EYE REGION PROCESSING: INSIGHTS FROM ACQUIRED PROSOPAGNOSIA

by

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Abstract

Face processing models propose a holistic representation of faces in the human brain. Additionally, behavioral studies in healthy individuals indicate a bias towards the eye region of faces, namely a Feature Salience Hierarchy. The exact mechanisms of this feature salience hierarchy are not known. Using behavioral face perception and neuroimaging experiments, we investigated the perceptual mechanisms and the neural correlates of the feature salience hierarchy, and the correlations of the human perceptual performance with the neural signal. Prosopagnosia studies also indicate an asymmetrical loss of the ability to deduce information from the eye region of faces. In a cohort of ten acquired prosopagnosia patients, we investigated and characterized the relationship between the structural brain damage and the behavioral face processing impairments. This dissertation examines the perceptual and neuroanatomical bases of the bias towards the eye region of a face in healthy individuals and the deviation from this bias in relation to the brain lesion locations in acquired prosopagnosia patients. Our findings confirm the dominance of the eyes in feature salience hierarchy in an adaptation aftereffects experiment. Investigation of the neuroanatomical correlates of the feature salience hierarchy shows that the activation pattern in Fusiform Face Area (FFA) correlates with the human perceptual performance, suggesting FFA's involvement in the feature salience hierarchy demonstrated for the eye region of faces behaviorally. Examination of the eye region processing in prosopagnosia patients shows that both apperceptive and associative variants of prosopagnosia can cause eye region processing deficits, yet apperceptive prosopagnosia patients with inferior occipitotemporal cortex lesions have significantly more severe deficits in eye region processing. Face scanning patterns in a learning and memory task with unlimited viewing times demonstrate

that both healthy and prosopagnosic individuals spend more time looking at the upper halves of faces while learning the faces, yet prosopagnosia patients spend significantly longer durations studying the faces. Our investigation of memory for half faces indicate that when presented in isolation, the upper and lower face halves do not have different contributions to face memory in healthy subjects. Prosopagnosia patients are similarly impaired in memory for upper and lower face halves.

Preface

I had sole primary role for experimental design, data collection, and data analysis for work described in Chapter 2.

I had equally shared responsibility with Joshua Lai for experimental design, data collection, data analysis, and manuscript preparation for work described in Chapter 3. Additionally, Dr. Jodie Davies-Thompson participated in experimental design, data analysis and manuscript preparation. Dr. Ipek Oruc participated in data analysis. A version of Chapter 3 has been published. Lai J*, Pancaroglu R*, Oruc I, Barton JJS, Davies-Thompson J. (2014). Neuroanatomic correlates of the feature-salience hierarchy in face processing: An fMRI-adaptation study. Neuropsychologia 53: 274-283. *equal contribution.

I had the primary role of data collection, and data analysis of the work described Chapter 4. Patients were recruited by Dr. Brad Duchaine. Alla Sekunova, Dr. Guiseppe Iaria, Dr. Sam Johnston and Dr. Jodie Davies-Thompson assisted in data collection.

I had the primary role of data collection, and data analysis of the work described in Chapter 5. Alla Sekunova and Charlotte Hills assisted in data collection.

I had the primary role of experimental design, data collection, and data analysis of the work described in Chapter 6. I was assisted by Jaya Viswanathan in experimental design and data analysis.

I had the primary role of experimental design, data collection, and data analysis of the work described in Chapter 7. Dr. Thomas Busigny assisted in experimental design.

Dr. Jason Barton provided a supervisory role in the experimental design, data collection, data analysis, and manuscript preparation for all the work described in Chapters 2-7.

The name of the particular UBC Research Ethics Boards, and the Certificate Numbers of the Ethics Certificates obtained for the research described in this thesis are: UBC Behavioral Research Ethics Board B04-0732 and UBC Clinical Research Ethics Board C05-0290.

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List of Abbreviations

AT: anterior temporal

B-AT: bilateral anterior temporal

B-ATOT: bilateral anterior temporal and occipitotemporal

B-IOT: bilateral inferior occipitotemporal

BOLD: Blood-oxygen-level-dependent

EEG: Electroencephalography

FFA: Fusiform Face Area

fMRI: functional Magnetic Resonance Imaging

IOT: inferior occipitotemporal

L-IOT: left inferior occipitotemporal

OFA: Occipital Face Area

pSTS: posterior Superior Temporal Sulcus

R-AT: right anterior temporal

R-IOT: right inferior occipitotemporal

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Dedication

This dissertation is dedicated to my dear parents Özel & Ahmet Kemal Pancaroğlu and to my dear husband Dr. Filip Louis Arsene Van Petegem.

Sevgili Anneciğim ve Babaciğim,

Başarabildiğim hersey, sizin sayenizde ve sizin icin. Hayatta başarilardan sayilan bu tezi, size ithaf ediyorum.

Liefste,

Dank je voor alles!

Chapter 1: Introduction

1.1 Face Processing in the Human Brain

Face processing is a classic example of high-level object processing in the human visual system. Human beings are highly skilled experts in processing faces. Accurate processing of faces, especially of the identity and expression aspects, is vital for human social interactions and communication. This vital component of human behavior is disturbed in patients with impaired face perception such as prosopagnosia (Barton 2003) and in individuals with developmental social disorders such as autism spectrum disorders (Hefter et al., 2005; Barton et al., 2007a). Studies of face processing provide insights for understanding the brain mechanisms involved in visual information perception as well as the general functional organization of the human brain. Additionally, discoveries from face processing studies are valuable for developing face processing rehabilitation programs for patients with brain damage (Powell et al., 2008), and for generating developmental face training programs for children with developmental social disorders (Tanaka et al., 2010). Given its significance in human social interactions and in understanding the functional organization of the human brain, face perception has been extensively studied by numerous research groups using various methods over the last decades. Although there have been multiple significant discoveries along with advancements in neuroimaging, the exact mechanism(s) of face perception in the human brain is not fully established.

Behavioral studies of face processing suggest that facial structure and configuration are represented as an integrated whole, or holistically, rather than individual parts of a face (Tanaka and Farah 1993; Farah et al., 1998, Goffaux and Rossion 2006). On the other hand, several

behavioral studies of face perception in healthy individuals indicate a bias towards the eye region of faces (Vinette et al., 2004; Henderson et al., 2005; Barton et al., 2006), namely a "Feature Salience Hierarchy" (Shepherd et al., 1981). Furthermore, a deviation from this bias towards the eye region has been observed in conditions affecting face processing such as prosopagnosia (Barton et al., 2007b) and autism spectrum disorders (Klin et al., 2002; Pelphrey et al., 2002). These findings suggest that there may be differences in the processing of the upper and lower parts, specifically the eye region, of faces. This behavioral bias towards the eye region of faces raises the question of the perceptual and neuroanatomical bases of the feature salience hierarchy. Studies so far demonstrate this bias, and humans subjectively experience it in daily interactions with conspecifics, yet it is not known whether this is simply a reflection of the low level physical properties of the face structure, e.g. different contrast levels across the face, a hardwired response to the invariant first-order configuration of face features, or the reflection of a top-down face network mechanism which could be task dependent and/or hardwired in the brain. If it is not a mere relay of the low-level physical properties of faces, where in the visual system does this bias arise? Which brain regions are involved in the computation of the spatial relationships of face features? There is recent neuroimaging evidence showing that the fusiform face area and the occipital face are sensitive to individual face parts (Liu et al., 2010). Is there a difference in the activation of these brain regions in response to different face parts? How do the activation patterns in these brain areas correlate with the perceptual behavioral patterns? This dissertation examines the contribution of the eye region in face processing in healthy individuals with the goal of determining the neuroanatomical correlates of eye region processing, and attempts to characterize eye region processing impairments in acquired prosopagnosia with the aim of determining the relationship of the eye region processing impairments and anatomical damage in

these patients. Previous studies indicate a dissociation of the processing of face identity and face expression in the human brain (Haxby et al., 2000; Barton 2003; Duchaine et al., 2003; Fox et al., 2009a, 2011). In order to avoid complications that could arise from including face expression tasks, and to simplify the interpretation of the findings, the scope of the dissertation has been restricted to the identity component of face processing.

This chapter summarizes the seminal findings and current models in face processing research, describes acquired prosopagnosia, and explains the evidence for feature salience hierarchy in face processing and how it could be disturbed in acquired prosopagnosia before stating the hypotheses driving the studies.

1.1.1 Configural Face Processing

Human beings can identify faces accurately, despite enormous variability in the conditions of observation and the physical properties of the observed face over the course of different life stages. The flawless expert-level face processing abilities of typical human viewers are considered to be achieved through configural processing of faces (Maurer et al., 2002). The configural face processing requires the detection of a face as "a face" based on the first-order relations of the face features, basically the positioning of two eyes on the upper half of the face under the eyebrows, a centrally positioned nose under the eye region, and a mouth located below the nose. A preference for stimuli similar to a first-order face configuration over other configurations is observed even in newborns and babies six weeks old (Morton and Johnson 1991; Mondloch et al., 1999; Simion et al., 2002).

It is suggested that along with the detection of the stimulus as "a face" based on its first-order relations, a face is processed as a gestalt, an organized whole rather than the sum of its

parts (Tanaka and Farah 1993). There are signature behavioral patterns demonstrated by human observers selectively for faces which support this holistic face processing view. One of these characteristics is the Face Inversion Effect. The processing of face identity is significantly impaired when a face is presented upside down, and the loss of this discrimination ability is disproportionally large for faces compared to other object categories (Yin 1969; Valentine and Bruce 1988; Sekuler et al., 2004). The Thatcher illusion is one of the most striking demonstrations of the loss of the ability to perceive faces properly in the upside down orientation (Thompson et al., 1980). In this demonstration, the individual features are not inverted and remain in their canonical upright orientation in an inverted face, but observers do not detect any peculiarity in the inverted face. Observers realize that the face looks grotesque only after the inverted image is rotated back to its upright orientation. These seminal studies and numerous repetitions of the face inversion effect in several follow-up studies indicate an orientation and configuration specific processing of faces, and have led to the idea that faces are processed by a unique expert mechanism (Diamond and Carey 1986).

Further behavioral studies have shown that subjects use the differences in the internal features, such as the eyes, nose, mouth of a face as well as the differences in the external features, such as hair, chin, jaw-line in face perception tasks (Ellis et al., 1979; Young et al., 1985; O'Donnell and Bruce 2001). The external features of a face can alter the perception of identity. The same internal features of a face can be perceived as a new identity when combined with the external features of another face (Young et al., 1985; Andrews et al., 2010). Merging the external features of a famous person with the internal features of another person can also cause the subjects to perceive the merged face as the famous person with those external features (Sinha and Poggio 1996). Furthermore, changing only the lower or the upper half of a face can cause the

subjects to perceive it as a new identity, which is known as the Composite Face Effect (Young et al., 1987; Goffaux and Rossion 2006; Rossion 2013). Subjects report the illusion of perceiving a new identity, and realize that only half of the face is different after the upper and lower halves of the composite face are misaligned.

Another important characteristic of face perception is the "Whole/Part Advantage". Experiments by Tanaka and Farah have shown that subjects are better at identifying the features of a learned face in a whole face presentation compared to the isolated presentation of the face parts individually (Tanaka and Farah 1993). These findings indicate that the presence and the successful encoding of the spatial relationships between the features of a face provide an advantage in learning and remembering faces. It has been suggested that processing of the second-order relationships between the features of a face are an essential component of face recognition (Diamond and Carey 1986; Rhodes 1988; Maurer et al., 2002). Indeed, healthy observers are very sensitive to small changes made to the relative position of the mouth or the eyes without changes in the individual features themselves (Barton et al., 2001a). Barton and colleagues suggested that the biggest effect of face inversion is the reduction in discrimination of second-order spatial relations of face features. This decline in the discrimination ability for second-order spatial relations of face features for inverted faces suggests that the processing of the second-order relations of face features in the upright configuration is an integrated component of holistic face processing, and is necessary for successful individualization of a face at the within-category level (Maurer et al., 2002).

Overall, the face inversion effect, the composite face effect, and the whole/part advantage are all considered as evidence that face structure and configuration are processed and represented

as an integrated whole, or holistically, rather than as a collection of individual face parts through a feature-based processing.

