CHAPTER 6

General Discussion
With my thesis, I have contributed to our current knowledge on the structural and functional properties of a visual system that is affected by homonymous hemianopia (HH) due to acquired brain injury (ABI). Furthermore, I have shown how the residual capacity of a visual system may reflect HH individuals’ recovery potential. The main findings of my thesis, in the context of HH due to ABI, are that:

- Post-geniculate visual pathway lesions can lead to widespread bidirectional transsynaptic degeneration along the entire visual pathway, in both the lesioned and non-lesioned hemisphere;
- a hemispherectomy can lead to small-scale reorganization of the visual system of the remaining hemisphere;
- functional MRI-based visual field (VF) mapping techniques can reveal residual visual processing that remains undetected by standard automated perimetry;
- the functional connectivity strength between the Precuneus and the Occipital Pole network reflects the effectiveness of Vision Restitution Training (VRT).

In the following sections, I discuss my findings and their practical implications for diagnostics and therapeutics.

6.1 The structural and the functional integrity of the visual system alter when someone has a HH due to ABI

In Chapters 2 and 3 of this thesis, I described how the structural [Chapter 2] and functional integrity [Chapter 3] of the visual system alters in the case of a HH due to ABI.

6.1.1 Post-geniculate visual pathway lesions lead to bidirectional transsynaptic degeneration along the entire visual pathway

In Chapter 2, I aimed to establish the presence of widespread collateral damage from a HH due to a post-geniculate lesion in terms of transsynaptic degeneration (TSD), by examining the integrity of the entire bilateral visual pathway (i.e., from the eyes to the visual cortex). In particular, I used Fixel Based Analysis (FBA) to evaluate the white matter (WM) properties of the visual pathway structures in the lesioned and non-lesioned hemispheres. Furthermore, I used Optical Coherence Tomography (OCT) to evaluate the thickness profiles of the macular Retinal Nerve Fiber Layer (RNFL), the combined Ganglion Cell - Inner Plexiform Layer (GCIPL), and the peripapillary RNFL in both eyes.
My findings showed lesion-induced TSD along the entire visual pathway, in both the lesioned and non-lesioned hemispheres. In the visual WM, the degeneration was reflected by axonal loss as well as fiber-bundle atrophy. Only TSD of the ipsilesional OT was related to the time-since-injury. Furthermore, in the eye on the same side as well as on the opposite side of the lesion, we observed layer-specific retinal thinning with high topographic correspondence to the VF defect. Together, this indicated a spread of degeneration towards the eyes (i.e., the ipsilesional OT, the ONs and the retinas) and the contralesional post-chiasmal visual pathway (i.e., the contralesional OT and the ORs), evidence for the occurrence of respectively retrograde and anterograde TSD following post-geniculate lesions.

With this work, I have contributed to our understanding of the collateral (i.e., indirect) pathological effects of post-geniculate lesions in HH participants by investigating degeneration at a larger scale and using more advanced methods than before. In particular, I involved all structures that comprise the visual pathway and applied FBA, a novel framework that includes higher-order DWI modeling. With this, I could, for the first time, demonstrate widespread bidirectional and bilateral TSD, affecting the entire visual pathway. Furthermore, I could provide biologically meaningful interpretations for the observed alterations of WM properties in terms of axonal loss and fiber-bundle atrophy. My finding of WM degeneration of the visual pathway structures in the non-lesioned hemisphere, in addition to that in the lesioned hemisphere, extends previous work showing WM degeneration of the OT in the non-lesioned hemisphere. Furthermore, the degeneration of the non-lesioned visual pathway complements observations of decreased visual performance in the seen VF that is subserved by this hemisphere. My finding of hemianopic retinal thinning, in which I found a layer-specific topographic correspondence in agreement with retinal anatomy, extends the many reports on retrograde TSD of the retina.

Based on the above, I conclude that post-geniculate lesions lead to collateral damage affecting the brain and the eye that is more widespread than previously thought. Furthermore, my finding of degeneration in the non-lesioned hemisphere highlights that one should not assume that this hemisphere is equipped for fully normal vision in HH individuals. This advance in our understanding of collateral damage from post-geniculate lesions to the visual system may shed light on HH individuals’ residual capacities and in turn their HH individuals’ recovery potential.
6.1.2 A hemispherectomy can lead to small-scale alterations in VF properties

In Chapter 3, I evaluated the functional organization of the visual system of an adolescent girl whose left hemisphere has been surgically removed at the age of three and who consequently experienced a right-sided HH. I evaluated her retino-cortical and cortico-cortical VF map projections, in terms of population Receptive Field (pRF) and Connective Field (CF) properties respectively, in comparison to control participants. My findings showed an enlarged foveal representation and more detailed foveal processing in the early visual areas, evident from a large number of small pRFs at low eccentricity. Furthermore, they showed a coarser sampling of the visual information in V1 by the extrastriate areas, evident from larger CF at all eccentricities. I interpreted these abnormal retino-cortical and cortico-cortical VF map projections in the remaining hemisphere as an indication of the occurrence of small-scale functional reorganization. It remained inconclusive whether the specific alterations in pRF and CF properties observed in this individual are a response to the presence of the HH or the absence of the other hemisphere. In the case of the first, the alterations might underlie adaptive visual processing and viewing strategies. In the case of the second, the alterations might have been induced by the absence of interhemispheric signaling.

