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STROKE OF THE VISUAL CORTEX

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DOCTORAL DISSERTATION

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ABSTRACT

Stroke is the leading cause of homonymous visual field defect (VFD), resulting from irreversible damage of the post-chiasmatic visual pathway. From 6 to 13% of ischaemic strokes affect the supply area of the posterior cerebral artery, including the visual cortex in the occipital lobe. Besides ischaemic injury, the visual cortex can be damaged by intracerebral haemorrhage (ICH), 10% of which reside in the occipital lobe. Since occipital stroke almost always disturbs vision but can leave motor and language functions untouched, it may remain unrecognised in the acute phase, withholding the patients from receiving recanalisation treatments. Moreover, only up to 25% of stroke-related VFD recover spontaneously, whereas the rest continue to hinder patients' independence in daily living and quality of life. Despite rigorous efforts, no evidence-based rehabilitation method to restore vision after stroke has been established.

The aim of this thesis was to study the recognition, clinical characteristics, rehabilitation, neural mechanisms, and outcome of occipital stroke patients with VFD. The retrospective part of the thesis consists of two cohorts. The first cohort comprised 245 occipital ischaemic stroke patients admitted to the neurological emergency department of Helsinki University Hospital due to visual symptoms in 2010–2015. We investigated their prehospital recognition and diagnostic delays and analysed the obstacles in their access to acute stroke treatment. The second retrospective cohort was the Helsinki ICH Study registry of 1013 consecutive non-traumatic ICH patients treated at Helsinki University Hospital in 2005–2010, among whom we searched for isolated occipital ICH patients and analysed their clinical characteristics, aetiology, outcome, and incidence of post-stroke epilepsy in comparison to ICHs of other location.

The prospective part of the thesis was based on the multicentre, randomised, sham-controlled exploratory REVIS (Restoration of Vision after Stroke) trial that studied rehabilitation of persistent VFD after chronic occipital stroke with different methods of non-invasive electrical brain stimulation. Altogether 56 patients were included in three 10-day experiments in three centres. The centres examined: 1) repetitive transorbital alternating current stimulation (rtACS) vs transcranial direct current stimulation preceding rtACS (tDCS/rtACS) vs sham in Germany, 2) rtACS vs sham in Finland, and 3) tDCS vs sham in Italy. In a functional magnetic resonance imaging spin-off study, resting-state functional connectivity of occipital stroke patients receiving rtACS or sham was compared to healthy control subjects at baseline and to each other after intervention.

We found out that the prehospital delay of occipital stroke patients ranged between 20 minutes and 5 weeks and only 20% were admitted within the 4.5-hour time window of intravenous thrombolysis. Consequently, only 6.5% received thrombolysis, which is the mainstay of acute stroke treatment. One fourth of the patients arrived through at

least two points of care and as many were assessed by an ophthalmologist before entering the neurological care, even though acute stroke patients should be transported directly to the neurological emergency department. The diagnostic delay was primarily caused by the patients' late contact to health care but was also attributed to poor recognition and misdiagnosis by health-care professionals.

The incidence of isolated occipital ICH was 1.9% of all non-traumatic ICHs and 5.3% of lobar ICHs. The patients with occipital ICH were younger and had more often vascular malformations as an aetiology of the bleeding than the non-occipital lobar ICH patients. They presented with milder symptoms and longer delay, and over 60% of the patients suffered solely from visual focal symptom. The haematoma volume in the occipital lobe was smaller and grew less compared to the non-occipital lobar haemorrhages. All in all, the occipital location of ICH was independently associated with favourable outcome at discharge among the patients with lobar ICH. The majority of the occipital ICH patients were able to return to independent activities of daily living, including driving a car and working, within a follow-up of a year. However, post-stroke epilepsy was as frequent as after non-occipital lobar ICH.

In the prospective REVIS trial, rtACS was mostly ineffective in vision rehabilitation according to behavioural vision tests. Neither did it affect resting-state functional connectivity in comparison to sham. Transcranial DCS alone increased the monocular visual field measured with standard automated perimetry. The combined tDCS/rtACS propelled some improvements in the secondary visual outcome measures but did not differ from the sham stimulation. All the stimulation modalities were tolerated well.

The functional connectivity of the chronic occipital stroke patients with VFD did not differ from the healthy control subjects when the whole brain network was considered in the analyses. However, a few occipital regions close to the infarct expressed lower local connectivity to the highly connected regions of the network according to the network graph metrics, whereas a lateral occipital region in the damaged hemisphere had higher network connectivity. These findings support the view that chronic ischaemic damage of the visual cortex affects functional connectivity within the visual network but leaves global connectivity unchanged.

In conclusion, occipital stroke patients are insufficiently recognised, and thus the awareness of visual stroke symptoms should be raised especially among the public but also among health-care professionals to provide the patients with timely acute treatment and to prevent permanent disability. Occipital ICH patients have relatively favourable outcomes, but a structural cause of bleeding should be searched. Non-invasive electrical brain stimulation with the examined modalities does not cause robust improvement in vision or functional connectivity of the brain networks after a 10-day treatment, but further experiments with tDCS-based methods, potentially in combination with vision training, may be worth pursuing.

TABLE OF CONTENTS

LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following publications referred to in the text by their Roman numerals:

I. Räty S, Silvennoinen K, Tatlisumak T. Prehospital pathways of occipital stroke patients with mainly visual symptoms. *Acta Neurol Scand*. 2018;137:51-58.

II. Räty S, Sallinen H, Virtanen P, Haapaniemi E, Wu TY, Putaala J, Meretoja A, Tatlisumak T, Strbian D. Occipital intracerebral hemorrhage – clinical characteristics, outcome, and post-ICH epilepsy. *Acta Neurol Scand*. 2021;143:71-77.

III. Räty S*, Borrmann C*, Granata G*, Cárdenas-Morales L, Schoenfeld A, Sailer M, Silvennoinen K, Holopainen J, Antal A, Rossini PM, Tatlisumak T, Sabel BA. Non-invasive electrical brain stimulation for vision restoration after stroke: An exploratory randomized trial (REVIS). *Restor Neurol Neurosci.* 2021;39:221-235.

IV. Räty S, Ruuth R, Silvennoinen K, Sabel B, Tatlisumak T, Vanni S. Resting-state functional connectivity after occipital stroke. *Neurorehabil Neural Repair.* 2022;36:151-163.

*These authors contributed equally to the respective work.

Publication II also appears in the dissertation of Hanne Sallinen, New insights into intracerebral hemorrhage, Faculty of Medicine, University of Helsinki (2020).

ABBREVIATIONS

ACS	alternating current stimulation
BOLD	blood oxygen level-dependent
CI	confidence interval
EMS	emergency medical service
EVT	endovascular thrombectomy
FC	functional connectivity
fMRI	functional magnetic resonance imaging
HICHS	Helsinki ICH Study
HRP	high-resolution perimetry
ICH	intracerebral haemorrhage
IQR	interquartile range
IVT	intravenous thrombolysis
LGN	lateral geniculate nucleus
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
OR	odds ratio
PCA	posterior cerebral artery
RCT	randomised controlled trial
ROI	region of interest
rsfMRI	resting-state functional magnetic resonance imaging
rtACS	repetitive transorbital alternating current stimulation
SAP	standard automated perimetry
tACS	transcranial alternating current stimulation
tDCS	transcranial direct current stimulation
tES	transcranial electrical stimulation
tRNS	transcranial random noise stimulation
V5/MT	visual area 5/middle temporal area
VFD	visual field defect

1. INTRODUCTION

Vision enables us to detect and interpret information about the surrounding environment based on light arriving on the retina of the eye. The visual system is highly complicated, and approximately one fourth of the cerebral cortex is dedicated to visual processing [1]. The primary visual cortex, as well as many of the secondary visual areas, are located in the occipital lobe [2,3], which receives blood flow from the posterior cerebral artery (PCA). The visual cortex is most often damaged by stroke [4,5]: ischaemic stroke due to occlusion of PCA or haemorrhagic stroke caused by bleeding from a ruptured intracerebral vessel. PCA strokes make up approximately 6 to 13% of ischaemic strokes [6-10], whereas intracerebral haemorrhages (ICH) affecting the occipital lobe represent about 10% of lobar ICH [11].

Unilateral occipital stroke typically results in homonymous hemianopia – a unilateral hemifield defect of both eyes [6,12-20]. Visual field defects (VFD) affect the ability to move independently, read, work and drive [21-24] and impair the quality of life after stroke [19,25]. They may recover spontaneously within the first few months, but the recovery is complete in only 5 to 25% and subsides by 6 months after stroke [19,26,27]. Patients do not recognise VFD as a sign of stroke [28] and visual deficits are not routinely included in the prehospital stroke scales used by emergency medical service (EMS) personnel to identify acute stroke patients [29]. Moreover, data on the acute recanalisation treatment of PCA strokes from randomised controlled trials (RCT) are scarce, so the treatment decisions are mostly based on the study results on anterior circulation stroke.

Due to the shortcomings of the acute treatment, the modest spontaneous recovery rate, and the toll to the quality of life, demand for effective rehabilitation of VFD after stroke is apparent. However, the evidence from RCTs is so far either low quality or lacking [30]. Most of the rehabilitation studies have focused on visual training methods that tend to be highly demanding for the patients and have provided mostly modest improvements in visual function. In recent years, non-invasive electrical stimulation methods have been introduced in the field of vision rehabilitation, namely repetitive transcranial alternating current stimulation (rtACS) for optic nerve damage [31] and transcranial direct current stimulation (tDCS) in combination with behavioural training after stroke [32-36]. Yet, the studies on stroke-related VFD have been small and preliminary.

During the past few decades, functional neuroimaging studies have produced data on neurophysiological changes associated with different brain disorders. One of the methods, resting-state functional magnetic resonance imaging (rsfMRI) can be used to investigate FC of brain networks [37]. After stroke affecting the visual system interhemispheric FC is disrupted in the acute phase and reverts along the clinical recovery [38]. Whether functional brain networks are altered in chronic stroke with persistent VFD remains unknown.

The aim of this thesis was to study occipital stroke and related visual field deficits. We wanted to embrace several blind spots of knowledge along the therapeutic path of these patients, ranging from acute recognition to rehabilitation and prognosis. First, we studied the prehospital recognition and diagnostic delays of occipital ischaemic stroke patients presenting with visual symptoms in a retrospective hospital-based cohort. Second, we investigated the clinical phenotype, outcome, and incidence of epilepsy after occipital ICH in a retrospective single-centre registry of consecutive ICH patients. Third, we evaluated FC of chronic occipital stroke patients suffering from persistent VFD in comparison to healthy control subjects with rsfMRI. Forth, we ran a multicentre, blinded, randomised, sham-controlled exploratory trial on rehabilitation of chronic VFD after occipital stroke with three non-invasive electrical stimulation methods, assessing both behavioural visual metrics and neurophysiological changes associated with rehabilitation.

2. REVIEW OF THE LITERATURE

2.1 The visual system

The visual system is responsible for receiving, relaying, forming, and interpreting visual perceptions from visual information of the surrounding world. Vision at daylight originates from cone photoreceptors that transduce photons to graded glutamate responses [39]. These signals stimulate bipolar and other intermediate cells and finally ganglion cells whose axons form the optic nerves (Figure 1). They cross in the optic chiasma where the fibres conducting information from the same hemifield of the eyes cross to the one side and fibres from the other hemifield to the other side. The post-chiasmatic fibres form the optic tracts that synapse in the lateral geniculate nuclei (LGN) of the posterior thalamus. From there, they diverge as the optic radiations that travel as an upper and lower division to the primary visual cortex, also called the striate cortex or V1, in the calcarine cortex of the occipital lobe; the neurons representing the lower visual field end to the upper bank of the calcarine sulcus and vice versa. This is called the retino-geniculo-striate pathway that mediates most of the neural output from the retinae. It consists of three cell types, called magnocellular, parvocellular, and koniocellular cells, that are classified according to their histologic appearance, convey different features of visual stimuli, and prevail anatomically segregated until the extrastriate visual areas [40].

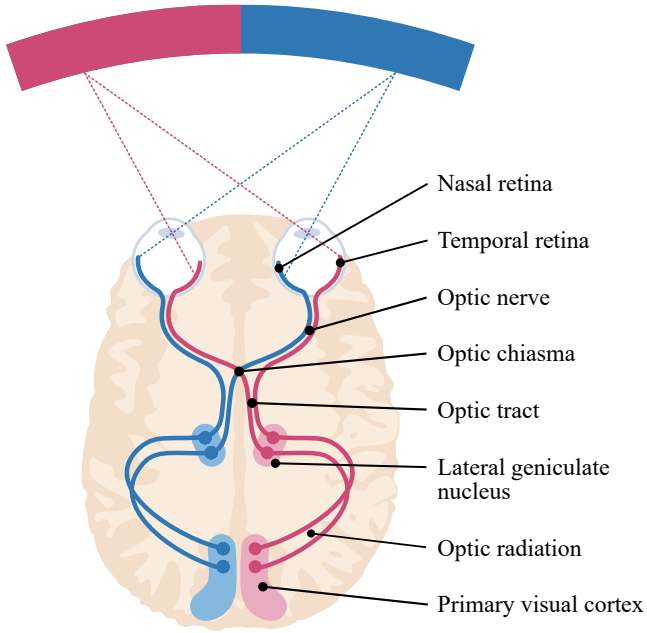

Figure 1. The retino-geniculo-striate pathway.

Much of the knowledge in the functional neuroanatomy of the visual cortex has been derived from animal studies, primarily from macaque monkeys and other primates [41], and later extended to humans based on functional imaging studies [42]. The neurons from LGN enter mainly into the fourth layer of the six-layered primary visual cortex that represents the lowest level of the hierarchical structure of the visual cortex [43]. From the primary visual cortex, they project towards the higher-order visual, or extrastriate, cortices along two separate routes, the ventral and dorsal stream [44]. The former is specialised in object recognition and includes areas in the occipito-temporal region extending towards the inferior temporal lobe, whereas the latter, covering areas in the anterior and middle occipital, dorsal parietal, superior temporal, and frontal lobes, processes spatial and movement information and participates in visual guidance of movements and attention. Altogether, approximately one fourth of the cerebral cortex is assessed to participate in visual processing [1].

All the way from the retina to the early visual cortex, the visual information retains its retinotopic organisation. This means that receptive fields of adjacent neurons are sensitive to stimuli from adjacent locations of the visual field. The neurons in the primary visual cortex respond to simple features in their relatively small receptive fields. However, downstream from the primary visual cortex the receptive fields become larger and the coding of visual information increasingly complex and specialised. Additionally, a neuron's response to stimuli within its receptive field is modulated by stimuli in the surrounding field – a process mediated via feedforward, feedback, and horizontal interactions that modify the signal coding at different levels of the visual system [45]. The retinotopic activation of nearby neuronal populations to different features of visual stimuli has been utilised to define cortical maps that divide the visual cortex into distinct hierarchical areas [42]. Besides hierarchical, the neural processing in the visual cortex is parallel and reciprocal and forms a highly complex and interconnected system with up to two thirds of possible intercortical connections existing [46]. Recent cortical maps have tried to tackle this complexity by incorporating topographical, functional, and connectivity data to model the architecture of the visual cortex (Figure 2) [47].

In addition to the retino-geniculo-striate pathway, there are subcortical projections from the retina to the extrastriate visual areas, bypassing the primary visual cortex (Figure 3). One route travels from the retina, via the colliculus superior or directly, to the pulvinar and further to the extrastriate cortex, including the visual motion area V5, also known as middle temporal (MT) area [48,49]. As observed from macaque studies, V5/MT also receives direct input from LGN [50], as do areas V2 and V4 [51,52]. The route from LGN equals 10% of the neurons projecting to V5/MT via the primary visual cortex and consists mainly of koniocellular cells [50]. Other subcortical structures receiving projections from the retina include the suprachiasmatic nucleus, the olivary nucleus of the pretectum, the terminal accessory optic nuclei, the nucleus of the optic tract, and the pregeniculate nucleus [53]. These pathways participate in more reflective visual functions, such as pupillary reflexes, circadian rhythm, or ocular movements.

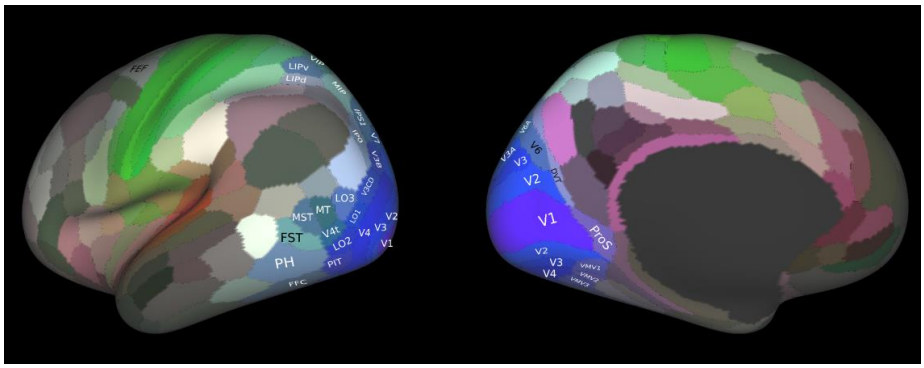

Figure 2. Human visual areas. The human brain is divided into 180 cortical areas according to Glasser et al. [47]. The striate and extrastriate visual areas (blue) and some of the visual association areas are annotated: V1–7, visual areas 1–7; MT, middle temporal area (V5); MST, medial superior temporal area; LO1–3, lateral occipital areas 1–3; PIT, posterior inferotemporal area; area FST; area PH; FFC, fusiform face complex; IPS1, intraparietal sulcus area 1; MIP, middle intraparietal area; VIP, ventral intraparietal complex; LIPd and LIPv, lateral intraparietal area, dorsal and ventral; IP0, intraparietal area 0; ProS, prostriate area; VMV1–3, ventromedial visual areas 1–3; DVT, dorsal visual transitional area. Frontal eye field (FEF) is also illustrated as it participates in controlling eye movements and visual attention. Figure has been created with the Connectome Workbench programme of the Human Genome Project (http://humanconnectome.org).

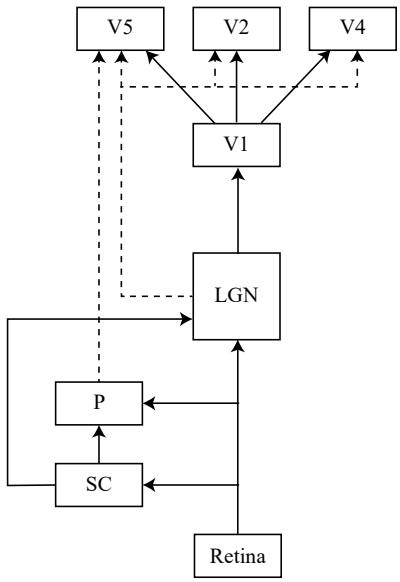

Figure 3. Pathways from the retina to the striate and extrastriate cortex. Dashed lines represent connections to the extrastriate cortex bypassing V1 (only the best-established connections are presented). Reciprocal connections are omitted. Based on data from Adams et al. [48], Lyon et al. [49], Sincich et al. [50], Lysakowski et al. [51], and Bullier et al. [52]. LGN, lateral geniculate nucleus; P, pulvinar; SC, superior colliculus.

2.2 Homonymous visual field defects

The prevalence of homonymous VFD is 0.8% in the population of over 50 years of age [54]. Given the neuroanatomy of the visual system, homonymous VFD is caused by unilateral damage to the post-chiasmatic visual pathway: the optic tracts, posterior thalamus, optic radiations, or occipital, temporal, or parietal lobe. In a study of 904 cases of homonymous VFD, the occipital, occipitotemporal, or occipitoparietal lobes were the most frequent lesion locations [4]. Approximately 89 to 94% of VFDs are unilateral and 55% affect the left visual field [4,5]. Homonymous VFD can range from scotoma to quadrantanopia to partial or complete homonymous hemianopia and can be either congruous (i.e., uniform in both eyes) or incongruous [4]. The defect can involve all visual modalities or save some of them, such as colour or form vision in hemiamblyopia [5].

Stroke is the most common aetiology of homonymous VFD with a percentage ranging from 70 to 76% (ischaemic stroke in 59–61% and haemorrhagic stroke in 11–15%) [4,5]. Other aetiologies, such as tumour, trauma, or demyelination are distinctly less frequent. Patients with ICH-related VFD are younger than ischaemic stroke patients, and the lesion affects more often the visual system beyond the occipital lobe [55].

The frequency of stroke-related VFD is 0.4 to 0.5% in a community-based elderly population and 5 to 8% if the patients report history of stroke [23,54]. In hospital-based cohorts, VFD affects around 20 to 50% of stroke patients in the acute phase [25,56,57]. If stroke patients are suspected to have visual impairments, the frequency of VFD increases to 52% [58].

Among stroke patients with VFD studied at a neuro-ophthalmology unit, 49% had isolated homonymous VFD without any other neurological deficits [55]. VFD was of occipital origin in 54% and congruous in 74% [55]. In contrast, among stroke patients treated at an acute stroke unit, VFD is associated with a more severe clinical entity and is most often caused by middle cerebral artery territory damage [57]. This distinction is likely to stem from the fact that severely neurologically disabled people are less likely to participate in detailed outpatient visual examinations and therefore are missed in studies with outpatient cohorts.

Visual field defects impair quality of life after stroke in comparison to either healthy population [59,60] or stroke patients without VFD [19,25]. Visual problems impact the ability to work, read, move, and drive a car, impair mental health, and reduce independence in daily living [21-24]. Visual ability has been assessed as one of the main predictors of life satisfaction after stroke [61]. The effect on quality of life depends on the side and extend of VFD [19], as well as on visual acuity [60]. Furthermore, the recovery of VFD is associated with improved quality of life [19].

2.3 Occipital stroke

2.3.1 Definition of stroke

According to the consensus statement of the American Heart Association and the American Stroke Association in 2013, stroke is defined as 'an episode of acute neurological dysfunction' of either ischaemic or haemorrhagic cause, 'persisting ≥ 24 hours or until death' [62]. It includes ischaemic stroke, ICH, and subarachnoid haemorrhage that make up approximately 80%, 10%, and 5% of stroke in high-income countries, respectively [63]. In ischaemic stroke, the permanent cell death in the central nervous system is attributable to ischaemia due to occluded blood flow of either an artery or a vein. ICH, on the other hand, is an intracerebral blood collection within the brain parenchyma or ventricular system, not caused by trauma [62]. The diagnosis of stroke can be based on either neuroimaging, pathological evidence, or clinical evidence and exclusion of other aetiologies.

2.3.2 Occipital ischaemic stroke

2.3.2.1 Definition, anatomy, and epidemiology

Ischaemic occipital stroke is caused by occlusion of PCA, the most distal branch of the vertebrobasilar circulation. It is divided to four segments according to its course around the midbrain and towards the occipital lobe (Figure 4) [64,65]. The first two segments of PCA, the P1 and P2 segments, provide deep perforator branches to the thalamus, hypothalamus, posterior limb of the internal capsule, midbrain, and rostral cranial-nerve nuclei (oculomotor and trochlear nerves). The superficial branches of PCA arise from the P2, P3, and P4 segments and include the temporal branches that supply most of the temporal lobe, particularly the inferomedial temporal region, the calcarine artery that supplies the occipital lobe, including the primary calcarine cortex, and the parieto-occipital artery. A common anatomical variant of PCA is the foetal PCA that continues as an extension of the internal carotid artery via a strong posterior communicating artery: approximately 10% of people have an absent P1 segment (complete foetal PCA) and 15% a hypoplastic P1 segment (partial foetal PCA) [66].

