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ALPHA OSCILLATIONS INDEX THE FUNCTIONALITY AND THE PLASTIC CHANGES OF THE VISUAL SYSTEM

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ABSTRACT

Brain oscillations in the alpha range have been shown to strongly influence visual awareness and support the intrinsic tendency of the visual system to process information periodically, suggesting that alpha rhythm may reflect a reliable index of the excitability and functionality of the posterior cortices, and hence of the visual system. Therefore, the present work described a series of studies aiming at investigating the role of alpha oscillations as a biomarker of the functionality of the visual system and as an index of the plastic modifications occurring in the visual system in response to the presence of lesions to the visual cortices or induced by external stimulations. The studies presented in chapter 5 and 6 provided strong evidence that posterior lesions induce consistent alterations in spontaneous alpha oscillations in hemianopic patients compared to controls, both in terms of reduced alpha reactivity at the opening of the eyes and decreased functional connectivity in the range of alpha. Moreover, damage to right posterior cortices was demonstrated to induce more severe alpha dysfunctions associated with alterations also in the theta range, suggesting a specialization of the right hemisphere in orchestrating alpha oscillations and coordinating the complex interplay among different brain rhythms. The study presented in chapter 7 investigated the role of rhythmical attentional sampling in modulating visual perceptual processing in healthy participants. The study demonstrated that the perceptual performance is strongly influenced by a rhythmical mechanism of attentional allocation, occurring at lower-alpha frequencies (i.e., 7 Hz), when a single spatial location has to be monitored, and at lower frequencies (i.e., 5 Hz), when attention has to be allocated to two spatial locations. Moreover, the two brain hemispheres seem to give a differential contribution to these rhythmical attentional sampling, with a dominance of the right hemisphere in distributing attentional resources to the entire visual field. Finally, the study presented in chapter 8 showed that prolonged trains of visual entrainment can induce long-term modulations of resting-state oscillatory activity in the range of alpha in healthy participants, suggesting that persistent modifications in the oscillatory functionality of the visual system are possible. Overall, the findings of the present project show that the functional processes and the plastic changes occurring in the visual system can be reflected in the alpha oscillatory patterns. Therefore, investigating and promoting the oscillatory activity in the range of alpha may give a substantial contribution for the development of rehabilitative protocols to ameliorate the alpha oscillatory patterns, and the hence the functionality of the visual system, in patients with brain lesions.

Chapter 1
Introduction

Human vision is based on extremely complex computations, characterized by both parallel and hierarchical information processing and by the activity of multiple pathways within the visual system. In the past few decades a wide body of evidence demonstrated that several visual abilities are susceptible to plastic modification, not only in the early stages of life (Norden, 1983; Kind, Mitchell, Blakemore, Bonhoeffer, Sengpiel, 2002), as it was previously thought, but also in the adulthood (Schoups, Vogels, Qian, Orban, 2001; Watanabe et al., 2002; Leh, Johansen-Berg, Ptito, 2006; Bridge, Thomas, Jbabdi, Cowey, 2008; Rees, 2008), due to the extraordinary ability of the visual system to change its functional and structural architecture, according to specific external requests. Crucially, more recent studies focused on investigating the oscillatory correlates of the functioning of the visual system, evidencing the existence of causal relationship between neural oscillations in the range of alpha (7-13 Hz), representing the intrinsic frequency of the posterior cortices (Rosanova et al., 2009), and visual processing (Klimesch 1997; Klimesch 1999; Cecere, Rees, & Romei, 2015; Samaha & Postle, 2015). In particular, these studies consistently showed that brain oscillations in the alpha range strongly influence visual awareness and support the intrinsic tendency of the visual system to process information periodically, within different temporal windows (Samaha & Postle, 2015), suggesting that alpha rhythm may reflect a reliable index of the excitability and functionality of the posterior cortices (Romei, et al. 2008a; Romei, Rihs, Brodbeck, &, Thut. 2008), and hence of the visual system. In line, recent electrophysiological investigations in patients with posterior brain damage and visual field defects reported the presence of dysfunctional changes in neural oscillatory activity of the alpha rhythm at rest (Pietrelli et al., 2019), suggesting that the posterior cortices have a pivotal role in the generation and distribution of these oscillatory patterns. However, these findings make also possible to hypothesize that the impairments in alpha oscillatory activity may be due to maladaptive postlesional modifications in the functional structure of the visual system and in particular, in the reverberating networks on which alpha oscillatory activity relies on. Despite of these results, suggesting the existence of dysfunctional rearrangements in the visual system following to lesion to the posterior cortices, on the other side, several studies on neurologically healthy participants provided evidence for efficient experience-dependent modifications in the adult visual system, induced by external experimental manipulation based on specific stimulation protocols. Specifically, the studies employing these protocols converged in demonstrating that a rhythmical stimulation administrated in a frequency included in the alpha band induces an effective modulation of the

spontaneous alpha oscillations, resulting in a concurrent enhancement in visual performance, a mechanism known as rhythmic entrainment (Mathewson et al., 2012; De Graaf et al., 2013; Spaak, De Langen, Jensen, 2014). It has been hypothesized that the enhancements in alpha oscillatory activity and in visual performance in entrainment paradigms may be due to the efficacy of the rhythmic stimulation in inducing plastic mechanisms in the oscillating networks, causing transient structural and functional changes in the visual system (Vossen, Gross, Thut, 2015). In light of these observations, it is of great relevance to investigate to what extent the adult visual system can be modeled through external stimulation, aiming at promoting its activity, or affected by the presence of a brain damage, disrupting its circuits and possibly resulting in maladaptive postlesional changes and how such modifications in the visual system reflect on the oscillatory activity of its intrinsic rhythms. Therefore, the present work aimed at investigating the role of alpha oscillations as a biomarker of the functionality of the visual system and an index the plastic modifications occurring in the visual system in response to the presence of lesions to the visual cortices or induced by external stimulations.

In particular, chapter 2 provided a description of the structural and functional organization of the visual system and of the visual field defects induced by a lesion affecting the primary visual pathway. In chapter 3 the elctrophysiological correlates and, more specifically, the oscillatory correlates of the functionality of the visual system were explained, providing a collection of evidence linking the oscillatory activity in the range of alpha to task performance and to the functionality of the visual system at rest. In addition, evidence about the existence of hemispheric asymmetries in orchestrating the alpha oscillatory patterns was also reported. In chapter 4, the mechanisms of cortical and subcortical plasticity in the adult visual system were described, with a report of relevant studies investigating plastic modifications of the visual system in neurologically healthy participants and brain lesioned patients. Importantly, chapter 5 describes the results of an EEG study investigating the effects of posterior brain lesions, disrupting the neural circuits of the visual system, on the residual functionality of alpha oscillations in hemianopic patients, by measuring the alpha desynchronization in the transition from the eye-closed to the eyes-open resting state. Then, in chapter 6, the effects of posterior brain damage on the alpha oscillatory activity in hemianopic patients at rest, were characterized at a network level in a EEG study assessing functional connectivity of brain rhythms. In chapter 7, the periodical structure of visual perception was investigated in healthy participants through a behavioural study, by employing a visual detection task. In particular, in this study attentional sources were manipulated to investigate the role of rhythmical attentional sampling in modulating visual perceptual processing and a lateralized target presentation was used to investigate possible different contributions of the two hemispheres in the rhytmic attentional sampling. Finally, chapter 8 describes the results of an EEG study in healthy participants, which aimed at investigating

whether long-lasting modulations of the alpha oscillatory activity can be achieved through a prolonged rhythmic sensory entrainment, exploiting possible plastic modifications in the underlying oscillating network of the visual system.

Chapter 2

The structure and the functioning of the visual system

2.1. The organization of the visual system

2.1.1 The visual pathway

Vision is the special sense of sight, which is based on the transduction of light stimuli, a complex information processing carried out within the visual pathway. The visual pathway starts from the eyes and includes the retina, the optic nerve, the optic chiasm, the optic tract, the lateral geniculate nucleus (LGN) of the thalamus, the optic radiations, and the visual cortex (see figre 2.1). The first cells in the pathway, the photoreceptors, convert light input into a neuronal signal that is transmitted to the bipolar cells and then to the ganglion cells, which are all contained in the retina. The axons of the ganglion cells exit the retina through the optic nerve, with the nasal fibers from each eye crossing in the optic chiasm and terminating in the opposite side of the brain. The optic tract carries these fibers from the chiasm to the LGN, where the next synapses occur. The fibers leave the LGN as the optic radiations that terminate in the visual cortex of the occipital lobe.

2.1.2 The eye

The eye is the primary sensory organ for vision, responsible for collecting light, focusing it, and encoding the first neural signals of the visual pathway (Prasad & Galletta, 2011). The eye is a hollow sphere made of three layers of tissue. The outermost layer is the fibrous tunic, which includes the white sclera and clear cornea. The sclera accounts for five sixths of the surface of the eye, most of which is not visible. The transparent cornea covers the anterior tip of the eye and allows light to enter the eye. The middle layer of the eye is the vascular tunic, which is mostly composed of the choroid, ciliary body, and iris. The choroid is a layer of highly vascularized connective tissue that provides a blood supply to the eyeball. The choroid is posterior to the ciliary body, a muscular structure that is attached to the lens by zonule fibers. These two structures bend the lens, allowing it to focus light on the back of the eye. Overlaying the ciliary body, and visible in the anterior eye, is the iris, the colored part of the eye. The iris is a smooth muscle that opens or closes the pupil, which is the hole at the center of the eye that allows light to enter. The iris constricts the pupil in response to bright light and dilates the pupil in response to dim light. The innermost layer of the eye is the neural tunic, or retina, which contains the nervous tissue responsible for photoreception. The eye is also divided into two

cavities: the anterior cavity and the posterior cavity. The anterior cavity is the space between the cornea and lens, including the iris and ciliary body. It is filled with a watery fluid called the aqueous humor. The posterior cavity is the space behind the lens that extends to the posterior side of the interior eyeball, where the retina is located. The posterior cavity is filled with a more viscous fluid called the vitreous humor.

2.1.3 The retina

The retina is a thin tissue composed of several layers, located near the optic nerve. The retina receives light and converts it into elettrochemical signals, through a layer of photoreceptor cells. This process, known as of phototransduction, is based on the activity of two types of phororeceptors, the cones and the rods (Levin, 2003). In optimal lighting conditions, vision is mainly mediated by three different cones that show an excellent response to various wavelengths of lights. Among the three cone photoreceptors, red cones (63% or 2.9 million), responding to long wavelengths, are more common than green cones (32% or 1.4 million), responding to middle wavelengths, and blue cones (5% or 0.2 million), responding to short wavelengths. The rods, instead, are more effective during night vision, due to their greater sensitivity to low-light condition (Sánchez López de Nava, Somani, Salini, 2022). The human retina contains approximately 4 to 5 million cones and 77–107 million rods (Wurtz, Kandel, 2000), which are not equally distributed across the retina (Osterberg, 1935). In particular, only cones are found in the foveola, whereas rods predominate outside the foveola in the remaining fovea and the entire peripheral retina (Ostier, 1999). The macula is located temporal to the optic disc and is about 1.5 mm in diameter (Kinkaid, Green, 1999). The most central part of the macula, the fovea, is formed by a central depression of 0.35 mm of diameter and represents the retinal region of greatest visual acuity (Oyster, 1999). Within the fovea, a sloping wall, the clivus, demarcates the foveola, which contains the highest density of cone photoreceptors (199,000/mm2). Here, the photoreceptor cells are narrowed and elongated to maximize light detection further (Curcio, Sloan, Kalina, Hendrikson, 1990). Moving in either direction from the central part of the fovea to the peripheral retina, there are fewer cones and more rods and, consequently visual acuity drops significantly. In the fovea each bipolar cell receives inputs from a single photoreceptor, supporting high spatial acuity. In contrast, in the peripheral retina, a bipolar cell summates the inputs from multiple photoreceptors. Bipolar cells then provide inputs to ganglion cells via direct, excitatory gluta-matergic synapses or indirect, inhibitory GABAergic connections (Flores-Herr, Protti, Wässle, 2001). The surface of the retina contains about 1.5 millions of ganglion cells taht share the property

of having long axons forming the optic nerve, optic chiasm, and optic tract, which extend into the brain. However, ganglion cells vary significantly in terms of responses to visual stimulation, depending on the part of the retina in which they are receiving the stimuli. Specifically, 80% percent of ganglion cells are P cells, 10% are M cells, and 10% are K cells, which organize in segregated visual pathway, the parvocellular, the magnocellular and the koniocellular pathways (Polyak 1941; Kaplan & Shapley, 1986), projecting to different layers of LGN. This peculiar organization, starting from the ganglion cells of the retina, is maintained through the entire visual system. P cells are highly concentrated in the fovea and have extremely small receptive field, therefore showing specialization for high spatial acuity, color vision and fine stereopsis (Livingstone & Hubel, 1988). On the contrary, M cells are more concentrated in the peripheral retina, and have larger receptive field with specialization for low spatial resolution (Croner & Kaplan, 1995), motion detection, coarse stereopsis, although blind to color differences (Livingstone & Hubel, 1988). As for the K cells, relatively little is known about them. However, K cells seem to be involved in color vision (Hendry & Yoshioka, 1994) and in the control of circadian rhythms, due to their sensitivity to changing in overall luminance level (Hattar et al., 2002). The information coming from the ganglion cells reaches the optic nerves, and then travels to the optic chiasm, where the optic nerve fibers of both eyes cross in the midline and then form the optic tract (Remington, 2012). Other retinal cells, such as horizontal cells, amacrine cells, and interplexiform neurons modify and integrate the signal before it leaves the eye (Sanchez-Lopez da Nava et al., 2022).

2.1.4 The optic nerve, the optic chiasm and the optic tract

The optic nerve is comprised of approximately 1.2 million retinal ganglion cell axons (Bruesch & Arey, 1942) and begins at the optic disc, a structure that is 1.5 mm in diameter, located at the back of the eye. The optic disc forms from the convergence of retinal ganglion cell axons as they pass out of the eye, while maintaining strict retinotopic organization (Hildebrand & Fielder, 2011). The central part of the optic disc, the optic cup, contains no retinal fibers and appears optically empty, giving rise to the monocular blind spot (Mariotte, Pecquet & Justel, 1668).

After passing through the optic disk, the retinal axons travel in the intraorbital (about 30 mm), the intracanalicular (5–12 mm), and the intracranial portions of the optic nerve (8–19 mm). Within the middle cranial fossa, the optic nerves from each eye, which convey information from the nasal (medial) and temporal (lateral) part of the retina, unite to form the optic chiasm (see Figure 2.1). At the optic chiasm, the nasal fibers decussate to join the temporal fibers of the contralateral optic nerve

to form the optic tract. Specifically, at the chiasm, fibers from the nasal half of each retina cross over to the contralateral optic tract, while fibers from the temporal halves remain ipsilateral. This arrangement is essential for producing binocular vision. Indeed, each nasal hemiretina receives visual information from the peripheral ipsilateral visual hemifield, whereas each temporal hemiretina receives information from the central contralateral part of the visual field. In this way, each following optic tract will propagates information from only the contralateral hemifield, specifically the visual information from the ipsilateral temporal hemiretina and the contralateral nasal hemiretina. Finally, the optic tracts project to the LGN, the superior colliculus, the hypothalamus, and possibly other brain structures (Levin, 2003). Some nerve fibers leave the optic tract without entering the LGN and instead enter the brain stem to provide information that ultimately determines pupil size (Gamm & Albert, 2015).

2.1.5 The subcortical nuclei

Most axons from the two optic tracts synapse in the ipsilateral LGN. Here, the retinotopical organization is still preserved (Kupfer, 1962), such that the central portion (hilum) receives macular fibers, whereas the lateral and medial horns receive fibers from the inferior retina and superior retina, respectively (see Figure 2.1). The LGN consists in six layers, which maintain the anatomical and functional segregation between the P, M and K pathways and between axons from the temporal and nasal hemiretinas (Chacko, 1948; Leventhal, Rodieck, & Dreher, 1981). The LGN is often described as critical relay station for visual information, which selects the amount and nature of input that is transmitted to visual cortex (Guillery & Sherman, 2002). Indeed, while retinal afferents represent only 5–10% of the synapses in the LGN (Van Hornet al., 2000), the LGN also receives extensive modulating connections from the thalamic reticular nucleus and layer 6 of the visual cortex (Prasad & Galòletta, 2011). Thus, the LGN plays a crucial role in modulating the flow of incoming visual inputs and in filtering relevant visual information (Prasad & Galetta, 2011). From the LGN, visual information is trasmitted to the primary visual cortex (V1) through the two optic radiations, while maintaining a retinotopical organization. In particular, each optic radiation is divided in a temporal branch that conveys visual information from the contralateral superior part of the visual field, and a parietal branch that conveys visual information from the contralateral inferior part of the visual field (Van Buren & Baldwin, 1958). A portion of the axonal fibers from the two optic tracts project into the ipsilateral Pulvinar nuclei of the thalamus. The Pulvinar receives extensive cortical projections from the visual cortex, in particular from layer 5 and 6 (Chalupa & Dreher, 1991), thus representing

a larger a higher-order relay for visual information. Importantly, the Pulvinar nuclei has also widespread connections with various subcortical and cortical areas, which provide to it a role in the modulation of brain activity according to spatial attentional requirements (Petersen, Robinson, & Morris 1987; Rafal & Posner 1987). Another portion of the axonal fibers of two optic tracts targets the ipsilateral Superior Colliculi (SC), which takes part in the programming and the generation of orienting behaviors. Specifically, the SC is involved in directing the eyes and the head movements toward sudden visual or other sensory stimuli (Prasad & Galletta, 2011). The SC are located in the dorsal midbrain and are anatomically and functionally divided in superficial and deep layers (see figure 2.1). The superficial layers of SC process only visual information and receive direct retinal input, consisting in a visuotopic representation of the contralateral visual field (Cynader & Berman, 1972). The deep layers of the SC, instead, receive inputs from multiple sensory modalities and help mediating saccadic eye movements through different connections with the ocular motor systems and the cortical areas involved in the generation of the saccades (Prasad & Galletta, 2011). Furthemore, each colliculi provide a magnified representation of the foveal vision, with over one-third of collicular neurons processing inputs from the central 10° of vision (Prasad & Galletta, 2011). Both superficial and deep layers of the SC exchange information with several thalamic nuclei, including the Pulvinar, and with the extrastriate visual cortices through connections that bypass the LGN (Sommer & Wurtz 2004a; Sommer & Wurtz 2004b). A relatively small portion of the axons of the two optic tracts projects into the Pretectal nuclei in the midbrain, which subserve the pupillary light reflex and regulate the size of the pupil. A newly identified type of retinal ganglion cells, which demonstrates an intrinsic responsiveness to light, not mediated by rod and cone photoreceptors, (Hattar et al., 2002) gives rise to a separate pathway through the optic chiasm and tracts. These fibers ultimately transmit light information directly to the suprachiasmatic nucleus (SCN), at the base of the anterior hypothalamus. The SCN is characterized by large receptive fields and provides sustained neural responses. These properties allow the SCN to monitor ambient light levels precisely. The SCN is also widely connected to the pineal gland, where melanine is released to drive circadian rhythms.

2.1.6 The primary visual cortex

The optic radiations arrive in the mesial surface of the occipital lobe. Here, the parietal fascicle of the optic radiations synapse in the superior part of the striate cortex (primary visual cortex, V1), whereas the temporal fascicle targets the inferior part (see Fifure 2.1). This allows a full representation of the visual field in V1, in an inverted way, both to the respect of the horizontal and vertical axes. Macular

projections make their synapse in the posterior pole of V1, such that the macular representation is greatly magnified in the V1 retinotopic map. All the axonal fibers of the optic radiations are connected to the layer 4 of V1 (Gennari, 1782). P and M pathways target the 4Cb and the 4Ca sublayers, respectively, maintaining their anatomical segregation (Hubel & Wiesel, 1962). Monocular inputs to V1 are organized in ocular dominance columns. The two eyes provide a different view of the visual space; therefore, their respective retinal images are slightly displaced. This retinal disparity forms the basis of cortical processing of stereoscopic depth, so that the monocular two-dimensional projection of visual space becomes a more complex three-dimensional perception (Wheatstone, 1838). Neurons in V1 are highly sensitive to specific orientations of luminance contrast. This represents the basic step for image contour detection and analysis (Hubel &, Wiesel 1962). In addition, V1 neurons support the initial processing of color, brightness, and direction of motion (Tootell, Switkes, Silverman, & Hamilton, 1988, Tootel et al., 1995). Along the dorsal and the ventral pathways, V1 sends visual information to the extrastriate cortices.

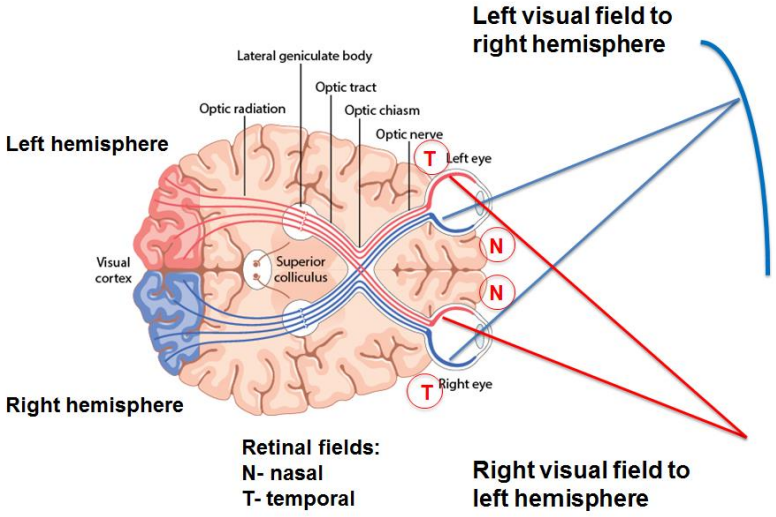

Figure 2.1. *Optic nerves feed into optic chiasm, where axons from the nasal retina cross and join axons from the temporal retina, and then feed into the optic tract to synapse in the LGN. From the LGN, the optic radiation reaches the visual cortex (Adapted from Guyton & Hall, 2020)*

2.1.7 The higher-order cortical visual regions

From V1, visual input reaches higher-order cortical areas. Here, visual information is further processed and integrated by higher-order neurons, characterized by expanded and more complex

receptive fields. Indeed, while neurons in the early visual areas have relatively small receptive fields, which are confined to the contralateral visual hemifield, neurons in higher-order visual areas have larger receptive fields that span both hemifields. In these higher-order areas, visual information loses its strict retinotopic representation. (Livingstone & Hubel, 1983). Each extrastriate visual area is specialized for the detection of specific attributes of the visual scene. In addition, the different extrastriate areas are organized into two parallel processing streams, which are anatomically and functionally segregated, the ventral stream and the dorsal stream. The ventral stream, also known as the "what" pathways, seems to mediate visual object recognition, whereas the dorsal stream, also known as the "where" or "how" pathway, seems to be specialized for the processing of spatial relationships and manipulation of objects (Mishkin, Ungerleider, &Macko 1983; Goodale, Milner, Jakobson & Carey, 1991). The ventral stream starts in the P pathway layer 4Cb of V1, continues to V2 and V4 and ultimately reaches the inferotemporal cortex (Zeki, 1980; Shipp & Zeki, 1985; Sincich & Horton, 2002). In parallel, the dorsal stream begins in the M pathway layer 4Ca of V1 and continues to V2 and V3 (Shipp & Zeki, 1985; Sincich & Horton, 2002). From V2 and V3 the dorsal stream goes to the motions specialized extrastriate areas V5/MT and ends in the posterior parietal cortex (Boussaoud, Ungerleider & Desimone, 1990; Tootell et al., 1995). Lesional studies helped defining the specific characteristics of these two pathways. Indeed, lesions to the macaques inferior temporal cortex, the higher-order region of the ventral stream, leads to severely impaired performance in visual discrimination tasks, specifically in objects recognition and in the discrimination of colors, visual patterns or shapes (von der Heydt, Peterhans, Baumgartner, 1984). However, performance in visuospatial tasks, such as visually guided reaching and discrimination of different relative distances between objects, was not affected at all (vonder Heydt et al., 1984). Coversely, a damage to the posterior parietal cortex, the higher-order region of the dorsal stream, induced the opposite behavioral pattern. Specifically lesions to these cortical areas led to a severe impairment in the performance to the same visuospatial tasks, whereas performance in the same visual discrimination tasks was preserved (Mishkin et al., 1983).

2.2 The visual system after brain damage

2.2.1 Visual field defects after brain damage

Following to a lesion that occurs along the visual pathway, visual field defects consisting in a loss of conscious vision in a portion of the visual field are usually experienced. In the majority of cases, the visual field defects are caused by stroke in the territory of the middle or posterior cerebral arteries,

although trauma or elective surgery in occipital cortex can also contribute to vision loss. Indeed, among the different etiologies, stroke represents the most common cause of visual field defect in the adult populations, with 52-70% of prevalence among patients with visual field defects and 8-10% of incidence of visual field defects among stroke patients (Zhang, Kedar, Lynn, Newman, Biousse, 2006). As for other etiologies, the 14% of visual field defect cases are due to a traumatic brain injury, whereas the 11% are due to tumor (Zhang et al., 2006). In children, instead, the most common cause of visual field defect is represented by tumor, with 27%– 39% of incidence, followed by brain injury (19%–34%), infarction (11%–23%), and cerebral hemorrhage (7%–11%) (Liu & Galetta, 1997; Kedar, Zhang, Lynn, Newman & Biousse, 2006). Depending on the location of the brain damage along the primary visual pathway, different types of visual field defects may occur. Specifically, a lesion to the optic tract induces a contralesional hemianopia, characterized by a loss of conscious vision in the contralesional visual field. A lesion to the temporal fascicle of the optic radiation, leads to a superior contralesional quadrantopia, in which the loss of conscious vision interests the upper contralesional quadrant of the visual field. On the contrary, a lesion to the parietal fascicle of the optic radiation causes an inferior contralesional quadrantopia, with a loss of conscious vision in the lower contralesional quadrant of the visual field. Lesions to the primary visual cortex, instead, are followed by different clinical manifestations. In particular, since the entire visual field is represented in the primary visual cortex, the loss of conscious vision will affect the part of the visual filed corresponding to the specific lesioned site within the primary visual cortex. However, the representation of the visual field is not equally distributed in the visual cortices. For instance, due to a large macular representation in the occipital lobe, the central 2-10° of the visual field are often spared after an occipital brain lesion (McFadzean, Brosnahan, Hadley & Mutlukan, 1994; Korogi et al., 1997). The sparing of macular field areas can also occur after a lesion of the optic tracts or the optic radiations (Zhang et al., 2006). Retrochiasmatic lesions never impair visual acuity, whereas retinal conditions affect it severely. In addition to the loss of conscious vision in a part of the visual field, retrochiasmatic lesions affect also higher-order visuospatial representation. Indeed, most of the hemianopic patients exhibit also an impaired oculomotor scanning behavior in the entire visual field, although more severely affected in the blind visual field (Chedru, Leblanc & Lhermitte, 1973; Zihl, 1995a; Ishiai, Furukawa &Tsukagoshi, 1987). This made possible to hypothesize that the ability to integrate different portions of the visual field into a high-order global representation of space can be impaired in hemianopic patients, resulting in a disturbed visual exploration and continuous visual information processing (Zihl, 1995). The visuospatial impairments, combined with the loss of conscious vision, have a negative impact over the patients' daily living. Indeed, hemianopic patients commonly experience reduced independence, inability to drive, considerably reduced ability of navigating in

crowded environments and in avoiding obstacles and difficulties in reading (Leff et al., 2000; Bowers et al., 2009; Goodwin 2014; Alberti, Peli & Bowers 2014;). Therefore, a prompt identification of the symptomatology, together with access to the currently available treatment options can significantly improve the quality of life of the hemianopic patients.

2.2.2 Residual visual abilities in hemianopic patients

In some rare cases, hemianopic patients do not suffer from a total of loss of vision in the contralesional visual field, but rather retain certain implicit visual capabilities that enable them to unconsciously detect, discriminate and respond to visual stimuli presented in the blind visual field, above chance level. These capacities are collectively known as blindsight (Poppel, Held & Douglas, 1973; 1973; Weiskrantz, Warrington, Sanders & Marshall, 1974). Over the past few decades, several studies revealed the presence of residual capacities in the blind field of blindsight patients using different kind of direct and indirect psychophysical approaches. Specifically, in direct approaches, such as the Alternative Forced Choice method (AFC), participants are asked to guess about the presence/absence or between different features of stimuli presented in their blind visual field, by choosing among a limited numbers of options. In indirect approaches, instead, participants are instructed to respond to stimuli presented in the healthy visual field while task-unrelated stimuli are presented in the blind visual field. Following this logic, if the performance for stimuli presented in the intact visual field is modulated by the presentation of stimuli in the blind field, then the unseen stimuli presented in the blind field must have been unconsciously processed.

AFC methods have demonstrated that blindsight patients can detect visual stimuli in their blind visual field (Fendrich, Wessinger, Gazzaniga, 1992) and localize such stimuli directing eye saccades (Zihl, 1980), or by pointing using their hands (Perenin & Jeannerod, 1975). In addition blindsight patients are able to detect moving stimuli (Riddoch, 1917), and discriminate among motion directions (Stoerig & Cowey 1989; Brent, Kennard & Ruddock 1994). Some blindisight patients were also shown to discriminate among different objects (Weiskrantz et al., 1974), colors (Stoerig & Cowey 1989; Brent et al., 1994), shapes (Perenin & Rossetti 1996) and facial expressions (Pegna et al., 2005). On the other hand, proof of residual blindsight abilities in some hemianopic patients was provided also by experimental paradigms based on indirect approaches. For instance, faster reaction times are found in response to stimuli presented in the intact visual field when an unseen stimulus is delivered concurrently in the blind visual field compared to when no unseen stimulus is delivered (Marzi, Tassinari, Aglioti & Lutzemberger**,** 1986; Corbetta, Miezin, Dobmeyer, Shulman, Petersen, 1990). In

particular, it was shown that the presentation of a grey stimulus in the blind visual field enhances reaction times and pupillary responses for stimuli concurrently presented in the intact field. These improvements were accompanied by an activation of the SC, suggesting a direct involvement of the SC in the visuomotor integration of grey stimuli presented between the two hemifields (Tamietto et al. 2010). In addition, it was also demonstrated that unseen words presented in the blind visual field are able to bias the semantic interpretation of words presented in the intact visual field (Marcel, 1998), suggesting that the influence of stimuli presented in the blind visual field can relay also on a higher level of unconscious processing. Other studies, based on both direct and indirect approaches, focused on investigating residual visual processing of emotional stimuli in absence of awareness in blindsight patients, a phenomenon known as affective blindsight. For instance, it was shown that one of the most studied blindsight patients, GY, could discriminate above chance level both in 2AFC and in 4AFC tasks, between happy, sad, angry and fearful faces (De Gelder, Voomen, Puortis, Weiskrantz, 1999). In addition, patients GY and TN were able to discriminate above the chance level in a 2AFC task between angry and neutral emotion delivered by body postures (Van den Stock & de Gelder, 2014), demonstrating that the affective blindsight discrimination abilities are not confined to facial expressions only, but occur also in the processing of emotional bodies. In another study, based on indirect methodology, patient GY showed faster reaction times in response to facial emotional expressions (i.e. sad, fearful or angry faces) presented in the intact visual field, when a congruent stimuli was presented concurrently in his blind visual field (de Gelder et al. 2000). Overall, these unconscious visual abilities, ranging from the simple motion detection to the discrimination of emotional facial expression, seem to be mediated by the activity of alternative visual pathways, which are usually spared after postchiasmatic lesions. Among the spared visual areas, the SC, which is involved in the programming and generation of saccadic eye-movements, may have a central role in determining blindsight responses driven by visually guided eye movements (Spering & Carrasco, 2015). Moreover, the SC may also be involved in the discrimination of motion stimuli presented in the blind field, due to its extensive connections with different subcortical and cortical brain structures relevant for processing of motion. Specifically, primate studies revealed the presence of connections between the SC and the V5/MT, a cortical area specialized in the processing of motion stimuli (Sommer & Wurtz 2004a; Sommer & Wurtz 2004b). Indeed, after the ablation of V1, primate V5/MT neurons still show a selective activation for different motion direction (Rodman, Gross, & Albright, 1990; Girard, Salin, & Bullier, 1992). In addition, a direct pathway between LGN and the middle-temporal visual area MT (Ajina, Pestilli, Rokem, Kennard, & Bridge, 2015), between the Pulvinar and MT (Bourne & Morrone, 2017) and projecting from the SC to MT, passing through the Pulvinar (Tran et al. 2019) were also proposed to have a role in motion-related blidsight. In affective blindsight

patients, instead, the sparing of the subcortical pathway projecting from the SC to the Amygdala, via the inferior Pulvinar (Tamietto, Pullens, de Gelder, Weiskrantz, Goebel, 2014; Rafal et al. 2015) seems to been involved in processing of visual emotional stimuli in absence of awareness.

Interestingly, although blindsight has been demonstrated in a limited number of patients with visual field defects, a series of more recent investigations revealed the presence of implicit visual processing also in hemianopic patients, not demonstrating blindsight in classical terms (i.e., in hemianopic patients unaware of the presence and the content of stimuli presented in their blind field and performing at chance level in 2AFC tasks with any kind of stimuli. For instance, in a recent EEG study, hemianopic patients without blindsight exhibited a selective alpha desynchronization for motion stimuli delivered in the blind visual field (Grasso et al., 2018). In particular, since alpha desynchronization is typically associated to visual cortex activation (Pfurtscheller ,2001; Romei et al., 2008a) and visual processing (Pfurtscheller, Neuper, & Mohl. 1994), this electrophysiological signature in hemianopic patients without blindisight may reflect an implicit visual processing of motion stimuli in the absence of awareness, relaying on the activity of a spared subcortical visual pathway. Specifically, authors suggested that the alternative pathway linking the retinal input to the motion sensitive extrastriate MT areas through the SC, may be the main candidate in sustaining such implicit visual processing of motion stimuli in hemianopic patients without blindsight (Grasso et al., 2018). An additional body of evidence revealed that hemianopic patients without affective blindsight (i.e. performing at the chance level in discriminating between different emotional facial expressions when presented in their blind field) retain an implicit selective visual processing for fearful faces presented in their blind visual field (Bertini, Cecere & Làdavas 2013; 2017; Bertini, Pietrelli, Braghittoni & Ladavas, 2018; Cecere, Bertini, Maier, Ladavas, 2014). Indeed, hemianopic patients without blindsight were shown to be faster in discriminating emotional faces presented in their intact visual field when concurrent fearful faces were presented in their blind visual field. On the contrary, no facilitation in response times was found when a happy of emotionally neutral face was concurrently delivered in their blind visual field (Bertini et al., 2013). In a subsequent ERP study, the presentation of fearful faces in the blind visual field led to an increase in the N170 amplitude evoked by emotional faces presented in the healthy visual field (Cecere et al., 2014). Therefore, since N170 is a well known ERP correlate of facial structural processing, these results indicate that the presentation of fearful faces in the blind field facilitate the visual analysis of facial expression presented in the healthy visual field. Based on these findings, it was hypothesized that such implicit processing, which is selective for fearful stimuli and induce a facilitation in the behavioral and electrophysiological responses to stimuli presented in the intact field (Bertini et al., 2013; Cecere et al., 2014; Bertini et al., 2017), may relay on the activity of a subcortical circuit encompassing the SC,

the Pulvinar and the Amygdala, spared after V1 damage (Tamietto et al., 2012; Rafal et al., 2015). In line with this hypothesis, it was also demonstrated that hemianopic patients with Pulvinar lesions do not exhibit the same response facilitation, suggesting that the Pulvinar covers a central role in conveying fear-related visual information (Bertini et al., 2018). On the one hand these findings suggest that hemianopic patients without blindisght may retain a capacity for implicit visual processing of emotionally relevant stimuli. On the other hand, these studies highlight also differences between the performance of hemianopic patients without affective blindsight (Anders et al. 2004; Bertini et al., 2013; 2017; 2018; Cecere et al., 2014) and the performance of patients with affective blindsight (De Gelder et al., 1999; de Gelder, Pourtois, van Raamsdonk, Vroomen, Weiskrantz, 2001). Indeed, patients with affective blindsight are able to discriminate between different emotional faces above the chance level and they show response facilitation for emotionally–congruent pairs of facial stimuli (De Gelder et al., 1999; de Gelder et al., 2001), despite of the type of emotion. On the contrary, hemianopic patients without affective blindsight show chance level performance in discriminating between different emotional faces, but, importantly, they show a response facilitation only when a fearful face is presented in their blind visual field (Anders et al. 2004; 2009; Bertini et al.,2013; 2017;2018; Cecere et al., 2014).

Based on these observations, it has been hypothesized that the implicit visual abilities in both affective blindsight patients and hemianopic patients without affective bindsight might be mediated by the subcortical retino-SC-Pulvinar-Amygdala circuit, which is thought to subserve implicit processing for emotional stimuli (Tamietto et al., 2012; Bertini et al., 2018). However, the peculiar implicit visual abilities of patients with affective blindsight might also involve other reorganized spared cortices (Gerbella, Caruana, & Rizzolatti 2019), suggesting that patients with blindsight and hemianopics without blindsight may represent two distinct neuropsychological profiles, supported by the activity of different neural substrates. Specifically, the residual visual processing abilities in hemianopic patients without blindsight may involve both the subcortical circuits conveying visual information from the retina to the SC and then projecting to the Pulvinar and Amygdala, which are relevant for processing threat-related information (Ledoux, 1998), and to the dorsal extrastriate areas, which play a crucial role in processing of motion stimuli (Albright, 1984; Huk & Heeger. 2002). In patients with blindsight, instead, showing evidence of implicit processing also in 2AFC and who demonstrate the ability of processing in the absence of awareness a wide range of different stimuli, the residual visual abilities seems to involve not only the contribution of the same subcortical SC-Amygdala and SC-dorsal extrastiate pathways proposed in mediating implicit abilities in patients without blindsight (Tamietto et al,. 2012), but also additional spared and functionally reorganized visual cortices. In particular, post-lesional plastic changes occurring to the subcortical V1-independent pathways and

their multiple connections with extrastriate areas, both within the dorsal and the ventral stream (Tamietto & Morrone, 2016), might represent a plausible account for the blindisght abilities in hemianopic patients, although their exact functional neuroanatomical correlates still need to be clarified. However, the presence of these spared abilities after lesions to visual areas consistently demonstrate the capability of the adult visual system to reorganize its circuits to preserve residual visual functioning.

