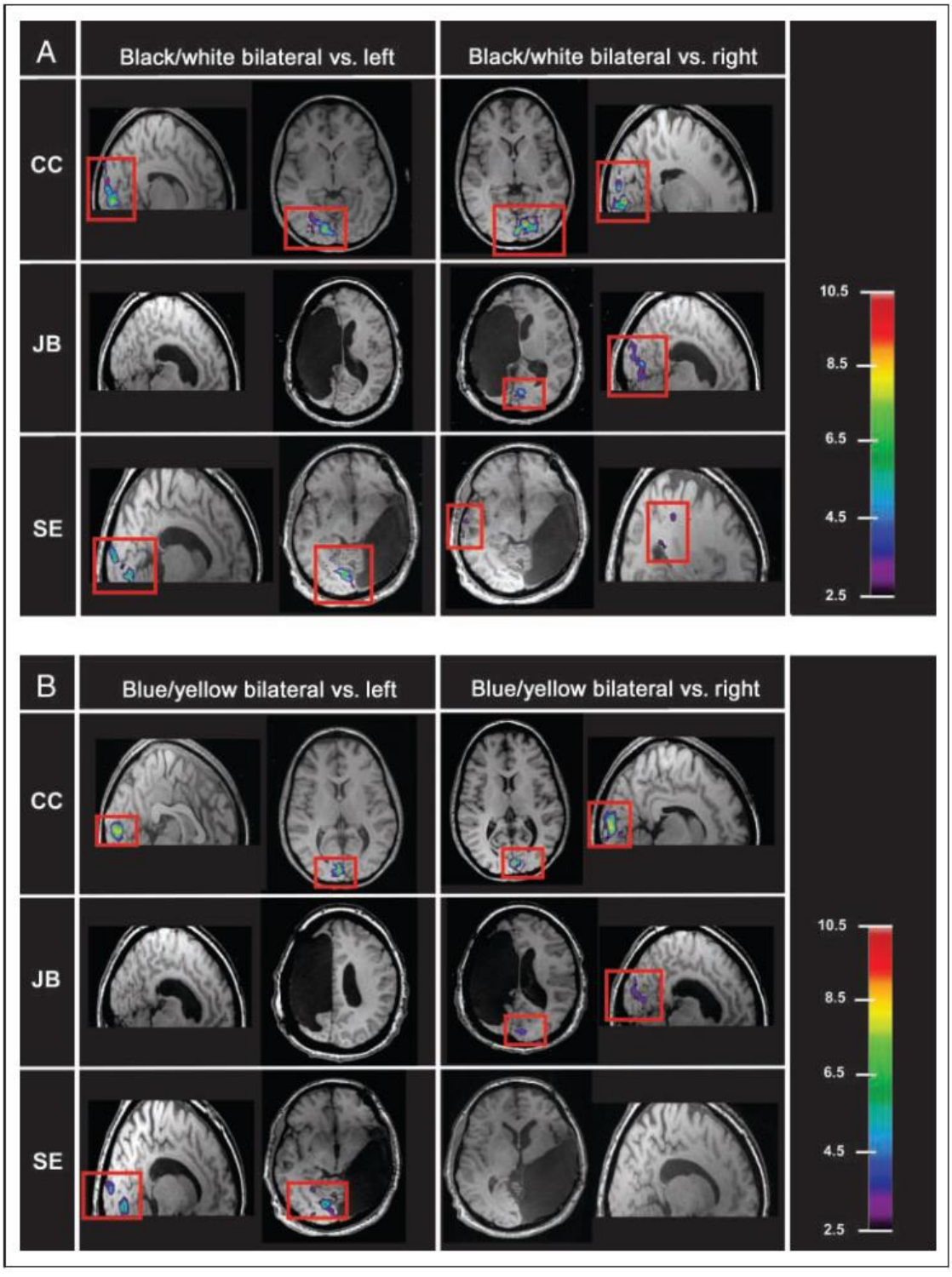
In a long series of experiments using monkeys with occipital resection who were subjected to larger cortical lesions and selective destruction of subcortical nuclei (Pasik & Pasik, 1985), it was shown that manual and saccadic localization depended on the midbrain, and were severely impaired when the superior colliculus was damaged in addition to V1 (Feinberg *et al.*, 1978; Mohler & Wurtz, 1977). While area MT+/V5, which is implicated in movement processing, maintains robust responses in non-human primates after both reversible inactivation via cooling (Girard *et al.*, 1992) and total ablation of V1 (Rodman *et al.*, 1989), its direction selectivity seems to depend on input from the superior colliculus, and responses are abolished

when it is lesioned (Rodman *et al.*, 1990). Furthermore, an fMRI study that investigated the neural substrates of 'aware' vs 'unaware' perceptual modes in GY revealed a shift in the pattern of activity, with unaware mode relying predominantly on subcortical structures, namely the superior colliculus (Sahraie *et al.*, 1997).

Several studies have demonstrated that the superior colliculus does not receive inputs from S-cones, rendering them blind to blue-yellow stimuli (Marrocco & Li, 1977; Savazzi & Marzi, 2004; Schiller & Malpeli, 1977; Sumner *et al.*, 2002). Using knowledge from these studies, a spatial summation paradigm was designed using achromatic and S-cone isolating stimuli to demonstrate the involvement of the superior colliculus in the processing of stimuli presented in the blind visual field of hemispherectomy patients. When blindsight subjects were presented with a stimulus in their intact visual field, their reaction times decreased when an achromatic stimulus was simultaneously presented in their blind visual field. Reaction time was however unaffected when a blue/yellow stimulus was used in their blind visual field. These results demonstrate the absence of S-cone inputs from the blind visual field, suggesting the involvement of the superior colliculus in blindsight (Leh *et al.*, 2006b).

In a follow-up study using fMRI, Leh and colleagues (2010) were able to show that the superior colliculus was in fact blind to S-cone input, responding to achromatic stimuli only. There was significant increase in activation of the visual areas in the ipsilateral cortex if bilateral achromatic stimuli were presented in the blind visual field of the hemispherectomy patient with previously demonstrated blindsight (SE) as compared to a unilateral stimulus (Figure 2.8). Such visual cortex activation in response to the achromatic stimuli was absent when presented in the blind visual field of a hemispherectomy patient who has never demonstrated evidence of blindsight (JB) (see also (Bittar *et al.*, 1999; Leh *et al.*, 2006a; Leh *et al.*, 2006b; Tomaiuolo *et*

al., 1997)). Similarly in GY, achromatic stimuli presented in the blind field resulted in selective activation of the superior colliculus and in occipito-temporal extrastriate areas, but when purple stimuli which draw on S-cones and are therefore invisible to the superior colliculus were projected instead, evidence of visuo-motor integration disappeared along with a significant drop in activation of the superior colliculus (Tamietto *et al.*, 2010). When TMS was used to artificially induce a scotoma in healthy subjects, their responses to visual stimuli presented within the blind area was affected considerably in tasks that directly rely on the superior colliculus such as initiating saccadic eye movements, thereby demonstrating its importance in the blindsight pathway (Ro *et al.*, 2004). In GY, diffusion tensor imaging was used to identify a direct anatomical pathway that connects the superior colliculus with the pulvinar in the damaged hemisphere, as well as bilateral tracts through the superior colliculi and corpus callosum that continued to the ipsilesional extrastriate areas (Tamietto *et al.*, 2012). Taken together, these findings suggest that the superior colliculus acts as an interface between sensory and motor processing and contributes to visually guided behavior in blindsight while remaining segregated from the geniculo-striate pathway.


A
Black/white bilateral vs. left
Black/white bilateral vs. right
CC
JB
SE
10.5
8.5
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B
Blue/yellow bilateral vs. left
Blue/yellow bilateral vs. right
CC
JB
SE
10.5
8.5
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FIGURE 2.8: Blindsight Mediated by the Superior Colliculus

Examples of enhanced activation pattern to two stimuli compared with a single stimulus in the right (left column) and left visual field (right column) are displayed as *t* maps for all subjects (CC, JB, and SE). Results for achromatic black/white stimuli are displayed in panel A, and results for S-cone isolating stimuli are displayed in panel B. Whereas subject CC (healthy control) showed an enhancement to two achromatic black/white and to two S-cone isolating stimuli compared to single conditions, JB (hemispherectomy subject with no blindsight) did not show this enhancement when a second stimulus was presented in his blind visual field. In contrast, SE (hemispherectomy subject with blindsight) showed enhanced activation patterns to two stimuli compared to a single stimulus if stimuli presented were achromatic black/white but not to S-cone isolating stimuli. Figure from Leh *et al.* (2010).

2.5.3 Lateral geniculate nucleus

Another structure often heavily implicated in the blindsight pathway is the lateral geniculate nucleus. Kisvarday *et al.* (1991) used a retrograde tracer in a unilaterally destriated monkey and showed projections from the ipsilesional lateral geniculate nucleus to the extrastriate cortices. In 2010, Schmid and colleagues used macaque monkeys with chronic V1 lesions to demonstrate its involvement in the processing mechanism of blindsight. While high contrast stimuli presented to the lesion-affected visual field produced significant fMRI activation in the extrastriate cortex and were correctly located in a detection task, reversible inactivation of the lateral geniculate nucleus abolished all fMRI and behavioural responses.

In blindsight subject GY, diffusion-weighted MRI was used to show that, like healthy controls, ipsilateral connections remain unchanged between the lateral geniculate nucleus and MT+/V5. However, additional contralateral pathways have been found connecting the lateral geniculate nucleus with MT+/V5 in subject GY, which are absent in controls (Figure 2.9) (Bridge *et al.*, 2008). In hemianopic patients without blindsight, the pathway between the lateral geniculate nucleus and MT+/V5 shows a deficit in white matter microstructure (Ajina *et al.*, 2015), and fMRI responses to motion stimuli in patients with V1 damage showed a direct functional connection between MT+/V5 and the lateral geniculate nucleus in the damaged hemisphere only in those who exhibited blindsight (Ajina & Bridge, 2018b). In a patient with bilateral V1 damage who showed activation in MT+/V5 comparable to healthy controls in response to high contrast stimuli, diffusion tractography showed a direct pathway between the lateral geniculate nucleus and MT+/V5 that maintained microstructure equivalent to that in the healthy control group (Ajina & Bridge, 2018a).

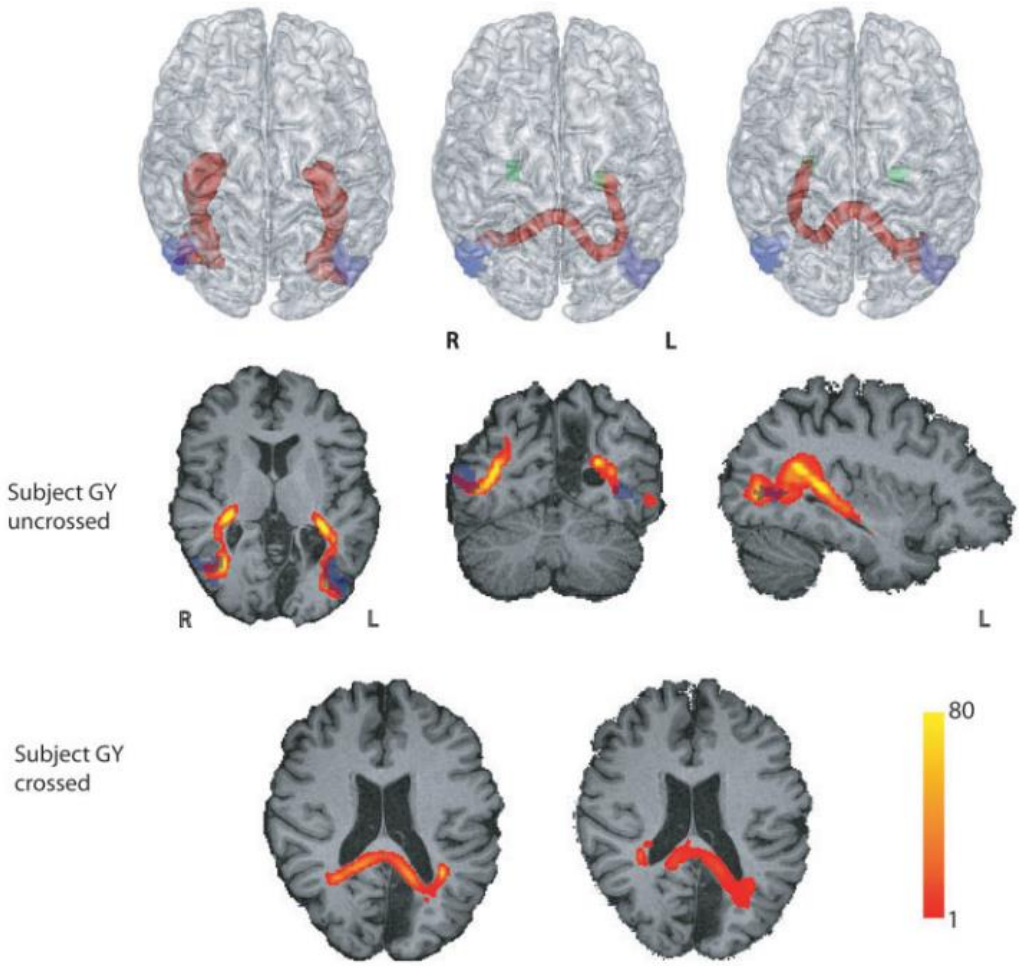

FIGURE 2.9: Connectivity of the Lateral Geniculate Nucleus in Blindsight

Blindsight subject GY has ipsilateral tracts from LGN (lateral geniculate nucleus) to MT+/V5, very similar to those of the controls (middle row, and left 3D brain). In addition, and most unusually, he has contralateral tracts both between the left LGN (lesioned side) and the right MT+/V5, and between right LGN and left MT+/V5. Slices showing these contralateral tracts can be seen on the left and right panels of the bottom row, respectively. These crossing tracts can be visualized in the 3D brains in the top row. Figure from Bridge *et al.* (2008).

2.6 Conclusions and present investigations

In summary, the residual visual functions that remain in the blind field of cortically blind individuals following primary visual cortex damage has been extensively researched for nearly 60 years and has been investigated in animal models as well as in humans. Studies have aimed to characterize these visual functions and have attempted to do so using a variety of techniques and approaches, some reflexive, some implicit, and some explicit. Despite the limitations in the research of this phenomenon introduced by individual variations, blindsight has faced and survived its criticisms over the years. With advances in imaging techniques and with the help of reversible inactivation and ablation in animals as well as hemispherectomy patients, it has become possible to investigate the underlying mechanisms that are responsible for these visual functions which has highlighted the brain's capacity for plasticity following damage and has changed the way we once thought of the organization of the visual pathways and the roles and connectivity of the structures within (Celeghin *et al.*, 2018). While our knowledge has come a long way since the 19th century (Figure 2.10), there is still much to uncover in this field.

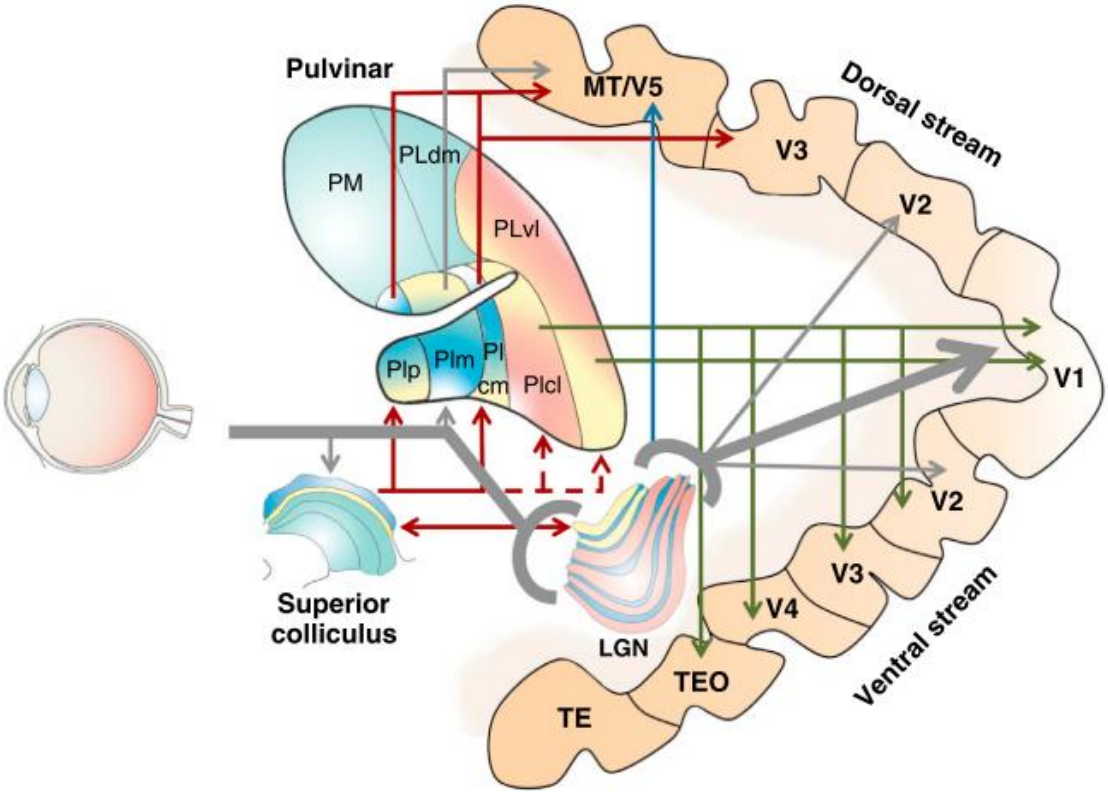

FIGURE 2.10: The Visual Pathways, Now

Gray arrows indicate direct projections for the eye, with thicker lines showing the major geniculo-striate pathway involving LGN (lateral geniculate nucleus) and targeting V1. Red arrows indicate projections originating from the superior colliculus and reaching the dorsal stream cortical areas via the pulvinar, with dashed lines showing disputed input to subdivisions of the pulvinar. Green arrows indicate projections from pulvinar subnuclei to areas along the cortical ventral stream. The blue arrow indicates projections from the koniocellular layers of LGN to area MT. In LGN and superior colliculus, yellow layers indicate magnocellular, blue koniocellular, and pink parvocellular channels. In the pulvinar these pathways are not clearly segregated and shaded blue-yellow; pink-yellow colors indicate the conjoint presence of the respective channels in given subdivisions. Light green denotes areas of the superior colliculus and pulvinar not interesting for the present purposes…. Figure from Tamietto & Morrone (2016).

In this thesis, I present three original studies aimed at expanding our knowledge of the neural mechanisms underlying blindsight. I studied a rare population of hemispherectomized subjects that have been tested extensively in the past and have consistently demonstrated strong evidence of blindsight. Since these subjects lack an entire functional cortical mantle in one hemisphere, they provide an incredibly unique opportunity for the study of blindsight because there is no possibility of remaining islands of functional cortex that can explain their residual vision in the blind hemifield. The goal of my thesis is to use a varied mix of techniques and approaches in order to investigate the capacity of the superior colliculus for encoding complex visual processing, to characterize changes in the retinotopic mapping and population receptive field sizes in the intact visual cortex, and finally to examine anatomical changes in the form of cortical thickness that may accompany this functional plasticity in the remaining hemisphere.

Chapter 3: Is the superior colliculus sensitive to stimulus numerosity and configuration?

