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Brain electrophysiological oscillations and vision loss in occipital stroke patients

Dissertation

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Kurzreferat

This study aimed to elucidate the correlation between functional visual parameters and the electrophysiological parameters and to learn more about the differences of EEG spectral power between the lesion hemisphere (LH) and the contra-lesion hemisphere (CH) in chronic occipital stroke patients.

Twenty-five patients with occipital lobe lesions were tested for visual acuity, contrast sensitivity, reading speed, dynamic vision, visual alertness, standard static perimetry and high resolution perimetry (HRP). In addition, a five-minute resting state EEG was recorded with eyes closed. The correlations were calculated between the performance in vision tests with EEG spectral power of different frequency bands and the electrophysiological status of different frequency bands within different regions-of-interest (ROIs) were compared between LH and CH.

The data indicates that while some vision parameters (contrast sensitivity, visual attention, foveal vision, dynamic vision, fixation control and fixation accuracy) were associated with oscillatory activity in the occipital and parietal lobes of both hemispheres, other parameters (visual acuity, reading speed or reaction time) were not. The EEG spectral power within alpha I, alpha II and whole alpha was higher in CH than in LH in the parietal and occipital lobes, while in the frontal lobes it was the opposite. Spectral power in the theta-band was higher in LH than in CH in the frontal lobes. That is, the spectral power from resting-state EEG was found to be changed not only in the lesion lobe but also in the functionally connected lobes. Thus, these findings indicate that the whole brain network was changed after a rather focal lesion.

Key words: occipital stroke, hemianopia, visual function, EEG, spectral power

Abbreviations

LGN	lateral geniculate nucleus
RT	reaction time
ARVs	areas of residual vision
PET	positron emission tomography
rtACS	repetitive transorbital alternating current stimulation
EEG	electroencephalography
VEP	visual evoked potential
LH	lesion hemisphere
CH	contra-lesion hemisphere
ROI	region-of-interest
HRP	high resolution perimetry
CS	contrast sensitivity
IResT	international reading speed texts
DDTV	Düsseldorf dynamic vision test
FIR	finite impulse response
FFT	Fast Fourier Transformation
FDR	false discovery rate
ERD	event-related desynchronization
ERS	event-related synchronization
ERP	event-related potential
MRI	magnetic resonance imaging
ICA	independent component analysis
EMG	electromyogram
IAF	individual alpha frequency
IAPF	individual alpha peak frequency
DTI	diffusion tensor imaging
PTJ	parietal-temporal junction
fMRI	functional magnetic resonance imaging
REM	rapid eye movement sleep

Contents

1. Introduction

1.1 General Background

According to the World Health Organization, 3 million women and 2.5 million men worldwide die from stroke each year. Stroke is the third leading cause of death in developed countries, exceeded only by coronary heart disease and cancer.

A stroke is caused by the interruption of the blood supply to the brain, which cuts off the supply of oxygen and nutrients and leads to damage of brain tissue. There are mainly two types of stroke: ischemic stroke and hemorrhagic stroke. An ischemic stroke occurs when blood flow to a certain part of brain is stopped by a blockage in a vessel, while a hemorrhagic stroke occurs when a weakened vessel tears or ruptures resulting in diverting blood flow from its normal course and leaking or spilling into brain tissue.

Stroke carries a high risk of death, and survivors can experience various symptoms, such as weakness or numbness of the face, arm or leg, difficulty in speaking or understanding speech, difficulty in seeing with one or both eyes, difficulty in walking, dizziness, loss of balance or coordination, confusion, fainting or unconsciousness. Current statistics of the stroke survival rate, which is published on the website of University Hospital Newark in New Jersey, shows that around 15% of stroke victims die shortly after the stroke, 10% require care in a nursing home with long-term care facility, 40% experience moderate to severe impairments requiring special care, 25% recover with minor impairments and only 10% recover almost completely.

The consequences of a stroke depend mainly on what causes the stroke, which part of the brain was injured and how severely it was affected. Posterior artery infarction results in occipital lesions and may lead to visual impairments which affect reading, orientation in space, visually-guided mobility, and especially driving [1, 2]. Such visual impairments are rather frequent and estimates are that between 20% to 57% of all stroke victims lose the ability to see some of the space in front of them, which is often one complete half or quarter of the normal field of vision [3]. The prevalence of vision deficit in stroke is about 11.0 Million worldwide and the incidence is 2.1 Million annually.

Before discussing the mechanisms of occipital stroke and vision loss, firstly in this thesis I explain which visual system structures are found in the brain and how the visual system works in normal subjects.

1.2 Anatomy and physiology of the visual system

The visual system is a part of central nervous system. It consists of the eyes (including the retina), the optic nerve, the optic chiasm, the optic tract, the lateral geniculate body, the optic radiation, the tectum (superior colliculus), the visual cortex, multiple other visual nuclei in associated cortex and their respective connections (Fig. 1).

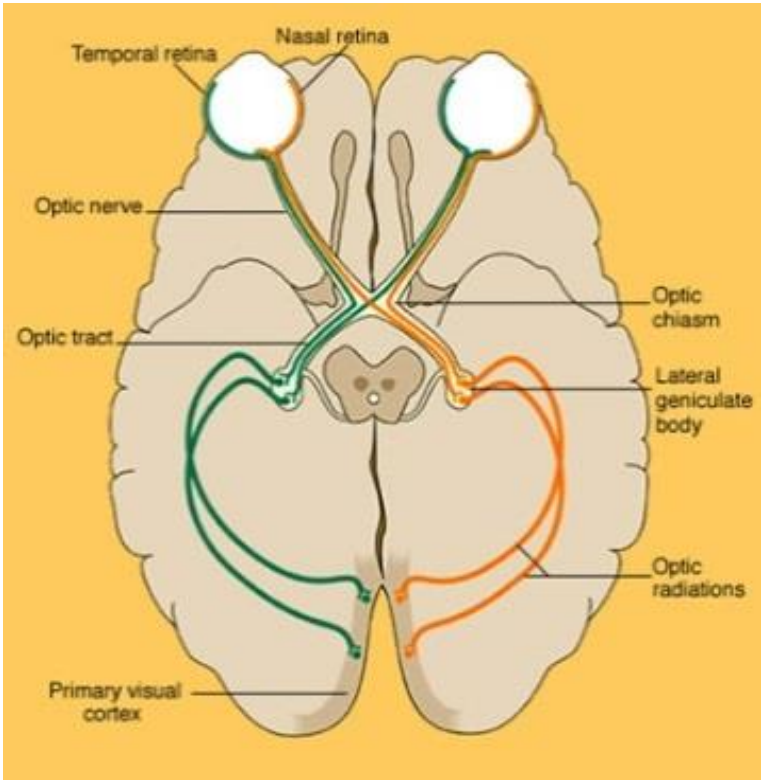

Fig.1. General anatomy of visual pathway. (Downloaded from internet. Originally created by Jonathan Trobe, M.D., University of Michigan Kellogg Eye Centre)

The visual system transmits neurophysiological information in response to visual stimuli from the eye into the brain. When the light reflecting from an object reaches the eyes, it triggers a series of neural events in the form of neural impulses, which travel up the visual system to different brain regions. Visual stimuli from the outside world pass through the eyeball and reach the retina, where there are two types of photoreceptors: cones and rods. Cones are colour-sensitive and important for colour vision in daylight. But they are less sensitive to dim light, which is the function subserved by the rods. Rods are sensitive to low levels of light and

important for the vision at night [4].

The signals from the photoreceptors are first processed by a collection of intermediary neurons called bipolar cells, horizontal cells and amacrine cells. Then the processed signals reach the ganglion cells where the final processing stage in the retina is carried out. Thereafter, the visual signals leave the eyes and follow their journey through an optic fibre bundle, known as the optic nerve. The optic nerve travels through the optic canal, through the superior orbital fissure in the orbit, into the cranial cavity. After reaching and forming the optic chiasm, the optic nerve fibres from the nasal hemi-retina decussate to join the nerve fibres from the contralateral temporal hemi-retina and join together to form the optic tracts. The optic tracts travel posteriorly and enter the brain in the lateral geniculate nucleus (LGN) of the thalamus, also known as the lateral geniculate body, where the retinal ganglion cells terminate with their neural synapses. While some fibres leave the LGN to connect directly to secondary visual structures, most nerve fibres leaving LGN form the optic radiations. A major part of optic radiation goes directly posteriorly reaching the ipsi-lateral visual cortex while a minor part firstly travels anteriorly and laterally, then turns posteriorly reaching the ipsi-lateral visual cortex as well.

The visual cortices locate in the occipital lobes, on the floor of the calcarine fissure, and are about only 1.5mm thick. The occipital lobes are primary and secondary visual areas and carry out the functions of sensation and interpretation of visual input.

Normal function of brain cortices depends on an adequate supply of oxygen and nutrients through brain arteries. The occipital cortices are supplied predominantly by the posterior cerebral arteries and particularly their calcarine branches. A parietal occipital branch supplies the superior calcarine lip, a posterior temporal branch supplies its inferior lip and a calcarine branch supplies the central region posteriorly. But visual cortex is also receiving blood supply from the middle cerebral arteries, which are found in the posterior aspect of the calcarine sulcus with an anastomosis between posterior and middle cerebral arteries, accounting for sparing of the macula in cases of posterior cerebral artery occlusion (Fig. 2). The region which receives dual blood supply is termed as “watershed area”. On one hand, this watershed area can be spared from ischemia due to the dual blood supply and on the other hand, both the blood supplies are from the most distal branches of the two large arteries, which are susceptible to ischemia [5].

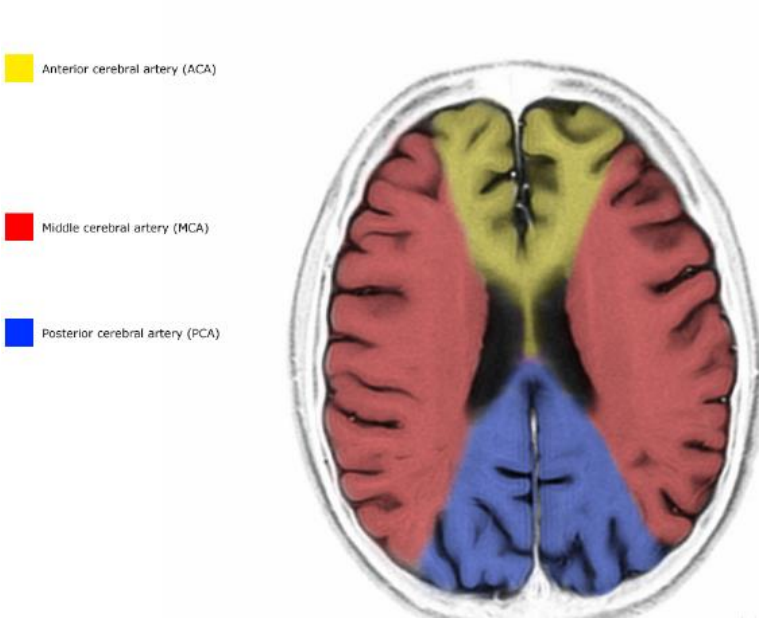

Fig.2.a. General cerebral vascular territories.
(Downloaded from internet; contributed by Dr. Frank Gaillard)

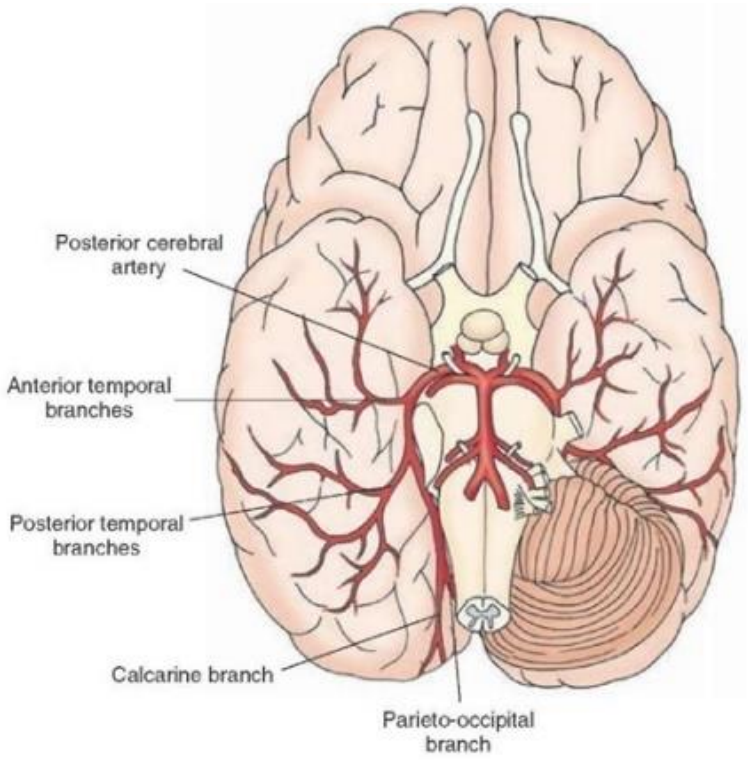

Fig.2.b. Branches of posterior cerebral artery.

(Downloaded from internet what-when-how.com)

1.3 Normal visual field and cerebral cortex

The visual field is the individually perceived vision that a person can see when fixating an object composing the normal visual field.

A normal eye can detect visual stimuli over a 120º range vertically and nearly a 160º range horizontally. When measured from the point of fixation, visual stimuli can be typically detected 60º superiorly, 70º inferiorly, 60º nasally, and 100º temporally. Yet, the true extent of the visual field depends on several features of the stimulus (size, brightness, motion) as well as the background conditions. Typically, no photoreceptors are present at the retinal position of 10-15º nasal to the fixation, which creates a normal absolute scotoma, called the normal "blind spot". Here, nerve fibres pass through the sclera and form the optic nerve head.

The visual field is often depicted as a three dimensional hill, with the peak sensitivity to stimuli occurring at the point of fixation under photopic conditions, decreasing rapidly within the 10º around fixation, then decreasing very gradually for locations further out in the periphery (Fig. 3).

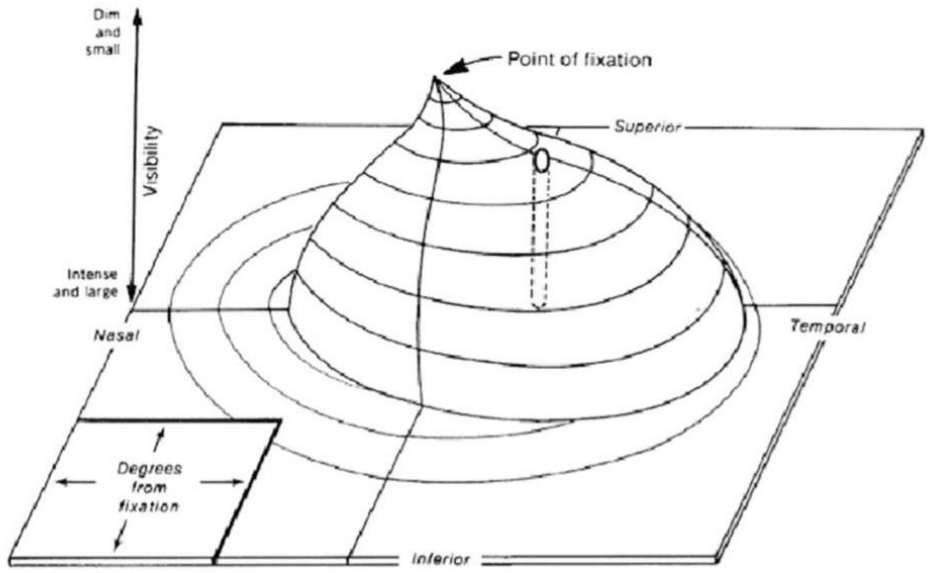

Fig.3.a. The three dimension hill of normal vision. The hill is highest at fixation, where visual sensitivity is greatest. The height of the hill declines towards the periphery as visual sensitivity diminishes. (Anderson DR: Perimetry with and without automation, 2nd ed. St. Louis, CV Mosby, 1987)

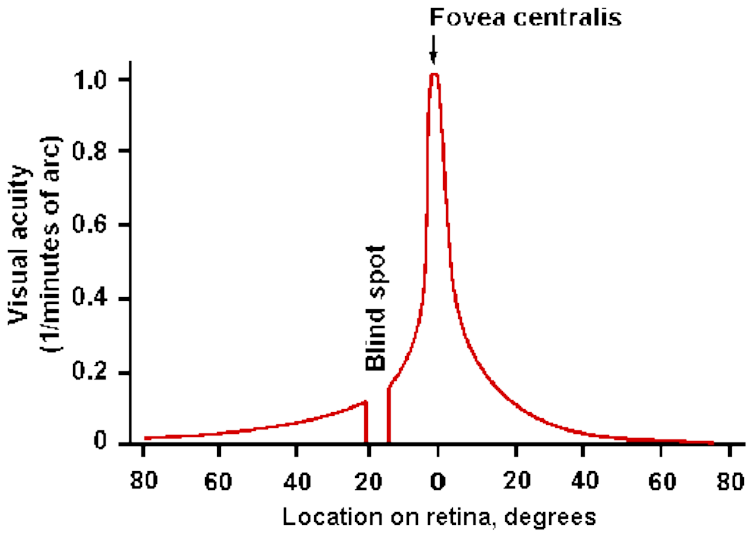

Fig.3.b. The rapid drop-off of visual acuity with retinal eccentricity. (Schmidt, R. F. (Ed.). (1981). Fundamentals of sensory physiology. Springer Science & Business Media)

In a normal observer, visual performance is maximal at the subject's point of fixation. That is, when asked to fixate at a point in space, normal observers move their eyes so that the point of interest is imaged on the region providing the highest resolution. The connection between fixation and optimal resolution, together with the histologic specialization of the retina, suggests that a normal individual will move the eye to place the image of the fixation point on the central part of the retina, which is known as the fovea. In the centre of the anatomic fovea, the inner retinal layers down to the outer nuclear layer are displaced, forming a pit, the foveola, with a diameter of about 0.35 mm (or about 1º of the visual field). The fovea and foveola are the anatomical structure at the posterior pole of the eyes. These structures are highly specialized to maximize visual acuity. The foveola contains cone cells only (rod-free area) and contains the highest density of cones in the retina (147,000 cones per mm^2). The retinal point of fixation and the foveola are assumed to be coincident [6]. The image of the fixation point is formed on the foveola in the normal eye. Here is the highest quality of vision and this is normally used when we look at an object. The resolving power of foveal vision is at its maximum at the point of fixation, even higher than in the remainder of the fovea [7].

The central 10º around fixation in the fovea have the best sensitivity, which can be explained by the fact that over half of the visual cortex is devoted to processing information from the nerve fibres corresponding to the central 10º around the fovea. This greater representation of central vision is termed "cortical magnification". Therefore, there are fewer nerve fibres which sustain peripheral vision than central vision, and sensitivity decreases with greater periphery of the visual field. Cortical magnification in human primary visual cortex correlates with acuity thresholds. Acuity thresholds are the lowest near the fovea, where cortical

magnification is the highest [8]. Cortical magnification decreases with eccentricity and visual acuity threshold increases with eccentricity.

There is a point-to-point localisation of the retina and the visual cortex as each area of the retina is precisely represented in the corresponding area of the visual cortex. The superior quadrants of both retinae are represented on the superior lip of the calcarine fissure, and the inferior quadrants are on the inferior lip. The central nerve fibres are represented in the extreme tip of the occipital pole, and the peripheral nerve fibres are represented by cells lying further forward in the occipital lobe. The most anterior part of the visual cortex represents the extreme nasal periphery of the retina, corresponding to the monocular temporal crescent of the visual fields. The nerve fibres that represent corresponding portions of the fovea of each eye and the immediately surrounding areas occupy a relatively large area in the striate area of the visual cortex in the occipital lobe.

Because of this anatomical structure of the visual system it is clear that when visual cortex is damaged, the shape and position of the visual field loss follow its retinotopic position.