Knowledge of the occipital stroke is mostly acquired from several moderate-size series of tens to a few hundred PCA stroke patients [6,7,9,12-18,20,67] (Table 1). Therefore, these series are not limited to the occipital lobe infarcts but typically comprise patients with ischaemic lesions anywhere within the supply area of PCA. PCA strokes can be categorised into superficial and deep PCA infarcts according to the affected branches, as well as into PCA and PCA plus strokes based on whether other vascular territories besides PCA are involved.

The estimated cumulative lifetime risk of ischaemic stroke is 18% [68], and PCA infarcts comprise approximately 6 to 13% of all ischaemic strokes [6-10]; of them,

isolated PCA infarcts make up 61 to 66% and PCA plus infarcts 34 to 39% [7,9,13]. In 26 to 51%, the lesion is limited to the superficial territory of the artery and in 35 to 48% to the deep territory, including the midbrain and thalamus while 14 to 26% consist of both superficial and deep infarcts [6,9].

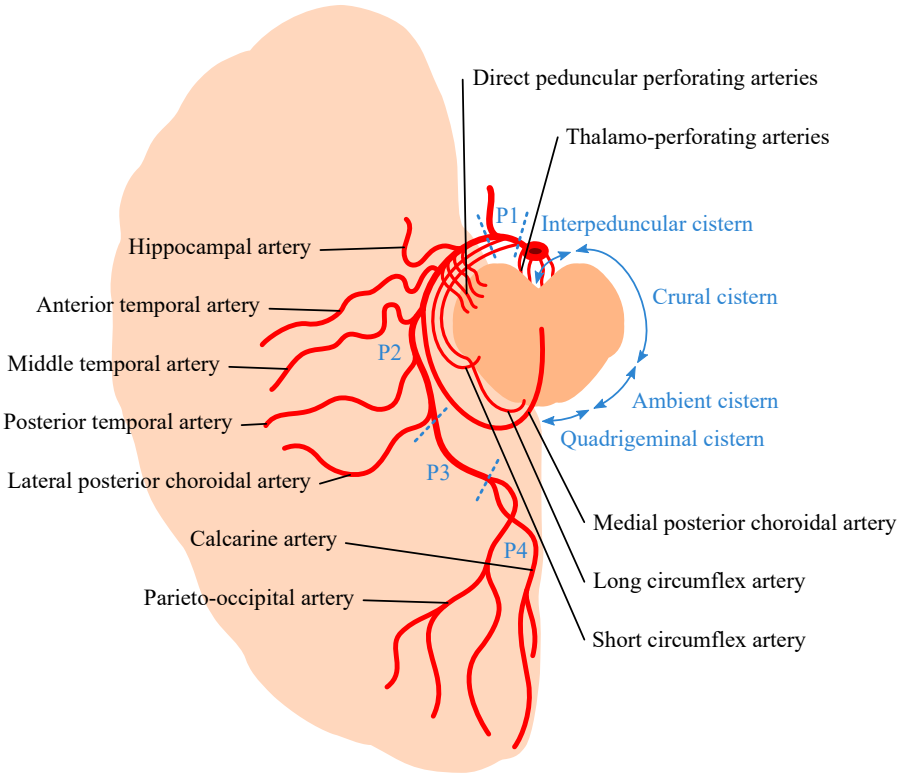

Figure 4. Schematic illustration of the anatomy of the posterior cerebral artery. The P1 segment reaches from the basilar artery to the entry of the posterior communicating artery within the interpeduncular cistern; P2 runs around the midbrain in the crural and ambient cisterns until the begin of quadrigeminal cistern; P3 travels in the quadrigeminal cistern and terminates as it enters the calcarine fissure; from there it continues as the P4 segment. The P2 segment can be further divided to two segments according to their course in the crural (P2A segment) and ambient (P2P segment) cisterns. Modified from Ciceri et al. [65].

2.3.2.2 Aetiology

The aetiology of PCA infarcts was first studied in a post-mortem series of posterior circulation stroke patients, among whom there were 30 people with PCA occlusions [69]. The cause of the stroke was embolic from atherosclerotic vertebral or basilar artery stenosis in 15 (50%), anterograde thrombosis from atherosclerotic basilar artery

occlusion in 8 (27%), isolated atherosclerotic PCA occlusion in 3 (10%), cardiac embolism in 1 (3%), and undetermined in 3 (10%). Since then, clinical PCA stroke series have reported the following aetiological distributions (Table 1): large artery atherosclerosis (13–50%), cardiac embolism (17–53%), other (3–23%), and undetermined aetiology (9–36%) [6,7,9,12-14,16-18,20]. The results vary depending on the diagnostic work-up, the aetiological definitions, and the selection of the included infarct distributions; for example, older series do not typically include small vessel disease as an aetiological entity. If only two of the more recent studies with over 200 PCA stroke patients are considered, one comprising only patients scanned with magnetic resonance imaging (MRI), small vessel disease appears as one of the most frequent (20–35%) aetiologies, especially in deep PCA infarcts [6,9].

Table 1. PCA infarct cohorts since 1985.

Cohort	Pessin 1987 [15]	Servan 1992 [20]	Milandre 1994 [18]	Brandt 1995 [12]	Steinke 1997 [17]	Yamamoto 1999 [13]	Cals 2002 [16]	Kumral 2004 [14]	Lee 2009 [9]	Ntaios 2011 [7]	Arboix 2011 [6]
N	35	76	82	127	74	79	117	137	205	185	232
Country	USA	France	France	Germany	Germany	USA	Switzer-land	Turkey	South Korea	Greece	Spain
Included PCA areas	sPCA± dPCA	sPCA± dPCA	sPCA or dPCA or both	sPCA± dPCA	sPCA± dPCA	sPCA± dPCA	sPCA	sPCA± dPCA	sPCA or dPCA or both	sPCA± dPCA±	sPCA or dPCA or both
PCA plus	no	yes	no	no	yes	yes	no	no	yes	yes	no
Prevalence (%)	-	-	13.7[a]	-	-	-	3.5[b]	2.9[b]	12.8[a]	8.1[a]	8.6[a]; 6.1[b]
Findings (%)											
VFD	100[c]	84	57	93	93	84	96	93	-	-	41
Sensory	20	32	46	29	14	15	14	47	-	-	51
Motor	17	-	34	28	20	29	19	34	-	-	39
Cognitive / behavioural	20	41	50	32	>55[d]	25	58	>36[e]	-	-	25[f]
Aetiology (%)											
LAA	17	23	43	28	30	41	13[g]	50	42	25	29
CE	29	35	18	33	31	41	44	17	20	53	22
SVD	-	-	16	-	-	-	-	-	20	-	35
Other	23	15	4	3	15	9	7	12	3	6	6
UD	31	27	20	36	24	10	35	21	15	16	9

[a] Of ischaemic stroke; [b] of all strokes; [c] VFD was an inclusion criterion; [d] memory deficit 55%, disorientation 35%, other 46%; [e] cognitive impairment 36%, visual inattention 13% etc.; [f] memory deficits; [g] aetiology was reported for 115 patients. PCA, posterior cerebral artery; sPCA, superficial branch of PCA; dPCA, deep branch of PCA; PCA plus, areas outside the supply area of PCA; VFD, visual field defect; LAA, large artery atherosclerosis; CE, cardiac embolism; SVD, small vessel disease; UD, undetermined.

In addition, some rare aetiologies of occipital infarction have been reported. In a cohort of patients with a first ever ischaemic stroke, the occipital lobe involvement was the only radiological finding independently associated with an unusual cause of stroke [70]. Rare causes with a proposed posterior predilection include mitochondrial disease [71,72] and migraine [73,74]. The relationship of occipital infarction and migraine has been debated: whether there is a causal link, such as in migrainous infarction [74,75], shared risk factors [76], or difficulty to differentiate the common symptoms of migraine and occipital stroke, including headache and visual symptoms, remains unresolved.

2.3.2.3 Clinical characteristics

The most common manifestation of PCA infarcts is homonymous VFD (41–96%), followed by sensory (14–51%), motor (17–39%), and neuropsychological (including visual cognitive) deficits (20–58%) [6,12-18,20] (Table 1). If only occipital ischaemic strokes are included, the frequency of VFDs is 79% [19]. Visual deficits after PCA stroke are typically complete homonymous hemianopias or (upper) quadrantanopias [14,16,77]. In approximately 10% of stroke-related VFDs, hemianopia spares the central visual field [16,55], which is suggested to be enabled by the collateral blood supply to the occipital pole [78]. Other visual disturbances associated with PCA infarcts include visuospatial processing problems, visual agnosia, visual neglect, visual hallucinations, problems of colour perception (dyschromatopsia), motion perception (akinetopsia), reading (alexia), and face recognition (prosopagnosia), inability to perceive multiple objects simultaneously (simultanagnosia), and deficits of eye movements [14,16,67,79]. Some of the deficits are extremely rare, as they require bilateral damage and may be missed without a detailed neuropsychological evaluation.

A particular symptom in patients with VFD after brain damage is hemianopic anosognosia, i.e., unawareness of the VFD. It is reported to be present in 16 to 62% of stroke patients with VFD and can appear in dissociation with neglect as well as in lesions restricted to the either-side occipital cortex, without a parietal extension [58,80,81]. In a population-based study by Gilhotra et al., up to 48% of elderly population with homonymous VFD due to stroke were unaware of either the VFD or their history of stroke [54]. Moreover, no more than 30% of those who knew they had suffered from stroke were aware of the VFD.

2.3.2.4 Outcome

Outcome data after PCA strokes are limited compared to anterior circulation stroke. Short-term (up to 1 month) mortality is reported to be 0 to 8% after isolated PCA stroke [6,7,16,18] and 25% after PCA plus stroke [7]. The respective long-term mortality reaches 4 to 11% and 40% at 6 months [7,14,15] and 55% and 73% at 10 years [7].

In stroke research, functional outcome is most often described according to the modified Rankin Scale (mRS), which ranges from 0 (no symptoms) to 6 (death) [82]. An mRS score 1 equals excellent outcome with some residual symptoms but no disability, whereas patients with an mRS score 3 need some help in their everyday life but can walk unassisted. Ntaios et al. have so far reported the most comprehensive data on functional outcome after PCA stroke, stratified by the affected vascular areas (Table 2) [7]. In their cohort of 185 patients, the outcome was associated with the extent of the stroke, being best when only the superficial PCA branches were affected and worsening as the deep PCA branches or vascular areas beyond PCA were damaged. In addition, Cals et al. observed excellent outcome (only minor sequelae or no disability) in 75% of superficial PCA strokes [16].

Table 2. Outcome after PCA stroke stratified by the stroke extent (based on data from Ntaios et al. [7]).

Lesioned areas	Superficial PCA	Superficial + deep PCA	Superficial PCA plus	Superficial + deep PCA plus
1 month				
mRS 0–1 (%)	56	29	33	18
mRS 0–3 (%)	84	54	47	29
Mortality (%)	8	8	22	30
6 months				
mRS 0–1 (%)	56	37	36	26
mRS 0–3 (%)	83	66	47	44
Mortality (%)	10	13	39	41

PCA, posterior cerebral artery; mRS, modified Rankin Scale.

2.3.2.5 Acute treatment and recognition

The mainstay of the modern acute ischaemic stroke treatment is immediate recanalisation, the removal of a thrombus occluding an artery, which can be achieved by two methods: intravenous thrombolysis (IVT) administered within 4.5 hours [83] and endovascular thrombectomy (EVT) for large vessel occlusion within 6 hours of symptom onset [84]. In recent years the time window of IVT has increased up to 9 hours [85] and of EVT up to 24 hours [86,87] for patients selected with advanced imaging. Although the research on IVT has focused on anterior circulation stroke, patients with acute posterior circulation stroke appear to achieve at least equally good outcomes [88]. Based on observational findings, occipital stroke patients with VFD seem also to benefit from IVT [89]. However, prospective studies addressing the question are lacking.

Patients with occipital stroke may present with sole VFD and therefore score low (1–2 points) in the National Institutes of Health Stroke Scale (NIHSS), which is the scale most often applied to rate the clinical severity of acute stroke [90]. A meta-analysis of the individual patient data from nine IVT trials concluded that IVT increases the odds for good functional outcome even for patients with minor stroke symptoms (NIHSS 0–4); yet symptoms deemed non-disabling were mostly excluded from the studies [91]. A later RCT investigated IVT in patients with minor non-disabling symptoms, defining disabling as a deficit that 'would prevent the patient from performing basic activities of daily living (i.e., bathing, ambulating, toileting, hygiene, and eating) or returning to work', and found no outcome favour with IVT [92]. Based on these findings, both the European Stroke Organisation and the American Stroke Association have recommended IVT for patients with minor disabling stroke symptoms [93,94]. Since the visual deficits were mostly regarded as disabling in the above studies, the guidelines can be interpreted to be in favour of IVT for patients with isolated VFD. Therefore, the current limited evidence does not support withholding IVT from these patients, even if individual consideration is warranted.

Up to now, the RCT evidence supporting EVT only exists for anterior circulation stroke [84]. Observational studies report comparable outcomes for the large vessel occlusions of the posterior circulation, but the proportion of isolated PCA occlusions included in the studies is no more than 3–4% [95,96]. A few relatively small observational studies on EVT for pure PCA occlusions have been conducted. One study compared retrospectively patients with proximal PCA occlusion (the P1 or P2 segment) treated with EVT to best medical treatment (IVT or conservative treatment) and observed a trend for better functional outcome and visual field normalisation in the former group [97]. In addition, the following outcomes have been observed for EVT-treated, mostly proximal PCA occlusion patients: 3-month mRS 0–2 in 60% [98,99] and mRS 0–1 in 55% [97] and discharge mRS 0–1 in 46% [100]. Mortality at 3 months has reached 7 to 16% [97-99]. In addition, a recent multicentre observational study compared retrospectively EVT to best medical treatment in a cohort of 184 patients with more distal PCA occlusions (the P2 or P3 segment) [101]. They discovered a trend for an early neurological improvement for the group receiving EVT; the subgroups benefitting were the ones with higher baseline stroke severity or contraindication for IVT. However, no difference in functional outcome at 3 months occurred. Hence, the evidence of whether PCA stroke patients should be treated with EVT is inconclusive.

Since occipital stroke patients may benefit from IVT (and in selected cases from EVT), they should be recognised as quickly as possible and transported to a unit providing the treatment. However, studies on posterior circulation stroke patients indicate that there are hurdles in their early diagnosis. Due to the different symptom distribution compared to anterior circulation stroke patients, they have lower NIHSS scores [102] and are more prone to be misdiagnosed at the emergency department

[103]. In a study of Ntaios et al., only 3.8% of PCA infarct patients received IVT, even though almost 50% arrived at the emergency department within 3 hours [7]. Patients with posterior circulation stroke also receive both IVT and EVT later than those with anterior circulation occlusion [95,104,105]. Furthermore, due to the frequently present visual anosognosia [58,80,81], patients with isolated VFD may not seek medical help urgently enough. Finally, the visual symptoms that dominate the clinical phenotype of occipital stroke are seldom included in the prehospital stroke scales used by EMS to recognise a stroke patient [29].

2.3.3 Occipital intracerebral haemorrhage

Intracerebral haemorrhages are rarer than ischaemic strokes with the estimated cumulative lifetime risk of 8% [68]. They are often classified based on the location of the bleeding either as lobar or deep ICH, the former residing in the lobes of the cerebrum and the latter in the basal ganglia, thalamus, internal capsule, brainstem, or cerebellum [106]. This classification has implications for the aetiology and outcome of ICH. Of the major aetiologies, cerebral amyloid angiopathy is more common in lobar ICH, whereas hypertension is associated with deep ICH [107-109]. Lobar ICH seems to have a better outcome than non-lobar ICH [110]. Other well-established factors associated with outcome comprise haematoma volume, clinical severity, age, and the presence of intraventricular haemorrhage [110-113]. Additionally, ICH during anticoagulation therapy has been reported to associate with higher and structural aetiology with lower mortality [114].

However, more detailed topographical analyses of ICH phenotype, aetiology, and outcome comparable to that acquired about ischaemic stroke have been scarce. A study used a voxel-based analysis to investigate the association of affected anatomical structures and outcome and observed that in lobar ICH, the location in the inferior parietal lobule or the posterior insula or extension to the posterolateral thalamus predicted higher mortality [115]. In contrast, no regions associated with reduced mortality were found. When it comes to the distribution of potential aetiologies of bleeding between the lobes, cerebral amyloid angiopathy has been most prevalent in the occipital lobe [116], whereas arteriovenous malformations are most frequently located in the parietal lobe [117].

Nevertheless, to the best of our knowledge, no cohorts of occipital ICH have been reported. The most comprehensive data so far come from Gerner et al. who conducted a retrospective study of 260 non-traumatic lobar ICH patients, among whom the isolated occipital location occurred in only 4.6% (n = 12) of haemorrhages, whereas occipital, occipitotemporal, and occipitoparietal ICH made up 10% [11]. In addition, isolated occipital ICH had the smallest average volume and grew least during the acute phase, and the patients had a lower NIHSS score on admission compared to those with other isolated lobar ICH locations. The same study reported that the occipital ICH patients had more often a favourable functional outcome, defined as mRS 0–3 at 3 and

12 months (83.3% of the patients at each time point) than the patients with more rostral haematoma location. In fact, the occipital location was an independent predictor of the favourable functional outcome at 3 months [11]. However, there have been no reports of aetiologies of occipital bleeding, nor of the presence of visual deficits after occipital ICH.

2.3.4 Post-stroke epilepsy

Epilepsy is defined as a long-term predisposition for spontaneous seizures, the aetiology of which can be genetic, metabolic, infectious, immune, structural, or unknown [118,119]. The diagnosis requires either at least two separate unprovoked seizures or one seizure and a markedly increased probability for further seizures, usually based on either neurophysiological or radiological proof [120]. Altogether 11% of epilepsies are of cerebrovascular origin [121], and the cumulative rate of post-stroke epilepsy reaches 9 to 12% among stroke patients within a follow-up of 8 to 10 years after stroke [122-124]. Post-stroke epileptic seizures can be divided into acute and late seizures. The former begin within a week of stroke onset, whereas the latter occur later than one week after stroke and predict future seizures as much as to justify the diagnosis of epilepsy [125].

Stroke characteristics affect the tendency to develop post-stroke epilepsy: haemorrhagic [122], large [123,126,127], severe [123,128], and cortical stroke [123,126,127,129] in younger patients [122,123,126] with previous early seizures [126,127,130] have been suggested to be associated with a higher risk of epilepsy. Yet, less is known about the association of a more precise lesion location with the incidence of post-stroke epilepsy. In ischaemic stroke, lesions involving the anterior circulation [123,127] and especially the posterior area of the lateral sulcus predicted late seizures, whereas the occipital location was not associated with either early or late seizures [131]. The data after haemorrhagic stroke are even scarcer. A study comparing 14 ICH patients with post-stroke seizures and 51 seizure-free ICH patients found an association between the frontal lobe location and seizures [132]. When it comes to stroke symptoms, the presence of VFD has not been independently associated with post-stroke epilepsy [123].

2.4 Recovery of visual field defects after stroke

Recovery after stroke alludes to the regain of a function impaired by irreversible loss of neurons. It can be either a partial or complete return to the pre-stroke functional state. In the scientific literature, the term often refers to both an adaptive function achieved by behavioural compensation and true recovery of the pre-stroke function [133].

Clinical studies have revealed that VFD caused by stroke can recover spontaneously for up to 6 months [27]. However, the recovery rate is highly variable,

and the improvement is mostly partial and occurs primarily within the first few weeks after stroke [19,25-27,134-137] (Table 3). Most recovery seems to occur within the lower quadrants of the visual field, which has been proposed to be due to the anatomic distribution of the collateral blood supply [26,138].

In a prospective hospital-based study by Gray et al., 99 hemispheric stroke patients with complete or partial hemianopia were studied with confrontation testing within 72 hours of stroke onset [137] (Table 3). At 28 days, 67% of the 57 survivals had experienced improvement in their visual field and 47% recovered completely. Tiel and Komel reported a prospective series of 69 PCA infarct patients with complete hemianopia who were tested with standard perimetry up to 3 weeks (mean 3.4 days) after stroke and then repeatedly until no more improvement was observed [26]. They discovered that 48% of the patients improved and 25% recovered completely. Emphasising the time course of recovery, 72% of the improved patients were first assessed within 48 hours and 87% within a week after the index stroke. On average, the improvement occurred within 25 days of the initial measurement, but the longest follow-up continued for 2 years. In a retrospective case series by Trobe et al. on 104 patients with homonymous VFD, 89% of which were caused by ischaemic stroke, only 18% of the patients improved [134]. However, the clinical course was only reported for the 51 patients who were followed up for at least 2 years, and the timing of the initial evaluation was withhold. Moreover, no modern neuroimaging was available during the study period and the diagnostic work-up was based on electroencephalography, lumbar puncture, skull x-ray, and clinical course. Both Tiel and Komel and Trobe et al. included only patients with isolated VFD, whereas patients in the study by Gray et al. suffered also from other neurological deficits. In a prospective study of 50 stroke patients with VFD by Messing and Ganshirt, the mean increase in the visual field among 37 survivors with no further strokes during the 3-year follow-up was 7% in partial hemianopia, 16% in complete hemianopia, and 37% in cortical blindness, mostly completed by 6 months [136]. Altogether 86% of the patients improved but only 3% recovered completely. However, the poorest improvement was reported by Zihl and von Cramon who found out that only 7% of 55 stroke and traumatic brain injury patients improved during a follow-up of at least 3 weeks succeeding the initial measurement within the first 2 weeks after the injury [135].

More recent studies on VFD recovery have mostly agreed with the previous results (Table 3). Zhang et al. analysed retrospectively 263 consecutive homonymous VFDs examined at least twice with conventional perimetry and found out that 38% improved and only 5% recovered completely [27]. The median time interval from the symptom onset to the initial measurement was 2 months. In a subgroup of 113 VFDs examined within the first 4 weeks of the injury, 55% improved and 9% recovered completely. The cohort included both stroke-related VFDs and those of other aetiologies. The stroke patients represented 73% in the early examined subgroup, and in the larger cohort where the sample of the study was derived from, stroke made up 70% of the

cases [4]. The recovery rate decreased along the first months and was non-existent after 6 months. Age, sex, lesion type and location, aetiology, and the presence of other neurological deficits were not associated with recovery. Tharaldsen et al. reported similar results in their smaller cohort of occipital infarction patients with a 55%-improvement rate at 6 months [19]. In their study, patients met a vision teacher, but whether this appointment included any rehabilitation interventions, was not addressed.

Table 3. Studies reporting spontaneous recovery of VFD.