1.1.2 Face Processing Network and Cognitive Models of Face Processing

Neuroimaging studies reveal a network of regions in the human brain that show activation in response to face stimuli. Studies so far show that face processing involves an extensive network of cortical regions with right hemispheric dominance (Sergent et al., 1992; Haxby et al., 2000; Ishai 2008; Fox et al., 2009b; Li et al., 2009). Within this extensive network, three regions in the occipitotemporal cortex which show higher response to faces than to any other object category are called the Core Face Processing Network. These regions are an area in the inferior occipital gyrus, known as the Occipital Face Area (OFA) (Gauthier et al., 2000a), an area in the lateral middle fusiform gyrus, known as the Fusiform Face Area (FFA) (Sergent et al., 1992; Haxby et al., 1994; Kanwisher et al., 1997; McCarthy et al., 1997), and an area in the posterior part of the Superior Temporal Sulcus (pSTS) (Puce et al., 1998; Hoffman and Haxby 2000). These regions are supplemented by an extended system which includes many other regions of the ventral visual pathway, such as the anterior fusiform gyrus, the posterior parahippocampal gyrus, the perirhinal cortex, the amygdala, and the anterior temporal pole (Ishai et al., 2005; Gobbini and Haxby 2007; Barbeau et al., 2008; Tsao et al., 2008; Fox et al., 2009b; Weiner and Grill-Spector 2010). A region of the tip of the collateral sulcus, named the anterior temporal face patch, has also been identified as a face-selective area in the human brain, and is a current area of interest as a past-FFA brain region for face processing in the human brain (Kriegeskorte et al., 2007; Nasr and Tootell 2012). In addition to the extended system regions in the ventral visual pathway, recently

an area at the junction of the right inferior frontal sulcus and the precentral sulcus has also been identified as a face-selective area in the lateral prefrontal cortex (Chan and Downing 2011).

Before data from functional neuroimaging studies were available, Bruce and Young proposed an elegant cognitive model for face processing. According to their model, face processing consisted of two parallel mechanisms (Bruce and Young 1986). The changeable aspects of faces, such as emotional expression, gaze direction, viewpoint were processed via one mechanism, and the invariant aspects of faces, mainly identity, was processed via the other. The model suggested a hierarchy of stages with an early stage of processing where the structural encoding of faces took place (Bruce and Young 1986). The output of this stage was then further processed by separate systems for face identity, emotional expression, and face speech analysis. In case of face identity, the output of the structural encoding generated a percept, which was then matched to a face from face memory stores named Face Recognition Units (FRUs). If there was an FRU match to the face percept, this activated person identity nodes (PINs), which in turn activated name recognition units (NRUs) and semantic information units (SRUs) which contained biographical information about the person. PINs, SRUs, and FRUs were proposed to be multimodal and activated by other cues than faces, such as voice, gait, or gestures (Bruce and Young 1986).

Haxby and colleagues combined the original model of Bruce and Young with results from neuroimaging studies and proposed a modular hierarchical model whereby the perceptual encoding of facial structure occurs in the OFA as the first stage (Haxby et al., 2000). It is considered that the OFA is more sensitive to representation of face parts than the full face configuration of face parts (Pitcher et al., 2007; Liu et al., 2010). The output from OFA is considered to be conveyed to the FFA and the pSTS in a parallel fashion. The response patterns

in FFA are correlated with detection and identification of faces (Grill-Spector and Malach 2004), and FFA is activated by face parts as well as the external features of faces (Liu et al., 2010). The response of FFA to faces is not affected by the size of the face stimulus (Schwarzlose et al., 2008). Based on these results, FFA is considered to be the brain region where the invariant aspects of a face are processed and the ultimate face identification takes place. Additionally, recent studies using multivariate pattern analysis have confirmed FFA's role in face identity, and have showed the involvement of a network of cortical regions in a face individuation task (Nestor et al., 2011). In pSTS, the changeable aspects of faces, such as expression are processed (Haxby et al., 2000). According to the Haxby model, the core face processing network connections are bidirectional and include direct connections of the FFA with the pSTS. The model suggests that the core network is linked to the extended face processing network with bidirectional connections. Another recent neuroimaging study has shown that both the FFA and the pSTS are sensitive to face identity while the anterior STS is sensitive to facial expressions (Winston et al., 2004). Later on, Fox and colleagues showed that FFA and pSTS are sensitive to both face identity and face expressions when the participants are attending to facial expressions in a task dependent manner (Fox et al., 2009a). Combining the results so far, current cognitive models of face processing propose that faces are represented in a modular hierarchical system which includes parallel, bidirectional, and interacting pathways for different aspects of face information such as identity and expression (Bruce and Young 1986; Haxby et al., 2000; Calder and Young 2005; Downing et al., 2006; Fox et al., 2009a).

In parallel with the findings from neuroimaging studies, electroencephalography studies using event-related potentials (ERPs) design revealed a negative potential in the EEG signal in response to face stimuli at around 170ms after stimulus onset (Bentin et al., 1996). This

response, named the N170, is significantly larger for faces than for other object categories and it is most consistently recorded over the right posterior temporal regions of the scalp (Bentin et al., 1996; Rossion and Jacques 2011). In addition, intracranial electrophysiological recordings in epilepsy surgery candidate patients recorded from the inferior surface of the right fusiform gyrus and the surface of the right inferior temporal sulcus revealed a negative potential response selectively for faces at 200ms after stimulus onset, named the N200 response (Allison et al., 1994).

Whether the regions involved in face processing are specific to faces reflecting a domain-specific modular processing (Kanwisher 2000), or shared by other non-face objects representing an expert-level object processing (Tarr and Gauthier 2000) is an ongoing debate. Gauthier and colleagues have shown that training subjects to expert-level familiarity with a category of computer generated objects called "greebles" results in increased activation in FFA in response to the greebles (Gauthier et al., 1999). In a separate study, they have also shown that bird and car experts showed higher activation in FFA in response to birds and cars respectively in comparison to other objects (Gauthier et al., 2000). Yet, another study showed that face identification specifically activated the FFA, whereas non-face object identification activated other areas of the ventral occipitotemporal cortex but not the FFA (Grill-Spector et al., 2004). One of the main obstacles in resolving this issue is the heterogeneity of the level of expertise among humans for object categories other than faces. In cases where neuroimaging studies of face processing in healthy individuals cannot establish the critical involvement and contribution of certain brain regions, studies in patients with acquired prosopagnosia have been useful to correlate the effect of the lesion on the face processing network with the behavioral deficits demonstrated by the patients (Barton et al., 2009; Fox et al., 2011). For example, although the exact role of FFA in

visual object processing and its specificity for faces remain to be established, brain lesions which include the anatomical location of this area result in prosopagnosia (Barton et al., 2002; Barton et al., 2008a; Fox et al., 2011), supporting FFA's significant involvement in face recognition.

1.1.3 Acquired Prosopagnosia

Prosopagnosia is defined as a visual disorder with the loss of the ability to recognize familiar faces or to learn new faces (Barton 2003). Individuals with prosopagnosia do not experience a sense of familiarity with faces they have seen before and are unable to identify the person to whom a face belongs. There have been reports of patients who could not recognize familiar faces in the literature as early as mid-19th century. Yet, the term prosopagnosia was first used by Bodamer when he proposed it as a selective visual recognition disorder specific to faces (Bodamer 1947). Even though some prosopagnosia patients may demonstrate a very minor object agnosia, basic object identification at the category level is generally intact in prosopagnosia. Prosopagnosia may involve deficits in high-level face perception, familiarity judgments, and access to semantic processing and facial memory (Barton 2011a), and cannot be explained by general deficits in low-level vision, memory, or cognitive function (Barton 2003). Therefore, an extensive neuropsychological examination of these patients is necessary in order to rule out general problems of perception, cognition or memory. Familiar faces tests using images of celebrities (Barton 2001), and standardized neuropsychological tests such as the Warrington Recognition Memory Test (Warrington 1984) and the Cambridge Face Memory Test (Duchaine and Nakayama, 2006a) are conducted to assess face recognition abilities in order to diagnose these patients. Prosopagnosia patients are typically able to recognize familiar people through other visual cues, such as hair, moles, body, gait, etc., and other sensory modalities, such as

voice (Barton 2011a). In addition, they have preserved semantic knowledge about people and access to names (Barton 2009).

Early case reports and reviews of patient studies stated that acquired prosopagnosia occurred after bilateral damage to the inferior occipitotemporal cortex (Meadows 1974; Damasio 1982), and also after unilateral damage to the right inferior occipitotemporal cortex (de Renzi 1986, Landis et al., 1986). In addition, there have been reports of prosopagnosia cases with damage to the anterior temporal lobes (Barton et al., 2002; Evans Heggs et al., 1995). In very rare cases, unilateral damage to the left inferior occipitotemporal cortex has been reported to cause prosopagnosia, notably in left-handed patients suggesting an anomalous hemispheric specialization in these left-handed patients (Tzavaras et al., 1973; Eimer and McCarthy 1999; Mattson et al., 2000; Barton 2008b). A more recent prosopagnosia case revealed left middle fusiform gyrus and right inferior occipital cortex damage with an intact right middle fusiform gyrus (Rossion et al., 2003). In most recent acquired prosopagnosia cases with clear neuroimaging data, there is a right hemisphere occipitotemporal lesion with or without an additional left hemisphere lesion (Barton et al., 2002), in agreement with the right hemispheric lateralization of the face processing network in healthy individuals (Kanwisher 1997). In summary, patient case studies complete with imaging data so far indicate that prosopagnosia can occur as a result of unilateral damage to the right hemisphere or bilateral damage.

Following the current models of face processing, which propose parallel hierarchical mechanisms for processing face identity and facial expression, it is considered that deficits in the processing of identity and expression could be dissociated in acquired prosopagnosia patients with different lesions, and that some types of face information processing may be preserved in prosopagnosia (Fox et al., 2011). Indeed, the acquired prosopagnosia patients examined in the

Fox study revealed intact abilities in processing emotional expression of faces. The perceptual face processing deficits present as the main issue in some prosopagnosia patients, while in others the perceptual face processing abilities are intact, yet there are problems in associating the perceived faces with existing face memory stores (de Renzi et al., 1991). The occurrence of different types of deficits and different brain damages resulting in prosopagnosia has led to a functional classification of two variants of prosopagnosia. These are proposed to be the apperceptive and associative variants of prosopagnosia (Damasio et al., 1990; de Renzi et al., 1991; Barton 2008a). Currently it is considered that apperceptive prosopagnosia occurs due to problems with structural coding of faces, whereas associative prosopagnosia results from problems with face memory. Previous work from our laboratory and others suggests that deficits in face structure encoding are caused mainly by damage to the occipitotemporal lobes that span the fusiform gyrus, whereas deficits in face memory and access to face memory are caused mainly by damage to the anterior temporal lobe (Damasio et al., 1990; Barton et al., 2002; Barton and Cherkasova 2003; Barton 2008). Supporting the parallel hierarchical processing mechanisms for face identity and expression, damage to the right STS impairs processing of face expression in a dissociated fashion from face identity (Fox et al., 2011). In cases of prosopagnosia with inferior occipitotemporal lesions, the FFA (Barton et al., 2002) and the OFA (Steeves et al., 2006; Rossion et al., 2003) may be damaged depending on the span of the lesion(s), whereas in patients with anterior temporal lobe lesions the core face processing network is preserved (Pancaroglu et al., in preparation).

The main structural face processing issues in apperceptive prosopagnosia are primarily deficits in spatial arrangements of face features (Barton et al., 2002; Joubert et al., 2003), and holistic face processing (Kimchi 1992; Bukach et al., 2006; Busigny and Rossion 2011). Some

prosopagnosia patients have demonstrated a feature-by-feature studying of faces instead of the holistic strategies demonstrated by healthy individuals (Levine and Calvanio 1989; Bukach et al., 2006). In addition, some prosopagnosia patients with occipitotemporal lesions are impaired in processing the configuration of face features (Barton 2002; Barton 2008a; Joubert 2003) which may be essential in processing the identity of an individual face (Rhodes 1988; Barton et al., 2001b). Some prosopagnosia patients with occipitotemporal lesions also show a loss of ability to use information from the eye region of faces. This particular problem with processing of the eye region of faces in prosopagnosia will be further described in the following subsection of this chapter (Section 1.1.3).