1.4 Stroke and hemianopia

Focal destruction of visual cortex produces a homonymous contralateral visual field defect. Defects are highly concurring, with virtually identical defects in the two eyes. A complete defect involving the left or right side of the vertical midline of the visual field is defined as hemianopia. It usually affects both eyes. A heteronymous hemianopia, in contrast, involves the opposite sides of the visual field from the two eyes. For example, a lesion at the optic chiasm typically produces bi-temporal heteronymous hemianopia. A homonymous hemianopia is a scotoma of the same side of the visual field in both eyes. For example, a post chiasmatic lesion typically produces homonymous hemianopia. Especially when an infarction occurs in the territory of the posterior cerebral arteries, patients may show a most notable symptom as homonymous hemianopia, a visual field defect which is opposite to the lesion of the occipital lobe. Besides a variety of other clinical symptoms, including hemianopia, colour blindness, failure to see to-and-from movements, it may also induce verbal dyslexia and visual pseudo-hallucinations [9]. About 90% of the cases of homonymous hemianopia are caused by an occipital lobe ischemia or infarct due to vascular occlusion in the territory of the posterior cerebral artery. And the causes for vascular occlusion are most commonly cardiac

emboli, vertebrobasilar occlusive disease or arteriovenous malformations. Other causes of homonymous hemianopia can also be trauma or brain tumor or brain haemorrhage in occipital lobes. It can be differentiated from ocular diseases by both normal pupillary light responses and normal funduscopic examination [10].

The anatomical basis for homonymous hemianopia is that the right hemisphere of the brain has visual pathways for the left visual hemi-field of both eyes, while the left hemisphere of brain has visual pathways for the right visual hemi-field of both eyes (Fig. 4). A very severe lesion may result in a bilateral and complete hemianopia with non-detectable peripheral visual field, complete loss of visual acuity and light perception.

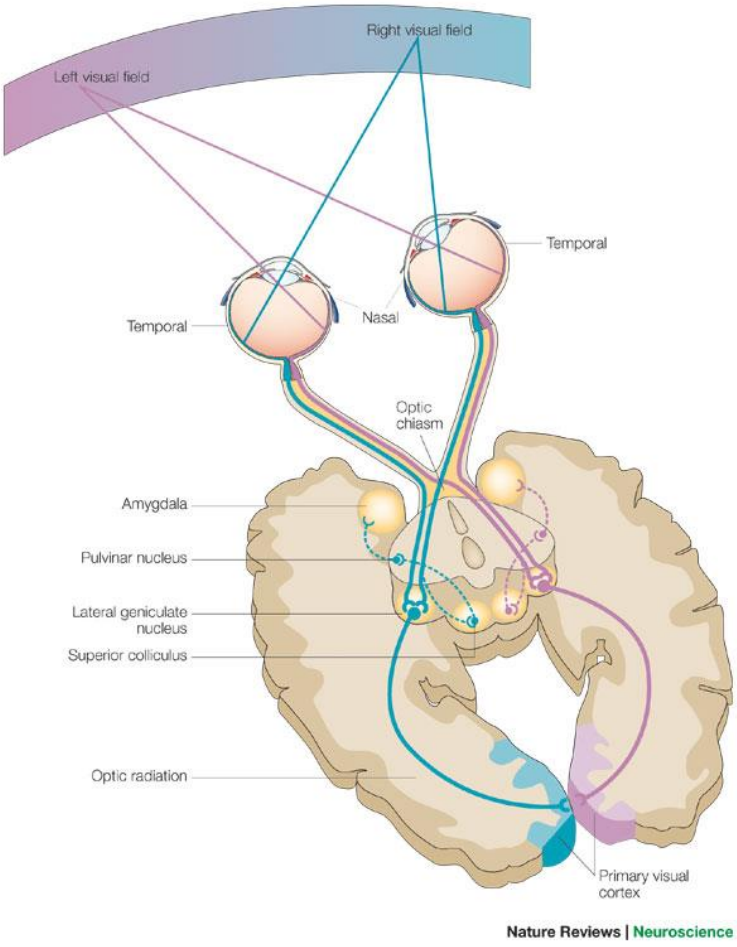

Fig.4.a. Subcortical visual pathway. (Hannula, D. E., Simons, D. J., & Cohen, N. J. (2005). Imaging implicit perception: promise and pitfalls. Nature Reviews Neuroscience, 6(3), 247-255.)

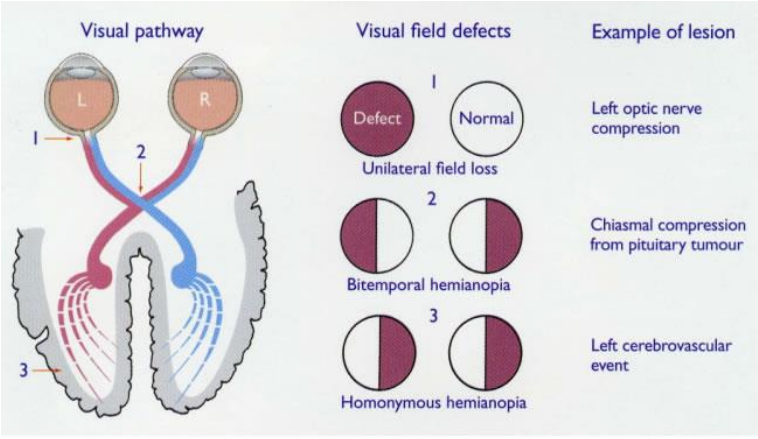

Fig.4.b. Vision loss due to different lesion locations in the brain.
(Downloaded from internet. sinaiem.org)

In this thesis, "lesion" refers to the infarcted tissue in the brain, while blind visual field is generally the homonymous hemianopia and the contra-lesion-side visual field is damaged. In contrast, the ipsi-lesion-side visual field refers to the so-called "intact" visual field (Fig.4.c).

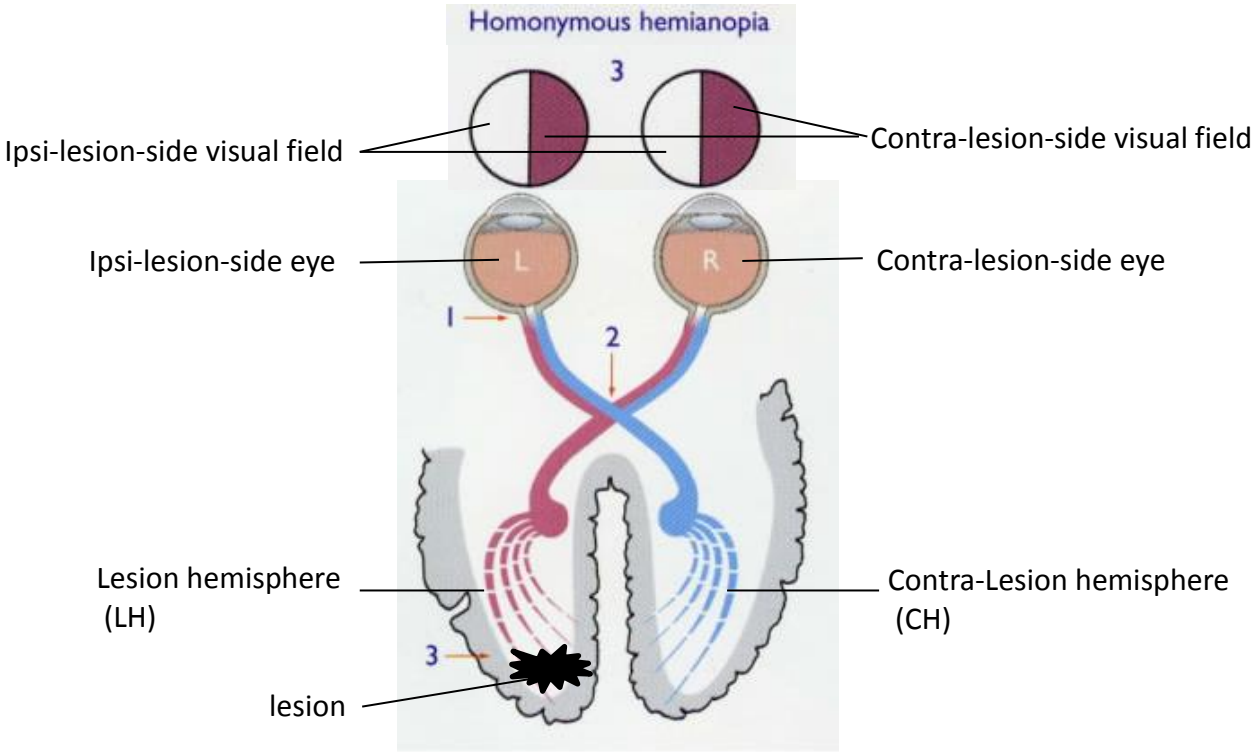

Fig.4.c. This figure illustrates the terms used in this thesis, such as "lesion hemisphere (LH)", "contra-lesion hemisphere (CH)", "ipsi-lesion-side eye", "contra-lesion-side eye", "ipsi-lesion-side visual field", "contra-lesion-side visual field".

Blindsight

Patients with hemianopia may have some residual ability to process visual stimuli which are presented in their blind visual field, even though they report not being aware of the stimuli.

Such a condition, in which patients with destruction of visual cortex retain some visual capacity to detect, localise and even discriminate visual stimuli within the clinically blind visual field, is called blindsight [11].

A study on functional magnetic resonance imaging (fMRI) showed that motion and colour-change stimuli presented in the hemianopic field produced activation in several extrastriate areas of the lesioned brain hemisphere, which were defined by using retinotopic mapping [12]. And there is the possibility that visual stimuli may be detected and located in the absence of striate cortex in man. Observations suggest that the visual capacity remaining after damage to striate cortex may be much greater than is commonly accepted [13]. There may remain in the visual cortex a representation of the visual field which is not revealed by ordinary perimetry but which is still accessible to a non-verbal orienting response [11].

Additionally, it is known that the midbrain receive a substantial and direct projection from retina which innervates the superior colliculus, and is kind of an alternative inter-hemispheric processing [14].

Sightblindness

In contrast to blindsight, many patients with visual field defects complain about perceptual difficulty in the areas where perimetric visual field test shows vision to be normal. Perceptual deficits in the “intact” visual field are likely to contribute to subjective vision loss in patients with visual field defect and this phenomenon is termed “sightblindness” [15].

There are several studies indicating the phenomenon of “sightblindness”. Findings from gestalt perception experiment revealed deficits in the early and late visual processing of gestalt pattern in the intact visual field of hemianopic patients when compared to healthy subjects [16]. Reduced sensitivity throughout the “intact” visual field of the hemianopic subjects was found unexpectedly [17]. Visual functions are impaired in the “intact”, ipsi-lesion-side visual field of patients with unilateral cortical lesions (homonymous hemianopia), such as elevated contrast thresholds, longer reaction times (RT) and more false positive responses when compared to normal subjects. Sightblindness can also be observed in tasks which demand more complex visual information processing, such as contour integration [15].

Explanations for sightblindness might be: the lesion-induced disturbance to inter-hemispheric projection and interaction, which might affect the visual information synthesis from both sides

of the visual field; the reduced or delayed activation in the lesion hemisphere, which might hamper the inter-hemispheric functional connectivity and synchronization; and finally the reorganization of the visual cortex, which occur in response to the cortical lesions [15].

Residual vision

The visual field of a hemianopia patient can be sorted into: the "absolute" defect (blind field), referring to the area where the patient does not consciously detect any visual stimuli, and it is usually found on the contra-lesion-side visual field; the "relative" defect, where some detection abilities for moving stimuli or stimuli with increased luminance remain and which is typically located at the border of the lesion but occasionally can also be found deep inside the blind field (islands of residual vision); and the "intact" region, referring the seeing field, where all visual stimuli can be normally detected.
Residual vision refers to the visual process which is generally non-conscious and usually spared when conscious vision is lost due to primary visual (striate) cortex damage. It is the detectable or usable vision remaining at the border of the scotoma or deep inside the blind visual field (islands of residual vision).

According to the "residual vision activation theory" [18], residual visual functions after damage can partially be reactivated because some residual structures are usually spared: (i) "areas of residual vision" (ARVs) at the visual field border or "islands of residual vision" inside the blind field, (ii) extra-striate pathways unaffected by the damage, and (iii) down-stream, higher-level neuronal networks. ARVs are characterized by a partial visual functionality, which are observed as (i) reduced probability of detection of above-threshold stimuli, (ii) increased perception thresholds when stimulating sub-threshold, and (iii) a slowing-down of reaction times.

All these general phenomena in hemianopia have a cortical basis, but they are by no means fixed or rigid. Rather, the visual cortex has the capacity to change according to experience, damage, training and certain treatment which is due to neuroplasticity. This plasticity is maintained throughout life.

1.5 Visual system plasticity

Brains with a stroke lesion in the occipital cortex still have the ability to adapt to the damage, which is called "post-lesion plasticity". It is invoked for encoding information during visual

perception and is involved in recovery of function. It can serve as a kind of positive plastic event which provides the basis for restorative plasticity after brain damage to recover some lost vision; but still, patients sustain clinical deficits to some extent.

A study on acute unilateral ischemic stroke showed a decrease in structure-function unity, where the regional neural activity was impaired by the anatomical lesion [19]. An fMRI study in stroke patients who had a homogenous structural pathology in the visual cortex and partially recovered hemianopia suggested extensive neuronal plasticity within the visual cortex [14]. It is a sign of some spontaneous recovery of vision following the brain lesion. Besides, patients with stroke-induced homonymous field cuts got modest but real expansion in visual field following vision restoration therapy, which was achieved by repetitive visual stimulation at the visual border zone adjacent to the blind visual field [20]. By applying positron emission tomography (PET) imaging before and after computer-assisted visual rehabilitation on a chronic stroke patients with homonymous right upper quadrant defect in the visual field, the results suggested that visual training might cause detectable plastic changes in the brain [21]. A recently emerging technique, non-invasive electric current stimulation, has also been shown to be helpful to visual restoration. Repetitive transorbital alternating current stimulation (rtACS) helped patients with chronic pre-chiasmatic visual system damage to improve their detection abilities and processing speed [22]. In the same study, electroencephalography (EEG) analysis revealed that the spectral power and the brain networks in higher alpha frequency band changed in patients when compared with normal subjects.

The study of EEG measurements has experienced a recent renaissance because of their excellent temporal resolution. In many recent clinical brain studies, EEG parameters served as biological markers. Because of these advantages, EEG can be employed to well characterize the brain's physiological response to visual cortex lesion, which is a major topic of this thesis.

1.6 Electroencephalography (EEG)

EEG recording has long been known. In 1875, Richard Caton reported using a galvanometer to observe electrical impulses from the surfaces of living brains in animals. In 1924, the German neurologist Hans Berger invented electroencephalography as he succeeded in recording the first human EEG. In 1929, he published his first paper which demonstrated the

technique for “recording the electrical activity of the human brain from the surface of the head”.

EEG is a non-invasive tool to record the electrical activity of the brain, which results from voltage fluctuations of the ionic current flowing within and between cells. EEG measures the transient, rhythmic activities of brain in the form of waves. The waves accompany all our thoughts, actions and feelings, indicating we are awake, relaxed, focused, or stressed and the EEG waves change when subjects are performing behavioural or mental tasks such as hearing, speaking or seeing. The EEG is usually recorded by attaching electrodes onto the scalp, getting the electrical signal amplified and displayed by a computer or other instrument. For special purposes, the EEG may be recorded by attaching electrodes directly onto the cortex or even by inserting the electrodes into the brain, such as during epileptic surgery. Psychologists mostly use scalp EEG to study its association of brain physiology with mental states and how information is processed by the brain. Clinicians may use EEG to diagnose disease and to identify certain patterns associated with specific pathological condition.

Although the EEG is an old tool, it is still being widely used both in science and in the clinic to explore brain activity. The EEG has two clear advantages for brain research: it is a non-invasive procedure and it has an extremely high time resolution. Today’s EEG technology can accurately detect brain activity at a resolution of milliseconds or even less, which is adequate to determine the brain’s very quick electrical activity changes. But, in contrast to modern imaging methods, such as magnetic resonance imaging (MRI), it has poor spatial resolution. Yet, recently there are more and more advanced techniques available to analyse EEG which allow more accurate estimates of the signal source and help uncover more information from EEG signals.

The brain’s electrical charge is maintained by billions of neurons. EEG activity therefore always reflects the summation of the synchronous activity of thousands of millions of neurons. Scalp EEG activity shows oscillations at a variety of frequencies. Several of these oscillations have characteristic frequency ranges, spatial distributions and they may be associated with different states of brain functioning. Theses oscillations represent synchronized activity over a network of neurons.

For analysis, the rhythmic activities measured by EEG can be divided into different bands by frequency, as delta (1-3 Hz), theta (3-7 Hz), alpha (7-14 Hz), beta (14-30 Hz), Gamma (>30 Hz). They have interesting and valuable properties [4].

Delta-band: The delta frequency tends to be the highest in amplitude and the slowest waves. It is the slow wave characteristic of deep, unconscious sleep and it is thought to reflect the brain of an unconscious person. Delta waves increase in relation to the decreasing awareness of the physical would.

Theta-band: Theta rhythms are observed during some sleep states, and in states of quiet focus, for example meditation. They are also manifested during some short term memory tasks, and during memory retrieval. Theta waves are thought to involve many neurons firing synchronously. They seem to communicate between the hippocampus and cortex in memory encoding and retrieval.

Alpha-band: Alpha waves arise from synchronous and coherent (in phase) electrical activity of large groups of neurons in the human brain. They are dominantly found to originate from the occipital lobe during periods of relaxation, with eyes closed but still awake. Conversely alpha waves are attenuated with open eyes as well as by drowsiness and sleep. The alpha-band can be divided into sub-bands: alpha I (7-11Hz) and alpha II (11-14Hz). Alpha I are important for inner self-awareness and balance, while alpha II are more involved with centring and healing. For more details, please see below in discussion.

Beta-band: Beta activity is 'fast' irregular activity, at low voltage. Beta waves are usually associated with normal waking consciousness, often active, busy, or anxious thinking and active concentration. Beta is usually seen on both sides of the brain in symmetrical distribution and is most evident frontally. Rhythmic beta may be associated with various pathologies and drug effects.

Gamma-band: Gamma waves are thought to signal active exchange of information between cortical and subcortical regions. It is seen during the conscious waking state and in REM (rapid eye movement sleep) dreams.

1.7 EEG markers of hemianopia

Despite the dominating relevance of vision in human behavior, very few studies have focused on the electrophysiological markers in patients with hemianopia and lesions in an occipital lobe. In 1986, Aldrich reported the EEG finding from 25 patients with homonymous

hemianopia and found visually detectable well-developed alpha rhythm were missing [10]. By measuring visual evoked potential (VEP) from 20 patients with occipital lobe lesions, Streletz confirmed a positive correlation between occipital lobe damage, homonymous visual field defects and the predominance of the P94 component in VEP ipsilateral to unilateral lesions [23]. One more recent study using VEP to study hemianopia showed differences in VEP amplitude and latency between the lesion hemisphere (LH) and contra-lesion hemisphere (CH) in the brain [24].

Because prior research has on the whole failed to investigate EEG markers of hemianopia, the present thesis was prepared to gain further insight to better understand the physiological nature of vision loss following occipital strokes.

1.8 Study questions

Few studies focus on chronic stroke in occipital cortex resulting in visual dysfunction and little is known about electrophysiological markers for visual functions. Therefore, I analysed EEG recordings, aiming at uncovering the correlation between functional visual loss and electrophysiological features in patients who suffer chronic occipital cortex damage and subsequent vision loss.

The specific study questions for my occipital stroke patients were as follows:

1. What is the correlation between the topographic visual field defect and other functional visual parameters?
2. Are there any correlations between the functional visual parameters and the electrophysiological parameters? The functional visual parameters are visual acuity, contrast sensitivity, reading speed, dynamic vision, visual alertness and topographic visual field. The electrophysiological parameters are the spectral power of EEG signal in different frequency bands in region-of-interest (ROI). We hypothesized that EEG markers would better correlate with the extent of central than with peripheral vision loss.
3. What are the differences of spectral power in resting state EEG between the lesion hemisphere (LH) and the contra-lesion hemisphere (CH)?

2. Material and Method

2.1 Study design and patient recruitment

This study was carried out in compliance with the ethical standards of the Declaration of Helsinki (1964) and approved as a clinical trial by the local ethics committee and national regulatory bodies.