Chapter 3

The functionality of the visual system: oscillatory patterns and possible hemispheric asymmetries

3.1.1 Electrophysiological correlates of the functionality of the visual system

Electroencephalography (EEG) is the measurement of the electrical activity of the brain through the placement of electrodes on the scalp. The resulting signal is the electroencephalogram, which represents the electrical activity from large populations of neurons. EEG is typically a non-invasive technique, suitable for laboratory settings and it is able to capture changes on the electrical activity of the brain at a millisecond-level. Due to such high temporal resolution, EEG has been successfully employed in cognitive neuroscientific research, representing an excellent tool to clarify the relationship between the electrical communication among numerous brain neurons and the different cognitive functions. Voltage fluctuations in neural electrical activity, as captured by EEG recording, can be characterized in terms of time-domain characteristics (i.e. Evoked Potentials and Event Related Potentials) or spectral components (i.e. EEG oscillatory rhythms). In particular, the Evoked Potentials (EP) represent the averaged EEG activity time-locked to the presentation of a visual, auditory or somatosensory stimulus, whereas Event Related Potentials (ERPs) represent averaged EEG responses time-locked to complex stimulus processing. In the past four decades, ERps have been extensively investigated in cognitive neuroscientific research, with successful results also in vision studies. Indeed, although their neural origins still need to be fully elucidated, more recently, specific aspects about their locations and latencies have been better clarified, making possible to relate them to the various steps of both conscious and unconscious visual processing (Lami, Salti, Bar-Haim, 2009; Foster, Koivisto, Revounso, 2020). In particular, it has been demonstrated that according to the increase of the latency, the locations of the ERP components interest larger areas, starting in the primary visual cortex, passing through the lateral occipital cortex and ending to the pariental cortex and the lateral occipito-temporal cortex (Hylliar & Anllo-Vento, 1998). Therefore, the earliest ERP components elicited by visual stimuli have been usually correlated to the processing of basic visual features like color (Liu et al., 2009) or shape (Gosling, Thoma, de Fockert., & Richardson-Klavehn, 2016), whereas later components have been typically related to more complex aspects of visual processing and manipulation of attention in visual tasks (Fu, Caggiano, Greenwood, & Parasuraman, 2004; Hietanen, Leppänen, Nummenmaa, & Astikainen, 2008).

The EEG oscillatory rhythms or brain weaves, on the other hand, reflect rhythmical fluctuations of the electric voltage between different parts of the brain, resulting in an electrical flow in different

frequency bands (e.g. theta band, alpha band), which can be spontaneous or driven by internal or externally induced computations. Importantly, in the recent years, several studies demonstrated the existence of a causal link between the spontaneous brain rhythms and different cognitive functions, renewing the interest in investigating the relationship between the various brain rhythms and cognitive processing. In particular, among all spontaneous brain frequencies, neural oscillatory activity in the alpha frequency band (7-13 Hz) has been consistently linked with various aspects of visual perception and visuospatial attention, suggesting that the neural oscillatory activity in this frequency band may reflect the complex interaction between the visual and attentional system in shaping visual perception, representing a reliable neurophysiological measure of the functionality of the visual system.

3.1.2 Oscillatory correlates of the functionality of the visual system: task-related alpha oscillatory activity

Different experimental studies have successfully employed EEG recordings in vision research, in order to enlighten the neural and electrophysiological correlates of the functionality of the visual system both in healthy participants and in brain lesioned patients. These studies have been consistent in demonstrating that neural oscillatory activity in the range of alpha (7-13 Hz) has a direct influence on visual awareness and that the different alpha oscillatory parameters (i.e. frequency, power and phase) are linked with various aspects of visuospatial processing (Klimesch 1997; Klimesch 1999; Romei at al.., 2008b; Cecere et al., 2015; Samaha & Postle, 2015) In particular, it has been hypothesized that increase in alpha oscillatory power may reflect inhibition of stimulus processing in cortical regions that are not functionally relevant in a given task (Bush & Van Rulen, 2010). In line with this hypothesis, a number of studies showed that a reduction of alpha power occurs during the processing of perceived (Pfurtscheller et al., 1994) and unperceived (Grasso et al., 2018) visual stimuli and the allocation of visuospatial attention (Thut, Nietzel, Brandt, & Pascual-Leone, 2006; Rihs, Michel & Thut 2009; Capilla, Schoffelen, Paterson, Thut & Gross, 2014).

Specifically, it was shown that the allocation of attentional sources to a given location results in a decrease in alpha power in the hemisphere contralateral to the attended visual field (Worden, Foxe, Wang, & Simpson, 2000; Sauseng et al., 2005), and an increase in power contralateral to the unattended visual field (Kelly, Lalor, Reilly, & Foxe, 2006). Accordingly, decrease in alpha power was shown to be correlated with enhanced target detection (van Dijk, Schoffelen, Oostenveld, & Jensen, O, 2008), strengthening the idea that alpha oscillatory power plays an active inhibitory

function in modulating visual perception and visuospatial attention (Jensen & Mazaheri 2010; Klimesch, Sauseng, & Hanslmayr, 2007).

In addition, variations in alpha power (Romei, et al., 2008b) and phase (Mathewson et al., 2009) were shown to reflect fluctuations in the excitability of the underlying oscillating neural sources and to result in a concurrent periodical modulation of visual processing within the visual system (Mathewson et al., 2009; VanRullen, 2016), favoring the notion that changes in alpha oscillatory activity, reflecting the excitability of the underlying neurons, correspond to fluctuations in perceptual performance and visual awareness (Mathewson et al., 2009).

These observations have recently given rise to the conceptualization that the variations in alpha oscillatory activity, and the concurrent fluctuations in cortical excitability, may be responsible for sustaining the intrinsic tendency of the visual system to process visual information periodically. Indeed, it has been widely proposed that visual perception is not continuous, as it was traditionally assumed, but rather periodic and consisting in a succession of perceptual cycles, which mirror the oscillatory activity of the underlying neural populations (Van Rullen, 2016). More specifically, it has been recently hypothesized that the periodical sampling of visual inputs occurs at favorable phases of the alpha rhythm (Michel, Dugué, Busch, 2020), in a way that a specific phase of each oscillatory cycle, at the time of stimulus presentation, enables a more efficient neuronal and perceptual processing, whereas the same processing is less efficient at the opposite phase (Van Rullen, 2016).

Other investigations provided additional evidence linking neural oscillatory activity in the alpha range to visual perception and, in particular, the periodical structure of visual perception. Indeed, a series of recent EEG studies demonstrated that alpha oscillatory frequency is related to the speed and the efficiency of the visual processing (Sadaghiani, Hesselmann, Friston, & Kleinschmidt, 2010; Morillon & Schroeder, 2015; VanRullen, 2016), suggesting a relationship between alpha rhythm and the tendency of the visual system to process information within different temporal windows. In particular, it was demonstrated that faster alpha frequencies are predictive of a more accurate flash discrimination in a two-flash illusion task (Samaha & Postle, 2015), indicating that the frequency of alpha rhythm is strongly related with the temporal resolution of visual perception.

Crucially, this accumulating evidence, revealing the existence of task-dependent variations in alpha parameters, usually accompanied by fluctuations in perceptual performance (Mathewson et al., 2009), pointed out that both oscillatory and perceptual activity are not invariant and stationary processes, but rather change during the course of an experimental session, according to task demands. This opened window on a promising avenue of research aiming at modulating alpha oscillatory activity by directly stimulating the underlying neuronal networks with controlled stimulation protocols. In this respect, promising results have been achieved by manipulating endogenous alpha oscillations through

rhythmic entrainment, a method based on a mechanism of temporal alignment of intrinsic brain oscillations to an external periodic stimulation, affecting also perceptual performance (Thut et al., 2011; Mathewson et al., 2012; de Graaf et al., 2013). Several studies employing different entrainment methodologies, such as transcranial magnetic stimulation (TMS) and sensory stimulation, demonstrated that periodic stimulation given at alpha frequency is effective in modulating alpha-band oscillatory activity both during the stimulation and at the stimulation offstet (Spaak et al., 2014), with a concurrent modulation of perceptual outcome (Mathewson et al., 2012; de Graaf et al., 2013; Spaak et al., 2014). For instance, a recent EEG investigation described an increased visual awareness for targets presented in-phase with a preceding 12 Hz visual stimulation together with a phase-locking of neural oscillatory activity during the stimulation, with maximum effect over the parieto-occipital scalp sites (Mathewson et al., 2012). Moreover, another study has recently demonstrated that an audio-visual entrainment, given at either 8.5 Hz or 10.5 Hz, resulted in a phase alignment of the perceptual performance across subjects and, importantly, in a shift of the average peak of the power spectrum towards the entrainment frequency that was employed in the stimulation (Ronconi & Melcher, 2017). Overall, this converging research provide strong evidence for a direct link between neural oscillatory activity in the range of alpha and various aspects of visual perception. Therefore, additional research investigating the relationship between alpha oscillatory parameters and visual perceptual processing may help further clarify how the neural oscillatory activity in this frequency band actively shapes visual perception.

3.1.3 Oscillatory correlates of the functionality of the visual system: resting-state alpha oscillatory activity

In addition to this wide body of research linking alpha oscillations to visual performance, neural oscillatory activity in the alpha range has also been reported since the earliest EEG studies in human research (Berger, 1929) as the dominant EEG rhythm in the healthy resting awake brain, with maximum amplitude over the parieto-occipital regions when the eyes are closed (Rosanova et al., 2009). Such increase in alpha power in a condition of eyes-closed resting-state was traditionally interpreted as a sort of brain standby state (Palva & Palva, 2007). Early observations of increased alpha power also during meditation (Travis & Wallace, 1999) and some states of coma (Niedermeyer, 1997; Ben-Simon et al., 2008) further supported this idea of alpha oscillations as the brain "idle rhythm". However, more recent findings have been taken in support to an alternative hypothesis, postulating that increased alpha power may be associated to tonic and distributed synchronous activity

of the underlying neural populations (Klimesch et al., 2007; Sadaghiani & Kleinschmidt, 2016). More specifically, according to this hypothesis, increased alpha power during eyes-closed resting state, as recorded especially over parieto-occipital electrodes, might represent an index of active suppression of neural predictions in the visual system (Sadaghiani & Kleinschmidt 2016), reflecting an active engagement of the neurons of the underlying oscillating networks.

Furthermore, a well known fundamental property of the alpha rhythm at rest is the reduction of the oscillatory power at the opening of the eyes, a phenomenon known as alpha desynchronization or alpha blocking (Berger, 1929), which has been often thought to represent a neurophysiological marker of widespread cortical activation in the transition from the eyes-closed to the eyes-open resting state (Barry, Clarke, Johnstone, Magee, & Rushby, 2007). Alpha desynchronization at opening of the eyes was shown to induce changes also in non-alpha frequency bands, which, however, have a more focal distribution (Barry et al., 2007; Barry & De Blasio, 2017) and may be associated with lower-level stimulus processing (Barry & De Blasio, 2017; Gevins, Smith, McEvoy & Yu, 1997; Grillon & Buchsbaum, 1986). More specifically, eyes-opening induced alpha desynchronization at rest may reflect a widespread cortical activation, which allows focal changes in non-alpha bands, to gather visual information (Barry & De Blasio 2017; Barry et al., 2007; Marx et al., 2003). In this perspective, it has been hypothesized that such complex interplay between widespread and local oscillatory changes at the opening of the eyes may rely on distributed cortical and subcortical interactions, reflecting increased active engagement of visual system at rest (Barry & De Blasio, 2017), indicating that alpha resting oscillatory activity represents a valuable index of the functionality of the visual system. Another important aspect that has been extensively acknowledged, is that the tonic alpha power measured at rest is associated with subsequent task-related phasic changes in alpha activity and has a positive correlation with perceptual performance (Klimesch ,1997; 1999; Mathewson et al. 2009; Cecere, et al., 2015), suggesting a relationship between efficient task execution and alpha oscillatory power at rest. Notably, a series of more recent EEG investigations on patients with posterior brain damage and visual field defects provided additional evidence linking alpha oscillatory parameters at rest to the functionality a of the visual system. Indeed, these studies revealed that posterior brain lesions, disrupting the neural circuits of the visual system and inducing visual field defects, resulted in a reduced speed of alpha oscillations and in an interhemispherically imbalanced alpha power, in favor of the intact hemisphere (Pietrelli et al., 2019). Crucially, these studies showed also that altered alpha activity in hemianopic patients was predictive of their perceptual performance in visual tests, suggesting that post-lesional changes in alpha oscillatory activity represents a valuable index of the functional integrity of the visual system. Overall, this converging evidence, helped shed light on the neural and electrophysiological correlates of the functionality of the visual system in the

healthy and in the lesioned brain, demonstrating that the different alpha parameters have a direct influence on various aspects of visuospatial performance and providing strong indication that alpha oscillatory activity, even at rest, may represent a reliable index to assess the functionality and the integrity of the visual system.

3.2 Hemispheric differences in the functionality of the visual system

A wide body of research supports the notion that the left and right brain hemispheres may give a differential contribution in perceptual and visuospatial processing (Duecker & Sack, 2015; Heilman & Van Den Abell, 1980; Kinsbourne, 1977).

In particular, several studies in healthy participants (Gitelman et al., 1999; Nobre et al., 1997) and a variety of investigations describing the behavioral consequences of brain damage have provided evidence for a dominant role of the right hemisphere in visuospatial abilities. These latter investigations focused on patients suffering from spatial hemineglect, a syndrome characterized by a failure to perceive and respond to stimuli on the contralesional hemispace and by a distorted representation of the contralesional part of space. Indeed, the hemineglect syndrome, which is caused by lesions to frontal, parietal, or subcortical structures, is more common and severe following right hemisphere lesions, compared to left hemisphere lesions (Bisiach & Luzzatti, 1978, Heilman & Valenstein, 1979; Heilman, Valenstein & Watson, 1984), suggesting the presence of a cortical asymmetry in the high-order representation of the visual field (Bisiach, 1978; Heilman, 1984).

Crucially, it has been demonstrated that also healthy participants exhibit a slight but consistent spatial bias toward the left visual field, showing the tendency to overestimate the left compared to the right part of the visual field, a phenomenon known as pseudoneglect (Bowers & Heilman, 1980). The magnitude of the pseudoneglect in healthy participants is smaller compared to the severe rightward bias observed in neglect patients. However, the pseudoneglect has been consistently reported across individuals in different experimental tasks (Jewell & McCourt, 2000), such as the line bisection task and the Greyscales tasks, demonstrating that the pseudoneglet interest both the perception of length (McCourt & Olafson, 1997) and of brightness across the horizontal axis of the visual field (Nicholls, Bradshaw, & Mattingley, 1999). In addition, healthy participant show also the tendency to have an overestimated perception of size and numerosity when items are presented in the left compared to the right visual field (Nicholls et al., 1999). Importantly, it has been observed that the same experimental manipulations induce the same modulation of the spatial bias in healthy participants and neglect patients. Specifically, both neglect and pseudoneglect biases are modulated in the same direction by

stimulus length, position along the horizontal and vertical midlines of the visual field and viewing distance (McCourt & Jewell 1999). This made possible to hyothesize that both neglect and pseudoneglect rely on the same neural mechanisms leading to a right hemisphere specialization in the mediation of visuospatial abilities. However, these mechanisms sustaining the asymmetry in visuospatial processing between the right and the left hemisphere have not been fully understood yet (Gitelman et al. 1999). In light of the accumulated evidence describing the prevalence of spatial hemineglect following to right compared to left hemisphere lesions, two classical theories attempted to explain the observed hemispheric asymmetries in visuospatial processing, the Heilman's hemispatial theory (Heilman & Valenstein, 1979; Heilman & Van Den Abell 1980) and the Kinsbourne's opponent processor model (Kinsbourne, 1977). The Heilman's hemispatial theory posits that the right hemisphere is able to represent both the contralateral and the ipsilateral visual hemifields, whereas the left hemisphere can represent the contralateral hemifield only (Heilman & Valenstein, 1979; Heilman & Van Den Abell, 1980). Based on this theory, a lesion of the left hemisphere would be expected not to affect the high-order representation of the entire visual field, due to the ability of the intact right hemisphere to represent both left and the right hemifield. In contrast, a lesion to the right hemisphere would severely impair the representation of the entire visual field, because the spared left hemisphere cannot concurrently represent both the contralateral and the ipsilateral visual field. The Kinsbourne's opponent processor model, instead, postulates that each hemisphere has a natural visuospatial bias toward the contralateral visual hemifield, with the left hemisphere inducing a stronger bias toward the right hemifield, compared to the bias toward left induced by the right hemisphere (Kinsbourne, 1977). In addition, according to this theory, the bias of the two hemispheres is typically balanced in healthy subjects, due to a mechanism of reciprocal interhemispheric inhibition. However, when a brain lesion occurs in one hemisphere, contralateral bias of the spared hemisphere is no longer counterbalanced by the other hemisphere bias, resulting in an impairment in the representation of one affected hemifield with a concurrent over activation of the spared hemifield. As a consequence, since the right hemisphere bias toward the left hemifield is not particularly remarkable according to this theory, a lesion occurring in the left hemisphere would not to severely impair the high-order representation of the visual field. In contrast, a lesion to the right hemisphere would severely affect the high-order representation of the entire visual field, because of the strong bias of the spared left hemisphere toward the right hemifield postulated by the Kinsbourne’s model.

Besides of these two classical theories, another theory proposing a functional-anatomical model of attentional control that accounts for the hemispheric asymmetries has been recently described (Corbetta & Shulman, 2002). Specifically, in this model, the attentional system is considered as the

result of the interaction of two different networks: a bilateral dorsal fronto-parietal network, and a right-lateralized ventral fronto-parietal network. The bilateral dorsal fronto-parietal network, including the frontal eye field and posterior parietal cortex, is involved in the endogenous shifts of spatial attention and the top-down modulation of sensory areas. The right-lateralized ventral fronto-parietal network, instead, which comprises the temporo-parietal junction and ventral frontal cortex, is involved in the exogenous disengaging of spatial attention when a salient stimulus occurs. Importantly, in the authors' view, the hemispatial neglect would be caused by lesions to the ventral fronto-parietal network, suggesting that the hemispatial neglect syndrome can be interpreted as an impairment in the exogenous reorienting of spatial attention. Because the ventral fronto-parietal network is right-lateralized, according to this model the hemispatial neglect would be then expected to be induced mostly by lesion occurring in the right hemisphere, rather than in the left hemisphere. Aside of these different theories, evidence about the asymmetry between the right and left hemispheres in the representation of space and modulation of spatial attention has been further supported by additional investigations employing non- invasive brain stimulation techniques. Indeed, it has been demonstrated that applying a TMS pulse on the right parietal cortex or right Frontal Eye Fields (FEF) induces a rightward bias in a line bisection task, whereas following to same TMS pulse on the left parietal cortex or left FEF no effect was observed (Fierro et al. 2000).

Similarly, proof for hemispheric asymmetries in visuospatial abilities was provided also by several neuroimaging studies. For instance, in a PET study, aiming at investigating the neural systems involved in shifting spatial attention to visual stimuli in the left or right visual field, two distinct responses were localized for attention to left and right visual field in the right superior parietal lobe (Corbetta, Miezin, Shulman & Petersen, 1993; Nobre et al., 1997). Another study reported the existence of a bilateral parieto-frontal network, previously described only in monkey, whose hemispheric lateralization predicted the degree of specialization of the right hemisphere for visuospatial attention. In particular, larger Superior Longitudinal Fasciculus (SLF) II volumes in the right hemisphere predicted greater bias to the left in the line bisection task (Thiebaut de Schotten et al., 2011) in healthy participants.

Overall, this converging evidence provides strong proof for the existence of a dominant role of the right hemisphere in visuospatial abilities. However, whether the two brain hemispheres may give a differential contribution also in supporting the oscillatory mechanisms behind the processing of visuospatial information is still debated. Indeed, in light of the evidence demonstrating a crucial involvement of alpha oscillations in shaping visual perception and visuospatial attention (Thut et al, 2006; Mathewson et al., 2009; Rihs et al., 2009; Capilla et al., 2014), it can be hypothesized that the right hemisphere may have a dominant role also in orchestrating these oscillatory mechanisms.

Nevertheless, hemispheric asymmetries in alpha oscillatory patterns still need to be fully elucidated. Indeed, hemispheric asymmetries in the alpha range were mainly investigated in frontoparietal networks and linked to psychiatric conditions (Ocklenburg et al., 2019; Stewart, Towers, Coan & Allen, 2011; Bruder, Tenke, Warner & Weissman, 2007 Bruder et al., 2005; Metzeger et al., 2004) to hand preference (Ocklenburg et al 2019; Papousek & Shoulter, 1999). However, more recently, a number EEG studies in healthy participants (Gallotto et al., 2020) and brain lesioned patients (Pietrelli et al., 2019), suggested that the right and the left brain hemispheres may give a differential contribution in sustaining the neural oscillatory mechanisms supporting visuospatial abilities in the alpha frequency band.

For instance, a recent EEG investigation on spatial orienting following directional cues in healthy participants described a decreased alpha power in the left hemisphere to facilitate visual processing in the contralateral field, whereas alpha activity in the right hemisphere was shown to both decrease to enhance cued stimulus detection in the contralateral field, and to increase to inhibit distractors in the contralateral field, when attention is cued to the ipsilateral field. (Gallotto et al., 2020). In addition, other studies reported imbalanced alpha resting activity, with evidence of greater alpha oscillatory power in the right hemisphere (O'Boyle & Benbow, 1991). Additional evidence suggesting a dominant role of the right hemisphere in orchestrating the brain oscillatory patterns that are linked to the functionality of the visual system comes from a series of EEG studies in patients with posterior brain lesion and hemianopia. In one of those studies, for instance, it was demonstrated that lesions to the right posterior cortices in hemianopic patients result in a more severely altered alpha oscillatory activity in an eyes-closed resting condition. In particular, it was demonstrated that hemianopic patients with right posterior lesions, compared to left-lesioned hemianopics, had a more pronounced slowdown of the individual alpha frequency peak (IAF) in both the intact and the lesioned hemisphere and a greater alpha power imbalance between the intact and the lesioned hemisphere, in favor of the intact one, which explained their perceptual performance (Pietrelli et al., 2019). This indicates that lesions to the right posterior cortices have more detrimental effects over the functioning of the visual system, in line with the notion that the right hemisphere has a dominant role in visuospatial processing (Heilman & Valenstein, 1979; Jewell & McCourt, 2000; Corballis et al., 2002; Nicholls et al., 2002; Nobre et al., 1997).

Overall, this accumulating evidence add to previous knowledge on hemispheric asymmetries in visuosptatial processing (Kinsbourne, 1977; Heilman & Van Den Abell, 1980) and help shed light on the different contribution of the left and the right brain hemispheres in sustaining the electrophysiological mechanisms underlying the functionality of the visual system in both healthy participants and brain lesioned patients, favoring the notion that the right hemisphere plays a

dominant role in perceptual and visuospatial processing (Bisiach & Luzzatti, 1978; Heilman et al., 1984; Gitelman et al., 1999; McCourt & Jewell, 1999; Jewell & McCourt, 2000; Corballis et al., 2002). However, the neural and the anatomical basis of the right hemisphere dominance in visuospatial processing are only partially known. Therefore, further investigations are needed for a better understanding of the mechanisms underlying the hemispheric asymmetries in visual perception and in visuospatial attention.

Chapter 4

Cortical and subcortical plasticity of the visual system in the healthy and in the lesioned brain

4.1 Plasticity of the visual system in the healthy brain

The structural and functional organization of the visual system is experience-dependent and can be effectively modeled to meet the environmental needs. In line with this view, several studies have consistently demonstrated that different visual functions in the adult healthy brain are susceptible to structural and functional modifications, based on mechanisms of neural plasticity. For instance, in perceptual learning paradigms, a repeated exposure to visual stimuli in detection or discrimination tasks induces enhancements in the perceptual performances and a functional reorganization of the visual system (Liu & Weinshall, 2000). In addition, it was shown that plasticity-related improvements in visual performance can be achieved also when visual stimuli are repeatedly paired with other perceptual information (Shams & Kim, 2012) in multisensory integration paradigms, or when brain intrinsic oscillatory patterns are promoted through external rhythmic stimulations (Thut et al., 2011; Mathewson et al., 2012; Ronconi & Melcher, 2017).

4.1.1 Learning-induced plasticity: visual perceptual learning

A well-known process associated with the plasticity of the visual system is the visual perceptual learning (VPL), defined as the mechanism through which the adult visual system shows long-term improvements in perceptual performance, resulting from a repeated visual experience (Sasaki et al., 2010). Several behavioral and physiological studies revealed the existence of long-term modifications in different brain areas after repeated exposure to visual input, suggesting that VPL involves distributed neural processes and neuronal plasticity. For instance, it was demonstrated that VPL training of primitive visual features, such as orientation (Schoups et al., 2001), motion (Ball & Sekuler, 1981) texture (Karni & Sagi, 1991) and Vernier acuity (Fahle & Edelman, 1993) lead to dramatic improvements in sensitivity and reaction times. In addition, it was shown that such improvements can be highly specific to the trained stimulus features, like orientation (Schoups et al., 2001) and direction (Watanabe et al., 2002), suggesting that the neural dynamics of VPL are mediated by modifications in the cortical circuits within the early visual areas solving the trained perceptual task (Fahle, 2005). This hypothesis has been further supported by extensive research describing

changes in early visual areas induced by repeated training. Several fMRI studies, for example, revealed an increased BOLD signal in regions of V1 corresponding to the location of the trained stimulus during contrast-discrimination tasks (Furmanski et al., 2004) and texture-discrimination tasks (Schwartz et al., 2002). In addition, single-cell recordings on monkeys, revealed enhanced responses of neurons in V1 with receptive fields lying on the contour, and suppressed responses for those on the noisy background, after repeated exposure to contour-detection task (Yan et al., 2014).

Although most of the experimental studies on VPL focused on the processing that takes place during the training, more recent investigations focused also on the consolidation phase occurring after the training, providing additional knowledge on the mechanisms through which VPL- induced changes are translated into stable modifications within the visual system and on the timing for such long-term modifications to be established. In this respect, it was shown that the consolidation of the improvement achieved through VPL requires sleep. For instance, it was demonstrated that sleep deprivation nullifies the effects of VPL (Gais et al., 2000), especially within the first 30 h after the training sessions (Stickgold et al., 2000), suggesting that sleep plays a fundamental role in the consolidation of VPL effects and, importantly, that there is a critical time window for such consolidation to occur, that seems to be shorter than 30 h in humans (Stickgold et al., 2000). However, it is still not fully understood which brain areas are involved in sleep-related VPL consolidation. Indeed, a fMRI study brought evidence of increased BOLD signal in trained regions of V1 during sleep after training, suggesting a plastic reorganization of primary visual cortex (Yotsumoto et al., 2009), but whether other brain areas are involved is VPL sleep consolidation remains unclear. This accumulated evidence emphasizes the role of V1 in both VPL training and consolidation phases. However, in a contour-shape discrimination task, it was shown that neural sensitivities to the trained shapes are enhanced also in higher visual areas along the ventral pathway (Kourtzi et al., 2005), suggesting that VPL-induced changes are likely to induce a global reorganization of sensory representations.

Another interesting aspect of VPL is that this mechanism seems to occur even in situations that lack attention and conscious effort (Baker et al., 2005). Nevertheless, active engagement in the task and focused attention on the stimulus feature seem to play a crucial role in driving neuronal plasticity in perceptual learning. . Indeed, focused attention is a well-known plasticity-inducing factor that may affect the learning process through the activation of neuromodulatory signals, such as acetylcholine and dopamine (Seitz & Dinse, 2007). In line, it was shown that learning-induced adaptations are also reflected in major modifications of functional connectivity between the visual cortices and the frontoparietal task networks (Lewis et al., 2009), giving rise to the conceptualization that VPL originates from a complex interplay across multiple cortical areas engaged in sensory processing, top-

down attentional control, and perceptual decision making. Nonetheless, the exact mechanisms behind VPL are not completely understood and still need to be fully characterized.

4.1.2 Multisensory-induced visual plasticity

Several studies reported the existence of multisensory-mediated enhancements in visual performance in different tasks, including visual detection (Bertini et al., 2008; Gleiss & Kayser, 2013), judgments on temporal duration or order (de Haas et al., 2013), visual orientation sensitivity (Caclin et al., 2011) and visual localization (Freeman et al., 2018). These investigations, describing multisensory-mediated improvements in visual performance, have been further supported by additional evidence, showing that a multisensory stimulation, evoking TMS-induced visual phosphenes, leads to an increase in visual cortex excitability (Convento et al., 2013). Based on human neuroimaging studies, it has been hypothesized that the multisensory interactions imply the activity of multiple brain pathways and structures, including the SC (Stein & Stanford, 2008), and early sensory and associative cortical areas (Ghazanfar & Schroeder, 2006). Interestingly, single neuron recordings in the SC suggested that multisensory integrative abilities may not present at birth and rather emerge and develop following to sensory post-natal experience (Stein et al., 2014). In addition, plastic adaptations in multisensory SC neurons were shown to occur throughout the adulthood, suggesting that multisensory integrative processes, relaying on complex interactions between subcortical and cortical sites of multisensory convergence, are ruled by mechanisms of neural ongoing plasticity (Stein et al., 2014). As previously discussed in chapter 4.1.1, repeated exposure to visual stimuli in VPL paradigms leads improved perceptual performance and functional modifications within the visual system (Sasaki et al., 2010). Based on these observations, it has been of great interest to investigate also the long-term effects of repetitive multisensory interactions on VPL. Indeed, a number of studies revealed improvements in rate and magnitude of VPL when combining visual signals with cues in other sensory modalities, compared to learning in the visual modality alone (for a review see Shams & Kim, 2012), demonstrating the existence of cross-modal facilitation of unisensory learning. In particular, it was shown that the repetition of a training in which a visual motion stimuli was paired with auditory stimuli moving in the same direction led to an increase in motion detection and discrimination abilities, compared to repeated exposure to training consisting in visual motion stimuli only (Seitz et al., 2006). However, when the visual motion stimuli were associated with incongruent auditory stimuli moving in the opposite direction, no facilitation in the performance was observed, suggesting that such facilitation might be not due to alerting effects induced by the sounds (Kim et

al., 2008). This evidence has been further supported by other studies, showing the existence of multisensory- induced plastic changes in visual discriminative abilities. In particular, it was demonstrated that a training in which participants were instructed to detect and perform a saccade towards repetitive audio-visual stimuli presented in spatial and temporal coincidence, caused an enhancement in motion discrimination, as well as an increase in the N1 ERP component related to visual discriminative abilities (Grasso et al., 2016a). Interestingly, the same post-training enhancement was not found in an orientation discrimination task, suggesting that the multisensory training produced selectively enhanced electrophysiological responses only in the dorsal stream. In addition, the relevance of multisensory integration processes in the observed results was confirmed by the lack of changes in the electrophysiological responses in a control condition in which the audio-visual training was administered using pairs of stimuli that violate the spatial rule of multisensory integration (Stein & Meredith, 1993). This has been proposed to be related to training-induced boosted activity in the multisensory subcortical circuit, conveying visual information from the retina to the SC and projecting to dorsal extrastriate areas. Another important aspect that has been enlightened in visual learning paradigms including multisensory-trainings, is that visual performance, relying on the dorsal stream, can be enhanced by a the repeated exposure to audio-visual stimuli that are completely unrelated to the visual task, therefore suggesting that training with paired audio-visual stimuli might change the effectiveness with which the brain process other visual signals (Rowland, 2016).

Overall, this converging evidence supports the notion that repetitive stimulation with stimuli in multiple senses can induce plastic changes in visual responses, enhancing visual performance. However, the exact brain mechanisms underlying this process are not fully understood. On the one hand, it has been hypothesized that the effects of multisensory trainings on visual learning might be based on a "learning threshold" mechanism. According to this hypothesis, multisensory processing would increase the unisensory representations by modulating the threshold of neural activation in visual areas needed for perceptual learning to occur (Kim et al., 2008; Shams & Kim, 2012). This can be achieved in many ways, including multisensory-induced increases in firing rate of unisensory neurons (Allman et al., 2008) or reducing response latencies of unisensory visual areas (Martuzzi et al., 2007). On the other hand, an alternative hypothes hypotheis postulates that multisensory facilitation of visual learning may rely on a "recruitment" mechanism. This would imply that the repeated exposure to multisensory stimuli may strengthen the functional connectivity between primary visual areas and other modality-specific sensory areas (Shams & Seitz, 2008; Shams & Kim, 2012). As a consequence, a larger network including multiple sensory structures would be recruited in multisensory training compared to training based on visual stimuli only, resulting in an greater

improvement in visual performance (Shams & Kim, 2012). Although the exact underlying mechanisms still need to be elucidated, the accumulated evidence of multisensory-mediated enhancements in VPL paradigms strongly suggest that the nervous system is equipped to respond to multiple sensory modalities and to adapt to plastic changes involving different sensory sources

4.1.3 Entrainment-induced visual plasticity

A large body of evidence has supported the hypothesis that our brain samples information periodically by discretizing visual inputs (Busch & VanRullen, 2010). This process may require fast changes in the functional architecture of the brain engaged networks, which possibly rely on dynamic interactions and plastic adaptations. As extensively discussed in chapter 3, several experimental studies showed that neural oscillations in the alpha (7–13 Hz) range are responsible for shaping visual perception through a mechanisms of pulsed inhibition of the ongoing cortical activity that relies on a precise spike timing (Busch et al., 2009). Indeed, alpha oscillations have an influence on the ongoing sensory processing and visual awareness (Thut et al., 2006; Van Dijk et al., 2008; Mathewson et al., 2009) and is related to the intrinsic tendency of the visual system to process information within different temporal windows (Sadaghiani et al., 2010; Samaha and Postle, 2015; VanRullen, 2016). In the absence of experimental manipulations, alpha oscillations are thought to spontaneously fluctuate around their mean frequency and power (Romei et al., 2008a; 2008b; Samaha & Postle, 2015). However, stimulus-dependent variations in alpha parameters (i.e. frequency and power), usually accompanied by fluctuations in perceptual performance, were shown to occur in the time course of an experimental session (Mathewson et al., 2009), suggesting that both oscillatory and perceptual activity are not invariant and stationary processes. These results strengthened the idea that variations in alpha oscillatory parameters, and the concurrent perceptual fluctuations, are likely to be explained by plastic adaptations in the underlying oscillating networks over time. As a consequence, it has been possible to hypothesize that such plasticity-related changes may be effectively modulated by directly stimulating the neuronal substrate with controlled stimulation protocols. Indeed, promising results have been obtained by manipulating endogenous oscillations through rhythmic stimulation protocols (entrainment), leading to a phase alignment of the intrinsic brain oscillations to an external periodic stimulation, with resonance also in perceptual activity (Thut et al., 2011; Mathewson et al., 2012; de Graaf et al., 2013). Although the exact brain dynamics underlying this phenomenon stillneed to be elucidated, several studies employing different forces including rTMS, transcranial alternate current stimulation (tACS) and sensory stimulation, convincingly demonstrated that periodic stimulation

given at alpha frequency results in a rhythmicity of alpha-band ongoing activity and, as a consequence, to a cyclic modulation of the perceptual performance (Mathewson et al., 2012; de Graaf et al., 2013; Spaak et al., 2014). For instance, it was shown that applying TMS at alpha frequencies affects oscillatory activity as measured by EEG responses (Thut et al., 2011) and perceptual performance (Romei et al., 2010). Similar results were achieved also in other types of paradigms, based on sensory stimulation procedures. In a visual stimulation protocol, for example, a 10 Hz sensory entrainment, but not an entrainment administrated at non-alpha frequencies, resulted in an effective modulation of alpha oscillatory activity within the visual cortex (Herrmann, 2001), suggesting that brain oscillating networks can be successfully entrained when stimulated at their preferential frequency. In line, another study described an increase in visual awareness for targets presented in-phase with a preceding 12 Hz visual stimulation together with a phase-locking of neural oscillatory activity during the stimulation, with greater effect over the parieto-occipital cortices (Mathewson et al., 2012). These findings were further supported by subsequent investigations showing that plastic rearrangements in alpha oscillating networks correspond to relevant variations in alpha oscillatory parameters. In this respect, it was recently demonstrated that an audio-visual entrainment, given at either 8.5 Hz or 10.5 Hz, leads to a phase alignment of the perceptual performance across subjects and, importantly, to a shift of the average peak of the power spectrum towards the entrainment frequency that was employed in the stimulation (Ronconi & Melcher, 2017). Crucially, such modulations occurring during the entrainment (i.e. online; Halbleib et al., 2012) were shown to occur also at the entrainment offset (i.e. offline), both at neural as well at perceptual level- Indeed, changes in ongoing oscillations, induced by brief periods of entrainment (~ 1 sec), were shown to shortly outlasts the stimulation train for approximately 300 ms (Mathewson et al., 2012; De Graaf et al., 2013; Spaak et al., 2014). In addition, it was demonstrated that participants exhibiting stronger effect during the entrainment (i.e increased alpha-power during the rhythmic stimulation) also tend to exhibit greater entrainment aftereffects (Helfrich et al., 2014). Still, an open question is which kind of neuronal plasticity the online and offline entrainment-induced modulations are based on. To address this controversial aspect, it has been argued that online entrainment process may reflect a neural mechanism of resonance that possibly induce synaptic plasticity at the entrainment offset. More specifically, it has been hypothesized that the activation of alpha oscillatory networks during online entrainment eventually leads to longer-lasting adaptations, which are based on a mechanism of spike-timing dependent plasticity (STDP; Zaehle et al., 2010) and translate into changes in alpha oscillatory parameters. Crucially, it has been also hypothesized that those effects can be induced only in specific resonant networks and when the stimulation frequency falls into a narrow range of frequencies, which might be equal or slightly higher or lower than the individual alpha peak (Zaehle

et al., 2010). Nonetheless, a suitable width of the stimulation-frequency window, giving rise to the strongest entrainment effects, has been not yet well established. Therefore, further research is needed to understand whether small or large deviations from the individual alpha frequency peak possibly induce differential outcomes in terms oscillatory neural and perceptual activity. Another noteworthy aspect that still needs to be disambiguated concerns whether prolonged stimulation protocols may lead to longer-lasting plasticity-induced modulations of neural oscillatory activity and perceptual performance. Although persistent post-stimulus entrainment effects have not yet been demonstrated, the accumulated proof of transient enhancements (~ 300 ms) in brain and behavioral activity as a result of short trains of stimulation (~ 1 sec) hold promise for prolonged entrainment paradigms to selective speed up or slow down visual processing and effectively impact visual awareness, through longer-lasting plastic reorganization of the underlying oscillating networks.

