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Domain-specific functional organization: neurocognitive characterization of a case of hemi-prosopometamorphopsia.

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Dissertação de Mestrado em Psicologia, área de especialização em Psicologia Clínica e da Saúde, subárea de especialização em Psicogerontologia Clínica, sob a orientação do Professor Doutor Jorge Almeida[1] e co-orientação da Professora Doutora Isabel Santana[2]

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Organização funcional por domínios específicos: caracterização neurocognitiva de um caso de hemi-prosopometamorfopsia.

Introdução: A forma como o cérebro está organizado para processar de forma eficiente informação relativa a objetos que tenham tido um papel fundamental para a nossa sobrevivência, tem sido uma questão central na investigação em ciência cognitiva. A existência de uma rede neuronal especializada no processamento de faces surge como exemplo desta organização cerebral por domínios específicos. Contudo, a forma como esta rede está organizada e o modo como as suas regiões cerebrais comunicam entre si não é ainda clara.

Objectivos: Fornecer evidências mais claras acerca da organização funcional do circuito de processamento de faces. Especificamente, estabelecer padrões de conectividade funcional entre as áreas principais do circuito e perceber como circula a informação entre elas.

Iremos estudar um paciente com hemi-prosopometamorfopsia - o Paciente AD. A hemi-prosopometamorfopsia é um défice na percepção visual raro, onde os pacientes reportam ver metade das faces distorcida. Estudar um caso de um paciente,com uma lesão no esplénio do corpo caloso e com este sintoma associado, poderá ser útil numa melhor caracterização da organização funcional do circuito de processamento de faces.

Métodos: O presente estudo foi dividido em três experiências. A primeira, um estudo volumétrico do hipocampo, que pretende estudar a integridade neuronal e cognitiva do Paciente AD e de um sujeito controlo, como uma forma de avaliar o envelhecimento neuronal. A segunda, uma experiência comportamental, que procura caracterizar a especificidade do défice perceptivo. A terceira, um estudo de fMRI, que pretende analisar os padrões de conectividade funcional entre as áreas do circuito de faces.

Conclusões: Os dados desta tese apontam para a importância das ligações entras as diferentes áreas da rede específica para o processamento de faces. Especificamente, o deficit do Paciente AD parece estar associado a uma disrupção na conectividade da área occipital de faces (OFA)esquerda com as outras áreas do circuito de processamento de faces. Estes resultados poderão fornecer informação acerca do papel desta área no processamento de partes da face. Para além disso, poderão ser úteis na compreensão do papel do esplénio do corpo caloso na conectividade das áreas de processamento de faces.

Palavras-chave: Processamento de faces; Conectividade funcional; Área occipital de faces (OFA); Hemi-prosopometamorfopsia.

Domain-specific functional organization: neurocognitive characterization of a case of hemi-prosopometamorphopsia.

Introduction: The way the brain is organized in order to more efficiently process categories that are important to our survival has been a central question in cognitive research. The existence of a neuronal network specialized on faces processing is an example of this domain-specific organization in the brain. However, the way this network is organized and how its regions are functional connected is not completely clear.

Objectives: To provide clearer evidence on the functional organization of face processing network. Particularly, to stablish patterns of functional connectivity between its core areas and to understand how the information flows between them.

To do this, we will study a patient with hemi-prosopometamorphopsia - Patient AD. Hemi-prosopometamorphopsia is a rare deficit in visual perception where the patients report to see half part of the faces distorted. Studying a case of a patientwith a lesion in the splenium of corpus callosum and with this symptom associated can help us to better characterize the functional organization of the face processing network.

Methods: This study was divided in three experiments. The first one, a volumetric study of the hippocampus, will study the neuronal and cognitive integrity of Patient AD and a control subject as a way of assessing the neural aging. The second one, a behavioral experiment, will characterize the specificity of the deficit. The third, a fMRI study, will analyze the functional connectivity of the face-selective areas.

Conclusions: The results of this thesis show that the connectivity between the different nodes of the face network are important for normal face perception. Specifically, Patient AD's deficit may be associated with a disruption in the connection of the left occipital face area (OFA) with the other areas of the face processing network. These results inform us about the role of the OFA on processing face parts. It can also shed a light on the role of the splenium of the corpus callosum in connecting face-selective areas.

Key Words: Face processing; Functional Connectivity; Occipital Face Area (OFA); Hemi-prosopometamorphopsia.

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Content

Introduction

The ability to recognize faces in a fraction of a second is central for adequate social interactions and has played an important role in our evolution and survival. The existence of a specialized neural network dedicated to face perception has been a question of great interest in cognitive research. However, it is not clear how the areas of this circuit are functionally connected, and how this connectivity affects our ability to process faces.

In this work we aim to study the functional organization of the face processing network by understanding how face-selective brain regions are connected with each other. We will study a patient – Patient AD – with a lesion in the splenium of corpus callosum and with an associated deficit in face perception. We want to understand how the information flows between the core areas in the face network.

Using behavioral and fMRI data we will try to characterize the deficit and understand at what level of face processing model the deficit occurs.

In the first section, **"Background"**, we will introduce some theoretical issues on the organization of object knowledge in the brain and on face processing. Then, after clarifying the purpose of this study, we will present a section **"Experiments"** where we will present more detailed characterization of the patient followed by the *procedure*, *results* and *discussion* of the three experiments that integrate this study. In the **"General Discussion"** section we will examine the results and confront them with the literature. And finally, we will conclude and present the major contributions of this study to the scientific field and address some future studies and perspectives.

I – Background

How is conceptual knowledge organized in the human brain?

One of the central issues in the cognitive neurosciences is to understand how conceptual knowledge about the world is organized in the human brain. Over the years many authors dedicated their work to studying the organization of information in semantic memory in the brain by testing brain-damaged patients with category-specific impairments (e.g. Hillis & Caramazza, 1991; Humphreys & Riddoch, 1987; Tyler et al., 2011; Warrington & McCarthy, 1983; Warrington, & Shallice, 1984). These patients present a selective impairment on tasks focusing on knowledge about one category of objects, whereas performance in tasks focusing on knowledge about other semantic categories remains intact (e.g., Capitani, Laiacona, Mahon, & Caramazza, 2003; Caramazza & Mahon, 2003). The fact that brain-damaged patients can show deficits that are specific to particular categories or domains suggests that different types of knowledge are represented in different brain areas independently (Shelton & Caramazza, 2001). The importance of these deficits

in our understanding of the neural organization of knowledge was initially stated by Warrington and colleagues (Warrington, 1981; Warrington & MacCarthy, 1983; Warrington & Shallice, 1984) with their reports on cases showing disproportionate impairment of the category of living things versus the category of non-living things. Since then, several studies have used this kind of evidence to provide empirical basis for theories on the organization of the conceptual knowledge in the brain.

We can distinguish between two types of theoretical approaches to the organization of the conceptual knowledge in the brain according to their underlying principle of organization: theories based on the correlated structure principle, which assumes that the organization of conceptual knowledge reflects the way objects properties are statistically related in the world; and theories based on the neural structure principle, stating that knowledge is organized according to representational constraints imposed by the brain (Capitani et al., 2003).

One example of the correlated structure approach is the Organized Unitary Content Hypothesis (OUCH; Caramazza, Hillis, Rapp, & Romani, 1990). This theory claims that conceptual knowledge is not organized by a semantic principle but by the degree that properties of the objects tend to co-occur in the world. According to this theory, categories that are compact enough in their conceptual space can be selectively damaged/spared and this selective damage will affect all types of knowledge of that category (Capitani et al. 2003).

Of the theories based on the neural structure principle, the one that has received more attention is the Sensory/Functional Theory (SFT). According to this theory, conceptual knowledge is organized into modality-specific components: the sensory/visual subsystem, responsible for the processing of visual characteristics of the objects, and the functional/associative subsystem, that stores information about non-sensory properties of the objects (e.g. how and for what they are used or where we can found them; Caramazza, 1998). SFT argues that the living category is more dependent on sensory features whereas the non-living category is more dependent on functional properties. Therefore, lesions to the sensory/visual knowledge subsystem will more likely lead to specific deficits for the living category, whereas impairments to the processing of non-living stimuli are believed to depend on damage to the non-sensory/functional subsystem (Warrington & Shallice, 1984). On this view, category-specific semantic deficits result from damage to different modality-specific systems and not from damage to category-specific structures *per se* (Santos & Caramazza, 2002). This approach also predicts that patients with an impairment for living things should have more difficulties processing their visual features, while patients with selective impairment in the non-living category should show more difficulties with the functional properties of objects (Caramazza, 1998).

Another theory that postulates a neural structure principle or organization is the Domain-Specific Hypothesis (DSH; Caramazza & Shelton, 1998). This approach argues that conceptual knowledge is organized by domain. These domains would be restricted to those that were most salient during our phylogenetic past. Evolutionary pressures led to the development of neural mechanisms specialized in recognizing certain types of categories allowing us to quickly solve survival problems like finding food, avoid predators or find conspecifics for physical and social needs (Almeida, 2007; Almeida, Pajtas, Mahon, Nakayama, & Caramazza, 2013; Shelton & Caramazza, 2001). Plausible categories are "animals", "fruit/vegetables", "conspecifics" and "tools" (Mahon & Caramazza, 2003; Marques, Raposo, & Almeida, 2013; Santos & Caramazza, 2002; Shelton & Caramazza, 2001).

The Domain Specific-Hypothesis predicts that (1) only a few categories can be selectively impaired after brain damage. Only the categories that were important in the evolutionary history will be represented in highly specialized brain areas and be associated with specific neural mechanisms. This explains why some patterns of impairment are not observed and why domain-specific deficits only occur with a limited number of categories (Caramazza & Shelton, 1998; Santos & Caramazza, 2002). As the underlying mechanisms are so specialized, recover from this kind of deficits will be poor since it won´t be possible for the function of one system to be recovered by other systems (Caramazza & Mahon, 2006); (2) that category-specific deficits result in equivalent impairments for visual and functional properties of an object. It assumes that the categorically organized system includes all types of information that is important to that semantic domain: both conceptual and perceptual (Caramazza & Mahon, 2003; Caramazza & Mahon, 2006; Caramazza & Shelton, 1998).