3.1 Prelude

In the first study entitled "*The superior colliculus is sensitive to gestalt-like stimulus configuration in hemispherectomy patients"* I used a modified version of the spatial summation effect paradigm in which reaction times to two bilaterally presented stimuli flashed simultaneously across the vertical meridian (whereby one stimulus falls within the sighted visual field, and the other in the blind visual field) are significantly faster than a single stimulus flashed in the sighted visual field only – termed 'redundant target effect'. This effect occurs in healthy subjects and has been used reliably to test unconscious visual functions in the blind hemifield of subjects with blindsight (see section 2.4.2). By introducing a component of stimulus numerosity (single v. quadruple) as well as configuration (gestalt-like coherent v. random), it was shown in a subject with V1 lesion that blindsight is sensitive to the stimulus numerosity only when the stimuli were presented in a gestalt-like pattern (Celeghin *et al.*, 2015c).

In this study, I tested two hemispherectomy patients with previously well documented blindsight using this paradigm with important modifications in order to address previous limitations. I hypothesized that because other retino-recipient subcortical and cortical structures in the damaged hemisphere are absent, if these patients are capable of demonstrating this effect, then the superior colliculus is the likely mediator of this non-conscious vision, and that it is sensitive to higher-order perceptual organization.

The superior colliculus is sensitive to gestalt-like stimulus configuration in hemispherectomy patients

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Published: **Cortex** ***(2016), Vol. 81, pp. 151-61***

3.2 Abstract

Patients with cortical blindness following a lesion to the primary visual cortex (V1) may retain nonconscious visual abilities (blindsight). One intriguing, though largely unexplored question, is whether nonconscious vision in the blind hemifield of hemianopic patients can be sensitive to higher-order perceptual organization, and which V1-independent structure underlies such effect. To answer this question, we tested two rare hemianopic patients who had undergone hemispherectomy, and in whom the only post-chiasmatic visual structure left intact in the same side of the otherwise damaged hemisphere was the superior colliculus (SC). By using a variant of the redundant target effect (RTE), we presented single dots, patterns composed by the same dots organized in quadruple gestalt-like configurations, or patterns of four dots arranged in random configurations, either singly to the intact visual hemifield or bilaterally to both hemifields. As reported in a number of prior studies on blindsight patients, we found bilateral stimulation yielded faster reaction times (RTs) than single stimulation of the intact field for all conditions (i.e., there was an implicit RTE). In addition to this effect, both patients showed a further speeding up of RTs when the gestalt-like, but not the random shape, quadruple patterns were projected to their blind hemifield during bilateral stimulation. Because other retino-recipient subcortical and cortical structures in the damaged hemisphere are absent, the SC on the lesioned side seems solely responsibly for such an effect. The present results provide initial support to the notion that nonconscious vision might be sensitive to perceptual organization and stimulus configuration through the pivotal contribution of the SC, which can enhance the processing of gestalt-like or structured stimuli over meaningless or randomly assembled ones and translate them into facilitatory motor outputs.

3.3 Introduction

Following unilateral damage to the visual cortex, patients experience clinical blindness in both halves of each eye in their contralesional visual hemifield (homonymous hemianopia). Despite clinical blindness, some patients retain nonconscious visual abilities for processing unseen stimuli in the blind hemifield (Ajina *et al.*, 2015; Barbur *et al.*, 1993; Blythe *et al.*, 1987; Bridge *et al.*, 2008; Celeghin *et al.*, 2015a; Corbetta *et al.*, 1990; Kentridge *et al.*, 2004; Kentridge *et al.*, 2008; Marzi, 1986; Pizzamiglio *et al.*, 1984; Pöppel *et al.*, 1973; Rafal *et al.*, 1990; Singer *et al.*, 1977; Stoerig *et al.*, 1985; Stoerig, 1987; Tinelli *et al.*, 2013; Torjussen, 1976; Torjussen, 1978; Weiskrantz *et al.*, 1974; Zihl & von Cramon, 1980). These residual nonconscious abilities, termed "blindsight" by Weiskrantz *et al.* (1974) have been described for different visual functions such as stimulus detection (Sahraie *et al.*, 1997; Weiskrantz *et al.*, 1995), shape or category-specific processing (Trevethan *et al.*, 2007; Van den Stock *et al.*, 2014; Van den Stock *et al.*, 2015), color and motion discrimination (Hervais-Adelman *et al.*, 2015; Kentridge *et al.*, 2007; Morland *et al.*, 1999), recognition of facial and bodily expressions (Bertini *et al.*, 2013; Celeghin *et al.*, 2015b; de Gelder *et al.*, 1999; de Gelder *et al.*, 2012) or gaze direction (Burra *et al.*, 2013). Moreover, preserved processing of such visual properties has been described under a variety of task demands, such as visually guided or goal directed behaviour (Buetti *et al.*, 2013; Celeghin *et al.*, 2015c; Pöppel *et al.*, 1973; Rafal *et al.*, 1990), yes-no or alternative forced-choice tasks (Azzopardi & Cowey, 1997; Tamietto *et al.*, 2009), and perceptual completion requirements (Torjussen, 1978) (see Tamietto & Morrone (2016) for a recent review).

Two kinds of strategies have been typically employed to assess blindsight: direct and indirect methods. The former makes use of forced-choice paradigms where the subjects make an

explicit decision regarding unseen attributes of the stimulus presented to their blind hemifield (Danckert & Rossetti, 2005; Stoerig & Cowey, 1989; Weiskrantz, 1990). Above chance performance, despite absence of awareness, is taken as indicative of blindsight. In contrast, the latter methods rely on the effect exerted by unseen stimuli presented to the blind hemifield on stimuli simultaneously presented to the intact counterpart. One of the indirect methods most often used for testing blindsight is the redundant target effect (RTE) (Marzi *et al.*, 1986). In healthy participants, the tachistoscopic presentation of two or more synchronous stimuli to both visual hemifields (BVF) across the vertical meridian results in faster reaction times (RTs) than a single stimulus presentation to one visual hemifield, either left (LVF) or right (RVF). This effect, also known as bilateral summation or redundancy gain, has been reported in many studies in healthy participants as well as in blindsight patients (Celeghin *et al.*, 2015c; Corbetta *et al.*, 1990; Leh *et al.*, 2006b; Marzi, 1986; Marzi *et al.*, 2009; Tamietto *et al.*, 2010; Tomaiuolo *et al.*, 1997). The main advantage of indirect methods is that patients make a choice about visual attributes they do not consciously acknowledge without being forced to do so, but are only required to respond as quickly as possible to the stimulus in their intact hemifield in a simple RT paradigm. Therefore, since patients have to respond to stimuli they can normally perceive, the range of visual operations that can potentially be investigated is wide and may include high-order visual operations.

Recently, Celeghin *et al.* (2015c) introduced a variant of the RTE to obtain insights on the influence of stimulus numerosity and configuration on visuo-motor responses in blindsight patients. Participants were presented with either unilateral or bilateral black dots. For each of these two conditions, the stimuli could be a single dot or a pattern of four dots. The latter were presented in either a variable random spatial configuration or a fixed one wherein the four dots

were arranged in a diamond-like shape. Notably, the two configurations subtended the same visual angle and had the same luminance. Orthogonal to the replication of the common RTE in the comparison between unilateral and bilateral conditions, the authors also found an additive effect of stimulus configuration with a speeding up of RT when the gestalt-like, but not the random shape, quadruple pattern was projected to the patients' blind field. These novel findings have allowed the establishment of a solid approach to study the influence of stimulus configuration on blindsight and its underlying neural structures, an issue that in the past has come under only desultory scrutiny. These results have provided initial support for the notion that nonconscious vision might be sensitive to perceptual organization, thereby enhancing the processing of gestalt-like or structured over meaningless or randomly assembled stimuli. Concerning the neuro-functional mechanisms of RTE, several studies in patients with unilateral destruction of the primary visual cortex (V1) or with removal of the entire cortical mantle in one hemisphere (hemispherectomy) have provided convincing evidence that the superior colliculus (SC) is necessary and sufficient for the RTE to occur (Leh *et al.*, 2006b; Leh *et al.*, 2010; Marzi *et al.*, 2009; Tamietto *et al.*, 2010). This raises the interesting, entirely unexplored, possibility that the SC responds differentially to higher-order perceptual properties, such as those involved in stimulus configuration, even in the absence of the geniculo-striate pathway that deprives vision of its conscious component. Although suggestive in a number of aspects, the previous results by Celeghin *et al.* (2015c) are not conclusive for two reasons. Firstly, the patients had intact portions of extrastriate visual areas as well as spared retino-recipient subcortical structures besides the SC, such as the lateral geniculate nucleus (LGN) and the pulvinar (Pulv). All these subcortical structures have been shown to receive direct input from the retina and to send (mainly) ipsilateral efferents to several extrastriate visual areas bypassing V1 (Ajina *et al.*, 2015;

Bridge *et al.*, 2008; Leh *et al.*, 2008; Lyon *et al.*, 2010; Schmid *et al.*, 2010; Sincich *et al.*, 2004; Tamietto *et al.*, 2012; Tamietto & Morrone, 2016). Therefore, the relative contribution of the SCS could not be disentangled from that of the other subcortical centers or their extrastriate targets, so that the SC specific role remains unresolved. Secondly, while a variety of random configurations were used in the original study, only one diamond-shape dot pattern was presented, thereby leaving the possibility that the effect found for the latter condition was due to familiarity and/or to spatially fixed versus variable stimulus configuration rather than to the presence of a gestalt-like dot pattern *per se*.

The aim of the present study is to tackle these questions by partially modifying the original experimental paradigm and by testing patients with hemispherectomy and blindsight. These patients had undergone removal of an entire cerebral hemisphere or of all the temporo-occipito-parietal cortices. Moreover, the LGN and Pulv in the affected hemisphere have been both removed leaving only the SC intact among retino-recipient subcortical structures. Therefore, testing the RTE in these patients has offered the unprecedented opportunity to examine the impact of perceptual configuration in nonconscious visually guided behaviour under the most stringent conditions in order to determine the putative crucial role of the SC.

3.4 Methods

3.4.1 Patients

Patient DR is a right-handed woman (40 years old at the time of testing) who presented with left hemiparesis since birth and began suffering from epileptic seizures at the age of 5 years CT and MRI scans performed at the age of 17 years revealed severe atrophy of the right cerebral hemisphere and EEG recording showed epileptiform activity over the right frontal-parietal-temporal regions. Cognitive testing indicated borderline intelligence scores: Full Scale Intelligence Quotient (FISQ), 77; verbal IQ, 92 and performance IQ, 65. At the same age, she underwent a functional hemispherectomy, which consisted of removing the temporal lobe invluding the mesial structures, the amygdala, the hippocampus, and a frontal-parietal corticectomy. The remaining cortical regions were left *in situ* but were disconnected from the rest of the brain by sectioning the white matter anteriorly and laterally, as well as posteriorly and laterally along the falx. Subsequent neuropathological investigation revealed an inflammatory process with diffuse gliosis characteristic of Rasmussen encephalitis. Follow-up assessments, at the age of 19 years, indicated that her level of intellectual function had increased to the low average range: FISQ, 83; verbal IQ, 87 and performance IQ, 83. MRI scans postoperatively, as well as further scans performed afterwards for research purposes and published elsewhere, showed the presence of intact left and right SC, whereas the presence of the Pulv was limited to the left (intact) hemisphere (Figure 3.1A) (Leh *et al.*, 2006a; Leh *et al.*, 2008; Leh *et al.*, 2010; Tomaiuolo *et al.*, 1997). Complete contralateral (left) hemianopia without macular sparing has been confirmed by computerized perimetry (Allergen, Humphrey), and her visual acuity was 20/25.

Patient SE is a right-handed man (49 years old at the time of testing) whose left hemiparesis was noted at birth. Seizure onset occurred at the age of 7 years. At the age of 23

years, CT and MRI scans showed a porencephalic cyst occupying the right temporal-parietal-occipital regions. EEG recordings detected epileptiform activity in the right occipital cortex alongside independent foci over the right temporo-parietal cortex. Neuropsychological testing revealed an FSIQ of 78; verbal IQ of 80 and performance IQ of 79. At the age of 25, he underwent a surgery to remove the congenital porencephalic cyst, and a temporal-parietal-occipital lobectomy included the hippocampus and the amygdala but spared the anterior portion of the frontal lobe. Postoperative neuropathological examination revealed a neuronal migration disorder (cortical dysplasia). MRI scans postoperatively, as well as further scans performed afterwards for research purposes and published elsewhere, showed the presence of intact left and right SC, but only presence of the Pulv on the left (intact) side (Figure 3.1B) (Leh *et al.*, 2006a; Leh *et al.*, 2008; Leh *et al.*, 2010; Tomaiuolo *et al.*, 1997). Follow-up cognitive testing, at the age of 26 years, showed an increase in IQ to an average range: FSIQ, 93; verbal IQ, 90 and performance IQ, 99. Contralateral hemianopia without macular sparing was confirmed by computerized perimetry (Allergan, Humphrey), and his visual acuity was 20/30.

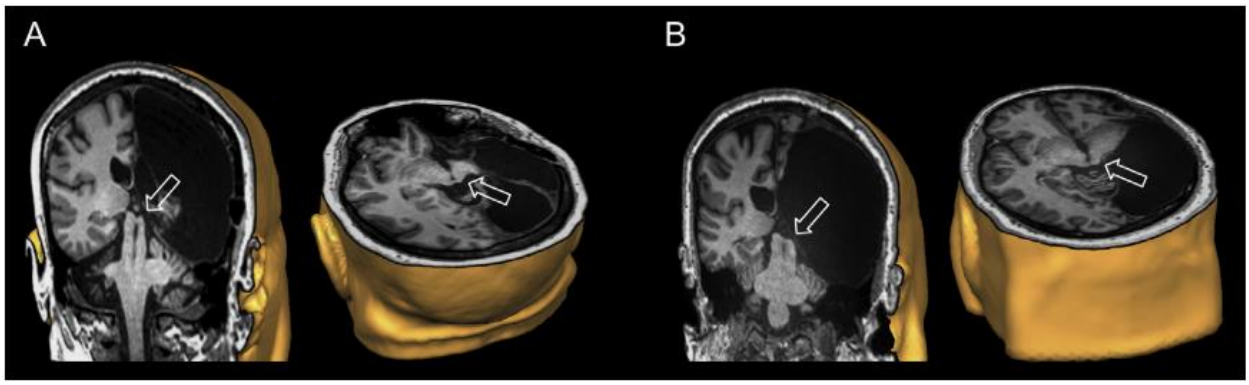

FIGURE 3.1: Patient DR and SE T1-weighted MRI

A) Coronal (left) and transversal (right) 3-D anatomical reconstruction of patient DR's brain; B) Coronal (left) and transversal (right) 3-D anatomical reconstruction of patient SE's brain. The white transparent arrow indicates the intact superior colliculus in the other damaged right hemisphere.

3.4.2 Stimuli and apparatus

The stimuli were black dots presented against a uniform gray background of 11.42 cd/m^2 luminance (RGB values = 126, 126, 126). The dots were presented either unilaterally, to the seeing RVF, or to BVF. For each of these two presentation conditions, there were three possible display types: a single dot, a quadruple pattern composed by the same dots organized in gestalt-like configurations, or a quadruple pattern of dots organized in random configurations. Quadruple arrays were displayed with the innermost dot at 6.5° of eccentricity with respect to the central fixation along the horizontal meridian (the same for single dot displays) and with the outmost dot at 8.5°. Gestalt-like configurations were of four different shapes: diamond, square, rectangles with longer vertical sides and rectangles with longer horizontal sides. Random configurations also consisted of the same dots organized in four different by equally meaningless combinations. In all BVF presentations with quadruple stimuli, the two patterns of stimuli projected to the two visual fields were of the same type, but not physically identical (e.g. a diamond shape in the LVF and a square shape in the RVF), in order to avoid any interpretation of the results in terms of bilateral symmetry (Figure 3.2).

The stimuli were projected on a 17’ LCD monitor (refresh rate: 16.7 Hz) using a MacBook Pro Notebook with exposure duration of 80 ms (5 refresh rates). The observer’s eyes were at a distance of 57 cm from the monitor. Stimulus presentation and response recording were controlled by means of the Presentation 16 Software (NeuroBehavioral Systems, Albany, CA).

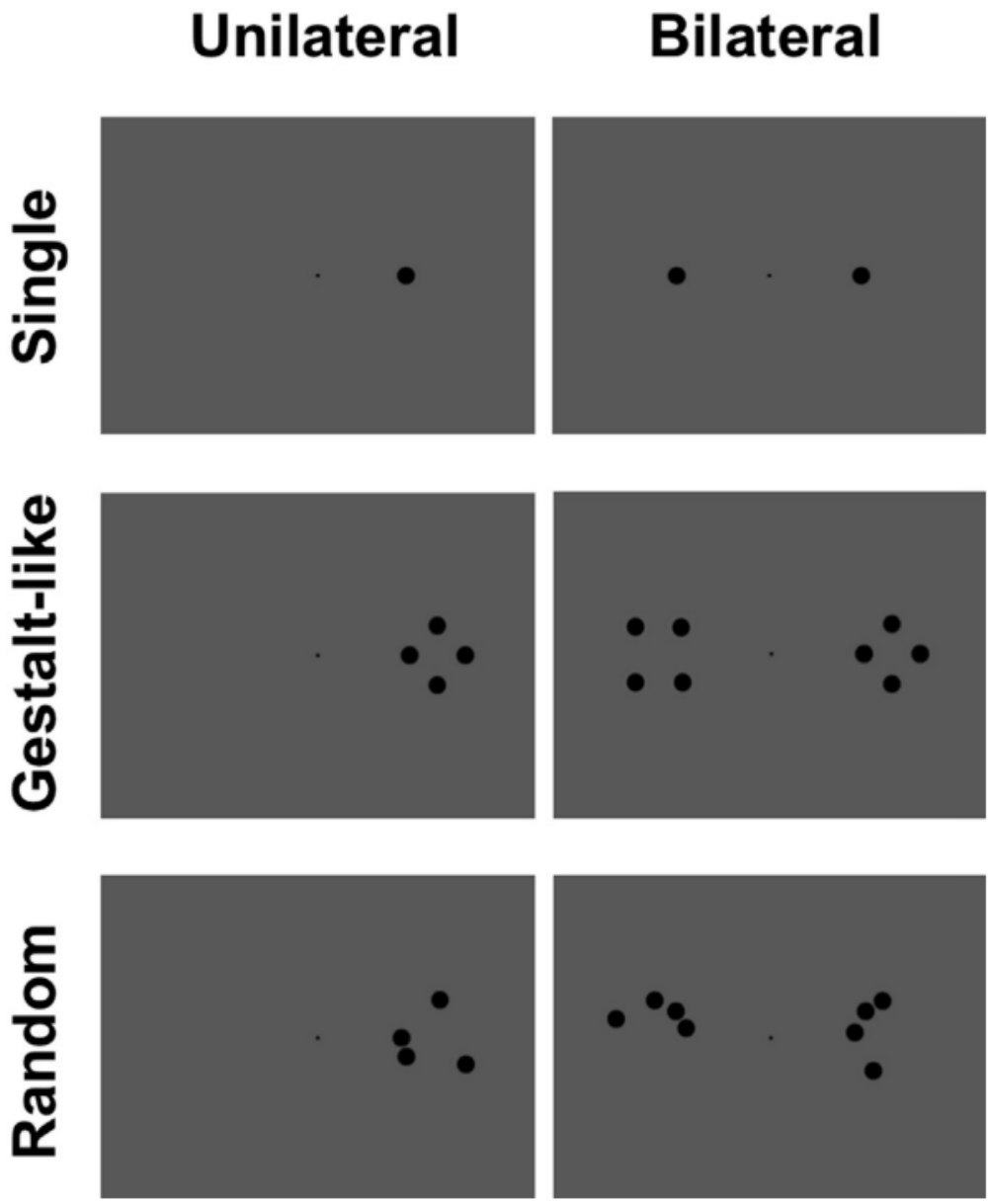

FIGURE 3.2: Modified RTE Stimulus

Examples of the stimuli and their spatial organization in different display types and a function of unilateral versus bilateral presentation, and for single, quadruple gestalt-like and random configurations. Note that in bilateral displays with gestalt-like or random configurations the two stimuli, while being of the same type, are not physically identical.