The study started from the beginning of 2014 and ended in March 2015. A total of 25 patients were recruited. All patients volunteered to take part in this study. Patients all had post-chiasmatic lesions, which resulted in marked visual field limitation, such as hemianopia or quadrantanopia. Most of the lesions were ischemic or hemorrhagic stroke and were at least 6-months old. The corrected visual acuity of each eye was required to be no less than 0.4 (logMAR) or 20/50 (Snellen). On admission to the study, the medical history was collected and assessed by a neurologist. A comprehensive examination, in particular of visual dysfunction, was carried out. The possibility of further participation in the study depended on the results of this preliminary investigation. The patients had to have some residual visual performance and typically a gradual transition between the blind area and the intact area of the visual field. This study helped to delineate physiological and functional changes that resulted from chronic brain damage (see Table 1).

As visual parameters, visual acuity (Standard-Snellen, with see-chart from Oculus) and contrast sensitivity (MARS Kontrast chart, MARS Perceptrix Corporation) were assessed; the visual field was measured by different methods, Standard Automated Static Perimetry (Twinfield, Oculus) and a high-resolution computer-based campimetric test with super-threshold stimuli (High Resolution Perimetry (HRP)). Visual cognitive tasks were International Reading Test (International Reading Speed Texts), Dynamic Vision Test (Düsseldorf Dynamic Vision Test) and TAP-Alertness test (Zimmermann and Fimm, 2008). A resting-state EEG (Geodesic EEG 128-channel system; Electrical Geodesics Inc) was collected as well.

ID	gender	age (years)	disease onset	lesion age at admission (month)	responsible lesion	side of vision loss
1	m	25	2010	45	infarction of left posterior cerebral artery	right
2	m	46	2009	61	infarction of left posterior cerebral artery	right
3	m	66	2012	20	infarction of left posterior cerebral artery	right
4	m	69	2010	45	ischemia in right occipital lobe	left
5	m	74	2012	19	infarction of left posterior cerebral artery	right
6	m	63	2011	28	infarction of left posterior cerebral artery	right
7	f	53	2004	117	ischemia in right occipital lobe	left
8	m	53	2011	29	infarction of right posterior cerebral artery	left
9	m	63	2012	25	infarction of left posterior cerebral artery	right
10	m	55	2001	156	infarction of left posterior cerebral artery	right
11	m	71	2012	21	infarction of right posterior cerebral artery	left
12	m	50	2013	11	infarction of right posterior cerebral artery	left
13	m	67	2010	49	infarction of right middle and posterior cerebral artery	left

ID	gender	age (years)	disease onset	lesion age at admission (month)	responsible lesion	side of vision loss
14	m	59	2012	27	intracerebral hemorrhage in right parietal-occipital lobes	left
15	m	61	2012	25	infarction of right posterior cerebral artery	left
16	m	73	2012	19	stroke in right occipital lobe	left
17	m	71	2013	12	intracerebral hemorrhage in left parietal-occipital lobes	right
18	m	46	2011	43	infarction of right posterior cerebral artery	left
19	m	54	2006	93	stroke in left occipital lobe	right
20	m	59	2014	6	infarction in left occipital lobe	right
21	f	55	2006	106	infarction of right posterior cerebral artery	left
22	m	55	2014	9	infarction in right side of brain stem	left
23	m	62	2014	6	infarction of right posterior cerebral artery and posterior inferior cerebellar artery	left
24	f	61	2014	7	infarction of right posterior cerebral artery	left
25	m	52	2014	10	infarction of right posterior cerebral artery	left

Table.1. Demographic and clinical characteristic of patient sample.

Inclusion and Exclusion criteria

Inclusion criteria: homonymous visual field defects (after posterior artery stroke) due to occipital cortex damage, stable visual filed defect (spontaneous recovery completed), lesion age ≥ 6 months, age > 18yrs.

Exclusion criteria: complete blindness, visual hemi-neglect, electrical or metal implants (e.g. heart pacemakers), any kind of epilepsy or photosensitivity, autoimmune diseases at an acute stage, psychiatric diseases (schizophrenia etc.), serious substance abuse, diabetic retinopathy or diabetes mellitus with average blood glucose level above 7mmol/l, high blood pressure above 160/100mmHg, instable or high level of intraocular pressure (more than 27mm of hg column), retinitis pigmentosa, pathological nystagmus, any serious ophthalmological disorders with high probability of ongoing vision loss, pregnancy, atrial fibrillation, risk for vascular thrombosis, arteriosclerosis with more than 75% stenosis, myocardiac infarction with high cardioembolic risk level, serious coronary heart disease including unstable angina pectoris, any operation targeting the heart, head or vascular system during the past 3 months.

2.2 Visual Acuity

Visual acuity is the ability to resolve spatial details. The measurement of visual acuity is a simple test to evaluate the general healthy state of the eyes, the visual pathway and the visual cortex. We tested the patients' visual acuity using standard Snellen eye charts, as done in routine ophthalmic examinations in the clinical context. It measures best corrected, binocular, near vision ability to recognize black, high-contrast Landolt 'C' on a white background, at a 40-centimetre distance. The Landolt 'C' is an interrupted circle, whose stroke width and gap width are one-fifth of its outer diameter. The two borders of the break in the ring are parallel. We took the decimal notation, which was the decimal expression of the Snellen fraction, and the number of correctly recognized "C" rings as well (Fig. 5).

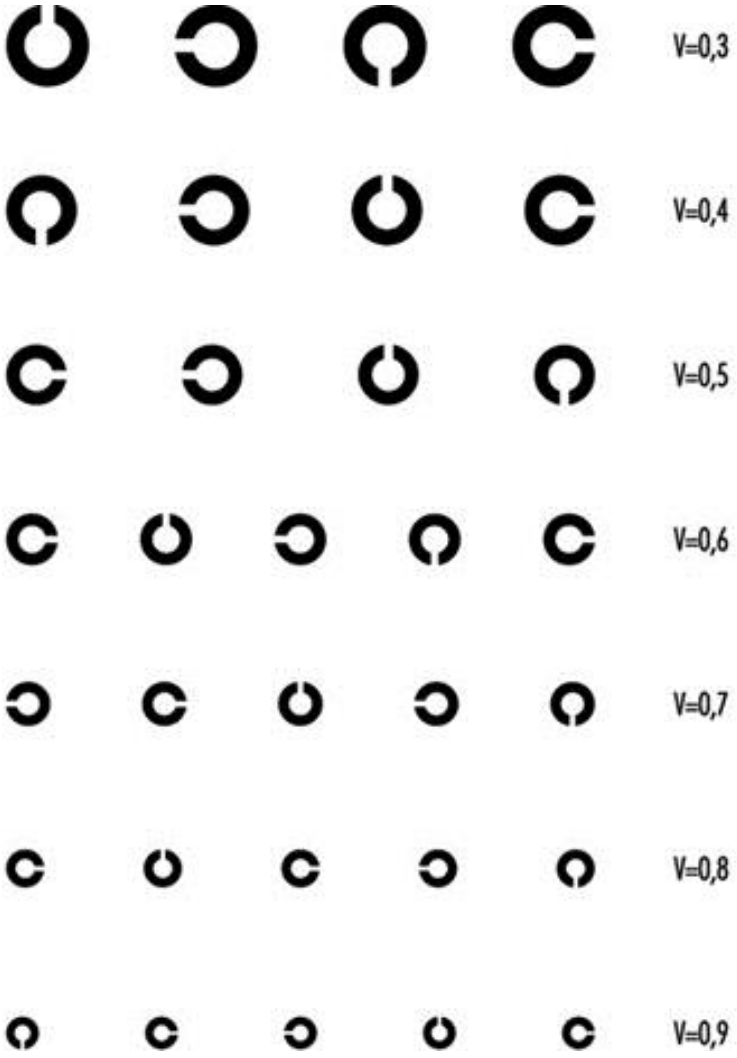

Fig.5. Standard Snellen eye charts.
(Downloaded from internet. iloencyclopaedia.org)

Visual acuity is a parameter which is frequently used to assess the overall vision. But even though visual acuity is normal, visual function can decrease because of diminished contrast sensitivity.

2.3 Contrast sensitivity (CS)

Contrast sensitivity is the visual ability to distinguish an object from its background. It defines the threshold between the visible and invisible. For contrast sensitivity measurements, the Mars Letter Contrast Sensitivity Test was used, since it is reliable, valid, broadly applicable in clinical research, low vision care, disease monitoring, and outcomes research [25]. Contrast sensitivity was evaluated binocularly, under the standardized conditions of a daylight lamp, at a distance of 50 centimetres. The test items were printed on resin-coated paper by halftone screening method, measuring 22.8*35.6 cm, and was mounted on plastic (Fig. 6). Each chart

form consisted of 48 letters, each subtending 2 degrees, in eight rows of six letters each. The contrast of each letter, from left to right and continuing on successive lines, decreased by a constant factor (0.04 log unit). The patients simply read the letters across lines and down the chart. The test was terminated when the patient made two consecutive errors. The score was the log CS of the final correct letter, minus 0.04 for any errors before that [26].

Fig.6. Mars Letter Contrast Sensitivity Test.
(Downloaded from internet. iovs.arvojournals.org)

2.4 International reading speed test

Reading plays an important role in daily life. Reading performance has been evaluated in several clinical trials which assessed the effectiveness of low vision rehabilitation [27]. To represent reading performance, reading speed is a key variable. To measure reading speed for a standard print size, we chose the International Reading Speed Texts (IResT). Its texts are sufficiently long to minimise the effect of reading "glitches", which should improve test-retest variability; its low within-subject variability supports good reliability. Reading whole paragraphs is closer to the demands of everyday reading. It is suitable for the assessment of reading speed for neurological reading disorders, e.g. hemianopia and for monitoring the impact of visual system disease and the effects of interventions [28]. But it was only tested in young normally-sighted readers (18-35 years old) [29].

As for this study, the patients read the same passage "Trees (Bäume)". I then calculated the normal reading speed minus the actual reading speed, then divided it by the standard deviation of the reading speed from normal subjects. This result was a relative reading speed for each subject.

2.5 Dynamic Vision Test

In order to study patients' visual performance which relies solely on motion cues without differences in luminance, I chose the Düsseldorf Dynamic Vision Test (DDTV). It employs aperture motion and displacement motion. Aperture motion: the form of a stationary Landolt ring was made visible through the motion of dots within the region of the ring. A fixation was maintained on a point in the centre of the ring so that an afferent motion stimulus results. With displacement motion, the entire ring moved across a stationary background. Thus, dynamic vision could be investigated under both afferent (fixation on a point in the centre of the display) and efferent (ocular pursuit of the ring) conditions which engage different motion mechanisms. It was a binocular test of detection of contours and the location of the gap in the ring relying on motion contrast (form-from-motion) instead of luminance contrast [30]. In the standard test, there were four motion contrasts and 20 trials per motion. Contrast conditions were administered for a total of 80 trials (four motion contrasts * 20 trials). Performance was tested by sequentially reducing the percentage of moving dots within the ring in four steps: 100%, 50%, 30% and 20%, while the surround pixels remained stationary throughout. The gap in the ring measured 0.36° and its position appeared randomly to the left, right, up, or down. The patients were seated 100 cm in front of the computer monitor with the head held stationary by a chin rest and asked to maintain strict fixation and to indicate the position of the gap in the ring verbally. The time allowed for an answer was unrestricted and no feedback was given to the subjects during measurements [31].

To calculate performance, we took each correct rate in the four gap positions by adding up the results from four motions, and then we calculated the overall averaged correct rate as the result for an individual patient.

2.6 TAP-Alertness test

TAP is a test to evaluate alertness. The visual alertness subsection from the test was used in this study. For each subject, the reaction times under two conditions were tested. One condition was that a crossing sign simply appeared on the screen at variable intervals; the reaction time was recorded from when the sign appeared till the patient pressed the button as fast as possible after the patient saw the sign (Fig. 7). This was the test for intrinsic alertness. The other condition was with the presentation of a visual warning signal, which served as a phasic arousal, before the crossing sign showing up. And the reaction time was recorded from

the crossing sign appeared till the subject pressed the button.

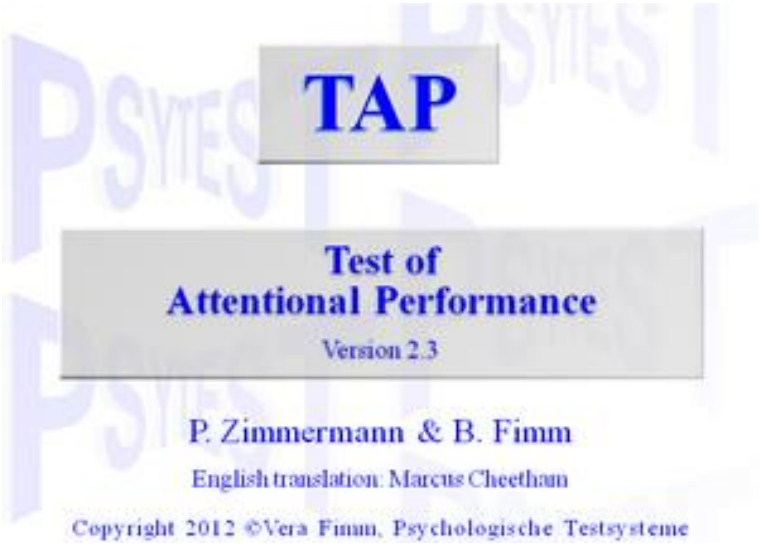

Fig.7.a. TAP-Alertness test.

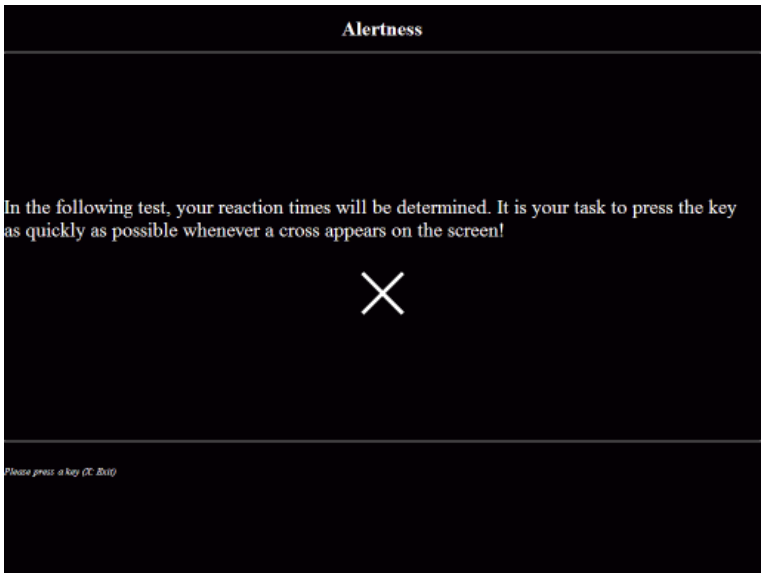

Fig.7.b. TAP-Alertness test.
(Both Fig.7.a and Fig.7.b were downloaded from internet. psytest.net)

With the consideration to balance tiredness effects, the test was regularly set in an ABBA-form. That is to say, the test contained four blocks and they were in the sequence “without warning signal”, “with warning signal”, “with warning signal”, “without warning signal”. Before each block, there was a cue to show whether the next block would have a warning signal or not.

As for the results, the mean value, the median, the standard deviation of reaction time, the number of right reaction were calculated. Additionally, a Kenn-value, “TAP-Kenn”, was

calculated for the phasic alertness. The formula was as follows:

$$(MD_{RZ.o} - MD_{RZ.m}) / MD_{RZ.ges}, \text{ where}$$

$MD_{RZ.o}$ = the median of reaction time from block 1 and 4 (without warning),

$MD_{RZ.m}$ = the median of reaction time from block 2 and 3 (with warning), and

$MD_{RZ.ges}$ = the median of reaction time from block 1, 2, 3 and 4 (all blocks of the test)

2.7 Perimetry

Perimetry is a systematic measurement of the limits and the sensitivity contours of a monocular visual field. It is an ophthalmology test to create a topographic map of the visual field in order to diagnose and evaluate diseases of the visual pathway. A standard static perimetry was involved in the study to test the central 30° of visual field. It was performed with a hemispherical surface onto which the visual field was projected. A white stimulus was projected on a white background to determine the threshold values. The size and location of a target were kept constant while the brightness was varied until the dimmest target the patient could still see at each of the test location (Fig. 8). Therefore, the lower the threshold, the better the vision. The examined eye of the patient was positioned at the geometric centre of the hemisphere, so that all points on its inner surface were equidistant from the eye [32]; that means all the stimuli were at equal distance to the eye.

Fig.8. Static automated perimetry test.

As for the perimetry results, the following parameters for each eye were taken for analysis: the threshold at fovea, the fixation performance, false positive reactions, the mean threshold difference between the patient and the normal value of the patient's age group, the number of absolute defect and relative defect. And the corrected threshold values of each testing location were added up in the central 30° and in the central 6°, for the left or right hemisphere from each eye, separately. Note: the lower the threshold at fovea, the better is the foveal vision.

2.8 High Resolution Perimetry (HRP)

Monocular visual fields were assessed with conventional threshold static automated perimetry, while binocular visual fields were tested by a special high-resolution computer-based campimetric test battery (High Resolution Perimetry (HRP)), which was developed by the Sabel laboratory [33]. This method fits best for the examination of the central visual field, up to approximately 25 degree of eccentricity. Yet, it is not useful in the more peripheral locations. It covers the visual field only up to ±12.5° vertically and horizontally. The patients were seated in a darkened room in front of a 17-in. monitor. The head position was stabilized by a combined head-chin rest. The distance between the eyes and the screen was approximately 40 cm. White-light stimuli were presented in a grid of 21 * 21 stimulus locations, each of which corresponds to 1.2° of the central visual field. The order of the stimulus was randomized. A fixation point was positioned at the centre of the screen and served as the frame of reference to set up the screen at eye level. The patients were instructed to keep looking at the fixation point and to press the space bar on the computer keyboard whenever either a target stimulus was detected or an isoluminant change in the colour of the fixation point occurred. A simultaneous control of eye movements was carried out by means of an eye-tracker. Stimulus detection as well as reaction times were measured by the program at all stimulus positions. For each patient, three measurements were performed, each with a duration of approximately 23 minutes. The visual field areas were categorized as intact (three correctly detected stimuli per location, white spots), partially damaged (one or two stimuli detected, gray spots) and absolutely impaired areas (no stimulus detected, black spots) [1].

From HRP, the following parameters were taken for analysis: fixation accuracy, acuity and reaction time, in right and left visual field, respectively.

2.9 EEG

2.9.1 EEG recording

The patients were seated in a darkened room with eyes closed. A resting-state EEG was recorded for five minutes using a 128 channel Electrical Geodesics Inc. system (EGI, Eugene, OR) (Fig. 9). The Geodesic Sensor Net is a lightweight, elastic structure, housing the silver/silver-chloride electrodes within a synthetic sponge on a pedestal. Sponges were soaked in potassium chloride prior to testing to promote conductivity. Sensor impedance was maintained below recommended manufacturer specification of 50kΩ.

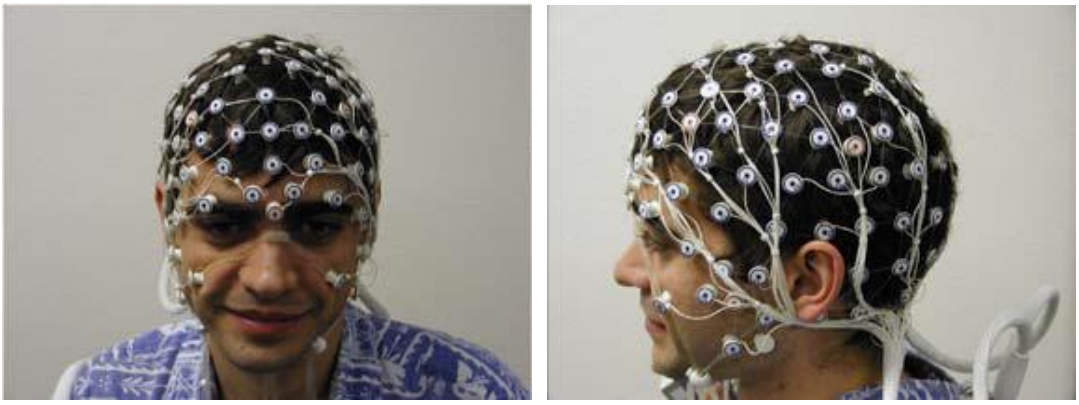

Fig.9. EGI 128-channel HCGSN, front (left) and side (right) views.
(The figures are from Geodesic Sensor Net technical manual.)

