UNIVERSITY OF PADOVA

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Final dissertation

Systematic review on the role of acquired brain damage in visuospatial perceptual deficits distinct from neglect

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Abstract

Visuospatial perceptual deficits refer to the inability to recognize faces or common objects, or to find those in direct view despite of good acuity. It is thought to arise due to aetiologies which include: cerebrovascular accidents, tumor, carbon monoxide poisoning, closed head injury, and central nervous system infections. In this narrative review work, we will be revolving around three disorders which are included in the array of visuospatial perceptual deficits, specifically metamorphopsia, hemimicropsia and hyperschematia and how such deficits could arise due to acquired neurological injuries. The case reports, with patients aged 35-73, will be further discussed, by systematically reporting information such as their medical history, the symptoms experienced and the locus of brain damage, and so on, in accordance with the deficit experienced out of the earlier mentioned ones. Furthermore, various neuropsychological tasks, which have been conducted on the above specified patients, will be comprised so as to ensure a clear understanding of their scope. Some examples of included tasks are: line cancellation, line bisection, drawing from memory, perceptual matching, drawing by copy. Moreover, neuroimaging and electrophysiological data will be also discussed, when available. By analysing the results, we will be able to understand the extent of impairment in specific cognitive abilities due to acquired brain damage. Additionally, we will create a broader neuroanatomical profile for each of those deficits to facilitate future research, which is the primary focus of this systematic review.

1. Introduction

The aim of the current systematic review will be to explore three distinct visuo-spatial deficits: metamorphopsia, hemimicropsia and hyperschematia. This work will also discuss how these conditions can develop through acquired brain damage in adult individuals. Following on, the general aspects of each disorder will be described in this section, such as their definition, characteristics, probable aetiologies and so on. Furthermore, I will describe the patients of interest in their complete medical profile, the neuropsychological tasks with which they have been typically tested in the literature, as well as results, all in concordance with the findings of each paper and the interpretations provided.

1.1. Metamorphopsia

Metamorphopsia has been stated as a form of distorted visual perception where linear objects are perceived incorrectly, curved or discontinuous (Hanumunthadu et al. (2021). Concerning the epidemiology of this disorder, 502 eyes have been studied and further analyzed, as such, the incidence of metamorphopsia has been estimated to range between 54% and 56.3% in diabetic macular edema (DME). An incidence of 45.4% has been reported in 33 patients with central serous chorioretinopathy (CSCR). In vitreomacular traction (VMT), it has been estimated as 18.9% (29.3% with concomitant epiretinal membrane). In some distinct cases, metamorphopsia has been found in patients with macular hole. However, there have been some reported cases in which patients did not have a significant scotoma due to the macular hole, and as a result, metamorphopsia was found to occur due to the eccentric displacement of photoreceptors.

In terms of its locus in the brain, structures that have been discovered in the close vicinity of, or in the occipital lobe, can be considered as metamorphopsia-micropsia-inducing sites, as stated by Ebata, Ogawa, Tanaka, Mizuno and Yoshida (1991). Furthermore, Lance (1976) has discovered that the parieto-occipital association areas of the cortex were strong predictors of metamorphopsic symptoms.

Turning to the deficits, it was analyzed and thus found that, individuals that suffer from macular diseases have expressed as having reduced visual acuity, an aspect that has posed difficulties in day to day activities that required visually-guided behaviors, appropriate examples of such activities being reading and face discrimination, as proposed by Rubin, Munoz, Bandeen-Roche and West (2000). Letter identification has been termed as being highly susceptible to spatial distortion, since it requires not only the detection and discrimination of high contrast stimuli, but also processing forms and shapes, a matter analyzed by Marmor (2000).

Regarding the treatments for metamorphopsia, we firstly have to consider the use of Amsler Grids, as Hanumunthadu et al. (2021) reported as being regularly used to detect and monitor symptoms of metamorphopsia, both in the clinic and at home setting. These grids could generate quantitative measures in perceived metamorphopsia prior and post treatment, providing so important knowledge in regard to the clinical trial evaluation of treatments for the disorder at hand. Commonly used treatments are surgery for the epiretinal membrane, according to Suh, Seo, Park and Yu (2009), and macular hole, as stated by both Christensen, Kroyer, Sander, Jorgensen, Larsen and la Cour (2010) and Itoh, Inoue, Rii, Hiraoka and Hirakata (2012). A significant correlation between visual acuity and recovery of foveal cone microstructures after macular hole surgery has also been explored, considering thus the positive implications of macular hole surgery in the course of treatment. Furthermore, it was noted that in regard to severe cases of symptomatic metamorphopsia, the need to endorse the use of occlusion therapy is highly necessary, since there are exceptional cases in which the previously stated treatments cannot be selected (Hanumunthadu et al., 2021).

1.2. Hyperschematia

Moving on to the second disorder, hyperschematia can be defined as an enlargement of object parts in an excessive manner, defined so by Vallar and Rode (2009) and typically left-sided disproportionate expansion of drawings by copy, as well as, object representation from memory, followed by an overestimation of left lateral extent when a leftward movement is required (Di Marco et al., 2019).

In terms of its characteristics, Rode, Revol, Rossetti and Vallar (2008) stated that hyperschematia is vastly explained as being primarily perceptual, known for occurring when operations (including planning and execution of motor acts in the left side of space) are required, and it can affect drawing of many different objects such as a daisy, a tree, a butterfly, a man, a house or scene, the whole of an object but also some parts of it. In regard to the etiology of brain damage, such disorder can be found in patients with damage to their right side of the brain, as specified by Di Marco et al. (2019). Adjacent to this idea is also the argument of Rode et al. (2014), who specified more in detail that damage to the frontal-temporo-parietal cortices, and subcortical structures, as well as in the vascular territory of the middle cerebral artery were noted as being primary factors that lead to the development of hyperschematia. For possible left brain damage locations, a left cerebral lesion could very well be of cause, with the majority of the damage being inflicted upon the middle cerebellar peduncle, which would subsequently give rise to ipsilesional spatial hyperschematia, according to Veronelli, Corbo, Brighenti and Daini (2020). Moreover, it is important to know that in order to acquire left spatial hyperschematia, damage to the basal ganglia and insula is not necessary, per Rode et al. (2008). Even more interestingly, Kew, Wright and Halligan (1998), as well as Podoll and Robison (2002) have documented the fact that hyperschematia tends to arise after paroxysmal cerebral disorders such as epilepsy, migraine and hypnagogic hallucinations. More interestingly, the fact that somatosensory loss can be caused by a local anesthesia deserves attention, as explained in the study of Gandevia and Phegan (1999) and Paqueron et al. (2003). Following on the above stated findings is the idea that, body image distortions have been proven to arise after brainstem lesions, or by a regional anesthesia, a fact which is supported by the findings of Rode (2012; 2018).