3.4.3 Procedure

Participants' head movements were minimized through the use of a head and chin rest. They were required to maintain fixation on a small black circle (diameter 0.3°, luminance: 0.82 cd/m^2) in the centre of the screen and to refrain from moving their eyes. Eye movements were also monitored online by one experimenter through an infra-red camera connected with an eye-tracking system, and trials were removed in the event of unsteady fixation. In this rare case (<5%) and additional trial was added to the end of the block. Moreover, to ensure fixation during stimulus presentation, each trial started with a warning acoustic signal (duration: 150 ms; frequency: 1000 Hz) followed by the visual stimulus after a randomized temporal interval (varying between 300 and 700 ms). The patients were testing monocularly with the (left) contralesional eye while an eye patch covered the (right) ipsilesional eye, and response was performed by pressing the space bar of the notebook with the (right) ipsilesional hand. Monocular testing with the dominant (left) eye was used for two reasons. First, in both patients the non-dominant (right) eye ipsilateral to the damaged hemisphere tended to deviate independently from the gaze direction of the dominant eye. This had potentially undermined the correct lateralization of the stimuli during fixation, as two different locations could be represented in the fovea of the two eyes and a stimulus assumed to be projected in the left blind hemifield might have actually fallen into the seeing field of the right eye. Second, naso-temporal asymmetries have been previously reported. For example, stimuli in the temporal hemifield (the left hemifield of the left eye) induce preferential gaze orienting or summon attention more readily than stimuli in the nasal hemifield (the right hemifield of the left eye) (Rafal *et al.*, 1991; Rafal *et al.*, 1989). These behavioural asymmetries have been proposed to indicate the contribution of the SC in such tasks. Anatomically, indeed, the superficial layers of the SC receive visual input predominantly from the nasal hemiretina, which samples the temporal

hemifield, whereas the connections from the temporal hemiretina constitute a relatively weaker retino-tectal pathway (Hubel *et al.*, 1975; Wilson & Toyne, 1970). This has been confirmed in an fMRI study showing higher activation of the SC following stimulation of the temporal rather than nasal hemifield (Sylvester *et al.*, 2007). Therefore, testing patients monocularly with the left eye ensured that the stimuli projected peripherally to the (left) blind temporal hemifield during bilateral conditions were processed uniquely by the nasal hemiretinas, and thus relayed to the right SC, ipsilateral to the damaged hemisphere, through the stronger of the two retino-tectal pathways (Figure 3.3). In contrast, the stimuli projected to the (right) intact nasal hemifield reached the left SC, ipsilateral to the intact hemisphere, through the weaker connections involving the temporal hemiretina pathway. This was done to counterbalance the potentially weaker representation of the (left) unseen over (right) seen stimulus during bilateral stimulation, as well as the overall weaker response in the (right) ipsilesional SC compared to the (left) SC in the intact side, which might have compromised the RTE.

The stimuli were presented in two blocks, each containing 84 randomized trials. Within each block, the six stimulation conditions and display types were equiprobably, and each was repeated for 14 trials (unilateral: single, quadruple gestalt-like, quadruple random; bilateral: single, quadruple gestalt-like, quadruple random). In total, each patient received 28 stimulus presentations per condition.

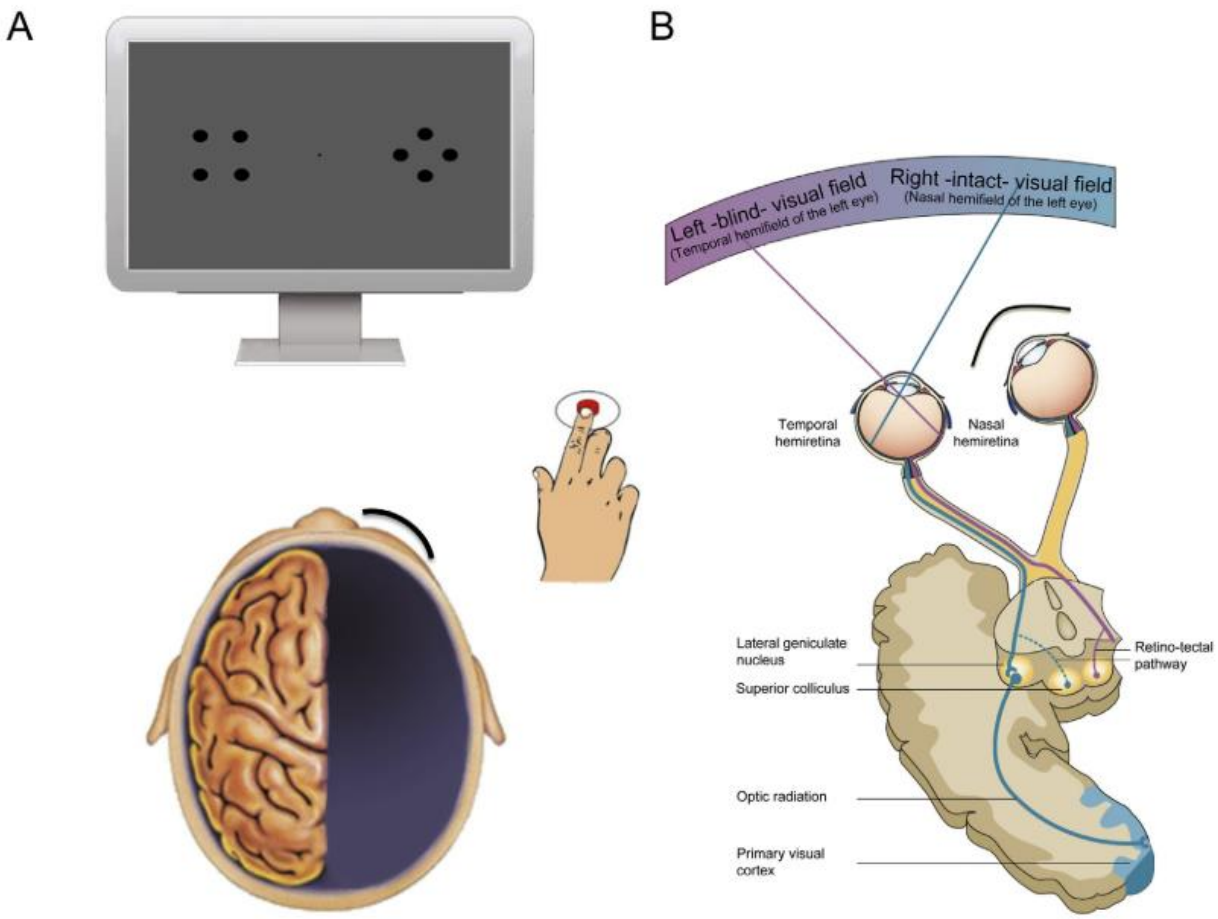

FIGURE 3.3: Experimental Set-up and The Retino-tectal Pathway

Schematic representation of the testing procedure. A) Illustration of the experimental set-up; B) Representation of the naso-temporal asymmetry in the retino-tectal pathway. The weaker pathway from the temporal hemiretina is represented by a blue dashed line, whereas the stronger pathway from the nasal hemiretina is represented by the purple continuous line.

3.5 Results

Based on previous reports on the same patients, only RTs in the time range 200-1000 ms were considered (Leh *et al.*, 2006b; Leh *et al.*, 2010; Tomaiuolo *et al.*, 1997). Patient DR responded to all 168 trials within the accepted range, whereas SE did not respond to 3 trials (1.8%), and had one anticipation (0.6%) while the responses to the remaining trials (97.6%) were within the accepted range. Mean RTs as a function of the six stimulus conditions are shown separately for patient DR and SE in Figure 3.4. Visual inspection reveals that RTs decreased in bilateral compared to unilateral presentations irrespective of the different display types and for both patients, although this decrease of RTs was particularly pronounced for gestalt-like configurations. Initially, a 2 x 3 repeated-measures ANOVA was carried out on RTs data with the within-subjects factors of Presentation Condition (Unilateral *vs* Bilateral) and Configuration (Single, Gestalt-like, Random). The same ANOVA was computed on the two patients separately.

Patient DR showed a significant main effect of Presentation Condition ($F(1, 27) – 47.507$, $p < 0.0001$], indicating that a RTE occurred for all display patterns. The main effect of Configuration was also significant [$F(2, 54) = 38.133$, $p < 0.0001$], but there was no significant Presentation Condition x Configuration interaction [$F(2, 54) = 1.777$, $p < 0.178$]. A post-hoc Bonferroni comparison performed on the Configuration factor revealed that RTs were significantly faster for gestalt-like patterns than for either single or quadruple random dot shapes ($t(55) \geq 6.31$ $p \leq 0.0001$], which in turn did not differ from each other significantly [$t(55) = 1.92$, $p = 0.149$].

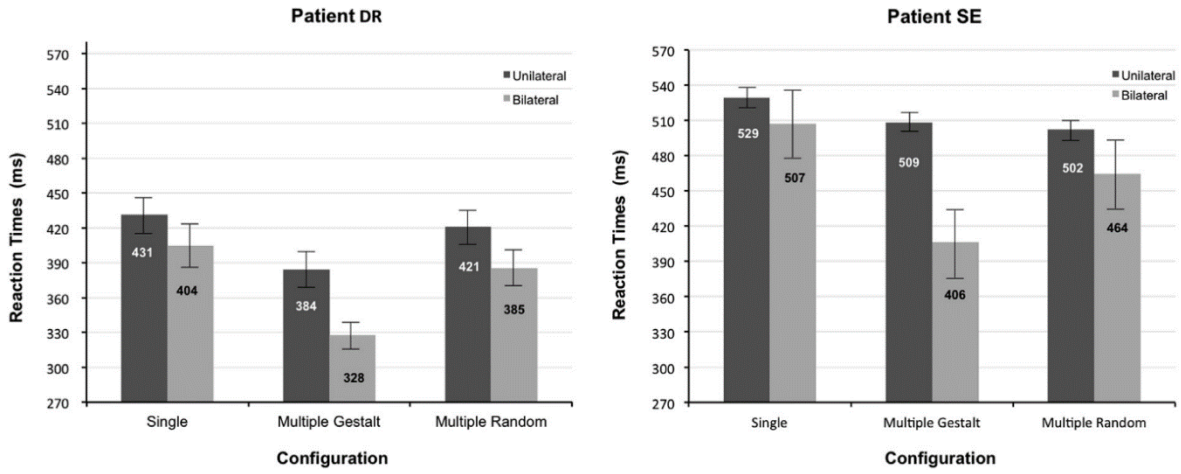

FIGURE 3.4: Reaction Time to Modified RTE Stimulus

Mean RTs for unilateral and bilateral conditions and as a function of the single, gestalt-like and random quadruple configurations for the two patients separately. Error bars represent SEM.

Two additional ANOVAs were computed separately for the unilateral and bilateral presentation conditions, each with the factor Configuration and the usual three levels (Single, Gestalt-like, Random). The aim of this additional analysis was to determine whether the presentation of gestalt-like configurations in the blind hemifield was pivotal for the effect to occur. This is because in unilateral trials the stimuli were projected in the patients' intact hemifield and any effect potentially observed thus reflects sensitivity for consciously seen stimuli. Conversely, in bilateral displays a stimulus was added in the blind hemifield, and any significant difference arising among conditions in this case can only be accounted for by the nature of the unseen stimulus. On unilateral trials there was a significant different between display conditions [$F(2, 54) = 12.47$, $p < 0.0001$]. Post-hoc tests showed that RTs for gestalt-like configurations in the intact hemifield were significantly faster than for single or quadruple random patterns [$t(27) \geq 3.22$ $p \leq 0.002$], while the latter two configurations did not differ from each other ($p = 0.864$). The ANOVA performed on bilateral trials was also highly significant [$F(2, 54) = 22.93$, $p < 0.0001$]. Post-hoc comparisons revealed a significant speeding up of RTs with bilateral gestalt-like patterns with respect to single or bilateral random configurations [$t(27) \geq 6.08$ $p < 0.0001$], while there was no significant difference between single and random patterns ($p = 0.334$).

Patient SE displayed a significant main effect of Presentation Condition [$F(1, 25) = 12.41$, $p = 0.002$] indicative of an RTE. The Configuration factor was also significant [$F(2, 50) = 41.26$, $p < 0.0001$], as well as the Presentation Condition x Configuration interaction [$F(2,50) = 40.48$, $p < 0.0001$]. Post-hoc comparisons on the interaction showed that the RTs for gestalt-like configurations were significantly faster than for either single or random patterns, but only in bilateral trials [$t(25) \geq 7.73$ $p \leq 0.0001$]. This significant interaction made it unnecessary to

compute the additional ANOVAs separately for unilateral and bilateral trials. Indeed, the interaction already indicates unambiguously that, unlike DR who was sensitive to gestalt-like patterns in both her intact hemifield (during unilateral presentation) and blind hemifield (during bilateral presentation), patient SE was differentially responsive to gestalt-like configurations only when the stimuli were projected bilaterally, and hence to his blind hemifield as well.

Additionally, we plotted the cumulative distribution functions (CDFs) of RTs for all six stimulation conditions and for both patients separately. This detailed graphical description enabled us to check whether the bilateral gain observed on mean values occurred throughout the whole RTs distribution. Furthermore, we carried out a Kolmogorov-Smirnov test of the CDFs, which represents a nonparametric version suitable for carrying out a single-subject analysis of Miller's inequality test (Miller, 1982), a mathematical tool to assess whether the RTE is more likely to be related to probability or neural summation. This further analysis is important, because only the latter type of bilateral gain postulates the existence of a neural centre where the visual input from the two hemifields is summed. In fact, observation of RTE on mean values is not *per se* conclusive of neural summation. Separate-activation or race models account for a bilateral gain by simply relying on the fact that the probability of a fast detection increases with the number of stimuli (Raab, 1962; Townsend & Ashby, 1983). Since speed of processing is a random variable, multiple stimuli are on average more likely to yield a faster RT than single stimuli for purely probabilistic reasons. In contrast, coactivation models assume the presence of a functional interaction or neural summation between perceptual channels that result in a reduction of RTs larger than that predicted by probability summation alone (Colonius, 1986; Colonius & Diederich, 2006; Miller, 1982). Note that violation of the inequality test unambiguously supports

neural summation, whereas no conclusion can be reached if the inequality is not violated, owing to the conservative nature of the test (Miller, 1982).

As displayed in Figure 3.5, when gestalt-like configurations were presented, RTs for the bilateral condition were faster than for the unilateral condition throughout the entire distribution and in both patients DR and SE ($p < 0.001$ by Kolmogorov-Smirnov test), thereby providing convincing evidence for an interpretation of the RTE in terms of neural summation. Conversely, the CDFs for unilateral and bilateral presentations when single or random dot configurations were displayed overlapped substantially and crossed, thus failing to support an interpretation of the RTE in terms of neural summation ($p \geq 0.1$ by Kolmogorov-Smirnov test). This latter finding confirms a previous study showing that it is not always possible to attribute the RTE for single dots to neural summation (Turatto *et al.*, 2004), but that its nature depends on stimulus and task factors. Nevertheless, the present results using CDFs indicate that, under identical conditions, neural summation for gestalt-like configurations was significantly more likely to occur than that for single or random dot configurations in both patients.

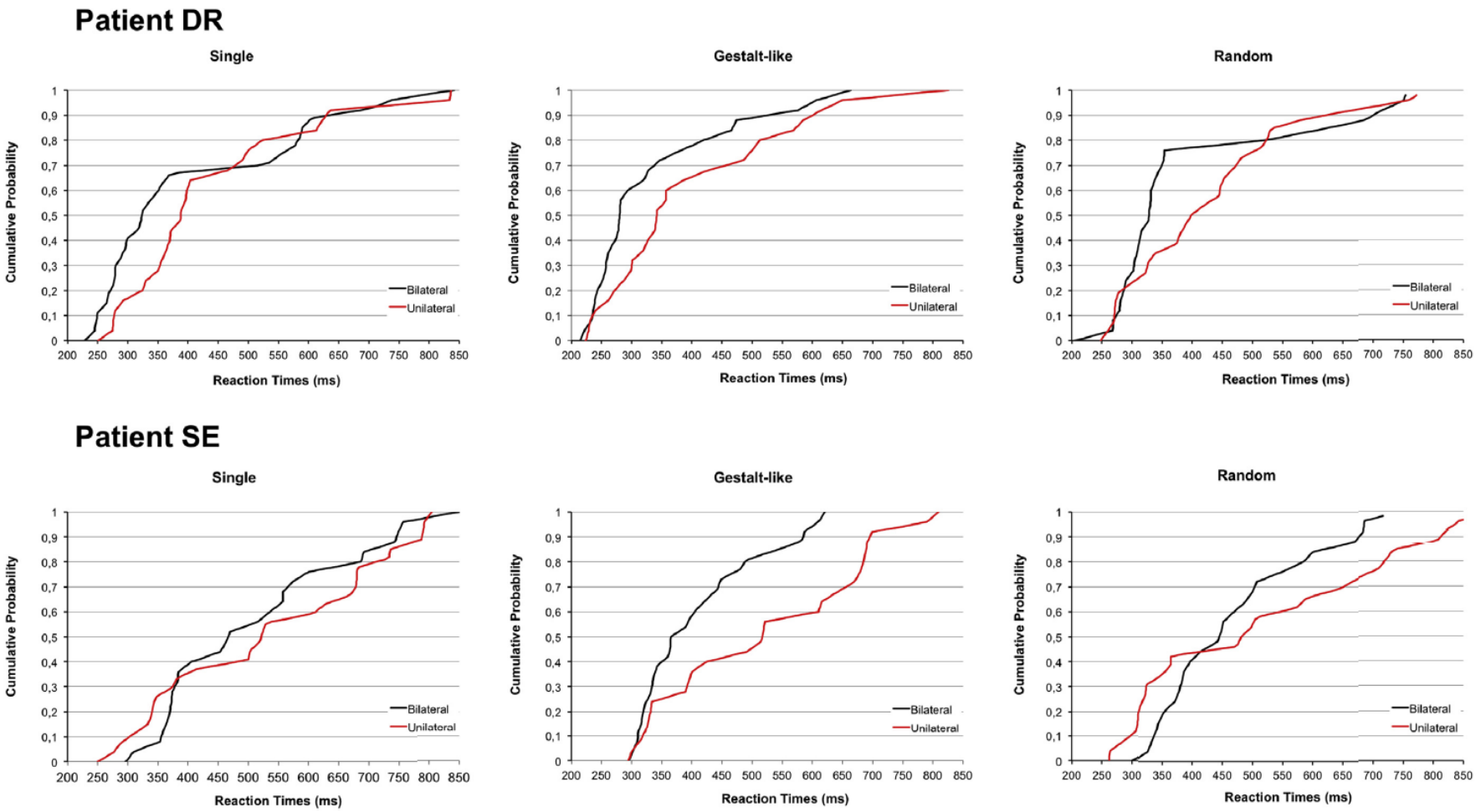

FIGURE 3.5: Cumulative Distribution Functions of the Reaction Times

Cumulative distribution functions (CDF) of RTs for unilateral and bilateral conditions as a function of single, quadruple gestalt-like and random configurations showing a significant bilateral gain throughout the entire distribution only for gestalt-like patterns.