2.9.2 EEG pre-processing

The EEG pre-processing and analysis were carried out in Matlab R2012b and EEGlab. Raw EEG signal was filtered with a high-pass (1Hz) finite impulse response (FIR) filter to exclude slow drifts, notch (48-52Hz) FIR filter to exclude 50Hz line noise, and a low-pass (100Hz) FIR filter to prevent aliasing during the following down-sampling to 250Hz. Electrodes which exhibited excessive artefacts were rejected and interpolated based on activity of nearby channels. EEG signals were re-referenced to the common average reference and screened again to reject periods of excessive artefactual activity.

2.9.3 EEG Spectral Power Analysis

Four regions-of-interest (ROI) channel groups on each hemisphere of the brain were taken for analysis from each patient's EEG recording (Fig. 10); each ROI consisted of five selected electrodes:

Left hemisphere:	Temporal lobe	[39, 40, 44, 45, 46];
	Frontal lobe	[19, 24, 27, 32, 33];
	Parietal lobe	[52, 53, 59, 60, 61];
	Occipital lobe	[65, 66, 67, 70, 71];
Right hemisphere:	Temporal lobe	[102, 108, 109, 114, 115];
	Frontal lobe	[1, 4, 122, 123, 124];
	Parietal lobe	[78, 85, 86, 91, 92];
	Occipital lobe	[76, 77, 83, 84, 90];

For each ROI, six frequency bands were extracted for analysis. They were delta (1-3Hz), theta (3-7Hz), alpha I (7-11Hz), alpha II (11-14Hz), alpha (7-14Hz), beta (14-30Hz).

Spectral power was calculated by the EEGlab function ***pop_spectopo***, which used Fast Fourier Transformation (FFT) to estimate the amplitude of the signal. The function plotted the mean logarithmic spectral power of the EEG signal at the selected channels of ROIs as the bundles of traces.

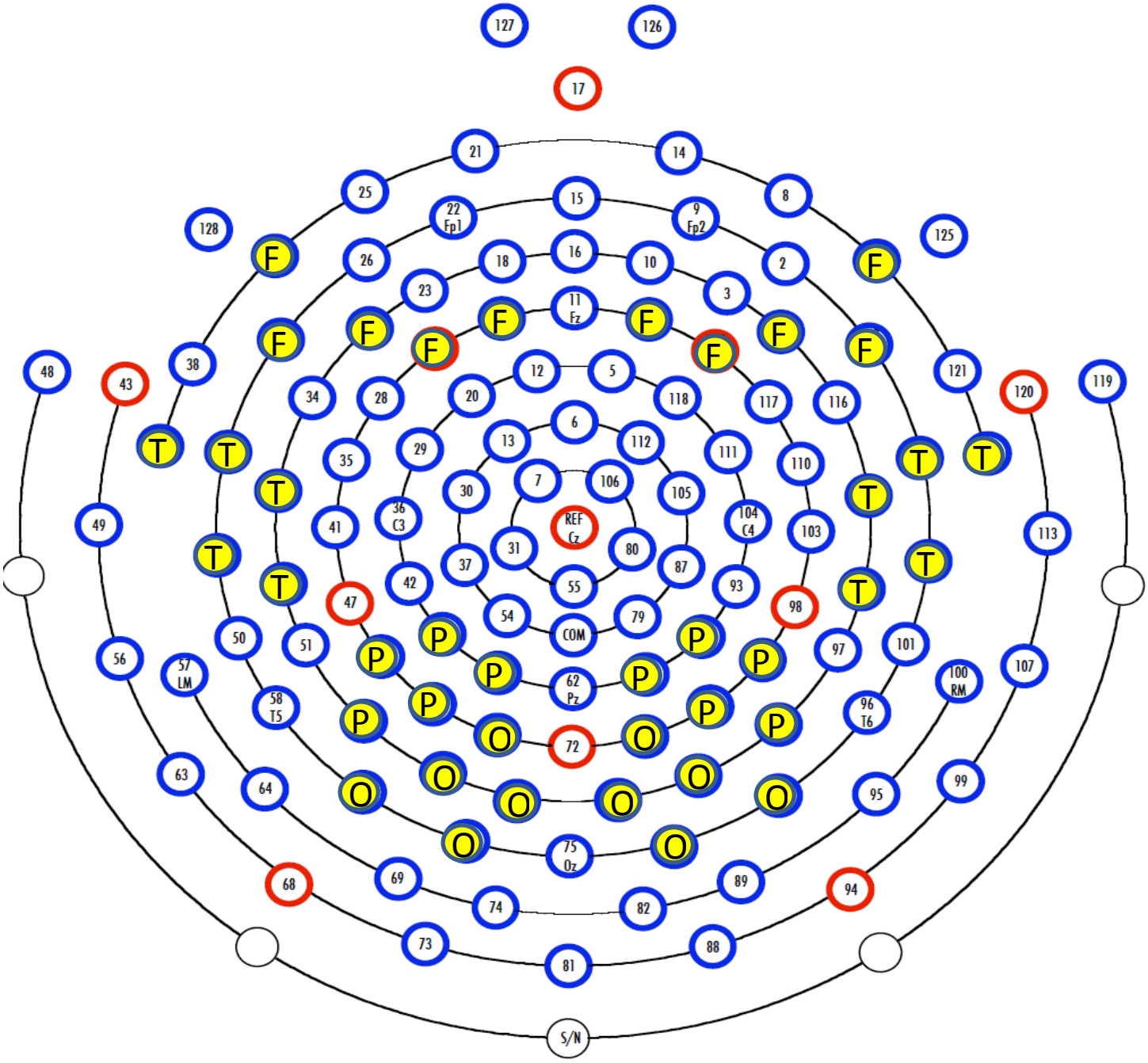

Fig.10. Regions-of-interest (ROIs). F=frontal lobe; T=temporal lobe; P=parietal lobe; O=occipital lobe.

2.10 Statistical Analysis

Firstly, to explore the correlation between topographic visual field and other functional visual parameters, the correlation between the functional visual parameters and spectral power of EEG as well, correlation analyses were carried out in SPSS 22. Multiple comparison corrections were taken into consideration by choosing a more conservative p-value at the level of 0.01 instead of 0.05 as a criterion for significance. Since this multiple comparison significance tests were used only for descriptive purposes, a relative stricter significant level was deemed appropriate [34].

Simultaneously, an approach controlling the false discovery rate (FDR) was applied, which was used to address the multiple-comparison problems [35]. A statistically significant p-value with the perspective of FDR control depends on the number of comparisons, the concrete situation of the individual p-values and the level of FDR control. In this study, the test results of the 90 parameters obtained from the 25 patients were calculated for correlations between each other, which resulted in a total of 4005 individual p-values. All these individual p-values served as input into Matlab function. As another input, the level of FDR control was set at 0.05. Calculated by the Matlab function, p-value should be $\leq$ 0.0124 to be considered statistically significant.

Based on the above two points, $p<0.01$ was deemed appropriate for the correct significance criterion so to adjust properly for multiple comparisons, since 0.0124 was close to the traditional two-decimal cut-off point of $p=0.01$.

Secondly, to compare the spectral power in the contra-lesion hemisphere (CH) and in the lesion hemisphere (LH), paired t-test was applied. Each frequency band for each ROI from CH and that from LH were set as a pair. The significance criterion was set at $\alpha=0.05$ and $\alpha=0.01$. The analysis was carried out in SPSS 22.

3. Results

3.1 Patients and lesion

For the 25 patients (22 male) recruited into the study the mean age was 57.6 ± 10.7 years and the mean lesion age was 39.4 ± 39.1 months. 10 patients had their lesion in the left hemisphere and 15 patients in the right hemisphere.

3.2 Results of the calculated parameters

Totally, 43 functional visual parameters as well as 48 EEG spectral power from 6 frequency bands in 8 ROIs were calculated for each patient.

For visual acuity, the mean of the patients was 1.2 ± 0.3 as the decimal expression by Snellen fraction and 100.0 ± 11.3 as the number of the corrected recognition.

For contrast sensitivity, the result was marked as MARS_logCS and its mean was 1.76 ± 0.05.

For the international reading speed test, the results were as follows: reading time 81.64 ± 76.23 seconds, error percentage 2.3 ± 3.1% and reading speed -4.10 ± 3.35 [The reading speed= (number of words a patient read per minute - number of words normal subjects read per minute) / standard deviation of normal subjects' reading speed].

For the dynamic vision test, the correct response percentages were as follows: when the gap position was pointing upwards 72.4 ± 30.4%; when the gap position was towards the right 81 ± 28.7%; when the gap position was pointing downwards 63 ± 31.2%; when the gap position was towards the left 64 ± 28.8% and the averaged percentage of correct responses of all four gap positions was 70.1 ± 26.5%.

For TAP-Alertness test, the mean value, the standard deviation and the number of right reaction of both without and with a warning signal were conserved as parameters. Furthermore, A TAP_kenn value was calculated for each patient. Its mean value for all patients was 0.03 ± 0.11.

For the HRP test, nine parameters were calculated as percentage values. The results were: for fixation accuracy 96.4 ± 5.5%, accuracy in the contra-lesion-side visual field 28.2 ± 20.5%, accuracy in the ipsi-lesion-side visual field 93.3 ± 14.5%, accuracy in the central 4.8 degree in the contra-lesion-side visual field 46.9 ± 34.3%, accuracy in the central 4.8 degree in the ipsi-lesion-side visual field 95.2 ± 17.3%; reaction time to the stimuli in the contra-lesion-side visual field 0.50 ± 0.07 second, reaction time to the stimuli in the ipsi-lesion-side visual field 0.43 ± 0.08 second, reaction time to the stimuli in the central 4.8 degree in the contra-lesion-side visual field 0.48 ± 0.08 second and reaction time to the stimuli in the central 4.8 degree in the ipsi-lesion-side visual field 0.42 ± 0.07 second.

For perimetry, sixteen parameters were calculated, which were foveal threshold of the contra-lesion-side eye 25.36 ± 2.20, foveal threshold of the ipsi-lesion-side eye 25.84 ± 1.93, fixation control of the contra-lesion-side eye 96.04 ± 8.21%, fixation control of the ipsi-lesion-side eye 95.48 ± 8.07%, the correct positive reaction of the contra-lesion-side eye 98.68 ±4.84%, the correct positive reaction of the ipsi-lesion-side eye 98.28 ± 6.82%, absolute defects of the contra-lesion-side eye 19.96 ± 8.58, absolute defects of the ipsi-lesion-side eye 21.88 ± 9.19, relative defects of the contra-lesion-side eye 6.08 ± 5.42, relative defects of the ipsi-lesion-side eye 5.88 ± 4.32, the mean threshold of the contra-lesion-side eye -4.49 ± 2.98 [the mean threshold of the patient minus the mean threshold of normal subject at the same age group], the mean threshold of the ipsi-lesion-side eye -5.32 ± 2.96 [the mean threshold of the patient minus the mean threshold of normal subject at the same age group], the deviation-corrected threshold of the contra-lesion-side visual field from both eyes -11.70 ± 3.80, the deviation-corrected threshold of the ipsi-lesion-side visual field from both eyes -1.15 ± 2.03, the deviation-corrected threshold of the central 6 degrees of the contra-lesion-side visual field from both eyes -9.26 ± 5.47, the deviation-corrected threshold of the central 6 degrees of the ipsi-lesion-side visual field from both eyes -0.11 ± 3.12.

For EEG recording, the spectral power ($10*\log_{10}(\mu V^2/Hz)$) of each of the six frequency bands regarding each of the eight regions-of-interest (ROIs) was calculated. The results were: in the temporal lobe on the CH, 1-3 Hz 3.94 ± 2.48, 3-7 Hz -0.50 ± 2.50, 7-11 Hz 1.45 ± 3.18, 11-14 Hz -2.39 ± 2.69, 14-30 Hz -5.85 ± 2.80, 7-14 Hz -0.14 ± 2.81; in the temporal lobe on the LH, 1-3 Hz 4.39 ± 2.49, 3-7 Hz -0.06 ± 2.75, 7-11 Hz 1.58 ± 2.95, 11-14 Hz -2.30 ± 2.60, 14-30 Hz -6.06 ± 2.49, 7-14 Hz -0.02 ± 2.55; in the frontal lobe on the CH, 1-3 Hz 6.08 ± 2.91, 3-7 Hz 0.67 ± 2.64, 7-11 Hz 1.58 ± 3.06, 11-14 Hz -3.11 ± 2.94, 14-30 Hz -6.25 ± 2.56, 7-14 Hz -

0.36 ± 2.85; in the frontal lobe on the LH, 1-3 Hz 6.47 ± 3.30, 3-7 Hz 1.31 ± 2.82, 7-11 Hz 2.20 ± 3.09, 11-14 Hz -2.63 ± 3.00, 14-30 Hz -6.03 ± 2.65, 7-14 Hz 0.20 ± 2.87; in the parietal lobe on the CH, 1-3 Hz 2.53 ± 2.01, 3-7 Hz -1.41 ± 2.51, 7-11 Hz 3.87 ± 3.84, 11-14 Hz -1.39 ± 3.60, 14-30 Hz -7.18 ± 2.66, 7-14 Hz 1.69 ± 3.32; in the parietal lobe on the LH, 1-3 Hz 3.16 ± 3.24, 3-7 Hz -1.11 ± 3.36, 7-11 Hz 2.66 ± 4.06, 11-14 Hz -2.28 ± 3.90, 14-30 Hz -7.43 ± 2.76, 7-14 Hz 0.62 ± 3.62; in the occipital lobe on the CH, 1-3 Hz 3.00 ± 1.90, 3-7 Hz -0.63 ± 2.52, 7-11 Hz 4.24 ± 3.46, 11-14 Hz -1.48 ± 2.98, 14-30 Hz -6.82 ± 2.15, 7-14 Hz 1.87 ± 2.90; in the occipital lobe on the LH, 1-3 Hz 3.18 ± 2.69, 3-7 Hz -0.81 ± 3.18, 7-11 Hz 3.00 ± 4.05, 11-14 Hz -2.27 ± 3.57, 14-30 Hz -7.10 ± 3.00, 7-14 Hz 0.82 ± 3.55.

3.3 Correlation between the topographic visual field parameters and the other functional visual parameters

No statistically significant and meaningful correlation was found between the topographic visual field parameters (the accuracies and reaction times in HRP test; the foveal threshold, the mean threshold, the deviation-corrected threshold, fixation control, the correct positive reaction, absolute defects and relative defects in perimetry test) and the other functional visual parameters (visual acuity, contrast sensitivity, reading speed, dynamic vision, phasic alertness). Thus, the size and position of the visual loss did not influence other visual parameters in occipital stroke patients.

3.4 Correlation between functional visual parameters and the EEG spectral power

The following sections describe which functional visual parameters correlated significantly with the EEG spectral power in certain ROI and certain frequency bands with $P<0.01$. Table 2 gives a summary of the results.

	correlation	1-3 Hz	3-7 Hz	7-11 Hz	11-14 Hz	14-30 Hz	7-14 Hz
Contrast Sensitivity	positive				O_LH	P_CH O_CH O_LH	
Phasic alertness	positive		P_CH P_LH O_LH	P_CH O_CH			
Foveal vision in perimetry in Contra-lesion-side eye	positive	O_CH O_LH	O_CH O_LH				
Foveal vision in perimetry in ipsi-lesion-side eye	positive	T_CH O_CH	O_CH				
Dynamic Vision	negative	O_LH					
Fixation control in perimetry in Contra-lesion-side eye	negative	P_CH P_LH O_CH O_LH	T_LH P_CH P_LH O_CH O_LH				
Fixation Accuracy in HRP Test	negative	T_CH P_CH P_LH O_CH O_LH	T_CH F_CH F_LH P_CH P_LH O_LH				

Table.2. The statistically significant correlations ($p<0.01$) between the functional visual parameters and the EEG spectral power. T= temporal lobe, F= frontal lobe, P= parietal lobe, O= occipital lobe; LH=lesion hemisphere, CH=contra-lesion hemisphere.

3.4.1 Contrast sensitivity

MARS_logCS showed a positive correlation with the 11-14 Hz and 14-30 Hz EEG signal. It correlated positively with 11-14 Hz in LH occipital lobe (r=.51, p=.009); with 14-30 Hz in CH parietal lobe (r=.54, p=.005), in CH occipital lobe (r=.60, p=.001) and in LH occipital lobe (r=.51, p=.010) (Fig. 11).

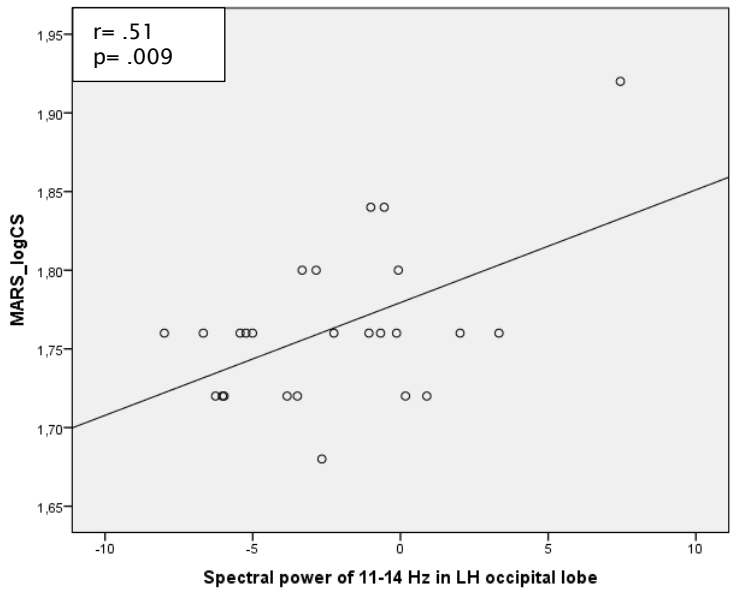

Fig.11.a. EEG spectral power in LH occipital lobe within 11-14 Hz.

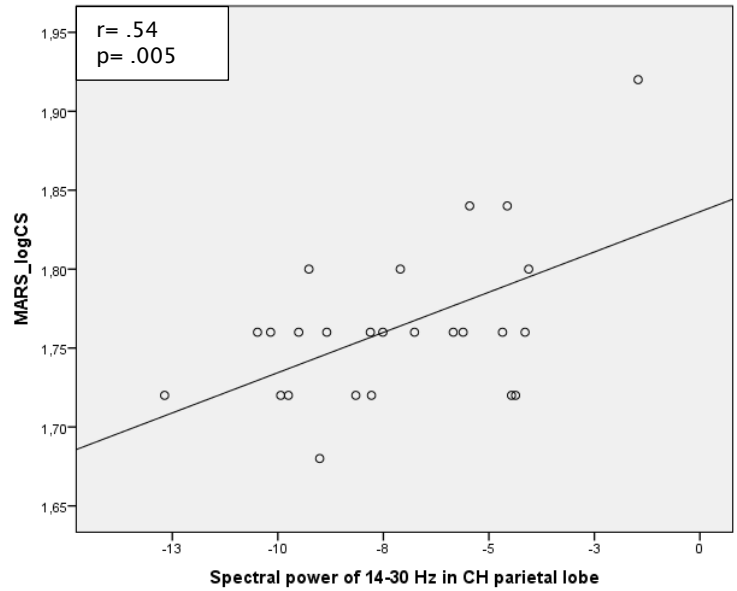

Fig.11.b. EEG spectral power in CH parietal lobe within 14-30 Hz.

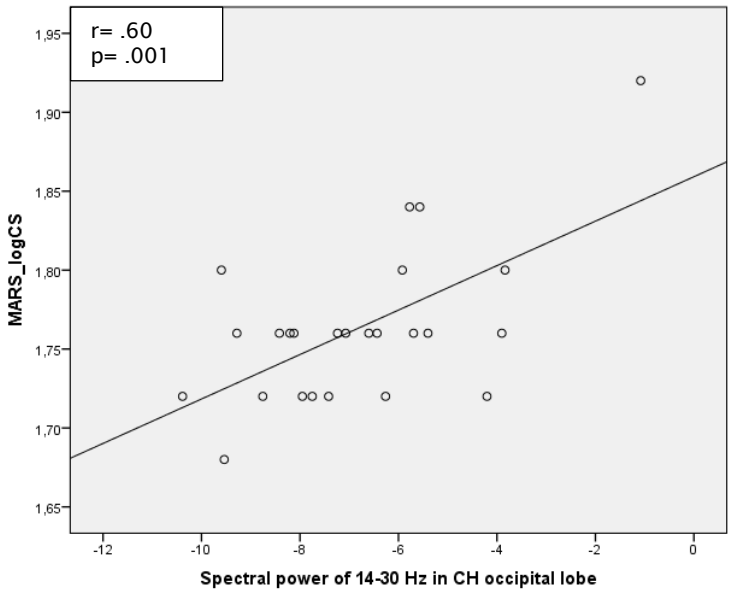

Fig.11.c. EEG spectral power in CH occipital lobe within 14-30 Hz.