Deviating retino-cortical projections in individuals with HH, either due to hemispherectomy or other types of ABI, have been reported before. Yet, in contrast to our observations, these studies observed smaller pRFs in the late visual areas\textsuperscript{24} or larger pRFs in the early visual areas.\textsuperscript{25} Regarding the cortico-cortical projections, I was the first to find deviating, i.e., abnormally large, CF projections in a HH participant due to hemispherectomy. A few other studies have examined the CF properties in clinical populations with visual deficits other than HH and showed either unchanged CF projections\textsuperscript{26,27} or smaller CF projections\textsuperscript{28,29} compared to a control group.

Based on the above, I conclude that the visual system is plastic and can functionally reorganize in response to HH due to a hemispherectomy. The fact that the deviations of retino-cortical and cortico-cortical VF map projections observed in my study are not in line with those reported previously suggests to me that HH due to ABI does not induce explicit plastic responses. Furthermore, such inconsistency in functional plasticity may reflect individual differences in the residual capacities and, in turn, the recovery potential of HH individuals’ visual systems.
6.2 Functional Magnetic Resonance Imaging (fMRI) based techniques can inform us on residual functional capacities of the visual system

In Chapters 4 and 5 of this thesis, I described how fMRI-based techniques can inform us about the residual capacities of the visual system [Chapter 4] and how residual capacities can reflect the recovery potential [Chapter 5] of HH participants.

6.2.1 fMRI-based VF mapping techniques can reveal preserved visual processing that remains undetected by automated perimetry

In Chapter 4, I examined the potential of two fMRI-based VF mapping techniques, i.e., the conventional pRF modeling and the novel Micro Probing (MP), to reconstruct the VFs of a group of HH participants. Interestingly, not only did I show that both techniques are capable of reconstructing a hemianopic VF, but they also seem to be able to reveal neural responses in the visual cortex in response to stimuli in the perimetrically 'blind' sections of the VF. Furthermore, compared to the pRF modeling, MP was able to uncover more voxels in the lesioned hemisphere for which a modest degree of visual sensitivity was retained.

My work extends the work of groups that showed the presence of neural activity in sections of the visual cortex corresponding to perimetrically blind regions of the VF.25,30–33 Yet, with my work, I expand on the previous by using the novel MP approach34,35 to map the VF.

Based on the above, I conclude that, as opposed to automated perimetry, fMRI-based VF mapping techniques are able to capture both conscious and non-conscious visual capacities. Hence, we can use fMRI-based VF reconstructions to gain better insights into the preserved visual processing, and in turn the HH individuals' recovery potential, of individuals with HH due to ABI. To this end, the MP approach has shown to be a more sensitive method, compared to the conventional pRF approach.

6.2.2 Functional connectivity strength between the Precuneus and the Occipital Pole network reflects the effectiveness of VRT in HH participants

In Chapter 5, I examined whether the functional connectivity (FC) patterns of five visual Resting-State (RS) networks of interest, assessed prior to VRT, are related to training
success in HH participants. I showed that individual differences in the FC strength between the anterior part of the precuneus and the Occipital-Pole network were associated with individual differences in training effects, i.e., a change in VF sensitivity. This association was specific to a training effect that was modulated by attention. Such a relationship was found neither for the other four visual RS networks nor for a training effect that was not modulated by attention. These findings suggest that 1) the precuneus plays a role in attention-modulated VF improvements, and 2) the prior-to-training FC strength between the precuneus and the Occipital-Pole network has the potential of identifying HH individuals that are most likely to benefit from the training.

Previous studies on VRT success showed that the variability in VRT success could be explained by residual visual capacities,\textsuperscript{32,36-42} or the timing of the intervention.\textsuperscript{4,43,44} Furthermore, the effect of VRT may be enhanced through the modulation of attention,\textsuperscript{45-47} or by the use of non-invasive brain stimulation.\textsuperscript{48-52} Our study adds to this current understanding by presenting an attention-related neural mechanism that may underlie the effect of VRT, i.e., the FC between the Precuneus and the Occipital Pole network.