3.6 Discussion

In the present study, we investigated the sensitivity of two blindsight patients with hemispherectomy to stimulus perceptual organization when the display is presented to the blind hemifield. We found that, in addition to the overall RTE often reported in previous studies in hemianopic patients, there was an RTE specific for gestalt-like stimulus configurations but not for spatially random patterns. These findings confirm and extend previous observations in patients with blindsight following lesions restricted to portions of the visual cortex (Celeghin *et al.*, 2015c), and also rule out extant alternative interpretations not related to stimulus configuration. A difference in stimulus familiarity or variability between gestalt-like and random configurations cannot account for the present results, since there were four different patterns counterbalanced for each of the two display types. Moreover, gestalt-like and random patterns were randomly intermingled and presented within the same block of trials, whereas in the previous study by Celeghin *et al.* (2015c), trials with these different configurations were administered in separate blocks always starting with gestalt-like configurations. Hence, this new procedure also rules outu the possibility that the original findings were partly due to fatigue or habituation determining the lack of effect for random patterns. While both patients exhibited similar overall results, they differed in that DR showed a speeding up of RTs also when gestalt-like patterns were presented unilaterally in her intact hemifield, whereas patients SE did not. This is possibly related to individual differences in sensitivity to consciously perceived gestalt-like configurations also present in the healthy population (Wagemans *et al.*, 2012).

Our present study provides the first causal evidence of the sensitivity of the SC for overall stimulus configuration, as witnessed by the facilitation exerted when a structured perceptual organization is translated into motor output. Since the SC in our patients is the only

intact visual structure remaining in the ipsilateral side of the otherwise damaged hemisphere, the contribution of other subcortical structures such as the LGN and the Pulv can be ruled out. This does not necessarily imply that the ipsilesional SC is solely responsible for the observed effect (i.e., does not support sufficiency for the SC for the effect to occur). In fact, visual information might well have been transferred from the (right) SC, ipsilateral to the damaged hemisphere, to the corresponding contralateral SC in the (left) intact side via the inter-collicular commissure or through other inter-hemispheric tracts, and from there to other subcortical structures such as the Pulv as well as extrastriate visual area in the (left) intact hemisphere. Prior Positron Emission Tomography (PET) (Ptito *et al.*, 1999) and fMRI (Bittar *et al.*, 1999) studies on the two patients tested here demonstrated activation in extrastriate visual areas of the (left) intact hemisphere following stimulation of the ipsilateral (left) hemifield, thereby documenting substantial neuronal plasticity and reorganization. Importantly, however, this activation does not seem to originate from cortical reorganization, e.g. owing to the expansion of the visual receptive fields in cortical areas of the intact hemisphere, but rather from the development of aberrant fibre tracts that connect the SC in the (right) damaged hemisphere to cortical areas in the opposite intact hemisphere (Leh *et al.*, 2006a). Hence, the critical point here is that the visual information concerning stimulus configuration must have been initially processed by the right SC ipsilateral to the damaged hemisphere, thus indicating its *necessity* in processing stimulus configuration and in visuo-motor integration, as other alternatives are not possible. In keeping with this notion, the crucial involvement of the SC in the RTE has been convincingly demonstrated behaviourally (Leh *et al.*, 2006b; Tomaiuolo *et al.*, 1997), and with combined behavioural and brain imagining studies in hemispherectomized patients (Leh *et al.*, 2010) as well as in an hemianopic patient with lesion confined to V1 (patient GY) (Tamietto *et al.*, 2010). However, it should be stressed

that all prior investigations used simple stimuli, whereas the present study used different perceptual configurations matched for stimulus intensity and position.

According to a traditional view, it may appear surprising that the SC is able to represent complex stimulus configurations and respond differentially to a gestalt-like perceptual organization. The SC is indeed a phylogenetically ancient visual structure considered to have coarse retinotopy, which receives visual information only from Magnocellular (M) and Koniocellular (K), but not from Parvocellular (P) ganglion cells, and has a relative differential sensitivity to low spatial frequencies (Merigan & Maunsell, 1993; Stone, 1984). However, recent neurophysiological evidence as well as previously somewhat overlooked findings from single-cell recordings in monkeys and rats clearly indicate otherwise. For example, several types of neurons in the superficial (i.e., retino-recipient) layers of macaque monkeys' SC respond very poorly to simple visual stimuli and their activation requires real objects or certain two-dimensional patterns (Rizzolatti *et al.*, 1980). Likewise, neurons in the monkey SC can separately encode faces or face-like patterns (Nguyen *et al.*, 2014). Furthermore, neurons in the most superficial lamina of the rat's SC perform sophisticated analysis of visual information and exhibit complex properties previously thought to be characteristic of visual cortical neurons only (Girman & Lund, 2007). Therefore, the SC seems to participate in early stages of figure-ground segmentation and the combined interaction of M and K channels can enable encoding of complex and high-level properties of the visual input. Moreover, early evidence of visuo-spatial localization and discrimination surviving hemidecortication has been provided by the seminal neuropsychological work of Perenin and Jeannerod (Perenin, 1978; Perenin & Jeannerod, 1978). These studies clearly underline the possibility that some degree of perceptual functions can be carried out by subcortical centers in the absence of the visual cortical mantle. Lastly, one

interesting issue concerns possible inter-hemispheric specialization for global versus local processing, which can contribute to the encoding of gestalt-like configurations. Deficits in global processing following right hemisphere damage (Hugdahl & Davidson, 2004). or due to unbalancing of the complementary functions of the two hemispheres (Negro *et al.*, 2015), have been repeatedly reported. In principle, the preserved sensitivity for gestalt-like configuration observed here despite right hemispherectomy could arise from the SC mirroring lateralized functions thus far reported primarily at the cortical level, or from lack of hemispheric specialization at the level of the SC. In the present study, both patients had undergone right hemispherectomy and it was thus not possible to compare the effects of right versus left hemispherectomy; an issue that awaits further investigation.

In conclusion, the present findings offer a clear demonstration that hemianopic patients as a result of hemispherectomy can be selectively sensitive to complex stimulus configuration within the context of the RTE task. The SC can act as an interface between structured perceptual organization and motor processing, thereby providing an essential contribution to visually guided behavior despite being functionally and anatomically segregated from the geniculo-striate or extrastriate pathway, and therefore entirely outside conscious visual experience. An important avenue for future research is to try to examine other higher-order visual functions that can be carried out in the absence of striate and extrastriate cortical areas and whether such sensitivity can be proficiently exploited to foster rehabilitation of cortical blindness (Chokron *et al.*, 2008; Perez & Chokron, 2014).

3.7 Acknowledgements

L.G. and A.P. are supported by the Natural Science and Engineering Research Council of Canada (NSERC: 37254-2011). M.T and A.C. are supported by a "Vidi" grant from the Netherlands Organization for Scientific Research (NOW) (grant 452-11-015), and by a FIRB – Futuro in Ricerca 2012 – grant from the Italian Ministry of Education University and Research (MIUR) (grant RBFR12F0BD). C.A.M is supported by a European Research Council (ERC) (grant 339939) Advanced Grant "Perceptual Awareness" under the European Union's Seventh Framework Programme.

Thanks to Matteo Diano for his help in the preparation of Fig. 1.

Chapter 4: Does the remaining visual cortex of a hemispherectomy subject show changes in retinotopic organization?

4.1 Prelude

In the second study entitled "*Functional reorganization of population receptive fields in a hemispherectomy patient with blindsight"* I investigated the retinotopic organization of the intact visual cortex of one hemispherectomy subject. It has been well established that the visual cortex is organized retinotopically to represent the visual field in multiple maps (Engel *et al.*, 1994; Engel *et al.*, 1997; Sereno *et al.*, 1995) with hierarchical organization that proceeds from V1 to parallel dorsal and ventral processing streams (Milner & Goodale, 1995; Ungerleider & Mishkin, 1982), and fMRI has proven to be an excellent non-invasive tool to characterize these maps with adequate spatial resolution. There is a long history in visual research of studying the spatial organization of retinotopic maps after direct damage (Horton & Hoyt, 1991; Inouye, 1909; Lister & Holmes, 1916; Spalding, 1952), and an fMRI study of the visual cortex in the presence of a central scotoma showed a loss of activation in the cortical areas representing the site of the atrophic lesion, demonstrating that retinotopic mapping can be successfully performed in patients with geographic atrophy (Sunness *et al.*, 2004).

In this study, I used population receptive field mapping which is a relatively new retinotopic mapping technique that not only allows us to delineate the visual areas using polar angle and eccentricity mapping, but also provides additional information concerning their response properties (Dumoulin & Wandell, 2008). This has allowed us to first examine the typical arrangement of the visual field maps and determine if they are preserved within the intact visual cortex of the hemispherectomy subject, and second to investigate the response properties of the early visual areas (V1, V2, V3), specifically the receptive field size within each voxel in these areas and how they vary as a function of eccentricity.

Functional reorganization of population receptive fields in a hemispherectomy patient with blindsight

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Published: **Neuropsychologia** ***(2019), Vol. 128, pp. 198-203***

4.2 Abstract

Blindsight refers to the ability of some patients with destruction of the primary visual cortex (V1) to respond to stimuli presented in their clinically blind visual field despite lack of visual awareness. Here we tested a rare and well-known patient with blindsight following hemispherectomy, DR, who has had the entire cortex in the right hemisphere removed, and in whom the right superior colliculus is the only post-chiasmatic visual structure remaining intact. Compared to more traditional cases of blindsight after damage confined to V1, the study of blindsight in hemispherectomy has offered the invaluable opportunity to examine directly two outstanding questions: the contribution of the intact hemisphere to visual processing without awareness, and the nature of plastic and compensatory changes in these remaining contralesional visual areas. Population receptive field (pRF) mapping was used to define retinotopic maps, delineate the boundaries between the visual areas, examine changes in the sizes of receptive field centres within each visual area, and their variability as a function of eccentricity. Aside from the dorsal visual areas showing blurred borders between V2d and V3d, not otherwise detected with perimetric mapping, the retinotopic maps of DR did not differ substantially from those of three matched healthy controls. Interestingly, those dorsal compartments showed a significant increase in the RF sizes toward values typical of higher-order processing cortices, while no differences were observed in the corresponding ventral visual areas. Findings showed that whereas receptive field sizes at foveal and parafoveal eccentricities (≤ 4°) were not measurably altered, the pRF size increased by ~ 270% at 4-6° of eccentricity, and the size difference reached ~ 300% between 8° to 10°. We interpret these findings to suggest that an increase in pRF sizes could be indicative of cerebral plasticity involving the retinotopic reorganization of the dorsal visual areas.

4.3 Introduction

Originally regarded as rather unchanging, the mature brain is now credited with substantial plasticity after injury. One major challenge in uncovering the brain's ability to undergo compensatory changes in the visual domain rests with the characterization of the functions of secondary pathways, whose contribution can be overshadowed by activity driven from the dominant input during physiological conditions. The human visual system is composed of an intricate network of areas implementing parallel functions with multiple inputs from different cortical and subcortical retino-recipient structures. Such organization makes it unique for studying the interaction of plasticity and stability in the aftermath of a lesion.

It has been more than a century ago that (Inouye, 1909) and (Holmes, 1918) independently identified that the spatial arrangement of an image in the retina is maintained in the primary visual cortex (V1). In this way, a lesion in a part of V1 determines clinical blindness in the corresponding (contralateral) part of the visual field. In the following decades, three major discoveries directly relevant for the present study followed. First, the existence of multiple maps that represent the visual field has been reported in the visual cortex of many species, including humans (Daniel & Whitteridge, 1961; Holmes, 1945; Horton & Hoyt, 1991; Van Essen *et al.*, 1984). In this context, functional magnetic resonance imaging (fMRI) has been determinant in characterizing with a non-invasive and spatially-resolved technique the location and properties of these multiple maps (Engel *et al.*, 1994; Engel *et al.*, 1997; Sereno *et al.*, 1995). Second, a hierarchical organization of the visual cortex, starting from V1 and proceeding along parallel dorsal and ventral processing streams, has been clearly documented (Milner & Goodale, 1995; Ungerleider & Mishkin, 1982). The division of labour along the cortical hierarchy thus offers a framework for interpreting the arrangement and functional meaning of multiple retinotopic maps.

Third, it has been shown that residual visual functions can be retained after damage to V1, despite the patient's denial of conscious perception (Pöppel *et al.*, 1973; Weiskrantz *et al.*, 1974). The initial discovery led Weiskrantz to coin the term 'blindsight' to denote this counterintuitive phenomenon, which remains of the utmost importance for studying compensatory changes and neural underpinnings of visual awareness.

Blindsight abilities have been documented in different patients, under a variety of task demands, and for a range of visual attributes, including detection and localization of targets (Blythe *et al.*, 1987; Zihl & von Cramon, 1980), motion discrimination (Barbur *et al.*, 1993; Hervais-Adelman *et al.*, 2015), line orientation (Weiskrantz *et al.*, 1974), visuo-motor transformation (Celeghin *et al.*, 2017), wavelength sensitivity (Stoerig, 1987), category discrimination (Van den Stock *et al.*, 2014) and emotion processing (Burra *et al.*, 2017; Celeghin *et al.*, 2015b; de Gelder *et al.*, 1999). Although the phenomenon is clearly established and survived possible methodological drawbacks in initial investigations, its neural bases remain disputed. In fact, several studies reported plastic changes in areas neighbouring V1 damage, as well as the presence of fragments or islands of functionally responsive striate cortex within the damaged V1 (Campion & Latto, 1985; Fendrich *et al.*, 1992). Accordingly, these authors have attributed blindsight functions to remaining, albeit altered, responses within V1 and therefore to functions and structures belonging to the canonical geniculo-striate pathway. Conversely, the traditional interpretation of blindsight and a wealth of successive studies advocate the role of extra-geniculostriate pathways bypassing V1 (Danckert & Rossetti, 2005; Perenin & Jeannerod, 1978; Rafal *et al.*, 1990). These V1-independent pathways include subcortical structures such as the superior colliculus or the pulvinar and their cortical targets in extrastriate visual areas (Leh *et al.*, 2006a; Leh *et al.*, 2006b; Tamietto & Morrone, 2016).

In addition to patients with circumscribed lesions to V1, blindsight has also been demonstrated in patients who have undergone hemispherectomy (Leh *et al.*, 2006a; Leh *et al.*, 2006b; Ptito *et al.*, 2001). Studying blindsight in hemispherectomy patients thus offers a particularly informative model to address these contentions and tease apart alternative interpretations on preserved visual functions. In such patients, the entire cortex in one hemisphere has been removed or disconnected surgically from the rest of the brain. Functionally, among other consequences, this leaves the patient with blindness in the contralateral visual field without macular sparing. Anatomically, the only retinal pathway remaining in the hemispherectomized side is the one coursing to the ipsilateral superior colliculus, and visual input can then cross the vertical midline through the inter-tectal commissure and project to extrastriate areas in the intact hemisphere via the pulvinar (Leh *et al.*, 2006a; Leh *et al.*, 2006b; Ptito *et al.*, 2001). Blindsight abilities in hemispherectomy patients have been shown especially, but not exclusively, in tasks requiring visuo-motor integration and spatial summation (Tomaiuolo *et al.*, 1997), properties processed mainly by the dorsal stream. Moreover previous neuroimaging studies in patients with blindsight and hemispherectomy lend support for a prominent role of the intact hemisphere, in conjunction with ipsilesional subcortical structures, in supporting residual functions (Bittar *et al.*, 1999; Celeghin *et al.*, 2017; Leh *et al.*, 2006b; Ptito *et al.*, 2001). In fact, fMRI activity has been observed in extrastriate areas of the intact hemisphere contingent upon stimulation in the blind ipsilateral visual field (Celeghin *et al.*, 2017; Leh *et al.*, 2010). Also, tractography reported enhanced and/or new fibre tracts that connect the superior colliculus in both sides of the brain with cortical areas in the remaining hemisphere (Leh *et al.*, 2006a).

Yet two pivotal questions concerning the nature and properties of neural reorganization sustaining blindsight in hemispherectomy remain unanswered. First, is the typical arrangement

of multiple visual maps that segment different visual areas (e.g., V1, V2, V3) preserved in the remaining hemisphere? Second, are the response properties within these areas altered or reorganized to compensate for the absence of one hemisphere? To our knowledge, no previous study addressed directly these questions. We therefore set about to investigate the spatial organization and response properties of early cortical visual areas in patient DR, whose blindsight functions following hemispherectomy have been repeatedly documented in different behavioural and neuroimaging studies (Bittar *et al.*, 1999; Georgy *et al.*, 2016; Leh *et al.*, 2006a; Leh *et al.*, 2006b; Ptito *et al.*, 2001; Ptito & Leh, 2007; Tomaiuolo *et al.*, 1997). We computed a model of population receptive field (pRF) in response to moving and flickering checkerboard bars. The pRF derives from the spatial and temporal dynamics of fMRI signal in response to visual stimuli a voxel-wise estimate of the visual field maps as well as other neuronal population properties, such as receptive field size (Dumoulin & Wandell, 2008). This forward-encoding approach enables detailed analysis of multiple retinotopic maps in visually responsive areas from a single data set, whereas classic phase-encoding methods require separate datasets for polar angle and eccentricity measures. Moreover, pRF provides information about the RF size within each voxel in different areas and its variation as a function of eccentricity.

4.4 Materials and Methods

4.4.1 Participants

Patient DR is a right-handed woman (43 years old at the time of testing) with a left hemiparesis since birth that began suffering from epileptic seizures at the age of 5 years. Prior to surgery, CT and MRI scans of the brain revealed severe atrophy of the right cerebral hemisphere and EEG studies showed epileptiform activity over the right frontal-parietal-temporal regions. Cognitive testing carried out at the time indicated borderline intelligence scores: full scale IQ of 77, verbal IQ of 92, and performance IQ of 65. At the age of 17 years, she underwent a functional hemispherectomy which consisted of removing the temporal lobe including the mesial structures and a frontal-parietal corticectomy. The remaining cortical regions were left *in situ*, but were disconnected from the rest of the brain by sectioning the white matter anteriorly and laterally, as well as posteriorly and laterally along the falx (Figure 4.1a). Subsequent neuropathological investigation revealed an inflammatory process with diffuse gliosis characteristic of Rasmussen encephalitis. Follow-up assessments indicated that her level of intellectual function has increased to the low average range: full scale IQ of 83, verbal IQ of 87, and performance IQ of 83. The presence of a complete contralateral hemianopia without macular sparing was confirmed by computerized perimetry (Allergan, Humphrey; Figure 4.1b), and her visual acuity was 20/25. DR's excellent fixation to target has been adequately reported in many publications, including most recently in Georgy et al. 2016.

Three healthy subjects served as controls (males, mean age: 32) (see Senden *et al.* (2014a) for details). The entire data set, including functional and anatomical MR measurements, and stimulus protocols are available at datadryad.org (doi: 10.5061/dryad.mb8h6).