Domain-specific neural systems consist of networks of brain regions in which each region processes a distinct type of information about the same domain or category of objects. Mahon and Caramazza (2011) propose that these domain-specific constraints may also be expressed by patterns of connectivity among regions that are necessary for the successful processing of a certain domain. This pattern of connectivity will differ from the processing of one category of objects to another. The ventral visual pathway plays a central role in this neural system. This pathway projects from early visual areas to lateral and ventral occipital-temporal regions and it is responsible for processing object shape, texture relatively independent of viewpoint, size and orientation (Cant, Arnnot, & Goodale, 2009; Grill-Spector & Malach, 2004; Mahon & Caramazza, 2011; Miceli et al., 2001). In other words, the ventral visual stream is responsible for extracting the object identity from early visual brain areas and transfer it to the rest of the brain (Mahon & Caramazza, 2011). Domain-specific constraints reflect the connections of the ventral stream and other brain areas specialized in processing information of the same class of objects. According to Mahon and Caramazza (2011) there are some good examples of this: 1) the organization

of the extrastriate body area (EBA), which responds differentially to body parts, is driven by the connectivity between somatomotor areas and regions of the ventral stream; 2) the organization of the visual word form area (VWFA), which is specialized for the processing of printed words, is dependent on the connectivity between left lateralized frontal language processing regions and ventral stream areas; and finally 3) the organization of the parahipocampal place area (PPA), which is specialized in the processing of visual scenes, is driven by the connectivity between ventral stream and regions involved in spatial analysis and ventral stream regions.

Importantly, data on category-specific deficits seems to best support the DSH model over the other hypotheses. Firstly, the living category can be damage independently of other categories. Secondly, this category seems to fractionate in two domains: that of animate (e.g. animals) and inanimate domains (e.g. fruits and vegetables). Thirdly, these deficits are associated with impairments in different categories of objects irrespectively of whether the damage is more apparent for sensory or functional properties. And finally, impairments on the processing of livings things doesn't seem to be associated with disproportional impairment in sensory types of knowledge (Capitani et al., 2003). Considering this, we decided to adopt the DSH as our model of organization of the conceptual knowledge in the brain. To test its principles, we will study one of the paradigmatic examples of category-specific organization: the face processing network.

Face Perception and Domain Specificity

The ability to rapidly and efficiently recognize a face is required for having adequate and successful social interactions and has probably been important to evolution and survival of our species. Following the assumptions of the domain-specific hypothesis, this has probably led to the organization of cognitive and neural specialized mechanisms. Supporting this hypothesis, fMRI studies have shown distinct face-selective regions in human cortex that respond stronger to faces than to other kinds of stimuli. Kanwisher, McDermott and Chun (1997) were the first to describe a face-selective area that became known as the Fusiform Face Area (FFA). In response to this finding, a discussion about the nature of the processing that occurs in this area and whether it is exclusive to this type of processing emerged in the literature.

An alternative view to this domain specific hypothesis argues that the mechanisms involved in face perception are not exclusive for the processing of faces but are related to a more general processing that can be important for other domains (Kanwisher & Yovel, 2006). The *individuation hypothesis,* for example, states that face-specific mechanisms can be activated whenever we need to make discriminations between exemplars of the same category. According to this, faces recruit a domain-general mechanism responsible for this kind of discrimination (Gauthier, Behrmann, & Tarr, 1999). Yovel and Kanwisher (2004) found evidence against this hypothesis finding three times

more activation in the FFA during a face discrimination task when compared to the activation during a house discrimination task.

Another important hypothesis is the *expertise hypothesis* that argues that we are all experts in discriminating faces and that if we had similar expertise in discriminating exemplars within other categories of objects, this discrimination effort would lead to similar activity patterns in the face network as those obtain under face-related tasks. That is, FFA is not specialized for faces *per se* but rather for any category that the subject has perceptual expertise in (Gauthier & Tarr, 1997). This hypothesis has gained some traction from data on the patterns of neural activation obtained for categories for which participants are experts (e.g., dogs, birds, etc.) – i.e., participants that are dog experts, and can discriminate between many different exemplars of dogs show similar activation patterns when seeing dogs and faces (Gauthier & Tarr, 1997). Moreover, Gauthier, Skudlarski, Gore, & Anderson (2000a) trained experimental participants to discriminate between different exemplars of novel stimuli called Greebles. These Greebles were created to have similar features to faces and so that discriminating between them would be as hard as discriminating between faces. Interestingly, participants that are trained to discriminate between Greebles exhibit face-like activations when presented with these stimuli. However, Kanwisher and Yovel (2006) showed that expertise effects are not restricted to the FFA and seemed to be substantially larger in non-face areas like the PPA (Rhodes, Byatt, Michie, & Puce, 2004). As such, Kanwisher and Yovel (2006) argue these data are not convincing evidence for the expertise hypothesis.

Importantly, data from face-related neuropsychology literature seems to be in accord with the DSH. For instance, strong evidence for distinct mechanisms involved in face processing comes from neuropsychological data from cases of acquired prosopagnosia. Prosopagnosic patients are unable to recognize previously familiar faces after brain damage, despite the fact that their ability to recognize objects remains intact (Kanwisher, 2000). Prosopagnosia is not a loss of the concept of the person, as these patients are still able to recognize individuals by their voice, verbal description or corporal aspects. Some prosopagnosic patients are still able to discriminate within the same category of objects – but not between faces. This is inconsistent with the individuation hypothesis and suggests the existence of different mechanisms responsible for the processing of faces rather than other objects. Other cases show normal acquisition of knowledge about Greebles, and normal Greeble discrimination performance, in the context of impaired face perception, strongly arguing against the expertise hypotheses.

Importantly, other brain-damaged patients present with the complementary functional dissociation and are impaired at recognizing objects but show normal performance in face processing tasks (e.g., Patient CK; Behrman, Moscovitch, & Winocur, 1994). This double dissociation between face and object recognition is proof of concept on the functional independence of these two domains, and strongly argues for a domain specific

approach for the processing of faces. Moreover, patient CK was a collector of (and an expert on) toy soldiers. Nevertheless, his deficit was also present for the recognition of these types of toys also lost his ability to discriminate this objects. That is, an expertise hypothesis for explaining the network of regions that support the processing of faces would have predicted that if the processing of the categories of objects in which the patient is an expert is impaired, then face processing should also be impaired. Taken together, the functional profiles of prosopagnosic and agnosic patients support the existence of domain-specific mechanism for face perception (Kanwisher & Yovel, 2006).

Face Perception Network

Several studies have shown that there is a network of regions that is dedicated to the processing of faces (when compared to other stimuli such as places or houses) that goes beyond right FFA. After the seminal paper of Kanwisher and colleagues on the FFA (Kanwisher et al., 1997), two more face-selective areas were found. The core system of face perception is composed by the following regions in the occipital and temporal lobes: the fusiform face area (FFA; Kanwisher et al., 1997), the occipital face area (OAF; Gauthier et al., 2000b) and the posterior superior temporal sulcus (pSTS; Hoffman & Haxby, 2000). This network is bilateral, albeit stronger on the right hemisphere.

According to Haxby, Hoffman and Gobbini (2000), the FFA seems to be responsible for the processing of invariant aspects of the face, holding a more holistically, and integrated representation of faces (Axelrod & Yovel, 2010; Duchaine & Yovel, 2015). It also seems to play a role in the processing of changeable aspects such as facial expression and gaze (Duchaine & Yovel, 2015). It is also important for the recognition of the identity of a face, and for the discrimination across different facial expressions (Duchaine & Yovel, 2015). pSTS seems to be responsible for the processing of dynamic changes in the face, such as expressions and mouth movements (Haxby et al., 2000), receiving information on motion and form from early visual areas (Dalrymple, Oruc, Duchaine, Pancaroglu, & Fox, 2011; Steeves et al., 2006). Finally, the OFA seems central in earlier face-processing stages, receiving input from early visual areas (Pitcher, Walsh & Duchaine, 2011). This area seems to preferentially represent parts of the face such as the eyes, the nose and the mouth (Liu, Harris, & Kanwisher, 2010; Nichols, Betts, & Wilson, 2010; Pitcher, Walsh, Yovel, & Duchaine, 2007). This representation of face parts seems to be prior to the processing of more complex facial aspects that occur in anterior cortical regions (Haxby et al., 2000). The connection between the OFA and pSTS is responsible for the processing of dynamic changes in the face, important to social interaction, whereas the connection between OFA and FFA is important for the representation of invariant facial aspects to be used in face recognition (Andrews & Ewbank, 2004; Davies-Thompson & Andrews, 2012; Hoffman & Haxby, 2000; Winston, Henson, Fine-Goulden, & Dolan, 2004). There are other regions that interact with this core system such as the amygdala, insula, medial prefrontal cortex, regions in the anterior

paracingulate cortex and the anterior temporal lobe (Gobbini and Haxby, 2007; Haxby et al., 2000; Scherf, Thomas, Doyle, & Behrmann, 2014).

Although models on face processing have focused on intrahemispheric connectivity, Davies-Thompson and Andrews (2012) found higher correlations between corresponding face regions in the left and right hemisphere than between different regions in the same hemisphere. This interhemispheric connectivity is mediated by the corpus callosum and damage in this structure reduces the correlated fMRI activity between hemispheres (Quigley et al., 2003). This issue will be discussed further in the next section.

Corpus callosum and the interplay between face-selective regions

The corpus callosum is the largest white matter tract in the brain. This interhemispheric commissure connects most of the neocortical areas. It is divided in four parts (listed here anterior to posterior): the rostrum, the genu, the body and the splenium. It is hypothesized to play a primary role in cognitive processing. For instance, low integrity of the corpus callosum seems to contribute to cognitive decline in aging (Hinkley et al., 2012). On the other hand, increased callosal thickness in childhood is associated with higher intelligence, faster processing speed and more efficient executive function abilities (for a review, see Hinkley et al., 2012). Moreover, Hinkley and colleagues showed that the absence of a fully development of corpus callosum alters the interactions within each hemisphere, and between the two hemispheres. The areas where this connectivity impairment would be more salient are regions within frontal, parietal and occipital lobes.