Turning to the symptoms of the above stated disorder, according to Vallar and Rode (2009), they consist of the perceptual overestimation of the entire body, or at times, for different parts of it. It was also discovered that patients with right hemispheric damage may sometimes show an impairment in drawing tasks, both from memory and by copy, further characterized by a disproportionate enlargement of putatively symmetrical objects such as a daisy, towards the left side, contralateral to the side of the lesion, as found by Rode et al (2008). It has also been highlighted that hyperschematic patients do not add gratuitous and unrelated details in cancellation tasks, such as a hen (Rusconi, 2002), or a goose (Bottini, G. 2002), but in turn, there is a tendency to enlarge the left-hand side of drawn objects, such as a church (Rode et al. 2007, p. 1807), a butterfly, or a pine tree, performance which was seemingly different compared to patients exhibiting perseveration (Rode et al. 2008). It should also be noted that, patients are unaware of the disorder (anosognosia) and that unilateral spatial neglect, or the deficit of perceptual underestimation of the lateral extent of objects located in the left hand-side of space, was not present in the patients diagnosed with hyperschematia (Rode et al. 2007).

When discussing about the treatments of this specific disorder, the most effective way of curing it is through the use of prism adaptation (PA), which proves to be rather promising through its effect upon the rehabilitation of post-stroke cognitive disorders, such as unilateral spatial neglect or constructional deficits (Di Marco, et al. 2019). In the course of treatment for hyperschematia, PA manages to reorient spatial attention towards the right side of space, with a relative rightward PA-induced unbalance, re-setting so the spatial representation to the left side of space, contralateral to the side of the lesion.

Such disorder has been proven to be highly comorbid with the vestibular syndrome, which arises due to damage inflicted upon the medulla oblongata and manifests itself through vertigo, irregular activity of the oculomotor reflexes, nausea and anxiety, transient auditory phenomena, and trigeminal pain, per discoveries reported by Vallar and Rode (2009). Similar feelings have been also noted in patients suffering from macrosomatoagnosia hallucinations, which are defined as the misperceptions that one or more parts of the body of the one who exhibits it are disproportionately larger (Rode et al. 2018). Such aspect could provide a better understanding of hyperschematia, since it is related to the vestibular syndrome, and through their correlation, showcasing a meaningful relation that it can have to macrosomatoagnosia.

1.3. Hemimicropsia

As for the third disorder, hemimicropsia has been coined as a term referring to a rare disorder of visual perception, characterized by an apparent reduction of the size of objects when presented in one hemifield. As such, it can be considered a limited violation of the size consistency principle respectively, termed so by Cohen et al. (1994).

Moving to its characteristics, it is highlighted as a reduction of the perceived size of objects in one visual hemifield, according to Rode et al. (2007). It can also have two primary causes that it can arise from: (i) a deficit in the ability to judge spatial relationships, both between and within objects, which is observed after a parietal lesion; (ii) a failure at an early stage of the processing of visual object features, which can follow a prestriate cortex lesion (Frasinetti et al., 1999).

In terms of the etiology of such deficit, it is without a doubt needed to highlight the importance of the prestriate cortex, or the V2 region, known as being anterior to the striate cortex in terms of anatomy (Gazzaniga et al., 2013). In line with the above stated information, is the idea that the prestriate cortex plays an important role, since it can compute size in order to maintain a constant representation of objects across variations of distance and position (Cohen et al., 1994). Moreover, hemimicropsia is believed to be caused by a lesion affecting the unimodal visual association cortex, excluding the probability that vascular lesions are of fault, since they are rarely restricted to this cortical region and as such, not posing themselves as a strong predictor for hemimicropsia. Another spot of interest from which hemimicropsia could arise, is located in the retinotopic reference frames of the visual field by Rode et al. (2007). Furthermore, it has also been found that the parietal cortex may be critical for processing size information, for the purpose of visuomotor control (Sakata et al. 1996).

In regards to the symptoms, they include the fact that patients with hemimicropsia, typically see objects in the contralesional hemifield smaller in size, compared with objects in the ipsilesional hemifield, but in most cases, they tend to compensate for the deficit. As such, they draw the contralesional side of objects larger than the ipsilesional side, and correct symmetric patterns, making so the contralesional side larger (Rode et al., 2007). Furthermore, those patients also tend to be aware of the deficit in their size perception, reporting that objects in the contralateral hemifield appear „smaller” or „somewhat shrunken and compressed”, or that „everything on the left side appeared distorted in its size”.

Treatment-wise, Kassubek et al. (1999) stated that, medication such as the anti-convulsant carbamazepine, can be used in the cases in which the hemimicropsia is caused by an epileptic activity, since it was shown that, after successful treatment, the previously reported visual deficits are not present anymore.

2. Methods

2.1. Inclusion Criteria

(i) Types of studies included: case reports of any of the above mentioned visuo-spatial perceptual deficits (i.e., Metamorphopsia, Hyperschematia and Hemimicropsia) which have been acquired through brain damage, written in English. Studies with animals, children and teen represented an exclusion criterion, altogether with possible cases where those disorders could have had been developed through genetic factors.

(ii) Participants: patients, both males and females, that have been diagnosed with one of the three stated visuo-spatial perceptual deficits, as a result of acquired brain damage.

1	*Visuospatial perceptual deficits*
2	*Metamorphopsia*
3	*Hemimicropsia*
4	*Hyperschematia*
5	*Horizontal dysmetropsia*

Table 1. Search terms

2.2. Searching Strategies

In my search, I have used 4 electronic databases, consisting of PubMed, Web of Science, Scopus and Clarivate, for relevant studies that have taken place in the last 35 years. The searching strategy and searching terms are listed in Table 1.

2.3. Study Selection

Nine articles were selected based on the inclusion criteria, as well as exclusion criteria and will be further reported in the review. The flow diagram that comprises Table 2 will further show the process of selection for the eligible studies analyzed. The table follows so the guidelines for The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al. 2020).

2.4. Data Extraction

The data extraction has been compressed into preset Word tables. Furthermore, the information that has been added to the tables includes: short descriptions of the patients, the past medical history, altogether with the accidents that the individuals have suffered, and the adjacent surgical procedures completed, as well as post-op evolution, distinct comorbidities noted for each of them, brain scans conducted, and lastly, the etiology and locus of brain damage. Moreover, following on the tables, the subsequent sections will present the neuropsychological tasks conducted on each patient, as well as their results.