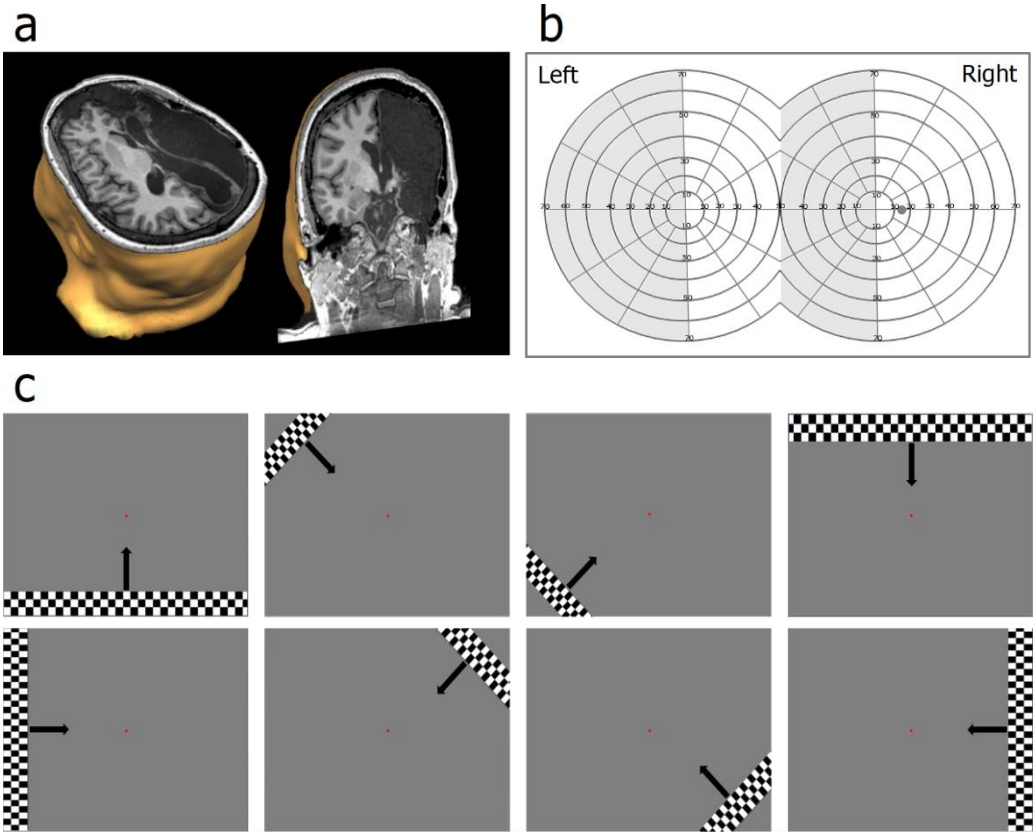

FIGURE 4.1: Patient DR T1-weighted MRI, Perimetry, and Stimulus

(a) Transverse (left) and coronal (right) 3-D anatomical reconstruction of patient DR's brain; (b) Perimetric map of DR's visual field, light grey indicates the left clinically blind field, dark grey circle indicates the blind spot in right visual field; (c) Stimuli samples, their spatial orientation and movement direction.

4.4.2 Visual Stimulus and Apparatus

The visual stimulus was adapted from Dumoulin & Wandell (2008) and consisted of a flickering black/white checkerboard bar (7.5 Hz; width = 1.5°) against a grey background (RGB=87, 87, 87). Patient DR was tested monocularly with her dominant, contralesional left eye while a patch covered her right eye. This was necessary because the non-dominant eye deviated from the gaze direction of the dominant eye in a way that could affect proper fixation and the lateralization of the stimulus, and hence interfere with the proper assessment of the resulting retinotopic representation. The subject was asked to fixate a red central circle and monitored online by an experimenter, while we measured responses to drifting bar apertures at various orientations; the bar moved in sequential steps in either a vertical, horizontal, or diagonal fashion (8 directions total) at each image volume acquisition (400 frames; Figure 4.1c). Note that the bars are not "phase-encoded" stimuli; there is no repetition of the stimulus because the bars change orientation and motion direction within a scan. The open source stimulus presentation tool StimulGL (v 2.1.0.0)[1] was used to present the visual stimuli to the subject. A Dell Inspiron 15 (5000series) computer with a screen resolution of 1366x768 pixels was used to present the stimuli at a resolution of 768x768 pixels through an InFocus LP840 Projector. The visual stimuli were first projected on a screen behind the bore of the magnet (120cm from projector screen to mirror) and then reflected by a mirror above the head coil (12 cm from the mirror the subject's eye). Overall, the projected stimuli covered 19° visual angle horizontally, and 18.5° vertically.

[1] https://sites.google.com/site/stimulgl/

4.4.3 MRI Acquisition Protocol

Data was acquired in the Brain Imaging Centre on of the Montreal Neurological Institute with a 3T Siemens Magnetom Tim Trio scanner equipped with a 32-channel head coil. Anatomical scans were collected with a T1-weighted MPRAGE imaging sequence (Repetition time [TR] = 2300 ms; Echo time [TE] = 2.98 ms; Flip Angle [FA] = 9°; Field of View [FOV] = 256 x 256 mm^2, 176 sagittal slices, 1 mm isotropic resolution). Functional scans were acquired using an echo planar sequence (TR = 2330 ms; TE = 30 ms; FA= 76°; FOV= 256 x 256 mm^2, 26 slices, 2 mm isotropic resolution). This project and all procedures employed therein were approved by the McGill University Health Centre (MUHC) Research Ethics Board (NEUPSY Panel; NEU-11-026).

4.4.4 Data Preprocessing & Analysis

Anatomical and functional scans of DR and the control subjects underwent basic preprocessing steps including 3D motion correction which spatially aligns all volumes to the subject's first volume using rigid body transformations in order to ensure minimal translation and rotation, temporal filtering which included linear trend removal, and a segmentation of the grey/white matter boundaries with manual checking. This was completed using standard BrainVoyager QX 20.6 processing parameters (Brain Innovation, Maastricht, the Netherlands, (Goebel *et al.*, 2006) and Matlab (The Mathworks, Natick, MA, U.S.A.) with the NeuroElf toolbox v0.9c (www.neuroelf.net; maintained and developed by Jochen Weber, Columbia University) as well as custom code. All interpolations were done using the sinc function in order to minimize any blurring or smoothing of the signal. pRF analysis was carried out using the procedure outlined in detail in Senden *et al.* (2014b) and Dumoulin & Wandell (2008) and implemented in BrainVoyager QX.

4.5 Results

4.5.1 Retinotopic maps

The retinotopic representation of the intact visual areas in DR's left hemisphere appears substantially unchanged and comparable to that of healthy controls. In fact, the boundaries between them reflect polar angle reversals in the expected locations. Similar to those found in healthy controls, DR's visual areas appear to have retained, albeit coarsely, their retinotopic maps with the dorsal visual areas in the left hemisphere (above the calcarine sulcus) corresponding to the contralateral (right) lower visual field quadrant, and the ventral visual areas in the left hemisphere matching the right upper visual field quadrant (Figure 4.2a). On this basis, it was possible to reveal the three maps near the calcarine sulcus, corresponding to V1 and to the additional maps V2 and V3 that encircle V1, these latter further subdivided into their dorsal and ventral components (V2d, V3d, V2v, V3v). Similarly, the pRF eccentricity maps showed that, as expected, the foveal representation was in the occipital pole while increasingly anterior locations corresponded gradually to more peripheral stimuli, with the maps showing a smooth and continuous phase progression (Figure 4.2b). These results show that no large-scale retinotopic distortions in the early visual areas of DR's remaining hemisphere occurred, although the retinotopic organization of the dorsal visual areas seems less clearly defined compared to that of the ventral visual areas. This lack of definition in the dorsal visual areas did not lead to any measurable visual deficits in the ventral visual field, at least as assessed with standard perimetry testing. However, subtle reorganization in the retinotopic structure of the intact hemisphere cannot be excluded and deserved a quantitative evaluation of the receptive field properties, as reported below.

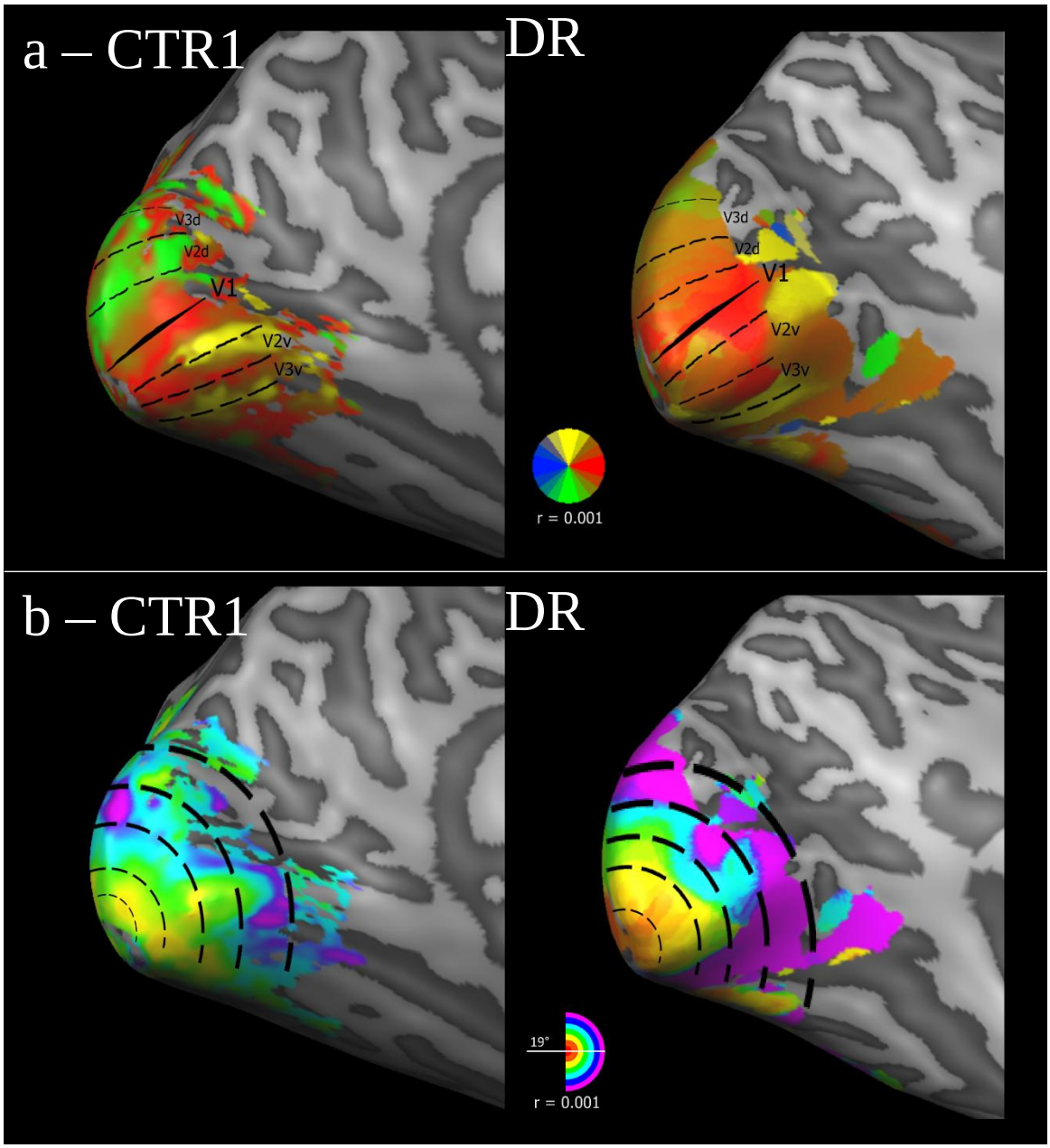

FIGURE 4.2: Retinotopic Mapping

Retinotopic maps of one representative healthy control (CTR1) versus patient DR. (a) Polar angle maps showing delineated visual areas V1, V2v, V3v, V2d, V3d; (b) Eccentricity maps.

4.5.2 pRF size

Quantitative pRF analysis was used in order to examine the differences between pRF centre sizes in DR's spared left hemisphere visual areas and those observed in the corresponding maps of the left hemisphere in healthy controls. Figure 4.3 displays the mean pRF size of all delineated striate and peri-striate visual areas for DR compared to three healthy controls (averaged across subjects). The pRF size in V1 of DR was comparable to that of controls, as well as size in ventral areas (V1d: $t(2) = 3.48$, $p = 0.07$; V1v: $t(2) = 2.34$, $p = 0.14$; V2v: $t(2) = 3.19$, $p = 0.09$; V3v: $t(2) = 1.73$, $p = 0.23$). However, we found that pRF size in DR shifted significantly toward larger values in V2d and V3d compared to controls (V2d: $t(2) = 5.77$, $p = 0.029$; V3d: $t(2) = 4.65$, $p = 0.043$). This increase may also partially explain the rather coarse delimitation within dorsal areas described above.

4.5.3 pRF sizes with increasing eccentricity

In order to examine whether the pRF sizes depend on eccentricity and distance from the occipital pole, we created regions of interest derived from the eccentricity maps from 0° to 10° at increasing intervals of 2° and plotted mean pRF size versus eccentricity for DR and control group, separately. This fine-grained distinction of the data at 2° resolution is adept to distinguish amidst pRF sizes at foveal (0°-2°), parafoveal (2°-4°), perifoveal (4°-6°) and extrafoveal (6°-10°) eccentricities. As expected, controls exhibited a moderate increase of pRF size with increasing eccentricities. In patient DR, mean pRF size for voxels between 0° to 4° of eccentricity was not statistically different from that of controls (0°-2°: $t(2) = 0.67$, $p = 0.57$; 2°-4°: $t(2) = 1.18$, $p = 0.36$). Conversely, at larger eccentricities (> 4°) the mean pRF size in DR was significantly expanded compared to controls (4°-6°: $t(2) = 3.78$, $p = 0.063$; 6°-8°: $t(2) = 6.08$, $p = 0.026$; 8°-10°: $t(2) = 5.89$, $p = 0.028$) (Figure 4.4).

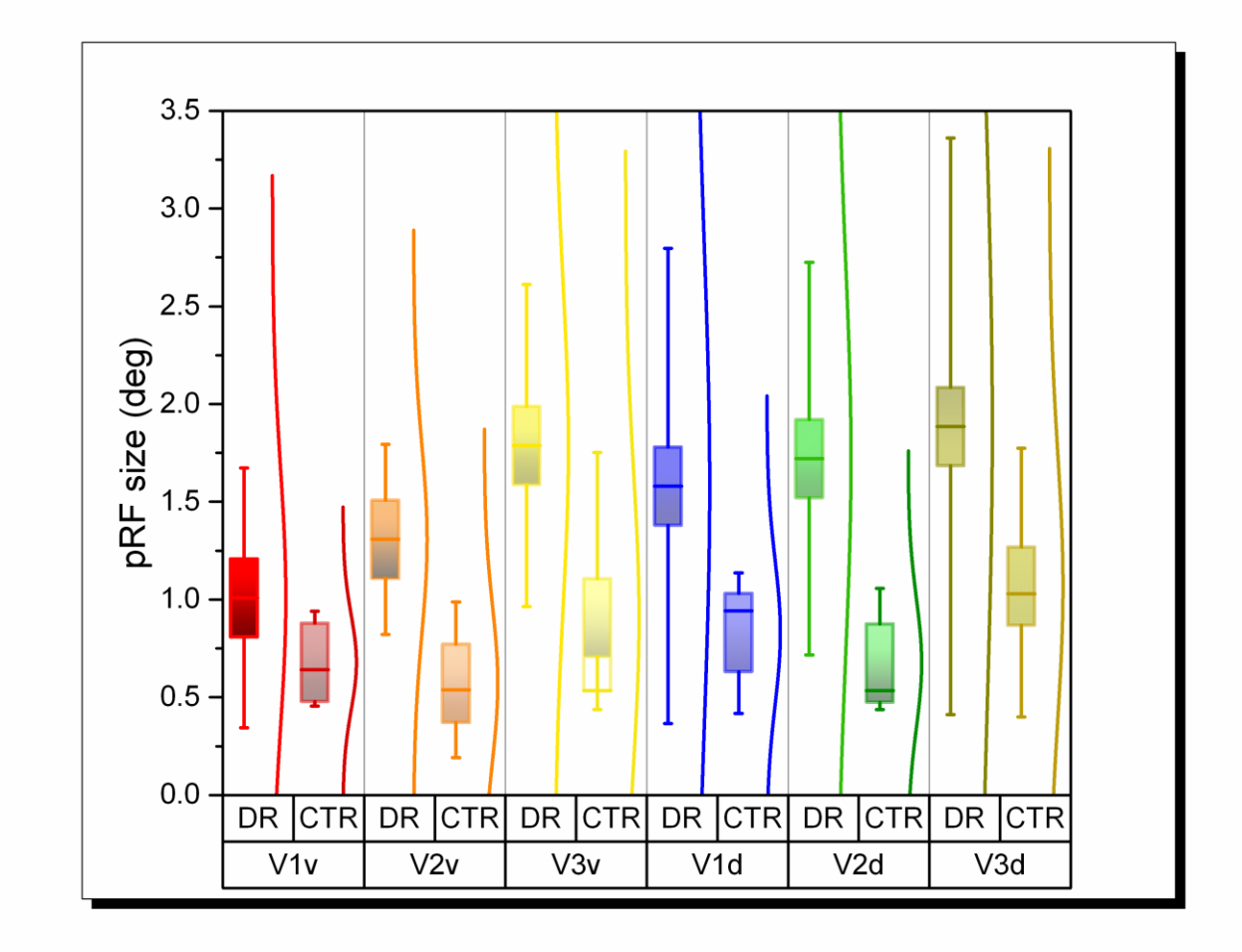

FIGURE 4.3: pRF Size in Visual Areas

Comparison of pRF sizes in all delineated visual areas between three averaged healthy controls (CTR) and patient DR. The central horizontal line within each box represents the mean value, the upper and lower margins of the box show ± 0.2 from the mean, the whiskers display min and max values, and, finally, the curve at the right of the box shows the distribution of each data point.