The corpus callosum is composed of function-specific pathways that differ in terms of their fiber composition. Aboitiz, Scheibel, Fisher, and Zaidel (1992) suggested that high-order processing areas (the so called “association areas”) tend to project to the corpus callosum by small axons, whereas visual and somatosensory areas tend to project through large axons. In terms of interhemispheric connection, the corpus callosum also seems to exhibit a functional specialization of its segments that topographically represent different cortical locations (Aboitiz et al., 1992). Specifically, the rostrum (the more anterior aspect of the corpus callosum) is responsible for connecting the orbital frontal cortices; the forceps minor (a fiber bundle that crosses the genu) connects medial and lateral surfaces of the frontal lobes; the anterior part of the splenium connects parietal and medial-temporal associative regions; finally, the posterior part of the splenium links primary sensory visual areas (occipital lobes) through a fiber bundle named forceps major (Knyazeva, 2013; Schmahmann, & Pandya, 2006). This u-shaped fiber projects to the occipital lobes through the splenium, and seems to be a major connection between lateral and inferior occipital regions related with face processing. Importantly, Avidan and Behrmann (2014) studied congenital prosopagnosic individuals and found reduced structural integrity of the forceps major, suggesting that abnormalities to this tract may be associated with abnormalities in the functioning of face related regions in the inferior and

lateral occipital cortex, such as the OFA (Avidan & Behrmann, 2014).

Studying a patient with a lesion in this structure and with a subsequent deficit in face perception could help us to better understand the role of forceps major on the face processing network. It can provide us evidence about how the face areas are connected and how the information flows between them.

II - Objectives

In this thesis we will focus on testing the domain-specific hypotheses of face processing, and particularly on understanding how different face-related processes come together neurally and functionally. To do so, we will study a brain-damaged patient – Patient AD – that suffers from hemi-prosopometamorphopsia.

Metamorphopsia is a visual perception deficit in which objects appear distorted in form, size and/or color (Miwa & Kondo, 2007; Trojano, Conson, Salzano, Manzo, & Grossi, 2007). In some patients, this distortion can appear restricted to faces. In these cases – prosopometamorphopsia – features of faces look dropped, afloat, protruded or shrunk (ffytche & Howard, 1999; Heacan & Angelergues, 1962). This deficit was first described by Bodamer's (1947) that reported a case of a patient who could recognize faces normally but perceived them disfigured. The distortion usually affects the whole face but more rarely can occur in just one side of the face. When the deficit is restricted to just one side of the face, the deficit is called hemi-prosopometamorphopsia.

In most of the cases, this deficit is due to a lesion on the right hemisphere either in the temporal lobe, occipital lobe or parietal lobe. However, lesions in the left hemisphere have also been reported (Lee, 2015; Miwa & Kondo, 2007). Interestingly, Lee (2015) reviewed seven cases of hemi-prosopometamorphosia due to a lesion on the splenium of the corpus callosum. It is hypothesized that this deficit is related with a callosal disconnection. However, the pathophysiologic mechanism of hemi-prosopometamorphosia remains unclear.

Importantly, studying Patient AD's performance in the processing of faces can provide invaluable clues to the understanding of the neural circuit that is specialized in perceiving faces. With this case study we aim to characterize the domain-specific nature of his deficit, and to understand its functional *locus* within the face processing network. We will use behavioral data and fMRI data to understand which brain areas are responsible for the perceptual distortion experienced by Patient AD, and how these areas are functionally interconnected. We will compare Patient AD's performance with the performance of an aged-matched healthy control, and conclude with a discussion section.

III - Experiments

This thesis includes three experiments. In the first experiment, we will explore age-related neural and cognitive changes in the brain of our patient and the healthy control as a way of assessing the course of neural aging. In the second experiment, we will test Patient AD's behavioral performance on a series of face-related tasks as a way of ascertaining the degree of domain-specificity of his deficit and further understand the functional *locus* of the deficit. Finally, in Experiment 3, we will uncover the neural underpinnings of Patient AD's deficit by exploring how face-specific areas are functional connected with one another, and comparing the data from Patient AD with the healthy control participant. We will first start by introducing the general approach taken in this thesis. We will then describe Patient AD and the healthy control. This will be immediately followed by each experiment.

The single case study approach – cognitive neuropsychology exploration of a hemi-prosopometamorphopsia deficit

In this thesis we will follow a cognitive neuropsychology case study methodology to study the processes at play during face recognition in Patient AD. The aim of cognitive neuropsychology is to study impairments of cognition to learn more about normal cognitive processes (Rapp & Goldrick, 2006). Influenced both by neurology and cognitive psychology, it tries to understand how the brain is organized in terms of cognitive abilities (McCarthy & Warrington, 1990). The data collected and analyzed by this discipline is the performance of brain-damage subjects. Hence, highly selective impairments observed in patients that suffered from brain damage represent an important clue to studying the organization and functioning of the brain. To serve this purpose cognitive neuropsychology uses case studies rather than group studies and studies functional symptoms rather syndromes (Caramazza & Coltheart, 2006). However, using single cases studies of patients with brain damage to study the normal cognitive functioning was not always a well-accepted method.

Buxbaum (2006) stated that "each patient may be as unique as a snowflake". When studied in detail, every case consists of a specific manifestation of the brain lesion: assuming that every component of the cognitive system can be damaged independently, the number of patterns of impairment are huge. This makes it very unlikely to gather a group of brain-damaged patients with the same pattern of impairment making it very hard to perform proper group analysis – that is why it makes no sense analyzing them as a group (Caramazza & Coltheart, 2006). Hence, if every patient is unique, how can we generalize the findings across normal population?

In defense of the single-case approach, Caramazza (1986) suggested that there are three assumptions that underlie almost all neuropsychological studies (Ward, 2015):

1. The *"universality assumption"*, that argues that there is no variation across the normal cognitive system used by a certain cognitive domain. Although from one patient to another there may be variations on their systems because of the damage, they had an identical system premorbidly (Caramazza & Coltheart, 2006);
2. The *fractionation assumption*, that states that brain-damage can result in selective cognitive impairments that can be used to inform about the theories of cognition (Ward, 2015);
3. The *transparency assumption*, stating that although lesions can affect a variable number of components in the premorbid system, they cannot result in a creation of a new cognitive system. The abnormal system is not the focus of cognitive neuropsychology research; our goal is to study the abnormal to understand the normal (Ward, 2015).

Importantly, cognitive neuropsychology do not aim to create theories from the observation of a single-case. Rather, theories about cognitive organization and functioning are created based on a large number of observations, from both normal and brain-damaged patients. Ward (2015) argues that it is very difficult to generalize from one case study to another but easier to generalize to some aspect of normal cognitive functioning.

Case Report – Patient AD – and an age and gender-matched healthy control

Patient AD is a 62-year-old right handed man that came to the Neurology Department of Centro Hospitalar e Universitário de Coimbra (CHUC) complaining of suddenly seeing the left half of people's faces distorted (including his own reflected in the mirror). He reports that the left eye, nose and the left corner of the people's mouth look like they are "melting down" and that the two halves of the face don't fit. No distortions in other objects or parts of the body were registered. However, he later reported that he started seeing the distortion in some animals' faces, like dogs. He has no problem in recognizing faces. As a result of his functional deficit, he has developed a reactive depressive syndrome which led him to leave his job and to become socially withdrawn, because he couldn't stare people in the face. He is now followed by the Psychiatric Department.

There is no record of relevant medical history or medication prior to his visit. The neurologic exam revealed no impairments and reported no alexia/dyslexia, no color anomia or changes in color perception (Ishiara 16/16), no optic aphasia, agraphia or other cognitive deficits. His visual acuity was normal (10/10 right eye; 9/10 left eye).

CT-scan has shown a hypointense lesion in the left lateral side of the splenium of the corpus callosum. MRI (3 Tesla) showed a T1 hypointense

lesion, hyperintense in DP/T2 and FLAIR. Five months later, the MRI showed central necrosis of the lesion but no increase in size. DTI evidence a reduction on the fractional anisotropy in the left side of the splenium of the corpus callosum, meaning that the white matter tracks are more diffused in this region. At the time of the current study, Patient AD underwent a new MRI session (see Figure 1, for a T1-weighted image of the patient's lesion). As can be seen in Figure 1, the lesion is located within the left part of the splenium of the corpus callosum.

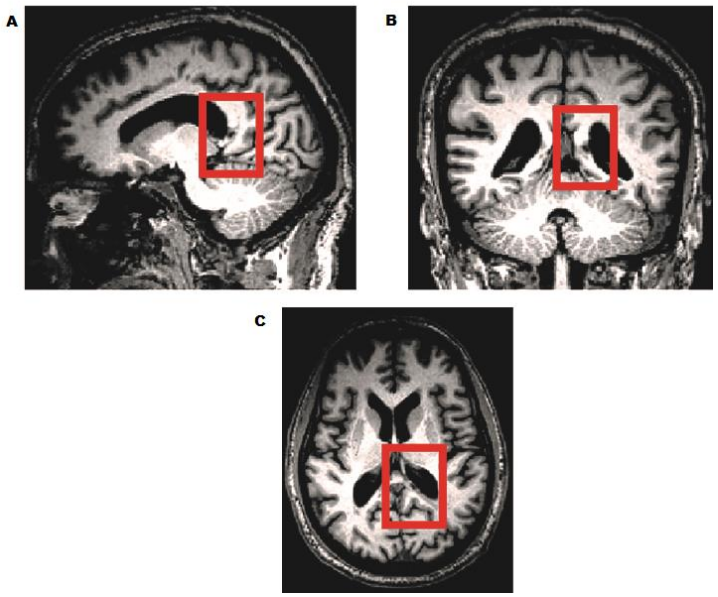

Figure 1. Location of the lesion. **A**. Sagittal view. Extension of the lesion: X=-20 to X=-9 (lateral/medial). **B.** Coronal view. Extension of the lesion: Y=-45 to Y=-37 (posterior/anterior). **C.** Axial view. Extension of the lesion: Z=16 to Z=8 (superior/inferior). Patient AD's brain was normalized into Talairach space (Tailarach & Tournoux, 1988).