Based on the above, I conclude that it may be possible to predict VRT success by measuring specific functional RS network connectivity patterns in HH participants. In particular, the strength of the connectivity may reflect the HH participants’ attention-related capacities and in turn, their recovery potential.

6.3 Clinical implications and future suggestions

Below I discuss, for each of the experimental chapters, the clinical implications of their results. Furthermore, I give suggestions for future studies.

6.3.1 Vision rehabilitation specialists should consider the consequences of widespread TSD of the visual pathway in individuals with HH

I have shown TSD of the visual pathway of HH participants that is more widespread than previously thought and even extends toward the non-lesioned hemisphere. I was left to speculate whether such alterations in the structural properties of the visual system impact the visual functioning of HH individuals. There is, however, mounting evidence for perceptual deficits in the ‘intact’ visual field of HH individuals (or ‘sightblindness’).\textsuperscript{5-10,12,53,54} My findings suggest that structural alterations of the contralesional visual pathway may
underlie such visual perceptual deficits. I further speculated that the extent of the collateral damage, and any associated functional consequences, may relate to interindividual differences in rehabilitation success. In support of this, the extent of OT degeneration has been shown to limit training-induced visual recovery in HH individuals. Therefore, for a future study, I suggest correlating measures of structural integrity with various measures of visual performance in HH participants. Such a study could give insights into whether the widespread bidirectional TSD of the visual pathway is associated with visual perceptual deficits. Furthermore, I suggest examining how the occurrence of TSD relates to HH participants' rehabilitation outcomes. By investigating the effect of TSD on the HH participants' residual capacities, fruitful insights into the individuals' recovery potential may be uncovered, and, potentially, a-priori predictions about their rehabilitation success can be made.

Although the exact functional consequences of the degeneration in HH individuals are yet to be determined, I have various reasons to suggest that vision rehabilitation specialists should consider the widespread TSD in HH individuals. First, it stresses the need for a careful evaluation of the treatment outcomes, in particular when assessing the visual functioning of the seen hemifield. Second, it may affect the rehabilitation therapists' decision on the type of rehabilitation interventions. For example, the presence of sightblindness advocates the need for an alternative rehabilitation approach that aims to also improve the visual functioning of the intact VF. Likewise, certain rehabilitation approaches may be waived. For instance, in case the TSD disturbs residual capacities that seem critical for successful rehabilitation, such as the neural correlate of VRT outcome identified in Chapter 5. Third, it may affect rehabilitation therapists' decisions on the timing of the rehabilitation intervention. Indeed, we found that OT degeneration was related to the time since injury [Chapter 2] which corroborates the suggested importance of on-time rehabilitation interventions. Furthermore, such time dependency underlines the importance of protecting anatomical structures that are integral to the visual system and advocates a need for neuroprotective or even-regenerative interventions.

6.3.2 Functional plasticity of the visual system may benefit vision rehabilitation therapy

Vision rehabilitation therapies may be more successful when they make effective use of the functional plasticity of the visual system of HH individuals. However, this capacity of the visual system to functionally adapt differs amongst HH individuals and cannot be
assumed. What causes the individual differences in functional plasticity remains unclear. In this thesis, I report on the occurrence of small-scale reorganization in the visual system of a girl who, at a very young age, had one of her hemispheres surgically removed. Such functional plasticity of the visual system may reflect adaptive viewing behavior, which in turn may benefit vision rehabilitation therapies.

Given the individual differences in the plastic functional capacity of the visual system, the alterations in VF projections specific to this case cannot be generalized to the larger population of hemispherectomy individuals. Therefore, an assessment of the VF projections in a larger cohort of hemispherectomy participants is warranted. However, due to the rarity of this surgical procedure, this might be hard to accomplish. Alternatively, including cases of HH with more common etiology (e.g., stroke) allows for the assessment of VF projections, in terms of pRF and CF measures, at a much larger scale. This would also allow for considering clinical or etiological features that may explain individual differences in the functional plasticity of the visual system.

Furthermore, future studies would benefit from correlating functional imaging and behavioral measures in HH participants (i.e., pRF and CF measures on the one hand, with visual performance measures on the other). Such studies may help to determine whether and how functional plasticity is indeed associated with adaptive visual processing or viewing strategies.