	Trobe et al. 1979 [134]	Zihl & von Cramon 1985 [135]	Messing & Ganshirt 1987 [136]	Gray et al. 1989 [137]	Tiel et al. 1991 [26]	Zhang et al. 2006 [27]	Ali et al. 2013 [25]	Tharaldsen et al. 2020 [19]
N	104	55	37[a]	99	69	263[b]	5978	52
Study design	Retrospective	Prospective	Prospective	Prospective	Prospective	Retrospective	Retrospective analysis of prospective data	Prospective
Time span	1939–1966	-	-	Feb 1985 – Sep 1986	1980–1989	1989–2004	-	Aug 2013 – Dec 2014
Cohort	Patients with isolated VFD in ophthalmo-logy unit	Patients with VFD in rehabilitation trial before intervention	Occipital stroke patients with VFD	Stroke patients with VFD at hospital <72 h of onset	PCA stroke patients with isolated CHH	Patients with VFD in neuro-ophthalmology unit	Acute stroke patients with >0 p in NIHSS item 3[c] in non-thrombolysis trials	Occipital stroke patients with VFD at hospital ≤7 d of onset
Aetiology	89% IS (86% PCA, 3% MCA)	80% IS (all PCA), 20% TBI	84% IS, 16% ICH	IS	IS	Multiple aetiologies (73% stroke in early group)	IS or ICH	IS
Baseline test	-	≤2 wk	≤7 d	≤72 h	Mean 3.4 d (range 0–21 d)	Median 2 mo	-	≤2 wk
Follow-up	>2 y	>3 wk	36 mo	28 d	≤2 y	Median 6 mo (range 1–120 mo)	3 mo	6 mo
Method of VFD assessment	SAP	SAP	SAP	CTest	SAP	SAP	CTest, NIHSS item 3	SAP
Any recovery	18%[d]	7%	86%	38% (67%[e])	48%	38% (55%[f])	72% of CHH, 55% of BHH	55%[g]
Complete recovery	-	-	3%	27% (47%[e])	25%	5% (9%[f])	55% of CHH, 69% of PHH, 47% of BHH	5%[g]

[a] The number of patients in the final cohort after excluding the ones who died or had recurrent stroke, originally 50; [b] homonymous VFDs among 254 patients; [c] item 3 of NIHSS: 1 p PHH, 2 p CHH, 3 p BHH (Cave! 1 point can be also acquired from visual neglect); [d] among 51 patients followed-up for ≥ 2 years; [e] among 57 survivors at 1 month; [f] among 113 patients examined < 4 weeks; [g] among 44 patients with available perimetry at 6 months. VFD, visual field defect; NIHSS, National Institutes of Health Stroke Scale; IS, ischaemic stroke; PCA, posterior cerebral artery; MCA, middle cerebral artery; TBI, traumatic brain injury; ICH, intracerebral haemorrhage; SAP, standard automated perimetry; CTest, confrontation testing; CHH, complete homonymous hemianopia; PHH, partial homonymous hemianopia; BHH, bilateral homonymous hemianopia.

Additional insight into the time course of visual recovery is provided by Ali et al. who studied acute stroke patients from the VISTA (Virtual International Stroke Trial Archive) registry, combining data from several clinical trials on acute stroke [25] (Table 3). The presence of VFD was evaluated based on the visual domain (item 3) in NIHSS assessed with confrontation testing at baseline and at 30 and 90 days. Of 11 900 patients, 5 978 (50.2%) had VFD in the initial examination: 34.9% had complete hemianopia (NIHSS 2 points), 14.5% had partial hemianopia (1 point), and 0.8% had bilateral hemianopia (3 points). By 90 days, 55% of the surviving patients with complete hemianopia, 69% with partial hemianopia, and 47% with bilateral hemianopia had recovered completely according to their NIHSS score and 72% of the patients with complete hemianopia and 55% with bilateral hemianopia had improved, resulting in a residual prevalence of 21% for any VFD among the surviving 9 338 patients of the whole cohort. Again, most recovery occurred within the first 30 days. The improvement was associated with IVT, younger age, and no history of diabetes and prior stroke. Both hemianopia at baseline and at 90 days were associated with poor functional outcome at 90 days when adjusted for confounders. The study was limited by the VFD assessment with only confrontation testing and by the representativeness of the study population, as most trials included mainly anterior circulation stroke patients. Furthermore, the timing of the baseline measurement was omitted but is often within the early hours of stroke in acute stroke trials, so the notable recovery rate may also reflect a high number of patients with transient ischaemic attack.

All in all, there are several obstacles when studying the incidence and recovery of stroke-related VFD, mainly:

1) The timing of the first visual field assessment: Most recovery occurs early and is missed if the baseline state is measured several days after the index event. Accordingly, the most reliable assessments of the point prevalence of VFD after stroke and the rate of spontaneous recovery can be achieved with studies targeting the first post-stroke days.
2) The method of assessment: The sensitivity of confrontation testing is no more than 70% in hemianopia and less in smaller defects when compared to conventional perimetries, so it cannot exclude VFD [139,140]. However, it is usually the only viable option in acute settings if severely injured stroke patients are included because their cooperation does not suffice to standard perimetry.
3) The study population: Some studies include patients evaluated at acute stroke centres, whereas others concentrate on patients referred to ophthalmology outpatient clinics. They often exclude patients with lowered consciousness, aphasia, or dementia, and therefore apply only to a subset of stroke patients with VFD. In addition, many older studies rely on clinical diagnosis of stroke and may therefore have included patients with other aetiologies.

2.5 Rehabilitation of visual field defects

2.5.1 Definitions

Because of the limitations of the acute treatment and the unsatisfying rate of spontaneous recovery, several rehabilitation methods have been investigated for patients with VFD after brain injury [141,142]. Rehabilitation strategies for post-chiasmatic VFD can be divided in three categories: 1) substitution, 2) compensation, and 3) restitution [143]. Substitution exploits optic aids and environmental modifications (e.g., prisms) to overcome the functional impairment caused by the deficit. Compensation has the same target by supporting an adaptive use of spared functions, such as training eye movements to improve the field of visual search on the side of the defective field. In contrast, restitution aims at regaining some of the impaired visual function without compensation. This can be attempted with behavioural training and/or neurostimulation methods and demonstrated as decreased VFD or as improvement in other visual metrics, such as motion discrimination or visual acuity. These rehabilitation approaches have been studied with several methods, but the next sections concentrate on restitution after a short introduction to compensatory methods. First, we will discuss behavioural rehabilitation and later move on to more novel neurostimulation methods. The section is finished with current controversies in vision rehabilitation. Although pharmacological interventions have been studied in both animals [144] and humans [145] with amblyopia, they have not so far been reported in vision rehabilitation after stroke beyond case reports and are thus not discussed here further.

2.5.2 Behavioural training

The best-established approach in vision rehabilitation, compensation, is applied to alleviate functional handicaps caused by VFD, including problems in visual exploration, ineffective scanning, and impaired reading. These methods comprise training for visual search, visual attention, eye movements, and reading strategies, to name a few [142]. The aim is to strengthen and adjust undamaged visual functions to compensate for the defective ones, mainly to intentionally shift patients' gaze towards the affected field. Up to a 30° improvement of the visual search field has been reported from non-controlled clinical trials [146], but the results of RCTs have been more cautious: a recent Cochrane review concluded that compensatory methods seem to improve quality of life after stroke-related VFD but may not affect the size of the defect, extended activities of daily living, reading, or scanning ability [30]. Yet, mainly compensatory methods are offered for patients after stroke affecting vision.

Restitution, on the other hand, is based on the idea of residual visual abilities that can be reactivated or strengthened after damage to the visual pathways. Repetitive stimulation of the visual system has been hypothesised to partially restore vision by

activating residual neuronal connections and inducing synaptic plasticity at the border and inside the damaged cortical area, its downstream networks, and at the unaffected extrastriate pathways [147-149]. The stimulation has most often been executed by means of repetitive visual training that can target either the visual field border area [150-158] or inside the blind field [159-168] and that differs according to the task (detection, discrimination, identification), type of presented stimuli, use of additional cues, duration, and timing [141,169,170].

The border area training and the blind field training are suggested to act by different mechanisms. The former targets relative field defects, also called 'areas of residual vision', at the transition zone of VFD where some, but not all, of the detection abilities are preserved [171]. The achieved visual field expansion is typically around five degrees, but the response rate varies greatly between individuals [147]. Restitution within these areas has been proposed to stem from small-scale neurological changes at the border or in islands of spared neuronal tissue within the damaged cortex as well as from more large-scale network alterations, including restoring interhemispheric imbalance [147,148].

The blind field rehabilitation, on the other hand, is founded on a phenomenon called 'blindsight', defined as a scenario where patients with damaged primary visual cortex can discriminate visual stimuli presented in their defective field unaware or with impaired awareness of this ability [172-174]. The stimuli captured by residual vision within the blind field are typically moving or of high luminance contrast and are traditionally tested with force-choice paradigms [53]. The blind field discrimination and its improvements seem to be dissociated from luminance detection and are not necessarily captured with traditional perimetries [168]. The blindsight has been proposed to be mediated through pathways bypassing the primary visual cortex, such as the one via the superior colliculi and pulvinar and the other consisting mainly of koniocellular neurons that project from LGN to the extrastriate cortex and especially to the motion-sensitive area V5/MT [53,175,176].

There have been several rehabilitation efforts for VFD after stroke, beginning from the work by Zihl and von Cramon reported over 40 years ago [135,151]. However, high-quality RCTs are still lacking. A meta-analysis by Pollock et al. found no interventions with a significant effect on the size of VFD, functional or extended activities of daily living, reading, or falls among nine studies comparing either restitutive, compensatory, or substitutive therapies to a group receiving placebo or no treatment [30]. There was only one study of 19 subjects that compared 6-month border area training to a placebo group [150]. The training required subjects to detect stationary stimuli of varying luminance presented in the border area of their VFD while maintaining central fixation. The control regimen comprised changing fixation within the central visual field. The study revealed no difference between the groups in the extent of VFD measured with standard automated perimetry (SAP) after the intervention. In contrast, VFD decreased more in the intervention group when assessed with high-resolution perimetry (HRP) presenting suprathreshold stimuli. However,

only ten of the subjects had stroke-related VFD and they were unevenly distributed between the groups.

In another rare restitutive attempt for VFD rehabilitation applying a controlled design, Elshout et al. studied 25 chronic stroke patients who trained either their defective or intact field, after which the treatment arms were changed [177]. The 8-week (40 hours) training period consisted of a computer-assisted discrimination task with high-contrast stimuli presented throughout the visual field and primed with attentional cueing. The study found out that the training of the defective field reduced VFD compared to the training of the intact field or a period of no training, assessed as a visual field border shift in Goldman perimetry.

However, most of the other studies on vision restoration have been observational or trials without a randomised control regimen. In recent years the emphasis has been on the blind field approach with some promising results from non-controlled studies [164,166,168]. All in all, the common chord for vision restoration studies is that the rehabilitation programme requires months of intensive training and is demanding for both patients and rehabilitation institutions.

Studies on vision restitution have tried to detect factors influencing the treatment response, but the results from small non-confirmatory studies are only suggestive. One determinant of the treatment response is suggested to be the size of the relative defect, with larger defects associated with greater visual field improvement [147,156,177]. Lesion age, on the other hand, has been argued not to affect recovery [154,166,178], which is counterintuitive concerning that the window of spontaneous recovery coincides early after the damage [26,27]. To challenge this notion, Saionz et al. observed that residual visual properties differ in subacute and chronic occipital stroke and that recovery of motion discrimination requires less training in the subacute phase [168]. Yet, most of the studies have recruited chronic stroke patients, with a few exceptions with subacute interventions [35,168,178]. This has been justified by methodological issues, as the chronic phase excludes the possibility of spontaneous recovery and alleviates the interpretation of results. Finally, recent studies have suggested new imaging markers for the rehabilitation response, including optic tract shrinkage at the chronic phase [179], pre-training V5/MT activity in functional magnetic resonance imaging (fMRI) [167], and resting-state functional connectivity (FC) between the precuneus and the occipital pole network [180].

2.5.3 Non-invasive brain stimulation

Non-invasive brain stimulation refers to neurostimulation methods applied outside the skull utilising either magnetic fields, ultrasound, or electrical currents. The last one is called transcranial electrical stimulation (tES), which comprises transcranial random noise stimulation (tRNS), tDCS, transcranial alternating current stimulation (tACS), and transcranial pulsed current stimulation. According to a recent consensus statement on the nomenclature of tES, distinct modalities have also been distinguished by the

waveform of current, intended outcome, and electrode montage [181]. A few of these tES methods are next reviewed in more detail.

Transcranial direct current stimulation is the most extensively studied low-intensity (≤ 2 mA) tES modality and has been increasingly deployed in various clinical indications [182]. In tDCS, the weak tonic current of constant polarity is administered through electrodes organised on the scalp according to the target region. The principle mechanism of tDCS is subthreshold modulation of neuronal excitability: it either enhances or reduces excitability by depolarisation or hyperpolarisation of underlying neuronal membranes, depending on the direction of current and the orientation and distance of target cell populations [183-185]. However, unlike transcranial magnetic stimulation, it does not induce action potentials. According to the polarity of current, the stimulation is either cathodal or anodal (Figure 5). In the visual cortex, anodal stimulation over the occipital midline (Oz according to the 10–20 international system) increases excitability whereas cathodal stimulation decreases it [186,187]. Besides the polarity of current and the electrode montage, the outcome of stimulation depends on current intensity, stimulation duration, and the ongoing activity of the target cell populations [182,188]. In healthy volunteers, tDCS over the occipital cortex has improved visual detection, including contrast sensitivity and perception of objects and faces [189,190]. The after-effects of tDCS last beyond the duration of stimulation [191], which is suggested to be based on synaptic plasticity, especially in glutaminergic synapses [182,188].

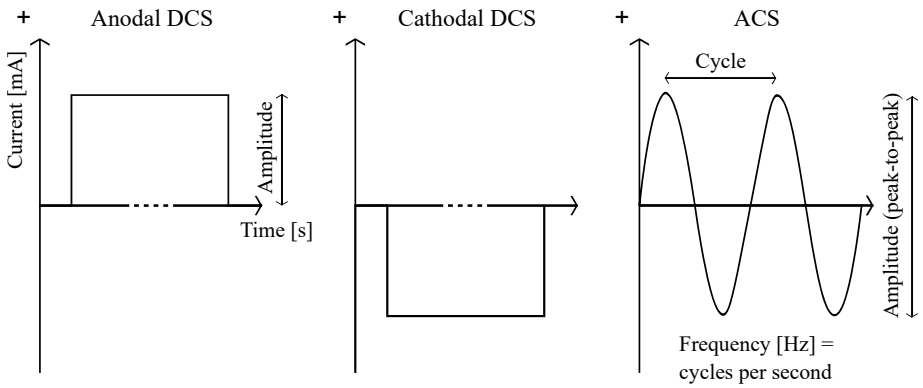

Figure 5. Stimulation paradigms of direct current stimulation (DCS) and alternating current stimulation (ACS). + sign indicates current direction towards the skull.

Transcranial direct current stimulation has been investigated in several neurological and psychiatric diseases, including chronic pain, depression, movement disorders, tinnitus, addiction, epilepsy, and stroke (mainly manifesting with motor and language deficits) [182]. However, the results in stroke rehabilitation have so far been modest

and inconsistent [182,192]. Recently, some research groups have turned to tDCS in vision rehabilitation after stroke (Table 4). Small pilot studies have reported positive findings on tDCS in combination with visual training in patients with subacute [35] or chronic occipital stroke [32-34,193-195]. Plow et al. studied 12 patients with homonymous VFD in a randomised controlled design. In their final analysis including eight patients, they found out that 3-month anodal tDCS over both occipital lobes in combination with vision restoration training targeted at the visual field border area expanded the visual field and improved vision-related activities of daily living in comparison to the training alone [32,33]. The extent of the visual field improvement after the 3-month regimen corresponded to the previous results achieved after 6-month vision restoration therapy [150,154], prompting the authors to propose that the combination therapy offers add-on benefit in vison restoration.

Olma et al. recruited 12 chronic occipital stroke patients to perform a daily motion discrimination task and to receive either 5-day tDCS or sham in a crossover design [34]. They measured motion sensitivity in the intact field and concluded that tDCS enhanced the learning effect achieved with the repetitive training alone. However, the affected field was not assessed even though the stimulating electrode was placed over the lesioned occipital lobe. Alber et al. applied tDCS and border area training to seven patients with subacute occipital stroke and compared them to a retrospective cohort of patients receiving routine rehabilitation, including training saccades and visual exploration [35]. The tDCS group achieved a greater relative visual field expansion after ten treatment sessions, although the treatment response varied markedly. The rest of the studies have included only one or two patients [193-195].

However, not all studies on tDCS in vision rehabilitation have been positive. Larcombe et al. investigated seven patients with VFD after chronic stroke of the primary visual cortex with considerably shorter 5-day blind field training with a motion direction discrimination task combined to either anodal tDCS over V5/MT, sham stimulation or no stimulation [36]. In this setting, none of the groups experienced improvement in motion detection ability or motion direction discrimination. All in all, the electrode placement, treatment duration, behavioural tasks, and outcome measures have varied widely, and larger confirmatory studies on the efficacy of tDCS in vision rehabilitation are still lacking.

In addition to tDCS, other tES modalities have been tested in vision rehabilitation after stroke. A preliminary study by Herpich et al. showed that tRNS in combination with visual training with a global direction discrimination task improved motion discrimination in both healthy subjects and patients with VFD [196]. The study recruited eleven stroke patients, three of whom received tRNS and training, two received sham stimulation and training, and in a non-randomised study arm, six were only trained. The patients treated with bilateral occipital tRNS improved approximately 10 to 30 percentage points (pp) in a motion discrimination task targeted at their blind field, whereas the other two groups did not benefit from the 10-day treatment.

Table 4. Transcranial electrical stimulation studies on stroke patients with hemianopia.

Publication	Study design	Patients	Time since injury	Intervention	Control	Duration	Stimulation intensity	Electrode montage[a]	Results
Halko et al. 2011 [193]	Non-controlled, observational	1 stroke	72 mo	tDCS + BAT (n = 1)	No	3 mo: 2 x 30 min 3 times/wk	2 mA	Anode: Oz; Cathode: Cz	VF increase 4° and BOLD activity shift from perilesional areas to occipital pole
Plow et al. 2011 [194]	Parallel, randomised, comparative, double blind	2 strokes[b]	Chronic phase	tDCS + BAT (n = 1)	Sham + BAT (n = 1)	3 mo: 2 x 30 min 3 times/wk	2 mA	Anode: Oz; Cathode: Cz	Greater increase in visual field border, reading speed, ADL, and QoL after tDCS, greater subjective improvement after sham, no statistical testing
Plow et al. 2012a [32]	Parallel, randomised, controlled, double blind	10 strokes + 2 surgical traumas[c]	>3 mo	tDCS + BAT (n = 4)	Sham + BAT (n = 4)	3 mo: 2 x 30 min 3 times/wk	2 mA	Anode: Oz; Cathode: Cz	Greater increase in visual field border, DA, and ADL after tDCS, greater subjective improvement after sham, no difference in QoL
Plow et al. 2012b [33][d]	Parallel, randomised, controlled, double blind	10 strokes + 2 surgical traumas[c]	>3 mo	tDCS + BAT (n = 4)	Sham + BAT (n = 4)	3 mo: 2 x 30 min 3 times/wk	2 mA	Anode: Oz; Cathode: Cz	As in Plow et al. 2012a but also greater improvement in DA at 1 month after tDCS, no change in contrast sensitivity or reading
Olma et al. 2013 [34]	Crossover, controlled, double blind	12 strokes	>6 mo	tDCS + MDT (n = 12)	Sham + MDT (n = 12)	1. block: 20 min/d for 5 d → 16 d without treatment → 2. block: as 1. block	1.5 mA	Anode: calcarine sulcus (IL); Cathode: Cz	Greater improvement in motion perception of intact field after tDCS that lasted to follow-up (up to 4 wk)
Alber et al. 2017 [35]	Parallel, open label, controlled	7 strokes + 7 historical controls	2.3 ± 1.6 mo (mean ± SD)	tDCS + BAT (n = 7)	Conventional therapy (n = 7)	10 d: 20 min/d (+ 66 d of BAT)	2 mA	Anode: O1/O2 (IL); Cathode: Cz	Greater increase in MS after tDCS
Matteo et al. 2017 [195]	Crossover, open label, controlled	2 strokes	>12 mo	tDCS + BFT (n = 2)	No stim. + BFT (n = 2)	1. block: 20 x 30 min (7 wk) → 2 wk without treatment → 2. block: as 1. block	2 mA	Anode: PO3/PO4 (IL); Cathode: supraorbital (CL)	Greater increase in visual field extension, MS, and DA after tDCS, no statistical testing
Larcombe et al. 2018 [36]	Parallel, randomised, controlled, double blind	7 strokes	>6 mo	tDCS + BFT (n = 3)	1. Sham + BFT (n = 3), 2. No stim. + BFT (n = 1)[e]	5 d: 15–30 min/d	1 mA	Anode: V5/MT (IL); Cathode: Cz	No improvement in motion discrimination in either group, less reduction of BOLD activity in V5/MT (IL) after tDCS
Herpich et al. 2019 [196]	Parallel, 1. randomised and 2. non-randomised arm	1. arm: 4 strokes + 1 TBI; 2. arm: 6 strokes	2.5–108 mo	1. arm: hf-tRNS + GDDT (n = 3)	1. arm: Sham + GDDT (n = 2); 2. arm: No stim. + GDDT (n = 6)	10 d: 20 min/d	0-mA offset	Stimulating electrodes: O1 and O2	Improvement in GDDT after hf-tRNS but not after sham or no stimulation, no between-group testing

[a] According to the international 10–20 system; [b] 1 patient same as in the study by Halko et al.; [c] 4 patients excluded from the analyses; [d] same patients as in the study by Plow et al. 2012a; [e] refused stimulation/sham. tDCS, transcranial direct current stimulation; BAT, border area training; BOLD, blood oxygen level-dependent; ADL, activities in daily living; QoL, quality of life; DA, detection accuracy; MDT, motion discrimination task; IL, ipsilesional; SD, standard deviation; MS, mean sensitivity/threshold; BFT, blind field training; CL, contralesional; TBI, traumatic brain injury; hf-tRNS, high-frequency transcranial random noise stimulation; GDDT, global direction discrimination task.

One rationale of tDCS in rehabilitation of unilateral brain damage relies on the model of hemispheric competition. After stroke the lesioned side is less active and its inhibitory effect via transcallosal fibres on the contralateral hemisphere decreases [197]. This results in hyperactivity of the intact hemisphere, which then exerts even more inhibition on the lesioned side and further down-modulates its excitability [198]. Therefore, anodal tDCS aims to excite the damaged hemisphere, whereas inhibitory cathodal tDCS is applied to suppress the hyperexcitation of the intact hemisphere, thus lifting the interhemispheric imbalance. However, this approach seems to mainly apply to mild to moderate strokes, whereas in severe strokes the increased activity of the unaffected hemisphere may support the recovery of the affected hemisphere [199].