2.5. Data Reporting

The data reporting process follows PRISMA guidelines, so as to improve the clarity of the systematic review.

3. Results

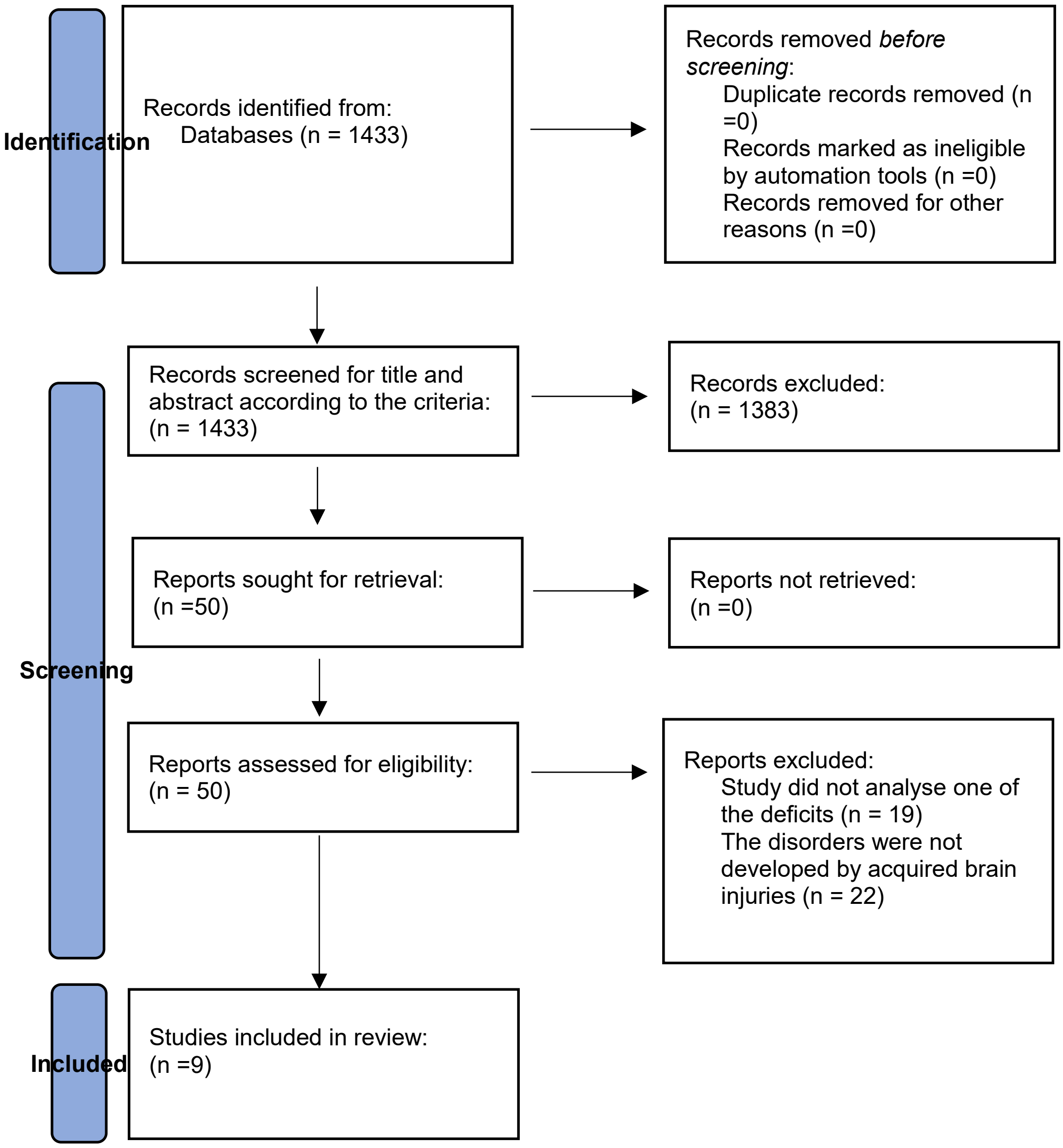

Table 2. The Flow Diagram

3.1. Study Overview

Nine studies, as stated in the previous section, have been considered as eligible and further described in the following sections thoroughly. The dates in which the articles have been published range from March 1991 to May 2019. A couple of those case reports have been conducted in the United States, while others have been done in

Italy, Germany and Japan. Moving on to the composition of the studies, 7 of those studies are single case reports, while the other 2 are double case reports, all of them showcasing patients that are both adult males and females, of different age groups, which have sustained distinct neurological accidents.

3.2. Description of the Patients

Counting the participants that have met the criteria, 11 patients will be presented further. In order to ease the understanding and overall the coherence of the topic at hand, Table 2, 3 and 4 will have the patients basic information, as well as further notions as to how the disorders of interest have occurred, the brain scans that have been used for each patient, while some others have not had any, the etiology of brain damage for each patient, in order to understand the zone of interest for each of those disorders, and lastly, it will also include the comorbidities found.

For hemimicropsia, there will be four patients included, aged 35, 50, 60, 71, with two of the patients having had the onset 48 hours following their respective neurological events, the patients aged 35 (Kassubek et al., 1999) and 71 aged (Frasinetti et al., 1999), respectively. The onset of the disorder happened four days after a stroke for the patient aged 60 (Cohen et al., 1994). Lastly, the onset for the patient aged 50 has happened in the first 24 hours after the accident (Cohen et al., 1994).

For hyperschematia, four patients, aged 45, 61, 63, 73 have been selected. Three of those patients have shown an immediate onset of hyperschematia following a stroke, patients aged 45, 61 (Rode et al., 2007) and 73 (Rode et al., 2008). As for the remaining individual, the one aged 63 (Di Marco et al., 2019), the onset of the disorder happened after one month since the occurrence of the stroke.

Lastly, for metamorphopsia, three patients were reported, with one patient having the age of 56, one aged 60, and the last one being 63. For the patient aged 56 (Miwa and Kondo, 2007), the onset of metamorphopsia was immediate, as well as for the individual aged 63 (Shiga et al., 1996), yet the symptoms for the latter one lasted only 3-4 days. For the remaining one, the patient aged 60 (Ebata et al., 1991), symptoms arose 11 years after the occurrence of the neurological event.