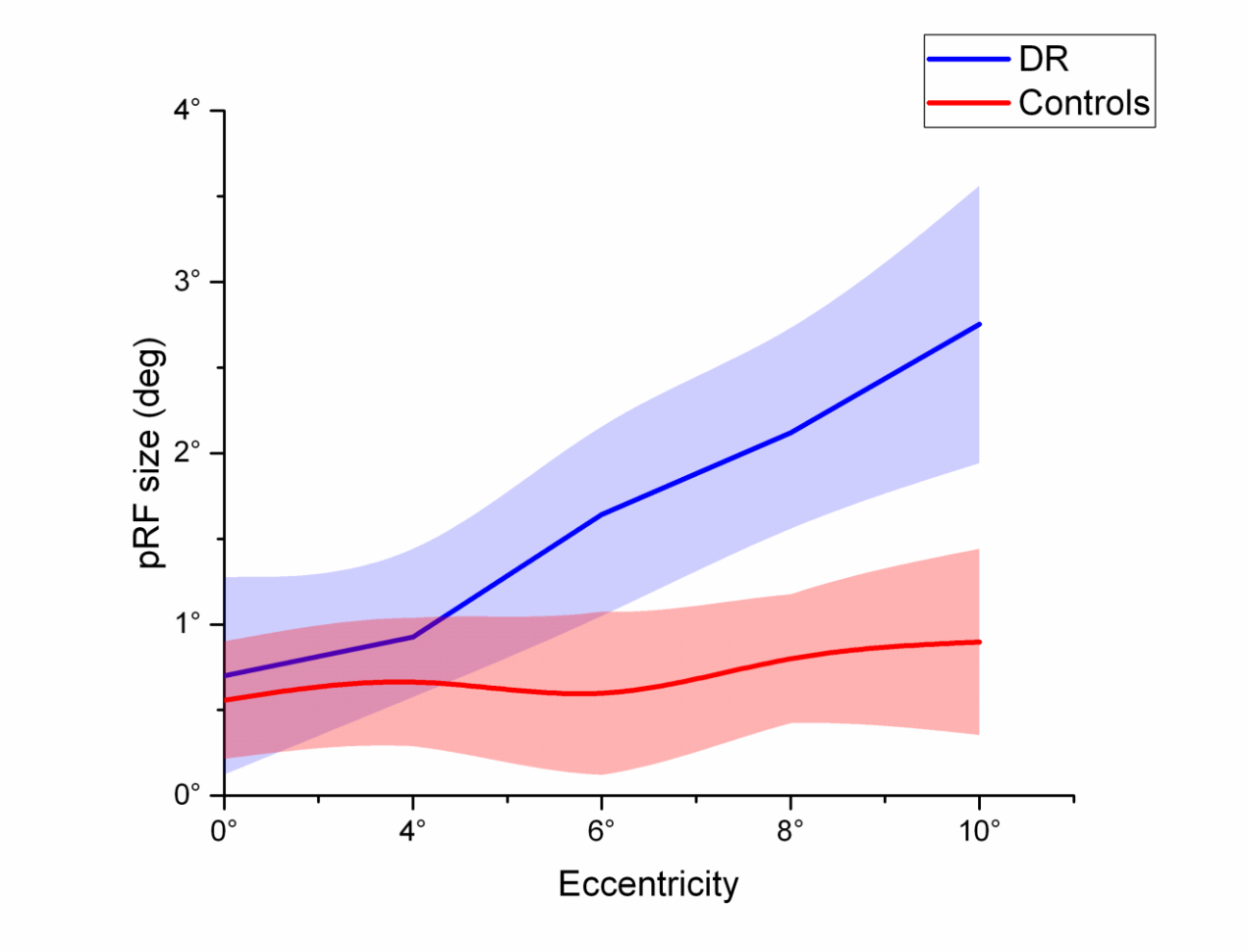

FIGURE 4.4: pRF Size with Increasing Eccentricity

Comparison of pRF sizes as a function of increasing eccentricity for three healthy controls (averaged) and patient DR. Solid lines indicate mean values and shadows indicate standard deviations.

4.6 Discussion

In the present study, we used pRF analysis in order to examine the retinotopic properties of early visual areas in the remaining hemisphere of one well-known patient with hemianopia and blindsight following complete hemispherectomy. We therefore derived retinotopic maps for dorsal and ventral components of V1, V2 and V3, and measured possible changes in the size and position scatter of individual receptive fields within a voxel, as a function of the different areas and of eccentricity. There were several noteworthy findings.

First, retinotopic organization in striate and peri-striate areas was substantially preserved in DR. Borders between V1 and V2, and between V2 and V3 remained reasonably stable, and the retinotopic maps showed a standard progression of phase. These findings indicate that no large-scale distortions of the retinotopic maps under investigation occurred. Accordingly, vision in the contralateral seeing field appears normal in DR, based on perimetry results and standard clinical tests. Previous findings do indeed show a gross retinotopic pattern of resting-state connectivity across V1, V2 and V3 in early blind and anophthalmic individuals (Bock *et al.*, 2015). However, we observed fuzzier borders in the delineation of dorsal compartments, primarily between V2d/V3d, which suggest possible plastic changes at finer levels of retinotopic organization. Second, by further investigating the receptive field properties within the delineated visual maps, we could find evidence of changes in the receptive field sizes of voxels in areas V2d and V3d. The increase is remarkable and of the magnitude of ~ 260% in V2d, and of ~270% in V3d. This selectivity in pRF size remodelling was further corroborated by the comparison as a function of eccentricity. In fact, whereas at foveal and parafoveal eccentricities ($\leq 4°$) receptive field size was not measurably altered, the pRF size increased of ~ 270% at 4-6° of eccentricity, and the size difference reached ~ 300% between 8° to 10°.

The present findings shed new light on the possible mechanisms of neuronal reorganization that compensate for early loss of vision due to hemispherectomy, as well as on pathways sustaining blindsight. Investigations of pRF in patients and animal models with a scotoma following V1 lesion have reported an expansion of receptive field size in the area surrounding the lesion (Eysel & Schweigart, 1999; Papanikolaou *et al.*, 2014). More interestingly for the present case, pRF size in the intact hemisphere also increased compared to controls and for eccentricities between 6° and 10°. Multiple mechanisms govern neuronal reorganization after brain damage, involving a complex interplay of factors that depend on the time and place of the lesion and the maturation status. The relative increase in pRF size observed in the intact hemisphere has been previously attributed to loss of input from interhemispheric connections (Henriksson *et al.*, 2007; Ptito *et al.*, 1999; Raninen *et al.*, 2007). There are also suggestions that subcortical input from superior colliculus and pulvinar may contribute to reorganize cortical maps (Ptito *et al.*, 2001; Ptito & Leh, 2007).

This evidence converges with previous observations in patients with blindsight along three different lines, and pleads in favour of a central role of the intact hemisphere in sustaining residual visual processing in the otherwise blind hemifield (Celeghin *et al.*, 2015a; Celeghin *et al.*, 2017). Neuroimaging data in the same patient have shown that stimulation in the blind field activates the ipsilateral remaining hemisphere at locations closely comparable to V2d and V3d where we found increased pRF size (Bittar *et al.*, 1999). Tractography studies have similarly identified enhanced tracts from the superior colliculus in the damaged side targeting, among others, striate and extrastriate areas in the dorsal stream of the remaining hemisphere (Leh *et al.*, 2006a). Behaviourally, visuo-motor blindsight has been clearly established in these patients (Georgy *et al.*, 2016; Tomaiuolo *et al.*, 1997) and linked to the contribution of the superior

colliculus and its cortical projections via the pulvinar (Leh *et al.*, 2008). There is also initial evidence from combined behavioural, neuroimaging and tractography studies on the critical role of the intact hemisphere in blindsight following damage restricted to V1 (Celeghin *et al.*, 2015a; Celeghin *et al.*, 2017).

It is thus tempting to interpret the changes in pRF as biomarkers of neuronal reorganization in the early visual areas of the intact hemisphere, whose functional role is linked to the presence of blindsight in the blind hemifield. This mechanism seems to operate by inducing an expansion of receptive field size in early dorsal visual areas, perhaps under mediation of subcortical input from the superior colliculus. A fundamental question for understanding principles of neuronal reorganization concerns whether the intact structures change their original response properties to take over those of damaged areas or restore their original tuning properties. Our results suggest that there is a progressive expansion of pRF size in dorsal areas at increasing eccentricities, which might help to process nonconsciously incoming information from the ipsilateral blind visual field. The present observations expand our knowledge on the neurofunctional bases of blindsight in hemispherectomy and can hopefully set a framework for further investigations on compensatory changes following cortical blindness, which may inform evidence-based clinical intervention targeting spared structures.

4.7 Acknowledgments

This work was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC: 37354-2011). L.G. is supported by a Canadian Institutes of Health Research doctoral research award (CIHR: 380343-2017). M.T. is supported by an ERC Consolidator Grant 2017 (LIGHTUP, project # 772953) and by a PRIN 2015 grant (2015NA4S55) from the Italian Ministry of Education University and Research (MIUR).

Chapter 5: Does the visual cortex in the intact hemisphere of blindsight subjects show changes in cortical thickness?

5.1 Prelude

In the third study entitled "*Changes in peri-calcarine cortical thickness in blindsight"* I wished to investigate whether the functional plasticity seen in the visual cortex of the intact hemisphere in blindsight patients was associated with anatomical changes. It has been well documented in cases of blindsight that the intact visual cortex plays an important role in maintaining residual vision by receiving visual information from the ipsilesional superior colliculus through inter-tectal connections (Leh *et al.,* 2006b), and more recent research has shown that functional compensation in blindsight occurs through the contribution of the intact hemisphere when performing visually guided responses (Celeghin *et al.*, 2017). Indeed, fMRI studies have shown that presentation of visual stimuli in the blind hemifield yields activity in the ipsilateral visual areas of the intact hemifield (Bittar *et al.,* 1999), and the study outlined in Chapter 4 clearly demonstrates a functional reorganization in the receptive field properties in the dorsal visual areas of the intact hemisphere (Georgy *et al.,* 2018).

In this study, I examined anatomical changes in the intact hemisphere of one patient with a complete right hemispherectomy, one patient with a partial right hemispherectomy, and one patient with a localized left V1 lesion, all three cases with well documented blindsight. Due to the large body of evidence supporting the role of the intact visual cortex in the functional compensation observed in the visuo-motor responses in blindsight, I performed a cortical thickness analysis restricted spatially to the visual areas in the intact hemisphere in order to determine if there were any measurable and consistent differences in grey matter thickness within these areas that persisted in the patients despite the large between-subject differences in the size and nature of their lesion.

Changes in peri-calcarine cortical thickness in blindsight

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Manuscript in preparation for submission

5.2 Abstract

Blindsight is the ability of subjects with primary visual cortex (V1) damage to process information in their clinically blind visual field in the absence of conscious awareness. In addition to patients with localised V1 lesions, a subset of subjects exhibiting this phenomenon have had a cerebral hemisphere removed or disconnected from the rest of the brain for the treatment of drug-resistant epilepsy (hemispherectomy). Research into the underlying neural substrates of blindsight has long implicated the intact visual cortex in maintaining residual vision and supporting visuo-guided responses to stimuli presented ipsilaterally within the blind visual field while operating outside the geniculo-striate pathway (Celeghin *et al.*, 2017; Leh *et al.*, 2006b). Indeed, functional magnetic resonance imaging (fMRI) studies have shown that presentation of visual stimuli in the blind hemifield yields activity in the ipsilateral visual areas of the intact hemifield (Bittar *et al.*, 1999), and a recent study clearly demonstrates a functional reorganization in the receptive field properties in the dorsal visual areas of the intact hemisphere (Georgy *et al.*, 2018) thereby supporting the compensatory role of the intact hemisphere in non-conscious visual functions. Here we used cortical thickness analysis to examine anatomical differences in the visual cortex of the intact hemisphere of three patients with varying degree of cortical damage: two subjects with a right hemispherectomy, one complete and one partial, as well as one patient with damage confined to the left V1, all of which have well documented blindsight. T1-weighted MRI data were obtained for the patients while control data were chosen from publicly available NKI-dataset to match closely the acquisition parameters of our blindsight cases. Our results show significant increases in cortical thickness in the visual cortex of all blindsight subjects compared to healthy controls, irrespective of age-onset, aetiology and extent of the damage. Our findings add to accumulating evidence from behavioral, functional imaging, and tractography studies of cerebral compensation and reorganization.

5.3 Introduction

Despite damage to their primary visual cortex (V1), which leads to clinical blindness in the corresponding portion of the visual field, some patients exhibit the ability to process and respond to visual stimuli presented in their cortically blind visual field independently of conscious awareness (Pöppel *et al.*, 1973). This phenomenon was labeled 'blindsight' by Weiskrantz (1974) and research into these functions uncovered the patients' abilities to detect and localize stationary and moving stimuli (Blythe *et al.*, 1987; Stoerig *et al.*, 1985; Zihl & von Cramon, 1980), to discriminate stimuli based on motion (Barbur *et al.*, 1993; Blythe *et al.*, 1986; Hervais-Adelman *et al.*, 2015; Morland *et al.*, 1999), line orientation (Weiskrantz *et al.*, 1974), colour (Danckert *et al.*, 1998; Morland *et al.*, 1999), form (Danckert *et al.*, 1998; Marcel, 1998), frequency (Magnussen & Mathiesen 1989), wavelength (Kentridge *et al.*, 2007; Stoerig, 1987; Stoerig & Cowey, 1989; Stoerig & Cowey, 1992), categories (Van den Stock *et al.*, 2014), as well as visuo-motor transformation (Celeghin *et al.*, 2017), semantic priming (Marcel, 1998), emotional processing (Burra *et al.*, 2017; de Gelder *et al.*, 1999; Pegna *et al.*, 2005; Van den Stock *et al.*, 2011), and navigational skills (de Gelder *et al.*, 2008). Further examination into blindsight has also uncovered evidence of an interaction between stimuli presented simultaneously to the blind and intact visual hemifields (Celeghin *et al.*, 2015c; Corbetta *et al.*, 1990; Georgy *et al.*, 2016; Marzi *et al.*, 1986; Marzi *et al.*, 1996; Tomaiuolo *et al.*, 1997).

This combined evidence demonstrates a clear bias of blindsight towards properties processed by the dorsal cortical visual stream leading to the idea that there are direct projections from the subcortical areas to extrastriate visual areas that bypass V1 in the undamaged hemisphere (Bridge *et al.*, 2008; Ptito *et al.*, 2001). Using a variety of imaging techniques, research into the underlying pathways involved in blindsight has implicated a variety of retino-

recipient subcortical structures like the superior colliculus (SC) (Leh *et al.*, 2006a; Leh *et al.*, 2010; Savazzi & Marzi, 2004; Tamietto *et al.*, 2010), the pulvinar (Pulv) (Leh *et al.*, 2008), and the lateral geniculate nucleus (LGN) (Ajina & Bridge, 2018b). In addition, some research has identified increased anatomical connectivity between LGN and motion area MT/V5 (Bridge *et al.*, 2008) not otherwise present in patients without blindsight (Ajina *et al.*, 2015), as well as connections between the superior colliculus, pulvinar, and amygdala (Tamietto *et al.*, 2012). In conjunction with evidence of plasticity involving these subcortical structures in blindsight, a wealth of functional and structural connectivity studies advocate for the role of the intact hemisphere in compensating altered visual functions (Bittar *et al.*, 1999; Celeghin *et al.*, 2017; Goebel *et al.*, 2001; Henriksson *et al.*, 2007; Leh *et al.*, 2006b; Ptito *et al.*, 2001; Tomaiuolo *et al.*, 1997). Recently, retinotopic mapping on a blindsight patient showed indeed functional reorganization of the population receptive field sizes within the dorsal visual areas of the intact hemisphere (Georgy *et al.*, 2018).

However, the question remains as to whether the functional changes associated with blindsight are also accompanied by anatomical modifications of grey matter microstructure of the visual cortex in the intact hemisphere. While patients with localized V1 lesions have offered a unique perspective on the study of the functional compensation contributed by the intact hemisphere which may be mediated through interhemispheric connections, hemispherectomy patients who have had an entire cerebral hemisphere disconnected anatomically or functionally for the treatment of intractable epilepsy offer an equally unique and rare opportunity to examine the compensatory effects mediated by input from subcortical structures, particularly through the superior colliculus which is the sole surviving retino-recipient structure in the otherwise damaged hemisphere. While this study does not directly aim to address the mechanism through

which anatomical changes in the visual areas of the intact hemisphere might be occurring, a characterization of these changes in individuals with varying lesions but who all exhibit blindsight appears important as a first step towards fully understanding this phenomenon.

Cortical thickness can be estimated from neuroimaging data based on the different magnetic resonance imaging (MRI) signals associated with grey and white matter. It is a brain morphometric measure of the distance between the pial surface and the grey/white matter boundary. This metric has been garnering interest recently for its use in clinical populations to identify cortical morphological changes (Engvig *et al.*, 2010; Hardan *et al.*, 2006; Jarnum *et al.*, 2011). In the present study we analysed cortical thickness to assess morphological differences in the visual cortex of the intact hemisphere of three subjects with blindsight due to either hemispherectomy or localized V1 damage.

5.4 Methods

5.4.1 Subjects

We studied three subjects with well documented blindsight: one complete right hemispherectomy patient: DR, one partial right hemispherectomy patient: SE, and one patient with a localized left V1 lesion: GY (Figure 5.1). DR is a right-handed woman (43 years old at the time of testing) with a left hemiparesis since birth who began suffering from epileptic seizures at the age of 5 years. Prior to surgery, CT and MRI scans of the brain revealed severe atrophy of the right cerebral hemisphere, and EEG studies showed epileptiform activity over the right frontal-parietal-temporal regions. At the age of 17 years, she underwent a functional hemispherectomy which consisted of removing the temporal lobe including the mesial structures and a frontal-parietal corticectomy. The remaining cortical regions were disconnected from the rest of the brain by sectioning the white matter anteriorly and laterally, as well as posteriorly and laterally along the falx. Subsequent neuropathological investigation revealed an inflammatory process with diffuse gliosis characteristic of Rasmussen encephalitis. The presence of a complete contralateral hemianopia without macular sparing was confirmed by computerized perimetry (Allergan, Humphrey), and she has consistently shown strong evidence of blindsight (Bittar *et al.*, 1999; Georgy *et al.*, 2016; Leh *et al.*, 2006a; Tomaiuolo *et al.*, 1997).

SE is a right-handed man (49 years old at the time of testing) whose left hemiparesis was noted at birth. Seizure onset occurred at the age of 7 years. At the age of 23 years, CT and MRI scans showed a porencephalic cyst occupying the right temporal-parietal-occipital regions. EEG recordings detected epileptiform activity in the right occipital cortex alongside independent foci over the right temporo-parietal cortex. At the age of 25, he underwent a surgery to remove the congenital porencephalic cyst, and a temporal-parietal-occipital lobectomy included the hippocampus and the amygdala but spared the anterior portion of the frontal lobe. Postoperative

neuropathological examination revealed a neuronal migration disorder (cortical dysplasia). MRI scans postoperatively, as well as further scans performed afterwards for research purposes and published elsewhere, showed the presence of intact left and right SC, but only the presence of the Pulv on the left (intact) side (Leh *et al.*, 2006a; Leh *et al.*, 2008; Leh *et al.*, 2010; Tomaiuolo *et al.*, 1997). Contralateral hemianopia without macular sparing was confirmed by computerized perimetry (Allergan, Humphrey), and he has consistently shown strong evidence of blindsight (Georgy *et al.*, 2016; Tomaiuolo *et al.*, 1997; Wessinger *et al.*, 1996a; Wessinger *et al.*, 1996b).

GY is a left-handed man (54 years old at the time of testing) who was involved in a traffic accident at the age of 8 years which caused a vascular incident that left him with a large unilateral lesion in the left medial occipital lobe. The striate cortex is absent in the left hemisphere, and the lesion includes the peripheral representation of V1 except at the occipital pole corresponding to about 3-4° of macular sparing. In addition to the occipital lesion, there is a smaller lesion in the right parietal lobe that has not been investigated behaviorally. GY's visual system has been highly investigated behaviorally and using fMRI (Baseler *et al.*, 1999; Morland *et al.*, 2004; Sahraie *et al.*, 1997) and he has consistently shown strong evidence of blindsight (Barbur *et al.*, 1980; Barbur *et al.*, 1988; Blythe *et al.*, 1986; Blythe *et al.*, 1987; Celeghin *et al.*, 2017; Jackson, 1999; Morland *et al.*, 1999; Weiskrantz *et al.*, 1991).

Control data were acquired from the NKI dataset, a cross-sectional sample of typical individuals from childhood to senescence; we selected from this sample all individuals within 15 years of our youngest and oldest cases. This comprised a set of 188 individuals.

This project has been approved by the McGill University Health Centre (MUHC) Research Ethics Board (NEUPSY Panel; NEU-11-026).