The associative variant on the other hand consists of relatively intact structural face processing, but the perceived faces cannot be linked to the existing face memory stores (Tranel and Damasio 1985; Damasio et al., 1990; de Renzi et al., 1991), either due to a loss of connection between face percepts and face memory stores or due to loss of face memory stores. These patients are quite impaired in answering questions about famous faces without actually seeing these faces in a face imagery task (Barton and Cherkasova 2003). Despite a general conservation of face processing abilities in associative prosopagnosia, it should be noted that some patients can still demonstrate some mild perceptual deficits, but these deficits are not as severe as the ones observed in patients with apperceptive prosopagnosia (Barton 2003). Patients with associative prosopagnosia demonstrate comparatively normal face perception and impaired face imagery and memory (Barton 2008a). Overall, there may be small overlaps in the impairments observed in patients with the two different variants of prosopagnosia through the stages of face processing from the perception of a face to the linking of that percept to a face from the face memory store, but ultimately apperceptive prosopagnosia is considered to present

with deficits in structural face perception and relatively intact face imagery and face memory, whereas associative prosopagnosia is considered to present with relatively intact face perception and deficits in face imagery and face memory (Davies-Thompson et al., 2014).

Acquired prosopagnosia, specifically the apperceptive variant of prosopagnosia with occipitotemporal lesions, often presents with certain comorbidities as a result of damage to the brain regions besides the face responsive areas. The most common comorbidity in patients with occipitotemporal lesions is visual field defects. Patients present with upper left or bilateral superior quadrantanopia and in some cases with left hemianopia (Barton 2003; Barton et al., 2004). In cases where the brain damage extends to the lingual gyrus and the medial fusiform gyrus, patients additionally present with achromatopsia (Barton 2011a). It should be noted that studies examining the effect of sensory impairment in recognizing faces have shown that the patients' difficulties in face recognition cannot be explained by their low-level visual impairments, such as visual field defects, in cases where they additionally suffer from these low-level visual comorbidities (De Haan et al., 1995). Another problem observed in patients with occipitotemporal lesions is difficulty in navigating in familiar surroundings (Davies-Thompson et al., 2014).

Integral to the face-specific processing versus expert-level object processing debate is the question of whether the face recognition difficulties of prosopagnosia patients are specific to faces as a result of damage to a region or a network of regions exclusively dedicated to face processing, or a consequence of generally impaired object processing at the within-category individualization level as a result of damage to a region or network of regions dedicated to expert-level object processing. As mentioned above, acquired prosopagnosia patients have generally preserved abilities in identifying objects at the basic category level, e.g., they can

differentiate a bird from a rabbit, etc. However, at the within-category level, examination of fruit and vegetable recognition revealed impaired performance from almost all acquired prosopagnosics tested (Barton 2004; Barton 2008a). It is not clear whether impairments of recognition of object categories other than faces are simply due to damage to regions involved in object processing in proximity to the face processing regions, or due to the damage to the same expert-object processing regions shared by faces and other objects. Neuroimaging data shows a large area of the human lateral occipital cortex in the vicinity of the face-responsive FFA activated in response to general object stimuli (Grill-Spector et al., 2001). These findings support the idea that impaired object recognition in acquired prosopagnosia could result from additional damage to these regions involved in general object processing. On the other hand, it is also possible that testing of acquired prosopagnosia patients generally shows preserved object recognition due to the heterogeneity of object category-specific expertise in the general population, as faces are unique in their necessity to be processed at the individual level unlike any other object category. One way to circumvent this heterogeneous expertise problem for other object categories is to derive a predicted score for visual object recognition abilities based on the acquired prosopagnosia patients' semantic knowledge of that same object category, with the assumption that the semantic knowledge should be intact in acquired prosopagnosia. Results from such an experiment looking at the relationship of a predicted visual performance score for cars based on semantic knowledge for cars and the actual visual test performance showed that most patients performed worse than predicted on the visual car recognition, indicating impaired visual recognition of cars (Barton et al., 2009). On the other hand, a very recent study showed that training prosopagnosia patients on a category of computer generated objects called "greebles" results in increased performance similar to controls for expertise with the greebles,

while the patients' performance did not improve for faces in a matched face training program (Rezlescu et al., 2014). These latest results indicate that the mechanisms involved in expert level object processing may be different than expert level face processing in these patients, supporting the idea that face are processed in a face-specific mechanism in the human brain.

Studies examining skin conductance changes and visually evoked potentials indicate covert face familiarity in acquired prosopagnosia patients (Bauer 1984; Tranel and Damasio 1985; Bauer and Verfaellie 1988; Renault et al., 1989). Behavioral studies with name-cued force-choice tasks are also utilized to reveal covert recognition of familiar faces (McNeil and Warrington 1991; Sergent and Signoret 1992; Barton et al., 2001b). The residual function of the damaged face processing network is considered to be responsible for covert recognition in acquired prosopagnosia (Farah et al., 1993; Barton et al., 2004). The involvement of an intact separate parallel dorsal occipitotemporal pathway to the amygdala via the superior temporal sulcus has also been suggested as an explanation (Tranel et al., 1995).

A limitation in generalizing findings from acquired prosopagnosia research is the uniqueness of each lesion since the size and the range of the lesion(s) vary in each patient. On the other hand, this very limitation can be advantageous in comparative patient studies where the differences in anatomical damage can be linked to differences in face processing abilities in order to establish the anatomical location of various cognitive functions involved. Subsequently, a full and clear taxonomy of the deficits resulting from different lesions is essential for designing effective rehabilitation programs that will target specific aspects of face processing.

In addition to the acquired version of prosopagnosia following brain damage, a developmental form of prosopagnosia in the absence of brain damage has also been identified (McConachie 1976), and is currently a progressing area of prosopagnosia research (Behrmann

and Avidan 2005; Susilo and Duchaine 2013). Similar to the cases of acquired prosopagnosia, individuals with developmental prosopagnosia have preserved face detection abilities, yet they are not able to recognize familiar faces (Duchaine and Nakayama 2006b) despite having no history of brain damage or impaired visual processing (Behrmann and Avidan 2005). Studies have indicated impaired holistic processing in developmental prosopagnosia (Avidan et al., 2011), and a recent study found that individuals with developmental prosopagnosia show the whole/part advantage, demonstrated for all face features by healthy individuals, for the mouth, but not for the eyes (DeGutis et al., 2012).

Loss of ability to use information from the eye region of faces may be an important aspect of the face perception issues in prosopagnosia. Some prosopagnosia patients have demonstrated reduced discrimination performance in the eye region (Barton 2008a), which is the reverse of the better discrimination performance for the eye region of faces demonstrated by healthy individuals. The next section of this chapter describes this bias towards the eye region of faces in healthy individuals and the observations of loss of this bias in some prosopagnosia patients in more detail.

1.1.4 Feature Salience Hierarchy

In his extensive investigations of eye movements of human viewers freely examining various classes of objects and symbols, such as human faces, natural objects, scenes, and words, Yarbus stated that a human viewer's eyes are usually drawn to the features of the face with little consideration of the other parts while observing a human face in paintings, photos, or sculptures (Yarbus 1967). Yarbus further noted that the eyes receive the highest number of fixations followed by the lips and the nose, mentioning that viewers direct their gaze almost exclusively to

the eyes while observing a neutral face. Additional quantitative measure of this observation came from another study which recorded the visual scan paths while viewers examined a face stimulus (Walker-Smith et al., 1977). Walker-Smith and colleagues showed that viewers directed most of their fixations to the eyes, mouth, and the nose of a face with 70% of their fixations directed to the eyes.

Various studies revealed the reflection of the face scanning patterns demonstrated by healthy individuals in their behavioral performance. Studies found that upper face half is more informative than the lower face half for identifying faces (Garneau 1973; Fisher and Cox 1975) and changes to the hair and eyes are more efficiently detected than changes to the mouth, nose, or chin (Baker 1967; Matthews 1978). A series of experiments by different groups measuring recognition accuracy in various tasks revealed a higher salience for eye region and/or the upper halves of faces (Shepherd et al., 1981). When only parts of a masked-face were visible through apertures in a face identification task, participants performed best when the apertures revealed the eye region (Haig 1985). Mean reaction times and mean error rates in an omission detection task were lower for the eye region than the nose and the mouth, indicating higher efficiency in processing the eye region (Fraser and Parker 1986). Altogether, these studies established that some face features were more important and salient than others in face processing, resulting in a Feature Salience Hierarchy (Shepherd et al., 1981; Fraser et al., 1990).

More recent eye-movement studies have reported that healthy subjects direct their gaze to the eyes when recognizing faces (Henderson et al., 2005). However, this pattern is task dependent, and subjects may shift their gaze to the lower face half when the task is to identify expressions (Malcolm et al., 2008). Another study which studied the pattern of fixations while controlling for difficulty across different regions of the face stimuli revealed that healthy subjects

scan the upper face half more (Barton et al., 2006). A series of studies using the "Bubbles" technique showed that the eyes contain the most diagnostic information when the task is the identification of a face (Vinette et al., 2004). This technique involves the random representation of only small parts of a face stimulus at a time to an observer and aims to infer mechanisms of face recognition from the utilization of these small windows of visual information presented (Schyns et al., 2002). Using the same technique, other face areas are detected to be more important when the participants engage in an emotional expression task (Smith et al., 2005), strengthening the idea that the eyes are more important in face identity tasks. Another study found that observers use the region near the eyes to successfully discriminate faces (Sekuler et al., 2004), and the behavioral performance in identity tasks most reliably correlates with the level of horizontal contour information from the eye region of faces (Pachai et al., 2013). Furthermore, modeling of the face scanning pattern of human observers suggests that looking precisely just below the eyes of a face stimulus is optimal for face recognition (Peterson and Eckstein 2012).

Single cell recordings from the fundus of the STS in rhesus monkeys revealed multiple face responsive neurons some of which had high response levels for the isolated presentation of the eyes or the mouth equal to the strong response levels for whole faces (Perrett et al., 1982).Using intracranial electrophysiological recordings in epilepsy surgery candidate patients, Allison and colleagues identified a negative potential response selectively for faces at 200ms after stimulus onset, named the N200 response, recorded from the inferior surface of the fusiform gyrus and the surface of the inferior temporal sulcus (Allison et al., 1994). Their subsequent intracranial recordings revealed regions in ventral occipitotemporal cortex which respond to isolated face parts at about 200ms after stimulus onset (McCarty et al., 1999). The amplitude of this signature N200 was larger for the eyes than for the mouth. The amplitude of the N200

response to the mouth was larger than the response to the nose. Scalp recordings on healthy subjects with the application of similar event-related potential designs by the same group revealed a negative potential change in the EEG signal in response to faces over the posterior temporal brain areas at about 170ms after stimulus onset, named the N170 response (Bentin et al., 1996). This N170 response was significantly larger for isolated eyes than whole faces, while isolated noses and mouths created smaller negative potentials at about 220ms after stimulus onset. Bentin and colleagues suggested that the significantly larger N170 response to isolated eyes may reflect an eye-sensitive cortex region in the human temporal cortex. Another study aimed to answer whether the N170 was indeed the result of an "eye processor" in the occipitotemporal sulcus by measuring responses to whole faces and faces without eyes (Eimer 1998). Eimer found that the amplitude of the N170 signal was not different for faces without eyes, but there was a significant delay in N170 latency for faces without eyes. He concluded that the N170 was most likely related to the structural encoding of face components rather than the activity of an eye-specific "eye processor" in the occipitotemporal sulcus. However, a more detailed analysis of the N170 response for faces and isolated eyes reported that both the amplitude and the latency of the N170 signal were larger in response to isolated eyes than to whole faces (Itier et al., 2005). Application of an adaptation procedure to examine the respective contributions of face parts to the N170 signal also revealed a larger adaptation aftereffect for the eyes (Nemrodov and Itier 2011).

Recent neuroimaging studies also indicate that OFA and FFA are sensitive to face parts, while the FFA is also sensitive to the invariant first-order configuration of faces (Liu et al., 2010). Beyond the core and the extended face processing network in the ventral pathway, a recently-identified face-selective area of the lateral prefrontal cortex, named the right inferior

frontal junction, is also activated by presentation of isolated eyes as well as whole faces (Chan and Downing 2011).

The higher saliency for the eyes of a face stimulus has been suggested to result from the higher contrast properties of the eyes (Gilad et al., 2008). One study has shown that FFA activity indeed reflects low-level physical properties of the face stimulus (Yue et al., 2011). However, other studies examining the response properties of FFA suggest that the activation patterns observed in the core face-processing network cannot be fully explained by low-level stimulus properties (Tong et al., 2000). On a behavioral face identity task, comparison of the better discriminative performance for the eyes demonstrated by human subjects and the performance output of an ideal observer algorithm which is based on low-level contrast properties of the face stimulus revealed that these performances were only partially correlated despite the fact that the eye region had the most diagnostic information for face identity for both the human observers and the ideal observer (Gosselin and Schyns 2001). These findings suggest that the bias for the eye region of faces demonstrated by human behavioral data may not simply reflect the low-level physical properties of the image.