Short description of the patient	*Brain Scans*	*Medical History and Evolution*	*Aetiology of Brain Damage*	*Commorbidites*
Man, age 50, right-handed (Cohen, L. 1994)		-Occasional opthalamic migraines at the age of 40 -Onset of a myocardial infarct at the age of 44 ->one hour later, right-sided throbbing headache began	-Hypodense area in the right occipital region(due to a migrainous stroke) -Hemorrhagic infarct in the right cerebral hemisphere - Destruction of Broadmann areas 18,19 -the depth of the inferior temporal and superior temporal sulcus was affected	-Left homonymous hemianopia -Prosopagnosia -Simultagnosia ->all due to the myocardial infarct (hemianopia dissapeared after two days, the other two receeded after one week)
Woman, age 60, right-handed (Cohen, L. 1994)		-Surgery for a deviated nasal septum->4 days after the surgery she presented with progressively increasing visual disorders->the condition worsened until the second day-> confusion, disorientation receded rapidly -> two years after, the patient only complained of minor sequelae	-bilateral occipitoparietal hypodense areas-> suggestive of bilateral brain infarction -left hemispheric lesion affecting the lower part of Broadmann areas 18 and 19 and the underlying white matter -small spot of high signal intensity in the white matter posterior to the lateral ventricle	-Anterograde amnesia -Unilateral Optic Ataxia -Ideomotor Apraxia -Simultganosia (present one week after post-surgery)
Patient P.S., Woman, age 71, right-handed (Frassinetti F., 1999)		-Hypertension+an ischaemic stroke in the left parieto-occipital region (sustained 3 years earlier) -A second stroke was diagnosed	lesions involved -> Brodmann areas 5, 6, 18, 19, 39 and 40 ->the lower part of the lateral aspects of the right occipital lobe -> right temporoparietal conjuction and the occipital white matter ->the prestriate cortex	-Right homonymous hemianopia (due to the ischemic stroke, later on it has dissapeared)
Male, age 35, right-handed (Kassubek, J., 1999)	-cranial computed tomography (CT) -two MRI -EEG -MR and cerebral catheter angiographies -FMRI -BOLD	suffered from severe occipital headache (dissapeared within a few days)-> six weeks later a conventional MRI investigation was conducted followed by the diagnosis of cavernous angioma	Hyper dense lesion in his right occipital lobe (suggestive of a hemangioma or cavernoma) The hemorrhage surrounding the cavernoma was accentuated at its superior and posterior parts, reaching well into the gray matter The cavernoma is located in the lateral part of Brodmann's area (BA) 19 of the right occipital lobe, bordering BA 37	episodes of dysmetropsia in the left hemifield (after the second headache)

Table 2- Hemimicropsia Patients

Short Description of the Patient	**Brain Scans**	**Medical History and Evolution**	**Aetiology of Brain Damage**	**Commorbidities**
Patient FV, Woman, aged 63, right-handed (Di Marco, J. 2019)		-arterial hypertension -thrombocythemia -right fronto-temporo-parietal hematoma	-right temporo-parietal white matter and overall white matter damage -Broadmann areas 17, 18, 19, 20, 21, 22, 37, 39, 40, 41, 42 -the ventral visual stream and a relative preservation of posterior callosal connections -disconnection between visual coordinates and attentional networks to the frontal lobe -The temporo-parietal junction + dorsolateral prefrontal cortex	-left hemiparesis, homonymous hemianopia, spatial neglect (their onset was due to the right fronto-temporo-parietal hematoma)
Patient 1, Man, aged 61, right-handed (Rode, G. 2007)	Computer Tomography (CT)->conducted 18 months after the onset of the stroke Cerebral Angiography	- hypertension -sudden onset of a left-sided weakness (onset of a stroke)->A neurologic examination showed a left hemiplegia	-extensive single lesion in the vascular territory of the right middle cerebral artery -lesion affecting: the temporoparietal region, the internal capsule, the head of the caudate nucleus, the putamen, the insula, the corona radiata (in the anterior part)-> discovered thanks to the CT Scan -complete obstruction of the right middle cerebral artery, right before its division into branches -> Cerebral Angiography	-left hemianesthesia, spatial neglect, spastic hemiparesis, severe left somatosensory deficit (three months after stroke onset)
Patient 2, Woman, aged 45, right-handed (Rode, G. 2007)	Magnetic resonance Imaging (MRI)-performed three months post stroke onset	sudden onset of a left-sided motor weakness-> onset of a stroke	Deep lesion involving: the head of the caudate nucleus, the putamen, the insula, the internal capsule, the frontoparietal paraventricular white matter-> found through the use of MRI	-moderate dysarthria -mild facial paresis -left hemiplegia (due to the stroke onset)
Man, aged 73, right-handed (Rode, G. 2008)	Magnetic Resonance Imaging (MRI)-performed six months post stroke onset	-admitted to a neurological unit for the sudden onset of left-sided weakness and confusion (onset of a stroke) - Four months after stroke onset, the patient showed no left-sided motor or somatosensory deficits, including tactile and proprioceptive sensation	Lesions involving-> the temporoparietal junction the superior and the middle temporal gyrus the inferior parietal lobule the occipital white matter the tail of the caudate nucleus the extra-striate visual cortex (all discovered through the use of MRI)	-left homonymous hemianopia and spatial neglect (caused by a temporoparietal hematoma which led to the occurence of the stroke)

Table 3- Hyperschematia Patients

Short description of the patient	***Brain Scans***	***Medical History and Evolution***	***Aetiology of Brain Damage***	***Commorbidites***
Woman, aged 60, right-handed (Ebata, S. 1991)	-CT -MRI -EEG -Cerebral Angiography -Proton Density Imaging	-hypertension (which has been kept under control for 30 years) -right putaminal hemorrhage (11 years before)	-small high density area in the right posterior part of the cingulate gyrus just behind the splenium -partial involvement of the corpus callosum -small low-density area in each putamen (right one most likely represents the putaminal hemorrhage) -high signal area in the right retrosplenial region extending into the part of the adjacent splenium itself (found through the use of proton density imaging)	-Prosopagnosia -Micropsia
Man, aged 63, right-handed (Shiga, K. 1996)	-Cranial Compute Tomography (CT) -VEP	-history of hypertension -acute right hemisphere hemiparesis, which led to his admission -on the third day, right homonymous hemianopia dissapeared -after one month of admission he was able to walk without assistance and was discharged from the hospital -left putaminal hemorrhage, without involvement of the parietal and occipital lobes (found through the CT scan)	-lesion in the left visual pathway posterior to the optic chiasm-> the lesion being accurately found in the left optic radiation	-Right homonymous hemianopia (resulted after a visual field examination -right inferior facial palsy -right hemiparesis without sensory involvment
Man, aged 56, right-handed (Miwa, H. 2007)	-Computer Tomography (CT) -Electroencelography (EEG) -Magnetic Resonance Imaging (MRI) -SPECT using ECD	-developed a generalized convulsion and high fever (dissapeared during transfer) while working and was admitted -a few days before he had a headache and general fatigue -showed a mild confusional state, probably postictal -stereotaxic absorption surgery was performed to drain the brain abscess -after the surgery, the patient recovered well with the use of antibiotics, while not having any sequels afterwards -seven months after being discharged, he developed generalized convulsions	-low density area occupying the right temporal lobe and a mass lesion surrounded by edema (found through CT)	-symptomatic epilepsy (diagnostic put thanks to the discovery of delta waves in the right temporal region following a EEG scan), kept in check throught the use of antiepileptic medication. No high spot suggestive of epilepsy focus through the use of SPECT ECD scan