Patient AD underwent several sessions of neuropsychological assessment in order to ascertain his general cognitive functioning. In the Mini-Mental State Examination (MMSE: Folstein, Folstein, & McHugh, 1975; Portuguese version: Guerreiro et al., 1994) patient AD scored 28 points (out of 30) which is a normal result for his age and education (6 years of education) (Freitas, Simões, Alves, & Santana, 2014). In the Montreal Cognitive Assessment (MoCA: Nasreddine et al., 2005; Portuguese version: Simões et al., 2008) patient AD's score was 21 points (out of 30). This score is two standard deviations bellow the normative values for his age and education, suggesting an impairment in its cognitive functioning abilities (Freitas, Simões, Alves, & Santana, 2011).

Furthermore, Patient AD went through a more comprehensive neuropsychological evaluation, and completed the Bateria de Lisboa para Avaliação da Demência (BLAD; Guerreiro, 1998). The scores were compared to normative values for the patient's age and level of education, and we used a particular scoring system: when the scores were 1 standard deviation below the mean, the patient was considered to be slightly impaired on the task; when

the scores were 1,5 standard deviations below the mean, the patient was considered to be moderately impaired on the task; and, when the scores were 2 standard deviations or more below the mean, the patient was considered to be severely impaired on the task. Patient AD's scores are summarized in Table 1.

Table 1.

Scores on Bateria de Lisboa para Avaliação da Demência (BLAD)

Task	Score	Normative Values	Classification
Mental Control (Cross of the letter "A")	4,85	5.91±1,61	Normal
Digit Span (total)	10	8,83±1,34	Normal
Verbal Initiative	17	17,33±2,87	Normal
Motor Initiative	3	2,92±0,29	Normal
Graphomotor Initiative	1	1,67±1,59	Normal
Following Instructions	4	4,00±0,00	Normal
Token Test	21,5	21,7±0,3	Normal
Writing	2	2,00±0,00	Normal
Orientation	15	14,83±0,39	Normal
Verbal Memory with Interference	7	11,83±2,33	Severe Impairment
Information	19	19,25±0,97	Normal
Associative Memory	12,5	15,29±2,68	Slight Impairment
Logical Memory	8	11,21±2,14	Moderate Impairment
Calculation	14	12,92±2,02	Normal
RPM	9	9,75±1,76	Normal
Verbal Reasoning	9	6,33±0,33	Normal
Right-Left Orientation	6	6,00±0,00	Normal
Delayed Associative Memory	8,5	-	No loss of material
Delayed Logical Memory	8	-	Discrete loss of material
TMT-A	62	60±29	Normal
TMT-B	161	131±67	Normal

RPM= Raven's Progressive Matrices; TMT= Trail Making Test. Normative values represented by mean ± standard-deviation and matched for subject's age and education.

We also assessed Patient AD's face processing abilities, with the use of the Benton Face Recognition Task (Benton, De Hamsher, Varney, & Spreen, 1992) and the Comprehensive Affect Testing System (CATS: Froming, Levy, Schaffer, & Ekman, 2006). The patient achieved a normal score in Benton Facial Recognition Test (he scored 46 out of a maximum of 54. This score is within the normal range that goes from 41 to 54 points) showing no problems in face recognition. In CATS he showed no evidence of faces discrimination deficits (emotion and identity) but revealed slight difficulty in the

discriminating emotional prosody. His scores, corrected for gender, are summarized in Table 2.

Table 2.

Scores on Comprehensive Affect Testing System (CATS)

Quotient	Score (Sex Corrected)	Classification
Affect Recognition Quotient (ARQ)	42	Z=-1,1 (Normal)
Prosody Recognition Quotient (PRQ)	18	Z=-1,5 (Normal)
Emotion Recognition Quotient (ERQ)	82	Z=-1,5 (Normal)

Z= standardized scores. Raw scores were gender corrected by intern commands of the test.

For some of the experiments described in this thesis, we also recruited a control participant. This control participant is a 60-year-old right-handed man with no known neurologic diseases and fitting the MRI inclusion criteria.

Both Patient AD and the healthy control participant were given extensive information about the experiments they were participating and gave written consent to their participation in the experiments according to the ethical committee of the Faculty of Psychology and Educational Sciences of the University of Coimbra, and the declaration of Helsinki.

Experiment 1 – Age related structural changes in the human brain

Aging, whether healthy or pathological, is currently one of the hottest debates in the social sciences. This is probably so because the average age of the population is increasing steadily and with it come a series of societal and medical challenges that have to be addressed. Importantly, it is now clear that the brain suffers dramatic changes under pathological aging, such as in neurodegenerative diseases, but also under healthy aging, as this is also associated with functional, structural and cognitive changes. Understanding how the healthy brain ages can lead us to a more efficient promotion of a sustainable aging.

As we age, our brain tends to shrink. Several MRI studies have focused on measuring these changes – both globally across the brain, and locally, in a region-by-region fashion. In general, the prefrontal cortex seems to be more significantly affected than other neocortical regions. Temporal regions also seem to be affected and occipital and parietal regions show smaller shrinkage effects (Raz, Rodrigue, Head, Kennedy, & Acker, 2004; Raz, Williamson, Michie, Gunning-Dixon, Head, & Acker, 2000). Some of the regions whose volume seem to be negatively correlated with age are the hippocampus, the amygdala, cerebellum and the neostriatum (Raz & Rodrigue, 2006). Good and colleagues (2001) suggest that the anterior cingulate cortex and striate cortex can also suffer from aging-related atrophy.

As described above, the hippocampus has been identified as one of the most vulnerable structures to the negative effects of aging. This area shows marked shrinking in healthy aging – the older the participant the more striking the hippocampal shrinkage is (Raz et al., 2005). This is extremely important because this structure plays a central role in cognition and in memory. In fact, volume loss within this area seems to play a role in pathological aging and has been identified as a predictor of many neurodegenerative diseases (Raz & Rodrigue, 2006). Finally, hippocampal dysfunction seems to be connected with mood disorders, such as the geriatric depression (Steffens et al., 2000).

Because of the centrality of the hippocampus during the aging process and the potential use of the volumetric analysis of this structure as a signature of healthy or pathological aging, in the first experiment we manually segmented the hippocampus on Patient AD and the healthy control's brain and compared the volume obtained with the average volume obtained from a group of healthy adults participants (Gur, Gunning-Dixon, Bilker, & Gur, 2002; Pruessner et al., 2000). This experiment will then help characterize Patient AD's age-related neural changes.

Methods

Participants

Patient AD and the healthy control participated in the first experiment.

Procedure

MRI Acquisition – MRI data was collected on a Siemens Tim Trio 3T MRI scanner with a 12-channel head coil at the Portuguese Brain Imaging Network. To acquire the high-resolution structural T1 weighted images, we use a magnetization prepared rapid gradient echo pulse sequence (repetition time [TR] = 2530msec, echo time [TE] = 3.29msec, flip angle = 7°, field of view [FOV] = 256mm, matrix size = 256×256, voxel size = 1×1×1mm, number of slices = 192 ascending interleaved).

Preprocessing of anatomical data and segmentation - Quantitative analysis of the differences in volumes of specific brain structures is an important method to evaluate age-related and disease-related effects. The aim of this analysis was to establish whether there were age-related changes (pathological or not) in the brain of Patient AD. In order to this, we defined the hippocampus as our target ROI, as it was one of the structures that the literature defines as being more affected by the aging process.

We manually defined the hippocampus bilaterally (left hippocampus and right hippocampus) using the T1-weighted images, aligned to Talairach space (Talairach & Tournoux, 1988) on both patient and control subject. We proceed with the analysis using the segmentation tool of Brain Voyager software package, following the protocol proposed by Moore et al. (2014). The segmentation started in the first slice where the hippocampus was visible.

The anterior border was defined as the disarticulation with the amygdala. The inferolateral separation border was defined by the horn of the lateral ventricle. The inferior border, which separate the hippocampi from the para-hippocampi gyri, was defined on the angular bundle and its imaginary extension to the ventricular cavity. Alveus and the fimbria compose the superior border. All the borders were traced posteriorly over the grey-matter limits (70 to 179 intensity values).

Results

With this analysis we want to evaluate possible age-related changes in the brain of Patient AD. Specifically, we aimed to compare the volume of his hippocampus with that of the hippocampus of the healthy control participant, and importantly, with a published database of mean hippocampus volume under healthy aging. For the volumetric analysis we manually segmented the hippocampus following a previously stablished protocol. In Figure 2 and 3 we present a set of images of the segmented hippocampi for each participant (patient and control, respectively). In red we represent the right hippocampus and in green the left.