4.2 Plasticity of the visual system in the lesioned brain

As it has been discussed above, the human visual system has an extremely complex, experience-dependent organization, which makes it capable to carry out sophisticated computations and to modify its functioning, connectivity and structure, based on mechanisms of neural plasticity. This ability, which is intrinsic and retrievable along the lifespan, can be externally modulated with different methods, which have been described in the previous paragraphs. However, the visual system is also capable to face adverse situations, rearranging itself both functionally and structurally also following to brain damage. In the lesioned brain, the activity of alternative visual circuits is unmasked when the functioning of the primary visual pathway is prevented. These circuits are thought to support visual functions when V1 is damaged in early life. However, these alternative pathways seem to be recruited also when the lesions occurs in the adulthood, supporting residual visual functions. Indeed, primate studies showed that when lesions to V1 occur in the first post-natal weeks, the visual pathway from the pulvinar to MT is maintained until the adulthood, supporting visual behavior pertaining to the dorsal stream (Warner et al., 2015). In addition, as extensively discussed in chapter 2, a series of human studies consistently showed that blindsight abilities and implicit visual processing after lesions to the visual cortex occurring in adulthood might rely on subcortical visual pathways connecting the SC or the LGN with extrastriate areas (Tamietto & Morrone, 2016), strengthening the idea that alternative subcortical visual circuits retain a crucial role in visual functioning also in adulthood and support the post-lesional plastic rewiring, allowing residual visual abilities. The recruitment of these alternative visual routes, independent from V1 and resisting after lesion, has also been proposed to

have a role in spontaneous visual field recovery (Sabel et al., 2011b). However, these alternative circuits are thought to play a crucial role also in the effects produced by compensatory rehabilitative trainings, aiming at implementing effective oculomotor exploratory strategies of the blind visual filed, based on plastic mechanisms (Dundon et al., 2015b; Grasso et al., 2016b).

Although evidence is accumulating on the role of this subcortical pathways in the development and the recovery of visual function, other studies based on restorative approach, which aim at promoting restitution of the defective visual function, enlightened that that both within-system and network plasticity and cortical reorganization may contribute to visual restorative mechanisms, as it will be discussed in the following paragraph.

4.2.1 Rehabilitation-induced plasticity: vision restorative training

According to the residual activation theory, brain lesions in the visual areas usually do not fully disrupt the affected tissue (for a review see Sabel et al., 2011a,b). Indeed, areas of spared tissue can be found within the lesion, although neurons in these residual areas have poor firing synchrony and synaptic strength, with consequent reduced visual functionality. In line with this theory and based on these observations, restorative approaches for visual rehabilitation aim to increase the sensitivity of the residual tissue, strengthening neural activity and synaptic plasticity, to expand the visual field itself (Sabel et al., 2011b). Converging evidence revealed the presence of transition zones of relative defects at the border between the damaged and intact visual field (Kasten et al., 1998b), functionally representing the cerebral areas with partial damage, that can be reliably detected through techniques of high resolution perimetry. Although, the quality of visual perception in visual residual areas is reduced, as demonstrated by increased response times to visual stimuli and poor discrimination abilities (Sabel & Kasten, 2000), neurons surviving the cerebral damage in transition areas are thought to retain plastic properties and, as a consequence, have been targeted by therapeutic intervention through vision restoration therapy (VRT; Sabel & Kasten, 2000). Specifically, in VRT, after the dentification of residual visual areas, patient undergo repetitive visual stimulation protocols in which they are asked to detect static stimuli presented in the target area, or dynamic stimuli appearing either in the in the intact or in the blind filed and moving towards the border of the area of residual vision (Kasten et al., 1998b). These training protocols, requiring daily sessions of 30–60 min for at least 6 months, are adaptive and visual stimulation progressively moves towards the blind field, according to patients' performance. Several studies described VRT-mediated visual field improvements (Dundon et al., 2015a), with average visual field border shifts of 5 of visual angle (Kasten et al.,

1998b). However, the efficacy of VRT is still debated, due to the possible presence of compensatory saccadic eye movements during visual field tests (Bouwmeester et al., 2007). Different plastic mechanisms have been proposed to underly vision restoration. Indeed, based on results of few animal studies, it has been argued that plastic adaptations of the residual tissue in the damaged visual system itself (i.e., within-system plasticity) may promote reactivation of surviving cells or enhancement of their synaptic transmission (Prilloff et al., 2007). In addition, it has been hypothesized that vision restoration may rely also on changes in the brain areas that are not directly affected by the injury which, however, suffer consequent functional differentiation. Interestingly, activity in the visual areas of the intact hemisphere has been observed after vision restoration (Henriksson et al., 2007). In addition, few investigations revealed that post-training activation to visual stimuli occur in a wide cortical network, including extrastriate areas (Ho et al., 2009), higher order visual areas in the occipito-temporal and middle temporal regions (Marshall et al., 2008), but also distant cingulate and frontal cortices (Marshall et al., 2008), suggesting that cortical reorganization may contribute to visual restorative mechanisms. At the cellular level, it has been hypothesized that both within-system and network plasticity may rely on mechanisms of neural plasticity such as long-term potentiation (LTP), which are typically involved in learning plastic processes. Indeed, high frequency and repetitive stimulus-driven activation of surviving cells both in the damaged areas or in the network-related spared visual structures seem to induce long-term enhancements in the cell response, leading to synaptic plasticity (Sabel et al., 2011b). Overall, this evidence suggests that both ì local and distant processes give a contribution in the recovery of the visual function after restorative trainings. However, further research is needed to better understand the mechanisms underlying vision restoration.

4.2.2 Rehabilitation-induced plasticity: compensatory training

As previously discussed, restorative trainings promote local and distant changes to induce plastic modification within the visual system itself. Compensatory therapeutic interventions in hemianopic patients, instead, aim to recruit spared cerebral areas to support effective saccadic eye movements, resulting in improved functional performance (Kerkhoff et al., 1994).

In rehabilitative protocols employing visual scanning trainings, for example, patients are instructed explore arrays of stimuli by performing voluntary saccadic eye movements, in order to promote compensatory saccadic strategies in the blind field (Zihl, 1995). These trainings were shown to result in increased and faster visual detections in the patients' blind field, with improved quality of life

(Nelles et al., 2001). However, these compensatory oculomotor strategies developed in visual scanning trainings seem to rely also on working memory abilities (Hardiess et al., 2010), suggesting that this rehabilitative method might be more suitable in patients with adequate residual cognitive resources. The improved ability to systematically scan the visual scene to compensate the visual field loss has been thought to imply plastic adaptations in cortical oculomotor structures. Indeed, activity in the fronto-parietal network, comprising the frontal eye fields, the supplementary eye fields and the parietal eye fields is typically preserved in hemianopic patients (Nelles et al., 2001). In addition, it was demonstrated that changes in the pattern of activation of the oculomotor network during a simple prosaccade occur after a saccadic training, with the recruitment of additional peristriate areas of the intact hemisphere, increased activation of the supplementary eye fields and decreased activity in the ipsilesional frontal eye fields (Nelles et al., 2001). This suggesta that the scanning compensatory interventions, which typically rely on unisensory visual stimulation, promote post-training functional reorganization of the large cortical network involved in performing saccades.

On the other hand, a number of studies on hemianopic patients revealed that also multisensory audio-visual stimulation, relying on the activity of spared subcortical structures, such as the SC, is greatly effective in boosting the oculomotor system for compensating visual field defects (Dundon et al., 2015b; Grasso et al., 2016b). Indeed, converging evidence provided strong indication that (the SC has a fundamental role in integrating convergent auditory and visual inputs into a unified percept (Stein & Meredith, 1993. Bertini et al., 2008). Importantly, the inverse efficacy principle, stating that the integration of weak unisensory stimuli leads to greater behavioral multisensory enhancement, suggests that the integrative abilities of this spared subcortical retino-collicular circuit might be of great relevance to hemianopic patients, showing unisensory visual defects (Bertini et al., 2016). In line with this principle, additional evidence revealed that unseen visual stimuli delivered in the blind field improve patients' ability to localize auditory stimuli in the same spatial position (Leo et al., 2008b). The same facilitation in auditory localization was also observed after passive exposure to repetitive audio-visual pairs of stimuli presented in the blind field during adaptation sessions of 4 min (Passamonti et al., 2009), indicating that unseen visual stimuli have an influence auditotory performance also with off-line effects. However, other investigations brought also evidence that auditory stimuli can enhance performance in the impaired visual modality. Indeed, a study on hemianopic patients, reported increased visual detection for light stimuli presented in the blind field, when concurrent auditory stimuli were presented in spatial proximity (Frassinetti et al., 2005). Similarly, in a patient with bilateral lesions to the striate cortex and early extrastriate cortices (Serino et al., 2014), looming auditory stimuli effectively enhanced visual detection performance in scotomatous areas (Cecere et al., 2014b). Overall, this evidence suggests that the preserved

responsiveness of the spared retino-colliculo-extrastriate pathway to degraded unisensory visual and auditory stimuli might be employed to compensate for visual field loss (Ladavas, 2008). Indeed, the SC is involved also in the generation and programming of saccadic eye movements related to both covert and overt attention (Krauzlis et al., 2013), suggesting that it cover a central role in promoting orienting behavior towards visual stimuli in the blind field. In line with this view, a rehabilitative training exploiting audio-visual integrative mechanisms has been developed for patients with visual field defects (Bolognini et al., 2005b). Specifically, in the training, patients are instructed to perform saccades towards audio-visual stimuli presented in spatial coincidence in both the blind and intact visual field, but with a prevalence in the blind field. In a number of studies, employing this rehabilitative trainings, patients were shown to exhibit improved performance in visual detection task in which central fixation was not required and enhanced visual exploration and reading abilities (Bolognini et al., 2005b). In addition, patients' showed also improved oculomotor parameters in visual search tasks, with reduced fixations and refixations, faster and larger saccades and a reduction in exploration time and length (Passamonti et al., 2009). This training was also proved to be effective in modulating the activity of visuo-spatial attentional networks, resulting in a reduction of attentional allocation towards the intact field (Dundon et al., 2015b; Grasso et al., 2016b). Interestingly, the treatment has been shown to be suitable for patients both at the chronic and at the acute stage (Keller & Lefin-Rank, 2010) and in childhood (for a review see Purpura et al., 2017; Tinelli et al., 2015, 2017), and to have stable effects on patients' performance over time, as demonstrated by follow-up studies carried out 1 year after treatment (Grasso et al., 2016b; Passamonti et al., 2009). Few studies based on animal models favored the hypothesis that the ameliorative effects of the audio-visual stimulations may rely on the activity of the retino- colliculo-extrastriate circuit (Jiang et al., 2015). Indeed, cat rendered hemianopic by unilateral visual cortex ablation, which lost visual capacities in their blind field and visual responsiveness in the deep layers of the ipsilesional SC, were shown to regain visual responses in the superficial layers of the SC following to an intensive audio-visual training. Importantly, the re-emergence of visual responsiveness in SC mainly interested multisensory neurons, suggesting that the effects of the training were mediated by integrative mechanisms, and were driven by influences of cortical associative areas crucial in multisensory processes (i.e., AES; Jiang et al., 2015). Similar plastic mechanisms, relaying on the activity of subcortical structures involved in multisensory integrative processes, are thought to mediate training-induced improvements also in hemianopic patients (Ladavas, 2008; Bertini et al., 2016). Indeed, the convergence of multiple sensory information from different sensory modalities is likely to promote and strengthen the connections between the SC and cortical structures relevant in oculomotor planning such as the frontal and parietal eye fields (Krauzlis et al., 2013), allowing the

implementation of efficient exploratory oculomotor patterns .In line, additional evidence on hemianopic patients revealed enhanced performance in visual detection tasks only when eye movements to compensate for the loss of vision were allowed, whereas no change in post-training visual detection performance was observed when patients are required to fixate centrally (Bolognini et al., 2005b; Dundon et al., 2015b; Grasso et al., 2016b; Passamonti et al., 2009). These findings seem to suggest that such amelioration does not depend on enlargements of the visual field, but rather on the implementation of effective compensatory eye movements towards the blind field. However, saccadic eye movements were also shown to elicit responses visual cortex neurons (Herrington et al., 2009) and to lower visual perceptual threshold, indicating that the audio-visual training might have also restorative effects exceeding the mere compensation of the visual field loss. In line, neural model investigations also predicted both compensatory and restitutive effects mediated by repetitive multisensory stimulation of the colliculo-extrastriate circuit in hemianopic patients (Magosso et al., 2017). Based on these converging findings, a prominent role of subcortical circuits, interacting with cortical structures promoting orienting behavior, has been proposed, although the neural mechanisms and the plastic modifications underlying the beneficial effect of multisensory-mediated rehabilitative trainings in hemianopic patients still need to be fully elucidated. Overall, evidence provided in chapter 4 convincingly demonstrates that the visual system retains capacity for neuroplastic adaptations throughout the entire lifespan. These plastic properties enable the system to modify its functional and structural arrangement according to the variable external needs. Proof for the ability of the visual system to rearrange itself in the adulthood, changing its structural and functional architecture, has been provided by a wide body of experimental studies in both neurologically healthy participants and brain damaged patients, as extensively discussed in this chapter. Indeed, following to posterior brain lesions, the damaged visual system has been shown to be able to reorganize itself and to undergo cortical and subcortical plastic modifications, responding to effective rehabilitative interventions (Kerkhoff et al., 1994; Sabel et al., 2011b; Dundon et al., 2015b; Grasso et al., 2016b). Crucially, in the past decade, promising entrainment paradigms have successfully driven the oscillatory mechanisms of the visual system in healthy participants, exploiting the plastic processes within the underlying reverberating networks. This resulted in consistent enhancements of the oscillatory activity of the intrinsic brain rhythms of the visual system, with concurrent improvements in the visual perceptual performance (Thut et al., 2011; Mathewson et al., 2012; de Graaf et al., 2013; Spaak et al, 2014). Due to the well-established link between neural oscillatory activity in the range of alpha and visual performance (Sadaghiani et al., 2010; Morillon & Schroeder, 2015; VanRullen, 2016), these results hold promise for such stimulation protocols to improve visual abilities also in brain lesioned patients with visual field defects, exhibiting altered oscillatory activity, as previously discussed in

chapter 3. Therefore, future experimental research could focus on developing effective stimulation paradigms, which can possibly enhance the residual functionality of the visual system of hemianopic patients, promoting the intrinsic oscillatory patterns and taking advantage of the spared plastic mechanisms in the damaged visual system.

Chapter 5

Altered reactivity of brain oscillations after posterior brain damage in hemianopic patients

5.1 Introduction

Neural oscillations in the alpha range (7-13 Hz) represent the dominant EEG rhythm in the healthy awake brain, with a prominent distribution over posterior regions of the scalp during an eyes-closed resting condition (Berger, 1929; Rosanova et al., 2009).

Several experimental findings have consistently demonstrated that oscillatory neurophysiological activity in the alpha range has a direct link with visuo-spatial performance and, in particular that the different alpha oscillatory parameters (i.e. frequency, power and phase) are related to various aspects of perceptual visual processing (Pfurtscheller et al., 1994). For instance, the individual alpha frequency of occipital oscillations represents a measure of temporal resolution of visual perception (Valera, Toro, John & Schwartz, 1981; Klimesch et al., 2007; Cecere et al., 2015; Samaha & Postle, 2015) whereas alpha power (Romei et al., 2008a; 200b) and phase (Mathewson et al., 2012; Bush, Dubois & Van Rullen, 2009; Mathewson et al., 2009) reflect variations in cortical excitability and visual awareness. However, recent perspectives have also proposed an association between alpha power at rest and the tonic and distributed synchronous activity of the underlying neurons (Klimesh et al., 2007; Sadaghiani & Kleinschmidt, 2016), possibly indexing active suppression of neural predictions in the visual system (Sadaghiani & Kleinschmidt, 2016) and, therefore, reflecting an active engagement of the neurons of the underlying neural population.

A well known fundamental property of alpha oscillations at rest is the reduction of the power at the opening of the eyes, a phenomenon known as alpha desynchronization or alpha suppression (Berger, 1929), which has been often thought to represent a neurophysiological marker of cortical reactivity in the transition from the eyes-closed to the eyes-open resting state (Barry et al., 2007).

This basic physiological response at the opening of the eyes, in normal conditions, is prominently observed over the posterior areas of the brain (Marx et al., 2003; Ben-Simon et al., 2012), but occurs all over the scalp without evident focal topographical changes (Barry et al., 2007; Barry & De Blasio, 2017). In addition to alpha suppression, the opening of the eyes also induces changes in non-alpha low-frequency bands, which typically show a more focal distribution (Barry et al., 2007; Barry & De Blasio, 2017). In particular, local desynchronization in the transition from the eyes-closed to the eyes-open condition has also been observed in the theta band and has been associated with low-level stimulus processing (Gevins et al., 1997; Barry & De Blasio, 2017). In this perspective, the typical

alpha desynchronization at the opening of the eyes represents a widespread cortical activation, enabling focal changes in non-alpha bands (e.g. in the theta band) to gather visual information (Marx et al., 2003; Barry et al., 2007; Barry & De Blasio 2017). The complexity of this global and local oscillatory changes at eyes opening may thus reflect increased active engagement of visual system (Barry & De Blasio, 2017) and this engagement has been linked to widespread cortical and subcortico-cortical interactions (Başar, 1999; Klimesch, 1999). Although investigations on alpha reactivity on clinical populations are limited, alterations in alpha reactivity were found in dementia (van der Hiele et al., 2008) and schizophrenia (Colombo et al., 1989). However, little is known about how brain lesions impact the EEG reactivity caused by eyes-opening. Notably, recent evidence on patients with posterior brain lesions and hemianopia, demonstrated that lesions of the posterior cortices result in a pathological resting eyes-closed alpha oscillatory pattern, with a slowdown of the individual alpha frequency peak (IAF) and a reduction of the amplitude in the lesioned hemisphere, which was more severe in hemianopics with right lesions, compared to hemianopics with left lesions (Pietrelli et al., 2019).

On the one hand, these observations confirm that alpha oscillations at rest might reflect the functionality of the posterior cortices and of the visual system (Klimesch et al., 2007; Sadaghiani & Kleinschmidt, 2016). On the other hand, they are in line with the previous research showing a pivotal role of the right hemisphere in generating and distributing brain rhythms that are relevant for visuospatial processing (Pietrelli et al., 2019; Gallotto et al., 2020) and support the longstanding theories which postulate a dominant role of the right hemisphere in orchestrating visuospatial abilities (Kinsbourne, 1977; Heilman & Valenstein, 1979; Heilman & Van Den Abell, 1980), as extensively discussed in chapter 3. However, the evidence showing that posterior lesions alter alpha oscillatory parameters (Pietrelli et al., 2019) raise the question whether the residual alpha recorded in hemianopic patients during eyes-closed resting state can retain some functionality and whether hemispheric asymmetries might be evident in this residual functioning. In addition, lesion studies on this topic, in patients with both left and right lesions, could be especially relevant to advance our understanding on the role of specific cortical sites and the contribution of each hemisphere to the generation, distribution and functionality of the alpha rhythm on the scalp. For this reason, the present study tested whether damage to posterior cortices results in disrupted or altered alpha desynchronization in the transition from the eyes-closed to the eyes-open resting state, investigating separately the effects of left and right hemispheric lesions. In addition, local changes in non-alpha bands (theta band) at the opening of the eyes were also investigated, since alteration in the widespread alpha suppression might also induce modifications in the typical patterns of changes in lower frequency bands. To this aim, a group of hemianopic patients with posterior left lesions, a group of hemianopics with posterior right

lesions, a control group of patients with more anterior lesions and a control group of healthy participants were tested, recording EEG during rest, both during eyes-closed and eyes-open conditions. Both widespread cortical reactivity in the alpha range and local oscillatory changes in the theta range at the opening of the eyes were assessed, to investigate the effects of both left and right posterior lesions on the complex interaction between global and local processes reflecting task-independent activation of the visual system. Last, visual performance in hemianopics was also tested, to investigate whether possible alterations in EEG reactivity at the opening of the eyes can relate to residual visual detection abilities.

5.2 Methods[1]

5.2.1 Participants

Four groups of participants took part to the study: 13 patients with visual field defects due to lesions to the left posterior cortices (10 males, mean age = 53.8 years, SD = 15.89; mean time since lesion onset = 12.7 months, SD = 11.85), 13 patients with visual field defects due to lesions to the right posterior cortices (10 males, mean age = 58.9 years, SD = 16.47; mean time since lesion onset = 12.5 months, SD = 14.18), a control group of 14 patients without hemianopia with fronto-temporal lesions sparing the posterior cortices (6 males, mean age = 47.9 years, SD = 11.49; mean time since lesion onset = 25 months, SD = 21.35), and a control group of 14 age-matched healthy participants (7 males, mean age = 54.3 years, SD = 6.65). No differences between the groups were found in terms of age ($F_{3,50} = 1.36$; $p = 0.212$) or time since lesion onset ($F_{2,37} = 2.58$; $p = 0.089$; for clinical details, please see Table 5.1).

[1] Part of the data presented in this study were also published in "Gallina, J., Pietrelli, M., Zanon, M., & Bertini, C. (2021). Hemispheric differences in altered reactivity of brain oscillations at rest after posterior lesions. *Brain Structure and Function*, 1-15.". Part of the data were preliminary analyzed and presented in Pietrelli, Mattia (2020) *Post-lesional functionality of the visual system in hemianopic patients*, [Dissertation thesis], Alma Mater Studiorum Università di Bologna. Dottorato di ricerca in Psicologia, 32 Ciclo. DOI 10.6092/unibo/amsdottorato/9478.

ID	Sex	Age	Onset	Lesion Site	Visual Field Defect	Aetiology
HEMI1	M	69	5	Left Occipital	Right hemianopia	Ischaemic
HEMI2	M	45	7	Left Temporal	Right hemianopia	Hemorragic
HEMI3	F	57	28	Left Fronto-Temporo-Insular	Right hemianopia	AVM
HEMI4	M	50	7	Left Temporo-Occipito-Parietal	Upper right quadrantopia	Ischaemic
HEMI5	M	81	9	Left Occipito-Temporal	Right hemianopia	Ischaemic
HEMI6	M	51	5	Left Fronto-Temporo-Occipital	Right hemianopia	Abscess
HEMI7	M	41	2	Left Occipital	Lower right quadrantopia	Ischaemic
HEMI8	M	45	41	Left Fronto-Parieto-Temporal	Right hemianopia	Hemorragic
HEMI9	F	29	26	Left Temporal	Upper right hemianopia	AVM
HEMI10	M	58	6	Left Temporo-Occipital	Right hemianopia	Ischaemic
HEMI11	F	32	4	Left Parieto-Occipital	Right hemianopia	Ischaemic
HEMI12	M	69	8	Left Temporo-Occipital	Right hemianopia	Hemorragic
HEMI13	M	73	17	Left Temporo-Occipital	Right hemianopia	Hemorragic
HEMI14	M	56	3	Right Occipital	Left hemianopia	Ischaemic
HEMI15	F	38	13	Right Parieto-Occipital	Left hemianopia	Hemorragic
HEMI16	F	37	4	Right Occipito-Temporo-Parietal	Left hemianopia	Tumor
HEMI17	M	58	18	Right Temporo-Occipital	Left hemianopia	Ischaemic
HEMI18	M	81	7	Right Occipital	Left hemianopia	Hemorragic
HEMI19	M	51	4	Right Occipital	Left hemianopia	Tumor
HEMI20	M	60	29	Right Temporo-Occipital	Left hemianopia	Ischaemic
HEMI21	F	73	8	Right Temporo-Occipital	Left hemianopia	Ischaemic
HEMI22	M	77	6	Right Fronto-Parietal	Left hemianopia	Hemorragic
HEMI23	M	30	53	Right Temporal	Left hemianopia	Hemorragic
HEMI24	M	59	5	Right Temporo-Occipital	Left hemianopia	Ischaemic
HEMI25	M	76	7	Right Occipital	Left hemianopia	Abscess
HEMI26	M	70	5	Right Occipital	Left hemianopia	Ischaemic
CON1	F	48	38	Left Fronto-Insular	No hemianopia	Ischaemic
CON2	F	44	40	Left Frontal	No hemianopia	Tumor
CON3	M	28	11	Left Fronto-Parietal	No hemianopia	Tumor
CON4	F	45	39	Left Frontal	No hemianopia	Tumor
CON5	F	46	12	Left Temporal	No hemianopia	Hemorragic
CON6	F	57	5	Right Fronto-Insular	No hemianopia	AVM
CON7	M	42	59	Right Frontal	No hemianopia	Abscess
CON8	M	62	7	Left Temporo-Insular	No hemianopia	Abscess
CON9	F	42	19	Right Frontal	No hemianopia	Tumor
CON10	M	34	7	Left Frontal	No hemianopia	Tumor
CON11	M	51	3	Right Temporo-Insular	No hemianopia	Tumor
CON12	F	50	71	Right Temporo-Fronto-Polar	No hemianopia	Traumatic
CON13	M	75	26	Right Temporo-Insular	No hemianopia	Tumor
CON14	F	47	13	Right Frontal	No hemianopia	Abscess

***Table 5.1**. Summary of clinical data of all patients that took part to the study. Legend: M = Male; F = Female; AVM = Arteriovenus Malformation.*

Mapping of brain lesions was performed using MRIcro. Vascular lesions and lesions after surgical exeresis in case of tumor patients were documented by the most recent clinical CT or MRI were traced onto the T1-weighted MRI template from the Montreal Neurological Institute provided with MRIcro software (Rorden, Karnath & Bonilha, 2007; Rorden & Brett, 2000), with the exception of HEMI7 and HEMI21 whose MRI scans were not available. Lesion volumes were computed for each patient in order to compare the extension of the lesions among the three patients' groups. No significant differences (one-way ANOVA, $F_{2,35} = 0.90$; $p = 0.414$) among left-lesioned hemianopic patients, right-lesioned hemianopic patients and control patients were found (see Figure 5.1). Patients with posterior lesions were recruited based on reported visual field defects, the availability of a visual field perimetry (see Figure 5.2) and CT/MRI reports of the lesion. In patients with right lesions, the presence of neglect was screened using the Behavioral Inattention Test (Wilson, Cockburn, & Halligan, 1987), to ensure performance was in the normal range.

All patients showed normal or corrected-to-normal visual acuity. Patients were informed about the procedure and the purpose of the study and gave written informed consent. The study was designed and performed in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Regional Health Service Romagna (CEROM; n.2300).

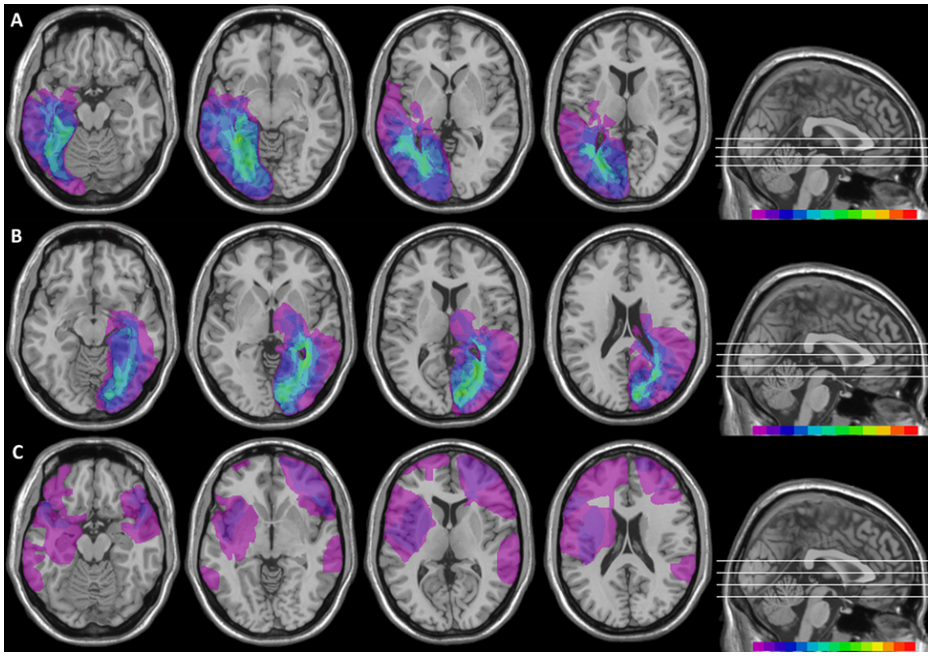

Figure 5.1. *Location and overlap of brain lesions of patients. The image shows the lesions of the hemianopic patients with left posterior lesions (A), hemianopic patients with right posterior lesions (B) and control patients with anterior brain lesions (C) projected onto four axial slices of the standard MNI brain. In each slice, the left hemisphere is on the left side. The levels of the axial slices are marked by white lines on the sagittal view of the brain. The color bar indicates the number of overlapping lesions.*

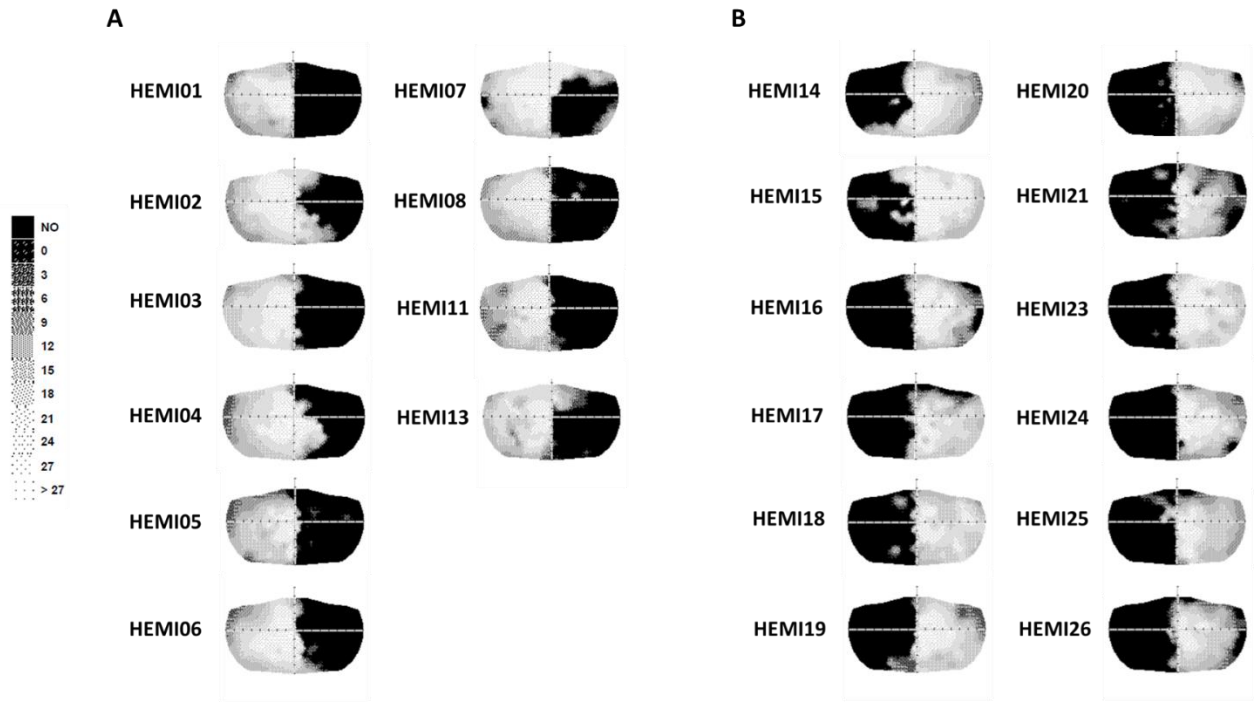

Figure 5.2. *Figure 5.2 automated binocular visual perimetries (Medmont M700 automated perimetry apparatus, Melbourne, Australia) in left-lesioned hemianopic patients (A) and right-lesioned hemianopic patients (B). Axial hash marks denote ten visual degree increments. Colourmap reports decibel values corresponding to each point in the grey scale. Images of the perimetries of patients HEMI09, HEMI10, HEMI12 and HEMI22 were not performed at our outpatient facility and, therefore, were not available for graphical representation. However, for these patients, perimetries performed at external facilities confirmed the presence of visual field defects.*

5.2.2 EEG during resting-state

Participants comfortably seated at rest in a sound-proof room in front of a 24'' LCD monitor (refresh rate 60 Hz) at a viewing distance of 57 cm. EEG signal was recorded in five sessions of one-minute for each of the two resting conditions: eyes-closed and eyes-open resting state. During the eyes-open resting state, participants were asked to fixate a white central fixation cross (0.5°) against a black background on the monitor. The two resting conditions were alternated among the one-minute session of recording. EEG data was acquired through a BrainAmp DC amplifier (BrainProducts GmbH, Germany) and Ag/AgCl electrodes (Fast'nEasy Cap, Easycap GmbH, Germany) from 59 scalp sites (Fp1, AF3, AF7, F1, F3, F7, FC1, FC3, FC5, FT7, C1, C3, C5, T7, CP1, CP3, CP5, TP7, P1, P3, P5, P7, PO3, PO7, O1, Fp2, AF4, AF8, F2, F4, F8, FC2, FC4, FC6, FT8, C2, C4, C6, T8, CP2, CP4, CP6, TP8, P2, P4, P6, P8, PO4, PO8, O2, FPz, AFz, Fz, FCz, Cz, CPz, Pz, POz, Oz) and the right mastoid. The left mastoid was used as online reference electrode, while the ground electrode was

placed on the right cheek. Vertical and horizontal electrooculogram (EOG) components were recorded from above and below the left eye, and from the outer canthus of each eye. Data was recorded with a band-pass filter of 0.01–100 Hz and digitized at a sampling rate of 1000 Hz, while impendences were kept under 5 KΩ. Raw EEG signal was off-line pre-processed and analyzed with EEGLAB (4.1.2b; Delorme & Makeig, 2004), using custom Matlab routines (R2017a; The Mathworks Inc., USA). Data from all electrodes were re-referenced to the average of all scalp electrodes (Lasaponara et al, 2018; Lasaponara, Pinto, Aiello, Tomaiuolo, & Doricchi, 2019, Pietrelli et al., 2019; Pirondini et al., 2020) and filtered with a band-pass filter of 1-100 Hz. The first 10 seconds of each one-minute recording session were excluded from the analysis, in order to avoid any contamination of the signal related to the transition from eyes-closed to the eyes-open resting condition. Continuous signal was segmented in epochs of 2 seconds. Horizontal and vertical eye artifacts were visually identified and removed by means of Independent Component Analysis (ICA), after data dimensionality reduction to 32 components based on Principal Component Analysis (PCA). On the cleaned EEG signal, a Fast Fourier Transformation (FFT) was computed on the 2-sec epochs, with a frequency resolution of 0.5 Hz. Then, the amplitude of alpha and theta oscillations was calculated as the average power (in dB) in each electrode between 7 and 13 Hz 4 and 6 Hz, respectively. In order to compare the lesioned and intact hemispheres across participants, electrodes were swapped cross-hemispherically for patients with lesions to the right hemisphere (i.e., the data were analyzed as if all patients were left-lesioned).

All the electrodes on the scalp were considered into the subsequent analyses, with the exception of the more anterior electrodes, to avoid contamination of the signal by the ocular artifacts, and electrodes on the sagittal midline, to provide a better segregation of the signal between the two hemispheres. The remaining electrodes were divided in six regions of interest (ROI), to perform statistical analysis on alpha and theta power on the entire scalp (Figure 5.3). Six right (P4, P6, P8, PO4, PO8, O2) and left (P3, P5, P7, PO3, PO7, O1) parieto-occipital electrodes were grouped in two ROIs representing the posterior regions of the intact/right hemisphere and the lesioned/left hemisphere, respectively. Similarly, centro-parietal right (C2, C4, C6, CP2, CP4, CP6, P2) and left (C1, C3, C5, CP1, CP3, CP5, P1) electrodes and anterior right (AF4, F2, F4, FC2, FC4, FC6) and left (AF3, F1, F3, FC1, FC3, FC5) electrodes were grouped in four ROIs representing central and anterior regions of the intact/right and lesioned/left hemisphere, respectively.

To test whether posterior brain damage might affect modulation of alpha and theta power induced by eyes- opening, the oscillatory EEG power in both frequency bands was analyzed with separate ANOVAs with CONDITION (eyes-closed, eyes-open), HEMISPHERE (lesioned, intact) and ROI (posterior, central, anterior), as within subject factors and GROUP (healthy participants, hemianopic

patients with left posterior lesions, hemianopic patients with right posterior lesions, control patients with anterior lesions) as between subjects factor.Post-hoc comparisons were performed with either Tukey or Tukey HSD, in case of unequal sample size.

5.2.3 Computerized visual field test

In addition to the EEG recording, during the clinical examination, visual detection abilities in hemianopic patients were also tested, to investigate a possible link between visual performance and EEG reactivity at the opening of the eyes. Patients were presented with a stimulus array of 52° x 45° (horizontally and vertically, respectively), projected on the wall at a viewing distance of 120 cm. Targets consisted of white dots (1°), presented for 100 ms at different positions on a black background. A red fixation cross (0.5°) was presented on the center of the screen. The total number of targets presented was 96 (i.e. 48 targets for each hemifield). No target was presented in 31 trials (i.e., catch trials). Patients were asked to press a response button after the detection of the target. The task was performed in two different conditions: when patients were not allowed to move their eyes to compensate for the visual field loss and had to keep their gaze on a central fixation cross (Fixed-eyes) and when patients were allowed to perform eye movements (Eye movements). The experimenter monitored the patients' gaze throughout the task. Visual detections and false alarms rates were measured. D prime (perceptual sensitivity) was calculated and used for subsequent correlational statistical analysis with EEG indices.