Table 4-Metamorphopsia patients

3.3. Symptoms reported by the patients before admission

In this section, I will highlight the symptoms experienced by each patient presented in the previous tables, before admission, specifically, those that have been reported by them as occurring in their day to day activities, some of them describing such impairments as rather difficult to live with, while others stated that they have not posed too many problems. As for the later sections, I will follow up on the symptoms that have subsequently risen through their implication in neuropsychological tasks, carried post admission into the medical units.

3.3.1. Hemimicropsia

According to the paper by Cohen et al. (1994), the first patient out of the double case report is the man aged 50, right-handed who exhibited hemimicropsia in the left hemifield. He reported having problems with objects that he saw in his left visual field, due to the fact that they appeared somewhat shrunk and compressed, resulting so into an immense struggle to perceive the depth, proportion and symmetry of objects, as well as pictures.

Moving on to the latter patient presented in this study, the woman aged 60, right-handed, she has exhibited hemimicropsia in the right hemifield, and had ongoing problems when spontaneously reporting that people's left eye was significantly smaller than the right one. Moreover, the right half of symmetrical objects, such as faces and pairs of hands, were consistently smaller than their left half. More so, she was not able to present her visual perception impediments graphically.

Turning to the patient presented by Frassinetti, Nichelli and di Pellegrino (1999), patient P.S., was a woman aged 71, right-handed, who showed a sustained hemimicropsia in the left hemifield, especially apparent when she noticed that everything on the left appeared smaller in size, shrunk and distorted, as if she "was looking at the reflections from a broken mirror". Furthermore, P.S. perceived objects projected on her left hemifield as smaller along their horizontal axis. Despite her deficits, she was aware of her visual problems and was able to report them. More interestingly, during her dream state, she did not perceive the objects imagined as being abnormal in size, symptom which is worth highlighting since it has not been found to occur in any of the other presented individuals.

Finally, Kassubek et al. (1999) paper describes a male patient, aged 35, right-handed, that has experienced hemimicropsia in the left hemifield, and as a result, he saw objects on his left smaller, shrunk and compressed and apparently farther away, though not altered in shape. At times, he had difficulties perceiving proportions, symmetry, and depth, thus explaining so why in one occurrence, he collided into the left side of the garage when he was parking his car. Surprisingly, objects extending into both hemifields appeared to be spatially disparate, reporting so that the left half was considerably farther.

3.3.2. Hyperschematia

I will describe the patients from the papers presented by Rode et al. (2007), (2008) and Di Marco et al. (2019) in the following sections, since their relevant symptoms have risen following post-submission, and more notably, in the course of their performance in the neuropsychological tasks.

3.3.3. Metamorphopsia

The patient presented by Ebata et al.(1991) who was aged 60, right-handed, has exhibited unilateral metamorphopsia of the face with features of micropsia, as such, the only alarming symptom that she has experienced until admission was that when she looked into a mirror, she realized that the left half of her face looked smaller than the right. Although the above stated symptom relates more to micropsia, it is known that in specific types of metamorphopsia, the individual can experience micropsia or macropsia (Stephen, J., 2013), proving to be so a necessary aspect worth of pointing out. Since the other symptoms of the patient have been found through the use of neuropsychological tasks, they will be further explained in the following sections. Both the patient from Shiga et al. (1996) and the patient from Miwa and Kondo (2007) will also have their symptoms presented in the neuropsychological tasks section.

3.4. Neuropsychological tasks that have been administered

In this section I will present in detail how the tasks that have been conducted for each of the patients work, in order to better understand their scope and implications.

3.4.1. Draw by copy

In this task, patients were asked to draw a copy of the symmetric images that were presented to them one by one (Cohen et al., 1994). This type of task was conducted on patient 1 (Man, aged 50, right-handed) by Cohen et al. (1994), the patient describe by Ebata et al. (1991), the patient shown by Di Marco (2019), patient 1 and 2 from Rode et al. (2007), the patient presented by Rode et al. (2008) and the two metamorphopsia patients presented by Shiga et al. (1996), and, Miwa and Kondo (2007).

3.4.2. Drawing from memory

No model is provided. The patient is required to draw what the practitioner is asking, with the only reference that the patient has depends on their mental representation of the item asked. This type of task has been used in the Di Marco et al. (2019) study, also for both patients in the Rode et al. (2007) paper, and on the patient from the Rode et al. (2008).

3.4.3. Quantified Size Comparison Task

A pair of horizontally aligned circles are presented on a computer screen, and the patient has to decide which circle is larger, with the larger circle being on the left for half of the trials, and on the right in the other half, the target circles were preceded so by a central fixation cross. As such, the patient was asked to press a key with their left hand if the circle on the left was larger, and to press another key with their right hand if the circle on the right was larger. The patient was also informed of the mismatch in size of the circles and that it was important to answer accurately and swiftly. This task had been used only on Patient 2 from Cohen et al. (1994) paper.

3.4.4. Perceptual Matching Task

Di Marco et al. (2019) and Rode et al. (2007), (2008) have used this task in order to assess the patient’s ability to judge the lateral extent of two rectangles. Twenty-five pairs of rectangles were presented in a pseudorandom series, in order to measure so the point of subjective equality between patterns placed in the left and in the right visual half-spaces. The subject’s task on each trial was to report verbally which was the longer out of the two rectangles. In terms of scoring, rightward errors were given a positive score, leftward errors were given a negative score.

3.4.5. Line Extension Task

Di Marco et al. (2019) and Rode et al. (2007, 2008) have implemented this task on their studies. The patient was asked to reproduce the length of the horizontal black line in two conditions. In the leftward movement condition, the line was placed in the right-hand side of the sheet, with its left end being aligned with the midsagittal plane of the body of the participant, who has received instructions to reproduce the perceived length of the segment with a leftward extension. In the rightward movement condition, the line was placed in the left-hand side of the sheet, with its right end being aligned with the midsagittal plane of the body of the participant, who was then asked to reproduce the perceived length of the segment with a rightward extension. The stimuli were horizontal black lines with three line lengths (4, 6, 8 cm). For the extension of each drawn line, a Laterality Index score (LI) was computed, thus, a positive value of the LI indicated overextension, while a negative score indicated under extension.