Some prosopagnosia patients, who have lost the ability to accurately identify faces, do not show the bias for eyes observed in healthy individuals, and have more problems perceiving changes in the eyes than in the mouth region (Caldara et al., 2005; Bukach et al., 2006, 2008; Barton, 2008a). When performing a face identification task, healthy individuals scan the upper face more, whereas some prosopagnosia patients demonstrate a reduced number of fixations to the eyes (Barton et al., 2007b). While healthy individuals are better in discriminating changes to the eyes than to other features, prosopagnosia patients do not show this bias to the eye region (Bukach et al., 2006, 2008; Rossion et al., 2009). They are impaired in discrimination changes in

the eye region, but they may still be able to successfully detect changes made to the mouth region of faces. Studies conducted on other prosopagnosia patients also indicate that the patients are particularly impaired in discriminating structural changes made to the eye region of faces (Barton et al., 2002; Barton 2008a). Application of the "Bubbles" technique where only parts of a face are visible through small gaze-contingent windows in a face identification task revealed that healthy individuals gathered most of the diagnostic information from the eyes of the stimulus faces whereas a prosopagnosic subject relied on the mouth region of the faces (Caldara et al., 2005).

Additionally, similar to acquired prosopagnosia patients (Busigny et al., 2010; Ramon et al., 2010), individuals with developmental prosopagnosia also show a deviation from the parts/whole advantage observed for the eye region in healthy individuals (DeGutis et al., 2012). In addition to the eye region, DeGutis and colleagues measured the parts/whole advantage also for the mouth region in individuals with developmental prosopagnosia, and found that the parts/whole advantage for mouth region was intact in these individuals. This study suggests that similar to acquired prosopagnosia patients, individuals with developmental prosopagnosia may also have a loss of capacity to process the eye region and therefore shift their focus to the mouth region.

A similar reduction of eye processing is reported in autism spectrum disorders (Klin et al., 2002; Joseph and Tanaka 2003; Hefter et al., 2005; Pelphrey et al., 2005), and currently Tanaka and colleagues are training their pediatric subjects diagnosed with autism spectrum disorders to look at the eyes of faces (Tanaka et al., 2010). The observations of reduced eye region processing in autism spectrum disorders are more noticeable for face expression processing than for face identity processing, and may have different origins such as an avoidance

of direct eye contact since it is perceived to be threatening (Tanaka and Sung 2013). Nevertheless, they point to a negative cost in face processing similar to that observed in prosopagnosia. Face processing abilities of individuals with autism spectrum disorders are being investigated to develop rehabilitative training strategies for affected individuals (Tanaka et al., 2010), and to increase our general understanding of mechanisms of face recognition (Golorai et al., 2006; Scherf et al., 2010; Weigelt et al., 2012).

Taken together, studies of healthy individuals and patient populations so far suggest that the eye region contains the most useful information for face identification, and that prosopagnosic patients may be particularly impaired in using information from the eye region. Lack of normal patterns of feature salience hierarchy in some prosopagnosia patients most likely reflects loss or damage to perceptual mechanisms which optimally process face identity from the eye region. This could be due to the loss of eye-specific processing if such a mechanism exists, or to a general loss of diagnostic capability from faces which results in the loss of salience of the eyes. Rossion and colleagues suggested that the lack of the feature salience hierarchy in prosopagnosia is due to the loss or reduction of holistic face processing (Rossion et al., 2009). They further suggested that the behavioral pattern of mouth region preference in some prosopagnosia patients could be explained by a larger effect of holistic processing impairment to the eye region since the eye region and the upper face half contains two eyes with eyebrows on top, whereas the mouth is the single standing feature in the lower face half. The demand of processing the second-order spatial relations of the features on the upper face half may overload the damaged face processing network in prosopagnosia patients, leading them to focus on the mouth where there is less demand in the integration of feature information. In multiple studies, impairments of the second-order relations of face features in acquired prosopagnosia has been

linked to damage to the fusiform gyrus (Sergent and Signoret 1992; Joubert et al., 2003; Barton et al., 2002; Barton 2008a; Riddoch et al., 2008; Busigny et al., 2010). These findings bring up the possibility that having lost the optimal holistic processing mechanisms for identifying faces (Ramon and Rossion 2010) prosopagnosia patients resort to a feature-by-feature processing of faces (Levine and Calvanio, 1989; Bukach 2006). Indeed, this strategy can pay off for both healthy individuals and patients on occasions when a particular feature of a familiar face is distinctive, such a big deviated nose or a mole (Ellis and Florence 1990; Duchaine 2000; Rotshtein et al., 2007). A recent study examining the configural and feature-based processing of face information in a classification task in developmental prosopagnosia showed that unlike the healthy individuals who are prone to interference between the two types of processing, prosopagnosics are able to attend to feature information without interference from the global configural information (Kimchi et al., 2012). This evidence suggests that developmental prosopagnosics process feature and configural information separately rather than integrating the face information holistically.

Despite many important discoveries in face processing, the neural basis and the exact mechanisms of the feature salience hierarchy and the exact roles of the brain regions involved remain elusive to this day.

1.2 Adaptation Aftereffects and Repetition Suppression in the Visual System

We used adaptation aftereffects in a behavioral experiment reported in Chapter 2, and a repetition suppression based fMRI-adaptation experiment in Chapter 3. Adaptation aftereffects, repetition suppression, and their use in face processing investigations are briefly described here.

Neural adaptation in general can be defined as the change in the operating properties of the nervous system in response to changes in its inputs (Clifford and Rhodes 2009). In different stages of the visual system, adaptation can occur over multiple temporal scales from milliseconds to minutes (Kohn 2007; Webster 2012). In terms of spatial domain, adaptation can be observed from the firing responses of a single neuron to the hemodynamic response measured as the combined output of a piece of brain tissue consisting of millions of neurons (Grill-Spector et al., 2006).

In the visual cortex, adaptation occurs for a variety of visual sensory attributes from motion (direction, speed) to pattern (orientation, spatial frequency) (Krekelberg et al., 2006). There are perceptual consequences of adaptation; adaptation to a certain stimulus reduces the responses in the neurons that are involved in encoding the adapting stimulus, and thus alters the detection thresholds and the perception of the test stimulus resulting in aftereffects (Levinson and Sekuler 1976; Clifford 2002; Webster 2011). These adaptation aftereffects manifesting as the effect of exposure to a stimulus on the perception of a subsequent stimulus result in a perceptual bias.

Adaptation paradigms provide a very useful tool in studies of face processing to elucidate the functional organization of the visual system (Clifford et al., 2007, Webster and MacLeod 2011). Application of an adaptation paradigm to face processing has revealed aftereffects specific to facial identity (Leopold et al., 2001). In this paradigm, a series of ambiguous morph faces are created between a base face and its ‘anti-face’, a face with the opposite structural properties with respect to the base face. After being exposed to the base face for a few seconds, subjects are briefly presented (<1s) an ambiguous morph test face about which they are asked to make an identity decision. Subjects are more likely to respond that the identity of the ambiguous

morph test face is the same as the identity of ‘anti-face’ after adapting to the base face (Leopold et al., 2005). Another study found similar aftereffects for a variety of other face properties including expression, gender, and ethnicity (Webster et al., 2004). These studies show that the perceived appearance of a face can be strongly affected by faces seen right before. Several studies by different groups have utilized this paradigm to study the perceptual underpinnings of visual processing in the human brain (Webster and MacLin 1999; Fang and He 2005; Jenkins et al., 2006; Fox and Barton 2007). These studies suggest that based on the aftereffect magnitudes created by a particular set of adapting stimuli, it is possible to deduce the range of the tuning properties of the neural population selective for that particular class of stimuli.

A series of elegant neuroimaging studies has shown that brief, repeated exposures to a visual stimulus generate adaptation, also named repetition suppression, to that particular stimulus in the ventral visual pathway and cause a reduction in the BOLD signal (Grill-Spector and Malach 2001). Although the exact mechanisms of this repetition suppression are not clear, it is considered to occur due to either the reduction or facilitation of the neural populations encoding that particular stimulus, or basically due to the sharpening of the tuning curves of the neurons responding to that stimulus (Grill-Spector et al., 2006). Once the repeated stimulus is replaced with a new stimulus of the same category, the reduced BOLD signal recovers to its original levels. This phenomenon provides a very useful tool to answer what classes of visual stimuli and which aspects of those stimuli are encoded by a particular region in the visual system. For certain questions, fMRI-adaptation paradigms have proven to be more sensitive than regular fMRI paradigms in studying the functional properties of cortical regions. After obtaining adaptation in a particular cortical region by repeated exposure to a stimulus it responds to, the function of that region can be tested as follows: when some aspect of the stimulus is varied, if the response of

that region remains at its adapted level, it indicates that the neurons in that region are not sensitive to the change, however, if the response of the region returns to its initial levels (recovery from adaptation), it indicates sensitivity to the change (Grill-Spector and Malach 2001). With this method, the functional involvement of a particular brain region can be assessed by varying different aspects of the stimulus. Previous fMRI-adaptation studies have revealed that there is a reduction of neural activity in the FFA in response to repeated exposure to the same face, and this adaptation is "released" when the face identity was different (Yovel and Kanwisher 2005). Other studies strengthened the evidence that FFA is involved in processing invariant properties of faces, such as identity, by showing that the FFA and the OFA show adaptation following repeated exposure to the same face (Winston et al., 2004; Mazard et al., 2006; Jiang et al., 2006), whereas repeated exposure to different views of the same face results in adaptation in more anterior fusiform regions (Eger et al., 2005). Investigating the neuroimaging correlations of the composite face effect, two fMRI-adaptation studies found that the BOLD signal in the FFA adapted in response to repeated exposure to the same face, and this adaptation was released when either the top or the bottom half of the face was changed (Schiltz and Rossion 2006; Schiltz et al., 2010). Furthermore, another fMRI adaptation study observed a complete release of adaptation in FFA in response to changing either the internal or the external features of a face (Andrews et al., 2010). These studies indicate FFA as the neuroanatomical correlate of face identity as well as the composite face effect which occurs when observers perceive a different identity if either the top or the bottom half of a face is altered.

In our current studies, we have applied the perceptual adaptation aftereffects paradigm to study the perceptual basis of the feature salience hierarchy in Chapter 2. In Chapter 3, we have

applied an fMRI adaptation paradigm to investigate the neuroanatomical correlates of the feature salience hierarchy.

1.3 Hypotheses

Previous results from behavioral studies of healthy individuals indicate a feature salience hierarchy, mainly demonstrated by the bias towards the eye region in healthy individuals. Studies in prosopagnosia patients indicate a deviation from this bias. Together, these findings suggest that there may be differences in the way upper and lower face regions are processed. What are the perceptual and neuroanatomical bases of the feature salience hierarchy? Where in the visual system does this bias arise? Which brain regions are involved in the computation of the spatial relations of facial features? How is this computation different for the upper face/eye region and the lower face/mouth region?

In order to investigate the neural representations underlying the feature salience hierarchy, we first applied an adaptation aftereffects paradigm with the aim of obtaining a quantifiable behavioral measure of the feature salience hierarchy in Chapter 2. We first asked: "Does the eye region bias observed in viewing faces involve a perceptual basis that could be accessed via adaptation aftereffects? Several studies have already confirmed adaptation aftereffects as a valid tool for studying face processing mechanisms (Webster et al., 2004; Fox and Barton 2007; Fox et al., 2008). Using this method, adaptation aftereffects are created in the perception of ambiguous faces based on the properties of the adapting face. Since adaptation creates a perceptual bias based on the representations of a particular face property in the human brain, a significant perceptual bias caused by an adapting stimulus indicates that the neural populations are sensitive to the properties of that particular adapting stimulus. Hence, different

adapting stimuli such as horizontally divided half faces or individual face parts can be used to examine the neural representations underlying the feature salience hierarchy by investigating the contributions of these adapting stimuli (upper and lower face halves) to the face identity aftereffect.