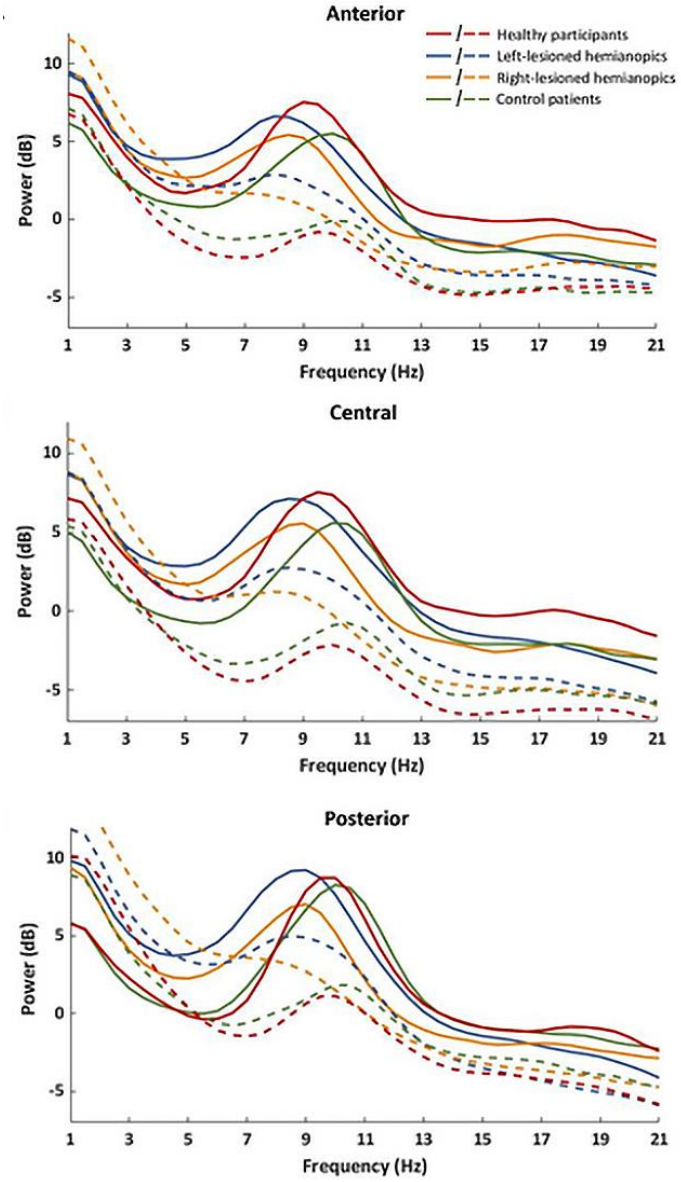

Figure 5.3. *Spectrograms of the mean power across electrodes of the anterior (A), central (B) and posterior (C) region of interest. Solid lines represent signal in the eyes-closed condition; dashed lines represent signal in the eyes-open condition.*

5.3 Results

5.3.1 Alpha power in the eyes-closed and in the eyes-open resting conditions

The overall ANOVA on alpha power revealed a significant main effect of CONDITION ($F_{1,50}$ = 157.73; $p < 0.001$; $\eta p^2 = 0.76$), with higher alpha power in eyes-closed condition (M = 3.97 dB) compared to the eyes-open condition (M = -0.53 dB; $p < 0.001$), showing the presence of a significant desynchronization of the power of alpha at the opening of the eyes. In addition, a significant main effect of ROI ($F_{2,100} = 61.09$; $p < 0.001$; $\eta p^2 = 0.55$) was found, explained by higher power in posterior regions (M = 2.81 dB), relative to central regions (M = 1.06 dB; $p < 0.001$) and anterior regions (M = 1.30 dB; $p < 0.001$). On the contrary, no significant main effect of GROUP ($F_{3,50} = 0.86$, $p = 0.467$; $\eta p^2 = 0.05$) nor HEMISPHERE ($F_{1,50} = 3.16$; $p = 0.081$; $\eta p^2 = 0.06$) was found.

Significant CONDITIONxGROUP ($F_{3,50} = 6.12$; $p = 0.001$; $\eta p^2 = 0.27$), HEMISPHERExGROUP ($F_{3,50} = 2.83$; $p = 0.048$; $\eta p^2 = 0.15$) and CONDITIONxHEMISPHERExGROUP ($F_{3,50} = 3.64$; $p = 0.019$; $\eta p^2 = 0.18$) interactions were also found. More importantly, the ANOVA revealed a significant CONDITIONxROIxGROUP ($F_{6,100} = 4.22$; $p < 0.001$; $\eta p^2 = 0.20$) interaction (Figure 5.3 and 5.4).

To investigate the distribution of alpha desynchronization over the regions of the scalp within each group, this latter significant interaction was explored, performing separate ANOVAs on each group of participants, with CONDITION (eyes-closed, eyes-open) and ROI (posterior, central, anterior) as factors.

The ANOVA on the group of healthy participants revealed a significant main effect of CONDITION ($F_{1,13} = 85.45$; $p < 0.001$; $\eta p^2 = 0.87$), with higher alpha power in the eyes-closed condition (M = 4.61 dB) compared to the eyes-open condition (M = -2.1 dB; $p < 0.001$), indicating a significant desynchronization all over the scalp at the opening of the eyes. Moreover, a significant main effect of ROI ($F_{2,26} = 20.46$; $p < 0.001$; $\eta p^2 = 0.61$) was found, with higher alpha power over posterior regions (M = 2.11 dB), relative to central regions (M = 0.48 dB; $p < 0.001$) and anterior regions (M = 1.13 dB; $p < 0.001$) and higher alpha power in anterior regions, compared to central regions ($p = 0.043$). Also, a significant CONDITIONxROI ($F_{2,26} = 47.81$; $p < 0.001$; $\eta p^2 = 0.77$) interaction was found. Post-hoc comparisons showed significantly higher alpha power in the eyes-closed condition compared to the eyes-open condition in posterior regions (eyes-closed M = 4.78 dB; eyes-open M = -0.56 dB, $p < 0.001$), central regions (eyes-closed M = 4.57 dB; eyes-open M = -3.61 dB, $p < 0.001$) and anterior regions (eyes-closed M = 4.47 dB; eyes-open M = -2.20 dB; $p < 0.001$; Figure 5.4). In addition, in the eyes-open condition, alpha power in posterior regions was significantly higher than in parietal regions ($p < 0.001$) and anterior regions ($p < 0.001$; Figure 5.4).

The ANOVA on hemianopic patients with left lesions revealed a significant main effect of CONDITION ($F_{1,12}$ = 23.14; $p < 0.001$; ηp^2 = 0.66) with higher alpha power in the eyes-closed condition (M = 4.69 dB) compared to the eyes-open condition (M = 1.46 dB; $p < 0.001$), again indicating a significant desynchronization all over the scalp at the opening of the eyes. In addition, a significant main effect of ROI ($F_{2,24}$ = 13.05; $p < 0.001$; ηp^2 = 0.52) was found, with higher alpha power in posterior regions (M = 4.26 dB), relative to central regions (M = 2.73 dB; p = 0.003) and anterior regions (M = 2.25 dB; $p < 0.001$). On the contrary, the CONDITIONxROI ($F_{2,24}$ = 1.89; p = 0.180; ηp^2 = 0.13) interaction was not significant (Figure 5.4).

Similarly to the ANOVAs on healthy participants and hemianopic patients with left lesions, the ANOVA on the group of hemianopics with right lesions showed again a significant main effect of CONDITION ($F_{1,12}$ = 30.12; $p < 0.001$; ηp^2 = 0.71), with higher alpha power in the eyes-closed condition (M = 2.92 dB) compared to the eyes-open condition (M = -0.20 dB; $p < 0.001$) and a significant main effect of ROI ($F_{2,24}$ = 11.64; $p < 0.001$; ηp^2 = 0,49), explained by higher alpha power in posterior regions (M = 2.38 dB), relative to central regions (M = 0.91 dB; $p < 0.001$) and anterior regions (M = 1.06 dB; $p < 0.001$). The CONDITIONxROI interaction ($F_{2,24}$ = 3.05; p = 0.066; ηp^2 = 0.20) was not significant (Figure 5.4).

Last, also the ANOVA on controls patient with anterior lesions showed a significant main effect of CONDITION ($F_{1,13}$ = 34.36; $p < 0.001$; ηp^2 = 0.72), with higher alpha power in the eyes-closed condition (M = 3.64 dB), compared to the eyes-open condition (M = -1.25 dB; $p < 0.001$) and a significant main effect of ROI ($F_{2,26}$ = 23.00; $p < 0.001$; ηp^2 = 0.64), revealing higher alpha power in posterior regions (M = 2.56 dB), compared to central (M = 0.24 dB; $p < 0.001$) and anterior regions (M = 0.79 dB; $p < 0.001$). No significant CONDITIONxROI ($F_{2,26}$ = 1.80; p = 0.185; ηp^2 = 0.12) interaction was found (Figure 5.4).

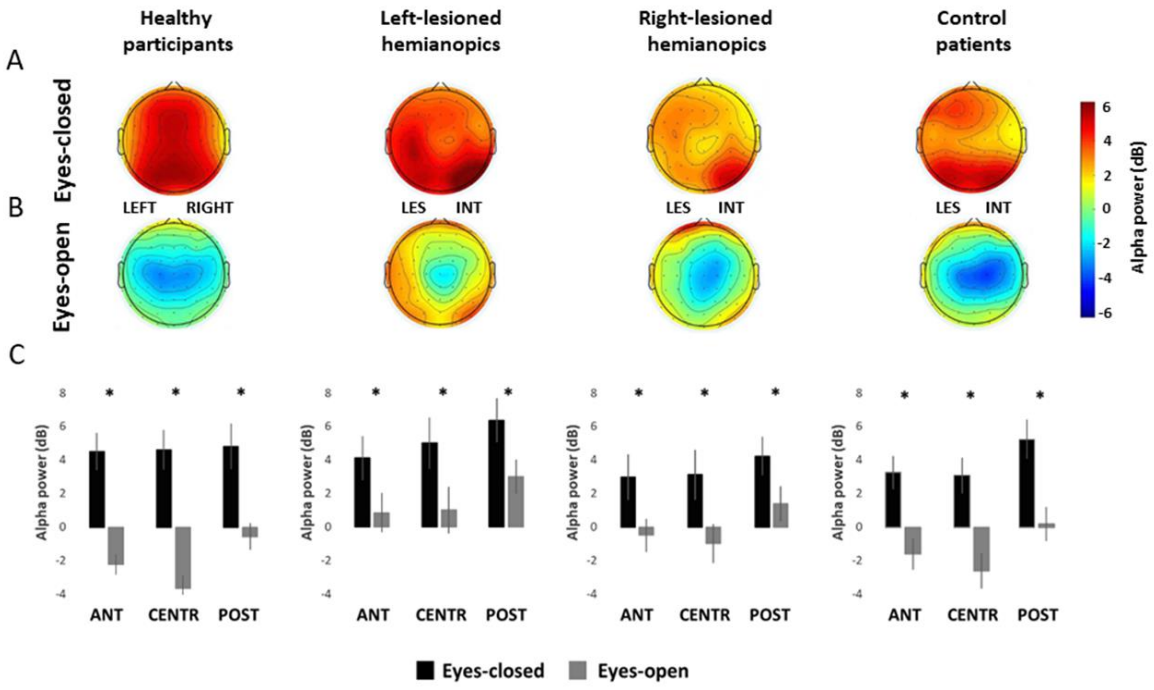

Figure 5.4. *Scalp topographies represent the scalp distribution of the alpha power (dB) within each group in the frequency window 7-13 Hz, in the eyes-closed condition (A) and in the eyes-open condition (B). For patients with lesions to the right hemisphere, electrodes were swapped cross-hemispherically, so that the lesioned hemisphere is represented on the left side. (C) Bar histograms show the mean alpha power (dB) in the eyes-closed and the eyes-open conditions, relative to anterior, central and posterior region of interest, within each group. Error bars represent standard error; asterisks are signaling the significant comparisons. Legend: ANT = Anterior region of interest; CENTR = Central Region of interest; POST = Posterior region of interest; LES = Lesioned Hemisphere; INT = Intact Hemisphere.*

5.3.2 Alpha power reactivity

The results of the statistical analysis on the alpha power in the eyes-closed and in the eyes-open conditions suggest the presence of a significant alpha power desynchronization induced by the opening of the eyes all over the scalp, both in healthy participants and in hemianopic and control patients. However, to compare the magnitude of the alpha desynchronization at the opening of the eyes between groups, an index of alpha reactivity was further calculated. The alpha reactivity index was computed by subtracting the mean power in the eyes-open condition to the mean power in the eyes-closed condition (alpha reactivity = mean alpha power eyes-closed minus mean alpha power eyes-open) in each ROI separately, for each group of participants.

One-way ANOVAs were performed for the posterior, the central and the anterior ROIs, with GROUP (healthy participants, hemianopic patients with left posterior lesions, hemianopic patients with right posterior lesions, control patients with anterior lesions) as between-subject factor.

The ANOVA on the posterior ROI revealed a significant main effect of GROUP ($F_{3,50} = 4.31$; $p = 0.009$; $\eta p^2 = 0.21$), pointing to a reduced alpha reactivity in right-lesioned hemianopic patients (M = 2.22 dB), compared to healthy participants (M = 5.34 dB; p = 0.018). In contrast, alpha reactivity in left-lesioned hemianopic patients (M = 3.08 dB; p = 0.096) and control patients (M = 4.75 dB; p = 0.917) was not significantly different relative to healthy participants. No other significant comparison was found (all ps > 0.081; Figure 5.5).

The ANOVA on the central ROI showed again a significant main effect of GROUP ($F_{3,50} = 4.31$; $p = 0.009$; $\eta p^2 = 0.20$). In this region reduced alpha reactivity was found both in left-lesioned hemianopic patients (M = 3.64 dB; p = 0.002) and in right-lesioned hemianopic patients (M = 3.47 dB; p = 0.001), compared to healthy participants (M = 8.17 dB). No significant difference in alpha reactivity was found between control patients (M = 5.34 dB; p = 0.073) and healthy controls. No other comparison was significant (all ps > 0.394; Figure 5.5).

Last, also the ANOVA on the anterior ROI showed a significant main effect of GROUP ($F_{3,50} = 5.75$; $p = 0.002$; $\eta p^2 = 0.26$). Similarly to the results on the central ROI a reduced alpha reactivity was found only in left-lesioned hemianopic patients (M = 2.96 dB; p = 0.006) and in right-lesioned hemianopic patients (M = 2.94 dB; p = 0.005), compared to healthy participants (M = 6.67 dB). No significant difference in alpha reactivity was found between control patients (M = 4.56 dB; p = 0.183) and healthy controls. No other significant comparison was found (all ps > 0.428; Figure 5.5).

Overall, these results suggest a reduced alpha reactivity only in hemianopic patients, with right-lesioned hemianopics showing a more global and widespread reactivity reduction, compared to left-lesioned hemianopics.

Last, to test whether the observed differences across groups in terms of alpha power reactivity could depend on the extent of the lesion, a correlational analysis was performed. Pearson's correlations were run between the patients' alpha reactivity indices in the anterior, central and posterior ROIs and the voxel-based lesion volume. No significant correlation was found (all ps > 0.645).

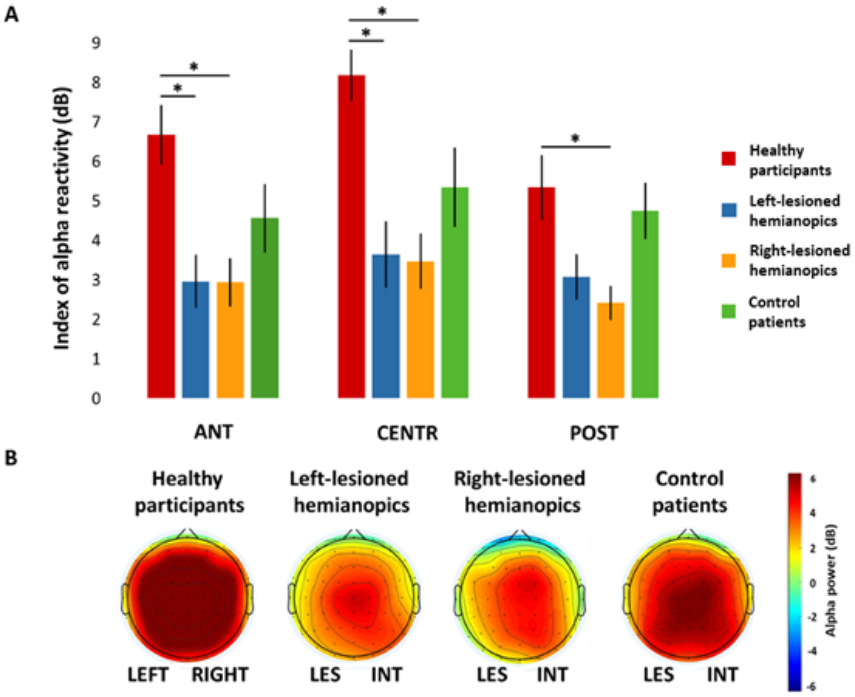

Figure 5.5. (A) *Bar histograms show the index of alpha reactivity (dB) within each group, relative to the anterior, central and posterior region of interest and represent the comparisons between each group, separately for each region of interest. Error bars represent standard error; asterisks are signaling the significant comparisons.* ***(B)*** *Scalp topographies represent the scalp distribution of the magnitude of alpha power reactivity (dB; alpha reactivity = mean alpha power eyes-closed minus mean alpha power eyes-open) averaged across participants in the frequency window 7-13 Hz, in each group. For patients with lesions to the right hemisphere, electrodes were swapped cross-hemispherically, so that the lesioned hemisphere is represented on the left side. Legend: ANT = Anterior region of interest; CENTR = Central Region of interest; POST = Posterior region of interest; LES = Lesioned Hemisphere; INT = Intact Hemisphere.*

5.3.3 Theta power in the eyes-closed and in the eyes-open resting conditions

The overall ANOVA on theta power revealed a significant main effect of GROUP ($F_{3,50} = 4.48$; $p = 0.007$; $\eta p^2 = 0.21$), with hemianopic patients with left lesions showing higher theta power (M = 3.00 dB) relative to the control group of patients with anterior lesions (M = -0.33; p = 0.041), while no other between-groups difference was evident (all ps > 0.075). Moreover, a significant main effect of CONDITION ($F_{1,50} = 4.33$; $p = 0.042$; $\eta p^2 = 0.08$) was found, explained by higher theta power in the eyes-closed condition (M = 1.80 dB) compared to the eyes-open condition (M= 0.82 dB; p = 0.038), indicating a significant desynchronization of the power of theta at the opening of the eyes. A significant main effect of HEMISPHERE ($F_{1,50} = 40.89$; $p = < 0.001$; $\eta p^2 = 0.45$), with higher theta power in the lesioned/left hemisphere (M = 1.72 dB) compared to the intact/right hemisphere (M =

0. 89 dB; $p < 0.001$) was also found. In addition, and a significant main effect of ROI ($F_{2,100} = 43.96$; $p = 0.007$; $\eta p^2 = 0.47$) was found, revealing lower theta power in central regions (M = 0.41 dB), compared to posterior regions (M = 1.94 dB; $p < 0.001$) and anterior regions (M = 1.57 dB; $p < 0.001$). Significant HEMISPHERExGROUP ($F_{3,50}= 4.59$; $p = 0.006$; $\eta p^2 = 0.22$) and HEMISPHERExROIxGROUP ($F_{6,100} = 2.51$; $p = 0.026$; $\eta p^2 = 0.13$) interactions were also found. More importantly, the ANOVA revealed a significant CONDITIONxROIxGROUP ($F_{6,10} = 3.0$; $p = 0.008$; $\eta p^2 = 0.15$, Figure 5.6) interaction. Similarly, to the analyses on alpha power, this interaction was further explored, performing separate ANOVAs on each group of participants, with CONDITION (eyes-closed, eyes-open) and ROI (posterior, central, anterior) as factors, to investigate the distribution of theta desynchronization over the regions of the scalp within each group.

The ANOVA on the group of healthy participants showed a significant main effect of CONDITION ($F_{1,13} = 6.05.$; $p = 0.028$; $\eta p^2 = 0.32$) with higher theta power in the eyes-closed condition (M = 1.03 dB) compared to the eyes-open condition (M = -1.07 dB; $p = 0.028$). In addition a significant main effect of ROI ($F_{2,26} = 14.09$; $p < 0.001$; $\eta p^2 = 0.53$) was found, with significantly lower theta power in central regions (M = -0.70 dB) relative to posterior (M = 0.31 dB; $p < 0.001$) and anterior regions (M = 0.32 dB; $p < 0.001$). Finally, a significant CONDITIONxROI ($F_{2,26} = 66.06$; $p < 0.001$; $\eta p^2 = 0.84$) interaction was found. Post-hoc comparisons revealed significantly higher theta power in the eyes-closed condition compared to the eyes-open condition in the anterior regions (eyes-closed M = 1.97 ; eyes-open M = -1.32 dB; $p < 0.001$ dB) and the central regions (eyes-closed M = 1.06 dB; eyes-open M = -2.45 dB; $p < 0.001$), but no significant difference between the two conditions was found in posterior regions (eyes-closed M = 0.06 dB; eyes-open M = 0.56; $p = 0.498$), indicating the presence of theta desynchronization only in anterior and central regions (Figure 5.6).

The ANOVA on hemianopic patients with left lesions did not show a significant main effect of CONDITION ($F_{1,12} = 2.27$; $p = 0.158$; $\eta p^2 = 0.16$), but a significant main effect of ROI ($F_{2,24} = 2.36$; $p < 0.001$; $\eta p^2 = 0.51$) with lower theta power in central regions (M = 2.06 dB) compared to posterior regions (M = 3.80 dB; $p < 0.001$) and anterior regions (M = 3.15; $p = 0.013$). In addition, the CONDITIONxROI ($F_{2,22} = 4.66$; $p = 0.020$; $\eta p^2 = 0.29$) interaction was also significant. Similarly to healthy participants, the subsequent post-hoc comparisons revealed significantly higher theta power in the eyes-closed condition compared to the eyes-open condition in the anterior regions (eyes-closed M = 4.01 dB; eyes-open M = 2.29 dB; $p = 0.001$) and in the central regions (eyes-closed M = 3.05 dB; eyes-open M = 1.06 dB; $p < 0.001$), but not in posterior regions (eyes-closed M = 4.02 dB; eyes-open M = 3.57 dB; $p = 0.822$; Figure 5.6).

The ANOVA on the group of hemianopic patients with right lesions did not show a significant main effect of CONDITION ($F_{1,12} = 0.59$; $p = 0.456$; $\eta p^2 = 0.045$), but a significant main effect of ROI

($F_{2,24}$ = 9.11; p = 0.001; ηp^2 = 0.43) explained by higher theta power in posterior regions (M = 3.70 dB) relative to central regions (M = 1.95 dB; p < 0.001), while no other significant difference among the regions was found (all ps > 0.102). In addition, the CONDITIONxROI ($F_{2,24}$ = 9.30; p = 0.001; ηp^2 = 0.43) interaction was also significant. However, in contrast to the results on healthy participants and left-lesioned hemianopics, post-hoc comparisons did not reveal any significant difference in theta power between the eyes-closed and the eyes-open conditions in the anterior regions (eyes-closed M = 2.89 dB; eyes-open M = 2.74 dB; p = 0.999) and the central regions (eyes-closed M = 1.97 dB; eyes-open M = 1.93 dB; p = 1.00; Figure 5.6). Moreover, a significant lower theta power in the eyes-closed condition (M = 2.51 dB) compared to the eyes-open condition (M = 4.88 dB; p < 0.001) was found in posterior regions, indicating the presence of a significant theta synchronization at the opening of the eyes (Figure 5.6).

Finally, in the control group of patients with anterior lesions, no significant main effect of CONDITION ($F_{1,13}$ = 1.26; p = 0.28; ηp^2 = 0.09) was found. In contrast, a significant main effect of ROI ($F_{2,6}$ = 13.77; p < 0.001; ηp^2 = 0.52) was evident, with significantly lower theta power in central regions (M = -1.43 dB) compared to posterior (M = 0.20 dB; p < 0.001) and anterior regions (M = 0.22 dB; p < 0.001). The CONDITIONxROI ($F_{2,26}$ = 5.43, p = 0.011; ηp^2 = 0.29) interaction was also significant. Again, similarly to healthy participants and left-lesioned hemianopics, post-hoc comparisons revealed a significant higher theta power in the eyes-closed condition relative to the eyes-open condition in the anterior regions (eyes-closed M = -0.95 dB; eyes-open M = -0.50 dB; p = 0.013) and the central regions (eyes-closed M = -0.54 dB; eyes-open M = -2.32 dB; p = 0.002), but not in posterior regions (eyes-closed M = 0.22 dB; eyes-open M = 0.18 dB; p = 0.999; Figure 5.6).

5.3.4 Theta power reactivity

Overall, the results of the statistical analysis on the theta power in the eyes-closed and in the eyes-open conditions suggest differences between groups in theta power changes induced by the opening of the eyes in the three ROIs examined. More specifically, no changes between the eyes-closed and the eyes-open conditions were found in the posterior regions in all groups, with the exception of right-lesioned hemianopics, who showed an atypical increase in theta power at the opening of the eyes, compared to the eyes-closed condition. Differently, in the central and the anterior regions, all groups showed a significant desynchronization at the opening of the eyes, again with the exception of right-lesioned hemianopics, who did not show any significant change between the eyes-closed and the eyes-open conditions. An index of theta reactivity at the opening of the eyes was calculated (theta

reactivity = mean theta power eyes-closed minus mean theta power eyes-open), to compare the magnitude of theta desynchronization at the opening of the eyes in the central and anterior regions among the groups of participants showing desynchronization (i.e., healthy participants, left-lesioned hemianopics and control patients with anterior lesions). Right-lesioned hemianopics were not included in this comparison, since they did not exhibit a significant desynchronization. Two separate one-way ANOVAs were performed for the central and the anterior ROIs, having GROUP (healthy participants, hemianopic patients with left posterior lesions, control patients with anterior lesions) as between-subjects factor.

Both the ANOVAs on the central ROI ($F_{2,38} = 0.83$; $p = 0.44$; $\eta p^2 = 0.004$) and the anterior ROI ($F2,38 = 1.19$; $p = 0.31$; $\eta p^2 = 0.006$) did not show a significant main effect of GROUP. This suggests that the overall pattern of theta desynchronization was similar between left-lesioned hemianopics, patients with anterior lesions and healthy participants. On the contrary, right-lesioned hemianopic patients revealed an atypical pattern of theta changes at the opening of the eyes, with no desynchronization in the central and anterior regions and the presence of theta synchronization in the posterior regions.

Finally, to test whether the extent of the lesion could account for the observed results, a correlational analysis was performed using Pearson's correlations between the patients' theta reactivity indices in the anterior, central and posterior ROIs and the voxel-based lesion volume. No significant correlation was found (all ps > 0.711).

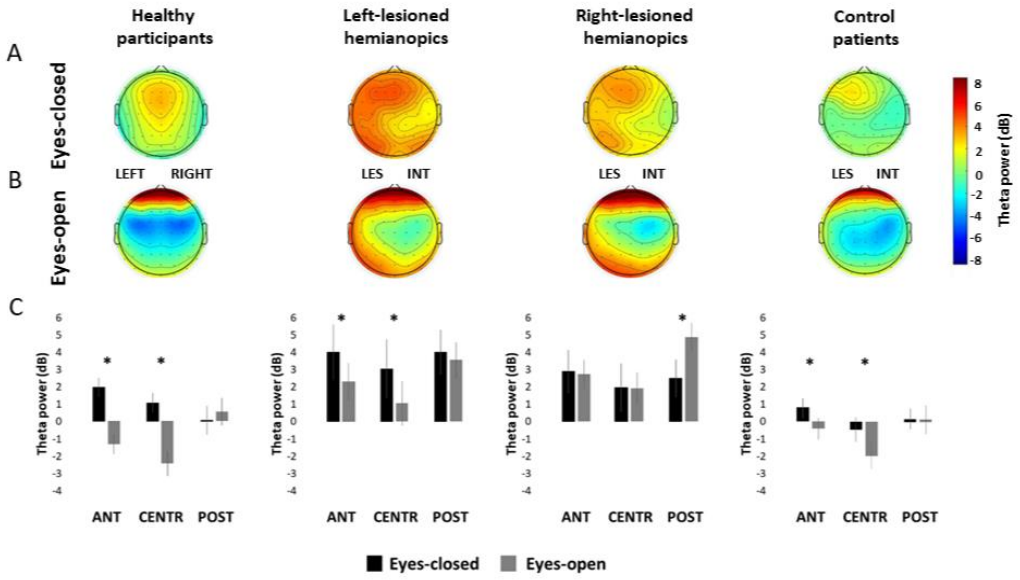

Figure 5.6. *Scalp topographies represent the scalp distribution of the theta power (dB) within each group in the frequency window 4-6 Hz, in the eyes-closed condition (A) and in the eyes-open condition (B). For patients with lesions to the right hemisphere, electrodes were swapped cross-hemispherically, so that the lesioned hemisphere is represented on the left side. (C) Bar histograms show the mean theta power (dB) in the eyes-closed and the eyes-open conditions, relative to anterior, central and posterior region of interest, within each group. Error bars represent standard error; asterisks are signaling the significant comparisons. Legend: ANT = Anterior region of interest; CENTR = Central Region of interest; POST = Posterior region of interest; LES = Lesioned Hemisphere; INT = Intact Hemisphere.*

5.3.5 Hemianopic patients' visual performance and reactivity in the alpha and theta band

Finally, we tested whether altered alpha and theta reactivity over the posterior, central and anterior ROIs can relate to behavioral performance in visual detection tests in hemianopic patients with both left and right lesions. To this aim, the relationship between hemianopic patients' perceptual sensitivity in their blind field at the Computerized Visual Field test in the Fixed-Eyes condition and their indices of alpha and theta reactivity was explored separately for each ROI. Simple correlations were performed and to account for multiple comparisons, p-values were adjusted with Holm-Bonferroni corrections. Adjusted p values (adj. p) are reported. No significant correlation between the mean D prime in the blind field and the indices of both alpha and theta reactivity was found in the three ROIs examined (all adj. ps > 0.171), suggesting that the residual alpha and theta reactivity in hemianopic patients is not associated with the sparing of their visual field. Additionally, the relationship between

hemianopic patients' perceptual sensitivity in their blind field at the Computerized Visual Field test in the Eye-movements condition and their indices of alpha and theta reactivity was explored separately for each ROI. Again, simple correlations were performed, and, to account for multiple comparisons, p-values were adjusted with Holm-Bonferroni corrections. Adjusted p values (adj. ps) are reported. No significant correlation between the mean D prime in the blind field and the indices of both alpha and theta reactivity was found in the three ROIs examined (all adj ps > 0.366), indicating no relationship between alpha and theta reactivity and patients' ability to compensate for the field loss with eye movements.

5.4 Discussion

The present EEG study compared eyes-closed and eyes-open resting conditions in posterior-lesioned patients with visual field defects and age-matched control anterior-lesioned patients and healthy participants. The results showed that all groups presented a significant desynchronization of alpha power at the opening of the eyes, across all scalp regions. Specifically, decreased alpha power during the eyes-open condition compared to the eyes-closed condition was found in posterior, central and anterior sites, in both the left and the right hemispheres. Nevertheless, alpha reactivity induced by eyes-opening was reduced in both left and right-lesioned hemianopic patients. This may indicate that hemianopics are characterized by altered task-independent activation of the visual system. More precisely, left-lesioned hemianopic patients exhibited a reduced alpha reactivity in the anterior and the central scalp regions, whereas right-lesioned hemianopics showed an overall reduction of alpha reactivity all over the scalp, i.e. in the anterior, central and posterior ROIs, suggesting a more pronounced and extended disfunction after lesions to the right hemisphere.

The altered alpha reactivity in hemianopics is in line with previous studies, demonstrating that left and right posterior brain lesions selectively impair alpha oscillatory parameters during eyes-closed resting state, resulting in a slowdown of IAF and an interhemispheric power imbalance, in favor of the intact hemisphere (Pietrelli et al., 2019). Importantly, the present results show that, regardless the presence of alterations to the baseline alpha oscillatory activity due to posterior lesions, hemianopic patients retain a residual reactivity in the alpha range to the opening of the eyes, which is evident, but reduced, after damage to the posterior cortices. This residual reactivity in the alpha band seems also in agreement with previous reports showing that hemianopic patients can retain stimulus-related alpha changes, induced by the presentation of stimuli in the blind field (Sanchez-Lopez et al., 2019; Grasso, Pietrelli, Zanon, Làdavas & Bertini, 2020). Converging evidence report that eyes-closed and eyes-

open conditions correspond to distinct neurophysiological states and functional connectivity patterns (Jao et al., 2012). More precisely, eyes-closed resting state has been linked to a state of greater network integration, with reduced modularity and increased global efficiency (Bianciardi et al., 2009; Xu et al. 2014). In contrast, eyes-open resting state has been associated with greater modularity, which is thought to facilitate increased local efficiency, subserving task dependent processing (Xu et al., 2014; Allen et al., 2018). In this perspective, the alpha desynchronization in the transition from the eyes-closed to the eyes-open condition might represent a widespread cortical activation, supporting the focal decreases in non-alpha bands, related to local processing which gathers visual information (Marx et al., 2003; Barry et al., 2007; Barry & De Blasio, 2017). Thus, the present findings indicate that focal unilateral lesions to posterior cortices can induce global and widespread alterations in alpha cortical reactivity, in line with the notion of a central role of low-level visual cortices in coordinating and propagating alpha oscillations in the visual system (Hindriks et al., 2015).

Notably, right hemispheric posterior lesions result in a more severe reactivity reduction, distributed all over the scalp, while in left-lesioned patients posterior cortices retain a normal alpha reactivity. This observation is in agreement with previous findings on hemianopics showing that posterior right lesions had more detrimental consequences on alpha oscillatory impairments, with stronger IAF reduction and interhemispheric power imbalance, relative to posterior left lesions (Pietrelli et al., 2019). This seems to suggest a specialization of the right hemisphere in generating and distributing alpha oscillatory patterns. In agreement, evidence has shown that the right hemisphere is capable of modulating alpha oscillations to both facilitate detection of visual stimuli and suppress visual irrelevant information (Gallotto et al., 2020), suggesting a more specialized role of this hemisphere in allocating visuo-spatial attentional resources and tuning visual perceptual abilities through alpha oscillatory patterns. In addition, in the present study, patients with right lesions also showed a peculiar pattern of reactivity at the opening of the eyes in the theta frequency range. More precisely, while healthy participants, control patients and also hemianopics with left lesions demonstrated a typical desynchronization in the theta range over centro-anterior regions at the opening of the eyes (Barry et al., 2007; Barry & De Blasio, 2017), hemianopics with right lesions revealed no significant change over central and anterior regions of the scalp and an atypical increase of theta power over posterior regions, in the transition from eyes-closed to eyes-open resting state. Focal alterations in the theta range after brain damage has been consistently reported in eyes-closed resting state, regardless the site of the lesion. Specifically, increased theta power in perilesional areas has been described in patients with stroke (Butz et al., 2004; Tecchio et al. 2005; Dubovik et al., 2012; Laaksonen et al., 2013; Chu, Braun & Meltzer, 2015), likely reflecting reorganization of the lesioned cortices (Carmichael & Chesselet, 2002; Rabiller, He, Nishijima, Wong & Liu, 2015). Previous reports

comparing hemianopics and control patients with anterior lesions also showed that post-lesional theta power increase at eyes-closed rest is evident after lesions both to posterior and anterior cortices (Pietrelli et al., 2019). However, the current findings show that theta reactivity to the opening of the eyes seems selectively compromised only after posterior right lesions, which adds to the right-lesioned hemianopics' reduced alpha reactivity.

The dysfunctional reactivity in the theta range observed in right-lesioned hemianopics might reflect the disruption of the typical focal oscillatory changes occurring at the opening of the eyes, which have been associated with stimulus processing and, hence, to low-level unstructured responses to visual stimuli during eyes-open resting state (Gevins et al., 1997; Barry & De Blasio, 2017;). The combination of impairments in the alpha and the theta range observed in hemianopics with right lesions suggests the presence of a stronger impairment in functional reactivity to the opening of the eyes, compared to hemianopic patients with left lesions, involving both global and local processes. Indeed, right posterior lesions seem to primarily weaken the typical reduction of alpha power at the opening of the eyes, reflecting the widespread cortical activation, gating and controlling visual inputs at the opening of the eyes; then, as a consequence, right lesions also impair focal theta reduction, which is linked with modular processing and local cortical activations (Grillon & Buchsbaum, 1986; Gevins et al., 1997; Barry & De Blasio, 2017).This seems in line with the notion that alpha oscillations propagating from posterior visual cortices to higher-order cortical sites (Hindriks et al., 2015), might play a special role in coordinating widespread oscillatory activity and orchestrating focal processing in non-alpha frequency bands, which might support visual processing at the opening of the eyes (Barry & De Blasio, 2017). In this perspective, the present findings suggest a possible role of the intact right hemisphere in compensating the disruption of alpha oscillatory reactivity due to left posterior lesions. Indeed, we can speculate that in left-lesioned hemianopics the right intact hemisphere might contribute to preserve alpha oscillatory activity in the posterior cortices, with a consequent spared normal reactivity in the theta range.

Although these results suggests that alterations in the reactivity patterns at the opening of the eyes are a dysfunctional feature of patients suffering posterior brain damage, it is notable that reactivity indices both in the alpha and in the theta band did not show any correlation with visual performance, both when hemianopic patients were required to fixate a central fixation point and when exploratory eye movements were allowed. This finding is in line with evidence showing that alpha desynchronization at the opening of the eyes occurs independently of external sensory input, for instance in blind individuals (Hüfner et al., 2009) and in condition of complete darkness (Boytsova & Danko, 2009; Marx et al., 2003; Ben-Simon et al., 2013). This is consistent with the hypothesis that alpha reactivity at the opening of the eyes does not reflect visual processing per se, but represents a prerequisite for

alpha visual-related modulation by external sensory stimulation (Klimesch et al, 2007; Ben-Simon et al., 2013). In line with this perspective, a wide body of research converges on the notion that various aspects of visual performance are rather linked with different alpha oscillatory parameters (Van Rullen, 2016; Brüers & Van Rullen, 2018), with individual alpha frequency representing a measure of temporal resolution of visual perception (Valera et al., 1981; Klimesch et al., 2007; Cecere et al., 2015; Samaha & Postle, 2015) and alpha power (Romei et al., 2008a; 2008b) and phase (Bush et al., 2009; Mathewson et al., 2009; Mathewson et al., 2012) reflecting variations in cortical excitability and visual awareness. In addition, alpha frequency and amplitude in a condition of eye-closed resting state were consistently shown to be linked to impaired visual abilities in hemianopic patients (Pietrelli et al., 2019), strengthening the evidence that the oscillatory activity in this frequency band at rest represents a reliable neurophysiological index of the integrity and the functionality of the visual system. As a consequence, the present findings suggest that EEG reactivity indices should be interpreted as intrinsic electrophysiological biomarkers of the functional effects of posterior brain lesions.