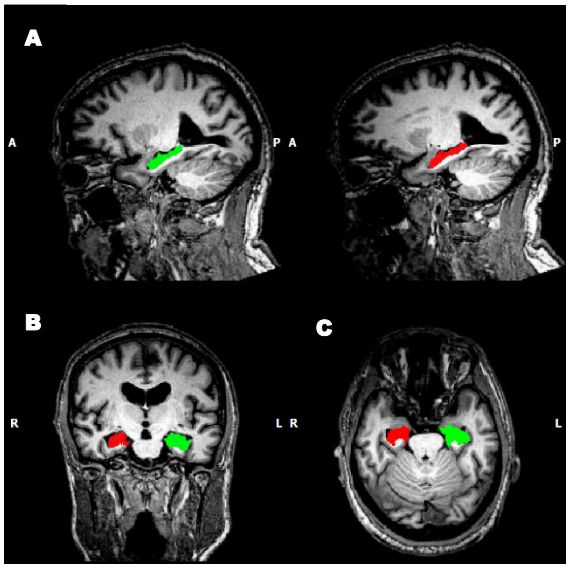

Figure 2. Patient's manually segmented hippocampus. Green=Left hippocampus. Red=Right hippocampus. Talairach Coordinates for:

A. Sagittal view: x=-26 (left); x=25 (right) **B.** Coronal view: y=-12 **C.** Axial view: z=-14

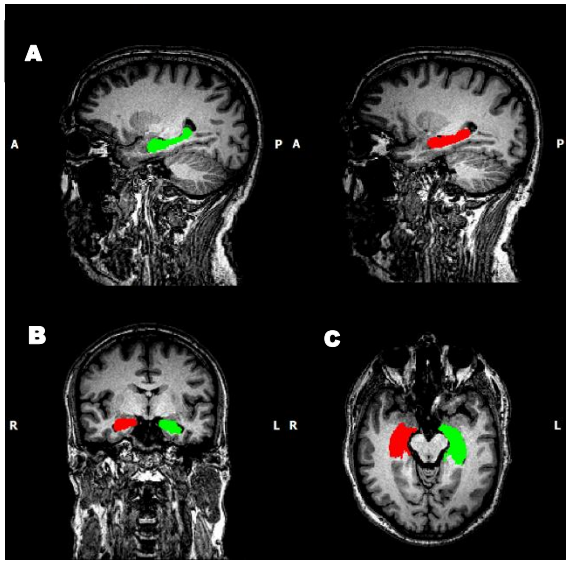

Figure 3. Control's manually segmented hippocampus. Green= Left hippocampus. Red= Right hippocampus. Talairach Coordinates for:

A. Sagittal view: x=-26 (left); x=25 (right) **B.** Coronal view: y=-12 **C.** Axial view: z=3

The approximate volume of the right and left hippocampus of both control subject and patient is summarized in Table 3 As can be seen, the patient presents numerically smaller hippocampi than the control.

Table 3.

Volume of Hippocampus for each subject

	Left Hippocampus	Right Hippocampus
Patient	4681	4213
Control Subject	4725	4876

All values are $mm^{3.}$

More importantly, we looked at published data on the size of the hippocampi in healthy adults. Pruessner and colleagues (Pruessner et al., 2000) tested 40 healthy individuals in terms of the size of the hippocampi. They found that the average volume for the left hippocampus was 4243.5 mm^3 (SD= 438.3), whereas the size for the right hippocampus was 4395.2 mm^3 (SD= 468.1). Moreover, Gur and colleagues (Gur et al., 2002), explore gender differences in the volumes of different brain structures over 116 healthy adults (57 men, 59 women), and observed average hippocampi volume sizes for male individuals to be similar to those obtained by Pruessner and colleagues. Specifically, they showed that average volume of the left hippocampus was 4320 mm^3 (SD=850), whereas the average volume of the right hippocampus was 4600 mm^3 (SD=1170).

Discussion

According to our neuropsychological assessment, Patient AD shows cognitive impairment – this is particularly true in the MoCA. In a more comprehensive neuropsychological assessment battery – the BLAD – Patient AD showed impairments in cognitive domains such as verbal memory with interference, logical memory and associative memory. This pattern of cognitive decline may have been influenced by Patient AD's depressive syndrome (Houston & Bondi, 2006). Other cognitive abilities are within the normal range for his age and education.

Interestingly, Patient AD's impaired performance is at odds with our data from Experiment 1 that seems to suggest that Patient AD, and the healthy control, present hippocampal sizes within the range typical of healthy aging. This suggests that no atypical structural age-related changes are present, and that Patient AD may be considered as within the normal aging process. Importantly, either Patient AD's impairment is visible only in neuropsychological assessment and not yet in neuroanatomical analysis, or his performance in the neuropsychological assessment is being amplified by his depressive syndrome (Houston & Bondi, 2006).

Experiment 2 – Behavioral characterization of the deficit

Categorical and functional boundaries of the Patient AD's deficit

Patient AD presented with a phenomenological complaint of seeing a distortion within the left part of the face. In this experiment we wanted to further characterize the functional deficit so that we could gain a deeper understanding of Patient AD's deficits. In particular, we wanted to understand two aspects: 1) is the deficit face-specific (Experiment 2a); and 2) can we delimit the deficit to certain aspects of face perception (Experiment 2b). Answering these questions would give us a better understanding of this patient's deficit and allow us to understand how typical face processing takes place.

Methods

Participants

In this experiment only Patient AD participated. The fact that Patient AD's deficit is not one of failing to recognize or to perform a particular task, but one related with a perceptual distortion was not amenable to being tested on a set of age-matched control individuals – i.e., Patient AD perceives a very particular distortion when he sees faces, and this phenomenon would be completely absent in a set of healthy controls.

Procedure

In Experiment 2a, we wanted to test the domain-specific nature of Patient AD's deficit. To this purpose we selected a set of greyscale pictures from the World Wide Web and from internal image databases. These were pictures of faces (4 frontal views of a face; 2 views of the right profile; 2 views of the left profile; 2 views of a face in ¾ to the right; 2 views of a face in ¾ to the left; 4 emotional faces; and 4 schematic faces), animals (4 pictures of animal faces, and 4 pictures of full-bodied animals), 16 pictures of artefacts (4 cars in a frontal view; 4 cars in a lateral view; 4 houses; and 4 tools) and 4 geometric shapes (e.g., a circle). One of the left profile faces was excluded from the study because it was considered by the patient to be too blurry to evaluate. As such, we used a total of 47 pictures. Each picture was presented one time and the order of presentation was random. Patient AD had to judge whether he could see any distortion in the stimulus depicted in each trial. His answers were annotated by an experimenter.

In Experiment 2b, we wanted to have a more complete understanding of Patient AD's functional deficit. Specifically, we wanted to test whether there were conditions where faces were presented but no distortion was perceived, or whether the deficit was restricted to a particular visual field or to the actual side of the face. In order to answer these questions, we randomly presented 125 pictures of faces that varied in several conditions. We presented 21 upright frontal faces; 19 inverted faces; 19 emotional faces; 16 left profile faces; 17 right profile faces; 18 faces with a 90º rotation; 19 faces with a 270º

rotation; 9 left half faces; and 6 right half faces. Importantly, the faces were the same across comparable conditions: the upright, inverted and rotated faces were the same exact faces, but rotated; the profiles were also the same exact faces but flipped so that they were the right and left profile; and finally the left and right parts of faces were also the same stimuli, but were also flipped to be either the left of the right part of faces. Each picture was presented one time in a random order. The patient had to report whether the distortion was present or absent, as well as where the distortion was located.

The different number of pictures presented in each condition can be explained by the fact that we had to stop the experiment because it was too uncomfortable to the subject.

The stimuli were courtesy of Michael J. Tarr, Center for the Neural Basis of Cognition and Department of Psychology, Carnegie Mellon University (http://www.tarrlab.org) Face Place database. The background of the pictures was changed so that it was equal to all images (grey tone; RGB: 128 128 128).

Results

In this experiment we used a Z-test for two proportions to compare our conditions of interest. In Experiment 2a, we compared the performance of Patient AD in perceiving a distortion in pictures of faces versus in pictures that did not have a face (i.e., animals, artifacts and geometric shapes). Patient AD reported seeing a distortion in the majority of the stimuli of the category "faces" (18/19). For the other categories the patient saw a distortion in a very small number of stimuli. Statistical values of the contrast of interest "faces" versus "non-faces" categories are represented in Table 4.

Table 4.

Experiment 2a – Statistical Analysis

Category	% of Distortion	Z-Score	p-Value
Faces	94.73	5.96	0.001
Non-faces	7.14		

These results show that there is a significant different in the presence of a perceptual distortion when Patient AD sees faces compared to non-face stimuli. Specifically, Patient AD perceives a distortion when presented with faces but not non-face stimuli.

A more qualitative analysis of the patient's performance on this task shows that he failed to see a distortion when only the right half of the face was presented. For the category of animals, the patient saw distortion in some of the animal faces, but none on the pictures depicting a whole body. Interestingly, the distortion was only seen in animal faces that more alike to the human face, such as monkey face. In the other categories ("artifacts" and "geometric shapes") no distortion was reported by Patient AD.

In Experiment 2b, we compared the patient's perception of a distortion in different types of face stimuli. All face presented in an upright position lead to the perception of a distortion – both for emotional and neutral expressions (upright frontal faces - 21/21; emotional faces - 19/19). We also tested whether face rotation attenuated the perception of a distortion in the target face. Faces presented in an inverted position almost always led to the perception of a distortion (17/19). Moreover, faces rotated in 90º and 270º also lead to the perception of a distortion in most faces (7/18, and 12/19 respectively). Importantly, when faces were presented either in profile or when only half of the face was presented – i.e., effectively when only one side of the face was presented – the results seemed to differ by side presented. Specifically, Patient AD tended to see a distortion when the left side of the faces was presented (left profile – 7/16; left side – 8/9), but not so much when the right side of the face was presented (right profile – 4/17; right side – 0/6).

We proceed with the statistical comparisons calculating the contrasts between different kinds of face stimuli that can be considered directly comparable: "upright" versus "inverted" faces; "left profile" versus "right profile"; "left half" versus "right half" of the face. Statistical values for this comparisons are represented in Table 5.

Table 5.

Experiment 2b – Statistical Analysis

Category	% of Distortion	Z-Score	p-Value
Upright	100	1.56	0.126
Inverted	89.5		
Left Profile	43.75	1.23	0.219
Right Profile	23.53		
Left Half	88.89	3.38	0.00072
Right Half	0		

This analysis shows that the difference between the left-half of the face and the right-half of the face is statistically significant. All the other comparisons did not reach significance.

Discussion

With this experiment we aimed to characterize the categorical and functional boundaries of Patient AD's deficit. The results of Experiment 2a show us that the deficit is specific for the category of faces. The rate of distortion reported by the patient for the category of faces is significant higher than for non-face stimuli.

Experiment 2b further specified, and characterized the deficit. The deficit occurs more often when the left side of the face is presented. For instance, when only half of the face is presented to the patient, Patient AD see the distortion only when presented with the left side of a face. Independently of the rotation or orientation of the pictures, Patient AD reports that the

distortion always occurs in the same elements of the face: left eye, nose and left corner of the mouth.