When tested in the whole face configuration, the eyes may have higher saliency merely due to their higher contrast compared to other features of a face, i.e., upper and lower face halves inherently may contribute equally to the perception of faces, and the eye region may have dominance only in the whole face configuration due to its low-level visual properties, such as higher contrast. One way to circumvent this issue is to use isolated face halves that are matched for their low-level discriminability as stimuli. If upper and lower face halves are equal in their individual saliency, then we would observe similar adaptation aftereffect magnitudes for upper and lower faces when they are presented separately. Additionally, if faces are represented only holistically in the human brain, then adapting to an isolated upper or lower face half matched for low-level physical similarity would have the same effect on the ambiguous test face since the face parts are considered to be integrated to achieve the holistic whole face perception. If on the other hand, the upper face/eye region indeed is processed differentially in the brain and has dominance in its isolated representation beyond its low-level visual properties, then we would expect differences in the adaptation aftereffects for upper and lower face halves even when they are matched for physical similarity. We would expect stronger adaptation aftereffects for upper faces and the eye region. In order to confirm the feature salience hierarchy in an adaptation aftereffects paradigm, we examined the differential role of the upper face and the eye region in face perception by separate presentation of isolated upper and lower face halves and isolated eye-region bands as adapting stimuli. We hypothesize that the top halves of faces will contribute

substantially to the identity adaptation aftereffects whereas bottom faces halves will not be sufficient to generate adaptation aftereffects.

Next question is whether there is a differential neural correlate for the eye region in the face processing network. If components of the core face processing network show a feature-salience hierarchy similar to that seen in the behavioral data, this would strengthen the evidence that neural activity in these regions plays a critical role in our perceptual experience of faces and face parts. In Chapter 3, the neuroanatomical correlates of the feature salience hierarchy are investigated using fMRI with the aim of locating the involved brain regions. Few studies so far have tried to investigate the neural correlates of the feature salience hierarchy despite the fact that various behavioral studies indicate differences in the perception of distinct face features. Two of these studies showed that the FFA and the OFA are sensitive to face parts (Harris and Aguirre 2008; Liu et al., 2010). Another study found that there was a release of adaptation when there were changes to the eyes but not when there were changes to the mouth (Harris and Aguirre 2010). However, this study did not take into account the correlation of these adaptation patterns with the perceptual performance of the participants, although it matched the stimuli for physical similarity. In our study described in Chapter 3, we include an ideal observer analysis to measure the physical properties of the stimuli, and a behavioral experiment to measure the perceptual characteristics of the stimuli, which we then correlate with the findings from the fMRI-adaptation experiment. We utilize a sensitive fMRI-adaptation paradigm (Davies-Thompson et al., 2013) to measure the sensitivity of the core face processing regions to alterations of different face parts. The fMRI-adaptation technique measures the reduction of the BOLD signal in the face processing regions of the brain in response to repeated face stimuli (Grill-Spector et al., 1999; Andrews and Ewbank 2004; Rotshtein et al., 2005; Yovel and

Kanwisher 2005). We introduce changes to the base stimuli by replacing the upper or the lower half of the face, and also by replacing the horizontal bands containing the eyes, the nose or the mouth separately. fMRI-adaptation is obtained by repeated presentation of the same base stimulus, and release from adaptation is measured in response to changes to the base stimulus in functionally localized core face processing regions, the OFA, FFA, and pSTS. The activation patterns of the face processing regions on fMRI are then compared to two measures: 1) efficiency scores of the same subjects, who participate in the neuroimaging experiment, in a behavioral same/different task using the identical face stimuli, which would reflect the perceptual discriminability of these different features in human subjects, and 2) level of physical similarity of the face stimuli, as assessed with an ideal observer technique, which simulates a contrast threshold task for face discrimination based on a Bayesian a posteriori maximization, which would reflect the low-level physical properties of the stimuli. We hypothesize that following fMRI-adaptation, the upper face and the eye region changes would result in higher release of adaptation in OFA and FFA.

Previous studies have reported that some acquired prosopagnosia patients may have difficulty particularly with eye region processing (Barton 2008a). Does this impairment of eye region processing occur only in the apperceptive variant of prosopagnosia that results from occipitotemporal lesions which include the anatomical location of the FFA? Earlier patient studies in the literature did not have the advanced neuroimaging tools available for characterizing the scope of the lesion(s), and the functional status of the intact face processing regions in these patients. Even today, current neuroimaging methods are not optimally advanced and new methods for analysis of macro-structure and the white-matter connectivity properties of neural tissue are still being developed and improved (Thomas et al., 2009; Phillips et al., 2012;

Mezer et al., 2013). There have been descriptive single case reports where the patient's eye processing difficulties were assessed (Rossion et al., 2009). There are also group reports where either the structural neuroimaging was not systematic, i.e., some patient's data resolution was at the CT scan level, whereas some were at the MRI scan level, or the functional neuroimaging data was not available (Barton 2008a). Additionally, individual variability in the lesion patterns of patients with prosopagnosia limits the generalization of findings from individual case studies. Therefore, systematic studies with larger patient cohorts with similar lesions are very valuable. To this day, there has been no systematic extensive examination of a patient cohort with combined neuroimaging and behavioral testing. We had the opportunity to recruit and examine a cohort of 10 acquired prosopagnosia patients with occipitotemporal and/or anterior temporal lobe lesions, and ran the same sets of experiments over the same time course on each patient. We performed structural neuroimaging to characterize the lesions, and functional neuroimaging to assess the functional status of the remaining face processing network, when applicable. We administered an extensive neuropsychological battery in order to assess the general cognitive abilities of the patients in order to rule out general cognitive impairments. We conducted a series of extensive behavioral tests in order to characterize the patients' perceptual impairments. In Chapter 4, we provide detailed descriptions of the patients in our cohort.

Impaired perception of the second-order relations of facial features has been previously linked to damage to the fusiform in prosopagnosia (Sergent and Signoret 1992; Barton et al., 2002; Joubert et al., 2003; Barton 2008a; Riddoch et al., 2008; Busigny et al., 2010). In Chapter 5, with the goals of 1) characterizing the feature processing deficits of acquired prosopagnosia patients, and 2) establishing whether the impairments of processing of second-order relations, mainly in the eye region, in acquired prosopagnosia generalize to our whole patient cohort with

different lesions, we examine the processing of individual face features and second-order relations of the face features in our cohort of 10 patients. We also study the processing of these second-order relations separately for the upper and lower face since some studies suggest that processing deficits may be specific to the eye region in some prosopagnosia patients (Caldara et al., 2005; Barton 2008a; Bukach et al., 2008; Rossion et al., 2009). Establishing the degree of feature processing abnormality in prosopagnosia patients and its correlation with the anatomical damage they have is very informative for defining the neural correlates of face processing and feature salience hierarchy in the human brain. In addition, a clear classification of the face processing deficits in the apperceptive and the associative variants of acquired prosopagnosia is essential for delineating the brain regions responsible for different aspects of face processing. It is also necessary for the development and improvement of rehabilitation programs targeted at improving the specific aspects of face recognition each variant of prosopagnosia is vulnerable to. For example, whether the structural encoding problems are the major issue for apperceptive variant of prosopagnosia needs to be established before proceeding with rehabilitation programs targeting to improve structural face processing for these patients. We hypothesize that the deficits of eye region processing follows the lesion pattern, i.e., that patients with the apperceptive variant of prosopagnosia which results from inferior occipitotemporal lobe lesions will demonstrate significant impairments in processing the eye region of faces, whereas patients with the associative variant of prosopagnosia which results from anterior temporal lobe lesions will not demonstrate significant difficulties with processing of eye region information..

In Chapter 6, we conduct an eye- movement experiment to study the scan abnormalities in our patient cohort. Previous eye movement studies have indicated that healthy subjects look more at the eyes when recognizing identities of faces (Vinette et al., 2004; Henderson et al.,

2005). It has also been reported that some prosopagnosia patients have lost this preference for fixating on the eyes, and have more problems perceiving changes in the eye region than changes in the mouth region (Caldara et al., 2005; Barton 2008a; Bukach et al., 2008). We investigate the degree of the abnormality of face scanning patterns in acquired prosopagnosia patients. We test both healthy subjects and patients from our cohort in a learning and memory task while we record their eye movements to measure the number of fixations and the durations of fixations on a given face region both in the learning and the recognition phases of the experiment. We hypothesize that patients with the apperceptive variant of prosopagnosia will have abnormal scanning patterns where they will not scan the upper faces similar to the healthy controls and that patients with the associative variant of prosopagnosia who have intact inferior occipitotemporal cortices and functionally intact FFA will not have any significant differences in their scanning patterns compared to healthy controls.

In Chapter 7, we investigate the performances of healthy controls and prosopagnosia patients in a half-face memory task. Would the feature salience hierarchy demonstrated by healthy individuals be reflected as better performance for the upper face half in a memory task where the upper and lower face halves are learned separately? Memory tasks have been systematically used to study the face recognition problems and have shown to be effective diagnostic criteria for face recognition difficulties (Warrington 1984; Duchaine and Nakayama 2006a). We aimed to explore whether the upper and lower face halves would result in differences in memory performance in a face memory task where subjects learn and recall the isolated upper and lower halves of a face separately. The face halves are presented separately so that there would not be a competition between the upper and the lower face halves that could occur in a whole face context. We hypothesize that the healthy population will demonstrate significantly

better face memory performance for upper face halves, while apperceptive prosopagnosia patients will obtain significantly lower scores for the upper face half memory than for the lower face half memory and associative prosopagnosia patients will be equally impaired in memory for upper and lower faces.

Finally, in Chapter 8, we combine the data from feature processing, face scanning, and half-face memory experiments from our prosopagnosia patients, and compare the results with the patients' anatomical damage delineated by a structural MRI scan and the preserved face network regions revealed by a functional dynamic localizer scan. The main goal is to establish the relationship of the eye region processing deficits with the brain lesions in order to determine which brain regions are involved in the eye region processing in the healthy human brain. We hypothesize that the patients with the apperceptive variant of prosopagnosia will demonstrate feature processing and face scanning difficulties, and the patients with the associative variant of prosopagnosia will demonstrate relatively preserved face processing and face scanning with possible difficulties in the half-face memory task. This dissociation would confirm the eye region processing as a part of the structural encoding of faces that is disrupted from damage to the inferior occipitotemporal cortex.

Overall, the aim of this dissertation is to investigate the perceptual and neuroanatomical bases of the feature salience hierarchy in healthy individuals and to characterize the feature processing deficits in a prosopagnosia patient cohort with the goal of establishing a link between the behavioral eye region processing deficits and the anatomical lesion locations in these patients.

Chapter 2: Perceptual Basis of the Feature Salience Hierarchy

The holistic face processing models suggest that faces are represented as an integrated whole rather than their individual components in the human brain. On the other hand, feature salience hierarchy demonstrated by human observers on various face identification tasks points to the dominance of the eye region in face processing. In order to investigate the neural representations underlying the behavioral manifestation of the feature salience hierarchy, we applied an adaptation aftereffects technique. This method, already proven to reliably and repeatedly create aftereffects in the perception of ambiguous test faces based on the preceding adapting face stimulus, enables the testing of various adapting stimuli for their ability to create adaptation aftereffects. We measured the aftereffect magnitude created by isolated upper and lower face halves separately to investigate their individual contributions to the face identity aftereffects. We also measured the aftereffect magnitude created by an eye band region in a separate experiment.

2.1 Methods

2.1.1 Participants

Sixteen healthy subjects (8 females, mean age = 29, age range 26-34) with normal or corrected-to-normal vision, no history of neurological, psychiatric disease or cognitive complaints participated in Experiment 1. The protocol was approved by the institutional review boards of the University of British Columbia and Vancouver General Hospital. All subjects gave written informed consent in accordance with the Code of Ethics of the World Medical Association, Declaration of Helsinki (Rickham 1964). Another set of sixteen healthy subjects (8 females,

mean age = 26, age range 18-32) with normal or corrected-to-normal vision, no history of neurological, psychiatric disease or cognitive complaints participated in Experiment 2.