Overall, the current results add to previous knowledge on hemispheric asymmetries in visuo-spatial abilities (Kinsbourne, 1977; Heilman & Van Den Abell, 1980; Duecker. & Sack 2015) and suggest a prominent role of the posterior cortices of the right hemisphere in organizing and distributing oscillatory alpha activity, to support the local functioning of the visual system at rest. This is in favor of a dominance of the right hemisphere in perceptual and visuo-spatial processing (Bisiach & Luzzatti, 1978; Heilman & Valenstein, 1979; Heilman et al., 1984; Mattingley et al., 1994; McCourt & Olafson, 1997; Nobre et al., 1997; Gitelman et al., 1999; Jewell & McCourt, 2000; McCourt & Jewell, 1999; Corballis et al., 2002; Nicholls et al.,2002) and emphasize the underlying role of complex oscillatory patterns.

Chapter 6

Alterations in resting-state functional connectivity after posterior brain damage reflect the functionality of the visual system in hemianopic patients

6.1 Introduction

Interactions between local and remote brain regions subserving cognitive functioning have been effectively studied in the domain of EEG research by functional connectivity, measuring the statistical interdependencies between EEG rhythms in a condition of resting state, between different pairs of electrodes (Aertsen, Gerstein, Habib, Palm, 1989; Stam, 2010). This electrophysiological marker of functional coupling is able to capture relationships among different brain regions, which are essential for brain functioning (Tononi & Edelman, 1998; Varela, Lachaux, Rodriguez & Martinerie, 2001). In line with this perspective, studies on the healthy brain have shown that spontaneous EEG fluctuations in the resting brain are typically highly organized and coherent (Greicius, Krasnow, Reiss & Menon, 2003). More recent findings have also described the complexity of brain connectivity using graph theory (Strogatz, 2001), a mathematical approach that quantifies topological properties of neural networks, defining a complex system of nodes (vertices) and edges (links), whose functional activity is characterized by a balance between local specialization and global integration (Tononi, Sporns, Edelman, 1994; Stam, Nolte, Daffertshofer, 2007). More precisely, among others, two specific graph theoretical parameters have been often used to quantify this network activity, namely Clustering coefficient (C), reflecting an index of functional segregation, and Characteristic path length (L), measuring functional integration (Caliandro et al., 2017; Vecchio et al., 2019a; 2019b) and a balancing between these parameters has been demonstrated to be an indicator of high functioning efficiency (Achard et al., 2006).

A variety of neurological (Babiloni et al., 2008; Melloni et al., 2015; Babiloni et al., 2016; Dottori et al., 2017;) and psychiatric (Haig et al., 2000; Dawson, 2004; Barttfeld et al., 2013) conditions have demonstrated to be associated to alterations of the typical pattern of functional connectivity, suggesting that these indices might represent a reflection of neural integrity. In line, investigations in patients with brain lesions have shown a wide range of postlesional changes in functional connectivity in different frequency bands. For instance, increase in the number (Castellanos et al., 2010) and the functionality (Castellanos et al., 2010; Dubovik et al., 2012) of the connections in the low-frequency bands (delta/theta) were reported in patients with acquired brain lesions, compared to controls. In contrast, various patterns of changes have been reported in the alpha range, showing both a

postlesional reduction of brain connectivity, especially in the ipsilesional hemisphere (Castellanos et al., 2010; Wu et al., 2011; Dubovik et al., 2012; Westlake et al., 2012;) but also increased alpha connectivity in the intact hemisphere or perilesional areas (Guggisberg et al., 2008; Wu et al., 2011; Westlake et al., 2012). Moreover, post-stroke reduced functional connectivity in the alpha band has also been related to more severe deficits in functional outcomes (Dubovick et al., 2012; Guggisberg, Rizk, & Ptak, 2015). Similarly, graph theory analyses have also described rearrangements of network topology following stroke, disrupting the balance between local and global processing, with changes in clustering and path length (Caliandro et al., 2017).

The variety of clinical and lesional profiles in the existing literature documenting alterations in connectivity has concurred to provide only partial and unselective proofs of changes in post-lesional connectivity at rest so far. However, as mentioned in the previous chapters, posterior lesions, targeting the structures of the visual pathways and resulting in visual field defects (Grasso, Gallina, Bertini, 2020), might induce specific alterations in oscillatory patterns. More precisely, as reviewed in chapter 3, posterior brain lesions in hemianopic patients have been shown to selectively reduce the alpha peak and power during rest, (Pietrelli et al., 2019), suggesting a role of posterior cortices in generating ad distributing alpha oscillatory activity at rest. Moreover, evidence reported in chapter 5, showed that lesions to posterior cortices alter also the reactivity in the alpha band observed in the transition from the eyes-closed resting state to the opening of the eyes (see chapter 5; Gallina, Pietrelli, Zanon, Bertini, 2021). Interestingly, a right posterior lesions induced compared to left posterior lesions, a more severe impairment in the alpha reactivity and a concurrent disruption in reactivity in the theta range at the opening of the eyes was also observed (see chapter 5; Gallina et al., 2021), suggesting a role of posterior cortices in coordinating widespread alpha oscillatory activity and organizing focal processing in the theta range and that lesions to these cortices and impairing the visual system might selectively disrupt this oscillatory activity. In line with this view, the relevance of posterior cortices in generating and distributing oscillatory activity, namely in the alpha range, has been widely reported (Bollimunta, Chen, Schroeder, Ding, 2008; Rosanova et al., 2009;Thut et al., 2011). In addition, activity in the alpha range has been reported to be linked to the excitability of the visual cortices (Romei et al., 2008b) and to be associated to aware (Pfurtscheller et al., 1994) and unaware (Grasso, Pietrelli, Zanon, Làdavas, Bertini, 2020) visual processing and visuo-spatial attention (Capilla et al., 2014), as extensively discussed in chapter 3. In this perspective, oscillations in the alpha range have been suggested to reflect, even at rest, the activity of the underlying neural populations (Klimesch et al., 2007; Sadaghiani & Kleinschmidt, 2016) and, thus, the functionality of the visual system. Moreover, alpha oscillations, propagating from posterior visual cortices to higher-order cortical sites

(Hindriks et al., 2015), might play a special role in coordinating widespread oscillatory activity and orchestrating focal processing in non-alpha frequency bands.

As a consequence, it is of great interest to study the effects of lesions to these cortices on oscillations also at the network level. Indeed, it is still unknown whether lesions to posterior cortices might induce specific post-lesional alterations of functional connectivity patterns in different frequency bands during resting state. Recent human fMRI studies on hemianopic patients showed a decreased brain functional connectivity in the Visual Network (Pedersini et al., 2020), suggesting postlesional changes in connectivity after posterior lesions, but providing no insight on possible alterations in specific frequency bands. Moreover, preliminary EEG investigations suggested the presence of some altered patterns of connectivity in the alpha range (Wang, Xiaoli, Sun, Jin, & Tong, 2012; Guo, Jin, Feng & Tong, 2014) after lesions to the visual cortices, but the consequences of posterior lesions on the complex pattern of alpha and non-alpha (e.g. theta) oscillatory processing at rest still needs to be elucidated. In addition, since previous investigations have revealed a different impact of posterior left and right lesions on resting oscillations, with right-damaged hemianopics showing a more severe impairments in alpha oscillatory patterns Pietrelli et al., 2019; Gallina et al., 2021; see also chapter 5). Therefore, the present study aims also at exploring whether posterior lesions affect the complex pattern of functional connectivity in different frequency bands and whether lesions to the left or the right hemisphere can differentially alter connectivity patterns.

To explore these hypotheses, EEG activity during eyes-closed resting state was recorded in patients with left or right lesions to the posterior cortices, in control patients with left or right more anterior lesions and in a group of healthy controls. Intrahemispheric connectivity indices were computed to measure post-lesional functional connectivity changes. In addition, clustering coefficient (C) and characteristic path length (L) were chosen as graph theory parameters to characterize local and global connectivity patterns. Connectivity indices and graph theoretical parameters were computed in theta (3-6 Hz), lower alpha (7-10 Hz) and upper alpha (11-13 Hz) bands, to inspect a broad range of oscillations (Caliandro et. al., 2017). Finally, the relationship between visual performance in hemianopics and connectivity indices was also investigated, to explore whether specific connectivity alterations might be linked to visual impairments in hemianopics.

6.2 Material and Methods[2]

6.2.1 Participants

Five groups of participants took part in the study: fourteen patients (10 males, mean age = 53.08 years, SD = 15.32; mean time since lesion onset = 12.64 months, SD = 11.59) with visual field defect due to lesions to the left posterior cortices, thirteen patients with visual field defect due to lesions to the right posterior cortices (10 males, mean age = 58.9 years, SD = 16.47; mean time since lesion onset = 12.47 months, SD = 14.18), a control group of nine patients without hemianopia with lesions to left fronto-temporal cortices, sparing the posterior cortices (5 males, mean age = 43.22 years, SD = 9.65; mean time since lesion onset = 19.56 months, SD = 14.83), a control group of nine patients without hemianopia with lesions to right fronto-temporal cortices, sparing the posterior cortices (4 males, mean age = 51.67 years, SD = 9.97; mean time since lesion onset = 23 months, SD = 25.15) and a control group of fourteen age-matched healthy participants (7 males, mean age 54.29 years, SD = 8.28). No differences between the groups were found in terms of age ($F_{1,54} = 2.12$; $p = 0.091$), or time since lesion onset ($F_{1,41} = 1.072$; $p = 0.371$; for clinical details, see Table 6.1).

Mapping of brain lesions was performed using MRIcro. Vascular lesions and lesions after surgical exeresis in case of tumor patients documented by the most recent clinical CT or MRI were traced onto the T1-weighted MRI template from the Montreal Neurological Institute provided with MRIcro software (Rorden, Karnath & Bonilha, 2007; Rorden & Brett, 2000), with the exception of HEMI L-LES 7 and HEMI R-LES 8 whose MRI/CT scans were not available. Although lesion reconstruction was not performed for these two patients, radiology MRI/CT reports were available and confirmed the presence of unilateral lesions limited to the posterior cortices. Lesion volumes were computed for each patient in order to compare the extension of the lesions among the four patients' groups. No significant differences (one-way ANOVA, $F_{1,39} = 1.61$; $p = 0.201$) in lesion volumes between the four groups of patients were found (see Figure 6.1).

[2] Part of the data presented in this study submitted to *Brain Structure and Function (*Gallina J, Zanon M, Mikulan E, Pietrelli M, Gambino S, Ibáñez A, Bertini C (accepted for publication). Alterations in resting-state functional connectivity after brain posterior lesions reflect the functionality of the visual system in hemianopic patients). Part of the data were preliminary analyzed and presented in Pietrelli, Mattia (2020) *Post-lesional functionality of the visual system in hemianopic patients*, [Dissertation thesis], Alma Mater Studiorum Università di Bologna. Dottorato di ricerca in Psicologia, 32 Ciclo. DOI 10.6092/unibo/amsdottorato/9478

Subject	Sex	Age	Education	Onset	Lesion site	Visual field defect	Aetiology
HEMI L-LES 1	M	69	11	5	Left-Occipital	Right hemianopia	Ischaemic
HEMI L-LES 2	M	45	13	7	Left-Temporal	Right hemianopia	Hemorragic
HEMI L-LES 3	F	57	13	28	Left Fronto-Temporo-Insular	Right hemianopia	AVM
HEMI L-LES 4	M	50	13	7	Left Temporo-Occipito-Parietal	Upper right quadrantopia	Ischaemic
HEMI L-LES 5	M	81	5	9	Left Occipito-Temporal	Right hemianopia	Abscess
HEMI L-LES 6	M	51	13	5	Left Fronto-Temporo-Occipital	Right hemianopia	Ischaemic
HEMI L-LES 7	M	41	13	2	Left Occipital	Lower right quadrantopia	Hemorragic
HEMI L-LES 8	M	45	13	42	Left Fronto-Parieto-Temporal	Right hemianopia	AVM
HEMI L-LES 9	F	29	15	26	Left Temporal	Upper right quadrantopia	Ischaemic
HEMI L-LES 10	M	58	8	6	Left Temporo-Occipital	Right hemianopia	Ischaemic
HEMI L-LES 11	F	32	16	4	Left Parieto-Occipital	Right hemianopia	Ischaemic
HEMI L-LES 12	M	69	13	8	Left Temporo-Occipital	Right hemianopia	Hemorragic
HEMI L-LES 13	M	73	12	17	Left Temporo-Occipital	Right hemianopia	Hemorragic
HEMI L-LES 14	F	59	11	11	Left-Mesial-Temporal	Right hemianopia	AVM
HEMI R-LES 1	M	56	18	3	Right Occipital	Left hemianopia	Ischaemic
HEMI R-LES 2	F	38	18	13	Right Parieto-Occipital	Left hemianopia	Hemorragic
HEMI R-LES 3	F	37	13	4	Right Occipito-Temporo-Parietal	Left hemianopia	Tumor
HEMI R-LES 4	M	58	8	18	Right Temporo-Occipital	Left hemianopia	Ischaemic
HEMI R-LES 5	M	81	8	7	Right Occipital	Left hemianopia	Hemorragic
HEMI R-LES 6	M	51	8	4	Right Occipital	Left hemianopia	Tumor
HEMI R-LES 7	M	60	18	29	Right Temporo-Occipital	Left hemianopia	Ischaemic
HEMI R-LES 8	F	73	5	8	Right Temporo-Occipital	Left hemianopia	Ischaemic
HEMI R-LES 9	M	77	8	6	Right Fronto-Parietal	Left hemianopia	Hemorragic
HEMI R-LES 10	M	30	16	54	Right-Temporal	Left hemianopia	Hemorragic
HEMI R-LES 11	M	59	18	5	Right Temporo-Occipital	Left hemianopia	Ischaemic
HEMI R-LES 12	M	76	13	7	Right Temporo-Occipital	Left hemianopia	Abscess
HEMI R-LES 13	M	70	18	5	Right Occipital	Left hemianopia	Ischaemic
CONT L-LES 1	F	48	13	38	Left Fronto-Insular	No hemianopia	Ischaemic
CONT L-LES 2	F	44	13	40	Left Frontal	No hemianopia	Tumor
CONT L-LES 3	M	28	18	11	Left Fronto-Parietal	No hemianopia	Tumor
CONT L-LES 4	F	45	11	39	Left Frontal	No hemianopia	Tumor
CONT L-LES 5	F	46	15	12	Left Temporal Pole	No hemianopia	Hemorragic
CONT L-LES 6	M	62	18	7	Left Temporo-Insular	No hemianopia	Abscess
CONT L-LES 7	M	34	13	7	Left Frontal	No hemianopia	Tumor
CONT L-LES 8	M	45	13	15	Left-Frontal	No hemianopia	Ischaemic
CONT L-LES 9	F	37	13	7	Left Frontal	No hemianopia	Tumor
CONT R-LES 1	F	57	13	5	Right Fronto-Insular	No hemianopia	AVM
CONT R-LES 2	M	42	18	59	Right Frontal	No hemianopia	Abscess
CONT R-LES 3	F	42	11	19	Right Frontal	No hemianopia	Tumor
CONT R-LES 4	M	51	8	3	Right Temporo-Insular	No hemianopia	Tumor
CONT R-LES 5	F	51	10	5	Right Temporal	No hemianopia	Tumor
CONT R-LES 6	F	50	5	71	Right Temporo-Fronto-Polar	No hemianopia	Traumatic
CONT R-LES 7	M	75	8	26	Right Temporo-Insular	No hemianopia	Tumor
CONT R-LES 8	F	46	8	13	Right-Frontal	No hemianopia	Abscess
CONT R-LES 9	M	51	13	6	Right-Frontal	No hemianopia	Tumor

Table 6.1. *Summary of demographic and clinical data of all patients that took part to the study. M = Male; F = Female; AVM = Arteriovenus Malformation. Details about age and education are reported in years; details about onset of brain lesion are reported in months.*

Patients with posterior lesions were recruited based on reported visual field defects and the availability of a visual field perimetry (see also table 6.2 for the hemianopic patients' detection rates in the blind field, in the Fixed-eye condition and in the Eye-movements condition, at the Computerized visual field) and CT/MRI reports of the lesion. In patients with posterior right lesions, the presence of neglect was screened using the Behavioral Inattention Test (Wilson, Cockburn, & Halligan, 1987), to ensure performance was in the normal range.

All patients showed normal or corrected-to-normal visual acuity. Patients were informed about the procedure and the purpose of the study and gave written informed consent. The study was designed and performed in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Regional Health Service Romagna (CEROM; n.2300).

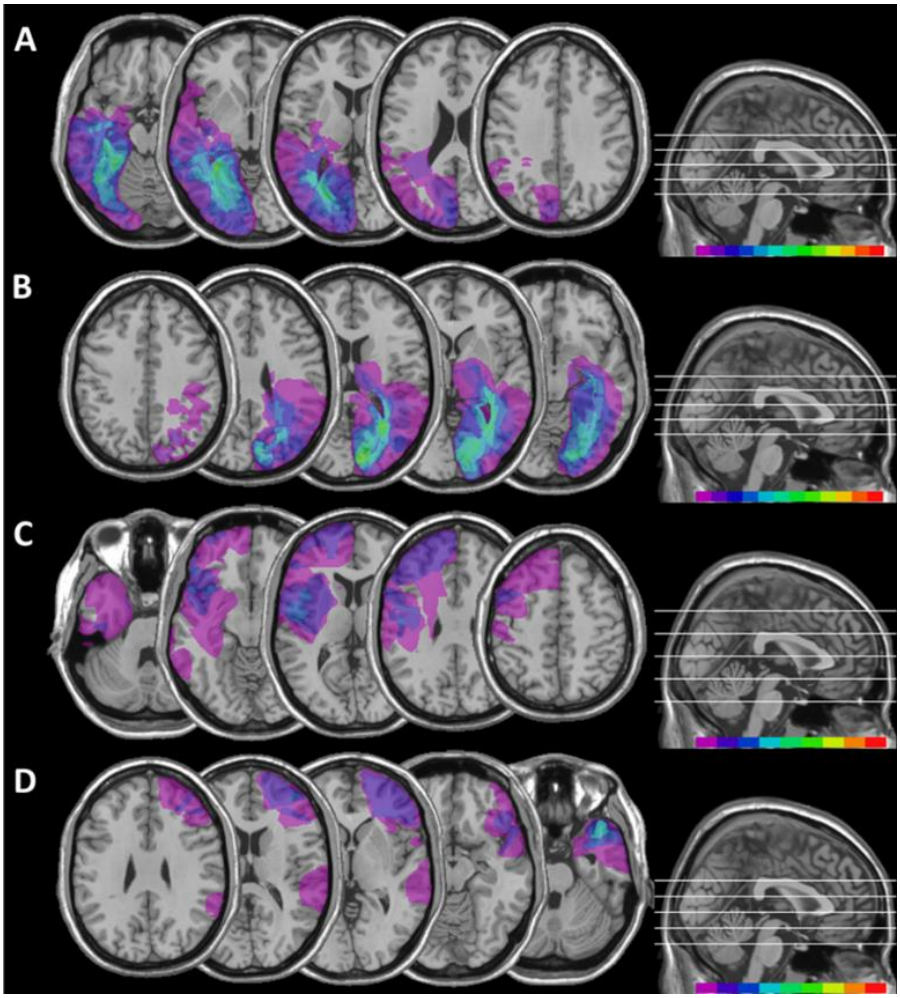

Figure 6.1. *Location and overlap of brain lesions of patients. The image shows the lesions of the hemianopic patients with left posterior brain lesion (A), hemianopic patients with right posterior brain lesion (B), control patients with left anterior brain lesion (C), control patients with right anterior brain lesion (D), projected onto four axial slices of the standard MNI brain. The levels of the axial slices are marked by white lines on the sagittal view of the brain. The color bar indicates the number of overlapping lesions.*

6.2.2 EEG recordings

Participants comfortably seated in a soundproof room, while EEG signal was recorded from 5 sessions of one minute each, in an eyes-closed resting state condition. EEG data was acquired through a BrainAmp DC amplifier (BrainProducts GmbH, Germany) and Ag/AgCl electrodes (Fast'nEasy Cap, Easycap GmbH, Germany) from 59 scalp sites (Fp1, AF3, AF7, F1, F3, F7, FC1, FC3, FC5, FT7, C1, C3, C5, T7, CP1, CP3, CP5, TP7, P1, P3, P5, P7, PO3, PO7, O1, Fp2, AF4, AF8, F2, F4, F8, FC2, FC4, FC6, FT8, C2, C4, C6, T8, CP2, CP4, CP6, TP8, P2, P4, P6, P8, PO4, PO8, O2, FPz, AFz, Fz, FCz, Cz, CPz, Pz, POz, Oz) and the right mastoid. The left mastoid was used as online reference electrode, while the ground electrode was placed on the right cheek. Vertical and horizontal electrooculogram (EOG) components were recorded from above and below the left eye, and from the outer canthus of each eye. Data was recorded with a band-pass filter of 0.01–100 Hz and digitized at a sampling rate of 1000 Hz, while impendences were kept under 5 KΩ.

6.2.3 EEG preprocessing

EEG recordings were processed off-line using EEGlab (v14.1.2; Delorme & Makeig, 2004) and custom scripts developed in Matlab (R2018a; The Mathworks Inc., USA). Data from all electrodes were re-referenced to the average of all scalp electrodes and filtered with a band-pass filter of 1-100 Hz. Continuous signals were segmented in epochs of 1 seconds. Horizontal and vertical eye artifacts were visually identified and corrected with an independent component analysis (ICA), after data dimension reduction by means of Principal Component Analysis (PCA). Data was down-sampled to 250 Hz and current source density (CSD) interpolation, using spherical splines (Kayser & Tenke 2015) was applied to minimize confounding effects in inter-electrode synchronization due to volume conduction and field spread (van Diessen et al. 2015; Cohen 2014). CSD transformation was performed in Matlab using the open-source CSD toolbox (version 1.1; http://psychophysiology.cpmc.columbia.edu/Software/CSDtoolbox/).

6.2.4. Functional connectivity analysis

A multi-step approach was used to investigate, separately for each frequency band and hemisphere, the effects of unilateral posterior or anterior brain lesions on functional connectivity and resting-state network topology.

6.2.4.1 Weighted phase-lag index

Functional connectivity was measured computing the weighted phase-lag index (wPLI, Vinck et al., 2011), which extends the phase-lag index (PLI, Stam et al., 2007) by weighting the contribution of observed phase leads and lags by the magnitude of the imaginary component of the cross-spectrum (Vinck et al., 2011). The wPLI is based on a consistent lag between the instantaneous phases of two electrodes and is less sensitive to zero-lag phase-relations typical for common sources (Bastos & Schoffelen 2016; Hardmeier et al., 2014).

To compute the wPLI, frequency decomposition was performed for all EEG channels, by using a multitaper method with digital prolate spheroidal sequence (DPSS) windows, implemented in Fieldtrip toolbox (v20210311) for EEG/MEG-analysis (for the details of the implementations, see Vinck et al., 2011). Complex Fourier coefficients were extracted for the frequency bands of interest, specifically in the theta (3-6 Hz), low alpha (7-10 Hz) and upper alpha (11-13 Hz) ranges and 59x59 connectivity matrix was constructed for each participant and frequency band of interest. Then, the wPLIs computed for all possible pairs of electrodes within the left (Fp1, AF3, AF7, F1, F3, F7, FC1, FC3, FC5, FT7, C1, C3, C5, T7, CP1, CP3, CP5, TP7, P1, P3, P5, P7, PO3, PO7, O1) and the right (Fp2, AF4, AF8, F2, F4, F8, FC2, FC4, FC6, FT8, C2, C4, C6, T8, CP2, CP4, CP6, TP8, P2, P4, P6, P8, PO4, PO8, O2) hemisphere were averaged across pairs of electrodes and participants, to obtain an index of intrahemispheric functional connectivity. Electrodes on the sagittal midline were excluded from the analysis, to provide a better segregation of the signal of the two hemispheres.

Intrahemispheric functional connectivity was compared among groups and hemispheres, separately for each frequency band (i.e., theta, lower alpha, upper alpha), with an ANOVA on mean intrahemispheric wPLI having *Group* (Healthy participants, Left-lesioned hemianopic patients, Right-lesioned hemianopic patients, Left-lesioned control patients, Right-lesioned control patients) as between-subjects factor, and *Hemisphere* (Left, Right) as within-subjects factor. Statistically significant interactions or main effects were subsequently explored through simple planned contrasts,

comparing connectivity in each group of patients against connectivity in the group of Healthy participants.

6.2.4.2 Graph theory

Two Graph Theory measures, the clustering coefficient (C) and the characteristic path length (L), were chosen to assess the functional network segregation and integration, respectively. In particular, the C represents the degree to which nodes in a graph are interconnected whereas the L reflects the average shortest path length between all pairs of nodes in the network (Watts & Strogatz, 1998). Graph indices were computed with custom scripts developed in Matlab, through the Brain Connectivity Toolbox (v1.1, Rubinov & Sporns, 2010). Specifically, the C and the L were calculated separately for each band of interest (i.e., theta, low alpha, high alpha), on undirected weighted network matrices without thresholding, putting wPLI values as the edge weights.
The C (Onnela, J. Saramäki, Kertész, Kaski, 2005) was defined as:

$$C^w = \frac{1}{n} \sum_{i \in N} \frac{2t_i^w}{k_i(k_i - 1)}$$

Where C is the clustering coefficient of a given node (for details, see Rubinov & Sporns, 2010).
The L (Runinov & Sporns, 2010) was defined as:

$$L^w = \frac{1}{n} \sum_{i \in N} \frac{\sum_{j \in N, j \neq i} d_{ij}^w}{n - 1}$$

Where L is the average distance between a given node and all other nodes (for details, see Rubinov & Sporns, 2010).
To test for differences in the functional integration and segregation within the two brain hemispheres, the C and the L parameters were separately computed for the left and the right hemisphere and averaged across participants. Electrodes on the sagittal midline were excluded from the analysis, to provide a better segregation of the signal of the two hemispheres. Then, possible differences among groups and hemispheres were tested separately for each frequency band (i.e. theta, low alpha, high alpha) with an ANOVA having *Group* (Healthy participants, Left-lesioned hemianopic patients, Right-lesioned hemianopic patients, Left-lesioned control patients, Right-lesioned control patients)

as between-subjects factor, and *Hemisphere* (Left, Right) as within-subjects factor. Statistically significant main effects or interactions were subsequently explored through simple planned contrasts, by comparing the mean C and L of each group of patients against the group of Healthy participants.

6.2.5 Computerized visual field test

In addition to the EEG recording, hemianopic patients' visual detection abilities were also tested (Grasso, Làdavas, Bertini, 2016 Passamonti, Bertini, Làdavas, 2009; Bolognini, Rasi, Coccia, Làdavas, 2005) during the clinical examination, to explore a possible link between visual performance and functional connectivity. Patients sat at a viewing distance of 120 cm, while a stimulus array of 52° x 45° (horizontally and vertically, respectively) was projected on the wall. Targets, consisting of white dots (1°) were presented on a black background for 100 ms, at random positions. A red fixation cross (0.5°) was displayed on the center of the screen. A total of 96 targets was presented (i.e., 48 targets for each hemifield). In 31 trials, no target was presented (i.e., catch trials). Patients were instructed to press a response button after the detection of the target. Patients'gaze was monitored throughout the task by the experimenter. The task was performed in two different conditions: when patients were not allowed to move their eyes to compensate for the visual field loss and had to keep their gaze on a central fixation cross (Fixed-eyes) and when patients were allowed to perform eye movements (Eye movements). Visual detections and false alarms rates for stimuli presented in the blind visual field were measured. D prime (perceptual sensitivity) was calculated and used for subsequent correlational statistical analysis with the patients' wPLI and Graph theory indices that resulted to be impaired, compared to healthy participants (for the details of the patients' dection rates at the Computerized visual field test, in the Fixed-eye condition and in the Eye-movements condition, see Table 6.2)

ID	Detection rate (%) Fixed-Eye	Detection rate (%) Eye-Movements
HEMI L-LES 1	21	40
HEMI L-LES 2	0	33,5
HEMI L-LES 3	21	66,4
HEMI L-LES 4	0	40
HEMI L-LES 5	10,5	29
HEMI L-LES 6	8,5	60,5
HEMI L-LES 7	16,5	52,5
HEMI L-LES 8	21	48
HEMI L-LES 9	0	32,5
HEMI L-LES 10	50	73
HEMI L-LES 11	48	89,5
HEMI L-LES 12	0	19
HEMI L-LES 13	23	85,5
HEMI L-LES 14	0	14,5
HEMI R-LES 1	27	50
HEMI R-LES 2	27	56,5
HEMI R-LES 3	6	63
HEMI R-LES 4	27	73
HEMI R-LES 5	15	50
HEMI R-LES 6	15	33,5
HEMI R-LES 7	8,5	50,5
HEMI R-LES 8	0	28,5
HEMI R-LES 9	0	0
HEMI R-LES 10	6,5	35,5
HEMI R-LES 11	29	48
HEMI R-LES 12	2	58
HEMI R-LES 13	13	46

***Table 6.2**. Hemianopic patients' detection rates (%) in the blind field at the Computerized visual field test in the Fixed-Eye condition and in the Eye-movements condition.*

6.3 Results

6.3.1. Functional connectivity in the theta band

6.3.1.1 wPLI

The ANOVA on wPLI revealed a significant main effect of *Group* ($F_{4,54} = 5.185$, $p = 0.001$, $\eta^2 = 0.277$). Moreover, a significant *Group* x *Hemisphere* ($F_{4,54} = 2.879$, $p = 0.031$, $\eta^2 = 0.176$; see Figure 6.2B) interaction was also evident, which was further explored through simple planned contrasts., in

which the intrahemispheric theta wPLI of each group of patients was contrasted against the group of healthy participants, separately for the left and the right hemisphere.

Planned contrast comparing the group of Left-lesioned hemianopics to Healthy participants showed no significant difference in the left hemisphere (Left-lesioned hemianopics M = 0.19, Healthy participants M = 0.18; p = 0.776) nor in the right hemisphere (Left-lesioned hemianopics M = 0.17, Healthy participants M = 0.16; p = 0.743). Similarly, planned contrast comparing Right-lesioned hemianopics to Healthy participants did not show a significant difference in the left hemisphere (Right-lesioned hemianopics M = 0.21; p = 0.141). However, Right-lesioned hemianopics showed a significantly increased wPLI in the right hemisphere (M = 0.25), compared to the right hemisphere of healthy participants ($p < 0.001$).

Planned contrasts comparing the group of Left-lesioned control patients against Healthy participants, showed no significant difference in the left hemisphere (Left-lesioned control patients M = 0.16; p = 0.28), nor in the right hemisphere (Left-lesioned control patients M = 0.16, p = 0.96).

Finally, planned contrast on the group of Right-lesioned control patients *vs* Healthy participants showed no significant difference in the left hemisphere (Right-lesioned control patients M = 0.14, p = 0.057) nor in the right hemisphere (Right-lesioned control patients M = 0.14, p = 0.314).

Last, to test whether the observed differences across groups and hemispheres in terms of intrahemispheric connectivity in the theta range could depended the extent of the lesion, a correlational analysis was performed. Pearson's correlations were run between the patients'intrahemispheric wPLI in the lesioned hemisphere and the voxel-based lesion volume. No significant correlation emerged (r = 0.003, p = 0.296).

6.3.1.2 Clustering coefficient and Characteristic path length

The ANOVA on C revealed a significant main effect of *Group* ($F_{4,54} = 5.249$, $p = 0.001$, $\eta^2 = 0.280$), and a significant *Group* x *Hemisphere* ($F_{4,54} = 2.591$, $p = 0.047$, $\eta^2 = 0.161$; see Figure 6.2C) interaction, which was further explored by performing planned contrast.

Planned contrast on the group of Left-lesioned hemianopcs against the group of Healthy participants did not show any significant difference neither in the left (Left-lesioned hemianopics M = 0.17, Healthy participants M= 0.17, p = 0.754) or in the right (Left-lesioned hemianopics M = 0.16, Healthy participants M= 0.17, p = 0.698) hemisphere. When comparing Right-lesioned hemianopics *vs* Healthy participants, planned contrast on the group of revealed no significant difference in the left hemisphere (Right-lesioned hemianopics M = 0.20, p = 0.132) but, importantly, Right-lesioned

hemianopics exhibited a higher theta C in the right hemisphere, compared to the right hemisphere of Healthy participants (Right-lesioned hemianopics $M = 0.22$, $p < 0.001$).

On the contrary, for the group of Left-lesioned control patients, planned contrast against Healthy participants revealed no significant difference in the left hemisphere (Left-lesioned control patients $M = 0.15$, $p = 0.278$) and in the right hemisphere (Left-lesioned control patients $M = 0.15$, $p = 0.976$). Last, also for the group of Right-lesioned control patients *vs* Healthy participants, planned contrast did not show any significant difference in the left hemisphere (Right-lesioned control patients $M = 0.13$, $p = 0.057$), nor in the right hemisphere (Right-lesioned control patients $M = 0.13$; $p = 0.316$).

To test whether the extent of the lesion could account fot the observed differences across groups and hemispheres in terms of theta clustering coefficent, a correlational analysis was performed. Pearson's correlations were run between the patients' C in the lesioned hemisphere and the voxel-based lesion volume. No significant correlation was found ($r = 0.024$, $p = 0.320$).

Looking at the results for the analysis on the L, the ANOVA showed a significant main effect of *Group* ($F_{4,54} = 4.445$, $p = 0.004$, $\eta^2 = 0.248$; see Figure 6.2D). Planned contrast revealed a significantly higher theta PL for the group of Right-lesioned hemianopics ($M = 0.15$) compared to Healthy participants ($M = 0.12$, $p = 0.015$).

In contrast, planned contrast performed on the group of Left-lesioned hemianopics ($M = 0.13$), Left-lesioned control patients ($M = 0.11$) and Right-lesioned control patients ($M = 0.10$) showed no significant difference, compared to Healthy participants (all $ps > 0.106$).

Also for the characteristic path length, a correlational analysis was performed to verify whether the observed differences across groups could be explained by the extent of the lesiosn. The patients' P indices of the lesioned and the intact hemisphere were collapsed and correlated to their voxel-based lesion volumes by performing Pearson's correlations. No significant correlation was found ($r = 0.268$, $p = 0.082$).

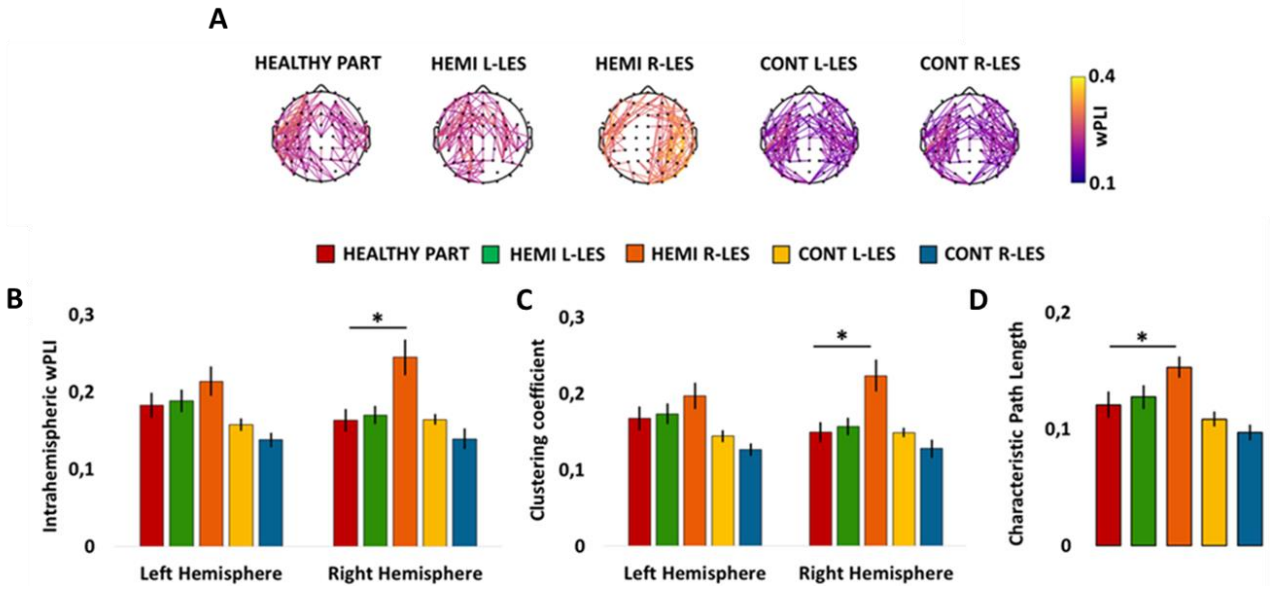

Figure 6.2. *Scalp maps (A) represent the strongest theta connections (n = 171, 10% of total connections) in the group of healthy participants (HEALTHY PART), hemianopic patients with left lesion (HEMI L-LES), hemianopic patients with right lesion (HEMI R-LES), control patients with left anterior lesion (CONT L-LES) and control patients with right anterior lesion (CONT R-LES) The color bar represents the wPLI value, so that higher values are associated with yellow color and lower values with blue color.*

Bar histograms show the mean theta (3-6 Hz) intrahemispheric wPLI relative to the left and to the right hemisphere, within each group (B), the mean theta clustering coefficient relative to the left and to the right hemisphere, within each group (C) and the mean theta characteristic path length within each group (D). Error bars represent standard error; asterisks indicate the significant comparisons

6.3.2 Functional Connectivity in the lower alpha band

6.3.2.1 Intrahemispheric wPLI

The ANOVA on the wPLI in the lower alpha band showed a significant *Group* x *Hemisphere* ($F_{4,54} = 3.162$, $p = 0.021$, $\eta^2 = 0.190$; see Figure 6.3B) interaction. Planned contrast performed on the group of Left-lesioned hemianopics *vs* Healthy participants revealed no significant difference between the two groups in the left hemisphere (Left-lesioned hemianopics M = 0.29, Healthy participants M = 0.32, p = 0.499), nor in the right hemisphere (Left-lesioned hemianopics M = 0.35, Healthy participants M = 0.31, p =0.349).

Similarly, when comparing the group of Right-lesioned hemianopics against Healthy participants, planned contrast did not show a significant difference in the left hemisphere (Rigth-lesioned

hemianopics M = 0.35, p = 0.408), nor in the right hemisphere (Rigth-lesioned hemianopics M = 0.29, p = 0.615).

Also when comparing Left-lesioned control patients against Healthy participants planned contrast showed no significant difference in the left hemisphere (Left-lesioned control patients M = 0.29; p = 0.479), nor in the right hemisphere (Left-lesioned control patients M = 0.29; p = 0.613).

Last, planned contrast on the group of Right-lesioned control patients *vs* Healthy participants showed no significant difference between the two groups in the left hemisphere (Right-lesioned control patients M = 0.34; p = 0.742), nor in the right hemisphere (Right-lesioned control patients M = 0.31; p = 0.992).