Although less well established, alternating current stimulation (ACS) has also raised interest in neurological rehabilitation for over a decade [200]. Unlike tDCS, it does not change the excitability of neurons tonically but modulates the ongoing oscillatory brain activity in a frequency-dependent manner and aims at influencing behaviour associated with brain oscillations [201]. The stimulation is administered as weak (< 2 mA peak-to-peak) currents of cyclically alternating polarity, the frequency, intensity, phase, and montage of which modify its effect. Its mechanism was first investigated in animal studies where low-intensity sinusoidal electric fields modified the rate and timing of endogenous neuronal spiking activity [202-204]. Since then, the ability of ACS to interfere with spontaneous brain oscillations has also been explored in humans: it strengthens [205-207] and entrains (phase-locks) [206] endogenous alpha power, induces flickering light perceptions called phosphenes [208], and modifies visual perception [206]. It has been suggested to affect network connectivity and thus behavioural processes by synchronising the phase coherence of oscillations in functionally related neuronal assemblies [209,210]. The neurophysiological after-effects of ACS on alpha power have been reported to last at least 70 minutes [211] and proposed to result from synaptic plasticity [205,212].

Alternating current stimulation is most often delivered transcranially to modulate the oscillatory activity of the underlying cortex. However, it can also be administered as repetitive transorbital ACS (rtACS), with stimulating electrodes placed near the orbits, to stimulate the retinae, the optic nerves, and the brain [181]. It has been applied to rehabilitate visual function after retinal or optic nerve injury, where rtACS has improved visual field detection ability and shortened reaction time in a visuo-motor task [31]. Here repetitive simply refers to the multiple sessions of the stimulation and has been historically used in the context of transorbital ACS studies – although other modalities of tES are also typically administered multiple times without this definition.

The mechanisms of rtACS are less studied compared to tACS. Whereas tACS seems to affect primarily the underlying cortical oscillations [213], the current flow in rtACS does not reach the occipital cortex but travels mostly through the frontal cortex and the eye toward the brainstem [31]. In rats, rtACS induces electrical evoked potentials along the visual pathway, including the thalamus, the superior colliculus,

and the visual cortex, and these evoked potentials are abolished by blockage of the retinal ganglion cells [214]. This alludes that the evoked potentials are caused by retinal stimulation, not by volume conductance of the current. Like tACS, rtACS produces phosphenes that most likely originate from the retina, as demonstrated with transcranial electrode montages [215,216]. These retinal phosphenes have been proposed to entrain the retino-thalamo-cortical pathway similarly to rhythmic photic stimulation that can entrain occipital oscillations of distinct frequency bands in the visual cortex [217]. Indeed, rtACS has strengthened the occipital alpha power [218,219] and the occipito-occipital and occipito-frontal resting-state alpha coherence [219], and the increased coherence has correlated with improved vision performance [219]. Thus, investigators have suggested that rtACS works by modulating cortical oscillations indirectly through the synchronised stimulation of the retino-thalamo-cortical pathway [31,214,218], a mechanism distinct from tACS.

As ACS is considered to modulate brain oscillations, their functional role is of interest. In the context of vision, most attention has been paid to the predominant oscillatory rhythm recorded over the visual cortex, the alpha band (7–13 Hz) [220]. The amplitude of occipital alpha increases when closing eyes and decreases at the presentation of visual stimuli or during demanding cognitive work. The amplitude, frequency, and phase of the alpha band impact visual perception: high alpha amplitude is associated with impaired stimulus detection [221,222], alpha frequency correlates with temporal visual resolution [223], and the phase of oscillations influences the probability of visual detection in a cyclic manner [224,225]. In the visual cortex, synchronous alpha and low beta oscillations dominate in the top-down feedback signalling, whereas gamma oscillations characterise the bottom-up feedforward processing [226,227]. Indeed, synchronised alpha has been proposed to participate in the top-down inhibition of task-irrelevant processes [228,229]. Although widely supported, this theory has also been questioned as too simplistic to fully explain the diverse state-dependency, topology, and inter-individual features of alpha responses; instead, alpha may have several functions in visual perception [220].

So far, tES-based methods have not thoroughly entered clinical use and their optimal parameters and underlying mechanisms are debated. The arguments concern 1) the ability of weak currents to reach the brain and to influence neural activity, 2) the role of peripheral stimulation in the observed effects, 3) the difficulty in targeting the stimulation both spatially and temporally, 4) the poor reproducibility of results, and 5) the obstacles in measuring the online neurophysiological effects due to abundant artefacts caused by currents [230,231]. Both the first and the second argument criticise the view that the behavioural effects of tES could be unambiguously explained by central mechanisms, as the produced currents may create larger electric fields to peripheral tissues, manifesting as skin sensations and phosphenes. Indeed, approximately 75% of the current is attenuated by peripheral tissues [232]. With the currents of 1 to 2 mA, the intracranial electric fields are very low (0.1–0.8 V/m) [233-236] and far under the strengths required to elicit action potentials [237]. Increasing

the current is usually limited by skin irritation and other side effects caused by the stimulation [238]. As a counterargument, alternating electric fields as low as 0.2 V/m have been demonstrated to be sufficient to modulate neural activity if carefully matched to endogenous oscillations [204].

The spatial resolution of tES is limited but its focality can be improved with smaller electrodes that are close to each other [239]. This, however, increases the amount of current attenuated by peripheral tissues and may reduce the strength of electric fields [240,241]. Moreover, intracranial electric fields are affected by individual properties of subjects [242] as well as by focal pathology [241]. Thus, computational models have been suggested for guidance of tES experiments.

Besides the above-mentioned factors, the final result of tES depends on the prevalent brain state and the related neural activity [207,211,243]. Ideally, the stimulation should be delivered to coincide with the specific phase and frequency of intrinsic oscillations, which would require electroencephalography or magnetoencephalography to define the individual intrinsic task-dependent oscillatory rhythm. However, tES causes substantial artefacts to neurophysiological measurements, which has prompted critics to question the reliability of online measurements [244].

2.5.4 Controversies in restitution of vision after stroke

The attempt to restore vision has not avoided criticism. First, the reasonability of trying to regain a lost function caused by permanent neural damage of the adult visual system has been questioned [245]. Another cause of dispute is the functional improvement achieved by vision restoration. Critics have pointed out that with the typical field expansion of approximately 5° reported from the border area training, the expected functional improvement in mobility and visual exploration remains low [146,246], even if there have also been opposite reports [153,157]. To complicate the issue further, the functional or quality of life gains reported from non-controlled studies do not always correlate with changes in the size of VFD [155] and can be argued to be by-products of increased attention and care during the length of the study. Although functional improvements propelled by a few-degree visual field expansion appear unlikely, an effect on reading performance would be more plausible. The border shift typically coincides within the parafoveal field that is crucial for efficient reading [247], and some studies have indeed observed improved reading performance after post-stroke vision restoration training [177,178,248].

On the other hand, the gain in the visual function may not be optimally measured with perimetry, which has been the most popular method to assess outcome in vision rehabilitation studies. Indeed, changes in perception after the blind field rehabilitation may concern other qualities of vision than the ones detectable with standard perimetry, such as in studies by Raninen et al. and Saionz et al. who trained flicker or movement discrimination of the blind field [160,168]. They showed that the subjects improved

in the trained tasks beyond the stimulated area, while their results in standard perimetry remained unchanged. Therefore, perimetry should be accompanied by other methods to assess the qualities of vision that may also support functional recovery. So far, several groups have introduced their own assessment tools that are not always easily comparable between studies [170]. The restoration efforts have also been criticised for only applying to the tasks and locations that are trained. This argument was challenged by Cavanaugh et al. who demonstrated that training a visual discrimination task can lead to improved luminance sensitivity beyond the trained area [166].

Yet another argument concerns the sufficient control of eye movements. As the restitutive approach aims at improving the visual field irrespective of facilitated eye movement strategies, the effect of unstable fixation must be ruled out. Hence, various methods have been proposed to control for fixation, including observation [151], changing attributes of the fixation point [150], laser scanning ophthalmoscope [155], microperimetry [152], or eye tracker [249]. However, some authors have argued that many of these methods are insufficient and that the field expansions achieved with the border area training may be attributed to eye movements [146,155,250]. Indeed, the experiments using more rigorous fixation control, such as a laser scanning ophthalmoscope, have produced no or minimal border shift [155,157]. Finally, the restitution programmes tend to be laborious and requiring for patients, which has undermined their clinical application – particularly considering that they have not demonstrated superiority to compensatory methods in the few comparative trials [165,251].

2.6 Neuroplasticity after stroke of the visual cortex

2.6.1 Plasticity after stroke

Most of the data on neurophysiological and biochemical changes after brain ischaemia are acquired from animal studies, but during the last few decades functional imaging of the human brain has increasingly contributed to the scientific knowledge. Thanks to the piling evidence, stroke recovery is believed to stem from structural and functional reorganisation of cortical networks, called neuroplasticity [133,252,253]. This reorganisation has been attributed to changes both locally and within the more distant neuronal networks: 1) remapping the representation of adjacent sensory or motor functions within the perilesional cortex, 2) remodelling structurally distant but functionally related circuits, as well as 3) rebalancing activity between the ipsi- and contralesional hemisphere [133,252,253]. The first mechanism is more likely to occur after minor strokes where nearby neurons conducting similar functions have survived [254], whereas the latter two may dominate after major strokes [255]. Disturbance in the normal lateralisation of neural functions is often detected in the subacute phase of

stroke, which seems to reflect the reduced interhemispheric inhibition from the damaged hemisphere and the increased, either supportive or inhibitory, influence from the contralesional hemisphere [256]. Return to the physiological lateralisation appears to be time-dependent and has been associated with functional improvement but its role in recovery is not completely solved.

Based on animal models, the proposed mechanisms behind the network reorganisation after ischaemic injury include re-establishing synaptic activity through increased excitability, enhanced axonal sprouting and dendritic spine production, upregulation of growth-promoting genes, changes in the extracellular matrix, and consolidation of functionally relevant connections by strengthening their synapses with concurrent activation of pre- and postsynaptic neurons [133,252,253,257]. The time window for the most efficient recovery when brain plasticity is at its greatest coincides early after stroke, whereas the spontaneous recovery seems to plateau after approximately 1 to 3 months, extending up to 6 months in the most severe strokes [258-261].

2.6.2 Plasticity of the visual system: animal studies

Most of the animal models, as well as human studies, on plasticity after stroke have focused on motor manifestations, whereas stroke of the visual cortex has been underrepresented. Instead, plasticity of the visual cortex has mainly been investigated during development and after retinal lesions [262,263]. The pioneer work of Hubel and Wiesel was first to demonstrate 'the critical period' in the developing brain, defined as the time period when the reorganisation of V1 ocular dominance was possible if the visual input was deprived temporarily by covering one eye [264-266]. However, the potential and extent of the primary visual cortex remapping in the adult brain has yielded supporting [267,268] but also opposing results [269] after visual pathway deafferentation. Interestingly, the early period of increased plasticity following stroke resembles the critical period in the adult brain [133,260]. Moreover, the re-emergence of the ocular dominance plasticity has been observed in adult amblyopic mice after administering selective serotonin uptake inhibitors [144].

To expand from the work of Hubel and Wiesel, Eysel et al. compared reorganisation after both retinal and cortical damage in cats [270]. After a V1 lesion neural activity was suppressed at the border of the damaged region and increased in the adjacent region until the activity returned to a normal level within 1–2 weeks. In vitro analyses revealed coinciding enhanced glutaminergic excitation and reduced GABAergic inhibition, which was interpreted as a sign of synaptic plasticity. These changes were followed by an increase in the receptive field size of the neurons surrounding the lesion.

In monkeys, damage of the primary visual cortex leads to retrograde destruction of afferent neurons from LGN within 3 months, followed by that of retinal ganglion cells [271-273]. The magnitude of the degeneration seems to depend on the extent of

the cortical damage to the extrastriate cortex and white matter tracts [274]. Later, evidence of a similar post-injury process has been observed in humans [275,276]. It has been hypothesised that the retrograde degeneration of the retino-geniculo-striate pathway impedes rehabilitation attempts in the chronic phase of occipital stroke and might favour targeting the extrastriate routes of residual vision [168,179]. These routes have been recently demonstrated to mediate the blindsight of monkeys, with evidence supporting both the pathway via the superior colliculus and the pulvinar [176] and the one from LGN to the extrastriate cortex [175].

2.6.3 Plasticity of the visual system: functional neuroimaging

In the recent decades functional neuroimaging has been established as a tool to investigate neural correlates of sensory, motor, and cognitive functions, as well as of different neuropsychiatric pathologies. One of these methods is fMRI which detects changes in regional blood flow by variations in a blood oxygen level-dependent (BOLD) signal [277,278]. The rationale of fMRI is based on the coupling of blood flow and neural activity. When neuronal populations fire, they consume glucose and oxygen. The metabolic change is anticipated by allostatic signalling from astrocytes, causing enhanced blood flow to the area [279]. This increases the local ratio of oxygenated (diamagnetic) and deoxygenated (paramagnetic) haemoglobin. As the former interferes with the MRI signal less than the latter, the enhanced flow results in an increased BOLD signal, detected in T2*-weighted MRI sequences. The peak blood flow, and therefore the BOLD signal, lags neural activity approximately 5 seconds, weakening the temporal resolution of the fMRI technique. Its spatial resolution, on the other hand, is among the best of non-invasive functional neuroimaging methods. Other strengths of fMRI comprise its non-invasiveness and lack of ionising radiation, whereas its limitations include various sources of noise produced by respiration, pulse, movement, and imaging-related artefacts.

Functional MRI is most often used in a task-dependent setting where neural, followed by haemodynamic, responses to tasks are studied. In vision research, task-dependent fMRI has been revolutionary in generating human retinotopic maps that link visual stimuli in different field locations to the activity of particular cortical regions of the visual cortex [2,280,281]. Besides measuring stimulus-induced neural phenomena, fMRI has been introduced as a technique to study intrinsic brain activity during rest. This resting-state method measures slow (< 0.1 Hz) BOLD signal fluctuations [282]. When the BOLD activity of remote brain regions is temporally correlated, it represents resting-state FC [37]. Regions that are activated by similar tasks seem to have correlated activity also during rest and form functional resting-state networks, such as visual, auditory, or language networks [283].

Several single-case and small studies have been conducted in subjects with visual cortex injury, the most famous one being the notoriously often studied subject GY who suffered from right homonymous hemianopia sparing foveal vision after a traffic

accident as a child [53,284]. Baseler et al. found out that when visual stimuli covered the full visual field of GY, including the fovea, the representation of his retinotopic maps was normal, but when the stimuli were restricted to the blind field, abnormal activation was shown, mainly manifesting in the dorsal extrastriate areas [285]. In a similar vein, Goebel et al. observed activation in the spared extrastriate area V5/MT but also in the ventral visual areas of GY and another patient FS who were mostly unaware of the stimulation of their blind field [286]. In both experiments, the activation of the extrastriate cortex occurred without concurrent activation of the ipsilesional striate cortex. Furthermore, other studies have supported the role of the extrastriate cortex, and especially the dorsal stream, in mediating residual vision with several neurophysiological imaging methods, including fMRI, magnetoencephalography, positron emission topography, diffusion tensor imaging, and transcranial magnetic stimulation [284,287-292]. The studies have demonstrated several potential pathways to the ipsilesional extrastriate cortex in humans: via 1) the ipsilateral LGN [288,292], 2) the contralateral LGN [288], 3) the contralateral extrastriate cortex [288], and 4) the contralateral early visual cortex [289]. The subcortical route via the superior colliculus and the pulvinar, although implied in animal studies [176] and in patients with hemispherectomy [293], has not been established in patients with occipital stroke [292]. Yet, many of the above-mentioned studies were performed on the famous GY and thus reflect neural processes after traumatic brain injury [284,287-289].

However, similar lines of evidence have been gained with fMRI from larger samples of occipital stroke patients. Nelles et al. compared chronic occipital stroke patients to healthy controls in their response to visual stimulation in the intact and blind field [294,295]. The blind field stimulation induced bilateral (ipsilateral > contralateral) activation of the extrastriate cortices without activation of the striate cortex among the patients, whereas the healthy control subjects displayed an activation pattern including the same structures and the contralateral striate cortex. Ajina et al. showed that after V1 damage the way the ipsilesional V5/MT responds to changes in coherence and contrast of blind field stimuli resembles that of the normal V1 [296,297].

The above results support the hypothesis that the extrastriate processing, bypassing the striate cortex, is behind residual visual abilities. There is also fMRI evidence from macaques to second the claim. Schmid et al. studied macaques with chronic V1 lesions and residual visual abilities before and after inactivation of LGN [175]. They observed widespread activation of the extrastriate visual areas when high-contrast stimuli were presented in the blind field of the animals before, but not after, the silencing of LGN. The detection task performance of the animals corresponded to the neurophysiological results. The results suggest that at least the blindsight in monkeys depends on intact geniculo-extrastriate connections.

However, alternative mechanisms for residual vision have also been proposed, including that it is mediated through small spared neuronal islands within the partially

damaged primary visual cortex [171,298,299]. To test this assumption, Morland et al. studied seven hemianopic patients with different aetiologies of brain damage [300]. They found out that two of the patients had residual movement discrimination abilities, one showing activity within the spared calcarine cortex and another within the extrastriate cortex during stimulation of their blind field. The authors concluded that at least two alternative parallel mechanisms can drive residual vision after brain damage, and thus the study did not proclaim superiority for one of the competing mechanisms. Papanikolaou et al. also observed two separate BOLD activation patterns when the blind field of occipital stroke patients was stimulated: one included activation in spared areas of V1 and V5/MT whereas the other showed only activity in V5/MT, potentially via subcortical connections bypassing V1 [301]. However, in this case, the activation did not manifest as residual visual abilities.

A few neuroimaging studies have observed longitudinal changes in cortical activity in the acute phase after stroke. Raposo et al. studied eight occipital stroke patients with VFD within a month of the injury and after a follow-up of 1 and 3 months [302]. They found out that as motion and colour perception of the subjects improved, initially absent activity in the ipsilesional V1 reappeared and bilateral extrastriate activity strengthened. The results were interpreted to support the importance of spared neuronal islands within the striate cortex for recovery of visual abilities. Brodtmann et al., on the other hand, scanned five occipital stroke patients within 10 days and at 6 months after stroke and compared them to healthy control subjects [303]. They discovered reduced activity bilaterally in the striate and ventral extrastriate cortices, whereas activity of the dorsal extrastriate cortices remained comparable to the control subjects. The authors proposed that the activity pattern reflects the increased influence of the dorsal stream in visual processing after stroke damaging the striate and ventral extrastriate areas.

In addition, some groups have investigated retinotopic maps after stroke. In a case report by Dilks et al., functional neuroimaging revealed a distortion of the retinotopic maps in the primary visual cortex in a quadrantanopic patient who had suffered a stroke affecting the post-chiasmatic visual pathway prior to V1 [304]. The finding was accompanied by altered perception in the adjacent intact visual field of the patient, prompting the authors to claim this as evidence of the reorganisation of the primary visual cortex. Another study by Papanikolaou et al. did not detect as extensive remapping in the early visual cortex in five chronic stroke patients with partial V1 injury [305]. They observed only modest reorganisation, including a small shift in the receptive field centres towards the scotoma and an increase in the receptive field size both within the ipsilesional and contralesional V1 in comparison to healthy control subjects. Finally, Reitsma et al. studied 27 subjects with chronic post-chiasmatic damage of different aetiologies [306]. They found atypical retinotopic organisation in three non-stroke subjects, whereas the stroke patients' retinotopic maps did not differ from healthy control subjects.

Although task-dependent fMRI studies on stroke affecting the visual system prevail, rsfMRI data on stroke patients have primarily concentrated on motor, and to a lesser degree, to somatosensory, attentional, and language deficits [307]. An rsfMRI finding recurrently demonstrated after stroke is impaired interhemispheric FC [308-310], but more extensive changes have also been observed both within [310-312] and between resting-state networks [308,313,314]. Additionally, several studies have shown that impaired connectivity correlates with behavioural deficits in the acute [308,309,312] and chronic phase [315]. Finally, return of FC closer to the pre-stroke state has been reported to occur spontaneously [310,312,314,316] or after rehabilitation [317], and this rebalancing seems to correlate with clinical recovery [312,314].

To our knowledge, there are just few rsfMRI studies on FC in hemianopia. One study investigated resting-state FC in occipital stroke patients and observed decreased interhemispheric connectivity between the occipital lobes compared to healthy control subjects and its improvement mostly within the first month after stroke [38]. Moreover, the early interhemispheric resting-state connectivity correlated with VFD recovery. Another study included both stroke and traumatic brain injury patients and reported mainly descriptive changes in the network topography of hemianopia patients compared to healthy control subjects [318], whereas the third one studied resting-state connectivity after visual training (see below) [319].

Functional MRI has been utilised to assess neurophysiological changes associated with vision rehabilitation. Changes observed after the border area training include a shift in the eccentricity of receptive fields within the early visual cortex [320], activation of the extrastriate attention-related brain areas [321], and strengthening of the resting-state attention network [319]. In addition, a single-case study reported that the border area training combined with tDCS induced a shift in perilesional activation of the damaged primary visual cortex [193].

When it comes to the blind field rehabilitation, a single-case study on flicker stimulation training revealed that stimuli presented in the blind field evoked a contralesional BOLD response within the striate and extrastriate visual areas, especially V5/MT, suggesting enhanced processing through transcallosal fibres and extrastriate pathways [322]. The neurophysiological changes were accompanied by improvement in flicker sensitivity of the blind field [160]. Another case study demonstrated increased activity in the ipsilesional V1 and V5/MT after training a motion coherence task [323]. The authors also detected a shift in the early retinotopic maps in the lesioned visual areas; however, similar changes were visible in repeated scans of an occipital stroke patient not receiving rehabilitation, which suggests that the change is not only due to training but represents post-stroke plasticity. Additional support for the V5/MT-mediated rehabilitation effect comes from a study that examined the blind field rehabilitation in six subjects with acquired occipital injury [167]. They observed increased BOLD activity in the ipsilesional V5/MT in response to blind field stimuli after training.

The fMRI studies on ACS have focused mostly on online or immediate after-effects of transcranial stimulation, whereas the data on the long-term effects and the impact of transorbital stimulation are lacking. The amplitude of posterior alpha-band oscillations has been shown to correlate negatively with the occipital BOLD signal [324,325] and with FC between the primary visual cortex and the rest of the brain [326]. Consistently, occipitally targeted tACS at alpha frequency has decreased online [327] and offline [328] visual task-dependent BOLD response in occipital regions, even if there have also been contradicting results [329]. The stimulation effect measured with rsfMRI is equally variable with reports of an increased local BOLD signal and augmented inter-network connectivity [330] or no change in BOLD activity [327]. Overall, the effect of tACS seems to be task-, frequency-, region-, and intensity-dependent, and to extend beyond areas in the immediate proximity of stimulation electrodes [329,330].