3.4.6. Prism adaptation procedure

The patient is exposed to a leftward optical deviation produced by prismatic lenses. The exposure period consisted so of 50 pointing responses to visual targets, which were alternatively presented 10% to the right or to the left of the objective body midline. During the prism exposure, the patient is asked to point at a fast but comfortable speed, allowing himself thus to see the target, the second half of their pointing trajectory and their terminal error, all while the practitioner records the terminal errors of each movement through the use of a thimble and further converts it into degrees of angular error. It is also worth noting that, the patient's head was kept aligned with the body's sagittal axis by a chin-rest and controlled only by the practitioner, the total duration of the exposure being about 3 minutes long. This task has only been used in the paper presented by Di Marco et al. (2019).

3.4.7. Open Loop Pointing Task

The after-effects of Prism adaptation were evaluated by means of open loop pointing (OLP) in the direction of a visual target. OLP accuracy measurement was carried out by asking the patient to point with their right hand in darkness to a target, a luminous visual target was aligned with the patient's sagittal axis. The instructions given to the patient was to place his right hand at the target drip-line, as precisely as possible but without time constraint, the goal being to distance themselves from the pointing conditions employed during exposure, with the aim of obtaining measurements of sensory-motor after-effects. This task can be found altogether with the Prism adaptation one in the Di Marco et al. (2019) paper.

3.4.8. Experiments conducted in the paper by Frasinetti et al. (1999)
Out of the eight experiments conducted, four of them have proved to be the most interesting ones in terms of the results produced, and as such, I will describe them further, in order to facilitate the understanding of their purpose and use.

Experiment 1 had the aim of quantifying Patient P.S.'s size perception of objects placed along the horizontal and vertical meridians. For each trial, a pair of empty circles was presented on the computer screen, with one circle larger than the other. The patient was free to move her gaze. Thus, ten pairs were aligned horizontally and ten were aligned vertically. As such, P.S. was required to enlarge the smaller circle by pressing the spacebar of the keyboard until the sizes of the two circles were identical (Frasinetti et al., 1999).

Experiment 5 was conducted with the purpose of investigating separately size distortion and size discrimination accuracy, followed by the comparison of the vertical and horizontal components of size distortion. Furthermore, three tasks were devised: horizontal line discrimination, vertical line discrimination and circle discrimination (Frasinetti et al., 1999).

Experiment 6 was meant to study the influence of the spatial location of stimuli upon P.S.'s size distortion. Each trial began with a fixation cross presented at the center of the display. When the subject was ready, the experimenter triggered the stimulus presentation. The stimuli were pairs of horizontally aligned circles presented for 250 ms, the midpoint of the distance between them was presented either at the center of the computer screen or 5 cm to the right or left of the center. A total of 324 pairs of circles were presented in a balanced random order at different spatial positions. Subject was informed that the two stimuli were never identical, as such, P.S. was asked to indicate the larger item out of each pair (Frasinetti et al., 1999).

Experiment 7 began with the presentation of one stimulus at a time, either to the left or to the right of fixation. P.S. was asked to examine a horizontal line in central vision without time limitation. When satisfied with her inspection, she pressed the space bar of the keyboard and a line for comparison was presented on the other side of fixation. There was no time constraint for examining the second line. The patient's task was to compare the length of the second stimulus with that of the previous one. Although the two lines were presented in different halves of space, as defined by head- or trunk-centered coordinates, they were projected to the same part of the retina. It was expect that, if P.S.'s hemimicropsia operated in retinal coordinates, then no deficit would be expected in this condition (Frasinetti et al. 1999).

3.4.9. Line bisection task

The following task was used and described by Rode et al. (2007). The stimuli included 18 lines, organized in 3 sets of 6 lines, so that one set would lay primarily on the left side of the page, one in the center, and one on the right side, each set containing so lines of 100, 120, 140, 160, 180, and 200 mm. The lines were organized so that the task was balanced with regard to the line length from top to bottom. Furthermore, two 150-mm lines, placed at the top and bottom (center), were used in communicating the instructions to the subject and were not included in data analysis. Subjects received instructions to mark the center of each line with a soft pen, without skipping any.

3.4.10. Epidiascope procedure

Decouples the direction of the hand movement from the subject's visual control of the display. As such, patients with a perceptual disorder would show a left-sided deficit with reference to their field of vision, independent of the direction of the movement of the arm and hand, while patients with a premotor disorder, would exhibit a left-sided deficit, with reference to the midsagittal plane of the body, independent of the normal or mirror-reversed field of vision. The patient that has gone through this type of task can be found in the Rode et al. (2007) paper.

3.4.11. Flickering checkboard

A random checkerboard display (50% dark checks, 50% light checks) that dynamically flickered (dark check changed to light and vice versa) was presented. The patient was instructed to view a central fixation point during stimulus presentation, in order to minimize eye movement. Kassubek et al. (1999) has implemented this task on his hemimicropsic patient.

3.4.12. Random dot motion

Sequences of random dots were presented in the expansion-contraction direction, randomly interspersed among the dots with the coherent direction, were dots with a random direction. Each dot remained on the screen for no longer than 3 s, at which time it disappeared and was replaced elsewhere by a new dot. Periods of stimulation were followed by periods of rest, during which the subject viewed a homogenous screen of the same luminance. Subjects were instructed to fixate a clearly visible central stationary spot, in order to suppress so the undesired eye movements during both rest and stimulation. The former (checkerboard) stimulus was used to activate primarily the striate and extrastriate cortex, while the latter (dot motion) stimulus was used to activate in addition, the V5 region (visual motion area). This task couples together with the flickering checkboard one in the Kassubek et al. (1999) study.

3.5. Results to the task administered

In this part, I will present the results to the above-described tasks, and, in order to classify the results promptly, I will devise them according to the disorders for which they have been used.

3.5.1. Hemimicropsia

For Patient 1 from Cohen et al. (1994), only the draw by copy task was used, his results have been then compared to those of the controls. As such, when presented with truly symmetrical drawings, he perceived that the left half is consistently larger than the right half of the drawings. In turn, when he was asked to correct the drawings to look symmetrical, he either expanded the left part of the pattern, or reduced its right part. Moreover, there was no mention of any anomaly of color or movement perception in his trials.