2.1.2 Stimuli

Two male face pairs with neutral expressions were selected from the Human Vision and Eye Movement Laboratory- Facial Identity, Viewpoint, Expression (HVEM-FIVE) database. Full faces in each pair as well as the upper and lower halves of each face were similar in discriminability as determined by an Ideal Observer face discrimination simulation based on contrast-thresholds (See Section 3.1.3 for details). Using Adobe Photoshop CS2 (www.adobe.com), all external cues, i.e., the hair, the ears, and the neck were removed from the faces, leaving only the internal features. An elliptical mask was applied to each face to remove the face contour cues. The face images were matched for luminance and converted to gray scale. Final size of the full face images was 600 pixels in width and 822 pixels in height. Full faces were segmented horizontally into an upper face-half and a lower face half, each with 600 pixels in width and 411 pixels in height. The upper face halves included the forehead, the eyebrows and the eyes, whereas the lower face halves included the cheeks, the chin, the mouth and the nose from below the nasal bridge. An eye-band region image consisting of the eyes and the eye-brows was prepared by selecting a rectangular box of 600 pixels width and 150 pixels height from the full face images. Images from this stage were used as adapting stimuli. The adapting stimuli for Experiment 1 were: full face A, full face B, upper-half face A, upper-half face B, lower-half face A, and lower-half face B (Figure 2.1). The adapting stimuli for Experiment 2 were: full face A, full face B, upper-half face A, upper-half face B, eye-band A, eye-band B (Figure 2.3). Next, a series of morphs with 2.5% increments between each face pair were created using Fantamorph

(www.fantamorph.com) from the full faces. The 13 images from the middle of each morph series, ranging from 65%Face1/35%Face2 to 35%Face1/65%Face2 were selected as the test morph stimuli (Figure 2.4). The final size of these images was16 500pixels in width and 684 pixels in height. Different adapting and morph test stimuli sizes were used in order to avoid low-level image matching.

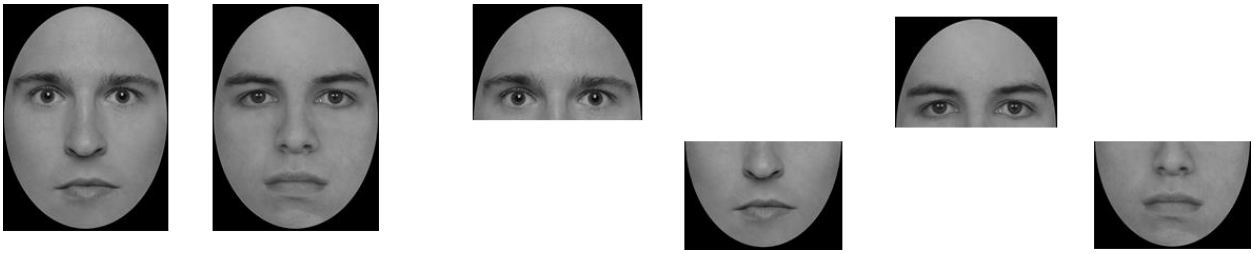


Figure 2.1 Adapting Stimuli of Experiment 1showing one series of the adapting stimuli.

2.1.3 Experimental Procedure

An IBM Levono notebook with 1280x800 pixels resolution at a 60Hz refresh rate was used to display the stimuli at a viewing distance of 57cm in a dimly lit room. The experiments were designed and conducted on SuperLab 4.5 (www.cedrus.com). In order to familiarize the participants with the experiments, each participant started with a practice run which included all possible adapting conditions with stimuli that was not used in the actual experiments. Total durations of Experiment 1 and Experiment 2 were each approximately 30 minutes.

Each trial began with a 5 second presentation of one of the six adapting stimuli. For Experiment 1 these were: full face A, full face B, upper-half face A, upper-half face B, lower-half face A, and lower-half face B. The adapting stimulus was then replaced by a Gaussian white noise mask

for 50 ms, followed by a white fixation cross for 150 ms. Following a black blank screen for 150ms, a morphed full face stimulus was presented for 500ms followed by another black blank screen for 150ms. Then the choice screen appeared on the screen and stayed until the participant responded on the keyboard. The choice screen displayed full face A and full face B, and their locations on the left or the right side of the screen were counterbalanced across subjects. The participants were instructed to look at all the face stimuli appearing on the screen and asked to report using a key-press whether the briefly presented second face (the morphed face) looked more like the face on the left or the face on the right on the choice screen (full face A or full face B) in a two-alternative forced choice task. The next trial started after the participant responded by a key-press. 13 morphs were shown once for each of the 6 adapting stimulus, resulting in a total of 78 trials for each face pair. Two face pairs were used with a total of 156 trials.

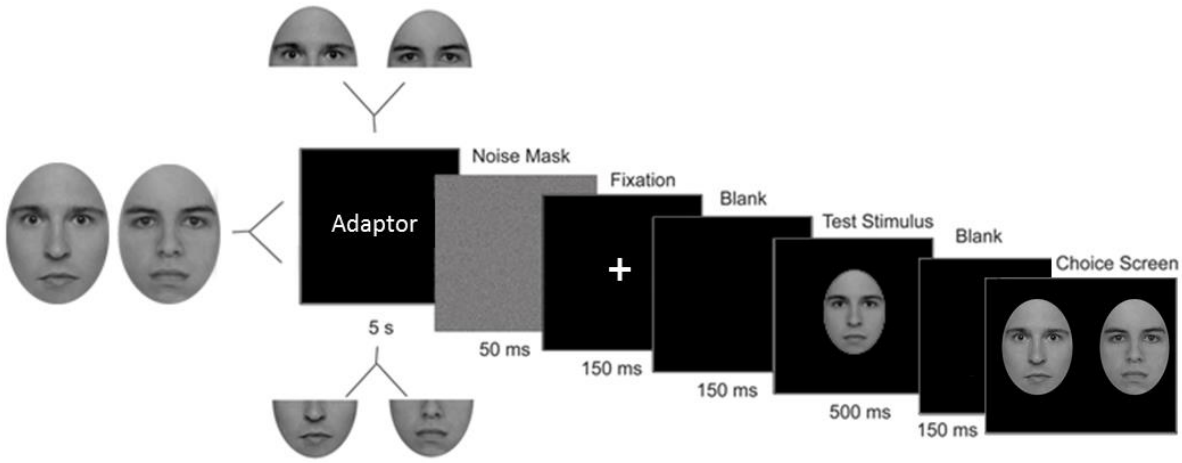


Figure 2.2 A Sample Trial Outline. Figure shows a sample trial with an adapting stimulus, followed by an ambiguous morph of the base face pair, and finally a choice screen with the intact full faces as the two choices.

Experiment 2 was identical except for the adapting stimuli. Each trial began with a 5 second presentation of one of the six adapting stimuli. For Experiment 2 these were: full face A, full face B, upper-half face A, upper-half face B, eye-band A, eye-band B. The adapting stimulus was then replaced by a Gaussian white noise mask for 50ms, followed by a white fixation cross for 150ms. Following a black blank screen for 150ms, a morphed full face stimulus was presented for 500ms followed by another black blank screen for 150ms. Then the choice screen appeared on the screen and stayed until the participant responded on the keyboard. The choice screen displayed full face A and full face B, and their locations on the left or the right side of the screen were counterbalanced across subjects. The participants were instructed to look at all the face stimuli appearing on the screen and asked to report using a key-press whether the fast-flashing second face (the morphed face) looked more like the face on the left or the face on the right on the choice screen (full face A or full face B) . The next trial started after the participant responded by a key-press. 13 morphs were shown once for each of the 6 adapting stimulus, resulting in a total of 78 trials for each face pair. Two face pairs were used with a total of 156 trials.

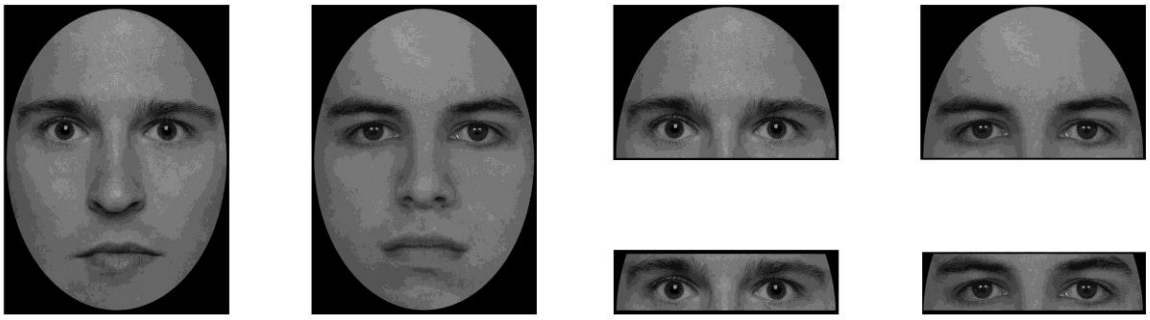
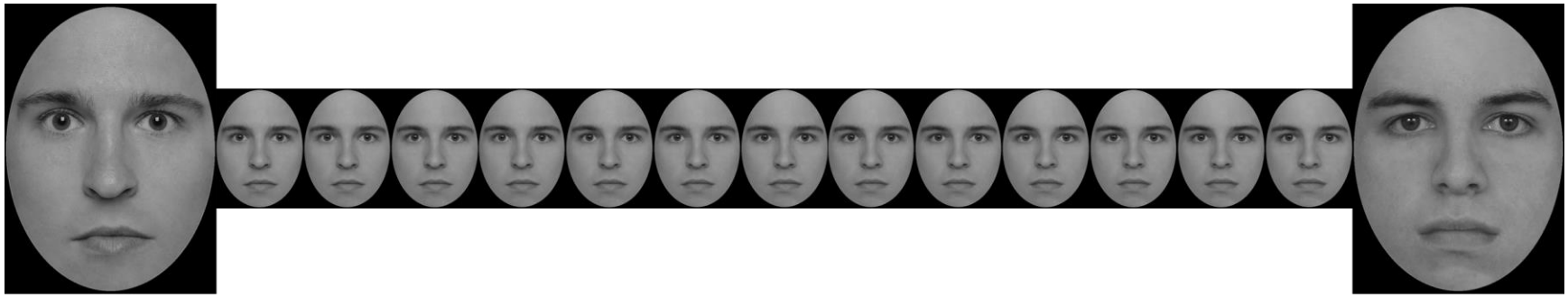


Figure 2.3 One Series of the Adapting Stimuli of Experiment 2.

2.1.4 Data Analysis

In order to determine the magnitude of the adaptation aftereffect, the number of trials in which the subject responded "Face A" were tabulated. As an index of the magnitude of the aftereffect, the frequency of "Face A" responses on the trials with an adapting image of face B minus the frequency of "Face A" responses on the trials with an adapting image of face A were calculated for each face pair and each adapting condition, and normalized by the number of test trials for each face pair (13). Adapting conditions were full face, upper-face half, and lower-face half for Experiment 1, and full face, upper-face half, and eye-band for Experiment 2. The results from the two face pairs were averaged for each condition, and then across subjects. One-sample *t*-tests were used to determine whether any of the three conditions were able to generate significant adaptation aftereffects. A 2X3 repeated measures ANOVA with Adapting Condition (Whole Face, Upper Face, Lower Face) and Face Pair(Pair 1, Pair 2) as factors and Subject as a random effect was performed in order to determine the significance of the effects of Adapting Condition and the face pair used. Paired-samples *t*-tests with Bonferroni correction for multiple comparisons were used to determine whether there was a pair-wise significant difference across conditions.

A



B

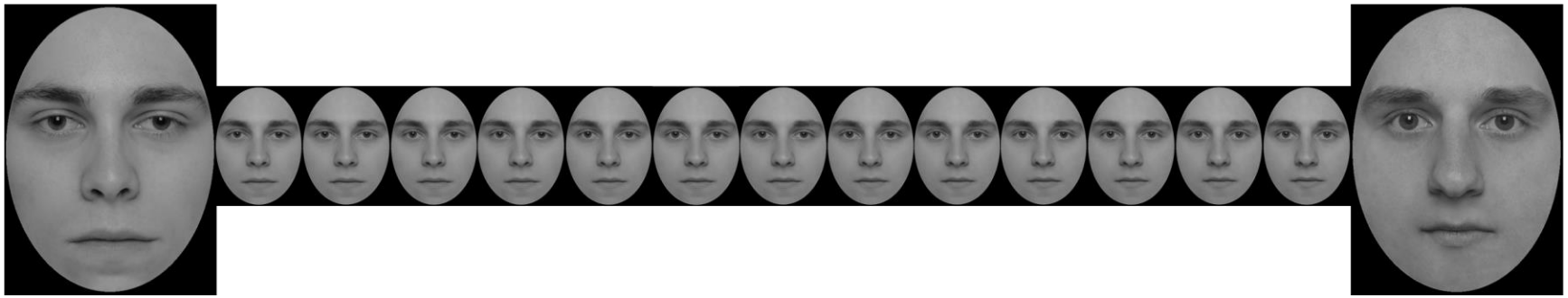


Figure 2.4 Morph Test Stimuli. (A) shows Face Pair 1 with the original faces at the ends and the 13 levels of morphs of the two faces in the middle. (B) shows Face Pair 2 with the original faces at the ends and the 13 levels of morphs of the two faces in the middle.