6.3.2.2 Clustering coefficient and Characteristic path Length

The ANOVA on the lower alpha C revealed a significant *Group* x *Hemisphere* ($F_{4,54}$ = 3.266, p = 0.019, η^2 = 0.193; see Figure 6.3C) interaction.

Planned contrast on the group of Left-lesioned hemianopics *vs* Healthy participants showed no significant difference between the two groups neither the left hemisphere (Left-lesioned hemianopics M = 0.27, Healthy participants M = 0.29, p = 0.462), nor in the right hemisphere (Left-lesioned hemianopics M = 0.31, Healthy participants M = 0.28, p = 0.416).

In a similar way, planned contrast on the group of Right-lesioned hemianopics vs Helathy participants did not reveal a significant difference in the left hemisphere (Right-lesioned hemianopics M = 0.32, p = 0.443), nor in the right hemisphere (Right-lesioned hemianopics M = 0.26, p = 0.514).

Also for the group of Left-lesioned control patients, planned performed contrast against Healthy participants revealed no significant difference in the left hemisphere (Left-lesioned control patients M = 0.26; p = 0.463), nor in the right hemisphere (Left-lesioned control patients M = 0.26; p = 0.604).

Finally, planned contrast for the group of Right-lesioned control patients *against* Healthy participants showed no significant difference between the two groups in the left hemisphere (Right-lesioned control patients M = 0.30, p = 0.714), nor in the right hemisphere (Right-lesioned control patients M = 0.28; p = 0.946).

In contrast, the ANOVA on the lower alpha P revealed no significant main effect or interaction (all ps > 0.123; see Figure 6.3D).

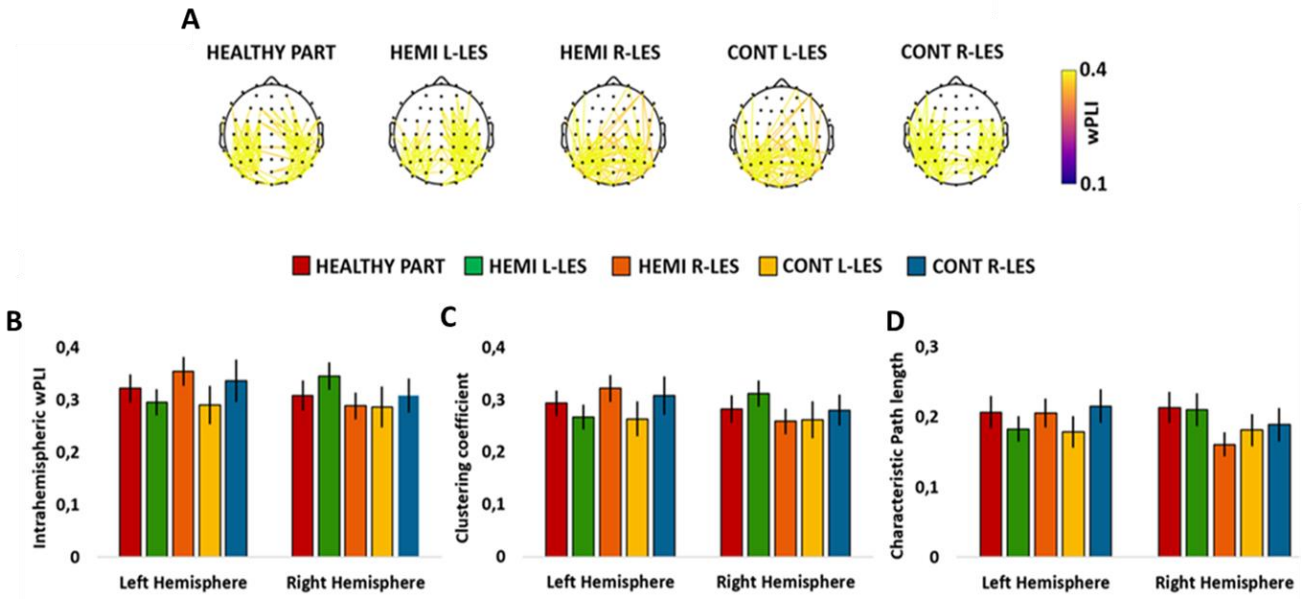

Figure 6.3. *Scalp maps (A) represent the strongest lower alpha connections (n = 171, 10% of total connections) in the group of healthy participants (HEALTHY PART), hemianopic patients with left lesion (HEMI L-LES), hemianopic patients with right lesion (HEMI R-LES), control patients with left anterior lesion (CONT L-LES) and control patients with right anterior lesion (CONT R-LES) The color bar represents the wPLI value, so that higher values are associated with yellow color and lower values with blue color.*

Bar histograms show the mean lower alpha (7-10 Hz) intrahemispheric wPLI relative to the left and to the right hemisphere, within each group (B), the mean lower alpha clustering coefficient relative to the left and to the right hemisphere, within each group (C) andthe mean lower alpha characteristic path length relative to the left and to the right hemisphere, within each group (D). Error bars represent standard error; asterisks indicate the significant comparisons.

6.3.3 Functional connectivity in the upper alpha band

6.3.3.1 Intrahemispheric wPLI

For the upper alpha band, showed a significant *Group* x *Hemisphere* ($F_{4,54} = 2.787$, $p = 0.035$, $\eta^2 = 0.171$; see Figure 6.4B) interaction.

Planned contrast for the group of Left-lesioned hemianopics *vs* Healthy participants showed a significantly decreased wPLI in the left hemisphere of Left-lesioned hemianopics (M = 0.24), compared to the left hemisphere of Healthy participant (M = 0.32, p = 0.020), whereas no significant difference between the two groups was found in the right hemisphere (Left-lesioned hemianopics M = 0.31, Healthy participants M = 0.32, p = 0.749). For the group of Right-lesioned hemianopics, planned contrasts revealed a significant decrease in wPLI both in the left (M = 0.25; p = 0.036) and in the right (M = 0.22; p = 0.019) hemisphere, compared to healthy participants.

Instead, when comparing the group of Left-lesioned control patients against Healthy participants no significant difference in the left hemisphere (Left-lesioned control patients M = 0.27; p = 0.186), nor in the right hemisphere (Left-lesioned control patients M = 0.30; p = 0.621) emerged.
Last, planned contrast on the group of Right-lesioned control patients against Healthy participants again showed no significant difference in the left hemisphere (Right-lesioned control patients M = 0.31, p = 0.899), nor in the right hemisphere (Right-lesioned control patients M = 0.30; p = 0.582).
Finally, to test whether the extent of the lesion could account for the observed differences across groups and hemispheres in terms of intrahemispheric connectivity in the upper alpha range, a correlational analysis was performed separately for the intact and the lesioned hemisphere. Pearson's correlations were run between the patients'intrahemispheric wPLI in the lesioned and in the intact hemisphere and the voxel-based lesion volume. Bonferroni-Holms corrections were applied to account for multiple comparisons. Adjusted p-values are reported. No significant correlation was found (all adj ps > 0.999).

6.3.3.2 Clustering coefficient and Characteristic Path Length

The ANOVA on the upper alpha C showed a significant *Group* x *Hemisphere* ($F_{4,54}$ = 2.958, p = 0.028, η^2 = 0.180, see Figure 6.4C) interaction.Planned contrast revealed that Left-lesioned hemianopics had asignificantly lower C in the left hemisphere of Left-lesioned hemianopics (M = 0.21), compared to the left hemisphere of Healthy participants (M = 0.29, p = 0.017), whereas no significant difference between the two groups was found for the right hemisphere (Left-lesioned hemianopics M = 0.28, Healthy participants M = 0.29; p = 0.727). In a similar way, the group of Right-lesioned hemianopics, planned contrasted revealed a significantly lower C in the left hemisphere (M = 0.22), compared to the left hemisphere of healthy participants (p = 0.041). Furthermore, Right-lesioned hemianopics exhibited also a lower C in the right-hemisphere (M = 0.20), compared to the right hemisphere of Healthy participants (p = 0.020).
In contrast, the group of Left-lesioned control patients exhibited no significant difference in the left hemisphere (Left-lesioned control patients M = 0.23, p = 0.142), nor in the right hemisphere (Left-lesioned control patients M = 0.27, p = 0.587), compared to Healthy participants.
Finally, also the group of Right-lesioned control patients, did not show any significant difference in the left hemisphere (Right-lesioned control patients M = 0.28, p = 0.908), nor in the right hemisphere (Right-lesioned control patients M = 0.27, p = 0.573), compared to Healthy participants.

To verify whether the extent of the lesion could account for the observed differences across groups and hemispheres in terms of upper alpha clustering coefficent, a correlational analysis was performed separately for the intact and the lesioned hemisphere. Pearson's correlations were run between the patients' C in the lesioned and in the intact hemisphere and the voxel-based lesion volume. Bonferroni-Holms corrections were used to account for multiple comparisons. Adjusted p-values are reported. No significant correlation was found (all adj ps > 0.999).

Last, the ANOVA on the upper alpha P showed no significant main effect or interaction (all ps > 0.080; see Figure 6.4D).

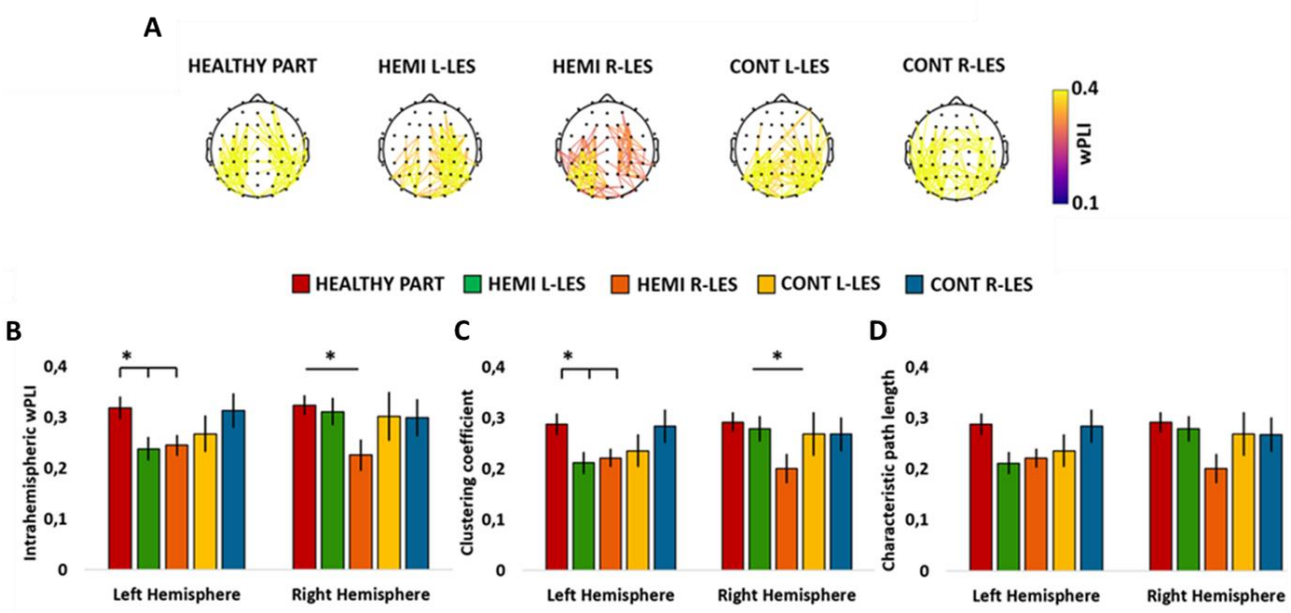

Figure 6.4. *Scalp maps (A) represent the strongest upper alpha connections (n = 171, 10% of total connections) in the group of healthy participants (HEALTHY PART) hemianopic patients with left lesion (HEMI L-LES), hemianopic patients with right lesion (HEMI R-LES), control patients with left anterior lesion (CONT L-LES) and control patients with right anterior lesion (CONT R-LES) The color bar represents the wPLI value, so that higher values are associated with yellow color and lower values with blue color.*

Bar histograms show the mean upper alpha (11-13 Hz) intrahemispheric wPLI relative to the left and to the right hemisphere, within each group (B), the mean upper alpha clustering coefficient relative to the left and to the right hemisphere, within each group (C) and the mean upper alpha Characteristic path length relative to the left and to the right hemisphere, within each group (D). Error bars represent standard error; asterisks indicate the significant comparisons.

6.3.4 Hemianopic patients' visual performance and functional connectivity

Finally, we tested whether altered theta and upper alpha functional connectivity can relate to behavioral performance in visual detection tests in hemianopic patients with both left and right lesions. To this aim, the relationship between hemianopic patients' perceptual sensitivity (D prime) in their blind field at the Computerized Visual Field test and their functional connectivity parameters that resulted to be impaired was explored. More specifically, hemianopic patients' D prime in both the Fixed-Eyes condition and in the Eye-Movements condition was correlated to the wPLI, the C and the L in the theta band and to the wPLI and the C in the upper alpha band, separately for the lesioned and the intact hemisphere. Pearson correlations were performed (Bonferroni-Holm corrections were used for multiple comparisons; adjusted p-levels are reported).

In the Fixed-Eyes condition, no significant correlation between the theta wPLI in both the lesioned and the intact hemisphere and the D prime was found (all ps = 0.100). Similarly, no significant correlation was found between visual performance and the theta C and L in both the lesioned and the intact hemisphere (all ps = 0.100). , therefore suggesting no relationship between connectivity parameter in the theta range and visual detection performance in the blind visual field when eye movements were restricted.

As for the upper alpha range, no significant correlation between the wPLI in the intact hemisphere and the D prime ($r = 0.225$, $p = 0.257$) was found, but, importantly, a positive significant correlation between the upper alpha wPLI in the lesioned hemisphere and the D prime ($r = 0.496$, $p = 0.016$, see figure 6.5A) was evident (i.e., the higher the upper alpha wPLI in the lesioned hemisphere, the better the performance in patients' blind field). In line, also a positive significant correlation between upper alpha C in the lesioned hemisphere and the D prime ($r = 0.541$, $p = 0.006$, see figure 6.5B) was found. In contrast, no significant correlation between the upper alpha C in the intact hemisphere and the D prime was found ($r = 0.264$, $p = 0.182$). Overall, these findings indicate that upper alpha functional connectivity in the lesioned hemisphere in hemianopic patients is associated with visual detection performance in their blind visual field.

Finally, in the Eyes-Movements condition, no significant correlation with hemianopic patients' D prime in the blind field was found (all ps > 0.074), suggesting that both the theta and the upper alpha functional connectivity are not related to patients' ability to compensate for the field loss when eye movements are allowed.

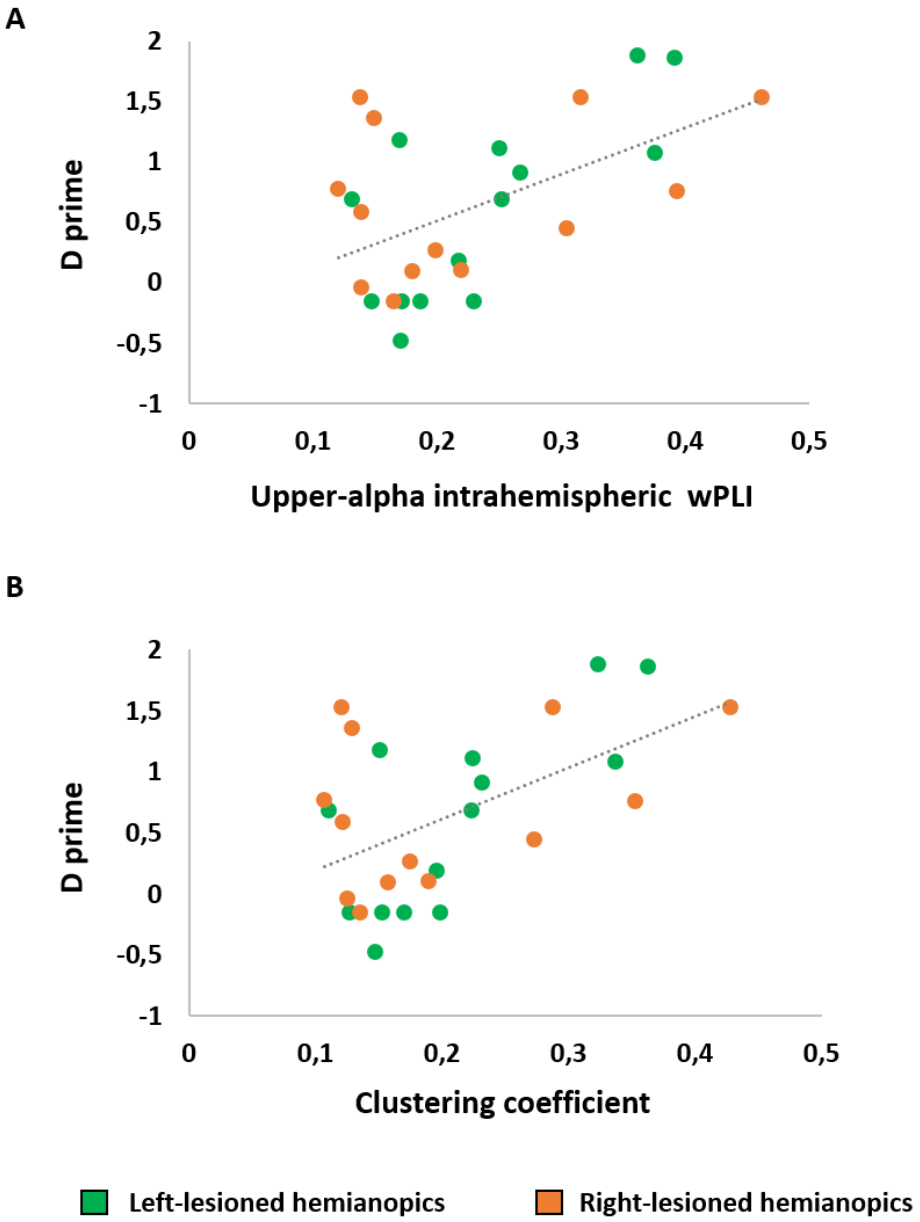

Figure 6.5. *Correlations between the hemianopic patients' visual performance in the Computerized Visual Field test in the Fixed-Eyes condition and functional connectivity parameters. Panel* ***(A)*** *depicts the correlation between D prime and upper alpha intrahemispheric wPLI; Panel* ***(B)*** *depicts the correlation between D prime and the upper alpha clustering coefficient.*

6.4 Discussion

The present study, exploring the hypothesis that specific lesional profiles might differentially alter functional connectivity, has revealed that posterior brain lesions selectively impair oscillatory brain connectivity at rest. More precisely, both hemianopics with left and right posterior lesions showed a reduction in intrahemispheric functional connectivity in the range of upper alpha (11-13 Hz) during resting-state, while control patients with anterior lesions revealed no connectivity change compared to healthy individuals. Moreover, posterior right lesions seemed to induce more severe alterations in the oscillatory connectivity patterns, with hemianopics with right lesions showing a reduced intrahemispheric upper alpha connectivity in both the lesioned and the intact hemisphere and additional abnormal increase in connectivity in the theta range. On the contrary, left-lesioned hemianopics revealed only a reduction in intrahemispheric upper-alpha connectivity limited to the lesioned hemisphere. These results suggest that lesions to posterior cortices, damaging the crucial hub for the generation and distribution of alpha oscillations, specifically impair connectivity in this frequency band, in line with recent evidence showing in this clinical population also a slowdown of the speed of a reduction of alpha peak), the occurrence of an interhemispheric power imbalance (Pietrelli et al., 2019) and, as showed in chapter 5, a reduction of alpha reactivity induced by eyes-opening (Gallina et al., 2021). In line with this view, posterior visual cortices have been demonstrated to be crucial in generating and propagating alpha oscillations in the visual system (Bollimunta et al., 2008; Hindriks et al., 2015) and oscillations in this frequency range have been reported to be linked to visual perception and visual cortex activity (Pfurtscheller et al., 1994; Romei, et al. 2008a, 2008b;). The observed alterations in alpha connectivity suggest that posterior lesions impair global resting-state integration mechanisms. Indeed, alpha oscillatory activity in functional neural connectivity has been suggested to represent one of the main mechanisms of global resting-state integration in the human brain (Guggisberg et al., 2015) and to reflect top-down processing, allowing the integration of local bottom-up information (von Stein & Sarnthein, 2000).

In the present findings, hemianopic patients with posterior lesions showed connectivity impairments only in the upper range of the alpha band. This seems consistent with previous evidence reportinga reduction of the individual alpha frequency in these (Pietrelli et al., 2019). Moreover, in line with this observation, converging evidence have also reported that occipito-parietal alpha generators, which might be impaired after posterior lesions, are more linked with oscillatory activity in the upper alpha band (Cantero, Atienza & Salas, 2002).Indeed, although consensus is scarce relative to the distinctive features of the low and high range of alpha, it has been suggested that activity peaking towards the slower components of the alpha band is more typical of the anterior than posterior cortical surface

(Nunez, 1974) and that this anterior alpha activity might depend on fronto-central generators, independent from the occipital alpha sources (Lehmann, 1971).

The present results also highlight the topological features of these postlesional connectivity changes, showing that the reduced connectivity in upper alpha, is characterized by a decrease in the clustering coefficient parameter, reflecting local functional segregation, with no associated change in the characteristic path length index, which represents a measure of global functional integration. Effective functional segregation has been reported to represent the ability of specific brain regions to integrate all the available information into complex specialized processes, through densely interconnected modules or clusters (Friston, 2011) and a balance between dense local clustering and short path length has been viewed as an index of network efficiency (Bassett & Bullmore, 2006; Sporns, 2011). Therefore, the observed postlesional changes in hemianopics suggest a decrease in network efficiency, mainly due to a weakened local functional specialization.

Our results also show a strong association between performance in clinical visual tests and connectivity patterns in the alpha range. Indeed, visual detection performance in the blind field, (Bolognini et al., 2005; Passamonti et al., 2009; Grasso et al., 2016) was positively correlated with connectivity index and clustering coefficient in the upper alpha range. In contrast, no association between alpha connectivity and visual performance, when compensatory eye-movements were allowed, was found. These findings suggest a strong link between alpha connectivity patterns after posterior lesions and the size of spared visual field. In contrast, compensatory visual mechanisms, such as visual exploration through eye movements, seem not related to these connectivity measures. Impaired pattern of alpha functional connectivity has also been observed in patients with visual loss due to pre-chiasmatic lesions (Bola et al., 2014) or retinal damage (Bola, Gall & Sabel, 2015). These findings altogether suggest that alterations in alpha functional connectivity during rest represents an index of impairment of the structural and functional integrity of the visual system, reflecting damage in posterior brain regions or in peripheral visual structures. This is in line with the evidence that alpha activity in a condition of eyes-closed resting state is strongly linked with visuospatial performance (Klimesch et al., 2007; 1999; 1997) and favors the notion that alpha oscillatory activity at rest may represent a valuable biomarker to assess the functionality of the visual system.

Interestingly, right posterior lesions led to a more profound impairment in oscillatory functional connectivity. Indeed, after lesions of the right posterior cortices, the reduction in alpha connectivity was bilaterally distributed all over the scalp; in contrast, after left posterior lesions, reduction in alpha connectivity was found only in the hemisphere ipsilateral to the lesion. Moreover, after right posterior lesions, the alpha connectivity alterations were also associated to an abnormal increase in theta connectivity. These observations are reminiscent of previous findings revealing at rest that

hemianopics with right lesions showed a stronger alpha peak reduction and a more pronounced alpha power interhemispheric imbalance, compared to left-lesioned hemianopics (Pietrelli et al., 2019). Similarly, evidence provided in chapter 5 showed that posterior right lesions also induced a more severe and distributed decrease in alpha reactivity at the opening of the eyes at rest, combined to a disruption in theta reactivity (Gallina et al., 2021, see chapter 5). The more severe impairments in oscillatory patterns after right posterior lesions in the present study and in the previously mentioned findings seems to suggest a specialization of the right hemisphere in the generation and distribution of alpha oscillations. A dominance of the right hemisphere in modulating alpha oscillations, has also been demonstrated during spatial orienting tasks with directional cues in healthy individuals (Gallotto et al., 2020). Indeed, alpha modulations in the right hemisphere have been demonstrated to serve both the enhancement of stimulus detection in the cued contralateral field (through a decrease of alpha power) and the inhibition of distractors in the contralateral field (through an increase of alpha power), when attention is cued to the ipsilateral field, while alpha oscillatory patterns in the left hemisphere have been shown only to decrease to facilitate visual processing in the contralateral field (Gallotto et al., 2020). This body of evidence, overall, seems to strengthen the notion of a role of alpha oscillatory patterns in the right hemisphere in allocating visuo-spatial attentional resources and tuning visual perceptual abilities.

Notably, graph theoretical analyses characterizing the impairment in theta connectivity in right-damaged hemianopics have demonstrated an increase in local segregated activity (i.e. increased clustering coefficient) and a decrease in global integration (i.e., higher path length), suggesting that a severe and bilateral reduction in alpha connectivity (as observed in right-damaged hemianopics) also induces impairments in local and global low-level processing in the theta range. In line, alpha oscillatory activity has been proposed to reflect widespread cortical networks' activity, regulating modular processes (Doesburg et al., 2009; Barry & De Blasio, 2017) and orchestrating oscillatory activity in different frequency bands (Hindriks et al., 2015). In this perspective, the present findings suggest that in case of left posterior lesions, spared activity in the right intact hemisphere, which shows normal alpha connectivity patterns, might be have a compensatory role and be sufficient to preserve normal connectivity also in the theta range. On the contrary, when lesions occur to right posterior cortices, such oscillatory regulatory mechanisms is disrupted, resulting in functional connectivity impairments also in the theta range, in line with the notion of a pivotal role of the right hemisphere in this mechanism. This seems in agreement with a longstanding range of evidence reporting a dominance of the right hemisphere in perceptual and visuo-spatial processing (Bisiach & Luzzatti 1978; Heilman & Valenstein 1979; Watson, 1984; Corballis et al., 2002; Nicholls & Roberts,

2002) and corroborate the notion that oscillatory mechanisms might play a role in this specialized function.

Overall, the present results suggest that different lesional profiles might induce different alterations in functional connectivity and show that lesions to posterior cortices specifically impair functional connectivity in the alpha range. This suggests that the connectivity in the alpha range might represent an index of the integrity of the underlying visual system and supports the role of alpha oscillations in regulating local and global oscillatory patterns in non-alpha frequency bands.

Chapter 7

Brain oscillations support rhythmical attentional sampling of lateralized visual stimuli in a visual detection task

7.1 Introduction

A wide body of evidence has consistently demonstrated that the visual system has an intrinsic tendency to process information periodically. This results in a succession of perceptual cycles, which possibly mirror the oscillatory activity of the underlying neural sources (VanRullen, 2016). Several experimental findings suggested that neural oscillations in the alpha (7-13 Hz) range play a crucial role in sustaining the cyclic structure of visual processing, such that the periodical sampling of visual inputs occurs at favorable phases of the alpha rhythm (Mathewson et al., 2009; Busch et al., 2009; Michel et al., 2020). This made possible to hypothesize that alpha oscillatory parameters (i.e. phase, power and frequency) reflect fluctuations in the excitability of the underlying neural population, resulting in a periodical modulation of visual processing within the visual system (Jensen et al., 2012; Van Rullen, 2016). More specifically, alpha oscillatory phase and power are thought to shape visual perception through a mechanism of pulsed inhibition of the ongoing cortical activity, leading to rhythmic fluctuations in cortical excitability (Busch et al., 2009, Mathewson et al., 2009). Indeed, changes in alpha oscillatory activity (i.e. enhancements in alpha power) have been linked to inhibition of stimulus processing in cortical regions that are not functionally relevant in a given task (Bush & VanRullen, 2010). In line, a series electrophysiological studies demonstrated that variations in alpha oscillatory power are typically accompanied by changes in attentional state (Worden et al., 2000; Sauseng et al., 2005; Thut et al., 2006), and visual awareness (Ergenoglu et al., 2004; Hanslmayr et al., 2007; Thut et al., 2006; Van Dijk et al., 2008), favoring the notion that alpha oscillatory activity plays an active inhibitory role in modulating visual perception (Klimesch et al., 2007; Jensen & Mazaheri 2010). However, more recent research provided additional evidence, revealing a direct link between endogenous alpha oscillations and rhythmical perceptual processing, resulting in a fluctuating performance. For instance, a recent EEG investigation revealed a relationship between increased alpha power and decreased target detectability in a metacontrast masking paradigm, suggesting that variations in alpha activity across the course of an experimental block correspond to fluctuations in behavioral performance and visual awareness (Mathewson et al., 2009). Although the specific role of alpha oscillatory phase still needs to be fully elucidated, this study enlightened another important aspect, showing that the specific alpha phase at the time of the stimulus onset resulted in a diminished target detectability (Mathewson, 2009), in line with previous

research indicating the specific phase at which the presentation of visual stimuli occurs has an influence on the ongoing visual perceptual processing (Gho & Varela, 1988).

This evidence linking neural oscillatory activity in the alpha range with the periodical structure of visual perception was further supported by other experimental studies, investigating the role of alpha oscillatory frequency in processing of visual information. In this respects, a series of EEG studies demonstrated that the frequency of alpha oscillations is related to the speed and the efficiency of the visual processing (Morillon & Schroeder, 2015; Sadaghiani et al., 2010), suggesting a relationship between alpha rhythm and the tendency of the visual system to process information within different temporal windows. In particular, it was demonstrated that faster alpha frequencies were predictive of a more accurate flash discrimination in a two-flash illusion task (Samaha & Postle, 2015), indicating that also the frequency of alpha rhythm is strongly related with the temporal resolution of visual perception. Overall, these observations have strengthen the idea that variations in alpha oscillatory activity, and the concurrent fluctuations in cortical excitability, may be responsible for sustaining the intrinsic periodical structure of visual perception.

However, aside of the electrophysiological methods, a more direct proof of a rhythmicity in visual perception was provided through behavioral and psychophysical measurements (de Graaf et al., 2013; Drewes et al., 2015; Ronconi & Melcher, 2017; Ronconi et al., 2018), which have been successfully applied in a wide range of experimental studies. Importantly, the results of these studies have further supported the notion of cyclic perception (also known as rhythmic or periodic perception), which implies that a particular phase of each oscillatory cycle, at around the time of stimulus presentation, results in a more efficient neuronal, sensory, or attentive processing, whereas the same processing is less efficient at the opposite phase (VanRullen, 2016). Frequently, these studies employ two separate stimuli, within or across sensory modalities. One stimulus is used to reset the postulated perceptual oscillation and to serve as a temporal reference, the other stimuli is meant to probe the state of this perceptual oscillation by measuring perceptual accuracy at various times after the reference (Landau & Fries, 2012; de Graaf et al., 2013; Drewes et al., 2015). A crucial aspect of these behavioral paradigms is the need to sample perception with a relatively high temporal resolution and, therefore, to use a large set of time intervals occurring between the reference and the probe stimuli. This methodological approach is reportedly known as ‘dense-sampling’ procedure, and the resulting fluctuations in behavioral performance can then be analyzed through the same spectral methods that are commonly reserved for electrophysiological signals (Landau and Fries, 2012). Many of the studies employing these methodologies demonstrated the existence of a periodicity in processing of visual stimuli, occurring at approximately 10-12 Hz (Van Rullen, 2016) that often implicate occipital channels, and might thus relate to sensory aspects of visual perception (Duguè et al., 2011; Drewes

et al., 2015, Mc Lelland et al., 2016, Van Rullen, 2016). However, it has been recently proposed that this sensory rhythm in the higher-alpha range may coexist with at least one more rhythm performing attentional sampling at lower frequencies (i.e. 7 Hz) (Bush et al., 2009; Duduè et al., 2015; Van Rullen, 2016; Ronconi et al., 2017), which was shown to imply to the activity of fronto-central or parietal electrodes (Bush et al., 2009; Duduè et al., 2015; Voloh et al., 2015; Van Rullen, 2016; Ronconi et al., 2018). Indeed, other studies recently enlightened the existence of a periodicity also in visual attention, by manipulating the endogenous and exogenous attentional resources during the course of the experimental session. Specifically, several investigations were consistent in describing a rhythmic attentional sampling in the lower-alpha range, at around 7-8 Hz (Bush & Van Rulen, 2010; Van Rullen et al., 2007) while other investigations reported a periodical attentional sampling in lower frequency bands, at around 3-4 Hz (Landau & Fries, 2012; Fiebelkorn et al., 2013; Song et al., 2014; Huang et al., 2015). To reconcile these two findings it has been argued that the experimental characteristics of these latter studies were explicitly or implicitly leading to a division of the attentional sources between two objects or locations (Landau & Fries, 2012; Van Rullen, 2016). Indeed, if attention does operate periodically by sampling information with an intrinsic rhythmicity at 7 Hz, it can be reasonably hypothesized that attentional sources focus on each possible object or location during alternate cycles. In this way, the periodicity measured at any one location would actually be one half, in case of two different spatial locations for instance, of the 7 Hz intrinsic rhythm of attentional sampling, therefore suggesting that the attentional system can periodically sample a single location or rapidly scan multiple items or locations, depending on the specific features of the experimental paradigm. Overall, the existing literature suggests the presence of an intrinsic rhythmicity in visual perception, showing that both sensory and attentional processing operate periodically, at different frequencies (i.e. 10-12 Hz, 7 Hz, respectively). In addition, there is strong indication that the intrinsic attentional rhythms can effectively support processing of visuospatial information when multiple locations or objects have to be attended, in a way that each possible object or location is scanned and sampled in alternate cycles at slower frequencies (e.g. 3-4 Hz).

Importantly, it has been hypothesized that that the specific characteristics of the experimental paradigms employed in the different studies may determine the prevalence of either the sensory or the attentional components of the perceptual sampling process (Van Rullen, 2016). For example, one central aspect that still needs to be elucidated is whether differences in periodical perceptual sampling of visuospatial information occur, depending on the side of stimulus presentation. In other words, it is not clear whether presenting a visual target to left or to the right visual hemifield may result in a different outcome in terms of the main frequency of the different perceptual rhythms in response to a lateralized target presentation. Indeed, in accordance with the current view of perceptual cycles, it is

possible to assume that the different rhythms of visual perception may depend not only on task characteristics or stimulus properties, but also on the brain circuits supporting these periodical mechanisms (Van Rullen, 2016). In addition, as it was extensively discussed in the previous chapters, a pivotal role of the right hemisphere in orchestrating the oscillatory activity of brain rhythms that are relevant for visuospatial processing (i.e. alpha rhythm, theta rhythm) has been reported in healthy participants (Gallotto et al., 2020) and patients with posterior brain lesions and visual field defects (Pietrelli et al., 2019; Gallina et al., 2021), as also described by evidence provided in chapter 5 and 6. Therefore, if both sensory and attentional cycles supposedly mirror the oscillatory activity of the underlying neural populations, the left and the right brain hemispheres may differentially support these mechanisms of sensory and attentional perceptual sampling.

To test this hypothesis, perceptual oscillations in response to the presentation of visual stimuli were assessed in two versions of a visual detection task, in a group of healthy participants. Specifically, in the first version of this task a visual target was presented at the contrast threshold and could appear exclusively to the left or to the right hemifield, with participants being instructed to monitor one hemifield only within the same block (*task 1*). In the second version of this task, the same visual target could appear randomly to the left or to the right hemifield, without any spatial cue, with participants monitoring both hemifields within the same block (*task 2*). In this way, participants' endogenous attentional sources were directed selectively to one single spatial location or split between two different spatial locations simultaneously. Similarly to what was previously done in other studies measuring perceptual oscillations (Ronconi & Melcher, 2017), participants' perceptual performance, in terms of percentage of detection accuracy, was then analyzed through a spectral decomposition as a function of the time interval occurring between a reference stimuli and the probe stimuli, following the logic of the dense-sampling method described above. Finally, the resulting spectral components were statistically tested by performing a permutation analysis, in order to characterize the main oscillatory components emerging in the task in response to stimulus presentation to the left and to the right hemifield.

7.2 Material and methods

7.2.1 Participants

Nineteen neurologically healthy volunteers aged 18-45 took part to the study. All participants showed normal or corrected-to-normal visual acuity and did not report history of neurological disorders or epilepsy. Participants were informed about the procedure and the purpose of the study and gave

written informed consent. The study was designed and performed in accordance with the ethical principles of the Declaration of Helsinki and was approved by the ethical committee of the Department of Psychology "Renzo Cansetrari" of the University of Bologna (Prot. 42483).

7.2.2 Apparatus and stimuli

Participants seated in a sound-proof room, positioned on a chin-rest at a viewing distance of 57 cm, in front 24-inch LED monitor (Acer) at 1080 × 980 pixels of spatial resolution with a vertical refresh rate of 144 Hz. Throughout the experimental procedure eye-movements were monitored and recorded with a Pan/Tilt optic eye-tracker (ASL 6000 eye-tracking apparatus), with a sampling rate of 60 Hz. All visual stimuli were displayed on a on a middle gray background and consisted of vertically oriented gabor patches sized at 0.5 × 0.5 cm, appearing at 15 cm at the right or the left to a black central fixation cross sized at 0.5 x 0.5 cm, on the midline. The contrast of the gabor patches was adjusted individually before the experiment to ensure that the stimulus was presented at threshold, with a Bayesian QUEST procedure (Watson & Pelli, 1983). The experiment was programmed in MATLAB (R2018a; The Mathworks Inc., USA) using the PsychToolbox (Brainard, 1997).

7.2.3 Experimental procedure

During the experimental session, participants were asked to complete two versions of a visual detection task that differ in terms of the type of target presentation, in respect to a central fixation cross. Participants were instructed to respond whether they saw the gabor or not, by pressing two different buttons on a keyboard. All participants were instructed to complete the experimental procedure using the same hand (i.e., 10 participants responded using the left hand, 9 participants responded using the right hand) and to keep their gaze on the central fixation cross, for the entire duration of the experimental session. Prior to task execution, participants were informed about the type of target presentation.

In *task 1* the gabor could appear only to the left or to right in respect to the central fixation cross, such that target stimuli would be presented always in the same hemifield, in each experimental block. In this way, participants had to attend a single hemifield at time, addressing their endogenous attentional sources to one location only, in absence of an exogenous spatial cue. In *task 2* the gabor could appear randomly in either the left or in the right hemifield, with equal probability, during the same

experimental block. In this way, participants had to monitor both the left and the right hemifield, simultaneously, directing their endogenous attentional sources to two locations at the same time, in absence of an exogenous spatial cue. Each participant could start the experimental session with either *task 1* or *task 2*, and the order of the session was counterbalanced across participants. All stimuli and apparatus were identical for *task 1* and *task 2*.