In conclusion, functional neuroimaging has revealed changed neural activity in patients with VFD after stroke of the visual cortex mostly 1) in the partially damaged V1, 2) in the ipsi- and contralesional extrastriate areas (especially V5/MT), and 3) within the visual resting-state networks, especially in the interhemispheric connectivity. Along spontaneous recovery or after rehabilitation the following changes have been found: 1) the reappearance or strengthening of activity within the ipsilesional V1, 2) the increased activity within the (dorsal) extrastriate areas with or without concurrent activity of V1, 3) the ectopic activation of the contralesional visual areas, 4) the shift in perilesional receptive fields, 5) the rebalancing of the interhemispheric connectivity, and 6) the strengthening of the attention-related network. The findings mainly follow the previously presented patterns of stroke recovery [133,252,253]. Overall, the greatest functional recovery after stroke has been associated with return to the normal neurophysiological activation pattern [253]. Yet, uncertainty remains about the causality between the neurophysiological changes and clinical gains.

Nevertheless, the number of subjects in the fMRI studies on stroke of the visual cortex has been small and most studies have used a task-dependent approach, whereas the effects on the resting-state networks have been less well documented. Notably, the inter-individual variability of neurophysiological findings has been large, which makes it difficult to track systematic changes at a group level. To some extent, this variability can stem from the technical uncertainties and varying analytical approaches of the relatively novel neuroimaging methods. However, it probably also reflects real differences in the underlying neural phenomena. Given the proposed routes of residual vision, the variability may be due to diverse lesion age, location, and extend – especially to the extrastriate cortex and subcortical structures. All in all, there are still a lot of gaps in the current knowledge in stroke of the visual cortex, challenging the recognition and treatment of these patients.

3. AIMS OF THE STUDY

The primary aim of the study was to investigate occipital stroke and VFDs: their clinical phenotype, recognition and acute treatment, neural mechanisms, rehabilitation, and prognosis. The more specific aims were:

I. to study the recognition and prehospital pathways of stroke patients presenting with visual symptoms and to define potential obstacles in the early diagnosis (I);

II. to investigate the clinical phenotype, functional outcome, and incidence of post-ICH epilepsy in patients with occipital ICH in comparison to other ICH patients (II);

III. to study the rehabilitation of homonymous VFDs after chronic occipital stroke with non-invasive electrical brain stimulation methods (III);

IV. to compare the resting-state FC of chronic occipital stroke patients with VFD to that of healthy adults and to explore if rtACS rehabilitation affects FC (IV).

4. PATIENTS AND METHODS

4.1 Occipital ischaemic stroke patient cohort (I)

Study I was a single-centre, retrospective, observational, registry-based study consisting of 245 acute and subacute occipital ischaemic stroke patients treated at the neurological emergency department of Helsinki University Hospital between 2010 and 2015. The subjects were screened from the hospital electronic medical database among all ischaemic stroke patients treated at the emergency department during the study period. Only patients with visual symptoms were included (excluding patients with other focal symptoms, such as hemiparesis, dysphasia, or lowered consciousness). The stroke diagnosis was confirmed with clinical criteria and either MRI or CT. Patients who had in-hospital stroke or who were treated first in another neurology unit were excluded.

We collected data on the patients' demographics, stroke phenotype, imaging results, and prehospital delay and route from the patient records. Time stamps of symptom onset or the time last seen well, the first contact to health care, and admission documented by a triage nurse were recorded, as well as the number of health-care units visited before admission. The time from symptom onset to admission to the neurological emergency department was defined as onset-to-door time. To further analyse the problems in recognition, we defined the number of patients with initial misdiagnosis, the patients who were referred to an incorrect health-care unit, the patients who were admitted within 4.5 hours of symptom onset and were therefore eligible for treatment with IVT, and the patients who eventually received IVT. If the onset-to-door time was longer than 4.5 hours, the primary reason for the delay was examined. The study was approved by the Helsinki University Hospital institutional review board (31.5.2013, 88/2013) as an observational registry study with no study-related patient contact. Therefore, no ethical approval was required.

4.2 Helsinki ICH study registry (II)

Study II used retrospective, observational, registry-based methodology. It studied 19 occipital ICH patients and compared them to 337 patients with non-occipital lobar ICH and to 994 patients with any non-occipital ICH. The study sample was drawn from the retrospective Helsinki ICH Study (HICHS) registry containing 1013 consecutive ICH patients treated at Helsinki University Hospital from January 2005 to March 2010 [114]. The registry excludes patients with traumatic ICH, tumour bleeding, haemorrhagic transformation of ischaemic stroke, and ICH caused by a ruptured aneurysm. It comprises data collected from the hospital electronic database, including demographics, patient history, all information concerning the hospitalisation due to ICH, functional outcome at discharge, aetiology of ICH according to the

SMASH-U (Structural, Medication, Amyloid angiopathy, Systemic disease, Hypertension, Undetermined) classification [114], and incidence of post-ICH epilepsy within a median follow-up of 2.7 years [126]. Mortality data at 3 and 12 months were derived from Statistics Finland.

The location of haemorrhage was assessed from the admission CT or MRI scan. All haematomas were classified according to the anatomical location (Figure 6). If the haematoma extended to both cortical and deep supratentorial structures, it was categorised according to the assumed origin if identifiable. Otherwise, the ICH location was labelled mixed. The occipital location was defined based on established anatomical landmarks, and only haematomas located exclusively in the occipital lobe were classified as occipital.

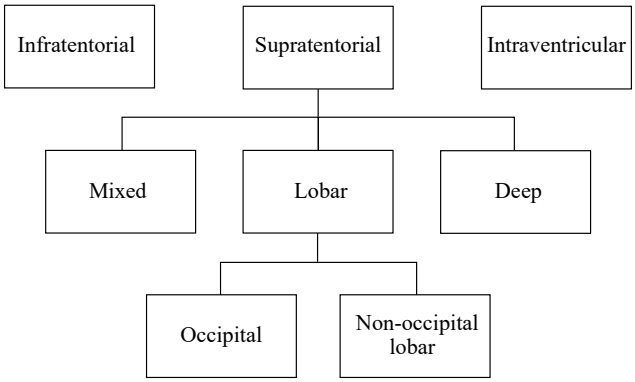

Figure 6. Classification of ICH according to the anatomical location (Study II).

In addition to the already existing HICHS registry data, we collected new data on occipital ICH patients from medical notes recorded at outpatient visits to a neurologist, a neurosurgeon, an ophthalmologist, a physiotherapist, an occupational therapist, a speech therapist, a neuropsychologist, or a general practitioner. From these data, we retrieved information on the patients' residual visual symptoms, perimetry results, recovery, return to work, ability to drive, and independence in daily living and constructed their functional outcome at 3 and 12 months after ICH. The Helsinki University Hospital institutional review board approved the study as an observational registry study.

4.3 Restoration of Vision after Stroke trial (III, IV)

4.3.1 Study design

The Restoration of Vision after Stroke (REVIS) trial was a randomised, sham-controlled exploratory trial accomplished by a consortium of Helsinki-, Magdeburg-, and Rome-based investigators that studied different modalities of tES in rehabilitation of homonymous VFD after chronic occipital stroke. The tES treatment was investigated in three separate experiments in the three centres (Magdeburg, Helsinki, and Rome): 1) rtACS vs rtACS with prior cathodal tDCS over the intact visual cortex vs sham, 2) rtACS vs sham, and 3) combined anodal/cathodal tDCS of the visual cortex vs sham. The subjects were randomised to receive either stimulation according to the local arm or sham treatment (Magdeburg: rtACS or tDCS/rtACS or sham 1:1:1; Helsinki: rtACS or sham 1:1; Rome: tDCS or sham 1:1). The patients and the study personnel performing the outcome measurements were blinded for the allocation.

The study was approved by the Ethics Committees of the Helsinki and Uusimaa Hospital District (No. 49/13/03/01/13, date 13/03/2013), the Medical Faculty of the University of Magdeburg (No. 173/13), and the University Policlinic of the Catholic University in Rome (No. 4/2013, date 20/05/2013) and executed according to the principles of the Declaration of Helsinki. All patients gave their written informed consent. The trial was registered to the clinicaltrials.gov (NCT01418820 and NCT02405143).

4.3.2 Patient selection

Patients were screened from the local hospital database of the centres. The following inclusion criteria were applied: 1) VFD (hemianopia or quadrantanopia) due to occipital ischaemic or haemorrhagic stroke, 2) age from 18 to 75 years, 3) lesion age 6 months or greater, 4) stable VFD across the baseline measurements, 5) the presence of residual vision (i.e., detectable gradual transition between the intact and the absolutely blind part of the visual field according to the evaluation of the clinician), and 6) the best corrected visual acuity of at least 0.4 (20/50 Snellen). Exclusion criteria were 1) known active malignancy, 2) ophthalmological or neurological diseases that might interfere with the study, 3) electronic implants, 4) intracranial or intraorbital metal artefacts, 5) expected low compliance, 6) epileptic seizures within 10 years and, 7) the use of antiepileptic or sedative drugs.

Altogether 57 patients were randomised, but one subject in the Helsinki arm was excluded prior to any intervention due to a late-appearing exclusion criterion. Consequently, the final treatment arms were (Figure 7):

Experiment 1 (Magdeburg): a) sham-tDCS/active rtACS (n = 8)
b) active tDCS/active rtACS (n = 8)
c) sham-tDCS/sham-rtACS (n = 8)

Experiment 2 (Helsinki): a) rtACS (n = 9)
b) sham (n = 9)

Experiment 3 (Rome): a) tDCS (n = 7)
b) sham (n = 7)

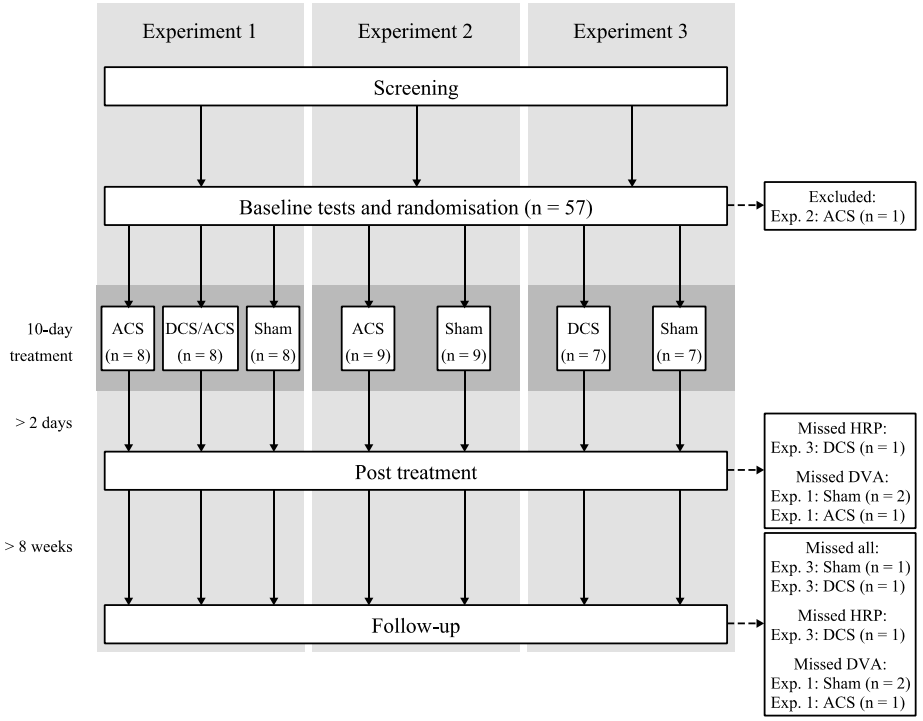

Figure 7. Flowchart of the REVIS study. Modified from Publication III. Reproduced with permission from IOS Press. ACS, alternating current stimulation; DCS/ACS, combined direct current stimulation/alternating current stimulation; DCS, direct current stimulation; HRP, high-resolution perimetry; DVA, dynamic visual acuity.

4.3.3 Outcome measures

The treatment effect was assessed with a variety of measurements of visual function at baseline, after the 10-day treatment, and after a 2-month treatment-free follow-up period (Table 5). Potential adverse effects were inquired and recorded. The primary outcome was change in VFD assessed with two methods: mean sensitivity measured with SAP and detection accuracy acquired with computer-assisted HRP [150]. Mean sensitivity is defined as the average sensitivity threshold of all test positions in SAP.

Detection accuracy, on the other hand, is the percentage of correctly observed stimuli in HRP. The variables describe the size and depth of VFD, but the perimetries study different aspects of vision: SAP evaluates near-threshold light detection in the monocular 30° visual field, whereas HRP tests suprathreshold visual detection of binocular central vision (12 × 12°) and is therefore potentially more prone to capture small changes within the VFD border area. As VFD can be incongruous [55], we analysed the SAP results of the ipsi- and contralesional eye separately.

Complementary visual measurements included near visual acuity, reading performance (International Reading Speed Texts, IReST, validated in Finnish, German, and Italian) [331], contrast sensitivity (Mars Letter Contrast Sensitivity Test) [332], and dynamic vision [333]. In addition, fMRI scans were acquired in Experiment 2 of the trial.

4.3.4 Intervention

The stimulation was administered with DC-Stimulator (MC4, NeuroConn GmbH, Ilmenau, Germany) in ten sessions during consecutive working days and delivered through rubber electrodes covered with saline-soaked sponges. During the treatment, subjects sat in a darkened room with their eyes closed. The stimulation modalities in each experiment had distinct electrode montages and stimulation parameters, which are described in Table 5. The novel combined tDCS/rtACS protocol was designed to test if reducing the interhemispheric imbalance by inhibiting the intact occipital cortex would enhance the effect of succeeding rtACS. The sham protocols matched the electrode montages and duration of the stimulation modalities of each arm but delivered only minimal stimulation to enable blinding.

Table 5. Intervention parameters and outcome measurements of the experiments (Study III).

	Experiment 1	Experiment 2	Experiment 3
Centre	Magdeburg	Helsinki	Rome
Treatment arms	rtACS vs tDCS/rtACS vs sham	rtACS vs sham	tDCS vs sham
Treatment montage			
Stimulation 1	sham-tDCS/rtACS: one stimulating rtACS electrode at Fpz and reference electrode on right upper arm	rtACS: two stimulating electrodes at Fp1 and Fp2 and reference electrode on right forearm	tDCS: stimulating cathode over intact and stimulating anode over damaged occipital cortex (O1/O2) with anodal and cathodal pairs at Fp1/Fp2
Stimulation 2	tDCS/rtACS: 1. cathodal tDCS over intact occipital cortex (O1/O2) with anode at Fpz, 2. rtACS as above	-	-
Sham	sham-tDCS/sham-rtACS: same as in active stimulations	sham-rtACS: same as in active stimulation	sham-tDCS: same as in active stimulation
Current parameters			
Stimulation 1	sham-tDCS/rtACS: rtACS frequency 5–30 Hz, amplitude 1.5 mA	rtACS: frequency 5–15 Hz, amplitude 100–150% of PT (0.45–1.5 mA)	tDCS: amplitude 2 mA
Stimulation 2	tDCS/rtACS: 1. tDCS amplitude 1 mA, 2. rtACS as above	-	-
Sham	sham-tDCS/sham-rtACS: 1. sham-tDCS: current ramped up for 30 s at first and ramped down for 30 s at the end, 2. sham-rtACS: 5-Hz burst every 1 min, amplitude at PT	sham-rtACS: 5-Hz burst every 5 min, amplitude at PT	sham-DCS: current ramped up for 30 s at first and ramped down for 30 s at the end
Treatment duration	10 + 20 min	sessions 1–5: 30 min sessions 6–10: 40 min	20 min
Primary outcomes			
High-resolution perimetry	400 positions, 21×21 grid, stimulus duration 150 ms, fixation control with online eye tracker	400 positions, 21×21 grid, stimulus duration 200 ms, fixation control with online eye tracker	400 positions, 21×21 grid, stimulus duration 150 ms, fixation ensured with microperimetry
Standard automated perimetry	Oculus Twinfield, Lynnwood, WA: 66 positions, stimuli (size: III, colour: white, duration: 0.2 s, luminance: 318 cd/m²/0 dB), background luminance 10 cd/m², fast-threshold strategy	Octopus 900, Haag-Streit Diagnostics: 59 positions, stimuli (size: III, colour: white, duration: 0.2 s, luminance: 1270 cd/m²), background luminance 10 cd/m², fast-threshold strategy	Humphrey Feld Analyzer II-i 750i: 76 positions, stimuli (size: III, colour: white), background luminance 10 cd/m², SITA-standard strategy
Secondary outcomes			
Reading test	IReST	IReST	IReST
Near VA	Oculus	Oculus	MNREAD
CS	Mars Letter CS Test	-	Mars Letter CS Test
DVA	computer-assisted DVA test	-	-
fMRI	-	resting-state fMRI	-

rtACS, repetitive transorbital alternating current stimulation; tDCS, transcranial direct current stimulation; PT, phosphene threshold; SITA, Swedish interactive thresholding algorithm; IReST, International Reading Speed Texts; VA, visual acuity; CS, contrast sensitivity; DVA, dynamic visual acuity; fMRI, functional magnetic resonance imaging.

4.4 Resting-state fMRI (IV)

In Study IV, we analysed the rsfMRI data of the prospective REVIS trial. Structural and functional images were acquired from 16 chronic occipital stroke patients participating in the Helsinki arm of the trial and 14 healthy control subjects who gave their informed consent. The study was approved by the Ethics Committee of the Helsinki and Uusimaa Hospital District (No. 49/13/03/01/13, date 13/03/2013 and no. HUS/576/2017, date 06/03/2017). The control subjects were examined by a neurologist who assessed their visual fields with confrontation testing. The flowchart of the study is depicted in Figure 8.

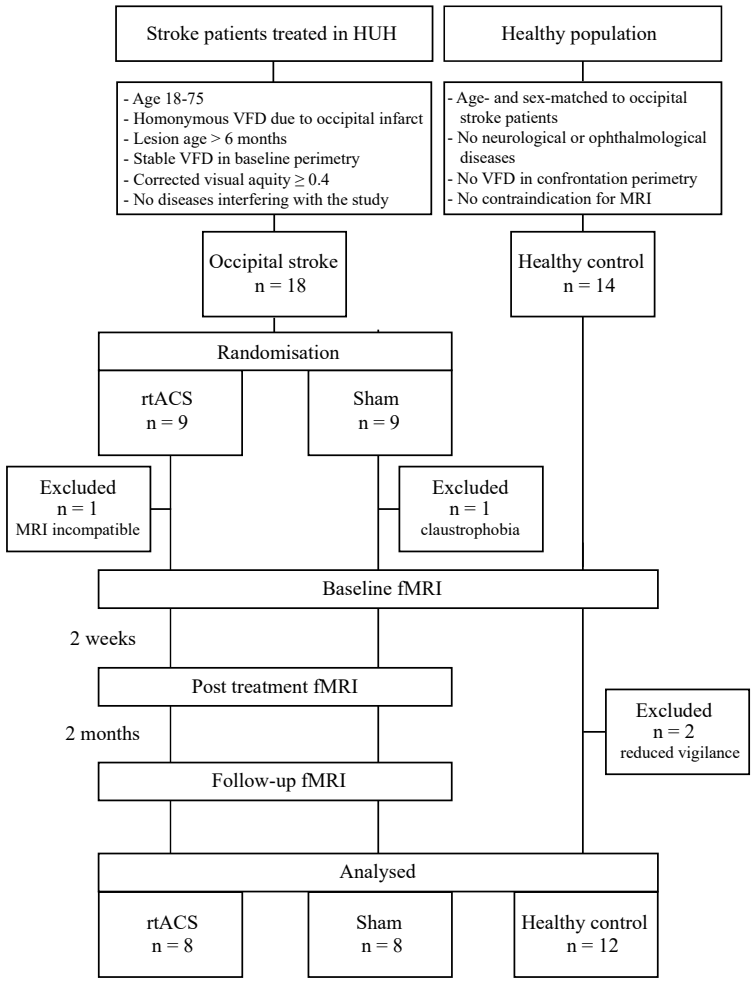

Figure 8. Flowchart of Study IV. Modified from Publication IV. Permission to reproduce granted by publishing terms by SAGE Publishing. HUH, Helsinki University Hospital; VFD, visual field defect; rtACS, repetitive transorbital alternating current stimulation; fMRI, functional magnetic resonance imaging.

The fMRI measurements were performed with 3T Siemens Magnetom Skyra scanner (Siemens, Erlangen, Germany) at the Advanced Magnetic Imaging Centre (Aalto University, Espoo, Finland) with a 30-channel coil (modified from 32-channel Siemens head coil). An fMRI session comprised anatomical images (high- and/or low-resolution T1, T2, FLAIR) and two 6-min rsfMRI runs. During the resting-state imaging, the subjects were advised to keep their mind empty of thoughts while they fixated on a cross on a back-projection screen. The fMRI sequences covered the occipital, parietal, and most of the temporal and frontal lobes, whereas parts of the inferior frontal and anterior temporal lobe and the cerebellum were excluded to optimise the images for visual cortical areas [1,42].

Functional and anatomical preprocessing were performed with tools from FSL [334,335], AFNI [336], and ITK-SNAP [337], integrated in a Nipype pipeline [338]. Preprocessing steps included skull stripping, deletion of the first six volumes to reach stable magnetisation, normalisation, slice timing correction, and transforming all images to the MNI152 standard space. In addition, we removed variance associated with several nuisance regressors, including temporal filtering and 24 motion parameters. Head movement was measured as framewise displacement [339]; its average magnitude in each run was calculated, and the higher of the two values was included in statistical analyses as a covariate to describe head motion.

We analysed the fMRI data with a method introduced by Craddock et al. [340]. The method is based on a multivariate regression connectivity model that uses a support vector regression analysis to calculate a predictive model for activity of a region of interest (ROI) based on time series of voxels outside the ROI. An advantage of the model is that it does not require a preselection of certain ROIs before analyses. For the connectivity analysis, we divided the brain into 74 cortical ROIs according to the Harvard-Oxford atlas [341]. The volume covered by infarcted tissue was excluded from the analysis with lesion masks. The support vector regression analysis was run consecutively for all ROIs. First it created a predictive linear model for the time series of the studied ROI based on the averaged time series data of all voxels outside the ROI from the first run of a rsfMRI session. Then it tested the model with data from the second run, and vice versa. Both runs produced one vector of prediction weight parameters. The analysis yielded correlation coefficients prediction accuracy and reproducibility for each ROI: the former between the predicted and observed time series and the latter between the two model vectors. The model is described in more detail in Figure 9.