For Patient 2 from Cohen et al. (1994), the quantified size comparison task was used. As a result, compared to the controls, when the right circle was slightly larger than the left circle, the patient perceived the two circles as identical, and randomly chose the left or the right key. Conversely, when the circles were identical, the patient showed no bias towards responding that the right one was smaller. Pairs of identical circles, as well as pairs with the right circle larger by 5%, would then be perceived by the patient as slightly asymmetrical.

Moving to Patient P.S. presented by Frasinetti et al. (1999), Experiment 1 has shown that compared to the control subjects, P.S. enlarged the left side one more, and the right side one less. Also, when circles were vertically aligned, P.S. performed almost as accurately as normal subject.

In Experiment 5, the point of subjective equality was classified as ‘left larger’ on 50% of the trials, while the just noticeable difference (JND), and was classified as ‘left larger’ on 75% of trials. Data has shown that the size discrimination accuracy of P.S. was the worst with horizontal and vertical lines, and much better with circles. Thus, the systematic bias in indicating the right stimulus larger than the left one, was much more evident with horizontal lines than with vertical lines (Frasinetti et al. 1999).

In Experiment 6, P.S. was as accurate as normal subjects in discriminating size at the center of the visual field, and that he appeared as being equally impaired in both hemifields. P.S. also had a systematic bias towards judging the left circle as smaller than the right one, more prominent especially when both stimuli appeared in the left visual field, and when the midline of their distance was presented at the center of the visual field. Moreover, when both stimuli were presented in the right visual field, there was no dysmetropsia, as such, dysmetropsia only occurred when either one or both stimuli in the comparison task fell into the left visual field (Frasinetti et al.1999).

Finally, Experiment 7 has highlighted the fact that, when the patient inspected each stimulus in central vision, there was no bias in reporting that the right stimulus was larger than the left. More noticeably, the size discrimination accuracy of the patient was much better when she was free to move her gaze. Moreover, P.S.’s left-sided hemimicropsia operated in retinal rather than body-centered coordinates (Frasinetti et al. 1999).

Turning to the last patient of this sub-section, the patient presented by Kassubek et al. (1999), the flickering checkboard and random dot motion showed that a strong response is evident in the primary visual cortices. The most lateral extensions of the activations corresponding to BA 1. Furthermore, in the random dot motion, BOLD effects were observed in a more lateral and anterior location, corresponding to the V5 area, in both hemispheres. Interestingly, this phenomenon did not occur in the flickering checkboard task when comparing the activation levels in both hemispheres. Rather, there was less activation on the side of the cavernoma. In a comparison across the left and right hemisphere, relative activation was lower in the right hemisphere (with the cavernoma) in both the flickering checkerboard condition (79%) and the coherently moving dots condition (76%), as compared to the left hemisphere (100%).

3.5.2. Hyperschematia

For patient FV studied by Di Marco et al. (2019), in the open loop pointing task, significant sensory-motor after-effect, directed towards the right side, was induced by Prism Adaptation.

For the drawing from memory task, which consisted in the drawing of a daisy, data showed a significant difference for both the laterality index and the number of petals in the first pre-test only. In the post-test, the mean laterality index was significantly reduced, showing a regression of left hyperschematia after prism adaptation, with a significant lowest number of left petals added. In comparison with the control data, and with the patient's performance immediately after prism adaptation (post-test), it was revealed that there was a significant difference for laterality index. This statistical difference was mostly due to a greater right-sided area and a greater number of petals in the right side of the drawings, leading to a reduction of left hyperschematia after prism adaptation (Di Marco et al., 2019).

For the drawing by copy task, the same results can be observed here as in the drawing from memory task, meaning that the patient exhibited a larger left-side drawn area, as well as a regression of left hyperschematia after prism adaptation, with a significantly lower number of left petals compared with those of the controls. As for the drawing from memory task, four days after prismatic adaptation, the patient copied a daisy with a significantly larger right-sided area, compared with controls, but with similar numbers of petals on the right side, suggestive so of an ongoing reduction of the left hyperschematia after prism adaptation, similar to that of the drawing from memory task. In the perceptual matching task, there were no significant differences observed between the patient performance and those of the controls (Di Marco et al., 2019).

Lastly, for the line extension task, the patient showed a leftward overextension for the three lines. While there was a significant increase of the mean rightward extension laterality index for the three lines lengths, there was no significant difference of the mean leftward extension laterality index for them. Finally, results showed that prism adaptation brought about a rightward overextension for the three lines, associated to a reduction of the leftward overextension for the longest line (Di Marco et al., 2019).

Turning to the patients presented by Rode et al. (2007), in the line bisection task, the mild rightward bias shown by Patient 1 is consistent with the clinical evidence of a left spatial neglect in the early stages of his disease.

For the drawing from memory task, the patients were asked to draw a daisy, with the same requirement being used in the Di Marco et al. (2019) study. A positive laterality index was observed for both patients, well outside the range of control subjects, indicating so that they have drawn the left-hand side of the daisy larger than the right-hand side. All daisy drawings done by Patient 1 had a positive laterality index score. Moreover, both patients drew more petals on the left side. Lastly, the number of petals drawn by Patient 1 were outside the controls' range (Rode et al., 2007).

In the epidiascope condition, both patients drew a larger left-hand side of the daisy, with reference to their field of vision and the direction of their hand movement being preferentially oriented towards the right side (Rode et al., 2007).

In the drawing by copy task, Patient 2 was not available for the task. For Patient 1 who drew a daisy, the laterality index and number of petals scores were outside the controls' range, a larger left-hand side of the model and more left-hand petals being noticed in his trials. In the perceptual matching task, both patients' scores were outside the controls' range, suggesting a relative perceptual underestimation of the lateral extent of the left-sided rectangle, compared to that of the right-sided rectangle. Finally, for the line extension task, both patients showed a leftward overextension, further noticing that patient 1 had a preserved performance in the rightward extension condition. The patients' performances in the adjacent tasks were compared with the control data, differences thus being found for both patients for leftward extension, but not for rightward extension (Rode, et al. 2007).

Following on, in the Rode et al. (2008) study, the perceptual matching task was utilized. As a result of the task, the patient has underestimated perceptually the lateral extent of left-sided rectangles, compared with the right-sided rectangles. Turning to the drawing from memory task, compared to the controls, the patient's daisies were larger on the left-hand side, and with more petals. Using also the drawing by copy task, the laterality index, the weight laterality index, and the number of petals have been measured for both the patient and the controls. As such, the positive scores obtained indicated that the modeled daisies were larger and heavier on the left-hand side, unlike those made by the controls. Finally, for the line extension task, the patient showed a major leftward overextension, with all line lengths, and a less pronounced rightward overextension, as in comparison to controls. More specifically, he showed differences for all leftward vs. rightward 6-cm and 8-cm extensions (Rode et al., 2008).