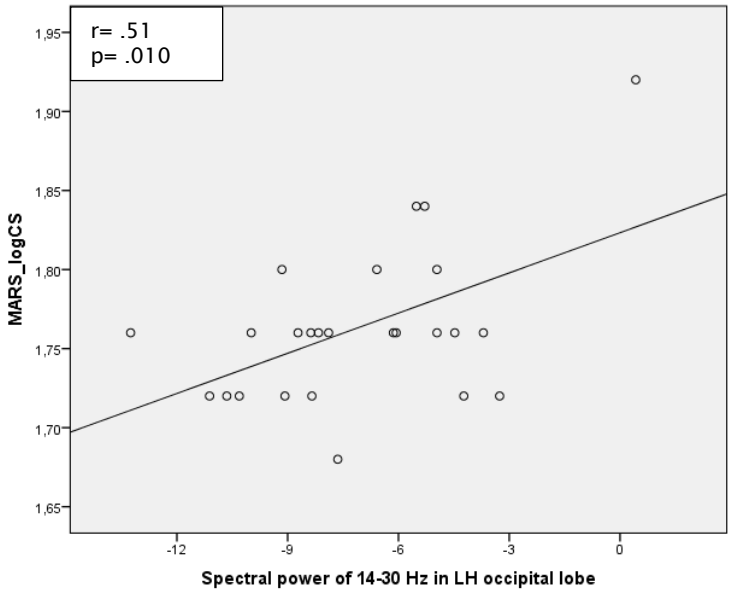

Fig.11.d. EEG spectral power in LH occipital lobe within 14-30 Hz.

Fig.11. Correlation of contrast sensitivity and the EEG spectral power.

3.4.2 Dynamic Vision Test

In the dynamic vision test, the averaged rate of correct responses correlated negatively with 1-3 Hz in LH occipital lobe (r= -.51, p=.009) (Fig. 12).

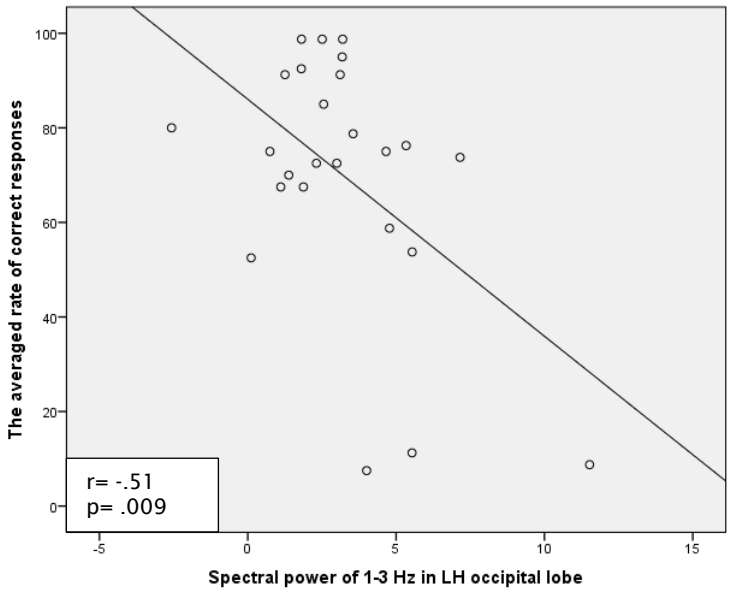

Fig.12. Correlation of dynamic vision and the EEG spectral power in LH occipital lobe within 1-3 Hz.

3.4.3 TAP-Alertness test

TAP_Kenn correlated positively with 3-7 Hz and 7-11 Hz EEG signal. It correlated positively with 3-7 Hz in CH parietal lobe (r=.58, p=.002), in LH parietal lobe (r=.53, p=.007), in LH occipital lobe (r=.60, p=.002); with 7-11 Hz in CH parietal lobe (r=.52, p=.008), in CH occipital lobe (r=.57, p=.003) (Fig. 13).

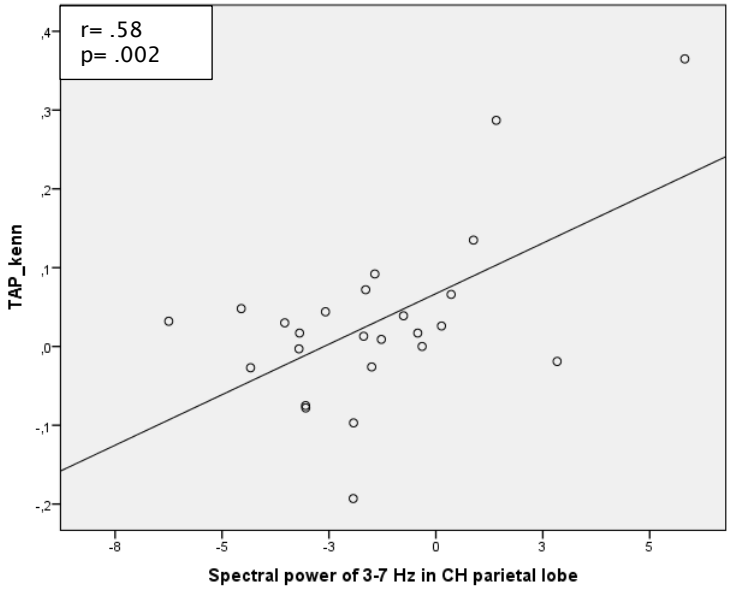

Fig.13.a. EEG spectral power in CH parietal lobe within 3-7 Hz.

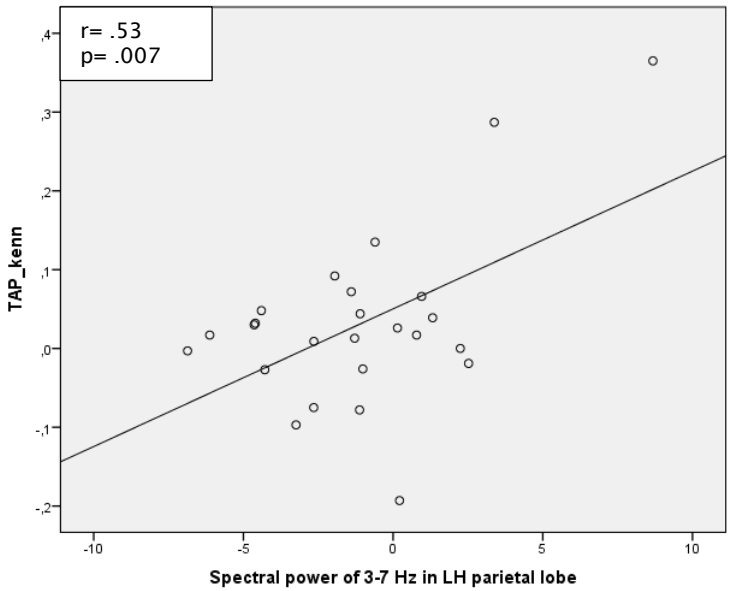

Fig.13.b. EEG spectral power in LH parietal lobe within 3-7 Hz.

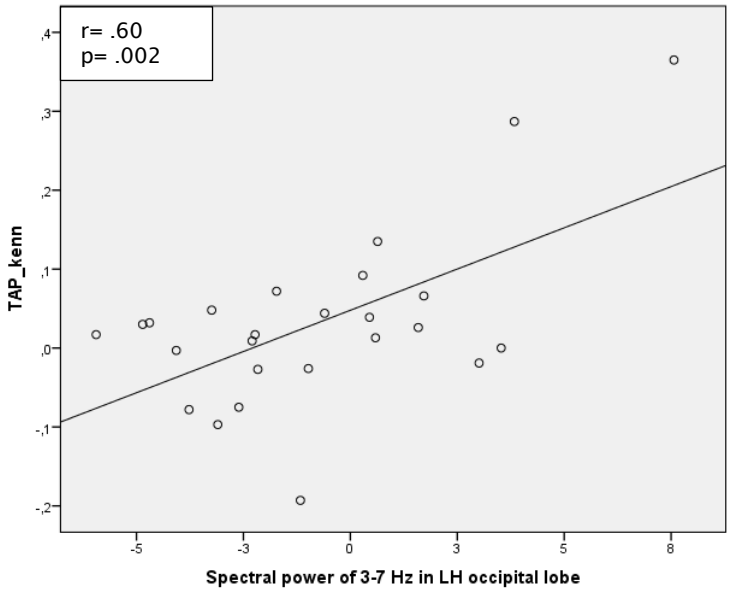

Fig.13.c. EEG spectral power in LH occipital lobe within 3-7 Hz.

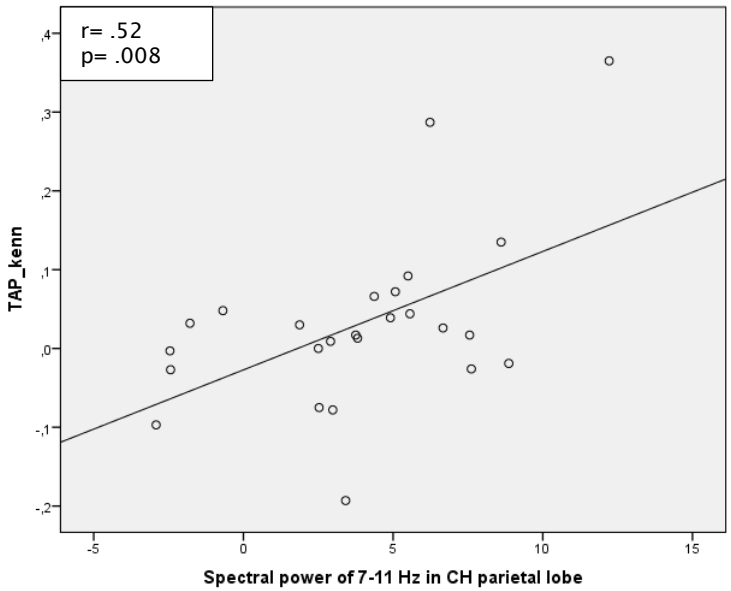

Fig.13.d. EEG spectral power in CH parietal lobe within 7-11 Hz.

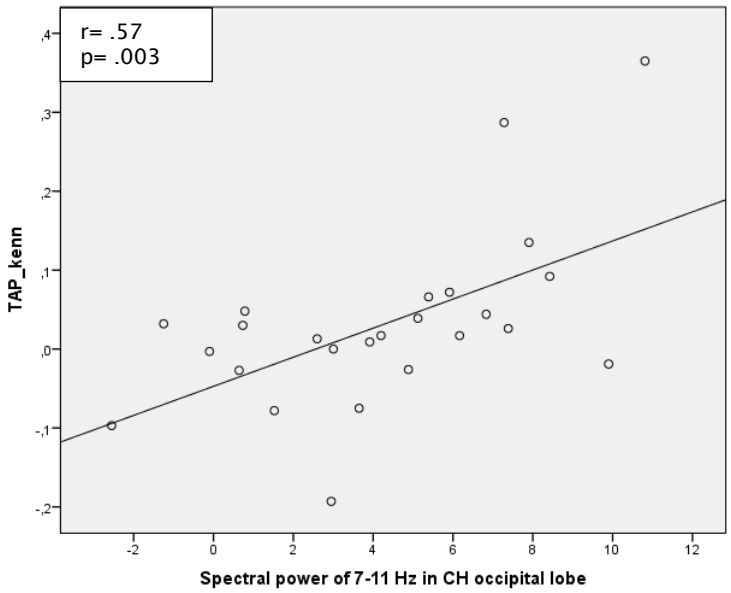

Fig.13.e. EEG spectral power in CH occipital lobe within 7-11 Hz.

Fig.13. Correlation of phasic alertness and the EEG spectral power.

3.4.4 Perimetry

3.4.4.1 Foveal threshold in perimetry in the contra-lesion-side eye

Foveal threshold in perimetry in the contra-lesion-side eye showed negative correlation with 1-3 Hz and 3-7 Hz in occipital. It correlated negatively with 1-3 Hz in CH occipital lobe (*r*= -.52, *p*=.008) and in LH occipital lobe (*r*= -.51, *p*=.009); with 3-7 Hz in CH occipital lobe (*r*= -.58, *p*=.003) and in LH occipital lobe (*r*= -.58, *p*=.002) (Fig. 14).

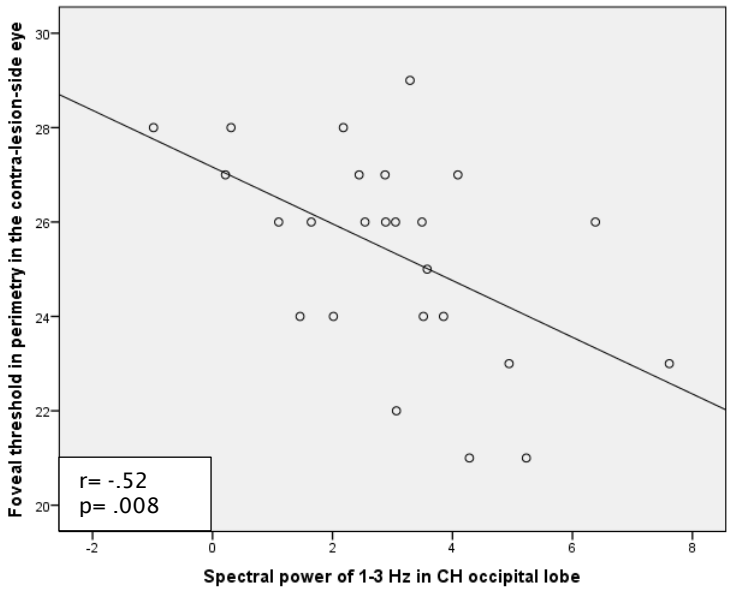

Fig.14.a. EEG spectral power in CH occipital lobe within 1-3 Hz.

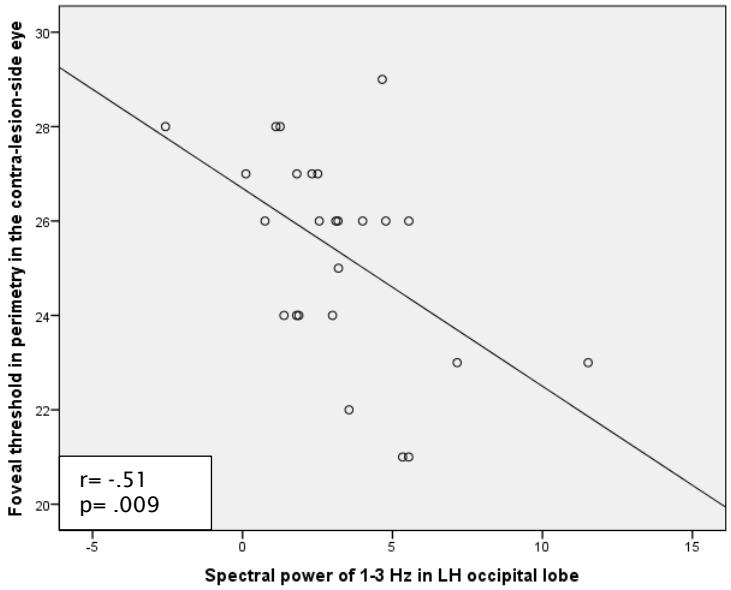

Fig.14.b. EEG spectral power in LH occipital lobe within 1-3 Hz.

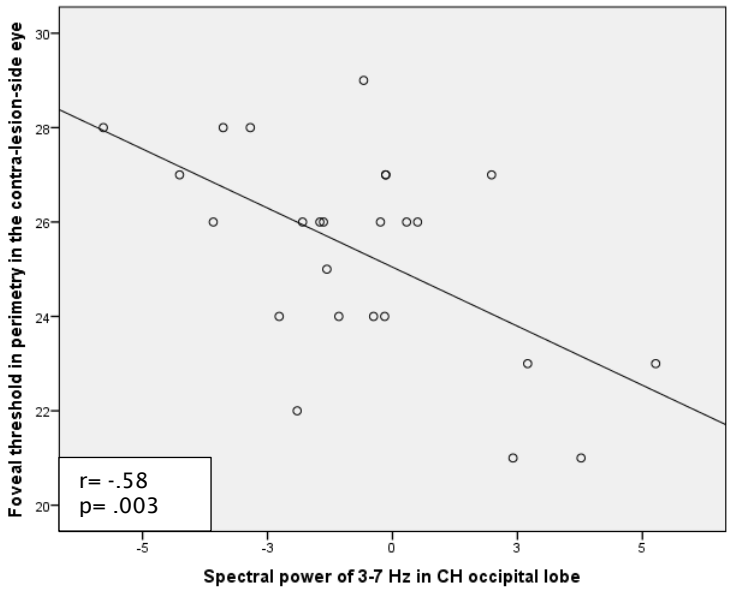

Fig.14.c. EEG spectral power in CH occipital lobe within 3-7 Hz.

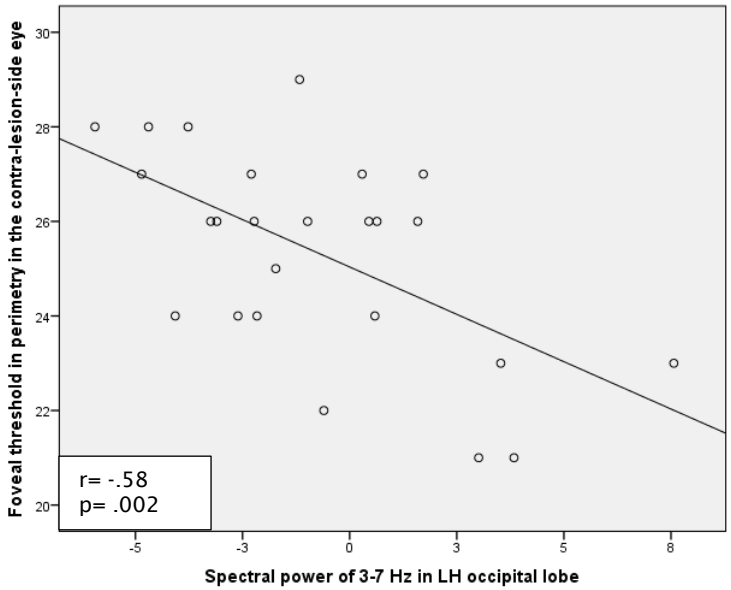

Fig.14.d. EEG spectral power in LH occipital lobe within 3-7 Hz.

Fig.14. Correlation of foveal threshold in the contra-lesion-side eye and the EEG spectral power.

The higher the foveal threshold was, the worse was the fovea vision. Therefore, the foveal threshold in the contra-lesion-side eye correlated negatively with the above EEG parameters, which means that the foveal vision in the contra-lesion-side eye correlated positively with such EEG parameters.

3.4.4.2 Foveal threshold in perimetry in the ipsi-lesion-side eye

Foveal threshold in perimetry in the ipsi-lesion-side eye showed negative correlation with 1-3 Hz and 3-7 Hz. It correlated negatively with 1-3 Hz in CH temporal lobe (r= -.51, p=.010)

and in CH occipital lobe (*r*= -.54, *p*=.006); with 3-7 Hz in CH occipital lobe (*r*= -.52, *p*=.008) (Fig. 15).