These results mean that the deficit is viewer independent/object centered not being related with any visual field deficit. This suggests that the deficit occurs in a more complex level of processing, posterior to the 3D perception of the face. This may indicate that specific neuronal mechanisms are involved in this high-level kind of processing.

Experiment 3 – Neural underpinning of Patient AD's deficit

In this last experiment we wanted to understand how faces were processed neurally in a patient that reported such a face-specific deficit, and compare it a healthy control. Patient AD presented a lesion in the splenium – and not within the actual nodes of the face network – so we expected that there would be functional and anatomical decrements at the level of the connections of the nodes. As such, we decided to test how the different nodes of the face-specific neural network were connected. Importantly, would it be possible to explain Patient AD's performance and phenomenological perception by looking at the neural processing of faces and the passage of information between the different nodes of the network? To test this we performed an fMRI experiment to test Patient AD's neural processing of faces.

Methods

Participants

Patient AD and the healthy control participated in the third experiment.

Procedure

MRI data acquisition – MRI data was collected on a Siemens Tim Trio 3T MRI scanner with a 12-channel head coil at the Portuguese Brain Imaging Network. In this experiment we used the same high-resolution structural T1 weighted images that were used in Experiment 1. For T2* contrast we use an EPI pulse sequence (TR=2000msec, TE= 30 msec, flip angle=90°, FOV=256 mm, matrix 256x256, voxel size=4x4x4 mm, slice thickness=4 mm; number of slice= 30 ascending interleaved). To achieve signal equilibration, the first two volumes of each run were discarded.

Localizer runs – We presented sequences of visual stimuli that were used to localize a series of face-related regions of interest (ROIs). This localizer included 8 conditions of stimuli: images of animals, faces, places, and tools, plus phase-scrambled versions of each category (i.e., phase-scrambled pictures of animals, of tools, of faces, and of places). There were 12 stimuli per condition and 8 exemplars of each item (which give us 768 different stimuli). These stimuli were presented in blocks by category. Each stimuli was presented for 500 ms. In each block all the 12 types were presented, and as such the block lasted for 6 seconds. Each block was immediately followed by a fixation block, where a fixation cross was presented in the middle of the screen, that lasted 6 seconds. The non-

scrambled were repeated 2 times within a run, while the scrambled conditions repeated 1 time per run. Both Patient AD and the healthy control went through two runs of the localizer.

Experimental runs – We presented a sequence of pictures of faces that varied across six conditions: face in an upright frontal view, faces in an inverted view, faces in a left profile view, faces in a right profile view, pictures of only left half of the face, and pictures of only the right half of the face. All the pictures were presented centrally. The stimuli used were those from Experiment 2b. There were 16 exemplars of each condition, in a total of 96 different stimuli. Each stimulus was on for 500 milliseconds. In each block all the 16 stimuli were presented, and as such the block lasted for 8 seconds. Each block was immediately followed by a fixation block, where a fixation cross was presented in the middle of the screen, that lasted 8 seconds. Each condition was repeated 3 times within a run, and the order of conditions was random. The total run time was approximately 5 minutes. Patient AD went through 4 runs, whereas the healthy control went through 2 runs. This is because the healthy control did not wish to continue the experiment.

A "simple framework" was used to control stimulus presentation in Psychtoolbox in MATLAB (Schwarzbach, 2011). The stimuli of both sequences were backprojected on a screen that participants viewed with a mirror attached to the head coil. The stimuli were viewed passively as no response was required.

Data Analysis

Preprocessing – fMRI data were analyzed with Brain Voyager software package 2.8.1 and in-house scripts drawing on the BVQX toolbox for MATLAB. We followed a typical data preprocessing sequence that included slice time correction (sinc interpolation), motion correction with respect to the first volume of the first run, and linear trend removal in the temporal domain (cut-off: two cycles within the run). Functional data were registered (after contrast inversion of the first volume) to high-resolution deskulled anatomy basis in native space. Echo-planar and anatomical volumes were transformed into standardized (Talairach & Tournoux, 1988) space. Functional data were smoothed at 6-mm (1.5 voxels) FWHM and interpolated to 3 × 3 × 3 mm voxels.

To fit beta estimates to the events of interest we used the general linear model (GLM). GLMs were created for each sequence (localizer and experimental runs) independently. The first derivatives of the six parameters describing volume-to-volume motion were added as predictors of no interest to attract variance related to head movement during the scanning. Experimental events were convolved with a standard two-gamma hemodynamic response function. For the Localizer, eight regressors of interest (plus the six motion regressors): animals, faces, places, tools, scrambled animals, scrambled tools, scrambled faces and scrambled places. For the Experimental runs there were six regressors of interest (plus the six

motion regressors): upright frontal face, inverted face, left profile, right profile, left half of the face and right half of the face.

Definition of the ROIs – We wanted to localize the face-selective network of areas in both the patient and the control participant. The ROIs were defined based on the analysis of the functional activation pattern within the localizer sequence. We were interested in localizing the clusters of voxels that showed a significantly higher response to faces than to the other categories of stimuli – specifically places. This clusters were then defined as the face-selective areas. To address this issue we computed a typical contrast in the face literature – that of faces > places. We used a statistical threshold of $p < 0.05$, with a standard FDR correction for multiple comparisons. We defined the typical face-selective areas: the right and left FFA and the right and left OFA. The analysis was done in each participant individually.

Functional Connectivity Analysis – Functional connectivity analysis consists of measuring the statistical association among two or more anatomically distinct areas of the brain. These analyses give us information about the functional interactions between different brain areas. In other words, it allows us to observe the activity patterns of a network of areas simultaneously (O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012). This analysis is computed over the averaged time course of all voxels in each of our previously defined ROIs. Time courses were extracted from preprocessed smoothed functional data that had also been regressed with the outputs from motion correction (change in head position across volumes) and the global mean time-course from the whole brain. Correlation between the named ROIs was then computed over the residuals from that model, and the R values obtained were fisher-transformed. The analysis was done individually for each subject and for each sequence.

Psychophysiological Interaction (PPI) Analysis – PPI analysis (Friston et al., 1997) is a particular type of functional connectivity analysis that allows us to identify the brain regions in which the functional coupling is dependent on the experimental context – i.e., on a particular experimental condition. It investigates task-specific increases in the relationship between different brain areas, by looking at which voxels in the whole brain increase/decrease their relationship with a seed ROI in a given condition. In other words, it identifies the areas whose level of activity differ according to an interaction between a psychological factor (the task) and physiological variables (the time course of a ROI; O'Reilly et al., 2012). This type of analysis was used to evaluate the connectivity patterns of our main ROIs when participants were processing faces (the category were the patient identify the distortion) compared to when they were processing places (were no distortion was reported).

First, we extracted the mean activity from the target ROIs and multiplied it with the contrast of interest (Faces vs. Places). We then convolved it with the HRF (haemodynamic response function) resulting in a

PPI predictor. Then, one GLM per ROI was computed with three predictors associated: the average time course of activity of the ROI, the psychological predictor and the PPI predictor. Analysis were Bonferroni corrected for multiple comparisons with a statistical threshold of $P < 0.05$.

Results

Definition of the ROIs – We used FDR corrected maps to define the face network in Patient AD and the healthy control by looking at voxels that were more active for faces than places. The average Talairach coordinates (Talairach & Tournoux, 1988) for the defined ROIs are summarized in Tables 6 and 7.

Table 6.

Patient AD -Average Talairach coordinates for the defined ROIs

Region-of-Interest	X	Y	Z	No. Voxels
Right FFA	40	-48	-16	1035
Left FFA	-45	-37	-17	181
Right OFA	39	-63	-11	507
Left OFA	-57	-66	-8	488

Contrast: faces > places. FFA= Fusiform Face Area; OFA= Occipital Face Area.

Table 7.

Control Subject - Average Talairach coordinates for the defined ROIs

Region-of-Interest	X	Y	Z	No. Voxels
Right FFA	37	-30	-10	561
Left FFA	-42	-30	-11	1021
Right OFA	32	-63	-14	3589
Left OFA	-42	-56	-16	208

Contrast: faces > places. FFA= Fusiform Face Area; OFA= Occipital Face Area.

As can been see, both participants exhibited a normal core face perception network. These regions were then used for the subsequent analysis.

Functional Connectivity Analysis – In Figures 4 and 5 we present a schematic model of the face network for Patient AD and the control respectively, where we show correlation values between our ROIs for both the Localizer and Experimental sequences. In both sequences, there was a clear difference in terms of the connectivity between face-selective areas for the control and Patient AD.

In the Localizer sequence, face-selective areas of the control subject were strongly and positively correlated (see figure 4A). Particularly, we found strong correlations between the right FFA and the left FFA (fisher transformed $R = 0.84$); the right OFA and the left FFA (fisher transformed $R = 0.76$); between the right FFA and right OFA (fisher transformed $R = 0.67$); between the right OFA and the left OFA (fisher transformed $R = 0.61$); between the

right FFA and the left OFA (fisher transformed R = 0.53); and finally between the left OFA and left FFA (fisher transformed R = 0.59).

In contrast, Patient AD's face-selective network was not so strongly connected (see figure 4B). There were strong and positive correlations between all areas except the connections that involved the left OFA. Specifically, we found strong correlations between the right FFA and right OFA (fisher transformed R = 0.91); between the right FFA and left FFA (fisher transformed R = 0.85); and between the right OFA and the left FFA (fisher transformed R = 0.79). Weak correlations were found in the connective paths between the left OFA and the left FFA (fisher transformed R = 0.28); between the left OFA and right FFA (fisher transformed R = 0.39); and between the left OFA and right OFA (fisher transformed R = 0.48).