2.2 Results

In Experiment 1, a repeated measures ANOVA showed that there was no significant effect of the Face Pair ($F(1,15) = 1.4668$, $P = 0.2444$). There were also no significant interactions between the Face Pair and the Adapting Condition ($F(2,30) = 0.022$, $P = 0.978$). There was a significant effect of the Adapting Condition ($F(2,30) = 4.053$, $p < 0.05$). In order to determine whether each condition generated a significant adaptation aftereffect, t-tests with the null hypothesis of the adaptation aftereffect equals to zero were run. t-tests showed that the full face adapting condition (20.19%, SE 5.13 , $t(15) = 3.936$, $P < 0.001$) and the upper-face half adapting condition (10.10%, SE 3.60, $t(15) = 2.808$, $P < 0.02$) were both able to generate a significant adaptation aftereffect, while the lower-face half adapting condition (6.29%, SE 3.55, $t(15) = 1.77$, $P = 0.097$) did not create a significant adaptation aftereffect (Figure 2.5). Paired-samples t-tests with Bonferroni correction for multiple comparisons showed that the adaptation aftereffects of the full face condition was significantly different than the adaptation aftereffects of the lower-face half condition ($t(15) = 2.553$, $P < 0.05$).

Experiment 1 confirmed the previously reported adaptation aftereffects for whole faces, mainly the fact that subjects were more likely to report that the ambiguous morph test stimulus looks more like Face A after they have seen Face B as the adapting stimulus. The upper-face halves were able to generate significant adaptation aftereffects similar to whole faces, but the lower-face halves were not able to generate a significant adaptation aftereffect. There was also a significant difference between the adaptation aftereffects levels in response to full face adapting condition and to the lower-face half adapting condition.

In Experiment 2, t-tests with the null hypothesis that the adaptation aftereffect was zero were run in order to determine whether each condition generated a significant adaptation

aftereffect. t-tests showed that the full face adapting condition (22.89%, SE 5.09 , $t(15) = 4.495$, $P < 0.0005$), the upper-face half adapting condition (22.39%, SE 4.31, $t(15) = 5.191$, $P < 0.0005$), and the eyes-band adapting condition (15.62%, SE 5.07, $t(15) = 3.082$, $P < 0.01$) all generated a significant adaptation aftereffect (Figure 2.5). A 2X3 repeated measures ANOVA showed that there was no significant effect of the Face Pair ($F(1,15) = 1.44$, $P = 0.709$). There were also no significant interactions between the Face Pair and the Adapting Condition ($F(2,30) = 0.004$, $P = 0.996$). There was a trend for the effect of the Adapting Condition ($F(2,30) = 2.744$, $P = 0.08$). Further exploration with linear contrasts showed that the adaptation aftereffects of the full face condition was significantly different than the adaptation aftereffects of the eye-band half condition ($t(15) = 2.320$, $P < 0.05$).

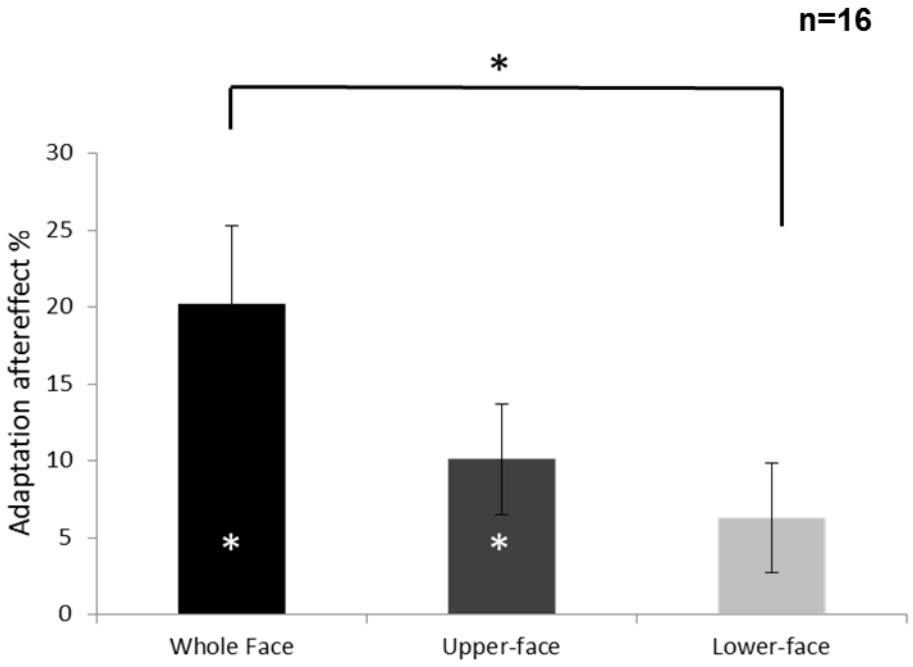


Figure 2.5 . Adaptation Aftereffects for Whole Faces and Face Halves in Experiment 1.

Experiment 2 confirmed both the previously reported adaptation aftereffects for whole faces and the significant adaptation aftereffects results for upper-face halves from Experiment 1. Additionally, the eye-band itself was able to generate significant adaptation aftereffects similar to whole faces and the upper-face halves. Although there were no significant differences between the adaptation aftereffects for the whole face and the upper-face half conditions, interestingly there was a significant difference between the adaptation aftereffects for whole faces and eye-band only.

2.3 Comments

We first tested the ability of the upper-face half to generate adaptation aftereffects similar to the full face adaptors. Our full face adapting condition was able to generate significant adaptation aftereffects in agreement with previous studies (Webster et al., 2004; Fox et al., 2008). The upper-face half adapting condition also generated significant adaptation aftereffects similar to the full face adapting condition. The lower-face half adaptors were not able to generate any significant adaptation aftereffects, in agreement with the feature salience hierarchy observed for the eyes and the upper face.

With the confirmation of the ability of the upper-face halves to generate significant adaptation aftereffects, we next asked whether the eye-band which included the eyes and the eyebrows, was able to generate the aftereffects on its own, and whether this adaptation aftereffect would be similar to the full face or upper-face half aftereffects in magnitude. The results showed that the eye-band itself was able to generate significant adaptation aftereffects. These results show that even when presented in isolation, the lower-face half is not able to generate any

significant adaptation aftereffects. This supports the idea that the dominance of the eye region in a full face cannot be explained by simple relay of low-level visual properties. Interestingly, there

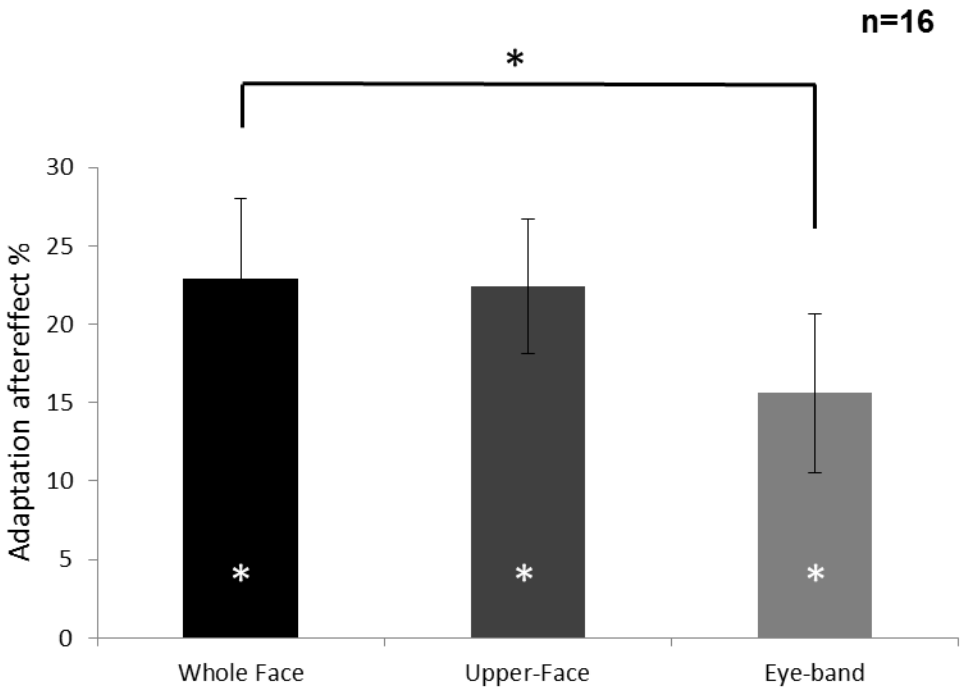


Figure 2.6 Adaptation Aftereffects for Whole Faces, Upper Face Halves, and the Eye Band in Experiment 2.

was a significant difference in the adaptation aftereffects created by whole faces and the eye-band, indicating that the magnitude of a full face adaptation aftereffects cannot be achieved by the eyes alone. Therefore, the eye region of a face cannot account for the total aftereffects generated by a whole face. These results support the idea of a crucial, yet only partial contribution of the eye region and are in agreement with the holistic face processing models integrating a differential contribution from the eye region.

A differential contribution from the eye region to the perceptual encoding of a face suggests that there are partial and differential contributions of separate face features to face processing, in agreement with other behavioral studies that indicate better discrimination performance for the eye region of faces. This brings up the question of the neural correlates of these differential contributions. The next chapter of this thesis examines the neural correlates of the feature salience hierarchy and the contribution of different facial features to the neural signal using fMRI-adaptation in combination with a behavioral face perception task in order to confirm the feature salience hierarchy and an ideal observer task in order to parse out the effect of the low-level visual properties of the face stimuli on the neural signal.

Chapter 3: Neuroanatomical Correlates of the Feature Salience Hierarchy

Previous studies suggest that faces are represented holistically in the human brain, yet the eye region of faces is more salient than other face parts for face recognition. The adaptation aftereffects study described in the previous chapter of this thesis examined the ability of upper and lower face halves to generate significant adaptation aftereffects in comparison with whole faces. The results showed that upper-face halves and the eye region were sufficient to create significant adaptation aftereffects. Interestingly, there was a significant difference in the magnitude of the adaptation aftereffects generated by whole faces and the eye region. These results support the idea that the eye region contributes only partially to face processing.

In the studies described in this chapter, we investigated the neural basis of the feature salience hierarchy and the degree of contribution of the eye region and other face features. We used an fMRI-adaptation experiment along with a behavioral discrimination task and an ideal observer analysis to investigate whether different face parts contribute different amounts to the neural signal in face responsive regions of the brain, and whether this correlates more with the behavioral performance of human subjects or the low-level physical properties of the face stimuli. Subjects performed a behavioral same/different discrimination task to confirm the feature salience hierarchy observed in previous studies, and to characterize their ability to detect changes when the whole face, the top half, the bottom half, the eyes, the nose, or the mouth changed. The same subjects participated in an fMRI-adaptation study, in which stimuli faces were repeated to achieve adaptation, then different parts of these faces were changed in alternating presentations to measure the release from adaptation in the face responsive regions which were determined using a separate functional face localizer scan. The ideal observer

analysis was run on the face stimuli set which was used on both the behavioral and the fMRI-adaptation experiments in order to establish the low-level physical image differences of the face stimuli with the main goal of establishing how much of the neural signal correlated with the low-level physical image properties of different features. Finally, we examined how the human behavioral performance and the ideal observer measures of the physical image differences of face parts correlated with the neural signal changes in the fMRI-adaptation experiment.

3.1 Methods

3.1.1 Participants

Twenty-five healthy participants with no history of neurological dysfunction, vascular disease or cognitive complaints participated in the fMRI and behavioral components of the study (14 females, mean age = 22.9, age range 20-29). All participants were right-handed and had normal or corrected-to-normal vision. The protocol was approved by the institutional review boards of the University of British Columbia and Vancouver General Hospital. Written informed consent was obtained from all subjects in accordance with the Code of Ethics of the World Medical Association, Declaration of Helsinki (Rickham, 1964).

3.1.2 Stimuli

Face-pairs with seven different conditions were created. In the whole-same condition, the first and the second faces were identical. In the whole-different condition, the first and the second faces were completely different. In the top face-half condition, the bottom halves of the two faces were identical, but the top halves were different. In the bottom face-half condition, the top halves of the two faces were identical, but the bottom halves were different. In the eyes

condition, a horizontal band containing the eye region was different, but the rest of the faces were identical. In the mouth condition, a horizontal band containing the mouth was different between the two faces, but the rest of the faces were identical. In the nose condition, a horizontal band containing the nose was different between the two faces, but the rest of the faces were identical.