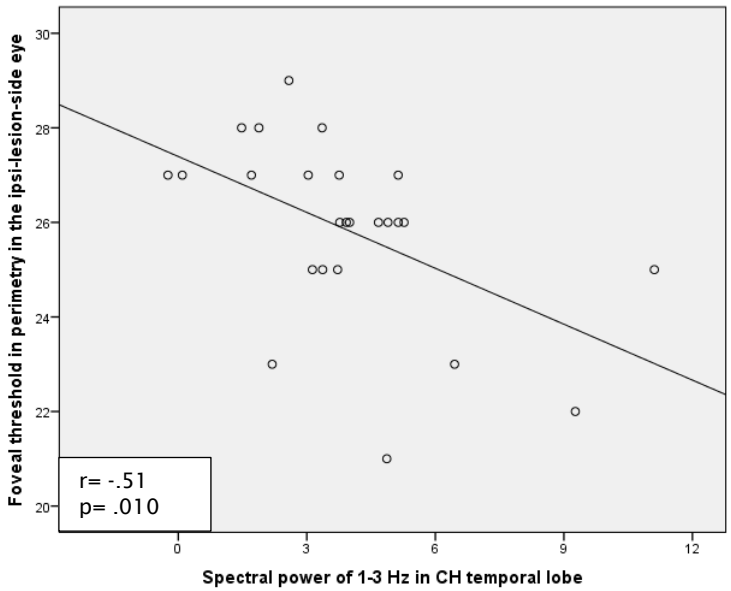

Fig.15.a. EEG spectral power in CH temporal lobe within 1-3 Hz.

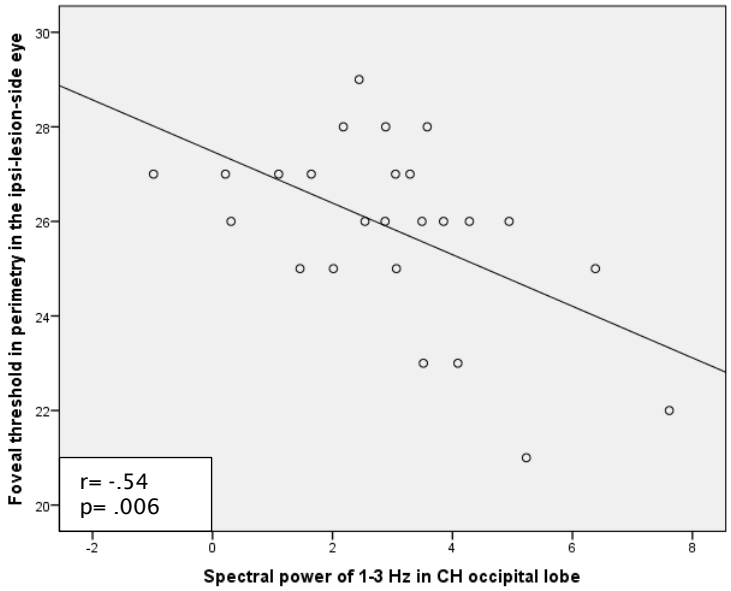

Fig.15.b. EEG spectral power in CH occipital lobe within 1-3 Hz.

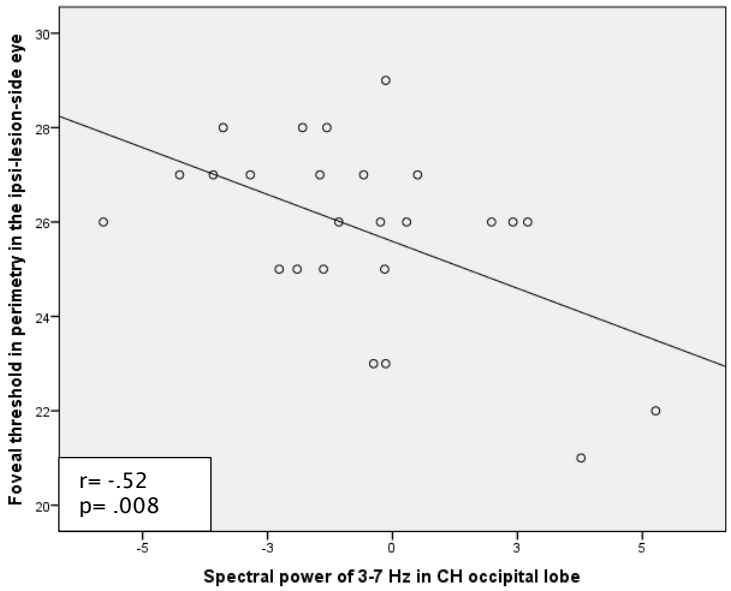

Fig.15.c. EEG spectral power in CH occipital lobe within 3-7 Hz.

Fig.15. Correlation of foveal threshold in the ipsi-lesion-side eye and the EEG spectral power.

Similarly, the foveal threshold in the ipsi-lesion-side eye correlated negatively with the above EEG parameters, which means that vision at the fovea in the ipsi-lesion-side eye correlated positively with such EEG parameters.

3.4.4.3 Fixation control in perimetry in the contra-lesion-side eye

Fixation control in perimetry in the contra-lesion-side eye showed a negative correlation with 1-3 Hz and 3-7 Hz EEG signals. It correlated negatively with 1-3 Hz in CH parietal lobe (r= -.51, p=.009), in LH parietal lobe (r= -.64, p=.001), in CH occipital lobe (r= -.53, p=.006), in LH occipital lobe (r= -.65, p=.000); with 3-7 Hz in LH temporal lobe (r= -.53, p=.006), in CH parietal lobe (r= -.53, p=.007), in LH parietal lobe (r= -.62, p=.001), in CH occipital lobe (r= -.52, p=.008), in LH occipital lobe (r= -.58, p=.003) (Fig. 16).

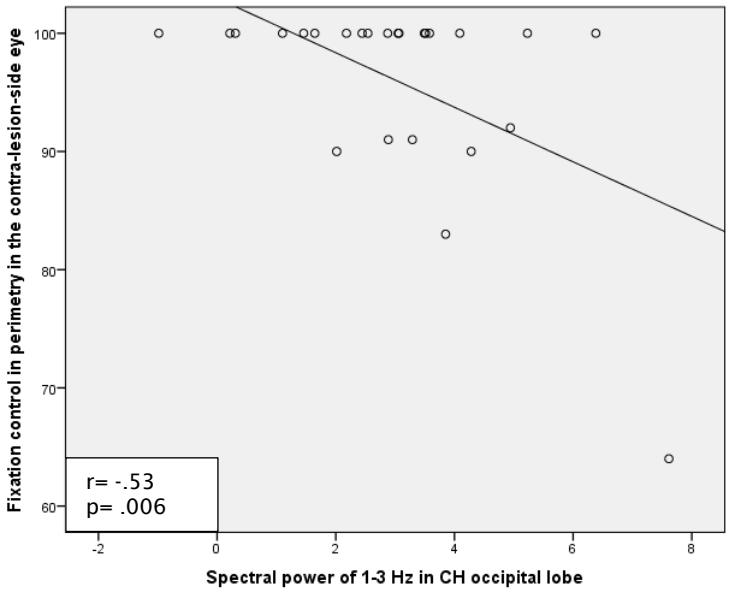

Fig.16.a. EEG spectral power in CH occipital lobe within 1-3 Hz.

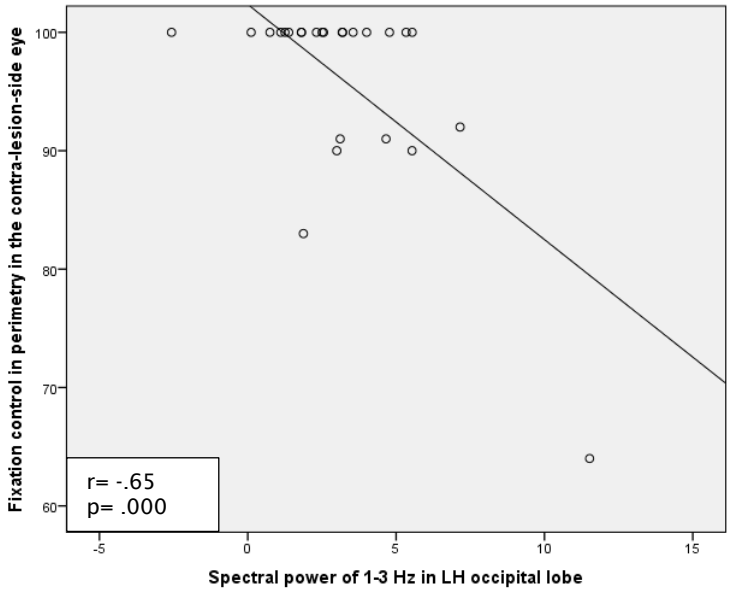

Fig.16.b. EEG spectral power in LH occipital lobe within 1-3 Hz.

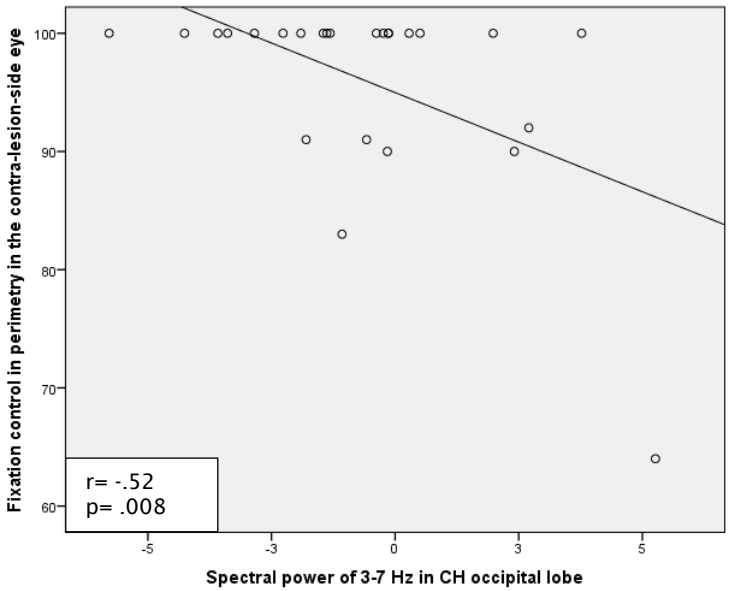

Fig.16.c. EEG spectral power in CH occipital lobe within 3-7 Hz.

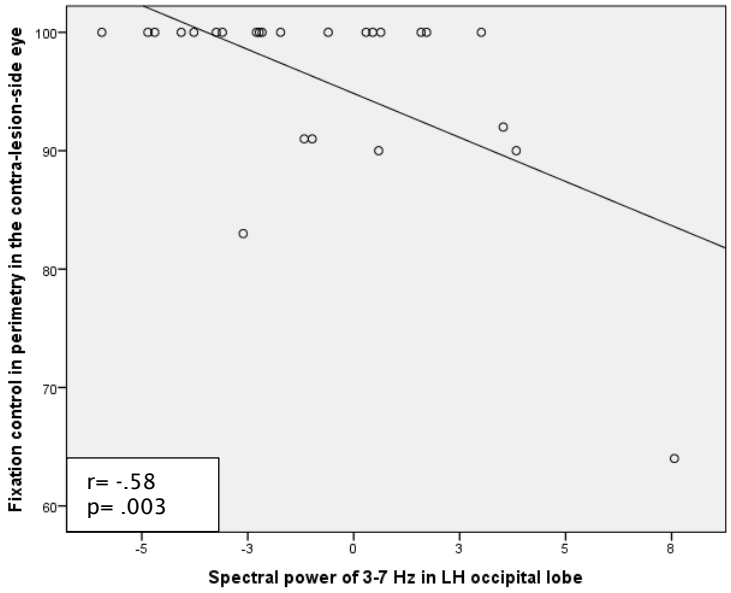

Fig.16.d. EEG spectral power in LH occipital lobe within 3-7 Hz.

Fig.16. Correlation of fixation control in the contra-lesion-side eye and the EEG spectral power. The plots of other correlated ROIs look similar as the four shown above. The other correlated ROIs were in CH parietal lobe within 1-3 Hz, in LH parietal lobe within 1-3 Hz, in CH parietal lobe within 3-7 Hz, in LH parietal lobe within 3-7 Hz, in LH temporal lobe within 3-7 Hz.

3.4.5 HRP

Fixation Accuracy in HRP showed a negative correlation with 1-3 Hz and 3-7 Hz. It correlated negatively with 1-3 Hz in CH temporal lobe (r= -.61, p=.001), in CH parietal lobe (r= -.72, p=.000), in LH parietal lobe (r= -.73, p=.000), in CH occipital lobe (r= -.62, p=.001), in LH occipital lobe (r= -.72, p=.000); with 3-7 Hz in CH temporal lobe (r= -.59, p=.002), in

CH frontal lobe (*r*= -.55, *p*=.005), in LH frontal lobe (*r*= -.51, *p*=.009), in CH parietal lobe (*r*= -.72, *p*=.000), in LH parietal lobe (*r*= -.73, *p*=.000), in LH occipital lobe (*r*= -.56, *p*=.004) (Fig. 17).

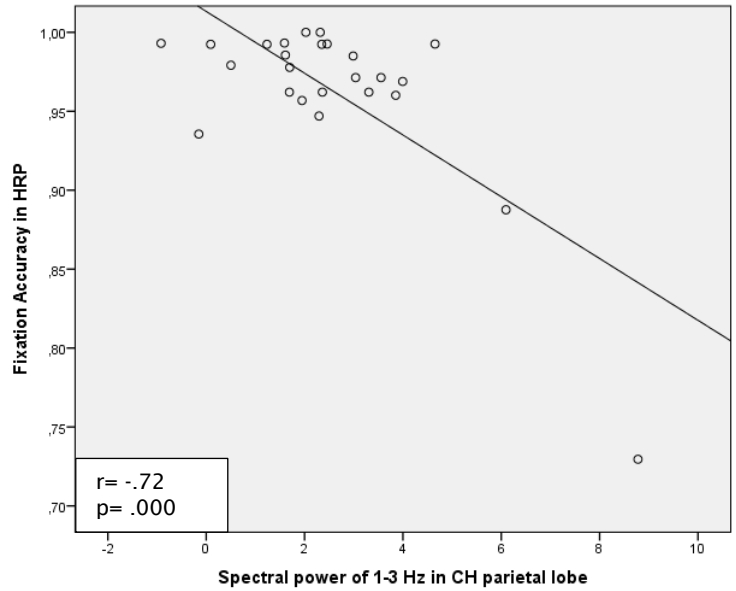

Fig.17.a. EEG spectral power in CH parietal lobe within 1-3 Hz.

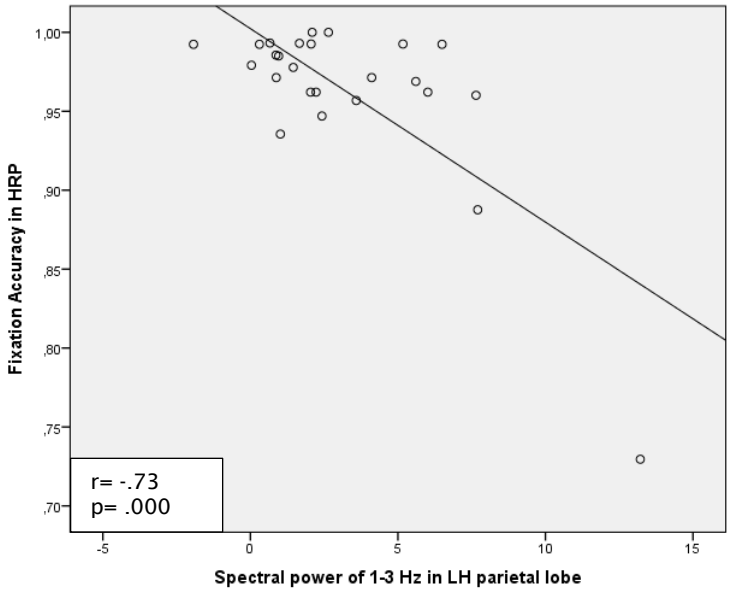

Fig.17.b. EEG spectral power in LH parietal lobe within 1-3 Hz.

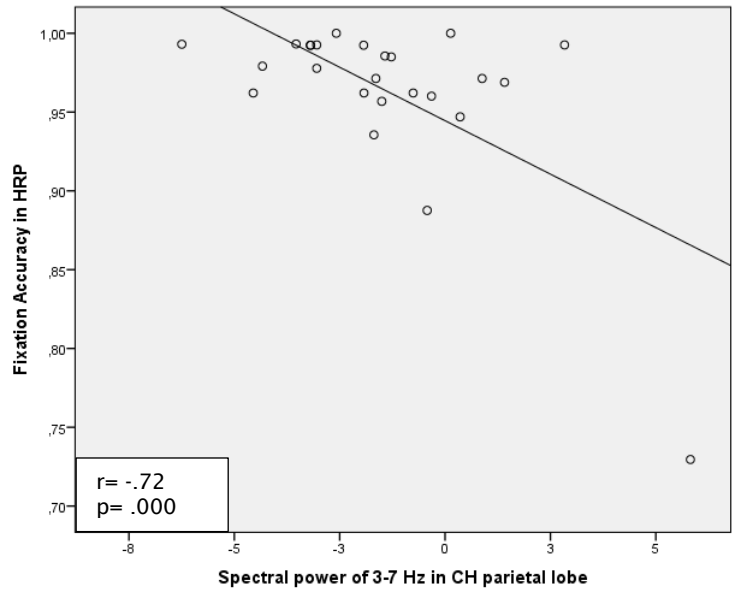

Fig.17.c. EEG spectral power in CH parietal lobe within 3-7 Hz.

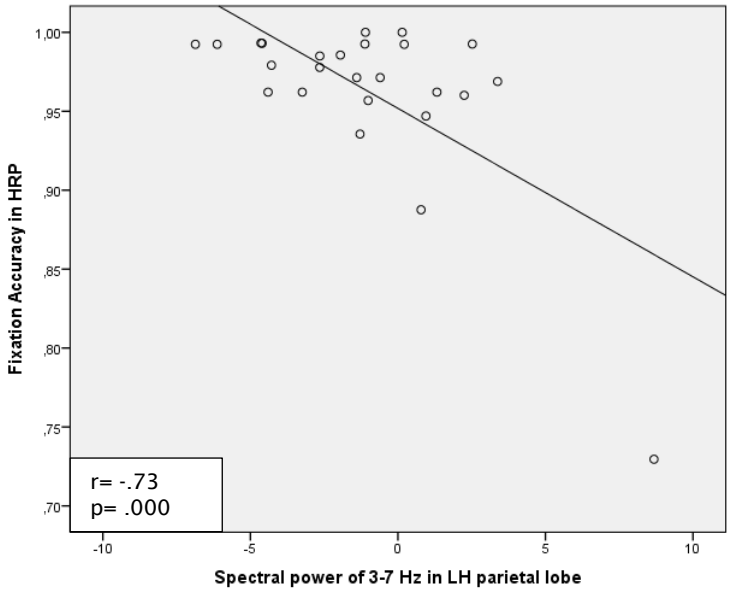

Fig.17.d. EEG spectral power in LH parietal lobe within 3-7 Hz.

Fig.17. Correlation plots of fixation accuracy and the EEG spectral power. The plots of other correlated ROIs look similar as the four shown above. The other correlated ROIs were in CH temporal lobe within 1-3 Hz, in CH occipital lobe within 1-3 Hz, in LH occipital lobe within 1-3 Hz, in CH temporal lobe within 3-7 Hz, in CH frontal lobe within 3-7 Hz, in LH frontal lobe within 3-7 Hz, in LH occipital lobe within 3-7 Hz.

3.5 Paired t-test for the differences between the spectral power in CH and LH

The spectral power of EEG signals in lesion hemisphere (LH) and contra-lesion hemisphere (CH) showed dominantly significant difference in the alpha I and total alpha bands in the parietal, occipital and frontal lobes. In parietal and occipital lobes, the mean spectral power

within alpha I (7-11Hz), alpha II (11-14Hz) and alpha (7-14Hz) in CH was higher than that in LH, while in frontal lobe, it was the opposite. The spectral power within theta (3-7 Hz) was higher in LH than in CH in the frontal lobes.

When setting the 2-tailed P-value at the level of 0.01, the following paired spectral power of EEG signal in LH and CH are statistically different: in parietal, alpha I (CH, 3.87±3.84; LH, 2.66±4.06 ; $t(24) = 4.35$, $p = .000$), alpha II (CH, -1.39±3.60; LH, -2.28±3.90; $t(24) = 3.69$, $p = .001$), alpha (CH, 1.69±3.32; LH, 0.62±3.62; $t(24) = 4.86$, $p = .000$); in occipital, alpha I (CH, 4.24±3.46; LH, 3.00±4.05; $t(24) = 3.57$, $p = .002$), alpha (CH, 1.87±2.90; LH, 0.82±3.55; $t(24) = 3.66$, $p = .001$) ; in frontal alpha I (CH, 1.58±3.06; LH, 2.20±3.09; $t(24) = -3.43$, $p = .002$), alpha (CH, -0.36±2.85; LH, 0.20±2.87; $t(24) = -3.31$, $p = .006$) (Fig. 18).