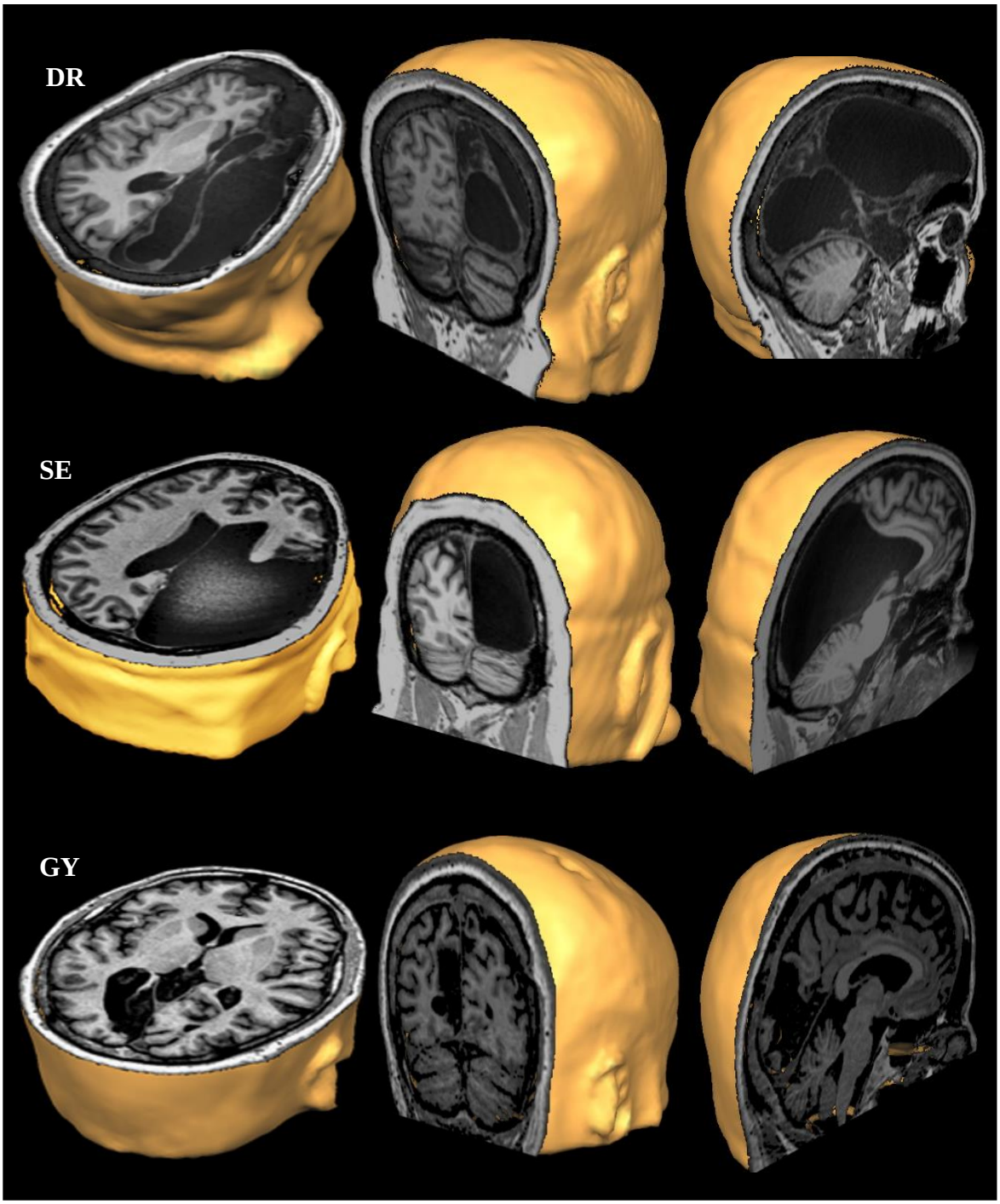


FIGURE 5.1: Blindsight Patients' T1-weighted MRI

Sections of T1-weighted 3T MRI anatomical scans of DR (top), SE (middle), and GY (bottom) showing the lesion of the visual cortex in transverse (left), coronal (middle) and sagittal (right) views.

5.4.2 MRI acquisition and processing

For all subjects, T1-weighted MR images were acquired using an MPRAGE sequence on a Siemens 3T scanner. All of the controls were scanned on a single Siemens Tim Trio 3T scanner. DR was also scanned on a Siemens Tim Trio 3T scanner; SE was scanned on a Siemens Prisma 3T scanner; GY was scanned on a Siemens Allegra 3T scanner.

All data were processed with CIVET-2.1.0[2] (released in October 2016) to extract cortical thickness measures. CIVET is a fully automated structural image analysis pipeline developed at the Montreal Neurological Institute. Intensity non-uniformities were corrected using N3 ; the input volume is aligned to the Talairach-like ICBM-152-nl template ; the image is classified into white matter, gray matter, cerebrospinal fluid, and background ; the white-matter surface is extracted via marching cubes, and adjusted to the center of the gradient at the inner edge of the cortical grey matter; the pial surface is positioned by walking outward from the white-matter surface to the CSF ; the surfaces are mapped to a common surface template (Lyttelton *et al.*, 2007), and thickness is measured as the Laplacian distance between the white- and grey-matter surfaces in native space.

In order to process the data for lesion patients, their lesions were filled with the corresponding portion of the non-linearly aligned MNI-152 template which was achieved by manually constructing a volumetric mask of the lesion for each subject; this was done using the manual segmentation tools in the MNI *Display* software[3]. This lesion mask was then subtracted from the brain mask obtained from the brain extraction tool *mincbet.* The resulting mask was then used to guide linear and non-linear registration of the MNI-152 template to overlay the subject's MRI, and then the lesion mask was used to fill in the lesioned portion of the subject's

[2] http://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET
[3] http://www.bic.mni.mcgill.ca/software/Display/Display.html

brain with the corresponding portion of the MNI-152 template. This composite brain was then processed by CIVET, and cortical thickness values extracted for the non-lesioned portions of the subject's brain. This procedure is illustrated in Figure 5.2.

5.4.3 Analysis

Statistical analyses were conducted using the SurfStat statistical toolbox[4], implemented in MATLAB. For each of the blindsight cases, a set of coefficients for the linear model

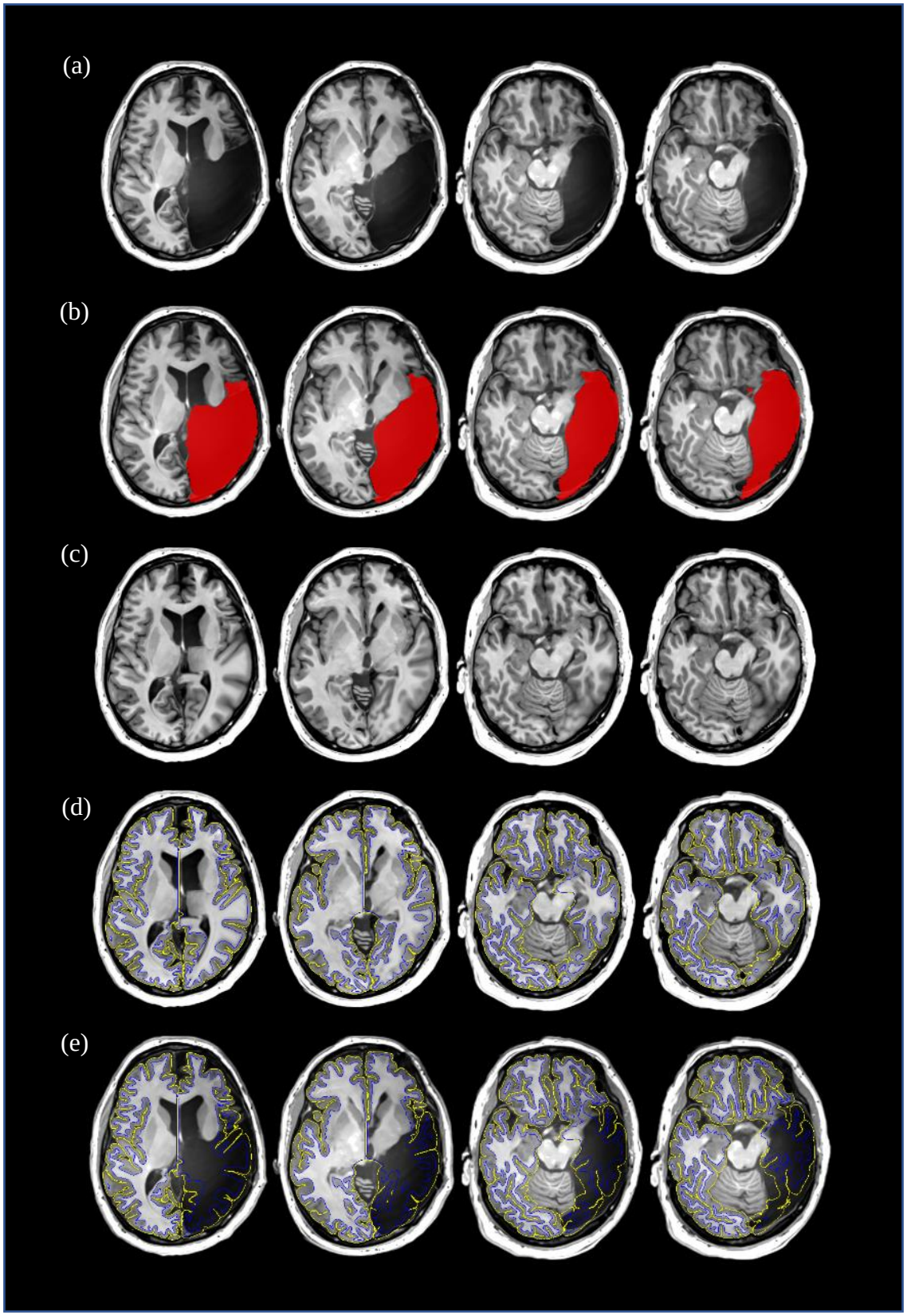
$$M = 1 + age + sex + age*sex + handedness$$

was generated based on the cortical thickness data from all control subjects, with age centered on the age of the particular blindsight case. The coefficients of this model were then used to predict the thickness of the blindsight cases based on their age, sex and handedness (predictedThickness). The studentized residual for the cortical thickness in the peri-calcarine region in the intact hemisphere of the blindsight patients was then calculated as:

$$studentizedResidual = (actualThickness - predictedThickness)/controlStddevs$$

where controlStddevs is the standard deviation of the residuals for the control data. The studentized residual was used to identify the set of vertices in each subject that were outliers with respect to the control population. To control for the proportion of Type 1 errors, a random field theory correction for multiple comparisons was performed (Worsley, 2007).

[4] http://www.math.mcgill.ca/keith/surfstat


(a)
(b)
(c)
(d)
(e)

…

FIGURE 5.2: Processing Pipeline

The processing procedure for patient SE. The lesioned MRI (a) is manually processed to create a lesion mask (b); the MNI152 template is registered to the lesioned MRI, and a composite brain is constructed by replacing the lesioned area of the brain with its MNI152 counterpart (c). The composite brain is then processed with CIVET to derive the white and grey surfaces (d) which provide measure of cortical thickness for the non-lesioned areas of the subject's brain (e).

5.5 Results

Our results demonstrate significant increases of cortical thickness in the visual cortex of the intact hemisphere in all blindsight cases compared to healthy controls. Figure 5.3 shows the studentized residual and the random field theory (RFT) corrected significance maps for each patient. DR shows increased cortical thickness in the anterior part of the calcarine fissure. The mean cortical thickness in this region in DR is 3.05; the predicted cortical thickness in this region for a right-handed 43-year-old female is 2.33. SE shows increased cortical thickness in a more posterior region of the calcarine fissure, extending into the neighbouring peri-striate cortex. The mean cortical thickness in this region in SE is 2.64; the predicted cortical thickness in this region for a right-handed 49-year-old male is 2.02. GY shows increased cortical thickness along the inferior bank of the calcarine sulcus extending into the lingual gyrus. The mean cortical thickness in this region in GY is 2.70; the predicted cortical thickness in this region for a left-handed 54-year-old male is 1.94. Note that in all three blindsight cases all regions showing an RFT significant alteration in cortical thickness are regions showing an increase in cortical thickness relative to controls.

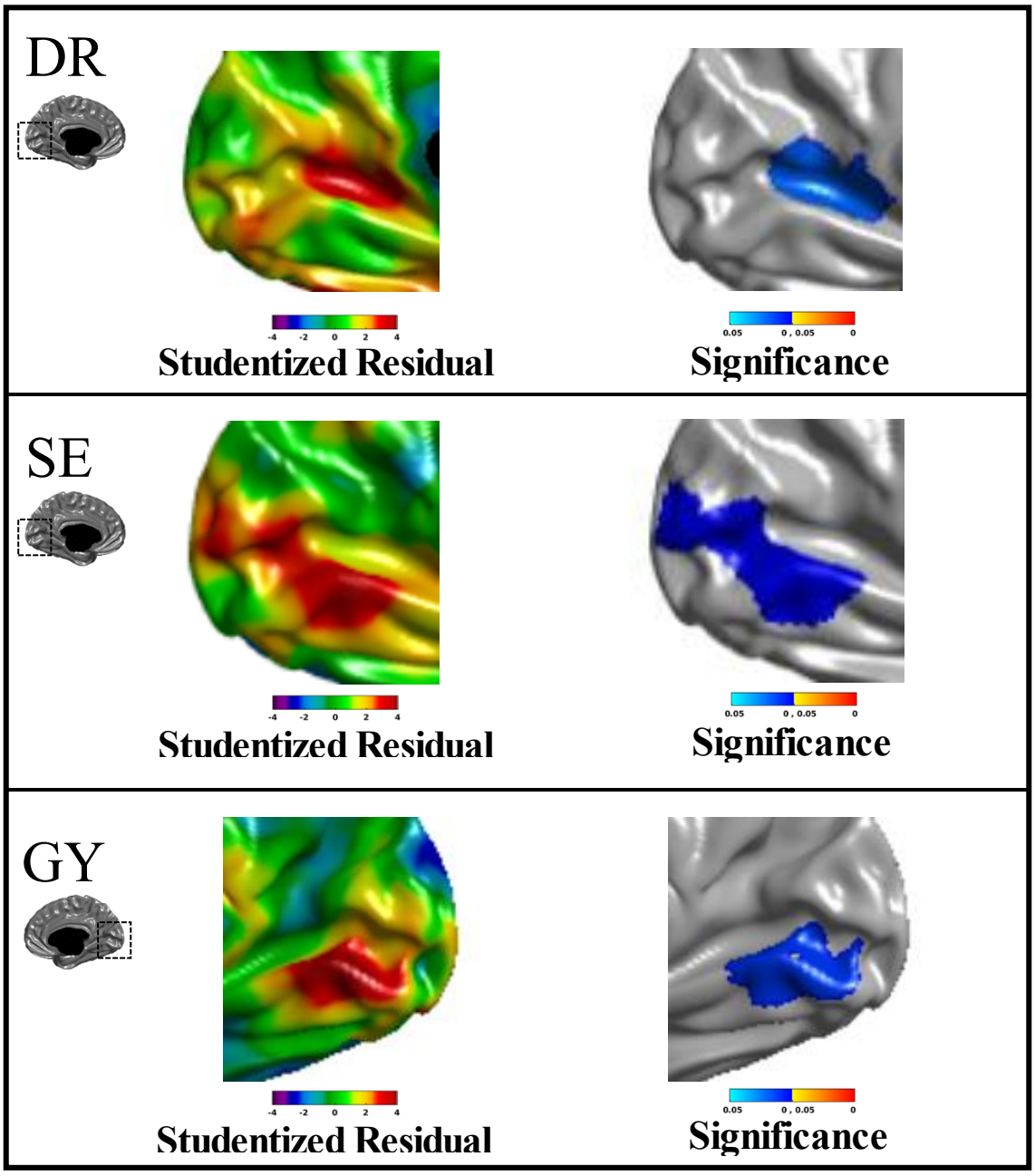


FIGURE 5.3: Peri-Calcarine Cortical Thickness

The studentized residual (left) shows the differences in the cortical thickness of the blindsight cases from what is predicted based on healthy controls. The significance maps (right), with multiple comparison correction via random field theory, show significant increases in peri-calcarine regions in each subject. Note that significance maps show vertex-wise significance (orange) and cluster-wise significance (blue).

5.6 Discussion

In this study, we aimed to explore whether there were any measurable changes in the cortical thickness in the visual cortex of the intact hemisphere in subjects exhibiting residual visual processing in their presumed blind field following damage to the corresponding primary visual cortex. In particular, we were interested in the visually responsive areas within the intact hemisphere which have been previously shown to be associated with the visual processing pathway implicated in blindsight. We assessed three subjects who exhibited blindsight: one who had undergone a complete right hemispherectomy (DR), one who had undergone a partial right hemispherectomy (SE), and one who had a circumscribed left V1 lesion (GY).

There have been a considerable number of findings implicating the intact visual cortex in the processing of visual information presented in the ipsilateral 'blind' hemifield in subjects exhibiting blindsight (see (Ptito *et al.*, 2001; Ptito *et al.*, 1999) for review). Furthermore, our group previously used fMRI to show in subject DR that visual stimulation of the blind hemifield yielded activation in the ipsilateral (intact) visual cortex (Bittar *et al.*, 1999), and that some functional reorganization of the receptive field sizes was taking place in these visual areas (Georgy *et al.*, 2018). In GY, transcranial magnetic stimulation (TMS) applied over the extrastriate areas in his damaged hemisphere was shown to modulate the appearance of phosphenes induced from primary visual cortex in the intact hemisphere indicating significant interhemispheric functional connectivity (Silvanto *et al.*, 2009).

Our results demonstrate clear anatomical differences in the striate and extrastriate visual cortex within the intact hemisphere of these subjects as compared to healthy controls; there were significant increases in cortical thickness along the calcarine sulcus which remain consistent across the three patients despite the varying age, nature, cause, and side of their cortical injury. The consistency of this finding, as well as its circumscribed nature rules out unspecific or general

plastic changes, suggesting a relationship between these anatomical differences and the functional role of the intact V1 in mediating blindsight functions.

These differences in cortical thickness, together with accumulating evidence from combined behavioral, functional imaging, and tractography studies on the critical role of the intact hemisphere in blindsight following damage to the primary visual cortex (Celeghin *et al.*, 2015a; Celeghin *et al.*, 2017) provide indications of morphological plasticity within the remaining visual cortex and lend support to the idea of a dynamic model of reorganization where sparing of visual functions following destruction of the primary visual cortex can be attributed to the compensatory role of cortical areas in the undamaged hemisphere, possibly mediated by existing neural pathways from subcortical nuclei.

Before discussing the specific implications of these findings, it is worth considering what changes in cortical thickness can imply about the brain, because while considerable thinning beyond the developmental epoch of synaptic pruning typically reflects loss or impaired function, interpretation of cortical thickening is not straightforward. Cortical thickness analyses provide a viable index for brain structure differences but the association of the metric to microstructural changes is unclear. Early studies in animals investigating the microstructure of the brain have shown that increases in cortical thickness are often a result of increased dendritic arborization (Kolb & Whishaw, 1989; Sholl, 1953) which are reliably reflected in higher synaptic but lower neuronal densities (Cullen *et al.*, 2010; Schuz & Palm, 1989). Imaging and histological work in humans have suggested that cortical thickness correlates to increases in soma size (Rajkowska *et al.*, 1998) and are inversely related to neuronal density in the occipital cortex (la Fougere *et al.*, 2011). From a behavioral standpoint, human patients with macular degeneration show increased cortical thickness in peripherally-responsive visual areas reflecting compensatory gain of

function leading to spared peripheral vision (Burge *et al.*, 2016). Considering the functional reorganization demonstrated in the intact visual cortex of blindsight subjects, it is reasonable to posit an explanation for these results of increased cortical thickness as a strengthening of cortico-tectal connections whereby input from remaining subcortical structures, such as the superior colliculus triggers changes in the microstructure of the intact visual cortex, such as increases in dendritic arborization and synaptic density that can support the processing of additional input of visual information from the ipsilateral, cortically blind visual field.