7.2.4 Visual detection task for target presented exclusively to the left or to the right hemifield (*task 1*)

All trials started with the presentation of a full-sized black screen of 21 ms of duration, which served to induce a phase reset of the ongoing functionally relevant oscillations within (i.e., from visual stimuli to visual areas; Landau & Fries, 2012) sensory modalities. This allows to measure fluctuations in behavior over time aligned to a putative reset point (Fiebelkorn et al., 2011; Landau & Fries, 2012). At the offset of the blank screen, target stimuli (i.e., gabor) appeared for 42 ms at different stimulus onset asynchrony (SOA), exclusively to the left or to the right hemifield. Specifically, in order to sample rhythmic perceptual activity, the SOAs randomly varied among 17 possible time points, ranging from 56 to 292 ms in regular step of 14 ms, following the logic of the dense sampling procedure (Fiebelkorn et al., 2011; Landau & Fries, 2012). At the gabor offset, when a black central question mark sized 0.5 x 0.5 cm replaced the central fixation cross, participants had to give their response. After the participants' response, the central fixation cross appeared again at a randomly varying duration (Intertrial Interval, ITI), ranging from 0.5 to 1.5 sec. Each experimental block consisted in 6 gabor presentation for each SOA, for a total number of 102 gabor presentations, and in 17 catch trials in which the gabor was absent, for a total of 119 trial per block. All participants completed 3 experimental blocks for each hemifield, for a total number of 357 trials per hemifield. Prior to the task execution, the contrast of the gabor was adjusted individually with a QUEST procedure, performed separately for the left and for the right hemifield. The QUEST procedure consists in an adaptive psychometric method that places each trial at the current most probable Bayesian estimate of threshold. The QUEST procedure takes advantage of the common finding that the human psychometric function, which describes the relation between some physical measure of a stimulus and the probability of a particular psychophysical response, is invariant in form when expressed as a function of log intensity (Watson & Pelli, 1983). The QUEST that was employed in the present study had the same characteristics of the visual detection task. However, the target stimuli

were always present. In particular, the QUEST consisted in 4 gabor presentations for each SOA, for a total number of 68 trials per hemifield.

7.2.5 Visual detection task for target presentated alternatively in the left or in the right hemifield (*task 2*)

The experimental procedure in *task 2* was identical to that of the *task 1*, except for the following changes.

Each experimental block consisted in 6 gabor presentation for each SOA, with the gabor randomly appearing at either the left or the right hemifield (i.e., 3 gabor presentation in the left hemifield and 3 gabor presentations in the right hemifield), for a total number of 102 gabor presentations (i.e. 51 gabor presentations in the left hemifield and 51 gabor presentation in the right hemifield), and in 17 catch trials in which the gabor was absent, for a total of 119 trials per block. All participants completed 6 experimental blocks, for a total number of 714 trials (i.e., 357 trials for each hemifield).

The QUEST consisted in 8 gabor presentation for each SOA (i.e., 4 gabor presentations for each hemifield), for a total number of 136 trials (i.e. 68 trials for each hemifield).

7.2.6 Data processing and analysis

All data processing and analysis were identical for *task 1* and *task 2*. Eye-movements recordings were stored and prepared for offline processing, with exception for 8 participants, whose recordings were not available. Due to the high number of artifacts, the eye-movements recordings of 1 participant could not be processed. However, for all participants that underwent the recordings, eye-movements were always monitored online for the entire duration of the experimental procedure, in order to assure that the gaze would be kept on the central fixation cross. During offline processing, trials in which participants' gaze was not kept on the central fixation cross were excluded from further analysis. In particular, in *task 1* 2.5% of the total number of trials were discarded for the left hemifield and 3 % of trials for the left hemifield; in *task 2,* 3.5% of trials were discarded fort he left hemifield and 3% of trials for the right hemifield. For each participant, all analysis was performed separately for the left and for the right hemifield. In the data analysis, the percent of accuracy exhibited in detecting the gabor was considered as a function of the SOA. Initially, all trials were sorted by the SOA. A linear detrend a moving average and a zero padding were applied to the resulting time series, to smooth out

random background fluctuations and to increase the frequency resolution, respectively. Then a Fast Fourier Transform (FFT) was computed for the aggregated data, similarly to what was done in previous studies measuring behavioral oscillations (Ronconi & Melcher, 2017; Ronconi et al., 2018). This made possible to characterize the perceptual oscillations in response to stimulus presentation, in terms of the main oscillatory component, across participants. Finally, the statistical significance of the resulting Fourier spectra was tested by performing a permutation analysis. In particular, for each individual dataset, 2500 permutations obtained from the real data by randomizing the SOA labels were calculated. Permuted data were analyzed with the same procedure described for real data (i.e., moving average and zero padding) before undergoing the FFT. The amplitude values, averaged across participants, of the 2500 permutated Fourier spectra represented the null distribution that was used to set the statistical significance for the frequency bins constituting the real Fourier spectra. Specifically, the frequency bins of the real FFT spectra resulting significantly above that of the permutation distribution (i.e. > 95° percentile; $p < 0.05$), represented the main sampling rhythms for detecting stimuli presented in the left or in the right hemifield.

7.3 Results

7.3.1 Visual detection task for target presented exclusively to the left or to the right hemifield (*task 1*)

When participants had to direct their attentional sources to one single hemifield within the same experimental block, the permutation analysis revealed a significant component falling in the upper theta/lower-alpha range, peaking at 7 Hz ($p < 0.05$ compared to the permutations distribution; magnitude 0.38; see figure 7.1) in response to stimuli presented in the right hemifield. Another oscillatory component, peaking at 14 Hz, could be observed in the real Fourier spectra, though not reaching the significance cut-off ($p > 0.05$, see figure 7.1). In contrast, in response to stimuli presented in the left hemifield, the permutation analysis showed no significant oscillatory component. However, two components, peaking at 5and at 10.5 Hz respectively, could be observed in the Fourier spectra, yet not reaching the significance threshold (all ps > 0. 05, see figure 7.1).

These results suggests that when attentional sources are allocated exclusively to one spatial location at time, the perceptual fluctuations measured in the visual detection tasks are represented by a main upper-theta/lower-alpha oscillatory component, which however is evident only in response to stimuli presented to the right but not to the left hemifield.

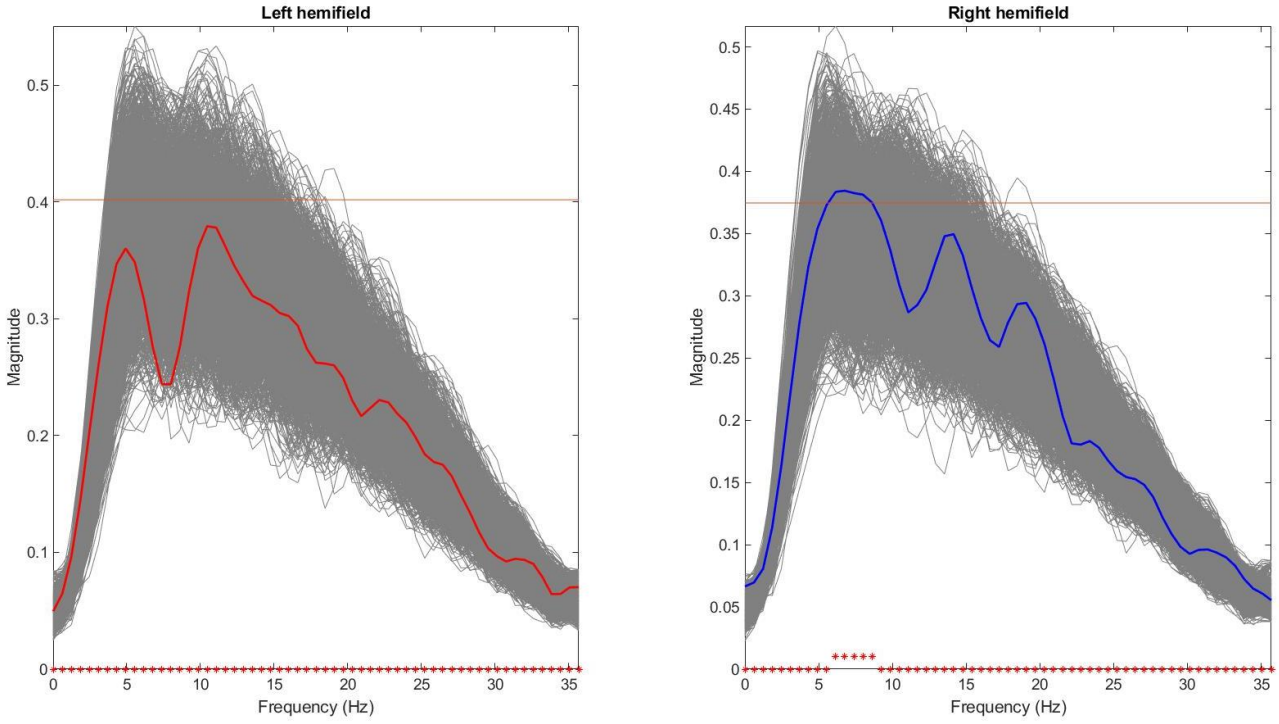

Figure 7.1. *Power spectrum (average of the individual power spectrums) of the perceptual oscillations in response to stimuli presented to the left hemifield (red solid line) and to the right hemifield (blue solid line). Spectra obtained from permuted data are represented by the grey lines. The orange horizontal line represents the significance cut-off signaling whether frequency bins in the observed spectrum are found to be significantly different compared to the spectrum obtained from the permutation test.*

7.3.2 Visual detection task for target presented alternatively in the left or in the right hemifield (*task 2*)

When participants had to monitor both the left and the right hemifield within the same experimental block, the permutation analysis showed a significant component falling in the theta range, which peaked at 5 Hz ($p < 0.05$, magnitude 0.46; see figure 7.2), in response to stimuli presented to the right hemifield. Another component, peaking at 10.5 Hz, was evident but not significant ($p < 0.05$, see figure 7.2). Similarly, also for stimuli presented to the left hemifield, the permutation analysis revealed the presence of a significant component falling in theta range, peaking at 5.5 Hz ($p > 0.05$, magnitude 0.43; see figure 7.2). This significant component was followed by another component peaking at 11.5 Hz, though not significant ($p > 0.05$, see figure 7.2). These results suggest that when attentional sources are simultaneously allocated to two different spatial locations, perceptual

fluctuations are represented by a main theta oscillatory component, which, importantly, is evident in response to stimuli delivered both to the right and to the left hemifield.

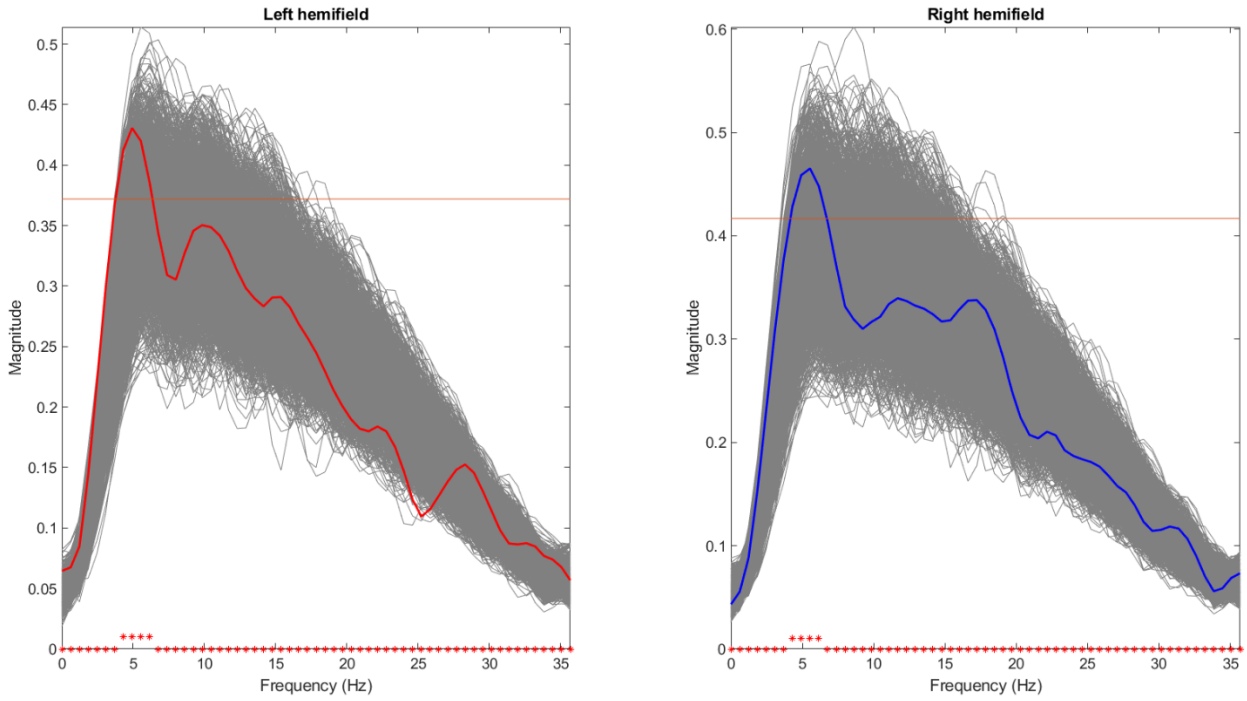

Figure 7.2. *Power spectrum (average of the individual power spectrums) of the perceptual oscillations in response to stimuli presented to the left hemifield (red solid line) and to the right hemifield (blue solid line). Spectra obtained from permuted data are represented by the grey lines. The orange horizontal line represents the significance cut-off signaling whether frequency bins in the observed spectrum are found to be significantly different compared to the spectrum obtained from the permutation test*.

7.4 Discussion

The results of the present study revealed the presence of distinct significant oscillatory components in response to visual stimuli presentation, that differ based on the specific attentional requirement of the two experimental tasks and on the side of the target presentation. Specifically in *task 1*, when visual stimuli appeared exclusively to the left or to the right hemifield within the same experimental block, and participants were instructed to monitor one single spatial location at time, in absence of an exogenous spatial cue, a significant oscillatory component peaking at 7 Hz emerged in response to stimuli presented to the right hemifield. In contrast, no significant oscillatory component was observed in response to stimuli presented to the left hemifield. These results are in line with previous

literature reporting the existence of a rhythmic sampling in the lower-alpha range, at around 7-8 Hz (Bush & Van Rulen, 2010; Van Rullen et al., 2007), that was shown to be related to the activity of fronto-central and parietal channels (Bush et al., 2009; Duguè et al., 2015; Voloh et al., 2015; Van Rullen, 2016; Ronconi et al., 2018) and was therefore interpreted as the intrinsic frequency at which attentional sampling of visuospatial information happens (Van Rullen , 2016). However, these findings provide additional knowledge, showing that differences in rhythmic perceptual sampling occur depending on the visual hemifield where the target stimuli appear, suggesting that the left and the right brain hemispheres might play a differential role in sustaining these sampling mechanisms. Indeed, it can be hypothesized that the observed significant component peaking in the lower-alpha range, in response to stimuli presented in the right hemifield, may represent a periodical processing of endogenous attention, relying on the synchronized activity of both brain hemispheres. In particular, such oscillatory component may result from the concurrent activity of the left hemisphere, which is reportedly involved in processing of visuospatial information in the contralateral hemifield, and of the right hemisphere, which is commonly thought to be involved in processing of visuospatial information in both the ipsilateral and the contralateral visual hemifield (Heilman & Van Den Abell, 1980). Following this logic, when the visual stimuli are presented in the left hemifield, an oscillatory component was visible, but not reaching significance. This could be due to a scarce synchronized activity, depending on the exclusively contribution of the contralateral right hemisphere. It is worth noting that, the not-significant oscillatory component for stimuli presented to the left hemifield peaked at approximately 5 Hz, differently from what has been observed in response to stimuli presented to the right hemifield peaking at 7h. Although the target stimuli were appearing exclusively to one spatial location, with participants being asked to attend the left visual hemifield only, this lower peak of frequency seems reminiscent of the rhythmic attentional sampling occurring when attentional sources are divided between two or more spatial locations (Landau & Fries, 2012; Fiebelkorn et al., 2013; Song et al., 2014; Huang et al., 2015). This makes possible to hypothesize that the right hemisphere has a peculiar and specialized role in modulating and directing attentional resources and, in particular, that the right hemisphere may be involved in monitoring both the contralateral left and the ipsilateral right hemifield, despite of the specific task requests. This interpretation is line with the longstanding theories about the dominance of the right hemisphere in spatial representation and visuospatial processing (Kinsbourne, 1977; Heilman & Valenstein, 1979; Heilman & Van Den Abell 1980) and is further supported by a large number of electrophysiological investigations describing a pivotal role of the right hemisphere in orchestrating the activity of brain oscillations that are relevant for processing of visuospatial information (i.e. alpha and theta oscillations), as extensively discussed in chapter 3 and shown by evidence reported in chapter 5 and 6. Indeed, evidence from healthy

participants revealed a greater involvement of the right hemisphere in modulating alpha oscillations during spatial orienting tasks, in order to allocate visuospatial attention and tune visual abilities (Gallotto et al., 2020). In keeping, a number of studies on patients with posterior brain damage and hemianopia revealed more severe impairments in resting state oscillatory activity of both alpha and theta rhythms when the lesions are located in the right hemisphere (Pietrelli et al., 2019; Gallina et al., 2021; see chapter 5). In particular, it was shown that right-lesioned hemianopic patients have a more severely reduced speed of alpha oscillations and in a greater alpha power imbalance between the intact and the lesioned hemisphere, in favor of the intact one (Pietrelli et al., 2019) and a greater impairments in functional connectivity of both alpha and theta oscillations (see chapter 6) at rest. Importantly, these studies showed also that such impaired alpha oscillatory activity was predictive of a more detrimental visual performance in hemianopic patients (Pietrelli et al., 2019; Gallina et al., 2021; see chapter 5). However, hemianopic patients with right lesions exhibited also more severe alterations in alpha reactivity, combined to a disruption in theta reactivity (Gallina et al., 2021; see chapter 5) in the transition from the eyes-closed to the eyes-open resting state, suggesting an additional specialization of the right hemisphere in orchestrating a complex interplay between alpha widespread oscillatory activity and other frequency bands that are associated to lower level local processing (Barry & de Blasio, 2017). Based on these observations, showing a greater involvement of the right hemisphere in supporting neural oscillatory activity in the alpha and in the theta range, it can be reasonably hypothesized the left and the right brain hemispheres give a differential contribution also in supporting the process of periodical perceptual sampling. Indeed, perceptual cycles are thought to reflect the oscillatory mechanisms of the underlying neural populations (Van Rullen, 2016), favoring the notion that the right hemisphere has a pivotal role in sustaining oscillatory activity at both neural and perceptual level. On the other hand, looking at the results of *task 2*, when the visual target could randomly appear in the left or in the right hemifield within the same experimental block and participants have to monitor two different spatial locations simultaneously, a significant oscillatory component emerged in response to stimuli presented to both hemifields. Specifically, it was possible to observe a main oscillatory component peaking at 5 Hz for stimuli presented to the right hemifield and, in similar fashion, a main oscillatory component peaking at 5.5 Hz in response to stimuli presented to the left hemifield. Similarly to what has been observed in *task 1* for stimuli presented to the left hemifield, these results are reminiscent of previous findings showing that the periodical sampling of visuospatial information becomes slower (e.g. 2-4 Hz), when the specific features of the experimental task explicitly or implicitly lead to a division of the attentional sources among two or more objects or spatial locations (Landau & Fries, 2012; Fiebelkorn et al., 2013; Song et al., 2014; Huang et al., 2015; Van Rullen, 2016). In this way, the intrinsic rhythm of

attentional sampling is effectively divided and distributed to any possible spatial location, at alternate cycles (Van Rullen, 2016). Based on that, it is reasonable to hypothesize that the different features and attentional requirements in *task 1* and *task 2* determined the presence of distinct patterns of periodical sampling, resulting in a significant component peaking at 7 Hz for stimuli presented to the right hemifield, when a single spatial location is attended (*task 1*), and in a significant oscillatory component peaking at 5-5.5 Hz for both hemifields, when two spatial locations are attended simultaneously (*task 2*). These results have important implications and suggest that the attentional system operates with an useful and effective functional flexibility. Indeed, depending on the specific characteristics of the experimental paradigm, the attentional system can periodically sample a single location, or rapidly scan multiple items or locations simultaneously and efficiently. Interestingly, the presence of a significant oscillatory component for stimuli presented to both the left and the right hemifield in *task 2* seem to suggest that when the endogenous attentional sources are divided between two different spatial locations, the left and the right brain hemispheres provide a sufficiently synchronized activity to support the split of attention in two different location. However, a qualitative inspection of the two Fourier spectra revealed that the magnitude of the significant 5 Hz oscillatory component in response to stimuli presented to the right hemifield (0.46) was greater than the magnitude of the significant 5.5 Hz component emerged for stimuli presented to the left hemifield (0.43). This tendency, yet not significant, seems to be in line with the hypothesis that the two brain hemispheres may give a differential contribution in sustaining the mechanisms of perceptual periodical sampling, strengthening the notion that right hemisphere has a dominant role in orchestrating these parsing processes. In this perspective, the greater magnitude observed for the significant oscillatory component in response to stimuli presented to the right hemifield may be due to the concurred synchronized activity of both the contralateral left and the ipsilateral right hemisphere in participating to the attentional sampling process. Following this interpretation, the significant oscillatory component for stimuli presented to the left hemifield would rely on a less synchronized activity, provided by the contralateral right hemisphere only, explaining why a smaller magnitude was observed for this latter component.

Another important aspect emerging in the present study is that the significant attentional components in response to lateralized stimulus presentation in both *task 1* (i.e. 7 Hz) and *task 2* (i.e. 5 Hz and 5.5 Hz) were followed by other oscillatory components peaking in the frequency spectrum that however were not significant. Specifically, in *task 1* a 14 Hz component in response to stimuli presented to the right hemifield and an 11.5 Hz component in response to stimuli presented to the left hemifield were observed. Similarly, in *task 2*, a 10.5 Hz and an 11.5 Hz oscillatory component emerged in response to stimuli presented to the right and to the left hemifield, respectively. These oscillatory components,

peaking in the higher-alpha range, may represent the sensory aspects of the periodical perceptual sampling, relying on the activity of more posterior areas of the two brain hemispheres. Indeed, a number of studies reported the existence a rhythmical processing of visual information, occurring at approximately 10-12 Hz (Duguè et al., 2011; Drewes et al., 2015, Mc Lelland et al., 2016, Van Rullen, 2016), implicating the activation of occipital channels, that might thus relate to sensory aspects of visual perception. Based on the results of the present findings and in line with the current view of perceptual cycles (Van Rullen, 2016) it can be then hypothesized that such sensory rhythm in the higher-alpha range and the observed attentional rhythm performing sampling of visuospatial information at 7 Hz and 5-5.5 Hz may operate together, representing different mechanisms and aspects of the periodical perceptual processing (Van Rullen, 2016). It can be speculated that the specific features of the two versions of detection task employed in the present study were crucial in determining the presence of significant attentional components only, whereas the oscillatory sensory components in the higher-alpha range were not significant. Probably, the presentation of lateralized visual stimuli in absence of an exogenous spatial cue in both *task 1*, when participants were instructed to attended one hemifield at time, and *task 2*, when participants were instructed to monitor both hemifields simultaneously, led to a greater activation of endogenous attentional networks supporting the attentional sampling of lateralized visuospatial information, resulting in a significant oscillatory components only at 7 Hz and at approximately 5 Hz, respectively. This may explain why the oscillatory sensory components in the higher-alpha range emerging in the frequency spectrum in response to stimulus presentation in both *task 1* and *task 2* were not significant. However, these latter speculations have to be taken with caution, since they refer to spectral components that do not reach significance and that, therefore, might not represent a perceptual or attentional process.

Overall, these findings strongly suggest that the attentional requirements of the experimental paradigm play a crucial role in determining the main frequency of the perceptual periodical sampling, although both sensory and attentional rhythms concur in the process of perceptual periodical sampling. In addition, the present findings showed that the main frequency of such periodical sampling is likely to be influenced also by the side of visual stimulus presentation and, as a consequence, by the different contribution of the left and the right hemisphere in supporting this process of rhythmic perceptual sampling. Overall, these results are in line with the existing literature on perceptual cycles and add new knowledge, suggesting that the different rhythms of visual perception, that reflect the activity of the underlying oscillating sources, may depend not only on task characteristics, but also on the different brain networks, within the left and the right hemisphere, supporting these periodical mechanisms (Bush, 2009; Van Rullen, 2016).

Chapter 8

A prolonged visual entrainment induces long-term modulations of resting alpha oscillations

8.1 Introduction

Alpha rhythm (7–13 Hz) is the prominent signal in the resting awake brain, characterized by a large amplitude when the eyes are closed. Subdivisions of the alpha rhythm based on cortical origin and/or functional role have been often proposed. However, in the past few decades, most of the investigations on the alpha rhythm focused on its link with the functionality of the posterior cortices and its active role in visual perceptual processing (Pfurtscheller et al., 1994). Indeed, several studies demonstrated that detection of visual stimuli varies with the power (Thut et al., 2006; Mathewson et al., 2009) and the phase of ongoing alpha oscillations (Mathewson et al., 2009; Busch et al., 2009). In addition, the frequency of alpha oscillations has been consistently related to the temporal resolution of visual perception (Valera et al., 1981; Klimesch et al., 2007; Cecere et al., 2015; Samaha & Postle, 2015). Under normal circumstances, alpha rhythm oscillates around its main frequency and power. However, changes in alpha power and frequency, accompanied by variations in the perceptual outcome (Klimesch et al., 2007; Matheson et al., 2009; Iemi et al., 2017), are typically observed during the course of an experimental session, according to task demands and cognitive state. These variations may require fast rearrangements in the functional architecture of the brain engaged networks, which are likely to rely on dynamic interactions and plastic adaptations.

These observations, showing that neural and perceptual activity represent dynamic, rather than invariant processes, gave rise to the conceptualization that the spontaneous brain rhythms can be externally promoted. In this perspective, a recent line of research aimed at driving alpha oscillatory activity and perceptual performance by directly stimulating the neural substrate through rhythmic stimulation protocols, taking advantage of the underlying mechanisms of neural plasticity within the visual system (for a detailed report on the plasticity of the visual system see chapter 4). Indeed, it has been widely demonstrated that applying a rhythmical external force through different techniques, like Transcranial Magnetic Stimulation (TMS), transcranial alternating current stimulation (tACS) or sensory stimulation, can effectively induce a temporal alignment of the endogenous brain rhythms to the rhythmical event, such that the stimulated neural substrate starts to oscillate with the same period as the external force (Thut et al., 2011a; Mathewson et al., 2012; Ronconi & Melcher, 2017). In this way, the spontaneous brain rhythms become synchronized, ore locked, to the external rhythmical stimulation and this typically results in a phase alignment (Mathewson et al., 2012) and amplitude

increase (Thut et al., 2011a; Mathewson et al., 2012; Spaak et al., 2014) of the ongoing neural oscillatory activity, a mechanisms known as rhythmic entrainment (Thut et al., 2011b).

The effects of the entrainment on the ongoing neural oscillation were shown to depend on several parameters. In particular, the frequency of the stimulation, relative to the frequency of the ongoing oscillations, seem to have an influence on the effects induced by the entrainment (Vossen et al., 2015). Indeed, due to the causal role that brain rhythms play on perceptual processing, the frequency of administration of the rhythmic entrainment should be confined to a narrow bandwidth and, in particular, the frequency of the stimulations should match the brain oscillations that are perceptually relevant for the targeted area (Thut, 2012). In this respect, the majority of the studies employing rhythmic entrainment protocols in vision research demonstrated that that the rhythmic stimulation of occipital or parietal areas results in selective and immediate variations of alpha oscillatory parameters, as well as in variations in perceptual performance, when the stimulation frequency is tuned to the preferred oscillation frequency of the visual system (i.e. alpha rhythm; Thut et al., 2011; Mathewson et al., 2012; Spaak et al., 2014). Specifically, due to this frequency-dependence, these studies were consistent in demonstrating that a rhythmical entrainment administrated at the participants' individual alpha frequency (IAF; Zahele et al., 2010b; Halbleib et al., 2012), or at other frequency included in the range of alpha (Matewson et al., 2012; Spaak et al., 2014; de Graaf et al., 2013), have strong effects on both EEG activity, typically in the posterior scalp sites contralateral to the stimulation, (Thut et al., 2011) and visual perceptual performance (Romei et al., 2010). Most of the experimental paradigms, investigating the effects of alpha-band rhythmic entrainment on neural activity and perceptual activity, have typically employed brief trains of rhythmic stimulation, of approximately 1 second of duration (Mathewson et al., 2012; de Graaf et al., 2013; Spaak et al., 2014). These short-term entrainment protocols were consistently shown to result in a phase synchronization (Mathewson et al., 2012), power increase (Mathewson et al., 2012; de Graaf et al., 2013; Spaak et al., 2014) or shift of the frequency (Ronconi & Melcher, 2017) of the ongoing neural oscillations, especially in the range of alpha, during the stimulation (i.e. online entrainment, Halbleib et al., 2012). In addition, it has been systematically reported that the power of the entrainment-driven alpha oscillation does not return to baseline levels immediately after the entrainment offset but remains relatively high for approximately 2/3 consecutive alpha cycles (i.e. offline entrainment, Halbleib et al., 2012; Mathewson et al., 2012; De Graaf et al., 2013; Spaak et al., 2014). In a visual entrainment protocol, for instance, a 10 Hz rhythmic stimulation was shown to induce the strongest neural entrainment in early visual areas, compared with other frequency bands, as demonstrated by a higher increase in alpha power at the entrainment offset (Spaak, 2014), favoring the notion that brain oscillating networks can be successfully entrained when stimulated at their preferential frequency.

Consistent with these results, another study reported a clear increase in visual detection for targets presented in-phase with a preceding 12 Hz visual stimulation as well as a phase-locking of neural oscillatory activity during the stimulation, with maximum effects over partieto-occipital scalp sites (Mathewson et al., 2012).In addition, it was recently shown that an audio-visual entrainment, given at either 8.5 Hz or 10.5 Hz, leads to a phase alignment of the perceptual performance across subjects and to a shift of the average peak of the power spectrum towards the entrainment frequency at which the stimulation was set (Ronconi and Melcher, 2017).Furthermore, it has been also demonstrated that individuals exhibiting stronger entrainment, as measured by greater increase in alpha-power during the rhythmic stimulation protocol, also tended to exhibit greater entrainment aftereffects (Helfrich et al., 2014).

This converging evidence provided strong proof for the effectiveness of alpha-band rhythmic entrainment in modulating alpha oscillatory parameters and visual perceptual processing. However, a suitable width of the stimulation-frequency window, giving rise to the strongest entrainment-induced effects, has not been established yet. It has been hypothesized that the observed entrainment-induced effects interest only specific resonant networks, when the stimulation frequency falls into a narrow range of frequencies which might be slightly higher or lower than the spontaneous alpha peak, (Zaehle et al., 2010), with maximum increase in alpha power following to the stimulation when the frequency of the entrainment correspond ds to the participants' IAF (Zaehle et al., 2010; Thut et al., 2011a). However, it is still not fully elucidated whether small or large deviations from the IAF possibly make a difference to the outcomes, both in terms of oscillatory activity and perceptual performance. Another important aspect that still needs to be disambiguated concerns whether prolonged stimulation protocols may lead to longer-lasting entrainment-induced modulations of alpha activity and perceptual performance. Indeed, as previously mentioned, the entrainment paradigms employed so far were commonly characterized by short trains of rhythmic stimulation (~ 1 sec), resulting in transient neural and perceptual aftereffect, shortly lasting at the entrainment offset (~ 300 ms) (Spaak et al., 2014).

A pioneering study demonstrated that a prolonged audio-visual 10 Hz entrainment of 8 minutes of durations resulted in either an increase or decrease of alpha oscillatory power, lasting for approximately 8 minutes after the entrainment offset (Rosenfled et al., 1997).

However, whether persistent modulations of alpha oscillatory parameters may be consistently achieved through prolonged trains of rhythmic stimulation is still open question.

Crucially, it is still debated whether the entrainment-induced effects on alpha oscillatory activity reflect local, rather than diffused or global processes. Indeed, based on the results of the above-mentioned studies employing short-term entrainment protocols, it has been argued that the effects of

the entrainment on the ongoing alpha oscillations are rather focal and observed especially in the posterior brain areas contralateral to the stimulation (Thut et al., 2011a; de Graaf et al., 2013; Spaak et al., 2014). Nevertheless, it is still largely unknown whether prolonged rhythmic entrainment protocols, differently of short-term entrainment protocols, may induce more diffused effects, possibly interesting brain areas ipsilateral to the stimulation and/or other brain regions.

To address these questions, the present study aimed at investigating whether a prolonged visual entrainment protocol administered in the right hemifield, at various frequencies included in the range of alpha, possibly induces specific long-lasting effects on the ongoing alpha oscillatory activity at the entrainment offset, and whether the entrainment-induced effects might be diffused, rather than local. In addition, since alpha-band entrainment was shown to selectively induce changes in ongoing alpha oscillation (i.e. increase of alpha power) at the entrainment offset (Thut et al., 2011b; Spaak et al., 2014), the effects of the entrainment on theta oscillatory power were also assessed, as a control analysis.

To this aim, EEG signal was recorded in a group of neurologically healthy participants before and after a protocol of rhythmic visual stimulation of 1 minute of duration, given at their IAF and at two frequencies higher and lower in respect to the IAF (i.e. IAF +2 Hz, IAF -2 Hz).

Alpha (7-13 Hz) and theta (3-6 Hz) power were then calculated at a baseline condition, prior to the rhythmic stimulation, and following to each of the possible entrainment conditions, in left and right posterior scalp regions, and in an anterior region.

8.2 Material and methods

8.2.1 Participants

Fourteen participants (10 males, mean age = 29.5 years) took part to the study. All participants showed normal or corrected-to-normal visual acuity and did not report history of neurological disorders or epilepsy. Participants were informed about the procedure and the purpose of the study and gave written informed consent. The study was designed and performed in accordance with the ethical principles of the Declaration of Helsinki and was approved by the ethical committee of the Department of Psychology “Renzo Cansetrari” of the University of Bologna (Prot. 42483)..

8.2.2 Apparatus and stimuli

Participants seated in a sound-proof room, positioned on a chin-rest at a viewing distance of 57 cm, in front 24-inch LED monitor (Acer) at 1080 × 980 pixels of spatial resolution with a vertical refresh rate of 144 Hz of. Throughout the experimental procedure eye-movements were monitored and recorded with a pan tilt ASL 6000 eye-tracking apparatus, with a sampling rate of 60 Hz.

EEG signal was acquired for the entire duration of the experimental session through a Brain Amp DC amplifier (BrainProducts GmbH, Germania) and Ag/AgCl electrodes (Acticap Slim, Brain Products GmbH, Germania) from 61 scalp sites (Fp1, AF3, AF7, F1, F3, F5, F7, FC1, FC3, FC5, FT7, FT9, C1, C3, C5, T7, CP1, CP3, CP5, TP7, TP9, P1, P3, P5, P7, PO3, PO7, O1, Fp2, AF4, AF8, F2, F4, F6, F8, FC2, FC4, FC6, FT8, FT10, C2, C4, C6, T8, CP2, CP4, CP6, TP8, TP10, P2, P4, P6, P8, PO4, PO8, O2, Fz, , CPz, Pz, POz, Oz). AFz and Cz were set as online reference and ground electrodes, respectively. EEG signal was recorded with a band-pass filter of 0.01-100 Hz and digitalized with a sampling-rate of 1000 Hz. Impedances were kept below 25 KΩ.

All visual stimuli were displayed on a middle grey background. The stimuli used for the rhythmic visual stimulation (entrainment) consisted in flickering white squares sized at 6 x 6 cm, presented at 15 cm of lateralization in respect to a central black fixation cross sized at 0.5 x 0.5 cm. For each participants the visual entrainment was administrated to the right in respect to the central fixation cross.

8.2.3 Experimental procedure

The experimental session started with the acquisition of the baseline eyes-closed resting-state EEG signal, consisting in 9 separate blocks of 1 minute of duration each. Following to EEG recordings at the baseline condition, the individual alpha frequency (IAF) of each participant was computed and visually inspected (for the details of the IAF processing and computation see 2.4.1), in order to determine the frequency of administration of the visual entrainment. After the computation of the IAF, the visual entrainment protocol, consisting in three conditions of stimulation, started. In particular, participants underwent the visual entrainment at three different frequencies. One frequency of stimulation corresponded to the participants' IAF, while the other frequencies corresponded to two frequencies higher (i.e. IAF +2 Hz) and lower (i.e. IAF – 2 Hz) in respect to the IAF. Each condition of stimulation (i.e. IAF, IAF + 2 Hz, IAF – 2 Hz) started with 1 minute of entrainment immediately followed by 1 minute of eyes-closed resting-state, in order to assess the effects of the visual

entrainment over the following eyes-closed resting EEG activity, compared to the baseline activity. This procedure (i.e. 1 minute of entrainment followed by 1 minute of eyes-closed resting-state) was repeated for 9 times for the IAF, the IAF + 2 Hz and the IAF – 2 Hz conditions of stimulation, for a total of 9 blocks of entrainment and 9 blocks of resting state for each condition of stimulation. The order at which each condition of stimulation was administered was randomized. Participants were instructed to maintain their gaze on the central fixation cross during the visual entrainment and to keep their head on the chin-rest for the entire duration of the experimental session.

8.2.4 EEG data processing and analysis

8.2.4.1 Pre-processing and computation of the IAF

EEG signal acquired at the baseline condition was off-line pre-processed and analyzed with EEGlab (v.4.1.1b, Delorme and Makeig 2004) and custom routines developed in Matlab (R2017a; The Mathworks Inc., USA). Data from all electrodes were re-referenced to the average of all scalp electrodes and filtered with a band-pass filter of 1–100 Hz. Continuous signals were segmented in epochs of 2 sec. After reducing data dimensionality to 32 components based on Principal Component Analysis (PCA), components representing horizontal and vertical eye artifacts were visually identified and discarded by means of Independent Component Analysis (ICA). Then, a Fast Fourier Transform (FFT) was computed on the clean EEG signal, with a frequency resolution of 0.5 Hz. Finally, in order to determine the frequency of stimulation to use in three entrainment conditions (i.e. IAF, IAF +2 Hz, IAF -2 Hz), the IAF of each participant was visually inspected and identified over six electrodes (P3, P5, P7, PO3, PO7, O1) representing the parieto-occipital Region Of Interest (ROI) contralateral to the stimulated hemifield (i.e. left hemisphere). The mean frequency of stimulation used in the IAF, IAF+2 Hz and IAF-2 Hz were 10.5 Hz, 8.45 Hz and 10.41 Hz, respectively.