Besides, when setting 2-tailed P-value at the level of 0.05, the following paired spectral power of EEG signal in LH and CH are also statistically different. In occipital, alpha II (CH, -1.49±2.98; LH, -2.27±3.57; $t(24) = 2.53$, $p = .018$); in frontal, alpha II (CH, -3.11±2.94; LH, -2.63±3.00; $t(24) = -2.23$, $p = .035$), theta (CH, 0.67±2.64; LH, 1.31±2.82; $t(24) = -2.52$, $p = .019$) (Fig. 18).

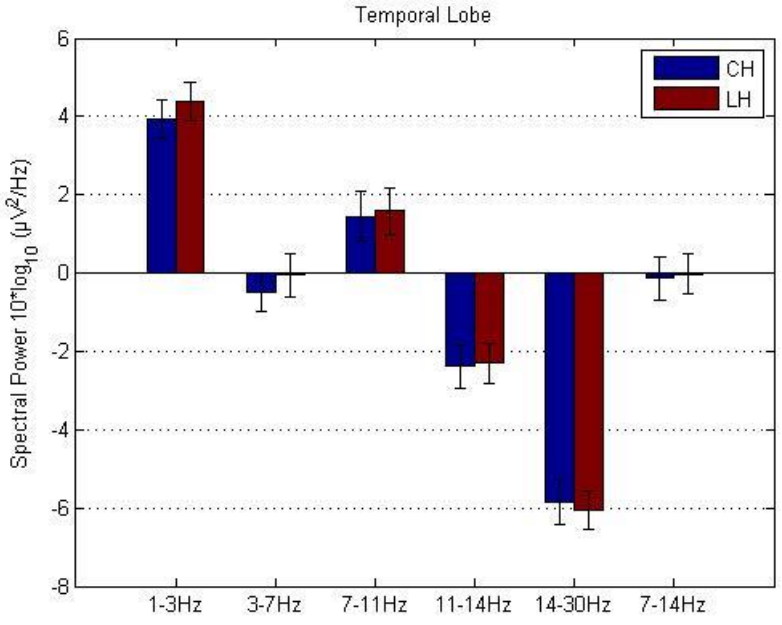

Fig.18.a. The EEG spectral power comparison between temporal lobes.

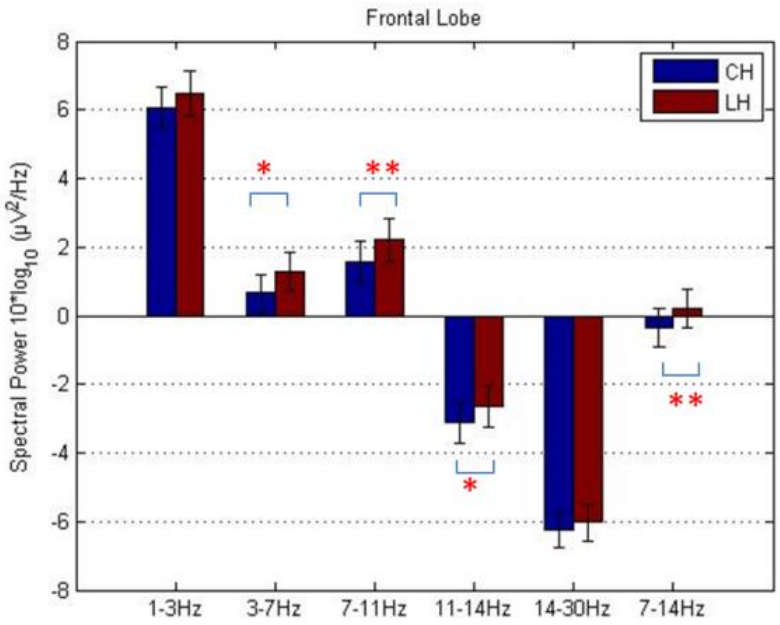

Fig.18.b. The EEG spectral power comparison between frontal lobes.

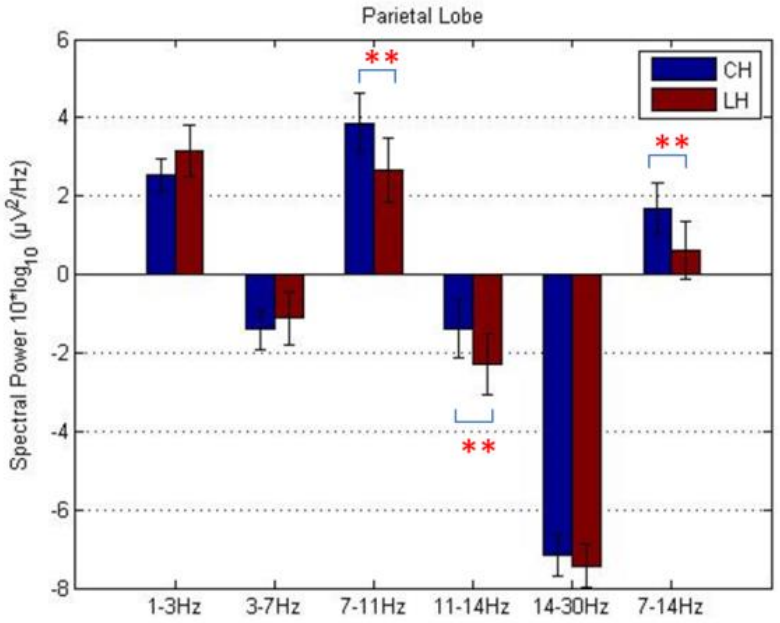

Fig.18.c. The EEG spectral power comparison between parietal lobes.

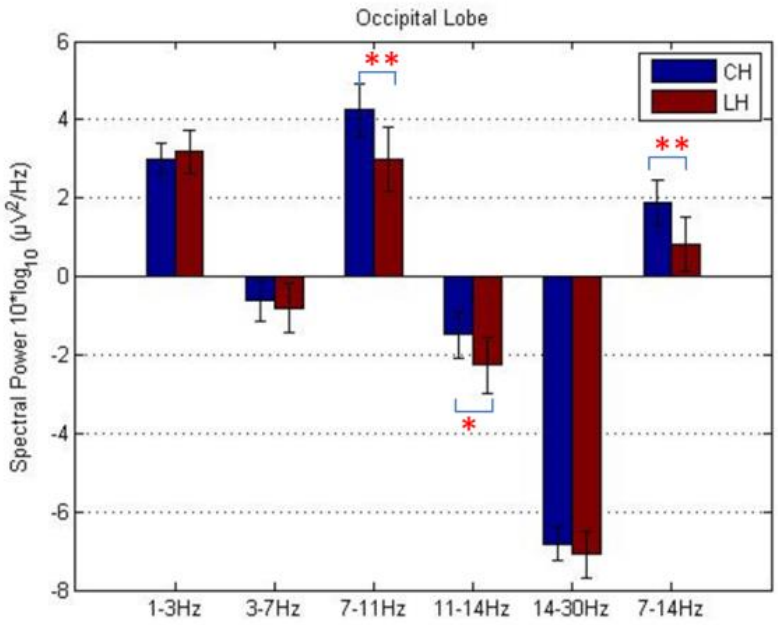

Fig.18.d. The EEG spectral power comparison between occipital lobes.

Fig.18. Comparison of the EEG spectral power between CH and LH by paired t-test. ** $P < 0.01$, * $P < 0.05$. The spectral power of alpha I (7-11 Hz), alpha II (11-14 Hz) and alpha (7-14 Hz) frequency bands showed statistically significant difference between CH and LH. The ones in parietal lobe and in occipital lobe were higher in CH than that in LH, while the ones in frontal lobe were the opposite. Additionally, the spectral power of theta (3-7 Hz) band in frontal lobe was higher in LH than that in CH.

4. Discussion

The study was designed to delineate in occipital stroke patients how the topographic visual field defect is related to other impairments of visual functions, how visual function impairment and electrophysiological markers are related with each other, and how occipital cortex stroke affects electrophysiological parameters of brain function.

4.1 Correlations between topographic visual field defect and other visual function parameters

There is an extensive body of literature on visual field defects in neurology and ophthalmology, but there is surprisingly little literature concerning the relationship between visual field loss, hereafter termed "topographic visual field defect" and other visual parameters. In this study, the hypothesis was that topographic visual loss, such as the average visual field threshold, the accuracy and the reaction time in the contra-lesion-side visual field and in the ipsi-lesion-side visual field, might correlate with other "non-topographic" visual dysfunctions, such as visual acuity, contrast sensitivity, reading speed, dynamic vision or phasic alertness. It is generally assumed that such non-topographic functions just require a central visual field to carry out the tasks. But because recent observations suggest that a local lesion in the visual cortex can lead to brain-wide network changes, the question arose as to the possible relationship between both types of visual dysfunction. Namely, it is conceivable that larger visual field defects may also lead to greater impairments of the "non-topographic" visual dysfunctions.

The results of the present study showed, however, that there were no statistically significant and meaningful correlations between the topographic visual field parameters and the other non-topographic functional visual parameters. Yet, some parameters which were obtained with different visual function tests and which share some common features showed statistically significant correlations. Specifically, one group of parameters (Group A) were found to positively correlate with another group of parameters (Group B). Group A parameters are those related to processing speed and attention, i.e. the mean and standard deviations of reaction time in the TAP-alertness test with the subtests "with warning" and "without warning". Group B parameters were the reaction times in HRP of the contra-lesion-side visual field, the ipsi-lesion-side visual field, the central 4.8° in the contra-lesion-side visual field and the central 4.8° in the ipsi-lesion-side visual field. Thus, group A and B

parameters had in common the reaction time to visual stimuli which were presented on the screen. This suggests that reaction time in different tasks (a measure of temporal processing) correlated with each other. This suggests that processing speed may be a basic mechanism in both types of tasks.

In addition, fixation accuracy in HRP and fixation control in both contra-lesion-side eye and ipsi-lesion-side eye in perimetry were significantly correlated with TAP_Kenn in the phasic alertness test and they were correlated with the correct rate when the gap position in the dynamic vision test was towards the right. These correlations can be best explained in that they share attention as an underlying mechanism. Fixation accuracy in HRP and fixation control in perimetry indicated how well patients could concentrate on the fixation point of the tests. And correspondingly, TAP_Kenn was aimed at measuring visual attention as well.

In brief, this study did not reveal any scientifically significant and meaningful correlation between the parameters representing topographic visual field and the other functional visual parameters. One reason might be that the visual field defect in occipital stroke patients are mostly hemianopia. The topographic visual fields of a group of hemianopia patients lack of gradual change. Perhaps some correlation could be found in other patient groups which show larger visual field defect gradient. Based on these observations a reasonable conclusion seems to be that, after all, a half intact visual field or even a half intact central visual field is sufficient for hemianopic patients to perform “non-topographic” visual tasks which are presented in the central visual field.

4.2 Certain visual functions correlate with specific EEG frequency bands

The results revealed statistically significant correlations between EEG spectral power parameters within specific frequency bands in certain ROIs and several visual parameters: contrast sensitivity, phasic alertness, foveal vision, dynamic vision, fixation control and fixation accuracy.

Most of these ROIs which correlated with visual parameters were found in occipital lobes and parietal lobes, where different types of visual functions correlated with different frequency bands. This is not unexpected because the primary visual cortex, localized in the occipital cortex, is the dominant vision processing centre in the brain. Previous studies found similar results that visuospatial attention produced a frequency-specific modulation of neuronal

oscillations in occipital and parietal cortices [36] and different EEG frequencies reflect different cognitive process [37].

But the occipital pole is not the only region where correlations between vision parameters and the EEG spectral power were found. In fact, several vision parameters were shown to correlate with different frequency bands also in the parietal lobes, which included contrast sensitivity, phasic alertness and dynamic vision. *Contrast sensitivity* correlated positively with EEG spectral power within alpha II in the occipital lobe of the LH and within beta in the occipital lobes both CH and LH, and in the parietal lobe of the CH. *Phasic alertness* correlated positively with the theta power band in the occipital lobe of the LH and in the parietal lobes of both CH and LH; and phasic alertness is also correlated positively with the EEG spectral power within the alpha I in the parietal and occipital lobes of the CH. The function of the phasic alertness test is to evaluate the level of alertness and attention. And this finding is coincident with former studies showing that lower alpha (alpha I) reflects attentional demands as alertness and expectancy [38-42]. *Dynamic vision* correlated negatively with the EEG spectral power in the delta band in the occipital lobe of the LH.

Interestingly, foveal vision correlated positively with the EEG spectral power in lower frequency bands of the occipital lobe, i.e. delta and theta. Fixation control and fixation accuracy correlated negatively with the EEG spectral power in delta and theta bands. But this negative correlation in delta and theta bands was actually much more widespread than for all other visual functions we tested as it affected all four lobes: occipital, parietal, temporal and frontal lobes all correlated negatively to some extent. Thus, it appears that fixation ability- as quantified by both fixation control in perimetry and fixation accuracy in HRP- is a very prominent functional correlate of electrophysiological activity in the brain. It engages more "brain space" than any of the other visual functions we tested. How could this be explained?

The fovea makes up only about 0.01% of the retina area, yet its representation is at least 8% of the striate cortex [43]. This explains its higher resolution for visual processing. It is, in fact, rather remarkable that the function of only 50% of the foveal retina can be seen in the volume conduction changes of EEG recordings covering the occipital processing centres of vision. Fixation control and fixation accuracy show how well patients can keep their eyes at the fixation point and react to colour or brightness changes at the fixation point. These processes rely both on good foveal vision and on being able to hold the eye movements steady in the right place. In addition, good fixation performance needs information integration and

judgement (“what colour is it?”). Therefore, proper fixation requires the combination of eye movement control, detection and cognitive ability, functions which are controlled by brain structures in different lobes and not just the occipital lobes. Parietal, frontal and even temporal lobes have regions critical for fixation including eye movements (frontal eye fields), parietal-temporal fields (attention control by the parietal-temporal junction, PTJ) and occipital regions (for detection and analysis). In perimetry and in the HRP test, a correct reaction to the visual stimulus presented on the screen is only possible if physiological and cognitive processes are synchronized, which involves a holistic network of functional connectivity in the brain and is not controlled by only one local brain region. A visual perception framework is required and we need to identify cortical regions associated with different functions and their integration: modality-specific processing (i.e. visual, auditory, motor, or olfactory), visual domain-specific processing (i.e. “what” versus “where”, or face versus visual context) and visual feature-specific processing (i.e. colour, motion, or spatial location). And there is also the visual memory which is a “constructive” process, in which features or components from disparate cortical regions bind together to form a coherent whole [44].

Moreover, fixation control and accuracy and perimetric foveal vision all correlate (mostly negatively) with the same EEG frequency bands, delta and theta. But there is one point difficult to explain: the foveal vision correlated positively with the lower EEG frequencies, while fixation control and accuracy correlated negatively with it. This is possibly because both event-related desynchronization and synchronization (ERD and ERS) are meaningful when facing different demands. They just play different roles in different situations. To clarify these finding, probably other parameters of brain oscillations should be considered, such as phase, coherence and connectivity. Since time or periodicity is an important element to investigate perceptual and cognitive processes [45], more dynamic analysis will be needed to obtain a more detailed understanding of the electrophysiological and functional relationship after stroke.

The change of multiple frequencies could be interpreted from a network perspective as follows: the entire brain is engaged in the task, as if the same frequency bands need to be lowered (“suppressed”) for fixation to work properly. This suppression may be termed “delta-theta silencing”. Perhaps this slow wave “silencing” is a direct (or indirect) requirement for information to be integrated more globally so that a unity of multiple aspects can be integrated to be able to fixate and respond to stimuli properly such as eye movement control, attention, detection and motor control for the manipulating the response button. How this

rather global EEG response of a “delta-theta silencing” fits to the proposal that during mental activity different neuronal networks may start to oscillate at different frequencies needs to be explained. Conceivably, the integration of higher frequency oscillations and lower ones is a complex affair and the volume analysis of spectral powers is not ideal to reveal sufficient insight into post-stroke visual disturbances of vision in the foveal region. Further, coherence analysis is called for to be able to obtain more and deeper information about the underlying mechanisms.

4.3 Electrophysiological features of the control vs. damaged hemisphere

None of the frequency bands in the temporal lobes showed statistically significant differences between the EEG spectral power in CH and in LH. In contrast, in the occipital, parietal and frontal lobes, differences in spectral power could be observed between both hemispheres. It means that the lesion in the occipital lobe did not affect the spectral power in the temporal lobe but that in the other lobes.

To interpret this result in the perspective of brain functions, the four lobes’ contribution to neuropsychological functions is as follows: the frontal lobe is involved in motor planning and motor output, while the prefrontal cortex is specifically needed for initiating activities, planning, holding critical information ready to use, changing mental set from one line of thinking to another, monitoring the effectiveness of one’s action, inhibiting plans and actions that are ineffective or self-defeating; the parietal lobe is a somatosensory region and the site for multisensory integration; the temporal lobe is the region where sound is processed and the region for auditory language and speech comprehension systems; and the occipital lobe is home to the visual cortex [4]. In fact, multisensory integration of auditory and visual information is achieved more in subcortical structures, such as superior colliculus in the midbrain [46]. The parietal lobes are involved in visuospatial processing and the frontal lobes manage eye-movements control. Furthermore, the correlations that could be observed give us some clues that both parietal lobes and frontal lobes must be tightly involved in visual processing.

Since vision is perhaps the most important sense in humans and requires most information processing of the brain, it is not hard to imagine that when the visual cortex in the occipital lobe is damaged by stroke, the functionally connected parietal and frontal lobes are affected as well. One study discovered the strong functional coupling between frontal and occipital brain

regions, possibly indicating the control of posterior cortical activation by anterior brain areas [47]. There are also neuroimaging studies on visuospatial working memory task indicating central executive processes related to the fronto-parietal network [48]. Posterior parietal cortex is engaged in selective attention [49]. Frontal lobe damage leads to diminished visual attention [50], and both frontal and parietal lobes contribute to competitive visual processing [51]. And the theta long-range network including frontal and parietal cortices were shown to indicate integration of sensory information into executive control components of motor behaviour [52].

Interestingly, the present study showed that the spectral power of alpha I (7-11Hz), alpha II (11-14Hz) and alpha (7-14Hz) were higher in the occipital and parietal lobes of the contra-lesion hemisphere (CH) than in the lesion hemisphere (LH), which was the opposite in the frontal lobes, where it was higher in LH. Additionally, the theta band spectral power in the frontal lobe was also higher in LH than that in CH, similarly as the alpha in frontal lobe. Similar findings were noted in a visual spatial attention task. It was found that frontal cortex showed stronger phase coupling with posterior sites that are contralateral to the attended hemi-field than ipsilateral sites, that a shift of attention selectively modulated excitability of the contralateral posterior parietal cortex and that the posterior modulation of alpha activity was controlled by prefrontal regions [53]. Another study provided evidence that during top-down processing in a working memory task, alpha power increased at prefrontal but decreases at occipital electrode sites, thereby reaching a state in which alpha power and frequency became very similar over large distances [47]. This “contralaterality effects” was confirmed in a magnetoencephalography study [36].

In fact, the spectral power of alpha I (7-11Hz), alpha II (11-14Hz) and alpha (7-14Hz) showed significant differences with $p<0.01$ in the occipital, parietal and frontal lobes between CH and LH. Note, however, that only for alpha II in the parietal lobes was the difference at a high level of significance $p<0.01$, whereas in the occipital and frontal lobes the significance level was at the lower $p<0.05$ level. Therefore, it was the alpha I frequency band that showed the greatest difference in the occipital, parietal and frontal lobes between CH and LH. In addition, the EEG spectral power in theta in frontal lobes also were different between CH and LH at $p<0.01$ level.

It should be noted that the EEG recordings in this study were obtained during a resting-state and they were not event-related potential (ERP). So far, little literature has directly illustrated

the relationship between the electrophysiological markers from resting-state EEG and different visual functions, but many ERP papers have revealed the spectral power change in different tasks and speculated the functional meaning of alpha band and theta band in visual cognitive processing, from which the possible functional meaning of alpha and theta could be deduced.