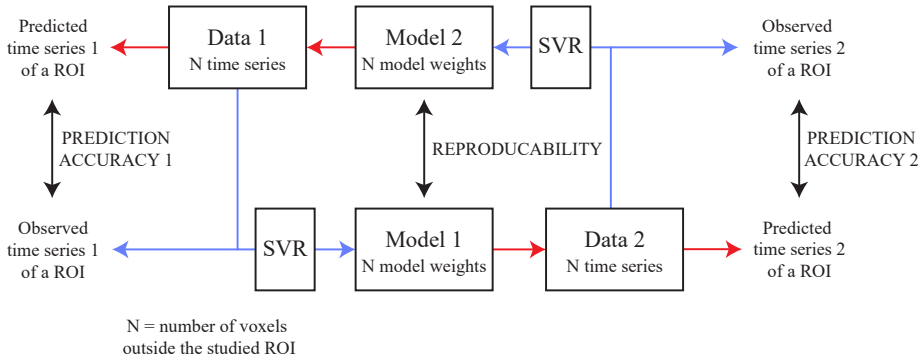

Figure 9. Schematic model of the multivariate regression method (modified from Craddock et al. [340]). Modified from the supplemental material of Publication IV. Permission to reproduce granted by publishing terms by SAGE Publishing. Data 1 and 2 depict two resting-state fMRI runs acquired during one session. Both data are divided in 74 regions of interest (ROI), which are examined one at a time. First, support vector regeression (SVR) analysis is applied to Data 1 to create a linear model (Model 1) for the activity of the ROI based on time series of all voxels outside the ROI (blue arrows). Next, Model 1 is applied to Data 2 to create a prediction of time series of the studied ROI in Data 2 by multiplying time series of the voxels outside the ROI with model weights (red arrows). The predicted time series of the ROI is then compared to the observed time series of the ROI from Data 2, and a correlation coefficient between these two is called Prediction accuracy. The same procedure is repeated for all ROIs and for both Data 1 and 2, resulting in two prediction accuracies for each ROI per session. For analyses, Prediction accuracy 1 and 2 are averaged. Reproducibility is the correlation coefficient between model vectors from Model 1 and 2. In the end, the analysis has yielded 74 Prediction accuracy and Reproducibility values per subject per session.

Furthermore, the model weights from the support vector regression analysis were used in a network analysis according to the graph theory [342]. In a directed and weighted graph, the ROIs represented nodes and the model weights edges between them. From the graph, we calculated four network parameters: centrality degree, centrality eigenvector, average shortest path, and clustering. Centrality degree is the sum of the edge weights that connect to a node [343], whereas centrality eigenvector sums not only the weights of a node but also the weights of the nearest nodes [344]. Average shortest path is the average length of the shortest paths between all possible pairs of nodes in the network, and clustering (clustering coefficient) reports the fraction of a node's nearest neighbours that are also neighbours to each other [343].

4.5 Statistical methods (I–IV)

In all studies, statistical analyses were executed with SPSS Statistics 22–25 (IBM Corp, Armonk, NY, USA). The distributions of continuous variables were assessed with histograms and the Shapiro-Wilk and Kolmogorov-Smirnov tests. Parametric tests were used for normally distributed variables and non-parametric tests for non-normally distributed variables. The significance level was two-sided $p < 0.05$. Odds ratios (OR) and 95% confidence intervals (CI) were calculated.

In Study I, to discover factors associated with early arrival, we compared the patients arriving within 4.5 hours to the ones who arrived later in their demographics, symptoms, findings, and diagnostic pathways with Fisher's exact test, Pearson´s χ^2 test, or the Mann-Whitney *U* test, when appropriate. Additionally, a multivariable analysis with binary logistic regression was run to detect independent predictors of the early arrival. Variables with $p < 0.2$ in the univariable analysis were included in the multivariable analysis. Data availability for all variables was > 97%.

In Study II, the occipital ICH patients were compared to other ICH patients in their clinical phenotype, mortality, dichotomous functional outcome (mRS 0–2 vs 3–6), and incidence of epilepsy with Fisher's exact test, Pearson's χ^2 test, or the Mann-Whitney *U* test. A binary logistic regression among the lobar ICH patients was performed to investigate if the occipital location was independently associated with the outcome variables when adjusted for confounding factors. The confounders were chosen based on the previous prognostic data [111-114].

In Study III, the treatment groups were compared within each experiment. In the between-group analyses, the absolute change in every outcome variable between the baseline and post-treatment and the baseline and follow-up measurements were compared between the treatment groups with the Mann-Whitney *U* test or the Kruskal-Wallis H test, in case of more than two groups. Post hoc pairwise comparisons were performed with Dunn´s test if the difference between the groups and the omnibus test were significant. Within-group comparisons were performed with the Friedman test and post hoc pairwise comparisons with the Wilcoxon signed-rank test. The Bonferroni correction was applied to the post hoc tests. Missing data at follow-up were replaced with the subjects' post-treatment results. However, if a subject had neither post-treatment nor follow-up data, they were excluded from the statistical analyses of that variable. The Hodges-Lehman estimator was applied to calculate estimates of median differences and 95%-CIs.

In Study IV, we compared the whole-network and ROI-wise prediction accuracy and network parameters of the patients before the intervention to the values of the control subjects to study the effect of the occipital lesion and VFD on the global and local FC. In addition, the stroke patients receiving rtACS were compared to the sham group at the post-treatment measurements to assess potential treatment effects. Multilevel modelling with either a linear or generalised linear mixed model [345] based on the distribution of the dependent variable was chosen to consider the

correlated nature of the data due to the repeated measures and the clustering of ROIs within subjects. The Fisher transformation was applied to the correlation coefficient prediction accuracy to enable linear statistical testing, whereas the network parameters were not transformed. The results were adjusted for head motion, age, and voxel count, and in the treatment-group analysis, also for baseline connectivity. The restricted maximum likelihood method was used for the model estimation, and the model selection was based on the Bayesian information criterion. Prediction accuracy and network parameters of single ROIs were compared with the Mann-Whitney *U* test between the groups and with the Friedman test with the post hoc Wilcoxon signed-rank test and the Bonferroni correction within the groups. The false discovery rate correction was executed to correct for multiple comparisons.

The correlation of the FC metrics with the behavioural primary outcomes (detection accuracy and mean sensitivity) of the REVIS trial and with potential confounding factors were tested with either the Pearson correlation or Spearman's rank correlation, based on the distribution of the variables. If significant correlations were found, connectivity variables were inserted into a simple linear regression model to test their independent association with the behavioural primary outcomes.

5. RESULTS

5.1 Prehospital pathways of occipital ischaemic stroke patients (I)

Among 10 775 ischaemic stroke patients treated at the neurological emergency department during the study period, there were 245 occipital stroke patients with mainly visual manifestation. Their onset-to-door time varied between 20 minutes and 5 weeks. Of the study population, 51 (20.8%) patients arrived within 4.5 hours (Figure 10) and 16 (6.5%) patients received IVT. As few as 56 (22.9%) patients arrived directly at the neurological emergency department whereas 120 (49.0%) patients arrived through one point of care and 67 (27.3%) patients through at least two points of care (Figure 10), mainly primary care. Only 49 (20.0%) patients were transported to their first point of care by EMS and 69 (28.2%) patients were assessed by an ophthalmologist before the correct neurological diagnosis (Table 6).

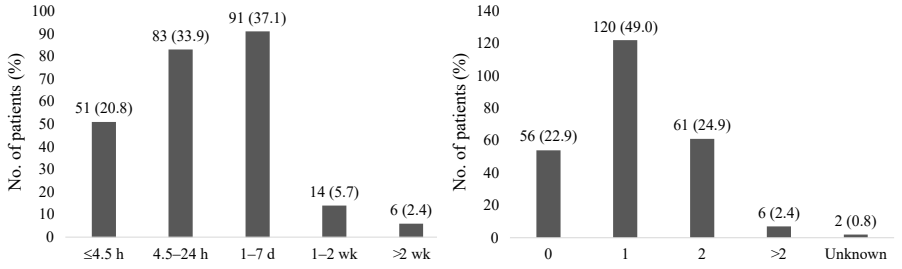

Figure 10. Distribution of patients according to the time from symptom onset to arrival (left) and the number of points of care visited before admission to the neurological emergency department (right). Modified from Publication I. Permission to reproduce granted by publishing terms by Wiley.

The most common reason for the delayed arrival was patients' late contact to any health-care unit (n = 143, 73.7% of the patients with onset-to-door time over 4.5 hours). For the remaining patients, the reason for the delayed arrival at the neurological emergency department was an unclear time window (n = 25, 12.8%), misdiagnosis (n = 11, 5.7%) or poor recognition of a potential thrombolysis candidate (n = 6, 3.1%) in health care, other reason (n = 3, 1.5%), or the reason was unavailable (n = 6, 3.1%). Health-care professionals initially suspected 80 (32.7%) patients to have other aetiology than stroke for their symptoms, most frequently ophthalmological disorder (n = 54, 22.0%) or migraine (n = 11, 4.5%).

Table 6. Demographics, symptoms, findings, and features of the prehospital pathway according to the delay to the neurological emergency department. Modified from Publication I. Permission to reproduce granted by publishing terms by Wiley.

	All (n = 245)	ODT ≤ 4.5 hours (n = 51)	ODT > 4.5 hours (n = 194)	*p*
Demographics				
Age (y)	68.0 (58.5–76.0)	66.0 (56.0–75.0)	68.0 (59.0–77.0)	0.558
Male sex	154 (62.9)	36 (70.6)	118 (60.8)	0.199
Previous stroke	38 (15.5)	11 (21.6)	27 (13.9)	0.179
Migraine	42 (17.1)	9 (17.6)	33 (17.0)	0.914
Ophthalmological disorder	69 (28.2)	10 (19.6)	59 (30.4)	0.127
Antiplatelet therapy	85 (34.7)	19 (37.3)	66 (34.0)	0.666
Anticoagulant therapy	26 (10.6)	8 (15.7)	18 (9.3)	0.186
Hypertension	160 (65.3)	36 (70.6)	124 (63.9)	0.373
Hyperlipidaemia	162 (66.1)	33 (64.7)	129 (66.5)	0.810
Atrial fibrillation	55 (22.4)	17 (33.3)	38 (19.6)	0.036
Other heart disease	77 (31.4)	18 (35.3)	59 (30.4)	0.504
Diabetes	53 (21.6)	9 (17.6)	44 (22.7)	0.437
Symptoms and findings				
Only positive visual symptom	6 (2.4)	0	6 (3.1)	0.349
Transient visual symptom[a]	8 (3.3)	0	8 (4.1)	0.211
Subjective monocular symptom	48 (19.6)[b]	9 (17.6)[b]	39 (20.1)[b]	0.682
Migraine-like symptom onset	27 (11.0)	4 (7.8)	23 (11.9)	0.415
Visual defect noticed by others	4 (1.6)	2 (3.9)	2 (1.0)	0.192
VFD in physical examination	210 (85.7)[b]	48 (94.1)[b]	162 (83.5)[b]	0.062
Headache	117 (47.8)	23 (45.1)	94 (48.5)	0.669
Nausea	30 (12.2)	4 (7.8)	26 (13.4)	0.281
Dizziness	37 (15.1)	7 (13.7)	30 (15.5)	0.758
Confusion	22 (9.0)	8 (15.7)	14 (7.2)	0.093
Imaging				
CT	175 (71.4)	33 (64.7)	142 (73.2)	0.232
MRI	27 (11.0)	5 (9.8)	22 (11.3)	0.755
CT + MRI	43 (17.6)	13 (25.5)	30 (15.5)	0.094
Additional CT/MR angiography	134 (54.7)	38 (74.5)	96 (49.5)	0.001
Imaging negative	11 (4.5)	2 (3.9)	9 (4.6)	1.000
Diagnostic pathway				
Use of EMS	49 (20.0)[b]	26 (51.0)[b]	23 (11.9)[b]	<0.001
Directly to neurological ED	56 (22.9)	33 (64.7)	23 (11.9)	<0.001
First misdiagnosed	80 (32.7)[b]	7 (13.7)[b]	73 (37.8)[b]	0.001
Examined by ophthalmologist	69 (28.2)	6 (11.8)	63 (32.5)	0.003

N (%) and median (interquartile range) are reported. Fisher's exact test, χ^2 test, or Mann–Whitney *U* test were used. [a] symptom duration less than 24 hours; [b] missing data < 1%. ODT, onset-to-door time; VFD, visual field defect; CT, computed tomography; MRI, magnetic resonance imaging; EMS, emergency medical services; ED, emergency department.

Factors associated with arrival within 4.5 hours were EMS utilisation, direct arrival at the tertiary centre, and atrial fibrillation (Table 6). On contrary, an ophthalmologist visit and initial misdiagnosis were predictors for onset-to-door time > 4.5 hours. Only direct arrival predicted onset-to-door time ≤ 4.5 hours in the multivariable analysis (OR 13.3, 95% CI 6.5–27.4, $p < 0.001$).

5.2 Clinical characteristics, outcome, and incidence of epilepsy after occipital ICH (II)

The HICHS registry of 1013 consecutive ICH patients contained 19 (1.9%) isolated occipital ICH patients. Their frequency among lobar ICH patients was 5.3%. The occipital ICH patients were younger (median 63 years) and had a lower NIHSS score on admission (median NIHSS 1) in comparison to the non-occipital lobar and all non-occipital ICH patients (Table 7). Their presentation delay was longer, and fewer patients arrived at the hospital by EMS. The median volume of the occipital ICH was smaller than that of the other lobar haematoma and did not grow between repeated imaging.

Table 7. Clinical and radiological characteristics, aetiology, and outcome of occipital ICH patients compared to patients with non-occipital lobar ICH or any non-occipital ICH. Modified from Publication II. Permission to reproduce granted by publishing terms by Wiley.

	Occipital ICH (n = 19)	Non-occipital lobar ICH (n = 337)	p^a	Non-occipital ICH (n = 994)	p^b	Missing data (occipital/ non-occipital lobar/ non-occipital)
Demographics						
Age (y)	63 (55–69)	71 (60–79)	0.007	68 (58–78)	0.04	0/0/0
Male sex	13 (68)	180 (53)	0.20	569 (57)	0.33	0/0/0
Hypertension	10 (53)	186 (55)	0.83	627 (63)	0.35	0/0/0
Diabetes	3 (16)	44 (13)	0.73	139 (14)	0.74	0/0/0
Coronary heart disease	3 (16)	57 (17)	>0.99	125 (13)	0.73	0/6/12
Atrial fibrillation	4 (21)	47 (14)	0.50	139 (14)	0.34	0/6/14
Dyslipidaemia	7 (37)	61 (18)	0.69	190 (19)	0.08	0/6/13
Previous ICH	1 (5)	26 (8)	>0.99	53 (5)	>0.99	0/8/18
Pre-ICH mRS	0 (0–0)	0 (0–0)	0.39	0 (0–0)	0.43	0/0/0
Prehospital route						
Presentation delay (d)	1 (0–2)	0 (0–1)	0.006	0 (0–1)	<0.001	0/0/0
Use of EMS	7 (37)	274 (83)	<0.001	859 (88)	<0.001	0/6/20

(*Table 7 continues*)

Clinical variables on arrival						
NIHSS score	1 (1–3)	8 (3–18)	<0.001	11 (4–20)	<0.001	0/0/0
GCS score	15 (15–15)	14 (10–15)	<0.001	14 (10–15)	<0.001	0/0/0
Systolic blood pressure (mmHg)	165 (141–176)	165 (144–187)	0.37	171 (149–193)	0.11	0/9/25
Diastolic blood pressure (mmHg)	96 (89–100)	87 (74–102)	0.07	90 (77–103)	0.23	0/11/29
Glucose (mmol/l)	5.9 (5.4–6.9)	7.5 (6.3–9.2)	0.003	7.3 (6.2–9.1)	0.005	2/32/95
Haemoglobin (g/l)	147 (132–157)	137 (127–148)	0.06	139 (128–150)	0.11	1/16/41
Platelet count (E9/l)	206 (171–249)	204 (164–253)	0.90	209 (171–253)	0.95	1/17/47
Radiological variables						
Imaging within 24 h of onset	9 (47)	233 (69)	0.048	757 (76)	0.01	0/0/0
Follow-up imaging	16 (84)	222 (66)	0.10	615 (62)	0.047	0/0/0
MRI	8 (42)	72 (21)	0.047	144 (15)	0.004	0/0/0
Any angiography	11 (58)	111 (33)	0.03	246 (25)	0.002	0/0/0
CTA	9 (47)	103 (31)	0.13	228 (23)	0.02	0/0/0
MRA	2 (11)	8 (2)	0.09	18 (2)	0.05	0/0/0
DSA	1 (5)	5 (2)	0.28	8 (1)	0.16	0/0/0
IVH	3 (16)	92 (27)	0.27	409 (41)	0.03	0/0/0
ICH volume at baseline (ml)	6.3 (4.1–11.7)	17.7 (5.4–39.5)	0.008	9.9 (3.7–28.0)	0.21	0/4/19
ICH growth to 2. scan (%)	-18 (-89–0.6)	0 (-50–41)	0.08	0 (-31–46)	0.03	5/136/424
Hospital stay						
Deterioration within 72 h	4 (21)	136 (40)	0.09	415 (42)	0.07	0/1/3
ICH evacuation	1 (5)	34 (10)	0.71	60 (6)	>0.99	0/0/2
Length of stay (d)	7 (3–14)	8 (3–14)	0.35	8 (3–14)	0.36	0/0/0
Aetiology[c]						
Structural lesion	5 (26)	22 (7)	0.01	46 (5)	0.002	0/0/0
Anticoagulation	2 (11)	52 (15)	0.75	140 (14)	0.74	0/0/0
Amyloid angiopathy	10 (53)	193 (57)	0.69	197 (20)	0.002	0/0/0
Hypertension	0	0	-	350 (35)	0.001	0/0/0
Systemic/Other disease	1 (5)	25 (7)	>0.99	48 (5)	0.61	0/0/0
Undetermined	1 (5)	45 (13)	0.49	213 (21)	0.15	0/0/0
Outcome						
In-hospital mortality	1 (5)	70 (21)	0.14	243 (24)	0.06	0/0/0
mRS at discharge	2 (1–2)	4 (3–5)	<0.001	5 (3–5)	<0.001	0/0/0
mRS 0–2 at discharge	16 (84)	81 (24)	<0.001	173 (17)	<0.001	0/0/0
Mortality at 3 months[d]	1 (6)	90 (27)	0.05	316 (33)	0.02	1/8/28
Mortality at 12 months[d]	1 (6)	111 (34)	0.01	357 (37)	0.006	1/8/28

N (%) and median (interquartile range) are reported. Fisher's exact test, χ^2 test, or Mann–Whitney *U* test were used. [a] occipital vs non-occipital lobar ICH; [b] occipital vs all non-occipital ICH; [c] according to SMASH-U classification; [d] patients lost to follow-up were excluded. ICH, intracerebral haemorrhage; mRS, modified Rankin Scale; EMS, emergency medical service; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; MRI, magnetic resonance imaging; CTA, computed tomography angiography; MRA, magnetic resonance angiography; DSA, digital subtraction angiography; IVH, intraventricular haemorrhage.

The most common aetiologies of the occipital bleeding according to the SMASH-U classification were as follows: amyloid angiopathy (n = 10), structural lesion (n = 5), anticoagulation (n = 2), systemic disease (n = 1), and other (n = 1) (Table 7). The distribution differed from the non-occipital lobar ICH patients in the frequency of structural causes, three of which were arteriovenous malformations and two were cavernomas.

Of the occipital ICH patients, 14 (74%) reported visual symptoms at the presentation and 12 (63%) suffered from no other focal neurological symptoms. Of the 18 patients assessed with confrontation testing, 15 (83%) had VFD in the acute phase. Other frequent manifestations included headache (n = 16; 84%), nausea (n = 5; 26%), motor hemiparesis (n = 2; 11%), and neglect (n = 2; 11%). One (5%) occipital ICH patient died during the hospital stay, but no other patient deceased within the following year. The follow-up data were available for 17 patients, 8 (47%) of whom continued to suffer from residual visual symptoms, including VFD, impaired perception in the neuropsychological or occupation therapy evaluation, or subjective visual symptoms. Ten (59%) patients underwent standard perimetry, which revealed two hemianopia/partial hemianopia, two quadrantanopia/partial quadrantanopia, one scotoma, and four normal visual fields in the final examination. Remaining seven (41%) patients were solely assessed with confrontation testing, six of which were normal at discharge or at the follow-up visit.

The median mRS of the occipital ICH patients at discharge was 2, and the number of patients achieving mRS 0–2 at discharge, at 3 months, and at 12 months were 16 (84%), 14 (74%), and 14 (74%), respectively. The functional outcome could not be defined for three patients at 3 months and for four patients at 12 months, either due to their out-of-province residence or lack of detailed enough description of their independence in activities of daily living in the patient records. Only one patient was unable to live at home and one could not return to their pre-ICH work. Two patients received permanent driving bans whereas nine were allowed to drive.

The functional outcome of the occipital ICH patients at discharge was significantly better compared to the non-occipital lobar and all non-occipital ICH patients, and the occipital location of lobar haematoma remained as an independent predictor of the favourable functional outcome at discharge in the multivariable model (Table 8). The mortality of the occipital ICH patients at 3 and 12 months was lower; however, the occipital haematoma was not independently associated with mortality when adjusted for age, sex, NIHSS on admission, haematoma volume, presence of IVH, and structural aetiology.

The incidence of acute seizures among the occipital ICH patients was 11%, and 18% developed post-ICH epilepsy within the median follow-up of 2.7 years. The occurrences of acute and late seizures were 20% ($p = 0.55$) and 16% ($p = 0.74$) among the non-occipital lobar ICH patients and 11% ($p > 0.99$) and 9% ($p = 0.19$) among all non-occipital ICH patients, respectively.

Table 8. Results of the multivariable analysis of favourable functional outcome and mortality in lobar ICH (n = 356). Modified from Publication II. Permission to reproduce granted by publishing terms by Wiley.

	Favourable outcome (mRS 0–2) at discharge[a]			3-month mortality[b]			12-month mortality[b]		
Covariates	OR (95% CI)	*p*	Wald	OR (95% CI)	*p*	Wald	OR (95% CI)	*p*	Wald
Occipital location	11.02 (1.55–78.20)	0.02	5.8	2.70 (0.29–24.8)	0.38	0.8	0.97 (0.11–8.33)	0.98	0.0
Age per year	0.93 (0.90–0.96)	<0.001	16.9	1.06 (1.03–1.10)	0.001	11.0	1.07 (1.04–1.10)	<0.001	18.2
NIHSS on admission per 1 point	0.80 (0.72–0.88)	<0.001	21.3	1.14 (1.09–1.19)	<0.001	34.0	1.11 (1.07–1.15)	<0.001	28.1
Baseline volume per ml³	0.86 (0.81–0.92)	<0.001	21.7	1.04 (1.02–1.05)	<0.001	18.0	1.03 (1.01–1.04)	<0.001	12.2
IVH	0.18 (0.03–1.04)	0.06	3.7	1.33 (0.60–2.93)	0.49	0.5	1.39 (0.68–2.84)	0.36	0.8
Male sex	1.50 (0.71–3.17)	0.29	1.1	3.11 (1.41–6.87)	0.005	7.9	2.51 (1.31–4.81)	0.006	7.6
Structural aetiology	1.37 (0.36–5.20)	0.65	0.2	0.00	>0.99	0.0	0.15 (0.02–1.01)	0.05	3.8

[a] Missing data 4/356 (1.1%); [b] missing data 13/356 (3.7%). mRS, modified Rankin Scale; OR, odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; IVH, intraventricular haemorrhage.

5.3 Non-invasive electrical brain stimulation for rehabilitation of vision after stroke (III)

Of the 56 randomised subjects, 52 underwent all post-treatment measurements and 50 all follow-up measurements (Figure 7). The primary outcomes were available for 55 subjects at post treatment and for 53 subjects at follow-up. Their baseline characteristics and measurements are presented in Table 9. Next, we present the main findings of the three treatment arms.