6.3.3 The VF regions with preserved visual processing as target regions for vision rehabilitation therapies

Ultimately, VF regions with preserved neural processing may be particularly amenable for vision rehabilitation therapy aiming at enhancing residual vision. In Chapter 4, I was able to uncover such extended areas of the VF, yet, due to study limitations, I was unable to confirm any residual visual processing in these areas. For example, it is possible that the preserved neural processing underlies ‘blindsight’, the ability of HH individuals to unconsciously detect stimuli presented in their VF defect. Therefore, future studies would benefit from additional behavioral visual performance measures, including blindsight tests, to confirm the presence of residual vision in these extended areas. Following that, I suggest that it would be worth further investigating the neural mechanism behind it. There are many theoretical frameworks that could explain our observation of the unconscious vision in HH participants, such as the presence of spared cortical tissue in V1, the presence of alternative processing pathways surpassing V1, or
modulation of attention.\textsuperscript{68,69} Better insight into the nature of the residual vision can inform us about which underlying mechanism to target during rehabilitation therapy. Furthermore, future studies would benefit from examining the amenability of these extended areas for rehabilitation. Towards this, Elshout et al.\textsuperscript{32} recently showed that VF sensitivity can be improved through VRT when particularly training those areas of the VF that are perimetrically blind but exhibit residual neural responses. Lastly, future studies would benefit from the fMRI reconstruction of a much larger part of the VF. A limitation of the fMRI-based VF mapping techniques used in Chapter 4 is that they only allow for a stimulation, hence a reconstruction, of the central part of the VF (i.e., 6.5° radius from central fixation). However, a hemianopic VF defect can involve regions way beyond this 6.5° and therefore may not be within reach of most current VF stimulation methods. Therefore, it would be worth exploiting possible methods that allow for an enlarged VF reconstruction\textsuperscript{32,70–72} and that enable the evaluation of a much larger part of the VF defect.

6.3.4 Functional resting-state connectivity as a predictor of VRT success

The observed relationship between functional resting-state connectivity of the visual brain and VRT success suggests that we may predict the success of VRT in HH participants from specific functional connectivity patterns in their brains. In particular, based on an examination of specific network connectivity patterns prior to the start of the training, we may select HH participants with an expected high training yield. Such selection would be very advantageous for both individuals, doctors, and rehabilitation workers, as VRT protocols tend to be long and demanding, both for individuals and their care professionals. Furthermore, a predictor for VRT success may optimize the cost-effectiveness of the rehabilitation as costs associated with VRT training protocols are usually higher than those associated with the procedure required to make the prediction, see below.

In Chapter 5, I was able to identify a post-hoc neural correlate for an attention-modulated effect of VRT with a potential predictive capacity for VRT success. Due to the explorative nature of the study, the FC strength between the Precuneus and the OP network as a predictor of VRT success still needs to be validated. Therefore, I suggest a study on a new cohort of HH participants who are scheduled for training. Based on FC strength prior to VRT, actual predictions about expected VRT outcomes can be made which can be validated after VRT. Furthermore, it would be interesting to determine the predictive potential for different training paradigms.
6.3.5 Towards determining the recovery potential of HH individuals

With this thesis, I have presented findings which I believe are of relevance when determining the recovery potential of HH individuals. In particular, I speculate that the 1) widespread TSD in HH individuals impedes their recovery potential; 2) functional reorganization of the visual system underlies adaptive visual processing that can be advantageous for vision rehabilitation; 3) VF regions with preserved visual processing are candidate target regions for VRT, and 4) the functional resting-state connectivity strength measured before training can be used to predict VRT success.

Future research is warranted to confirm the above and examine whether these observations indeed underlie interindividual differences in HH individuals’ recovery potential. With that, other aspects that may contribute to the recovery potential should be considered as well. For example, an early start of the rehabilitation intervention may be key to boosting the HH individuals’ recovery potential. Additionally, the age of the HH individual at the time of injury should be considered given the structural and functional age-related changes to the visual system and the accompanying changes in plastic capacity. Furthermore, the extent of the visual cortex damage should be considered. After all, a locally damaged visual system may permit more resources for residual capacities compared to a total absence of half of the visual pathway, for example in the case of a hemispherectomy.

6.4 Concluding remarks

In summary, by investigating the structural and functional properties of the visual system in the case of a HH due to ABI I have shed light on aspects that may be critical for determining the HH individuals’ recovery potential. In particular, I have advanced our understanding of changes in the structural and functional integrity of the visual system, reflected by widespread TSD and functional reorganization. Furthermore, I have shown how fMRI-based techniques can inform us about residual visual processing by revealing regions of the ‘blind’ VF with preserved visual processing and finding a neural correlate of VRT outcome. Based on the above, I conclude that when assessing an individual’s recovery potential, one should consider alterations to various structural and functional properties of their visual system. In particular, the recovery potential may be impeded by bidirectional TSD along the entire visual pathway or benefit from a functional reorganization. Furthermore, the recovery potential may be inferred from fMRI-based VF reconstructions or resting-state functional connectivity patterns. Future studies are...
warranted to determine the exact relationship between the findings presented in this thesis and the recovery potential. Ultimately, in my view, the careful determination and consideration of the recovery potential of HH individuals may aid in developing and selecting successful and individually tailored rehabilitation interventions.
References


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