4.4 Interpretation of alpha and theta frequency bands

4.4.1 Interpretation of the function of alpha frequency band

The alpha band is the dominant rhythm in the human brain during conditions of mental inactivity [47]. The alpha-band oscillations have two roles, inhibition and timing, which are closely linked to two fundamental functions of attention (suppression and selection) and enable controlled knowledge access and semantic orientation [54, 55].

Synchronous alpha oscillations reflect a basic processing mode that controls the access system. Particularly during a decrease in alpha power, they reflect topographically specific neural network activity that is related to the access of semantic information [56]. During an early stage of perception, alpha "directs the flow of information" to those neural structures which represent information that is relevant for encoding. Alpha enables access to stored information by inhibiting task-irrelevant neuronal structures and by timing cortical activity in task-relevant neuronal structures [57]. In that sense, one could think of the alpha band as a kind of "noise filter".

Recent studies revealed that cross-frequency phase coupling and modulations of alpha power dissociate between retention of relevant and suppression of irrelevant information in visual working memory [58]. Different parameters of ongoing oscillatory alpha activity (~10 Hz) can predict whether a visual stimulus will be perceived or not [59]. In a visual discrimination task, good perceptual but not memory performance was related to low resting alpha amplitudes, which showed that low alpha amplitudes might be an indicator for good perceptual performance [60].

As in the present study, in most psychophysiologcial studies the alpha band is usually divided into lower alpha and upper alpha bands. The lower alpha band (alpha I) is more sensitive to reflect expectancy, alertness and attentional processes [38-40], while the upper alpha (alpha II)

band is particularly sensitive to semantic memory demands as encoding and processing semantic information [37, 61, 62].

A significant task-related power change that responds selectively to semantic processing demands was found for the upper alpha band and over the left side of the scalp [39]. Long-term (semantic) memory demands and performance are positively correlated with task-specific desynchronization (decrease or suppression of power) in the upper alpha band [41, 63].

While upper alpha may be important for the reactivation of long-term memory codes in short-term memory, theta reflects working memory functions [64]. Both alpha and theta bands reflect cognitive and memory performance. Good performance is related with an increase in alpha power but a decrease in theta power and a phasic (event-related) decrease in alpha but increase in theta [41].

In the present study, the lower alpha band (alpha I) was found to be an indicator of attention and increase in the higher alpha band (alpha II) power was linked with better performance in contrast sensitivity. The amplitude of resting-state alpha band was also shown in this study to be significantly changed due to a lesion in the occipital lobe in hemianopia patients, which stresses alpha band's key role in vision.

4.4.2 The subdivision of alpha (7-14Hz) into alpha I (7-11Hz) and alpha II (11-14Hz)

The correlation results showed that contrast sensitivity correlated positively with the EEG spectral power in alpha II frequency band and phasic alertness correlated positively with alpha I. But neither of them showed correlation with total alpha (7-14Hz), whose frequency width was the sum of alpha I plus alpha II. Therefore, it is meaningful to split alpha into alpha I and alpha II during calculating and analysing, in order to find out the respective relationship.

The concept to divide alpha into lower alpha and upper alpha has been accepted by the academic world for decades [38]. And the sub-division can already be considered to be classic as it contributed to the discovery of many functional correlations. If all the frequency bands could be ideally divided correctly according to the actual functional narrow frequency fragments, it might be possible to find out more correlations between visual functional parameters with the EEG spectral power.

Furthermore, I hypothesize that different univocal brain function would depend on the electrophysiological activity within different specific narrow frequency fragments rather than the standard delta, theta, alpha and beta frequency bands. Tasks usually require more than just one single piece of brain function, so that the tasks or the test results could be found to correlate with more than one EEG frequency fragment.

4.4.3 Interpretation of the function of theta frequency band

The thalamus can act as an independent pacemaker of alpha and theta rhythms [65]. On one hand, theta influences neural network activity; on the other hand, it is important for successful performance of several cognitive tasks, such as pattern recognition, memory, sequence learning and navigation [66].

Theta band oscillation and synchrony is involved in mechanisms underlying sensorimotor integration. Theta synchronization in the limbic system provides voluntary motor systems with updated feedback to the changing environmental (sensory) conditions [67]. Furthermore, intracranial recording from human cortex revealed evidence of high-amplitude theta oscillations throughout the brain, including the neocortex [68]. And “frontal theta” is a major oscillation of the human frontal cortex and has a response-controlling function [69].

Theta frequency is the dominant frequency of the hippocampal formation and reflects hippocampal activity [37]. Theta oscillations functionally associate with memory processes [70] and are positively correlated with the ability to encode new information [41]. Memory information is stored within a distributed theta network and matched with an incoming sensory trace at posterior brain areas [42]. Short-term (episodic) memory demands lead to a synchronization (increase in band power) in the theta band [63]. Phase-locked theta (i.e. the synchronization with a stimulus) reflects top-down regulation processes mediating information between memory systems and is partially involved in the modulation of the visual P2 component [71]. In addition, theta oscillation plays a functional role in the representation and processing of spatial information for navigation [72].Theta oscillation can be conceived as the navigation rhythm through both physical and mnemonic space, facilitating the formation of maps and episodic/semantic memories [73].

Even though the complexity of the role of different frequency bands is an important topic, it would go beyond the scope of this thesis to solve their complex interactions. Yet, based on the

present findings, together with some educated guesses and speculations, it is worth considering how the brain works as a whole to mediate (residual) vision after stroke.

4.5 A holistic hypothesis of how the brain mediates residual vision in stroke

From all the results of this study, I come up with a sketchy hypothesis on the rules how the damaged brain mediates visual functions after stroke.

The brain contains different functional centres, like the visual centre in occipital lobes, auditory centre in temporal lobes and body sensorimotor centre in parietal lobes. However, the brain functions are not executed by one single functional centre or a single lobe, but by a more coordinated process involving many different functional centres in the brain, which need to be coordinated. This coordinating process consists of information spreading throughout the brain network and/or orders from the multiple centres to collect and integrate information. Most of the messages which travel through the brain are carried by electrical signals, although chemical/hormonal and other modulators exist. The electrophysiological messages may contain many elements. The precision to accurately pass the messages and their respective elements would depend on the electrical signals within specific frequency fragments. The following analogy might help to understand the function of such complex information streams which spread throughout the brain:

Let us consider electrophysiological frequency streams to act like an individual gossip newsboy knocking at each attracting door to spread news and to collect news. Very often, several newsboys would wander through the streets in communities together as a group. But not all residents in each community would respond to all newsboys, but residents would only respond to the newsboys if they carry their target news. One house with its resident in the community takes charge of one certain element of the many different messages. But which resident would open their door for which newsboy who carries the right target information? This would depend on the attractiveness of the news content that the newsboy carries. Afterwards, the residents in different houses in the community integrate their separately collected elements of the messages in their own way, and then spread out signals to other functionally connected communities after integrating all the messages they received from different newsboys. Similar to this newsboy analogy, a piece of message in the brain would be delivered by a group of different frequency fragments. The group of frequency fragments

would travel through the brain, bringing the outside information to the corresponding neurons assembly responsible for handling this kind of functional information and/or collecting the orders from the functional neurons in the brain. But which functional neuron assembly might react to which frequency fragment? It would possibly depend on the amplitude of the matching frequency fragment which contributes to the overall spectral power.

In this study, I could only observe the sum of all activity which can be recorded by a few electrodes; so the information of my study can only be rather course. The physiological signal that could be recorded is thus the cluster or sum of many near-to-each-other located functional neurons which may or may not form a functional centre in the brain. Therefore, the scalp EEG displays only an integrated electric signal with very low spatial resolution which is far below the resolution needed to uncover all the functional elements of the system to detect, how one functional centre carries information and spreads it to other functional centres in the brain. Therefore, even though it is not possible to untangle all the individual elements of the neurophysiological network, the results of my study still reveals important basic information how a brain lesion in the central visual system affects other regions of the brain. It shows that the disturbance of a local region has widespread consequences for the system, i.e. the brain network, even in regions which are rather remote from the acute damage site and which are not considered to be "visual".

To use another analogy, a lesion in the brain's cortex, for example a hematoma or an infarction, is like an accident destroying houses and their residents inside. The corresponding elements of the messages cannot be collected from newsboys and the community suffering destroyed houses would have the problem of not being able to integrate information and even spread out the information to other communities. As for the recovery process, if the accident destroys only a single house or few houses, the residents nearby might be able to compensate for the lost function by collecting and processing the newsboy information they obtain. After all, the newsboys still deliver the information to whomever they meet, yet now the information is being processed by other members of the community. In other words, if the brain tissue is only partially damaged, the information can be processed, though perhaps not with the same precision or speed; but if a whole community is destroyed (complete damage), then it is not possible to recover the function through compensation by other community members.

In prior studies by others, the integration and functional coupling between the activated cortical regions during human action observation has already been discovered, indicating the extent of interregional communication between different brain regions [74]. And many detailed mechanisms are now being discussed concerning the role of "phase coupling" between brain sites, phase synchronization across frequencies and phase-locking to external events [75]. Cross-frequency phase synchronization has been viewed as a brain mechanism of memory matching and attention [42], and the loss of phase coupling and synchronization is also one consequence of vision loss [76].

4.6 Limitations of this study

The present study has several limitations which need to be considered when interpreting the findings and their meaning. One limitation of the present study is the low spatial resolution of the EEG signals. Although a better resolution would be preferable, yet different new insights were made with regard to functional correlations of brain activity. And the reader should also be aware of other limitations of the present experiment.

Another limitation concerns the behavioural assessments. The international reading speed test (IResT) has so far only been tested in young normally-sighted readers (18-35 years old) [29], but the patients recruited in this study had an average age of 57.6 ± 10.7 years. This limitation could be overcome in future studies by using a normal, age-matched control group who carries out the same test.

Another limitation concerns the pre-processing of the EEG signals, in which I did not employ the independent component analysis (ICA). However, I considered the manual pre-processing to remove artefacts in the EEG signal as sufficiently adequate given the course spatial resolution of the signal. In any event, any errors in artefact removal would have increased the variability of the correlations and hence would have biased the EEG results against my hypotheses. I therefore argue that even if the manual pre-processing would be flawed, I still discovered rather consistent correlation patterns, which argues for, and not against, the power of my analysis. Furthermore, there is no comparison of the patients' results with age-matched controls. Collecting data from normal control subjects would have revealed if any EEG recordings in the CH were any different from the normal brain state. This should be considered in future studies.

4.7 Outlook

Given the results and the acknowledged limitation of this study, further studies might include the following aspects:

- recruiting age-matched healthy subjects as a control group,
- carrying out coherence and connectivity analyses of the EEG data,
- adding MRI analyses in order to quantify the volume and precise locations of the lesions and to differentiate higher visual associations,
- To combine the EEG and MRI analysis in order to take advantage of both methods together, and
- To study the potential of different treatment methods to alter the course of vision recovery.

5. Conclusions

Previously, little has been known about the electrophysiological markers of visual functions and dysfunctions in chronic occipital stroke patients. It was the aim of this study to elucidate the correlation between functional visual parameters and the electrophysiological parameters and to learn more about the differences of EEG spectral power between the lesion hemisphere (LH) and contra-lesion hemisphere (CH) in the chronic occipital stroke patients.

Twenty-five patients with occipital lobe lesions were tested for visual acuity, contrast sensitivity, reading speed, dynamic vision, visual alertness, standard static perimetry and high resolution perimetry (HRP). In addition, a five-minute resting state EEG with eyes closed was recorded to be able to correlate between the performance in vision tests with EEG spectral power of different frequency bands. In this manner, I could also calculate the EEG spectral power of different frequency bands within different regions-of-interest (ROIs) and compare the LH and CH electrophysiological status.

The data indicates that while some vision parameters (contrast sensitivity, visual attention, foveal vision, dynamic vision, fixation control and fixation accuracy) are associated with oscillatory activity in the occipital and parietal lobes of both hemispheres, other parameters (visual acuity, reading speed or reaction time) are not. The EEG spectral power within alpha I, alpha II and whole alpha was higher in CH than in LH in the parietal and occipital lobes, while in the frontal lobes it was the opposite. Spectral power in the theta-band was higher in LH than in CH in the frontal lobes. That is, the spectral power from resting-state EEG was found to be changed not only in the lesioned lobe but also in the functionally connected lobes. Thus, the whole brain network was changed after a rather focal lesion.

Further studies are now needed to characterize more subtle changes in the brain, such as functional activity network alteration. With the benefits of the present findings, I hope to have laid the groundwork of better understanding the mechanism of vision loss after stroke, which could be a starting point to come up with more effective ways to help vision restoration and recovery.

Summary

Background: Lesions in the occipital lobe lead to hemianopia, but it is unknown to what extent parameters of vision loss relate to brain electrophysiological activity and what the electrophysiological changes are in the lesion hemisphere (LH) compared to the contra-lesion hemisphere (CH).

Aims: To investigate the correlation between different parameters of visual functions and the brain-wide spectral power of different frequency bands from resting state EEG in hemianopia patients and to compare the EEG spectral power between LH and CH.

Methods: Twenty-five patients with occipital lobe lesions were tested for visual acuity, contrast sensitivity, reading speed, dynamic vision, visual alertness, standard static perimetry and high resolution perimetry (HRP). A five-minute resting state EEG with eyes closed was recorded as well. The correlation between the performance in vision tests and the EEG spectral power of different frequency bands was calculated with $p<0.01$. The EEG spectral power of different frequency bands within different regions-of-interest (ROIs) were compared between LH and CH by paired t-test.

Results: Different functional visual parameters correlated with the EEG spectral power of specific frequency bands: 1. *Contrast sensitivity* correlated positively with alpha II (11-14 Hz) and beta (14-30 Hz) in the occipital and parietal lobes. 2. *Phasic alertness* correlated positively with alpha I (7-11 Hz) and theta (3-7 Hz) in the occipital and parietal lobes. 3. *The foveal vision* correlated positively with delta and theta in the occipital lobes. 4. *Dynamic vision* correlated negatively with delta (1-3 Hz) in the occipital lobe. 5. *The fixation control in perimetry* correlated negatively mainly with delta and theta in the occipital and parietal lobes. 6. Finally, *fixation accuracy in HRP* correlated negatively with delta in the occipital and parietal lobes, and with theta in the parietal and frontal lobes. Other functional visual parameters showed no correlation with the EEG spectral power such as visual acuity, reading speed, and different perimetry measures including detection accuracy and reaction time in both visual field halves in HRP, mean threshold, absolute and relative defects and correct reaction in standard static perimetry test.

The EEG spectral power within alpha I (7-11 Hz), alpha II (11-14 Hz) and total alpha (7-14 Hz) was higher in the parietal and occipital lobes of the CH than in LH, while in the frontal lobes this was reverse, where the spectral power of theta was higher in LH than in CH.

Conclusion: While some vision parameters (contrast sensitivity, visual attention, foveal vision and dynamic vision) are associated with oscillatory activity in the occipital and parietal lobes of both hemispheres, other parameters (visual acuity, reading speed, accuracy or reaction time) are not. Thus, not all aspects of vision loss are related to occipital/parietal oscillatory activity as measured by spectral power. Furthermore, spectral power from resting-state EEG is changed not only in the damaged lobes but also in the non-damaged lobes. This is compatible with the proposal that local visual system damage has widespread consequences for the whole brain. Studies are now needed to characterize more subtle changes in the brain, such as functional connectivity network alteration and their relationship to parameters of vision loss.

Key words: occipital stroke, hemianopia, visual function, EEG, spectral power

Zusammenfassung

Hintergrund: Läsionen im Okzipitallappen führen zur Hemianopsie, aber es ist nicht bekannt, inwieweit Parameter dieses Sehverlusts auch hirnelektrophysiologische Aktivität beeinflussen und welche elektrophysiologischen Veränderungen in der geschädigten Hemisphäre (LH) im Vergleich zur ungeschädigten, kontralateralen Hemisphäre (CH) zu finden sind.

Ziele: Es soll nunmehr die Korrelation zwischen verschiedenen Parametern der visuellen Funktionen (Verhalten) und der gehirnweiten EEG-Power unterschiedlicher Frequenzbänder im Ruhezustand (Physiologie) bei Hemianopsiepatienten untersucht werden, einschließlich des Vergleichs der EEG-Spektralmuster zwischen LH und CH.

Methoden: Fünfundzwanzig Patienten mit Hirnläsionen im Hinterhauptslappen wurden auf die Sehschärfe, Kontrastempfindlichkeit, die Lesegeschwindigkeit, dynamische Vision, visuelle Aufmerksamkeit, Standard statische Perimetrie und hoher Auflösung Perimetrie (HRP) hin geprüft. Darüber hinaus wurde ein Fünf-Minuten Ruhezustand EEG mit geschlossenen Augen aufgezeichnet. Die Korrelation zwischen der Sehleistung und der EEG Spektralmuster unterschiedlicher Frequenzbänder wurde mit $p < 0.01$ statistisch berechnet. Die EEG power unterschiedlicher Frequenzbänder wurde in verschiedenen vorher definierten Hirnregionen (ROIs) zwischen LH und CH mittels gepaartem t-Test miteinander verglichen.

Ergebnisse: Verschiedene funktionelle, visuelle Parametern korrelierten signifikant mit EEG Spektralmustern bestimmter Frequenzbänder: 1. Kontrastempfindlichkeit korrelierte positiv mit alpha II (11-14 Hz) und beta (14-30 Hz) okzipital und parietal; 2. phasische Alertness korrelierte positiv mit alpha I (7-11 Hz) und theta (3-7 Hz) okzipital und parietal; 3. das foveale Sehen korrelierte positiv mit delta- und theta okzipital; 4. dynamisches Sehen korrelierte negativ mit delta (1-3 Hz) okzipital; 5. Fixationskontrolle in der Perimetrie korrelierte negativ vor allem mit delta und theta okzipital und parietal; und 6. Fixationsgenauigkeit bei HRP korrelierte negativ mit Delta okzipital und parietal und mit theta temporal und frontal. Bei anderen visuellen Parametern fanden sich keine Korrelationen mit der EEG Spektralleistung; das betraf die Sehschärfe, Lesegeschwindigkeit und verschiedene HRP-Perimetriewerte wie Entdeckungsgenauigkeit und Reaktionszeit in beiden Gesichtsfeldhälften. Und es fanden sich keine Korrelationen mit der durchschnittlichen Wahrnehmungsschwelle, absoluten und relativen Defekte und richtig Reaktionen in der statischen Perimetrie.

Die EEG Spektralleistung in alpha I (7-11 Hz), Alpha-II (11-14 Hz) und Gesamt-Alpha (7-14 Hz) waren sowohl in den Scheitel- und Hinterhauptslappen der CH als auch in der LH höher, während es sich im Frontallappen umgekehrt verhielt: hier war die Spektral-Power von theta in der LH höher als in der CH.

Fazit: Während einige visuelle Parameter (Kontrastempfindlichkeit, visuelle Aufmerksamkeit, foveales und dynamisches Sehen) Oszillationen im EEG okzipital und parietal beider Hemisphären zugeordnet werden konnten, fanden sich keine Korrelationen zwischen EEG und anderen Parametern der Sehleistung (Sehschärfe, Lesegeschwindigkeit, Genauigkeit und Reaktionszeit). Daher können nicht alle Aspekte des Sehverlustes in einen Zusammenhang mit Oszillationen okzipital/parietal gebracht werden, die durch Spektralanalysen sichtbar gemacht werden können. Darüber hinaus sind die Power-Spektren im Ruhe-EEG nicht nur in lädierten sondern auch in nicht-lädierten Hirnarealen verändert. Dieser Befund unterstützt die Hypothese, dass „lokale“ Läsionen des visuellen Systems weitreichende, *globale* Konsequenzen für das ganze Gehirn haben. Es werden nun Studien zu subtileren Veränderungen im Gehirn benötigt, insbesondere in Bezug auf mögliche Veränderungen funktioneller Konnektivität globaler, neuronaler Netzwerke.

Schlüsselwörter: Schlaganfall, Okzipitallappen, Hemianopsie, Sehfunktion, Perimetrie, EEG, Spektralanalysen

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Ehrenerklärung

Ich erkläre, dass ich die der Medizinischen Fakultät der Otto-von-Guericke-Universität zur Promotion eingereichte Dissertation mit dem Titel:

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ohne sonstige Hilfe durchgeführt und bei der Abfassung der Dissertation keine anderen als die dort aufgeführten Hilfsmittel benutzt habe.

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