Table 9. Demographics and baseline measurements of the treatment arms in Experiments 1, 2, and 3. Outcome variables measured in only a subset of centres are omitted. Modified from Publication III. Reproduced with permission from IOS Press.

	Experiment 1					Experiment 2				Experiment 3			
	All (n = 24)	Sham (n = 8)	rtACS (n = 8)	tDCS/rtACS (n = 8)	*p*	All (n = 18)	Sham (n = 9)	rtACS (n = 9)	*p*	All (n = 14)	Sham (n = 7)	tDCS (n = 7)	*p*
Demographics													
Age (y)	58 (51–66)	64 (59–67)	54 (51–66)	52 (45–64)	0.12	58 (36–67)	57 (36–69)	59 (34–66)	0.71	68 (60–73)	65 (57–68)	72 (67–81)	0.06
Male sex	21 (87.5)	6 (75.0)	7 (87.5)	8 (100.0)	0.75	13 (72.2)	7 (77.8)	6 (66.7)	1.00	10 (71.4)	6 (85.7)	4 (57.1)	0.56
Infarct side, right	14 (58.3)	5 (62.5)	5 (62.5)	4 (50.0)	1.00	10 (55.6)	5 (55.6)	5 (55.6)	1.00	12 (85.7)	7 (100.0)	5 (71.4)	0.46
HRP													
Detection accuracy (%)	55.9 (53.0–63.9)	57.0 (49.9–73.6)	54.0 (47.4–57.9)	58.0 (55.4–67.1)	0.31	74.0 (60.0–78.8)	76.0 (62.0–81.0)	72.0 (60.0–79.5)	0.85	70.0 (51.5–78.3)	55.7 (25.7–72.7)	74.3 (65.3–80.0)	0.16
Response time (ms)	439 (401–477)	437 (392–523)	435 (397–471)	441 (405–470)	0.96	416 (380–476)	418 (395–521)	414 (370–447)	0.55	488 (429–550)	515 (436–589)	468 (405–537)	0.62
Fixation accuracy (%)	98 (96–99)	97 (96–100)	97 (96–100)	99 (96–99)	0.59	98 (95–100)	98 (92–100)	98 (95–100)	0.41	90 (65–97)	93 (66–97)	88 (61–97)	0.88
False positives (%)	1.1 (0.4–2.1)	1.6 (0.5–4.1)	0.7 (0.4–1.5)	0.8 (0.4–3.0)	0.64	1.0 (0.8–2.0)	1.0 (0.5–2.5)	1.0 (0.5–1.5)	0.48	2.3 (1.5–4.3)	1.7 (1.0–3.0)	3.3 (1.7–5.3)	0.33
SAP													
Mean sensitivity, ILE (dB)	12.6 (10.3–15.0)	12.7 (10.5–16.5)	11.5 (8.6–15.2)	12.6 (11.5–13.7)	0.59	17.7 (14.9–19.2)	17.7 (14.3–19.4)	17.7 (14.9–18.6)	0.75	17.5 (12.7–22.2)	19.1 (9.0–21.6)	15.9 (13.5–23.2)	0.54
Mean sensitivity, CLE (dB)	13.5 (11.6–15.7)	14.0 (11.9–16.6)	12.9 (8.9–16.2)	13.5 (11.9–14.9)	0.77	18.2 (16.3–20.3)	17.6 (15.1–20.8)	18.7 (16.1–19.8)	0.98	16.8 (12.8–22.0)	17.3 (10.5–22.3)	16.4 (13.5–21.9)	1.00
Foveal sensitivity, ILE (dB)	26.0 (25.0–27.0)	26.0 (25.3–26.8)	25.5 (22.8–27.0)	27.5 (25.3–28.0)	0.18	32.0 (26.8–32.3)	32.0 (26.5–33.0)	31.0 (26.5–32.0)	0.32	35.0 (30.8–37.0)	35.0 (30.0–37.0)	35.0 (32.0–36.0)	0.81
Foveal sensitivity, CLE (dB)	26.0 (24.0–27.0)	26.0 (22.3–26.0)	26.0 (23.3–27.8)	26.5 (24.3–27.8)	0.39	32.0 (29.5–33.0)	32.0 (29.0–32.5)	32.0 (30.0–33.0)	0.41	35.0 (31.3–36.3)	36.0 (29.0–38.0)	35.0 (33.0–36.0)	0.51
Visual acuity (decimal)	1.4 (0.8–1.4)	1.3 (0.8–1.4)	1.4 (0.8–1.4)	1.2 (0.8–1.4)	0.94	1.1 (0.8–1.4)	1.4 (0.9–1.4)	1.0 (0.8–1.4)	0.58	1.3 (1.0–1.3)	1.3 (1.0–1.3)	1.0 (1.0–1.3)	0.43
Reading speed (words/min)	126 (93–150)	130 (84–148)	109 (82–183)	129 (120–145)	0.90	122 (98–137)	117 (78–138)	122 (101–134)	0.78	137 (104–160)	138 (58–156)	128 (120–171)	0.90

N (%) and median (interquartile range) are reported. Between-group *p* values for continuous variables were calculated with Mann-Whitney *U* test or Kruskal-Wallis H test in case of more than two groups and for dichotomous variables with Fisher's exact test. rtACS, repetitive transorbital alternating current stimulation; tDCS, transcranial direct current stimulation; HRP, high-resolution perimetry; SAP, standard automated perimetry; ILE, ipsilesional eye; CLE, contralesional eye.

5.3.1 Experiment 1: rtACS versus tDCS/rtACS versus sham

Of the primary outcomes, the median changes of detection accuracy and mean sensitivity in the ipsilesional eye did not differ between the treatment groups (Figure 11). Mean sensitivity in the contralesional eye decreased between the baseline and post-treatment assessments −0.3 dB (IQR −1.0–0.2) in the rtACS group (n.s.), increased 0.4 dB (IQR −0.2–0.7) in the tDCS/rtACS group (n.s.), and increased 0.7 dB (IQR 0.1–1.2) in the sham group (adjusted p = 0.018), resulting in a significant difference between the sham and rtACS groups (estimated median difference 1.1 dB [95% CI 0.2–0.9], adj. p = 0.040). No changes persisted at the 2-month follow-up.

The tDCS/rtACS group experienced several improvements in the secondary outcome measures. The absolute defect in the contralesional eye diminished by −0.8 pp (IQR −2.7–1.5) (n.s.) to the post-treatment assessment and −1.5 pp (IQR −5.7–1.5) to the follow-up (estimated median difference −3.0 pp [95% CI, −5.3–−0.8], adj. p = 0.026). Reading speed increased 4.6 words/min (IQR −6.8–19.2) to the post-treatment visit (n.s.) and 14.5 words/min (IQR 5.3–21.0) to the follow-up visit (estimated median difference 14 words/min [95% CI, 6.5–27.0], adj. p = 0.005). Average dynamic visual acuity improved 5.0 pp (IQR 1.9–9.7) to the post-treatment measurement (estimated median difference 5.3 pp, [95% CI, −5.0–10.6], adj. p = 0.037). In addition, false positive responses in HRP reduced to the post-treatment assessment (estimated median difference −0.6 pp [95% CI −1.0–−0.2], p = 0.026). None of these changes, however, differed significantly from the results of the other treatment groups.

Of the secondary outcomes, foveal sensitivity of the ipsilesional eye decreased −0.5 dB (IQR −1.0–0.0) in the sham group and increased 1.0 dB (IQR 0.0–2.0) in the rtACS group, with a significant between-group difference immediately after the intervention (estimated median difference 2.0 dB [95% CI, 1.0–2.0], adj. p = 0.013).

5.3.2 Experiment 2: rtACS versus sham

There were no changes in the size of VFD or in the other visual variables within either of the groups or between them (Figure 11).

5.3.3 Experiment 3: tDCS versus sham

Mean sensitivity of the contralesional eye increased 0.8 dB (IQR −0.2–2.1) to the post-treatment assessment (n.s.) and 1.3 dB (IQR 0.5–3.3) to the follow-up measurement (n.s.) in the tDCS group and decreased −0.7 dB (IQR −1.0–0.5) and −0.5 dB (IQR −1.7–0.3) (both n.s.) in the sham group (Figure 11). Despite the non-significant within-group changes, this yielded a significant difference between the groups at the 2-month follow-up (estimated median difference 2.2 dB [95% CI, 0.6–5.0], p = 0.017) and a trend for difference immediately after the intervention

(estimated median difference 1.5 dB [95% CI, 0.02–5.2], $p = 0.053$). No such changes were detected in the ipsilesional eye, nor in the binocular detection. The secondary visual outcome variables were also neutral.

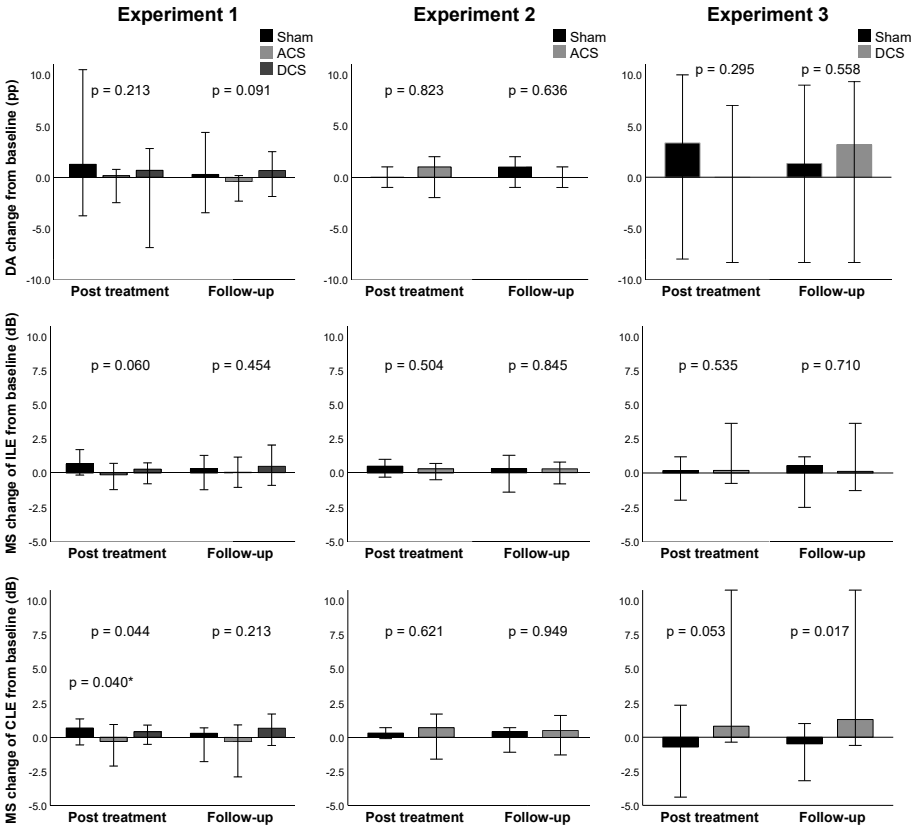

Figure 11. Results of the primary outcomes in Experiments 1, 2, and 3. Median changes from baseline, 95%-CIs, and between-group *p* values, calculated with Mann-Whitney *U* test or Kruskal-Wallis H test in case of more than two groups, are given. Modified from Publication III. Reproduced with permission from IOS Press. *Sham vs ACS, calculated from post hoc pairwise comparison. ACS, alternating current stimulation; DCS/ACS, combined direct current stimulation/alternating current stimulation; DCS, direct current stimulation; DA, detection accuracy; MS, mean sensitivity; ILE, ipsilesional eye; CLE, contralesional eye.

5.3.4 Adverse events

No serious adverse events occurred. The most common adverse events in Experiments 1 and 2 were mild skin irritation under the stimulation electrodes (n = 22), metallic taste (n = 9), other skin sensations (n = 8), tiredness (n = 7), paroxysmal phosphene-like phenomena between the sessions (n = 6), mild headache (n = 4), chills (n = 4), myokymia (n = 2), and transient discomfort (n = 2). In Experiment 1, the composite

numbers of adverse events in the rtACS (median 1.0 per subject [IQR 0–2.5]), tDCS/rtACS (median 0 per subject [IQR 0–1.5]), and sham group (median 0.5 [IQR 0–1.8]) were similar ($p = 0.431$). Neither was there difference in Experiment 2 where the composite numbers were 3.0 per subject (IQR 2.0–5.5) in the rtACS group and 4.0 per subject (IQR 1.5–5.0) in the sham group ($p = 0.194$). In Experiment 3, all patients reported mild skin sensations, but adverse effects were not collected systematically.

5.4 Functional connectivity after occipital stroke (IV)

5.4.1 Baseline characteristics

The average age was 54 years among the stroke patients and 49 years among the control subjects and 75% were men in both groups (Table 10). The stroke patients had more often a history of hypertension and antiplatelet medication, whereas there was no difference in other cardiovascular diseases. Ten (63%) stroke patients had other old infarcts in addition to the occipital one but no related permanent neurological deficits. The volume of the cerebral cortex was smaller among the patients, which was apparent both in the ipsilesional and contralesional hemisphere. None of the baseline characteristics differed between the two treatment groups.

Table 10. Baseline characteristics of the patients (rtACS and sham group) and controls. Modified from Publication IV. Permission to reproduce granted by publishing terms by SAGE Publishing.

	All patients (n = 16)	Controls (n = 12)	*p*	rtACS (n = 8)	Sham (n = 8)	*p*
Age (y), mean ± SD	54 ± 17	49 ± 18	0.452[a]	51 ± 19	57 ± 15	0.477[a]
Male sex, n (%)	12 (75)	9 (75)	1.000[b]	7 (88)	5 (63)	0.569[c]
Hypertension, n (%)	9 (56)	0	0.003[c]	4 (50)	5 (63)	1.000[c]
Diabetes mellitus, n (%)	2 (13)	0	0.492[c]	1 (13)	1 (13)	1.000[c]
Atrial fibrillation, n (%)	4 (25)	1 (8)	0.355[c]	2 (25)	2 (25)	1.000[c]
Vascular degeneration, n (%)	3 (19)	1 (8)	0.613[c]	2 (25)	1 (13)	1.000[c]
Antiplatelet medication, n (%)	11 (69)	1 (8)	0.001[b]	6 (75)	5 (63)	1.000[c]
Time since stroke (mo), median (IQR)	30 (19–54)	-	-	46 (20–62)	22 (19–42)	0.344[d]
Other infarcts, n (%)	10 (63)	-	-	5 (63)	5 (63)	1.000[c]
Cortex volume (cm^3), mean ± SD	472 ± 43	512 ± 32	0.013[a]	467 ± 45	477 ± 43	0.667[a]
Ipsilesional (left) cortex volume (cm^3), mean ± SD	232 ± 24	255 ± 15	0.006[a]	232 ± 22	232 ± 27	0.976[a]
Contralesional (right) cortex volume (cm^3), mean ± SD	241 ± 21	257 ± 17	0.036[a]	235 ± 24	245 ± 17	0.352[a]
Head motion (mm), mean ± SD	2.8 ± 0.7	1.7 ± 0.4	<0.001[a]	2.7 ± 0.5	2.8 ± 0.9	0.670[a]

Significances are calculated with [a] *t* test, [b] χ^2 test, [c] Fisher's exact test, or [d] Mann-Whitney *U* test. rtACS, repetitive transorbital alternating current stimulation; SD, standard deviation; IQR, interquartile range.

5.4.2 Functional connectivity of patients versus control subjects

There was no difference in the whole-network prediction accuracy between the occipital stroke patients and the control subjects at baseline (median 0.64 [IQR 0.56–0.78] vs 0.68 [0.55–0.78]; adj. p = 0.552). Likewise, none of the network parameters differed between the groups: average shortest path (6.17 [5.21–7.27] vs 5.98 [5.21–6.98]; adj. p = 0.419), centrality degree (19.0 [15.9–22.4] vs 19.4 [16.7–22.5]; adj. p = 0.415), centrality eigenvector (0.11 [0.10–0.13] vs 0.10 [0.09–0.12]; adj. p = 0.835), or clustering (0.10 [0.09–0.12] vs 0.10 [0.09–0.12]; adj. p = 0.376).

When it comes to individual ROIs, no significantly altered prediction accuracy was found. However, the patients had lower centrality eigenvector in the ipsilesional lingual gyrus (median 0.12 [IQR 0.10–0.13] vs 0.14 [0.14–0.15]; corrected p = 0.015) and in the ipsilesional intracalcarine cortex (0.12 [0.10–0.13] vs 0.14 [0.14–0.15]; corr. p = 0.003) and higher centrality eigenvector in the superior division of the ipsilesional lateral occipital cortex (0.14 [0.13–0.16] vs 0.12 [0.11–0.13]; corr. p = 0.046). Centrality degree and average shortest path showed similar trends in the ipsilesional intracalcarine cortex and in the superior division of the ipsilesional lateral occipital cortex, as did clustering in all three ROIs. To confirm the altered local connectivity in the occipital region, we analysed 16 occipital ROIs jointly and adjusted the results for voxel count and head motion. In this analysis, centrality eigenvector of the patients remained lower (0.12 [0.10–0.13] vs 0.13 [0.11–0.14]; $p < 0.001$).

5.4.3 Functional connectivity of patients receiving rtACS versus sham

The rtACS treatment led to decreased whole-network prediction accuracy at the post-treatment assessment (Table 11). In contrast, prediction accuracy increased in the sham group; yet no significant between-group difference was detected. Neither of the observed changes remained at the 2-month follow-up. Of the network parameters, average shortest path decreased in both groups between the baseline and post-treatment analyses and remained shorter at follow-up, but no between-group effect occurred. In a similar vein, centrality degree and clustering increased within the sham group, whereas the rtACS group remained unchanged. Again, the changes were not large enough to result in significant between-group differences. No changes in individual ROIs were observed within either groups or between them.

Table 11. Global network statistics of the rtACS and sham groups at the three assessments. Modified from Publication IV. Permission to reproduce granted by publishing terms by SAGE Publishing.

	BASELINE		POST TREATMENT		POST TREATMENT – BASELINE			FOLLOW-UP		FOLLOW-UP – BASELINE		
	Median (IQR)		Median (IQR)		Within-group p^c		Between-group p^d	Median (IQR)		Within-group p^c		Between-group p^d
	rtACS (n = 592)	Sham (n = 592)	rtACS (n = 592)	Sham (n = 592)	rtACS	Sham		rtACS (n = 592)	Sham (n = 592)	rtACS	Sham	
PA[a]	0.70 (0.58–0.78)	0.67 (0.54–0.77)	0.67 (0.54–0.78)	0.68 (0.54–0.77)	0.041	<0.001	0.270	0.70 (0.57–0.78)	0.63 (0.47–0.74)	1.000	1.000	0.771
ASP[b]	6.18 (5.17–7.23)	6.16 (5.23–7.33)	5.98 (4.99–7.05)	5.47 (4.71–6.35)	0.006	<0.001	0.115	6.15 (5.11–7.47)	5.40 (4.55–6.27)	0.028	<0.001	0.203
CD[b]	19.3 (16.1–22.6)	18.8 (15.7–22.2)	19.4 (16.6–22.8)	21.3 (18.4–25.0)	0.081	<0.001	0.062	18.9 (15.8–22.5)	21.5 (18.7–25.1)	0.157	<0.001	0.239
CE[a]	0.11 (0.10–0.13)	0.11 (0.10–0.13)	0.12 (0.10–0.13)	0.11 (0.10–0.13)	ns[e]	ns[e]	ns[e]	0.12 (0.10–0.13)	0.11 (0.10–0.13)	ns[e]	ns[e]	ns[e]
CL[a]	0.10 (0.09–0.12)	0.10 (0.09–0.11)	0.10 (0.09–0.12)	0.12 (0.10–0.13)	0.051	<0.001	0.060	0.10 (0.09–0.12)	0.12 (0.10–0.13)	0.224	<0.001	0.194

Significances were calculated with [a] a linear mixed model or [b] a generalised linear mixed model using the gamma target distribution and the log link function based on the distribution. There are 592 data points per group (74 ROIs within 8 subjects). [c] Adjusted for head motion. [d] *p* values counted for post treatment and follow-up and adjusted for baseline value, voxel count, and difference in head motion between sessions. [e] Group, session, and interaction terms were non-significant, so not post hoc analysis was performed. IQR, interquartile range; rtACS, repetitive alternating current stimulation; PA, prediction accuracy; ASP, average shortest path; CE, centrality eigenvector; CL, clustering; ns, non-significant.

5.4.4 Correlation with behavioural results and confounding factors

At baseline, the median prediction accuracy of the stroke patients correlated with the two primary outcomes of the REVIS trial: detection accuracy of the central 12° visual field (Pearson's *r* 0.56, $p = 0.023$) and binocular mean sensitivity of the 30° field (Pearson's *r* 0.79, $p < 0.001$). The network parameters did not correlate with the behavioural results. Voxel count correlated with prediction accuracy (Spearman's *rho* 0.27, $p < 0.001$), as well as with average shortest path (Spearman's *rho* 0.39, $p < 0.001$), centrality degree (Spearman's *rho* −0.25, $p < 0.001$), and clustering (Spearman's *rho* −0.17, $p < 0.001$), whereas age, head motion, and cortex volume did not. In a linear regression model with voxel count as a covariate, global prediction accuracy proved to be an independent predictor of mean sensitivity (β 0.36; 95% CI 0.16–0.55; $p = 0.002$) but not that of detection accuracy ($p = 0.108$).

6. DISCUSSION

6.1 Main results in the context of the existing literature

This study covered several aspects of occipital stroke ranging from prehospital recognition to rehabilitation and outcome. We focused on the most prevalent symptom of occipital stroke, homonymous VFD, because it is often neglected in clinical practice and has received relatively little attention in post-stroke rehabilitation.

6.1.1 Prehospital pathways of occipital ischaemic stroke patients (I)

Prehospital pathways of occipital ischaemic stroke patients observed in Study I were highly variable, as the onset-to-door time ranged from 20 minutes to 5 weeks and the point of cares prior to the neurological emergency department up to more than two health-care units. The percentage of patients arriving within the 4.5-hour time window of IVT was no more than 20.8%, which is considerably low compared to the previously reported 25 to 60% in 3 to 4.5 hours for all strokes [28,346,347] and 54 to 56% for posterior circulation strokes [104,348]. Consequently, the IVT rate was only 6.5%, which is slightly higher than the 3.8% previously reported for PCA strokes [7] but lower than the 9.9% among posterior circulation strokes [348] and the 26.9% among all ischaemic stroke patients of the same tertiary centre during the same time period [349]. This is unfortunate considering that the current guidelines recommend IVT also for mild but disabling stroke symptoms [93,94].

The main obstacle for arrival within 4.5 hours in this cohort was the poor recognition of visual stroke symptoms, especially by the patients but also by the health-care personnel. The patient-driven delay has previously been demonstrated to be the primary determinant of late admission [350] and seems to be emphasised when it comes to the recognition of visual stroke symptoms, as these patients use less often EMS [28]. This is also supported by our findings from Study II, where the occipital ICH patients had a longer prehospital delay and used less frequently EMS compared to the other ICH patients. However, VFD has not been associated with a longer delay in all previous studies [351].