3.5.3. Metamorphopsia

For all of the patients presented in this section, only the drawing by copy task was used.

For the patient presented by Ebata et al. (1991), prior to the drawing by copy task, she was acutely aware that the right half of the examiner’s face looked smaller than that of the left. In regards to her performance on the task, her drawings of the face showed some distortions, more specifically, those distortions where exhibited in the distance between the right eye and the center of the face, which were far wider, accompanied with the fact that the right half of the face was noticeably smaller.

Moving on to the patient presented by Shiga et al. (1996), right before the conduction of the task, he described that „the right half of the curtain in front of me suddenly transforms into an animal’s face. It rotates there for a while and finally flows to the right, and then disappears. At the next moment, another face springs up at the very portion and...” .Turning to the two models used for the drawing by copy task, the doctor’s face and hands, as well as a curtain, it was noticed thereafter when analyzing the drawing of the doctor’s face and hands that his left cheek was scraped ,and some of his fingers from his left hand were missing, while for the curtain drawing: “a fold of the lace seemed to have been transformed into an animal’s face and it seemed to flow to the right...”.

Lastly, the patient from Miwa and Kondo (2007) showed that when he observed a person’s face, the lower half of it appeared swollen. This type of symptom was exhibited in his drawings as well, and thus correlates with a type of metamorphopsia restricted only to the right side of the faces of the people in front of him, which was also exhibited only when he saw round faces. Interestingly, the above stated difficulties were not present when he came across objects, nor thin faces.

4. Discussion

In this part I would like to highlight some curious aspects that were noted in the papers, according to their findings, but more so to possible aspects which can be further looked into in future studies.

4.1. Hemimicropsia

Starting with the papers about hemimicropsia, specifically with Cohen et al. (1994), he noted in his findings that hemimicropsia should result from lesions affecting the posterior part of the ventral pathway, aspect which can strengthen the etiological portrait of the disorder, as well as, simplify the diagnosis of future cases similar to the ones specified by him.

Moving to the study done by Frasinetti et al. (1999), she noted that for patient P.S.'s occipital lesion, it involved anatomical areas which resembled those damaged in the cases of hemimicropsia reported by Cohen et al. (1994). Noting this similarity, we can understand a pattern of evolution in acquiring this deficit. Besides the experiments that were conducted in this study, it was also emphasized that it might be useful to also test the size comparisons of two vertically separated circles presented in a single hemifield.

Finally, on the paper written by Kassubek et al. (1999), it was stated that visuospatial processing appears to involve in large the "dorsal stream", which continues into the parietal cortex, with the areas of motion processing residing at the junction of the ventral and dorsal stream, thus providing a useful view as to how visuospatial processing functions. Moreover, he suggests that a region neighboring V5 must be involved in size consistency. As such, further exploration of this idea could prove to be beneficial in assessing the importance of this region.

4.2. Hyperschematia

Moving to the papers which had their topic based upon hyperschematia, Di Marco et al. (2019) noted that left hyperschematia has exhibited left visuo-spatial neglect in the acute and subacute post-stroke phase, as such, it could prove to be interesting for future studies to see if these results could be replicated as well to right hyperschematic patients. More importantly, for future studies, the author suggested that those who may want to use the perceptual matching task used here, could further implement it in studies that explore the effects of prism adaptation in neurologically unimpaired participants.

On the double case study carried out by Rode et al. (2007), both patients reported that they were entirely unaware of their deficit in drawing, similar to the patients suffering of unilateral spatial neglect. It would be interesting to see whether this phenomenon happens casually, and if it is restricted only to drawing tasks. More so, for those same two patients, the deficit experienced, which was termed contralateral hyperschematia for extrapersonal space, was associated with damage to the right hemisphere, thus identifying the importance of this brain region of concern for possible future cases that will tackle this disorder.

Following this study, another hyperschematic patient was presented by Rode et al. (2008). It was noted that hyperschematia's nature is primarily perceptual, so as to better understand the area of impairment. Moreover, he stated that hyperschematia is not a core component of the neglect syndrome, even in tasks that require a computation of the metric of horizontal objects, such as the line bisection task. Finally, it is thought that hyperschematic patients do not add gratuitous and unrelated details in cancellation tasks.

4.3. Metamorphopsia

Lastly, focusing on metamorphopsia, and on the paper written by Ebata et al. (1991) specifically, who highlighted the fact that unilateral metamorphopsia of the face, experienced by their patient, is a distinct neurological symptom different from generalized metamorphopsia or partial prosopagnosia. It was also noted that the responsible site for it might be in the contralateral retrosplenial region.

With another case of a patient suffering from metamorphopsia, Shiga et al. (1996) found in their analysis that their patient had a lesion occurring in the left optic radiation. According to the authors, this was the first report that such a lesion could elicit metamorphopsia. They further added that, through their analysis, many reports attribute the cause of metamorphopsia to lesions in the occipitoparietal cortex, as well as chiasmatic and retrosplenial cortex. Through this, they proposed that any lesion along the visual pathway, from the retina to the occipitoparietal cortex specifically, could elicit metamorphopsia, since this study showcased the first case of a metamorphopsic patient resulting through left optic radiation. Thus, it would be interesting for future studies to explore this topic more in depth.

Finally, the article by Miwa and Kondo (2007) noted that the actual mechanism underlying metamorphopsia in the face, in their patient, was quite unclear, since it was described that his metamorphopsia occurred in the lower half of the face and did not occur with thin faces, suggesting that his pathophysiological mechanism was significantly different compared to other case reports highlighted in the study at hand. More so, it was speculated that maybe a dysfunction of the symmetry-based process in face perception could be the cause, proving that this topic could be of interest for further searching, since the literature at the time was scarce and, to the best of our knowledge, no other similar case has been described.

Moreover, as it has been seen through the patients discussed, as well as the general explanation of it, hyperschematia has not been observed in pure perception, thus it would be interesting for future studies to delve more into this idea.

Conclusion

The studies presented in this thesis work offer a wide array of analyses on the deficits of interest, which have been developed so by a subsequent neurological accident. Moreover, it is worth considering that further research is needed on all three topics, as suggested in the discussion section, with particular emphasis on the possibility to observe hyperschematia in pure perception, since such cases have not been published in the literature so far. Overall, each work reported here managed to highlight distinct aspects which should be further tackled, with the scope of creating a more diverse literature for each of these three deficits.

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