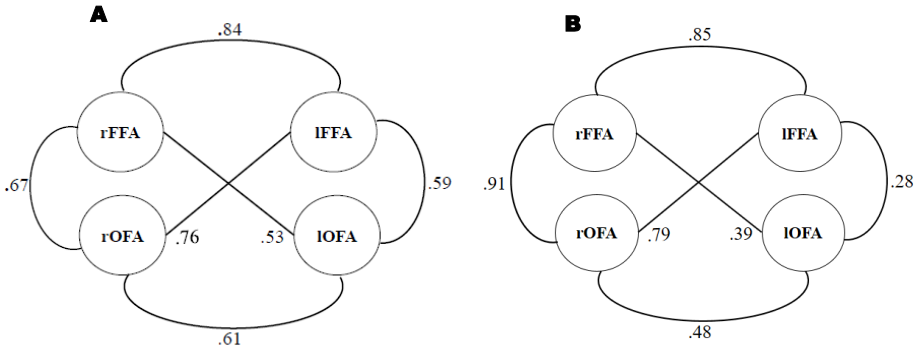

Figure 4. Functional Connectivity Circuit of the Localizer sequence **A.** Control's correlation values. **B.** Patient's correlation values

A very similar pattern of connectivity between face-selective regions was obtained when we used the Experimental sequence. As in the localizer sequence, face-selective areas in the control participant's brain were all strongly and positively connected (see Figure 5A). Specifically, the right OFA and the left FFA (fisher transformed R=.77); the right FFA and the left FFA (fisher transformed R = 0.76); the right FFA and the right OFA (fisher transformed R= .75); the right OFA and the left OFA (fisher transformed R= .74); the left OFA and the left FFA (fisher transformed R= .68); and the right FFA and the left OFA (fisher transformed R= .64). On the other hand, Patient AD's face network seemed to have a normal cluster that included the FFAs and the right OFA, that was weakly connected with the left OFA (see Figure 5B). We found positive and strong correlation between the right FFA and the right OFA (fisher transformed R= .95; the right FFA and the left FFA (fisher transformed R= .89); the right OFA and the left FFA (fisher transformed R= .88). Lower correlations values were found between left OFA and right OFA (fisher transformed R= .53); left OFA and left FFA (fisher transformed R= .51); and left OFA and right FFA (fisher transformed R= .50).

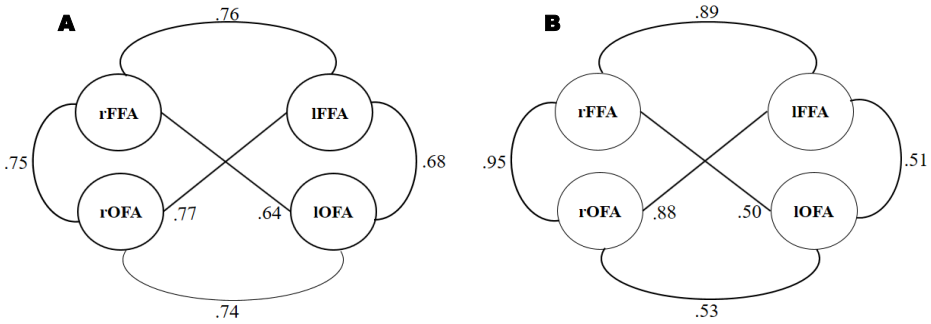

Figure 5. Functional Connectivity Circuit of the Experimental sequence **A.** Control's correlation values. **B.** Patient's correlation values

PPI Analysis – We then used PPI analysis to test whether this disconnection between left OFA and the remaining areas in Patient AD (that contrasted with our control participant) was dependent on the processing of faces (when compared to the processing of a control category – places). We wanted to know how other clusters of voxels in the brain increase their association with each seed ROI when processing this specific category of stimuli. We used each ROI as a seed region for a PPI analysis and used a stringent correction for multiple comparisons (Bonferroni correction).

In Figure 6, we can see the areas that show heightened connectivity with the **right FFA** for face processing when compared to the processing of places. In both participants these areas are restricted to areas that match almost completely the other face selective ROIs (right OFA, left FFA, and left OFA). Importantly though, Patient AD's face-specific network does not include the left OFA.

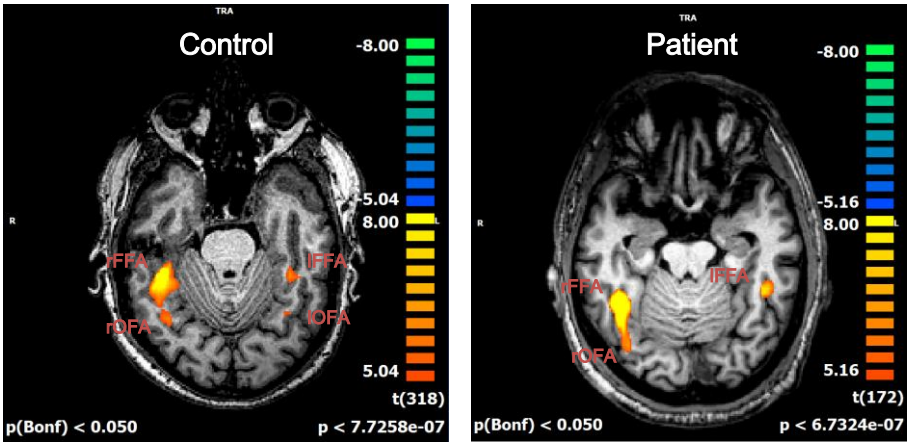

Figure 6. PPI analysis with the right FFA as seed ROI.

In Figure 7, we can see the PPI results for when we use the **left FFA** as a seed region. As for the previous seed region, the control shows heightened connectivity between all of the other face-selective ROIs and the seed region when processing faces compared to when he is presented with places, whereas Patient AD shows heightened connectivity between the seed and all the other face regions except the left OFA.

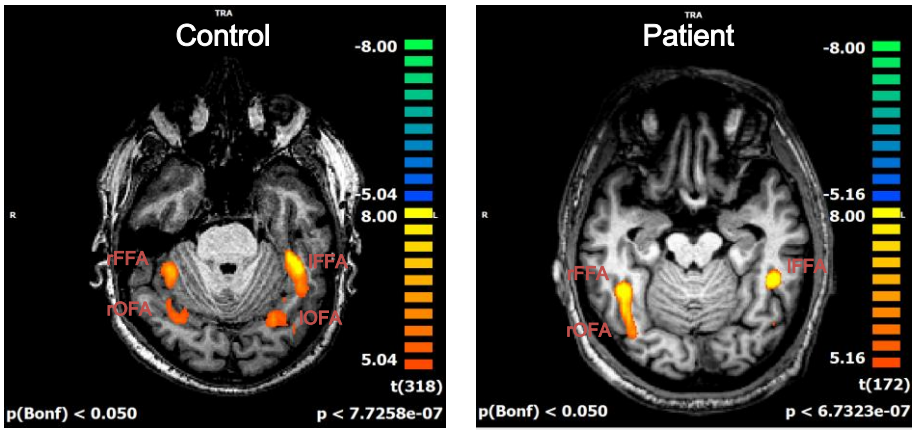

Figure 7. PPI analysis with the left FFA as seed ROI.

In Figure 8, we show the pattern of activity between the **right OFA** and the whole brain when processing faces, when compared to processing places. Once again, while the control's network shows heightened connectivity between the seed region and the other face-selective ROIs, this is not true for the face-selective network of Patient AD. The connectivity between his right OFA and his left and right FFA increases when he perceives faces, when compared to places, but no such increase in connectivity is visible between the seed region and the left OFA.

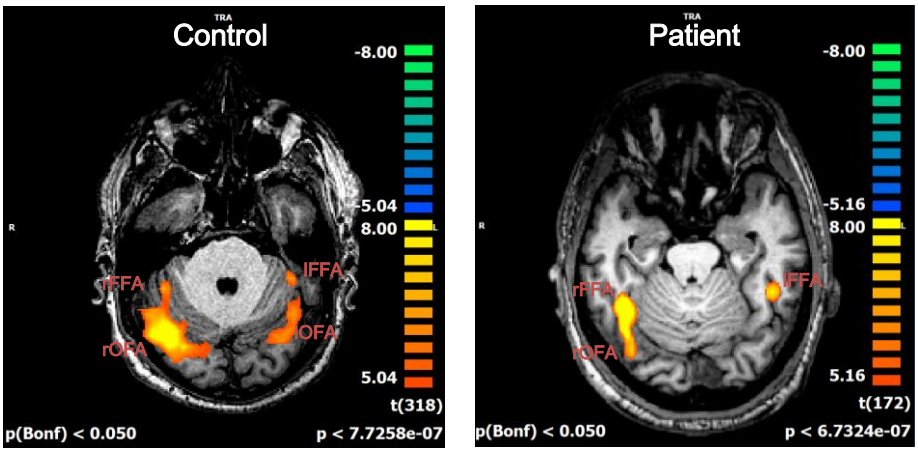

Figure 8. PPI analysis with the right OFA as seed ROI.

Finally, in Figure 9 we focus on the connectivity between the **left OFA** and the whole brain. The pattern of this analysis is striking – no area in the brain shows heightened connectivity with the left OFA when Patient AD is processing faces compared to when he is processing places. This is in contrast with the control's face-specific connectivity network. All areas, with the exception of the right FFA show increases in connectivity with the left OFA during face processing.

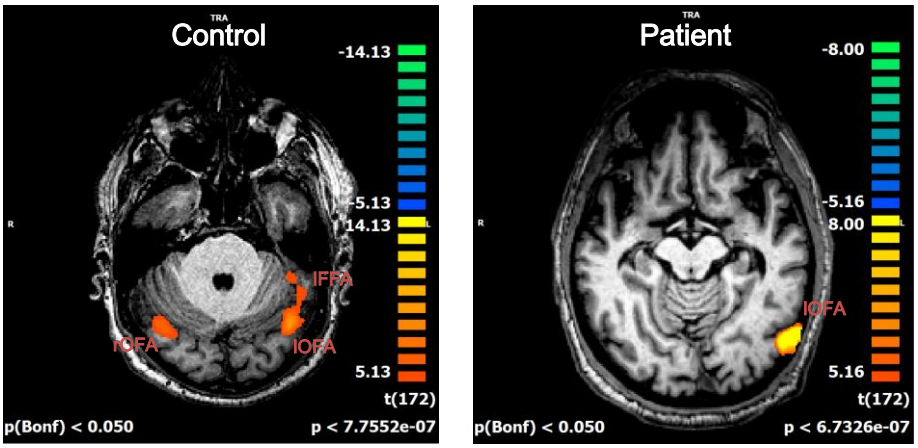

Figure 9. PPI analysis with the left OFA as seed ROI.