The number of initial misdiagnoses by health-care professionals rouse to approximately one third, which agrees with the results reported for posterior circulation stroke but are clearly higher than the 22% among all stroke patients [103]. The clinical characteristics that may prove especially confusing when diagnosing occipital stroke were the high frequency (20%) of patients reporting monocular symptoms, which usually suggest an ophthalmological problem, as well as the positive, transient, or migraine-like descriptions of visual complaints. However, 86% of the patients had VFD detectable with confrontation perimetry, which underlines the importance of careful examination of visual function, even if the sensitivity of confrontation testing is little over 70% in hemianopia and lower in smaller defects

[139,140]. Considering that almost every second elderly patient with homonymous VFD may be unaware of their stroke [54], it is likely that some of the patients with stroke-related VFD within the catchment area of our study remained unrecognised and were not included in the cohort. Whether it is due to visual anosognosia [299], patients not contacting health care, or misdiagnosis, can only be hypothesised. All in all, our results demonstrate only a fraction of problems associated with the diagnosis of occipital stroke.

The factors associated with arrival at the emergency department within 4.5 hours were prior atrial fibrillation, the use of EMS, the correct first diagnosis, not being examined by an ophthalmologist, and direct arrival at the definitive point of care, but only the last one remained significant after the multivariable analysis. Since the patients are predominantly admitted either by referral from another health-care unit or directly by EMS if recognised as a neurological emergency, raising the patients' and relatives' awareness of VFD as an emergency stroke symptom might be the most effective way to shorten the prehospital delay.

6.1.2 Clinical characteristics, outcome, and incidence of epilepsy after occipital ICH (II)

Study II revealed that isolated occipital ICH were rare with the frequency of 1.9% in the cohort of consecutive ICH patients. Occipital ICH represented 5.3% of lobar haemorrhages, which is almost equal to the previously reported 4.6% – the least frequent lobar location even when adjusted for the size of the lobes [11]. One explanation for the smaller than expected prevalence might be the lower arterial pressure gradient compared to the anterior circulation [352], which may also be the reason for the smaller haematoma volume and growth. The majority (63%) of the patients suffered only from visual focal symptoms, which in the context of the findings of previous studies [54], as well as of those from Study I, suggests that some of the patients with occipital ICH may remain unrecognised.

Amyloid angiopathy was the most frequent aetiology of occipital ICH in this study, which is in line with its known occipital predisposition [116]. Yet, its frequency was still lower than among non-occipital ICH, which might reflect the tendency of amyloid angiopathy-related haemorrhages to expand beyond one lobe. In contrast, the second most frequent aetiology, a structural cause, stood out with a distinctly higher prevalence among the occipital ICH patients. Most of the structural lesions were arteriovenous malformations, 20% of which have been reported to reside occipitally, whereas parietal (42%) and frontal location (25%) are more common [117]. This corresponds to the HICHS cohort where 16% of the bleeding due to arteriovenous malformations were occipital. Thus, the absolute number of structural causes of ICH is not higher in the occipital lobe but the other aetiologies are rarer. This aetiological distribution has probably contributed to the lower median age of the occipital ICH patients [353].

The outcome of the occipital ICH patients was overall favourable. Both 3- and 12-month all-cause mortality were 6%, and functional independence (mRS 0–2) was achieved by 84% at discharge and by 74% at 3 and 12 months. The numbers closely resemble the results of Gerner et al. who observed that 83% of the occipital stroke patients had an mRS score of 0–3 at 3 and 12 months [11]. In addition, the more robust markers of functional outcome, including the high rates of independent habitation, return to work, and ability to continue to drive, support the favourable vision-related recovery that could be overlooked by mRS which emphasises mobility [354]. Altogether 9 out of 15 (60%) patients with VFD at the acute phase recovered completely or partially either based on normal or improved standard perimetry or later normal confrontation perimetry. Other studies have reported improvement in 48 to 55% and full recovery in 5 to 25% of patients examined within a month of injury [19,26,27]. The incidence of post-stoke epilepsy did not differ from the other lobar ICH patients but was non-significantly higher than among all non-occipital patients, which agrees with the previously observed association of cortical lesion location and a higher epilepsy rate [126].

We found the occipital haematoma location to independently predict favourable outcome at discharge, as did Gerner et al. at 3 months. The favourable outcome after occipital ICH is in contrast to the prognosis of all ICH survivors, 33 to 42% of whom achieve mRS 0–2 at 6 months and 17 to 25% at 12 months [355]; yet, it is in line with the results obtained after superficial PCA infarcts with 6-month mRS 0–3 in 83% [7] and short- and long-term mortalities of 0 to 8% [6,7,16,18] and 4 to 11% [7,14,15]. Therefore, occipital stroke, whether haemorrhagic or ischaemic, seems to carry a relatively positive prognosis, at least when assessed with mRS.

The outcome advantage of the occipital ICH location might stem from several factors. The patients were younger, structural aetiology more prevalent, symptom severity at presentation milder, and haematoma smaller, which are all known predictors of good outcome [110-114]. However, the results remained for functional outcome at discharge even after adjusting for all these confounders. One hypothesis is that the favourable prognosis is based on the organisation of functional and structural networks in the occipital lobe. As about one fourth of the cerebral cortex seems to be dedicated to visual processing [1], the visual functions may have redundancy that enables better functional recovery after an occipital lesion than after similar anatomical damage in the anterior brain. Furthermore, the ratio of grey and white matter in the occipital lobe is higher compared to the more anterior brain [356]. This may impact recovery, as poor functional outcome has been predominantly associated with stroke lesions damaging white matter tracts [357]. Finally, even a small haematoma in the frontal or parietal lobe can damage the attention network, which may result in widespread network effects concerning several functional domains [358,359].

6.1.3 Non-invasive electrical brain stimulation for rehabilitation of vision after stroke (III)

The main results of the REVIS trial were neutral, as the visual field of the chronic occipital stroke patients did not improve either after rtACS or tDCS/rtACS in comparison to the sham treatment and the improvement after tDCS was visible in only one primary outcome. However, there were some positive changes in the monocular visual parameters in the tDCS and tDCS/rtACS groups, whereas rtACS alone was mostly ineffective and in some respects even inferior to sham. All procedures were tolerated well.

The overall efficacy of the tES methods did not fill the cautious expectations set by the earlier pilot studies on tDCS in rehabilitation of post-chiasmatic VFD [32,33,35]. The most evident difference to the REVIS trial was that the previous studies had administered tDCS in combination with visual training, which was absent from our protocol. In addition, our intervention lasted only 2 weeks compared to the 3 months in the studies by Plow et al. [32,33]. Thus, our results suggest that sole tES without any behavioural training in the current setting is not enough to induce meaningful vision restoration. We hypothesise that tES may temporally modify the cortical excitability but probably requires repetitive visual inputs (training) to enable long-lasting functional reorganisation of the cortical circuitry. Whether this is possible with tES combined with training, is to be confirmed by new controlled trials with larger samples.

Unlike after optic nerve injury [31], rtACS showed no efficacy in vision rehabilitation after damage of the visual cortex. Since the protocols resembled each other closely, the difference in efficacy may derive from the distinct origin of the injury. In rtACS, the current reaches the anterior visual pathway but not the occipital cortex [31], unlike occipitally applied tDCS. It has been hypothesised to elicit synchronous activation of retinal ganglion cells that propagates along the retino-geniculo-striate pathway and thus strengthens alpha coherence of the brain networks [31,214,218,219]. However, when the lesion affects the primary visual cortex, this indirect stimulation may not be enough to affect the occipital oscillations, at least not as much as to increase the sensitivity of the visual system for visual input and to produce behavioural change. Moreover, we did not define the patients' intrinsic alpha frequency before treatment, so the stimulation frequency was not individually adjusted but instead covered a wider range than the occipital alpha band.

Another persistent question plaguing the vision rehabilitation field is the timing of the rehabilitation. Similarly to most previous rehabilitation studies, we targeted chronic stroke patients in order to eliminate the effect of spontaneous recovery on our results. Yet, restoration attempts might be futile after the first few months as the rate of spontaneous recovery declines [26,27] and the retrograde degeneration of the retino-geniculo-striate pathway proceeds [276]. The results of the few studies on vision restoration in the subacute phase of brain injury have produced mixed results

about the benefit of early rehabilitation; however, they have not initiated the treatment until at 6 to 7 weeks after the insult, which may not be early enough to explore the full potential of neural plasticity [168,178].

Nonetheless, some cautiously positive results were observed after the tDCS and tDCS/rtACS treatments. The former improved the visual field of the contralesional eye measured with SAP in comparison to sham, whereas the latter reduced the absolute field defect of the contralesional eye, increased dynamic vision, and improved reading from the baseline within the group but did not differ from sham. However, the results should be interpreted with caution, as the sample size was small and there was a lot of inter-individual variability in the treatment response, which was reflected in the wide CIs. Hence, one can only speculate the possible mechanisms of the observed changes. The improvement of the contralesional eye over the ipsilesional eye could be due to different anatomical outputs from the temporal (defective hemifield of the contralesional eye) and nasal hemifields (defective hemifield of the ipsilesional eye). The temporal hemifield covers most of the peripheral vision, including the monocular temporal crescent. Interestingly, the peripheral visual field is relatively more extensively represented in the human dorsal stream area V6 compared to the representation in V1 [360]. Moreover, a recent macaque study demonstrated direct projections from the pulvinar and LGN to V6, bypassing V1 [361]. Thus, tDCS-based stimulation methods might mainly impact the direct subcortical pathways to the dorsal stream, potentially to V6. This subcortical effect would comply with the proposed mechanism of the blindsight phenomenon [53] and with the improvement in dynamic vision, which relies, among other things, on peripheral awareness [362]. However, the relative overrepresentation of the visual periphery has not been confirmed in V5/MT [363,364], which is the dorsal stream area most often associated with the blindsight [53]. All in all, drawing any conclusions on the mechanism of tDCS or tDCS/rtACS in post-chiasmatic vision rehabilitation requires further investigations, including a closer examination of peripheral vision.

6.1.4 Functional connectivity after occipital stroke (IV)

Study IV reported the rsfMRI results of the Helsinki arm of the REVIS trial. We found no difference in the global FC between the chronic occipital stroke patients and the healthy control subjects in our analysis using a multivariate regression connectivity model. There are only a few previous studies concentrating on FC after occipital lesions. One study on stroke patients with VFD found decreased interhemispheric FC between the visual areas in the acute phase, and its recovery mostly within a month, after which FC no longer differed from control subjects [38]. Therefore, it is possible that we did not detect difference in the global FC due to the timing of the study. Another study investigated various behavioural impairments, including visual, and how well they were predicted with models based on either FC metrics or lesion topography [365]. They found out that only a small fraction of the variance in visual

performance was explained by an FC-based model, whereas a model based on lesion topography predicted it to a much greater extend. In addition, most of the FC alterations that differed from control subjects occurred locally within the visual resting-state network [365]. These findings imply that a second possible explanation for the lack of global FC changes in our study is that chronic VFD may not be associated with extensive global connectivity alterations but more with local changes. This agrees with the proposed primate cortical connectivity graph that describes sensory networks, such as the visual network, as peripheral nodes in the whole-brain network [359].

In conclusion, the negative global result may reflect one or more of the following explanations: 1) a true lack of extensive changes in FC in patients with VFD after occipital stroke, 2) already normalised global FC in the chronic phase, or 3) dilution of FC changes in the group statistics due to inter-individual variance. Factors that may have increased variance include head motion and the different spatial distribution of stroke lesions, although the former was carefully modelled during the preprocessing and the statistical analyses.

Despite the negative global result, our study revealed ipsilesional modifications in the network parameter centrality eigenvector: its decrease in the ventral occipital areas and increase in the more dorsal region. Similar but non-significant changes were seen in the other network parameters. Our finding suggests that occipital stroke lesions cause a systematic shift in FC to the more connected nodes of the visual network. We hypothesise that this could reflect a diminished role of the ventral occipitotemporal areas with an unchanged or increased role of the dorsal stream areas of the network, which is a phenomenon previously reported for both occipital stroke patients [303] and monkeys after inactivation of V1 [366] but not so far shown in resting-state connectivity.

The study revealed no robust changes in the global, nor in the local prediction accuracy after the rtACS treatment, which is in line with the negative behavioural results of the REVIS trial. Although prediction accuracy of the rtACS group decreased between the baseline and post-treatment measurements, the absolute change was small and there was no between-group difference to sham. As we recorded fMRI a few days and 2 months after rtACS had ended, our results indicate a lack of long-lasting plasticity-mediated network changes. However, we cannot rule out immediate entrainment-driven effects of rtACS, previously reported after occipital tACS [330]. Interestingly, some of the global network parameters altered along the study, more so in the sham group. This finding in combination with the small behavioural changes within the sham group of Experiment 1 (Study III) imply that the infrequent ACS pulses delivered during the sham stimulation may influence the brain functional networks. This underlines the importance of a carefully designed sham condition without any residual treatment effect yet ensuring the blinding.

6.2 Strengths and limitations

The strengths of the present work include its diverse approach to occipital stroke and associate visual field disturbances, which are topics often neglected in the research of both acute stroke and stroke rehabilitation. The cohorts of Studies I and II were consecutive and well characterised but encompassed the usual disadvantages of retrospective observational methodology. Studies III and IV complement the research field of stroke-related VFD rehabilitation, where the need for RCTs has been evident [30], with a randomised, double-blind, sham-controlled design. Several early positive results from non-RCT pilot studies have been published during the last few decades. Although the REVIS study with its exploratory aspects does not bring this discussion to a close, it offers RCT-based data on the effectiveness of tES on vision rehabilitation after chronic stroke. The investigational procedures of the trial were versatile, including several behavioural visual measurements and functional neuroimaging, and enabled the evaluation of both visual parameters and functional networks. The perimetric measurements included several methods to control for fixation, which has been one of the main causes of debate in vision rehabilitation research. The amount of missing data throughout the studies was small and the patient dropout minor. The analysis method of Study IV allowed examining the whole brain without preselection of only a few ROIs, which is an advantage in explorative rsfMRI research even though it renders the comparison to other rsfMRI studies less straightforward.

The conclusions drawn from the studies of the thesis are restricted by the relatively small sample sizes and mostly single-centre cohorts, which in Studies I and II were also retrospective. In Study I, we had no access to the diagnostic pathways of patients treated at outpatient clinics, nor of those who had never access to the neurological assessment, so the whole picture of the diagnostic obstacles of occipital infarction patients remains unravelled. In addition, not all patients were scanned with MRI, so some occipital infarcts may have remained undiagnosed. Therefore, the results probably underestimate the challenges in the recognition of occipital infarction patients.

In Study II, we could not define retrospectively functional outcome for all ICH patients at 3 and 12 months, so no statistical comparison of these outcomes between the occipital and non-occipital ICH patients were performed. In addition, mRS of the occipital ICH patients at the above-mentioned time points was defined retrospectively, so its accuracy was sufficient for only categorical description and was not attainable for all patients. Accordingly, the long-term outcome analysis of the occipital ICH patients was mainly descriptive. Furthermore, due to the retrospective design, the diagnostic imaging work-up and the assessment method of VFD varied. Particularly, as patients with occipital stroke are often less severely disabled in the acute phase compared to other stroke patients, they may be capable of giving a more detailed patient history and undergoing a more comprehensive diagnostic work-up, including MRI. This could have affected the aetiological distribution of ICH since many of the

structural lesions require MRI for diagnosis. In addition, not all patients of Study II underwent SAP or a neuropsychological evaluation, so the presence of residual visual symptoms in these cases relied on the patients' subjective report or on confrontation testing.

The REVIS trial comprised many limitations. In Study III, tES consisted of three experimental protocols that enabled exploration of different modalities but did not allow their direct comparison between the centres. The experimental arms were small, reducing the power to detect a true effect within the arms with positive trends. However, in the rtACS arm, there was no trend towards superiority to sham, so increasing the sample size would probably not have affected the results. In addition, the investigational methods comprised slight differences, complicating the comparison between the centres. Our primary outcome measures were directed to identify changes in luminance detection in the visual field border area, which may not have been an optimal approach to capture changes in discrimination performance within the blind field. Furthermore, some of the secondary outcomes, including dynamic visual acuity and contrast sensitivity, were recorded in only a subset of the centres. Finally, the adverse effect data were incomplete from one of the centres (Rome); however, tDCS has been widely studied so its safety profile is already well established.

In the spin-off fMRI study, there were some technical limitations. The resting-state images did not cover the basal frontal and anterior temporal regions of the brain, which might have resulted in missing FC changes within those areas and which caused technical challenges for the registration of the images. Neither did we study subcortical connections. The healthy control subjects were not examined with perimetry, so VFDs undetectable with confrontation testing could not be excluded. The small sample size renders our longitudinal results more susceptible to decreased test-retest reliability [367], even though multivariate analysis methods are suggested to suffer from this problem less than univariate methods [368]. Finally, the ununiform localisation and size of the occipital infarcts and the old infarct lesions of a few patients might have caused additional inter-individual variance to the FC network, despite similar phenotype.

6.3 Implications for future research

Although some moderate-size cohorts of PCA infarct patients have been gathered throughout the years, larger prospective multicentre cohorts of both ischaemic and haemorrhagic occipital stroke patients are still required, because these patients make up only a subset of cases in the general stroke cohorts. In addition to confirming the clinical characteristics and functional outcome of occipital stroke, the cohort studies should collect prospective perimetric and neuropsychological data on stroke-related visual deficits and their recovery early after stroke. The previous cohorts consist of either hospital-based acute stroke populations or of patients with VFD referred to an

ophthalmological outpatient evaluation. The former usually lack systematic follow-up of vision recovery, whereas the latter miss patients not undergoing further investigations due to poor condition, pessimistic prognosis, undiagnosed visual problems, or administrative reasons.

The problems in the acute recognition of visual stroke symptoms are evident, so the next investments should be made in enhancing the prehospital pathway of these patients. Mass-media campaigns could be launched to raise the awareness among the public. An example of such campaign is FAST (Face, Arm, Speech, Time) that presented three stroke symptoms, none common for occipital stroke, and reduced prehospital delay, increased EMS utilisation, and improved IVT rates of acute stroke patients [369,370]. Moreover, recognition of occipital stroke patients by EMS and primary care physicians should be improved. To respond to this need, a few scales designed for stroke recognition either at the emergency department or in prehospital use have included VFD among their scoring items [371,372]. These scales report high sensitivity but their diagnostic accuracy, and especially specificity, vary depending on the study population [29]. One of the more established scales, ROSIER [372], was not superior to a scale not including an assessment of visual fields when used by EMS [373]. However, only 4% of the cohort, consisting of patients suspected to have stroke by EMS, had posterior circulation stroke, and there were no patients with isolated VFD. Similar findings have been made from other prehospital cohorts of suspected stroke [374,375], alluding that either posterior circulation stroke symptoms do not raise a suspicion of stroke in EMS or the patients do not contact EMS in the first place. Hence, studies on the accuracy of stroke scales comprising VFD assessment should target all prehospital patients with an acute-onset neurological focal symptom, including those with a sole visual complaint.

More research efforts for vision rehabilitation after occipital stroke should be made. Although the primary outcomes of the REVIS trial were mostly negative, some positive signs from the tDCS-based stimulation modalities encourage further research. These should preferably combine tDCS with behavioural training, considering the modulatory mechanism of the stimulation and the results of the earlier pilot studies [32,33,35]. Based on both the results of the recent rehabilitation studies [164,166-168] and some behavioural and neuroimaging signals from the current thesis, vision training targeted at the blind field, whose effects may be mediated via the extrastriate pathway and especially the dorsal stream, seems to be a viable option. In addition, occipital tACS, as well as pharmacological interventions, are yet to be investigated in vision restoration after stroke. This may change in the future as these approaches have recently been proposed by a few groups [376,377]. All in all, vision rehabilitation studies should aim at confirming the results of pilot studies in larger multicentre samples while maintaining proper control groups and a randomised design.

One of the remaining questions in tES research concerns the suitable sham condition that would ascertain blinding but avoid any stimulation effect. Thus, computational models should be utilised when designing treatment and sham

conditions to optimise their parameters. At the same time, neurophysiological mechanisms of tES should be explored in order to understand its network effects. The electroencephalography recordings of the REVIS trial are still to be analysed and will hopefully shed light on the oscillatory effects of tES on stroke patients.

Another question to consider in vision rehabilitation research is the timing of the intervention. Stroke rehabilitation is ideally implemented at the early stages after the injury. A randomised controlled design should eliminate the confounding impact of spontaneous recovery, and occipital stroke patients would be ideal for early interventions because they are often less functionally disabled than many other stroke patients and could thus engage in demanding rehabilitation. However, vision restoration studies are yet to target the early post-stroke state.

Future functional neuroimaging studies on diseases of the visual cortex should confirm the absence of global resting-state network disturbances in larger samples, preferably with several analytical approaches. This will be easier as fMRI data are increasingly available in shared databanks. In addition, multimodal studies could further investigate the local FC disturbances and their time dependence. The careful modelling of movement remains one of the staples throughout the preprocessing and the analysis of rsfMRI data to exclude its confounding effect on the results.

7. SUMMARY AND CONCLUSIONS

This study revealed that occipital stroke-related visual symptoms are sub-optimally recognised at the acute phase, and therefore the patients seldom have short enough prehospital pathways to allow for acute recanalisation treatments. Most occipital ICH patients present with exclusively visual focal symptoms and are younger, have lower haematoma volumes, more frequent structural aetiology, and a better outcome compared to other lobar ICH patients but have an equal rate of post-stroke epilepsy. However, up to 50% continue to report residual visual symptoms. Chronic occipital stroke patients demonstrate altered perilesional FC measured with fMRI but do not differ from healthy control subjects at the whole-network level. Non-invasive electrical stimulation does not cause robust recovery of VFD or induce subclinical FC changes in chronic occipital stroke patients when delivered as a 10-day schema without concurrent behavioural training.

The findings of the thesis suggest that there is space for improvement along the treatment chain of occipital stroke patients, since they are too often withheld from both state-of-art acute treatments and rehabilitation. The awareness of visual symptoms as a sign of stroke should be improved among both the general public and health-care professionals to increase the number of immediate direct contacts to EMS by patients and to cut down the number of referrals to an ophthalmologist instead of a neurologist from primary care. Shortening the prehospital delay would enable more patients to be admitted while still eligible for recanalisation treatments, which might reduce permanent disability. In case of acute occipital ICH, the patients should undergo a careful diagnostic work-up to detect treatable causes, such as structural lesions, and be offered counselling and suitable follow-up for residual visual symptoms; however, they should also receive information about the favourable outcome.

For patients with irreversible VFD despite acute treatments, continuing effort should be made to establish evidence-based rehabilitation options. Further studies could investigate the combination of visual training and tDCS-based stimulation methods with large enough samples and a control setting without minimal stimulation, preferably early after stroke. The scientific community should strive for confirming the preliminary results of pilot studies, accompanied with neurophysiological evidence, in order not to be caught permanently in promising but preliminary findings. Meanwhile, the patients are left with no clinically established rehabilitation to support the recovery of their visual function.

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