8.2.4.2 Pre-processing and computation of the alpha and theta power

EEG signal from all electrodes acquired at the baseline condition and following to three entrainment conditions (i.e. IAF, IAF +2 Hz, IAF -2 Hz) was re-referenced to the average of all scalp electrodes and filtered with a band-pass filter of 1–100 Hz. EEG data, consisting in 9 eyes-closed resting state separate blocks of 1 minute each, was merged and then segmented in epochs of 1 sec, for a total of 540 epochs for each experimental condition. Components representing horizontal and vertical eye

artifacts were visually identified and discarded through ICA, after reducing data dimensionality to 32 components based on PCA. A FFT was computed on each of the 540 epochs of the clean EEG signal, with a frequency resolution of 0.5 Hz For each epoch, alpha power was calculated as the mean power (in dB) in the 7-13 Hz window, in each electrode. Then, as a control analysis, theta power was calculated following the same procedure, in the 3-6 Hz window. The power in each epoch was averaged across blocks, resulting in 60 epochs for each experimental condition. Finally, to assess the duration of the effects of the entrainment over the following 1 minute of resting-state activity, the averaged 60 epochs were grouped in three segments of 20 epochs each. For the statistical analysis, to assess whether the effects of the prolonged visual entrainment might induce diffused, rather than focal, effects over neural oscillatory activity, two posterior ROIs, one in the hemisphere contralateral to the stimulated hemifield (i.e. left hemisphere, P3, P5, P7, PO3, PO7, O1) and one in the hemisphere ipsilateral to the entrainment (i.e. right hemisphere P4, P6, P8, PO4, PO8, 02) and one anterior ROI (Fp1, Fp2, AF3, AF4, AF7, AF8, F1, F2, Fz, AFz) were selected. In order to test fot possible differential effects of the three entrainment conditions over the resting EEG activity, compared to the baseline condition in the posterior ROIs, across segments of epochs, a repeated measures ANOVA, having Condition (Baseline, post IAF, post IAF +2 Hz, post IAF -2 Hz), Segment (1, 2, 3) and Hemisphere (Left, Right) was performed separately on the alpha and the theta power. Similarly, a repeated measures ANOVA having Condition (Baseline, post IAF, post IAF +2 Hz, post IAF -2 Hz) and Segment (1, 2, 3), was performed for the anterior ROI, separately on the alpha and the theta power. All post-hoc comparisons were performed with Tukey HSD test.

8.3 Results

8.3.1 Effects of the visual entrainment on the alpha power

For the posterior ROIs, the ANOVA on the alpha power revealed a significant main effect of Segment ($F_{2,26} = 6.42$, $p = 0.005$) and a significant main effect of Hemisphere ($F_{1,13} = 16,47$, $p = 0.001$). Importantly, the ANOVA showed also a significant main effect of Condition ($F_{3,29} = 3.13$, $p = 0.036$, see figure 8.1). Post-hoc comparisons showed a higher alpha power following to the IAF condition ($M = 8.92$ dB), compared to the baseline condition ($M = 7.29$, $p = 0.0456$), suggesting that the entrainment administered at the IAF effectively induces an increase of the alpha power. A similar tendency emerged when comparing the alpha power in the baseline condition to alpha power following to the IAF-2 Hz condition ($M = 8.81$ dB, $p = 0.068$), although not significant. No other significant comparisons were found (all ps > 0.453).

Interestingly, the ANOVA did not show a significant Condition x Hemisphere ($F_{3,39} = 1.39$, $p = 0.262$) interaction, suggesting that the modulations of the alpha power induced by the entrainment, compared to the baseline condition, are irrespective of the hemisphere.

In addition, also the Condition x Segment ($F_{6,78} = 2.37$, $p = 0.895$) interaction was not significant, indicating that the effects of the entrainment on the alpha power did not differ across the three segments of epochs and, as a consequence, are sustained over time.

In line, also the Condition x Segment x Hemisphere ($F_{6,78} = 0.487$, $p = 0.816$) interaction was not significant.

For the anterior ROI, the ANOVA on the alpha power did not reveal a significant main effect of Segment ($F_{2,26} = 2.86$, $p = 0.075$), but a significant main effect of Condition ($F_{3,39} = 4.02$, $p = 0.014$), pointing to a higher alpha power in the post IAF condition ($M = 3.47$ dB, $p = 0.016$) and in the post IAF-2 Hz condition ($M = 3.38$, $p = 0.039$), compared to the baseline condition ($M = 2.74$ dB). This suggests that the entrainment administrated at both the IAF and the IAF-2 Hz results in an increased alpha power, compared to the power in the baseline condition. All the other comparison were not significant (all ps > 0.368).

Last, similarly to what was found in the posterior ROIs, the ANOVA showed no significant Condition x Segment interaction ($F_{6,78} = 0.91$, $p = 0.489$), indicating that the modulations of the alpha power induced by the entrainment do not differ depending on the segments of epochs. This suggests that, also in the anterior ROI, the effects of the entrainment are sustained over time.

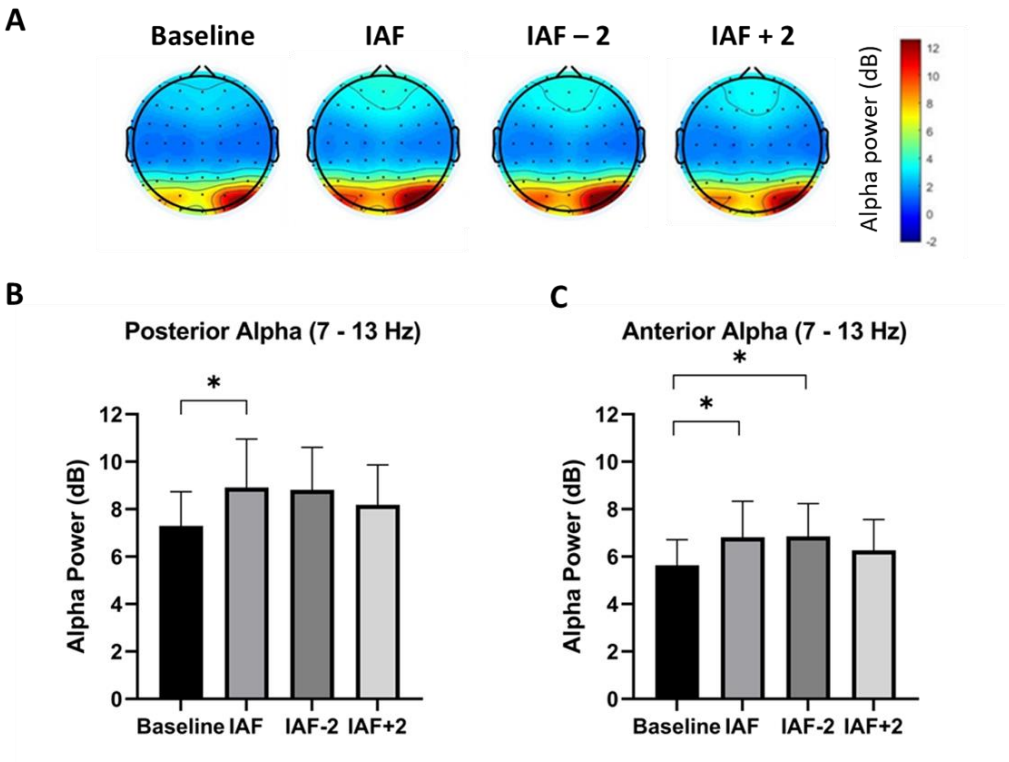

Figure 8.1. *Scalp topographies represent the scalp distribution of the alpha power (dB) the frequency window 7-13 Hz, in the baseline condition (Baseline), the Post-IAF condition (IAF,) in the Post-IAF -2 Hz condition (IAF -2) and in the Post-IAF+2 Hz condition (IAF +2). Bar histograms show the mean alpha power (dB) in the posterior regions (B) and in the anterior region (C), relative to the baseline condition (Baseline), the Post-IAF condition (IAF) in the Post-IAF -2 Hz condition (IAF -2) and in the Post-IAF+2 Hz condition (IAF +2). Error bars represent standard error; asterisks are signaling the significant comparisons.*

8.3.2 Effects of the visual entrainment on the theta power

In contrast to what was found for the alpha power, the ANOVAs on theta power, performed as a control analysis, showed no significant main effect nor interaction in the posterior ROIs (all ps > 0.129, see figure 8.2) This indicates that the entrainment administered at IAF, IAF +2 Hz and IAF-2 Hz, does not induces any modulation of the theta power in the posterior ROIs.

Similarly, also in the anterior ROI no significant main effect or interaction emerged (all ps > 0.487), suggesting that none of the entrainment conditions have an effect on the theta power in the anterior ROI.

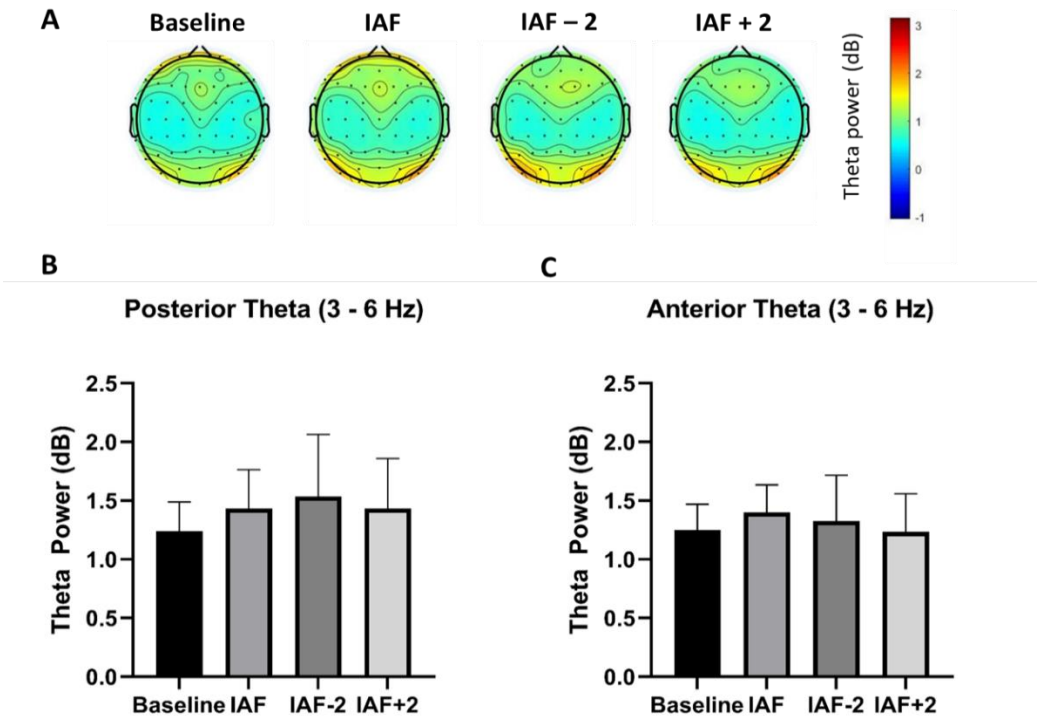

Figure 8.2. *Scalp topographies represent the scalp distribution of the theta power (dB) the frequency window 3-6 Hz, in the baseline condition (Baseline), the Post-IAF condition (IAF,) in the Post-IAF -2 Hz condition (IAF -2) and in the Post-IAF+2 Hz condition (IAF +2). Bar histograms show the mean alpha power (dB) in the posterior regions (B) and in the anterior region (C), relative to the baseline condition (Baseline), the Post-IAF condition (IAF) in the Post-IAF -2 Hz condition (IAF -2) and in the Post-IAF+2 Hz condition (IAF +2). Error bars represent standard error.*

8.4 Discussion

The present study aimed at investigating whether a prolonged alpha-band visual entrainment, given at the right hemifield at the participants' IAF and at two frequencies higher and lower than the IAF (i.e. IAF +2 Hz, IAF -2 Hz), may induce persistent and frequency-specific modulations of the resting-state oscillatory activity, with possible differential outcomes depending on the frequency used for the stimulation.

In addition, the presented study aimed at investigating whether such prolonged visual entrainment protocol may result in diffused, rather than focal, changes in neural oscillatory activity, with possible entrainment-induced aftereffects in different brain regions.

The results showed that the prolonged alpha-band visual entrainment can selectively induce persistent and diffused modulations of the neural oscillatory activity in the alpha, but not in the theta, frequency band, in all examined scalp regions. In particular, the visual entrainment administrated at the

participants' IAF was shown to result in a significantly increased power of alpha oscillations, compared to the power observed at the baseline condition, with comparable aftereffects in both the left and the right posterior regions. Similarly, a tendency to an increased alpha power was observed also in the anterior scalp region, although not significant.

Similar results, pointing to a distributed alpha power enhancement following to the entrainment given at the participants' IAF, were found also for the alpha oscillatory activity recorded after visual stimulation administrated at the IAF -2 Hz. Indeed, coherently with what was found following to the IAF stimulation, a significant increase in alpha power emerged in both left and right posterior regions, without any differential outcome between the left and the right hemisphere. Consistent with this, a significant entrainment-induced increase in alpha power was found also in the anterior region, strengthening the evidence in favor of a tendency to enhanced alpha oscillatory activity in the anterior scalp region observed after the IAF entrainment.

Overall, these results are in line with previous literature investigating the effects of rhythmic entrainment on the spontaneous brain rhythms, and provide additional proof of the efficacy of an alpha-band visual entrainment in increasing the power of the ongoing neural oscillations in the alpha range (Thut et al., 2011a; Mathewson et al., 2012; Spaak et al., 2014).

However, differently of what has been widely reported so far, the results of the present study provide strong indication that the effect of the visual entrainment can be diffused and distributed, rather than focal and limited to the posterior cortices contralateral to stimulation (Thut et al., 2011a; Mathewson et al., 2012; Spaak et al., 2014).This may be due to the fact that the previous studies typically employed short-trains of rhythmic entrainment of approximately 1 second of duration, which may be too brief to induce more distributed entrainment aftereffects, although resulting in consistent modulations of the alpha oscillatory activity in more restrained scalp sites. In contrast, in the present study, the observed increased alpha oscillatory power in both posterior areas contralateral to the stimulation (i.e. left posterior region) and ipsilateral to the stimulation (i.e. right posterior region), combined with an increase in alpha power also in anterior regions, give strong indication that more distributed entrainment aftereffects can be found when the rhythmic entrainment is characterized by a prolonged succession of stimuli.

Based on these observations, it can be hypothesized that such prolonged visual rhythmic stimulation may be effective in promoting the activity of widespread cortical networks, interesting not only posterior visual areas, but also more anterior cortical regions, leading to a diffused enhancement in alpha oscillatory activity. This process, ultimately leading to a spread alpha power increase, may involve mechanisms of neural plasticity both within and outside the visual system, promoting wiring

and activation of distributed reverberating circuits and resulting in diffused changes in cortical excitability (Vossen, 2015).

Remarkably, our results strongly suggest that the prolonged visual entrainment employed in the present study effectively led to long-lasting entrainment aftereffects in all examined brain areas. Indeed, the observed enhancement in alpha power in both posterior regions and anterior region did not differ across blocks of EEG epochs, suggesting that the effects of the prolonged entrainment are sustained over time. This finding add relevant knowledge to previous literature on rhythmic entrainment, showing that the well-known effects of the entrainment over the oscillatory activity can be persistently observed if proceeded by prolonged trains of rhythmic stimulation.

Indeed, although the effects of short-trains of rhythmic entrainment on the activity of alpha rhythms have been consistently and widely described (Thut et al., 2011a; Mathewson et al., 2012; Spaak et al., 2014) in literature, whether a prolonged rhythmic stimulation might lead to persistent entrainment-induced aftereffects has been largely unknown so far.

It has been argued that both the online and offline transient modulations of neural oscillatory activity observed after short trains of rhythmic entrainment may relay on the same mechanisms of neural plasticity (i.e. long term potentiation, LTP) supporting enhancement in neural oscillatory activity (Vossen, 2015). Based on that, it can be hypothesized that the persistent alpha power increase observed in the present study may relay on the same mechanisms of LTP that supposedly sustain transient entrainment aftereffects. However, due to the scarce evidence about the effects of prolonged stimulation protocols on neural oscillatory activity, this assumption remains speculative.

Another noteworthy aspect that emerged from the present study is that the entrainment given at two frequencies higher than the participants' IAF (i.e. IAF + 2 Hz) did not induce any modulation of the alpha power, compared to the power recorded at the baseline. These results seem to be in line with a recent theoretical model postulating that a rhythmic stimulation administered at the IAF or at a slower stimulation, relative to IAF, enhance alpha oscillations in resonating circuits based on mechanisms of LTP, leading to synaptic strengthening (Vossen, 2015). In contrast, according to this model, when neurons of the reverberating circuits are stimulated at a faster frequency relative to the IAF, a weakening of the synapses may occur (Vossen, 2015), explaining why, in the present study, no significant increase of the alpha power emerged following to the IAF + 2 Hz entrainment condition. In addition, it can be also hypothesized that the prolonged entrainment given at the participants' IAF effectively induces a plasticity-related enhancement of alpha activity of the oscillating networks within the posterior cortices, whose frequency of resonance is represented by the IAF itself, which would then spread to more diffused networks, reaching anterior brain areas. Conversely, the entrainment given at the IAF -2 Hz would result in long-term increase of alpha activity in fronto-

central reverberating networks, which are thought to oscillate at other preferential frequency in the in the lower alpha range (Lehmann, 1971; Nunez, 1974), spreading to the posterior cortices.

Crucially, the prolonged visual entrainment did not induce any modulation whatsoever of theta oscillatory activity. This result seems to be in line with the evidence that alpha-band rhythmic entrainment effectively results in selective variations of alpha oscillatory parameters when the frequency of the stimulations matches to targeted brain oscillations (Thut, 2011b) and strengthen the notion that no significant aftereffects over nearby frequency-bands should be observed following to an alpha rhythmic stimulation (Vossen 2015).

Overall, the present study provided proof for sustained and distributed increase in the power of alpha oscillations, following to a frequency-tuned prolonged visual entrainment. This observed enhancement of alpha oscillatory activity possibly relays on mechanisms of neural plasticity in widespread cortical networks, both within and outside the visual system, leading to synaptic strengthening and increased cortical activation.

This adds new knowledge to previous literature on rhythmic entrainment which has shown that short-term rhythmic stimulation results in transit entrainment induced online and offline effects (Spaak et al., 2014), demonstrating that prolonged trains of visual entrainment can induce persistent modulations of resting-state oscillatory activity in the alpha frequency band.

In addition, since neural oscillations in the alpha range are reportedly linked to various aspects of visual perceptual processing and are thought to represent a reliable index of the functionality of the visual system even at rest (Klimesh et al., 2007; Sadaghiani & Kleinschmidt, 2016), the result of the present study hold promise for prolonged entrainment paradigms to selectively enhance visual processing and effectively impact visual awareness, by means of plastic reorganization of the underlying oscillating networks. Crucially, eyes-closed resting state activity in the range of alpha has been widely proposed as a biomarker of the functionality of the visual system and has been strongly linked to visual performance both in healthy participants (Samaha and Postle, 2015; Cecere et al., 2015) and in patients with posterior brain lesion and hemianopia (Pietrelli et al., 2019). Therefore, prolonged entrainment paradigms may represent a valuable tool with possible rehabilitative applications in patients with posterior brain damage and visual field defects, characterized by an impairment in eyes-closed resting-state alpha oscillatory activity.

Chapter 9
General discussion

Human visual system is characterized by an incredibly complex organization, consisting in multiple visual pathways and both parallel and hierarchical information processing. Such complex organization strongly depends upon experience and maintains capacity for neuroplastic adaptations throughout the entire lifespan, enabling the system to modify its functioning, connectivity and structure according to the variable external needs. Proof for the ability of the visual system to rearrange itself in the adulthood, changing its structural and functional architecture, has been provided by a wealth body of experimental studies in both neurologically healthy participants and brain damaged patients (for a detailed review, see chapter 4). Therefore, it is of a great interest to further investigate to what extent the activity of the visual system can be modeled and promoted through external experimental interventions or affected by the presence of a brain damage, disrupting its circuits and possibly resulting in dysfunctional postlesional changes. Crucially, there is strong indication in literature that neural oscillations in the alpha range (7-13 Hz) play an active role in shaping visual processing and in sustaining the intrinsic periodical structure of visual perception (Bush et al., 2009; Mathewson et al., 2009), having a direct link with timing and temporal resolution of visual perception (Samaha & Postle, 2015; Cecere et al., 2015) and visual awareness (Matewson et al., 2009), representing a reliable index of the efficiency of the visual system and the functionality of the posterior cortices (Romei et al., 2008a; 2008b).In line, a series of electrophysiological studies in hemianopic patients described the presence of maladaptive functional and structural changes in the visual system following to posterior brain lesions, revealed by alterations in neural oscillatory activity of the alpha rhythm at rest (Pietrelli et al., 2019), suggesting that the posterior cortices have a pivotal role in the generation and distribution of these oscillatory patterns. On the other hand, in the healthy adult brain, several visual functions have been shown to be susceptible to plastic modification, leading to improvements in the visual perceptual outcome. In particular, in the past few years a recent line of research has aimed at modulate the intrinsic oscillatory patterns of the visual system in the frequency range of alpha, by directly stimulating the underlying reverberating networks trough rhythmic entrainment, exploiting the underlying mechanisms of neural plasticity within the visual system, with concurrent cyclic enhancements in visual perceptual performance (Mathewson, 2012; de Graaf et al., 2013; Spaak et al., 2014).

In light of this evidence, the present thesis aims at investigating the role of alpha oscillations as an index reflecting the functionality of the visual system and the plastic changes occurring in response to the presence of lesions to the posterior cortices or induced by external stimulations.

To this perspective, based on previous studies showing the presence of consistent impairments in alpha oscillatory activity after posterior brain lesions disrupting the circuits of the visual system, with a detrimental reduction of alpha frequency and power (Pietrelli et al., 2019), chapters 5 e 6 aimed at further characterize these oscillatory alterations, investigating their residual functionality and network connectivity of alpha oscillations in hemianopic patients.

In particular, the study presented in chapter 5 investigated whether a damage to the posterior cortices in hemianopic patients results in disrupted or altered alpha desynchronization in the transition from the eyes-closed to the eyes-open resting state, representing a functional measure of cortical visual system reactivity at rest. To this aim, EEG signal was recorded in eyes-closed and in eyes-open resting state conditions in hemianopics and controls. The results showed that, following to both left and right posterior lesions, hemianopic patients retain a residual cortical reactivity at the opening of the eyes, as shown by the presence of a significant alpha desynchronization, which was however altered and significantly reduced, compared to healthy participants, suggesting that the posterior cortices play a crucial role in the functionality of the alpha rhythm. Importantly, this observed alteration in the eyes-opening induced alpha desynchronization was more pronounced and distributed over the scalp in the group of right-lesioned hemianopics, Furthermore, right-lesioned hemianopic patients showed an additional atypical pattern of theta reactivity at the opening of the eyes. These combined impairments in the alpha and the theta range observed in right-lesioned hemianopics suggests the presence of stronger postlesional alterations in functional reactivity at the opening of the eyes involving both global and local processes.

In addition, the study presented in chapter 6 aimed at investigating whether lesions to the posterior cortices in hemianopic patients affect also the complex pattern of functional connectivity at rest in different frequency bands, with possible detrimental effects both at a global and at a local level. To this aim, EEG signal was acquired in a condition of eyes-closed resting-state in hemianopics and controls. Intrahemispheric connectivity indices were computed to assess post-lesional functional connectivity changes. In addition, clustering coefficient (C) and characteristic path length (L) graph theory parameters were chosen to characterize local and global connectivity patterns. The results showed that posterior lesions decrease intrahemispheric upper-alpha connectivity compared to healthy participants, with left-lesioned hemianopic patients showing a reduction in connectivity only in the lesioned hemisphere, and hemianopic patients with right lesions showing a more diffuse impairment, with reduced intrahemispheric upper alpha connectivity in both hemispheres. At a

network level, the reduced connectivity in upper alpha was characterized by a decreased network efficiency, with reduced local functional segregation (i.e., clustering coefficient) and no associated change in global functional integration (i.e., characteristic path length). Crucially the altered functional connectivity in the upper alpha range was shown to be positively correlated with the patients' visual detection performance in the blind field, suggesting that post-lesional changes in alpha functional connectivity at rest represent an index of impairment of the structural and functional integrity of the visual system. Furthermore, in chapter 6 right-lesioned hemianopic patients showed an abnormal increase in theta connectivity, characterized by an increased local segregated activity (i.e. increased clustering coefficient) and a decreased global integration (i.e., higher path length), suggesting that a severe and bilateral reduction in alpha connectivity also induces impairments in local and global low-level processing in the theta range.

Overall, the results of the studies presented in chapter 5 and 6 provide strong evidence for consistent alterations in the spontaneous alpha oscillations in patients with posterior lesions and hemianopia, strengthening the notion that alpha oscillatory activity may represent a reliable biomarker of the functionality and the integrity of the visual system. However, in chapter 5, no significant correlation between hemianopic patients' functional reactivity in the alpha range and visual performance was found, suggesting that alpha desynchronization at the opening of the eyes may not be related to visual processing per se, but rather represents a basic physiological response of stimulus-independend activation induced by the opening of the eyes. In contrast, in chapter 6, upper alpha functional connectivity in a condition of eyes-closed resting state was direlectly linked with hemianopic patients' visual abilities, favoring the evidence of a direct role of alpha oscilaltory activity at rest in shaping visuospatial processing.

In addition, the results presented in chapters 5 and 6 suggest that the posterior cortices give a substantial contribution in coordinating and propagating alpha oscillations in the entire visual system, from lower to higher-order visual areas (Bollimunta et al. 2008; Hindriks et al. 2015). Consistent with this interpretation, oscillatory activity in the alpha range has been reportedly described as the natural frequency of resonance of the posterior cortices, representing the intrinsic neural rhythm of the visual system (Rosanova et al., 2009). In line with this, alpha oscillatory power, phase and frequency were shown to have a strong influence on visual awareness and to be directly correlated with the temporal resolution of visual perception (Mathewson et al., 2009; Bush et al., 2009; Samaha & Postle, 2015). In addition, neural oscillations in the range of alpha have been recently thought to be responsible to sustain the discrete nature of visual perception, through a mechanism of pulsed cortical inhibition relying on fast dynamic interactions within the visual system (Bush et al., 2009).

Moreover, the results of the studies presented in chapter 5 and 6 enlighten the presence of more severe and prominent impairments of alpha oscillatory activity in right-lesioned hemianopic patients, which were consistently combined with altered oscillatory activity also in the range of theta. Overall, the presence of these concurrent alterations in alpha and theta oscillatory patterns following to right posterior lesions, strengthen the hypothesis that alpha oscillatory activity may reflect widespread cortical processes, regulating modular processes in lower frequency bands (Doesburg et al., 2009; Barry & De Blasio, 2017). This seems in line with the notion that alpha oscillations propagating from posterior visual cortices to higher-order cortical sites (Hindriks et al., 2015) play a crucial role in coordinating widespread oscillatory activity and orchestrating focal processing in non-alpha frequency bands (i.e., theta), supporting visual processing (Barry & De Blasio, 2017) and add to previous literature suggesting a specialization of the right hemisphere in coordinating this complex interplay among different brain rhythms.

These converging results convincingly demonstrate the presence of altered alpha oscillatory activity in patients with posterior brain damage and visual field defects, strengthening the evidence for a causal role of alpha oscillation in modulating efficient visual processing, and strongly suggest that the left and the right brain hemisperes differently contribute to these oscillatory mechanisms. Based on this evidence, the study presented in chapter 7 aimed at investigating the role of these oscillatory patterns in determining processing of visual information in healthy participants, investigating the possible differential role of the two brain hemispheres in supporting these oscillatory processes also at a perceptual level. Indeed, a large body of evidence has demonstrated that the visual system is characterized by an intrinsic tendency to process information in a periodical way, through rhythmic fluctuations in cortical excitability, which mirror the neural oscillatory activity of the alpha rhythm (Bush et al., 2009). In line, alpha oscillatory power, phase and frequency have been shown to have a strong influence on the detectability of visual stimuli (Mathewson et al., 2009) and to have a direct link with the temporal resolution of visual perception (Valera et al., 1980; Samaha & Postle; Cecere et al., 2015). In this perspective, several studies demonstrated the existence of a periodicity in the processing of visual stimuli, occurring in the range of upper-alpha at approximately 10-12 Hz (Duguè et al., 2011; Drewes et al., 2015, Mc Lelland et al., 2016, Van Rullen, 2016) and it has been reported that this sensory rhythm may coexist with at least one more rhythm, performing attentional sampling at lower alpha frequencies (i.e., 7 Hz) when attention is allocated to a single spatial position (Bush et al., 2009; Duduè et al., 2015; Van Rullen, 2016) or at lower frequencies at alternate cycles (e.g. 2-4.Hz), when multiple spatial positions have to be attentionally monitored (Landau & Fries, 2012; Fiebelkorn et al., 2013; Song et al., 2014; Huang et al., 2015). Specifically, this study aimed at measuring perceptual oscillations in response to the presentation of visual stimuli in a visual detection

task, manipulating the allocation of attentional resources and, thus, exploring the influence of the rhythmic attentional sampling on perceptual visual processing. Moreover, a lateralized presentation of the visual targets in the left or right visual hemifield was used to investigate possible different contributions of the two hemispheres in the rhythmic attentional sampling.

To do so, a behavioural methodological approach known as 'dense-sampling' procedure was used, which is able to sample perception with a relatively high temporal resolution, allowing the resulting fluctuations in behavioral performance to be analyzed through the same spectral methods that are commonly reserved for electrophysiological signals (Landau and Fries, 2012). In particular, in one version of the task, participants had to detect a visual target at threshold contrast appearing exclusively to the left or to the right hemifield (*task 1*), while in the second version of the task the target could randomly appeare to the left or to the right hemifield (*task 2*), in absence of an external spatial cue. This allowed a manipulation of the participants' endogenous attention, such that their attentional sources were directed to one single spatial location at time, or split between two different spatial locations simultaneously.

In line with previous findings, the detection performance revealed the presence of different oscillatory attentional components in the two tasks. Indeed, when a single spatial position had to be monitored in task 1, an oscillatory attentional component peaking in the lower alpha range at 7 Hz was evident, while when attention had to monitor two concurrent spatial positions in task 2, an oscillatory attentional component was observed in a lower frequency range at around 5Hz. This observation is consistent with previous literature showing that the perceptual sampling of visual information is strongly influenced by a periodical mechanism of attentional allocation, which effectively distribute attention to any possible spatial location, suggesting that the attentional system operates with an useful and effective functional flexibility.

Moreover, the results showed that differences in rhythmic attentional sampling occur depending on the visual hemifield where the target stimuli appeared, suggesting that the left and the right brain hemispheres might play a differential role in sustaining these sampling mechanisms. In particular, the oscillatory attentional components were more evident in response to stimuli presented in the right visual field in both tasks. Indeed, in task 1, the lower-alpha component (7Hz) reached significance only when participants detected visual targets in the right visual field, while no similar significant components were observed in response to visual stimuli on the left visual field. Furthermore, in task 2, at a qualitative level a greater magnitude for the 5 Hz oscillatory component in response to stimuli presented to the right was observed, compared to the 5.5 Hz component in response to stimuli presented to the left hemifield. The observation that these attentional components are more prominent in response to visual stimuli in the left visual filed may depend on the concurrent activity of both

hemispheres. Namely, this might reflect a cooperation of the activity of the left hemisphere, which is reportedly involved in processing visuospatial information in the contralateral hemifield, and of the right hemisphere, which is commonly thought to be involved in processing visuospatial information in both the ipsilateral and the contralateral visual hemifield (Heilman & Van Den Abell, 1980). This is in line with the hypothesis that the two brain hemispheres may give a differential contribution in sustaining the mechanisms of perceptual and attentional periodical sampling and favors the notion that right hemisphere has a dominant role in orchestrating these parsing and attentional processes, distributing attentional resources to the entire visual field.

Interestingly, this evidence and the previously reported findings of chapter 5 and 6 emphasize a specialized function of the right hemisphere in orchestrating and distributing brain oscillatory patterns. These observations are consistent with previous findings showing that posterior right lesions induced stronger IAF reduction and interhemispheric power imbalance in hemianopic patients (Pietrelli et al., 2019). In keeping, evidence on healthy participants revealed that the right hemisphere is involved in modulating alpha oscillations to promote detection of visual stimuli and to inhibit irrelevant visual information (Gallotto et al., 2020), suggesting a fundamental role of this hemisphere in allocating visuospatial attentional resources and tuning visual abilities through alpha oscillatory patterns. This is in line with the well-known theories about the existence of hemispheric asymmetries in visuospatial abilities and strengthen the notion that the right hemisphere has a greater involvement in perceptual and visuospatial processing, compared to the left hemisphere (Bisiach & Luzzatti, 1978; Heilman & Valenstein, 1979; Heilman et al., 1984; Mattingley et al., 1994; McCourt & Olafson, 1997; Nobre et al., 1997; Gitelman et al., 1999; McCourt & Jewell, 1999; Jewell & McCourt, 2000; Corballis et al., 2002; Nicholls et al.,2002). Nevertheless, few studies have recently enlightened the presence of impaired spatial processing in chronic stroke patient with left hemisphere damage when testing them in a condition of attentional load, suggesting that hemispheric asymmetries in spatial processing and spatial representation, in favor of the right hemisphere, may be less pronounced than previously assumed (Blini et al., 2016).

The results of the studies presented in chapter 5, 6 and 7 helped also understand the effects of posterior brain damage over the activity of different oscillatory brain patterns, enlightening the presence of global and local dysfunctional postlesional changes in the damaged visual system, and clarify the periodical nature of visual perception in healthy participants. In addition, these studies helped shed light on the role of the different brain rhythms in sustaining the functioning of the visual system and the processing of visual information, strengthening the evidence for a pivotal role of alpha oscillatory activity in supporting these processes.

Crucially, a noteworthy aspect to be investigated concerns whether these oscillatory patterns can be effectively modulated through experimental interventions, aiming at promoting possible long-lasting plastic changes in the underlying networks. Indeed, it is well known that the spontaneous oscillatory activity in the range of alpha can be externally promoted through specific frequency-tuned stimulation protocols (i.e. rhythmic entrainment), which lead to transient functional modifications in the visual system (Spaak et al., 2014), resulting in consistent, but spatially restrained, enhancements in alpha parameters and in the perceptual outcome (Thut et al., 2011; Mathewson et al., 2012; de Graaf et al., 2013; Spaak et al., 2014). However, it was still not elucidated whether persistent modifications in the functional structure of the visual system, leading to more diffused and long-lasting modulations of the alpha oscillatory activity, can be effectively achieved through prolonged stimulation protocols. Therefore, the study presented in chapter 8, aimed at investigating the effects of a prolonged rhythmic visual entrainment on the resting-state oscillatory activity in a group of healthy participants. To this aim, eyes-closed resting state EEG signal was recorded before and after the administration of a visual entrainment, given at different frequencies included in the alpha range (i.e. IAF, IAF +2 Hz, IAF – 2 Hz). The results showed that visual entrainment administrated at the participants' IAF and at IAF - 2 Hz condition selectively induced an increase in the alpha power in posterior scalp regions, with comparable aftereffects in both the left and the right hemisphere, and an increased alpha power also in the anterior scalp region. In contrast, no significant modulation of the theta power was observed, in line with previous research showing that no significant aftereffects over nearby frequency-bands should be observed following to an alpha-band rhythmic entrainment (Vossen, 2015). Based on these findings, it can be hypothesized that the observed enhancement of alpha oscillatory activity possibly relays on mechanisms of neural plasticity in widespread cortical networks, both within and outside the visual system, leading to long-term synaptic strengthening and increased cortical activation. This adds new knowledge to previous literature on rhythmic entrainment, demonstrating that prolonged trains of visual entrainment can induce long-term modulations of resting-state oscillatory activity in the range of alpha.

In addition, as previously mentioned, neural oscillations in the alpha range are reportedly linked to various aspects of visual perceptual processing, supporting the periodical structure of visual perception (Bush et al., 2009; Mathewson et al., 2009; Samaha & Postle, 2015; Cecere et al., 2015) and are thought to represent a reliable index of the functionality of the visual system even at rest (Klimesh et al., 2007; Romei et al., 2008b; Sadaghiani et al., 2010). Therefore, the result of the present study hold promise for prolonged entrainment paradigms to selectively enhance visual processing and effectively affect visual awareness, by means of plastic reorganization of the underlying oscillating networks. This evidence may be of particular relevance in light of the results provided in

chapter 5 and 6, showing alteration in the alpha range after posterior brain lesions, and suggests that prolonged entrainment paradigms may represent a valuable tool with possible ameliorative outcomes in patients with posterior brain damage and visual field defects, characterized by a residual impaired resting-state oscillatory activity. In particular, such entrainment protocols may be highly effective in modulating the eyes-closed resting state oscilaltory activity in the alpha range, which represents a reliable biomarker of the functionality and the structural integrity of the visual system and which was shown to be strongly linked to visual performance in hemianopic patients (Pietrelli et al., 2019; see chapter 6). This may induce long-lasting rehabilitative effects in patients with hemianopia, resulting in an improved eyes-closed resting state alpha activity (e.g., increased alpha functional connectivity), with subsequent possibile enhanchments in the patients' visual abilities.

Overall, the findings of the present work provided strong evidence for a pivotal role of the alpha rhythm in regulating visual perceptual processing and strengthen the notion that neural oscillations in the alpha range represent a valuable biomarker of the functionality of the visual system. The present results provide also additional knowledge, suggesting the existence of a differential contribution of the two brain hemispheres in orchestrating these oscillatory patterns, possibly reflecting the well-known hemispheric asymmetries in visuospatial processing, and emphasize a dominant role of the right hemisphere in supporting these oscillatory mechanisms. In addition, the present work provides also evidence that these oscillatory patterns can be effectively modulated and promoted through external stimulations, suggesting that the alpha oscillatory activity is susceptible of long-lasting plastic changes.

In conclusion, the studies presented in this dissertation converge in enlightening the relevance of investigating the intrinsic oscillatory processes of the visual system, in order to have a deeper understanding on the mechanisms that regulate its activity. This growing and promising avenue of research, exploring the role of alpha oscillations in shaping visual processing, hold promise for future experimental studies to further define the functional and structural properties of the visual system.

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