Our first ROI analysis suggests that the processing of faces is performed in all core areas of the face processing network. Right FFA, left FFA, right OFA and left OFA show a higher response for faces versus places in both control subject and Patient AD. We then used these ROIs in our functional connectivity and PPI analysis. Functional connectivity analysis show that all the core areas of the two participants are positively related with each other. Strong to moderate correlations were found in all the control subject ROIs connections, both in the Localizer and Experimental sequences. However, Patient AD results show weaker correlations in all the left OFA connections for the two sequences.

The PPI analysis also suggest a problem in the connections of Patient AD's left OFA with the remaining regions of the face processing network. The activation of this area doesn't seem to be influenced by the activity of the other areas and doesn't seem to influence the activity of other areas in the brain as well. In contrast, the control's data show that all the face-selective areas seem to increase their activity together with each seed ROI.

Taken together our results suggest that although Patient AD's left OFA shows increased response when processing faces, there may be a problem in the passage of information between this area and the remaining face-selective areas. Interestingly, the OFA is responsible for the processing of specific elements of the face (e.g. eyes, nose and mouth). This functional connectivity pattern demonstrates a failure in integrating the information coming from the left OFA in the face-processing circuit – i.e., face parts in the left part of the face. This connectivity failure is then probably responsible for the abnormal perception presented by Patient AD. Patient AD's holistic processing faces seems to be preserved - he shows no problem in recognizing faces, even when only half of the face is presented. This type of processing is potentially supported by the FFAs.

IV – General Discussion

The domain-specific hypothesis states that the brain is organized in a specific way in order to facilitate efficient processing of categories of objects that are important to our survival. It argues that evolutionary pressures led to the emergence of neural networks specialized in the recognition of this type of categories (Caramazza & Mahon, 2006; Caramazza & Mahon, 2011; Caramazza & Shelton, 1998). To be able to recognize faces instantly is an essential ability in our social networking toolbox and facilitates successful social interactions. Because of that, and following the assumptions of the domain-specific hypothesis, we have probably evolved with a particular network that is specific for the processing of faces. However, the way these areas are functionally connect, and this connectivity impacts how we process faces is not clear.

In this thesis we studied a case of a patient with hemi-prosopometamorphopsia restricted to the left side of the face due to a lesion in the splenium of the corpus callosum. The study of this highly specific deficit can lead us to better understand the functional organization of face processing network. Using behavioral and fMRI data we aimed to characterize the functional *locus* of the deficit.

Patient AD, a 62 year-old right handed man, reported seeing the left half of people's faces distorted. Particularly, he claims that the left eye, left side of the nose and left corner of people's mouth seems to be dropping down. The neurologic exam shows no relevant medical history or medication, no cognitive deficits or problems in visual acuity. On neuropsychological assessment Patient AD evidences some decline in verbal memory with interference, logical memory and associative memory. This pattern of impairment may be due to the depressive syndrome that he developed in reaction to the hemi-prosopometamorphopsia (Houston & Bondi, 2006). On face recognition assessment (Benton Facial Recognition Test and CATS) he shows no problems in recognizing faces.

Our first experiment, a volumetric study, aimed to study Patient AD neuronal integrity and possible age-related effects on its cerebral volume. We decided to segment the hippocampus because the volume of this structure is highly (and negatively) correlated with healthy and pathological aging (Raz et al., 2005; Raz & Rodrigue, 2006). We manually segmented the left and right hippocampus of both the patient and the control participant and compared it with data from volumetric studies using large samples of healthy participants (Gur et al., 2002; Pruessner et al., 2000). Results show us that the volume of the hippocampi of Patient AD is within the normal range for his age, suggesting that there are no significant pathological age-related changes.

We then characterized Patient AD's deficit in terms of its categorical specificity, and put forth a behavioral experiment – Experiment 2 – to characterize the deficit. In Experiment 2a we presented a sequence of stimuli

belonging to either the category of faces or to categories other than faces. Patient AD had to report whether he saw a distortion in the stimuli or not. Results indicate that the deficit is specific for faces. In Experiment 2b, we aimed to characterize the deficit further in terms of where the distortion is located within the perceived face. We presented 125 pictures of faces varying in several conditions such as upright, inverted, left half of the face, right half of the face, left profile and right profile. Results show us that the deficit more significantly occurs in the left side of the face, even when only half of the face is presented, and independently of its rotation or orientation. Moreover, the patient always reported seeing the distortion in the same face elements: the left eye, the nose, and the left corner of the mouth. These data suggest that the deficit is object centered, occurring in a more complex level of processing posterior to the 3D perception of the face.

In Experiment 3, an fMRI study, we aimed to characterize the face processing network in terms of its functional connectivity, in the context of the behavioral performance of Patient AD. We started by using a Localizer sequence to define which areas respond more to faces than to other categories of objects (we used the typical contrasting category of places/houses). Results show that despite his face deficit, Patient AD presented all of the core face processing areas when we contrasted the activation for face stimuli *versus* house/place stimuli (particularly the right OFA, right FFA, left OFA, and the left FFA). We then analyzed functional connectivity patterns between these areas, based on their time course, when processing two sequences of stimulus: the Localizer sequence (with different categories of stimuli) and the Experimental sequence (where only faces were presented). We found that all the face-selective areas were positively connected with one another in both the control participant and Patient AD. Strong to moderate correlation values were found between all the face areas for the control participant, whereas for Patient AD, all areas but the left OFA were strongly correlated with one another.

We then conducted a PPI analysis in order to identify other clusters of voxels in the brain that increase their association with each face-selective region when the participants were processing faces in comparison to when they were processing a control category (places). In the control participant's data we observed that all the core regions seem to show increased connectivity with each other when he was processing face stimuli versus when he was processing place stimuli. In other words, all of the face-selective areas seem to be fully communicating in order to process faces. When analyzing Patient AD's data, we observe that his left OFA does not seem to be connected with the other regions of the face processing circuit – i.e., irrespectively of the seed region used in the PPI analysis over Patient AD's data, the left OFA never showed increased connectivity with the seed region during the processing of faces when compared to the processing of places. Moreover, when we used the left OFA as seed region, no other brain areas seem to increase their connectivity with this region during the processing of faces. From this functional connectivity pattern we can conclude that, although all the core

areas of the face processing network showed a selective response for faces, there seems to be a problem in the connection of the Patient AD's left OFA with the remaining areas of his face processing network.

Patient AD's deficit may be then explained by the role of the OFA within the face processing network, and the fact that in Patient AD this region seems to be disconnected from the face network. As previous studies suggest (Liu et al., 2010; Nichols et al., 2010; Pitcher et al., 2007), the OFA is associated with the processing of face parts like the eyes, the nose and the mouth. Interestingly, these face elements correspond to those that the patient reports seeing distorted. Because of the apparent disconnection between the left OFA – the area that putatively processes face parts in the part of the face that is typically on the right hemisphere, i.e., the left part of the face – and the remaining face-selective regions, there may be a failure to correctly register the information on the specific face elements with the holistic understanding of the face. Interestingly, his 3D processing of the face seems to be spared – Patient AD shows no impairment in recognizing faces (even when only half of the face is presented). This may be explained by the fact that this holistic representation of the face is supported by the FFAs, where no impairment was observed. That is, the problem may be in the integration of the information of faces parts coded by the OFAs (specifically the left OFA) with the holistic perception processed by the FFAs.

But how does a corpus callosum lesion lead to a face-specific deficit? The posterior part of the splenium is crossed by a fiber bundle – the forceps major (Knyazeva, 2013; Schmahmann, & Pandya, 2006). This bundle connects the occipital regions of the brain and seems to match the location of the Patient AD lesion. Our hypothesis is in line with studies from Avidan and Behrmann (2014) which suggest that abnormalities on this tract seem to be associated with deficits in the functioning of the OFA and the passage of the information to the other parts of the face network.

Limitations and Future Directions

The study of a very rare clinical condition typically introduces a set of limitations. Hemi-prosopometamorphopsia is a highly rare symptom, which makes it very unlikely to find similar cases to study that could improve the reliability of our results. Note however, that the single case methodology rests on the idea that these patient's performance constitutes proofs of concept that can disprove extant theories. One possible option to circumvent this problem is to collect more data from these types of patients. In the case of Patient AD, his deficits has also forced him to withdraw from regular social interactions. He feels extremely uncomfortable when he has to focus on faces – this has limited the amount of data we could collect from this patient at a single time. Nevertheless, we will certainly collect more data in the future. Moreover, we will also collect data from a larger sample of control participants.

As for future directions of this study, we are currently analyzing DTI data that will be useful for testing our hypothesis on the functional and neuroanatomical deficit of Patient AD – i.e., is deficit is a consequence of a problem in the connection between the left OFA and the other face-selective areas. This analysis may help to clarify the pattern of disruption caused by the lesion on the splenium of the corpus callosum. Finally, another important research direction is to focus on the representational content of each individual area to ascertain whether this is just a connectivity issue, or whether this connectivity problem also impacts the actual functional organization of the left OFA.

V – Conclusions

Our results suggest that the hemi-prosopometamorphosia defict is associated with a disruption in the connection of the left OFA with the remaining areas of the face processing network. The distortion perceived in specific elements of the face (eye, nose and mouth) may be explained by the fact that OFA is responsible for the processing of face parts. Moreover, the left OFA should process face aspects that are typically within the right visual field – i.e., the left part of the face. This is exactly what Patient AD shows. Our data suggests that there is a problem in registering the information processed within the left OFA – face parts on the left part of the face – with the remaining face-selective regions. In patient AD, this registration is certainly not complete and leads to a distortion specific to the parts of the face. That is, this part-based processing is not fully integrated with the holistic processing supported by the FFAs.

The pattern of functional connectivity observed in Patient AD may be associated with the location of his lesion on the splenium of the corpus callosum. There may be a disruption in the forceps major - the fiber bundle that crosses this brain structure - that seems to be associated with the connection of the occipital face-selective areas.

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