Several studies have used cortical thickness assessment techniques in order to observe neuroplasticity in the human occipital cortex (Elvsashagen *et al.*, 2017; Hardan *et al.*, 2006), and shown that the visual areas and associated cortices are capable of change under a variety of circumstances. For example, Rogge et al. (2018) found evidence of increased cortical thickness in the visual and vestibular cortical areas induced by balance-training exercises that rely on extensive vestibulo-visual stimulation. Additionally, this measure has been used to investigate cortical changes that accompany brain disorders or that appear as a consequence of brain injury. Findings show clear anatomical differences in the functionally defined visual areas that correlate with visual processing abnormalities in behavioral and neural measures in disorders such as schizophrenia (Butler *et al.*, 2008; Javitt & Freedman, 2015; Reavis *et al.*, 2017). Cortical thickness within the primary visual cortex has also been heavily studied in blind subjects, showing consistently that changes in visual experience can induce changes in the cortical thickness of V1 (Anurova *et al.*, 2015). Considerable research into these alterations has suggested that congenitally blind and early blind individuals show a thicker V1 compared to that in sighted controls (Bridge *et al.*, 2009; Jiang *et al.*, 2009; Park *et al.*, 2009; Ptito *et al.*, 2008; Voss & Zatorre, 2012). There is compelling evidence from the literature which suggests that

congenitally or early blind subjects activate their visual cortex in nonvisual tasks, demonstrating that occipital recruitment mediates heightened abilities in their remaining sensory modalities (Merabet & Pascual-Leone, 2010; Noppeney *et al.*, 2005; Noppeney, 2007; Ptito & Kupers, 2005; Voss *et al.*, 2010). In an attempt to relate these functional changes to the anatomical changes resulting from sight loss, Voss & Zatorre (2012) gathered cortical thickness measures in blind and sighted subjects along with several nonvisual behavioral measures. Group contrasts confirmed a thicker occipital cortex in the early blind which correlated with superior behavioral scores in two tasks, demonstrating a direct link between increased cortical thickness in the visual cortex and adaptive cross-modal reorganization which occurs in the brain of the visually deprived (Pascual-Leone *et al.*, 2005). The study of cortical morphometry in these pathological cases and more such as epilepsy (Tang *et al.*, 2019), mental retardation (Zhang *et al.*, 2011), and Alzheimer's disease (Thompson *et al.*, 1998) demonstrates a high variability in the extent of these neuroanatomical changes, and that the thickness of the cortex is associated with meaningful functional differences and in some cases, behavioral enhancement.

However, the loss of interhemispheric connections between the striate cortices could potentially provide an alternate explanation for our results. It could be possible to attribute the increases in cortical thickness in the intact visual cortex of our hemispherectomy subjects to a decrease in invading myelinated fibers that would normally connect the visual cortices such that a loss might move the surface at the inner edge of the cortex further inward. Nevertheless, we see the same effect of cortical thickening in our localized lesion patient who shows no deterioration in the posterior corpus callosum and interhemispheric connections between the undamaged visual areas surrounding the lesion and the contralateral hemisphere (Celeghin *et al.*, 2017; Silvanto *et al.*, 2009). Still, we can not exclude the possibility that the loss of V1 in the damaged

hemisphere leads to an increase in cortical thickness that is not functionally driven; this question would require further histological work in hemispherectomy and lesion patients *post mortem.*

An important avenue for future research is to examine changes in cortical thickness in other visually responsive areas, particularly those that mediate visuo-motor response such as the temporal visual areas, and posterior parietal and frontal premotor areas. Also, it is important to note that while our study shows anatomical changes that persist in three patients who have little in common outside total unilateral destruction of V1 and well documented blindsight, it is not possible to unequivocally attribute these increases in cortical thickness to either the damage and subsequent compensatory changes, or to the underlying functional reorganization that mediates blindsight. It will therefore be important to compare the findings reported here to cortical thickness changes in the visual cortex of the intact hemisphere in hemispherectomy and/or lesion patients who do not demonstrate evidence of blindsight.

5.7 Acknowledgements

A.P. and L.G were supported by the Natural Sciences and Engineering Research Council of Canada (NSERC: 37354-2011). L.G. is supported by a Canadian Institutes of Health Research doctoral research award (CIHR: 380343-2017). M.T., M.D., and A.C. are supported by a “Vidi” grant from the Netherlands Organization for Scientific Research (NOW: 452-11-015) and by a FIRB – Futuro in Ricerca 2012 – grant from the Italian Ministry of Education University and Research (MIUR: RBFR12F0BD). JDL, GB, and AE were supported by grant ANRP-MIRI13-3388 from the Azrieli Neurodevelopmental Research Program in partnership with the Brain Canada Multi-Investigator Research Initiative (to ACE). The research also benefited from computational resources provided by Compute Canada (www.computecanada.ca) and Calcul Quebec (www.calculquebec.ca).

Chapter 6: Conclusions

6.1 Summary and Implications

Blindsight is a phenomenon whereby visual deficits owing to primary visual cortex damage are compensated for by an alternate neural pathway that bypasses V1, and therefore consciousness. This alternative route allows cortically blind patients to maintain visuo-motor processing of stimuli presented in their blind visual field despite the lack of awareness of a visual percept. Since its discovery, there has been a rising interest in exploring blindsight as it provides insight into the plasticity of the brain and its remarkable capacity for change and compensation following injury.

The first study outlined in Chapter 3 successfully confirms a spatial summation effect in two hemispherectomy patients with documented blindsight by using a redundant target paradigm. When presenting a single dot, bilateral presentation that stimulated both the seeing and the blind visual fields yielded a faster reaction time than unilateral presentation in the seeing visual field alone, a finding that confirms previous reports in these patients (Leh *et al.*, 2006b; Leh *et al.*, 2010; Tomaiuolo *et al.*, 1997). Additionally, this study used a variant of the stimulus which introduced a factor of numerosity, by presenting quadruple dots, and configuration, whereby the dots were either arranged randomly or in a spatially coherent shape, referred to as a gestalt-like stimulus. The results show that in both patients, blindsight was indeed sensitive to the stimulus numerosity, i.e. there was a faster reaction time to quadruple than single dots, but this effect was present only when the dots were arranged in a gestalt-like shape. While the influence of stimulus numerosity and configuration on the visuo-motor responses in blindsight patients was previously tested by Celeghin *et al.* (2015c), the experiment was conducted on patients with intact portions of extrastriate visual areas as well as spared retino-recipient subcortical structures besides the superior colliculus (such as the lateral geniculate nucleus and the pulvinar), so it was

not possible to determine the relative contribution of the superior colliculus to this processing, and therefore its specific role remained unresolved. Our study examines blindsight patients who have undergone a hemispherectomy; since these patients have had an entire cortical cerebral hemisphere removed or disconnected, including the temporo-occipito-parietal cortices, the lateral geniculate nucleus and pulvinar on the side of the affected hemisphere, the only remaining retino-recipient subcortical structure is the superior colliculus. Testing these patients using this modified experimental paradigm not only provided further support for the notion that nonconscious vision is sensitive to perceptual organization, but offered a clear demonstration that the superior colliculus can facilitate a visuo-motor response that is selectively sensitive to coherent stimulus configuration, and thereby providing an essential contribution to visually guided behaviour despite its functional and anatomical segregation from the geniculo-striate and extrastriate pathways and being outside the reach of conscious visual experience.

The second study outlined in Chapter 4 takes advantage of recent advances in retinotopic mapping techniques in order to investigate the functional reorganization that occurs in the intact hemisphere since the contralesional visual areas have been previously implicated in blindsight through a wealth of studies that advocate for the role of extra-geniculostriate pathways that bypass V1 (Danckert & Rossetti, 2005; Perenin & Jeannerod, 1978; Rafal *et al.*, 1990). In hemispherectomy patients, the entire cortex in one hemisphere has been removed or disconnected meaning that the only retinal pathway remaining on the damaged side is the one projecting to the ipsilateral superior colliculus; visual information then crosses the inter-tectal commissure to reach the extrastriate areas in the intact hemisphere (Leh *et al.*, 2006a; Leh *et al.*, 2006b; Ptito *et al.*, 2001). While fMRI activity has been reported in the extrastriate areas of the intact hemisphere when stimulating the blind ipsilateral visual field (Leh *et al.*, 2010), and

tractography has shown enhanced and new fibre tracts that connect the superior colliculus on both sides of the brain with cortical areas in the remaining hemisphere (Leh *et al.*, 2006a), the nature of the neural reorganization within these remaining visual areas that presumably underly and sustain blindsight in hemispherectomy patients was yet unknown. By computing a model of the population receptive fields (pRF) in the early visual areas of the remaining hemisphere of one hemispherectomy subject with blindsight it was possible to derive the retinotopic maps and examine their response properties. Overall, the findings indicate no large-scale distortions in the retinotopic organization of the remaining hemisphere. However, blurred boundaries between the dorsal compartments V2 and V3 which were otherwise undetected by conventional perimetry warranted additional investigation. Indeed, further observation uncovered evidence of a marked increase of the pRF size within the voxels in these very same dorsal areas, and the receptive field sizes tended to increase significantly at higher eccentricities. Our results suggest that progressive expansion of the pRF sizes in the dorsal areas can help process the incoming visual information from the ipsilateral blind visual field and contribute to the fundamental search for understanding neuronal organization showing that intact structures can change their original response properties to compensate for damaged areas. It is important to note that previous retinotopy work has shown a tendency both in animals (Dow *et al.*, 1981; Hubel & Wiesel, 1974; Wilson & Sherman, 1976) and in humans (Dumoulin & Wandell, 2008; Smith *et al.*, 2001) for the increase in receptive field sizes with increased eccentricity by a factor of 3-4 between V1 and V3 due to magnification, a finding we see in our patients, but not significantly so in any of our controls. This could perhaps be an artefact of individual variation in this particular cohort of controls, but it warrants further investigation (discussed further in the following section).

Finally, the study outlined in Chapter 5 aims to examine whether anatomical changes occur in the visual cortex of the intact hemisphere of blindsight patients. As discussed previously, the intact hemisphere has been functionally implicated in mediating unconscious residual vision not only in hemispherectomized patients who lack an entire cortical mantle in the damaged hemisphere (Bittar *et al.*, 1999; Leh *et al.*, 2006a; Leh *et al.*, 2010), but also, and perhaps unexpectedly, in a case of a localized V1 lesion where extrastriate areas remain intact in the damaged hemisphere (Celeghin *et al.*, 2017). In this recent study, Celeghin *et al.* (2017) showed that despite the fact that surviving extrastriate areas in the hemisphere deprived of V1 are receiving visual input through the ipsilesional projections from subcortical structures and transferring this information to motor and pre-motor areas within the same hemisphere, visually guided behaviour of simple movements was mediated by functional compensation of the intact hemisphere. Together, these data suggest a key role of the visual areas in the intact hemisphere in mediating blindsight, regardless of the extent of the lesion (localized or generalized) in the damaged hemisphere, and furthermore, the study outlined in Chapter 4 clearly demonstrates a functional reorganization and expansion of receptive field sizes in the intact visual cortex of a hemispherectomy patient with blindsight. For this reason, we chose to investigate anatomical changes in the visual areas of the intact hemisphere by performing cortical thickness analysis in two hemianopic patients, one with a partial and the other with a full hemispherectomy, and one patient with a localized V1 lesion. We extracted cortical thickness measures for each patient separately and compared them to a predicted cortical thickness measure from healthy controls based on age, sex, and handedness. The results show a significant increase in the cortical thickness of the peri-calcarine regions of the intact hemisphere in each of our three patients compared to healthy controls, which pass the random field theory correction for multiple

comparisons. While there are expected variations in the pattern of increased cortical thickness in the visual areas between the patients given their individual differences, the presence of such consistent morphological changes in the same visually responsive areas in all three subjects is compelling as it persists irrespective of age-onset, etiology, or extent of damage. These results provide further support for the involvement of the intact hemisphere in blindsight, and add to the accumulating evidence from behavioural, functional imaging, and connectivity studies that advocate for the presence of cerebral reorganization and plasticity following damage.

Through the series of experimental studies reported here, I was able to determine that the superior colliculus, a major known player in the blindsight pathway, is in fact sensitive to, and likely responsible for the processing of higher-order perceptual functions such as stimulus configuration. Using neuroimaging, I was able to demonstrate both functional and anatomical changes in the visual areas of the intact hemisphere, which further highlights its involvement in the compensatory functions mediating blindsight following damage to the contralateral primary visual cortex. Our body of work contributes to the existing literature on the topic and furthers our understanding of blindsight and its underlying neural substrates.

Some studies on cortically blind patients have shown that with daily discrimination training over a period of months it is possible to increase sensitivity in the blind visual field (Bridgeman & Staggs, 1982; Henriksson *et al.*, 2007; Sahraie *et al.*, 2006; Sahraie, 2007; Stoerig, 2006) despite limited reported perceptual awareness of the stimuli, indicating that cortical blindness can be at least partially reversible with training, and that the threshold for visual attention is not fixed but can be altered through the brain's intrinsic plasticity, even in the adult (Schwiedrzik *et al.*, 2009). However, in order to design the most efficient and effective rehabilitation programs, it is important to first identify the underlying mechanism, to understand

how the structures involved in this pathway can change, and what they are sensitive to perceptually so that we can solicit their functions optimally (for example using achromatic, low frequency, moving stimuli). It is also important to continue to use these rare and unique populations to investigate the brain and the roles of these lesions to better understand how structures contribute to certain processing pathways, and the effect their damage has on normal brain functioning.

6.2 Future Directions

While the studies outlined here offer new insights into the neural substrates of blindsight, particularly in hemispherectomy subjects, much is yet left unknown. While the results in the first study outlined in Chapter 3 demonstrate that the superior colliculus in hemianopic subjects is capable of encoding complex properties of visual input, it is important to continue to examine other higher-order visual functions to determine whether they can be carried out in the absence of striate and extrastriate cortical areas in hemispherectomy patients.

A commonly used experimental paradigm for information processing is a same-different judgement task that requires the subject to discriminate letter pairs based on either their nominal identity (name) or physical identity (shape) as the decision criteria (Posner & Mitchell, 1967). This design has been used often in healthy subjects in order to investigate the cognitive processing mechanism for such stimuli through the close scrutiny of the reaction time, which has resulted in a number of interesting theories and cognitive models (Proctor, 1981). Since the hemispherectomy subjects tested in Chapter 3 clearly show a facilitation to processing higher-order visual stimuli through the superior colliculus, it would be interesting to test them using this paradigm to determine if they are capable of correctly classifying the letter pairs presented across the vertical meridian (one in the “blind” and another in the “seeing” visual fields) as same or

different based on the nominal or physical criteria. This would specifically test whether the superior colliculus is capable of encoding name information which contains a learned language aspect, or whether it is simply concerned with shape information. Additionally, since there has long been a debate about some of the proposed asymmetries between the hemispheres in language processing, the use of hemispherectomy patients might shed light on this issue (Eviatar *et al.*, 1994).

With regards to the second study outlined in Chapter 4, as previously mentioned, it is important to investigate further our findings of significant difference in the pRF sizes between the hemispherectomy subject and the healthy controls at increasing eccentricities. Since an increase is expected in the pRF sizes at higher eccentricity simply due to magnification, it is possible that the results outlined in *4.4.3* are an artefact of the controls exhibiting smaller than expected receptive field sizes unlike the patient who shows an increase within reasonable values. In addition to verifying these results by using a different group of controls and blindsight subjects, it would be of interest to examine these changes at higher eccentricities beyond those tested here, and to repeat this experiment using blindsight subjects with localized V1 lesions in order to determine if the plasticity seen here as a significant increases in pRF sizes in the dorsal visual areas is directly related to blindsight in hemispherectomy or if this compensation can also be seen in those with blindsight due to circumscribed lesions. Lastly, since the superior colliculus (Schneider & Kastner, 2005) and lateral geniculate nucleus (Schneider *et al.*, 2004) are both retinotopically organized and have been heavily supported in their involvement in the blindsight pathway, it would be interesting to perform pRF mapping on these structures in order to examine whether they show any differences in their retinotopic organization.

Finally, since the last study outlined in Chapter 5 was premeditatively focused on the peri-calcarine visual areas in the intact hemisphere of blindsight patients and found significant increases in the cortical thickness in this region, a natural follow-up is to extend our analysis to other visually responsive areas that have been previously implicated in the visuo-motor processing underlying blindsight. Research into the substrates of blindsight has previously implicated the premotor cortex as a key player in sensory-motor integration during the processing of visual stimuli (Leh *et al.*, 2006a; Tamietto *et al.*, 2015). Despite having no primary visual cortex, and no awareness of the stimulus presented in the blind visual field, blindsight subjects have nevertheless been able to show above chance responses by carrying out an action towards the blind field stimulus such as pointing, reaching, grasping, scaling, or initiating saccades – functions that were termed 'action blindsight' (review (Danckert & Rossetti, 2005). It is therefore worthwhile to investigate changes in the cortical thickness of areas along the dorsal visual stream such as the middle-temporal visual area (MT), a cortical area best known for its role in motion processing, as well as posterior parietal and frontal premotor areas. As mentioned previously, this study focuses on patients who, despite their varying lesions, all nevertheless demonstrate strong blindsight responses. Despite the increase in cortical thickness in the visual areas of the intact hemispheres in all three subjects, it is not possible to attribute these changes to blindsight since it may be possible that they are an effect of the lesion in the contralateral hemisphere, and therefore independent of the functional plasticity shown within. In order to address this, it will be important to perform cortical thickness analysis on lesion and/or hemispherectomy patients who do not exhibit blindsight. Additionally, we have yet to determine if there are volumetric changes in the subcortical structures that have been heavily implicated here and elsewhere in the blindsight pathway, such as the superior colliculus and lateral

geniculate nucleus. Studies have focused on their connectivity to other structures and have shown significant associated plasticity in blindsight, but it remains to be seen if these changes are reflected in their size, and how that could be interpreted in terms of increases in synaptic connections.

6.3 Concluding Remarks

There is, perhaps, no target for research in physiology of greater importance or complexity than the functions of the brain, and for centuries, scientists observed the damaged brain by various means to gain insight into how its countless parts communicate and relate to each other to support those complex functions. Through the study of the blindsight phenomenon in hemispherectomy patients, much was uncovered about the visual system and how it adapts following damage to the primary visual cortex. In this thesis, I presented an overview of the existing literature followed by three chapters outlining novel findings that contribute to the current knowledge about the role of the superior colliculus and its connectivity within the blindsight pathway, as well as the functional and anatomical plasticity observed in the intact visual cortex as it mediates residual visual functions in the ipsilateral, blind hemifield. Our results show that 1) blindsight is sensitive to higher-order perceptual organization that is mediated by the superior colliculus, 2) while the intact visual cortex maintains its coarse retinotopic organization, the dorsal compartments show an increase in receptive field sizes which is likely mediating residual vision in the blind hemifield, and 3) the visual areas in the intact hemisphere of blindsight subjects show marked anatomical changes through a significant increase in cortical thickness in peri-calcarine regions as compared to healthy controls.

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