Frontal view face photographs of eight young Caucasian males with neutral expressions were selected from the HVEM-FIVE database. Images were converted to grayscale and distinguishing features (moles, facial hair) were removed using Adobe Photoshop CS. Next, the images were matched for luminance using Matlab (www.mathworks.com). A gray mask with an oval aperture was placed over each face in order to remove external features (hair, ears, chin), resulting in an oval facial image of 547 pixels in height and 400 pixels in width.

Upper and lower half face stimuli were created by cropping the oval images exactly at midpoint approximately above the tip and below the dorsum of the nose of each face stimulus. In order to create face pair stimuli in which the top and the bottom halves were similar in degree of dissimilarity, the physical discriminability between any two top face-halves or any two bottom face-halves was assessed using an ideal observer technique (Section 3.1.3). Top face half pairs were linked with bottom face half pairs that matched in terms of similarity in discriminability.

In order to generate the faces with eyes, mouth, or nose changes for the face part conditions, "feature bands" were created by dividing the face into three horizontal bands containing an equal number of pixels. Pairs of faces differing only in one feature band were created by inserting one feature band from another face and keeping the other two feature bands constant (Figure 3.1). To avoid the presence of lines with sharp contrast arising from alignments,

we used the "Patch" tool in Photoshop to evenly blend a small (10 pixel width) area around the alignment line, and then added a 7.5% Gaussian noise mask to the entire image.

3.1.3 Ideal Observer Analysis of the Stimulus Face Pairs

Face stimuli were evaluated by an ideal observer analysis in order to determine the physical differences between a pair of face stimuli. The ideal observer is a simulation of a two-alternative forced-choice task in which contrast threshold for face discrimination at 82% accuracy is measured (Fox et al., 2008). On each trial, one face randomly chosen out of two alternatives is presented as the test stimulus at a contrast that is determined by a psychological staircase, and embedded in Gaussian white noise with fixed variance. The ideal observer has knowledge of the complete face stimulus set, the contrast level on each trial, and the statistics of the noise. It responds at minimum distance between the noisy test stimulus and the two alternatives which are equally likely to be chosen. Under the given conditions, this decision rule is equivalent to Bayesian *a posteriori* maximization and thus is statistically optimal (Tjan et al., 1995). Hence, the ideal observer's response in each trial is based on the equation $\mathbf{argmin}_i \Sigma(S - cF_i)^2$, where S is the noisy stimulus, c is the contrast at a given trial, and F1 and F2 are the two possible faces in a given session.

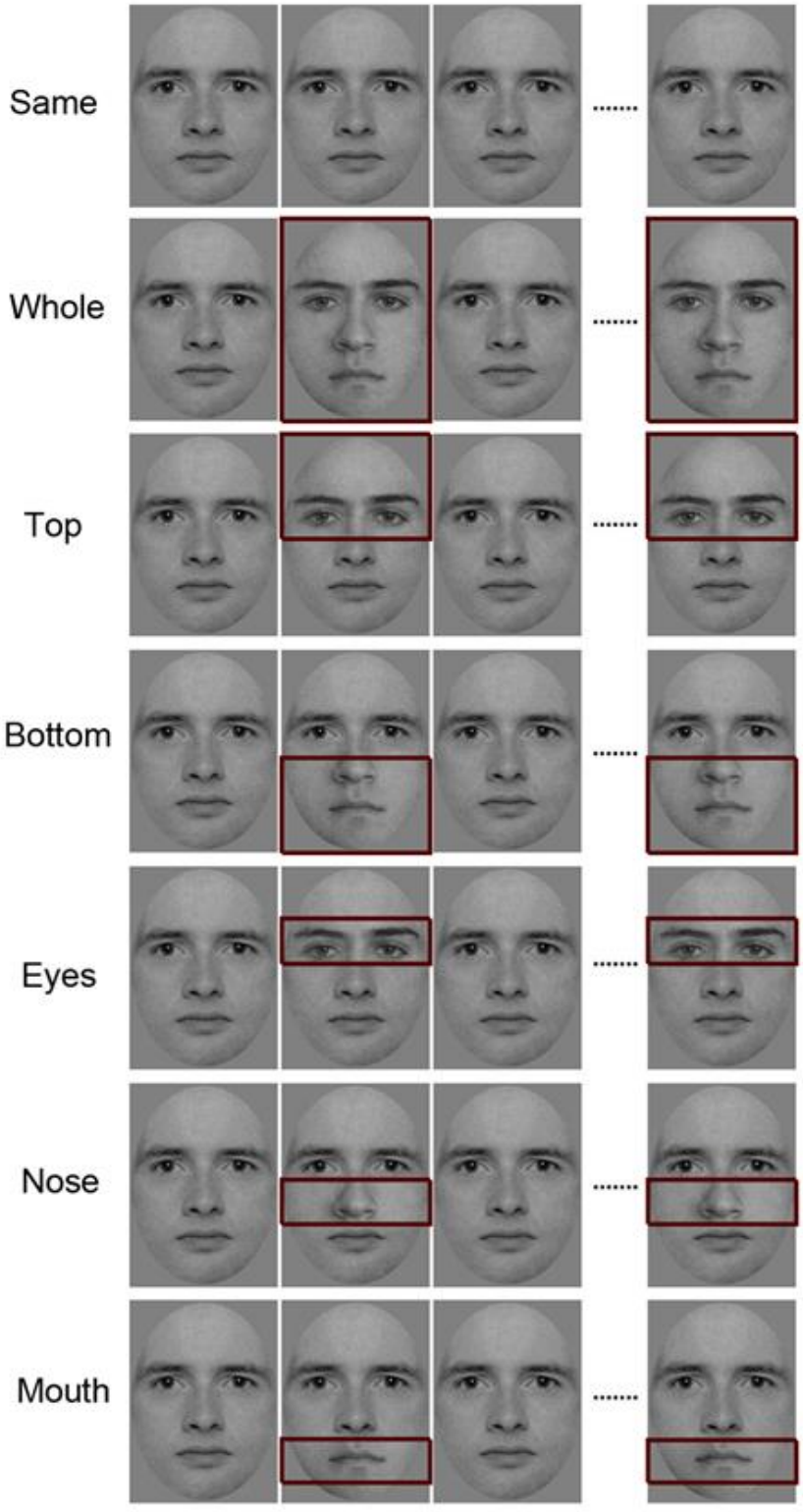


Figure 3.1 . Examples of the Different Face Conditions.

3.1.4 Human Behavioral Experiment

In order to examine how humans perceive the changes between the face pair images, each subject who participated in the fMRI experiment also completed a same/different task using the same face stimuli. Participants were tested at least one week after their fMRI session. On each trial, two faces were presented sequentially for 900ms each, separated by an inter-stimulus interval of 100ms. These were the same stimulus timing parameters of the fMRI experiment. The presentation of the faces was followed by a response period of 2s. In order to reduce contributions from low-level visual processes, the first face in each pair was located centrally, while the second face within each pair was spatially moved to the left by 2.4^{o} horizontally and to the top by 2.4^{o} vertically with respect to the central position of the first face. Subjects were asked to respond whether the two faces were the same or different. There were a total of 192 trials; 96 "same" and 96 "different" face pairs, presented in a pseudo-random order. Each of the 6 different conditions was tested in a separate block in a randomized order across participants with 16 trials for each different condition. Accuracy and reaction times were measured and combined into a single efficiency score which is a more reliable measure of behavioral performance (Townsend and Ashby 1983; Morein-Zamir et al., 2007), calculated for each participant for each condition using the formula Efficiency = Accuracy/log (Latency).

After the behavioral experiment, each participant was asked the strategy they used to perform the task. All but one participant stated that they scanned the entire face. One participant reported that he adopted a strategy of looking exclusively at the mouth. As a result, his efficiency scores were higher for the mouth and lower faces, and his measure for upper versus lower face efficiency was more than three standard deviations away from the other participants. Therefore, his data was excluded from the behavioral analysis and the correlation part of the fMRI analyses.

Two other participants who were excluded from the fMRI analyses due to excessive motion were also excluded from the behavioral experiment and the correlation analyses.

3.1.5 fMRI Experiment

3.1.5.1 Imaging Parameters

Participants were scanned in a Philips 3.0T scanner at the UBC MRI Research Centre. T2*-weighted functional scans using echo planar imaging were used to collect data from 36 interleaved axial slices (TR 2000ms, TE 30ms, FOV 240X216mm, 3mm thickness with 1mm gap, voxel size 3X3mm, 128 reconstruction matrix, reconstructed voxel size 1.88X1.6mm). These were co-registered onto a T1-weighted anatomical image gradient echo sequence (170 axial slices, FOV 256X200mm, slice thickness 1mm, voxel size 1X1mm) from each participant.

3.1.5.2 Face Localizer Scan

The HVEM Dynamic Localizer scan was run twice on each participant to identify the face-selective regions of the visual cortex (Fox et al., 2009). The localizer consisted of grayscale video clips of faces, body parts, objects, Fourier-phase scrambled faces, and Fourier-phase scrambled objects. Each stimulus block included 6 video clips lasting 1.5s separated by a 500ms blank screen. Stimulus blocks were separated by a 12s fixation cross block. Each condition was repeated 5 times per run. In order to confirm that the subjects attended to the stimuli, participants were asked to press a button on an MRI-compatible button-box when the same video was presented twice in a row.

3.1.5.3 Adaptation Experiment

In order to determine the contribution of different face parts to the neural signal in face-responsive regions of the human brain, the adaptation paradigm included the 7 face-pair conditions, (1) same condition, (2) whole-different condition, (3) top face-half different condition, (4) bottom face-half different condition, (5) eyes different condition, (6) mouth different condition, (7) nose different condition. An alternating (AB) block design was used to present the stimuli (Figure 3.1). This alternating AB presentation was employed based on the recent findings that two alternating images are sufficient to obtain adaptation, reflected by reduced BOLD signal for repeated stimuli, and the release of adaptation, reflected by the recovery of the bold signal (Davies-Thompson et al., 2012). The first face (Face A) was presented for 900ms, followed by a 100ms blank and the second face (Face B). The second face was presented for 900ms followed by a 100ms blank. This alternating pattern was repeated four times (ABABABAB) resulting in 8 face images per block. Each stimulus block was separated by a fixation block, during which a grey fixation screen with a central cross hair was presented for 8s. Each block was repeated 8 times for each condition, resulting in a total of 56 stimulus blocks. Using Presentation (www.neurobs.com) software, the stimuli were back-projected onto a screen located inside the scanner bore, approximately 68cm away from the participant's eyes. The stimuli covered approximately 11^{o} of visual angle. In order to control for effects of attention across conditions and to ensure that the participants were actually looking at the face stimuli, the participants were given a size change detection task. They were asked to press a button on the button-box when they saw a face that was smaller than the other faces within the block. Each block had one target face that was 8% smaller than the other faces. The order of the smaller-size target face in the sequence of 8 faces on each block was pseudorandom and counterbalanced

across the possible positions. Before the start of the scan, each participant took part in a practice session in order to familiarize them with the task. The practice consisted of six blocks of face stimuli which were not used in the experiment.

3.1.5.4 fMRI Analysis

All data was analyzed with Brainvoyager QX (www.brainvoyager .com) software. The preprocessing of the fMRI data consisted of slice time correction (cubic spline interpolation), 3D motion correction (trilinear/sinc interpolation), and high-pass temporal filtering (GLM-Fourier, 2 sines/cosines). Out of the 25 subjects, two were removed from further analysis due to excessive movement during the scans. Preprocessed functional data for the two face localizer scans were combined together for each subject. Face responsive regions-of-interest (ROIs) were determined for each subject individually with the contrast "Faces> Objects" at $p<0.05$, Bonferroni corrected for multiple comparisons. The core face-network areas were defined as contiguous clusters of at least 10 voxels located (a) on the lateral surface of the inferior occipital gyrus, and designated as the OFA, (b) on the lateral middle fusiform gyrus, and designated as the FFA, and (c) on the posterior banks of the superior temporal sulcus and designated as the pSTS.

In order to investigate whether the responses in the face responsive regions were reflecting low-level visual processing, the peak response for each condition was measured in an early visual region, namely the occipital pole, which encompassed the central striate cortex. An occipital pole box mask was drawn around the calcarine fissure of each subject (Talairach coordinates from x = 14, y = 67, z = 8 to x = -14, y = -96, z = -12). Additionally, in order to determine whether the effects were specific to the face selective ROIs or due to a general response pattern of the fusiform voxels, we defined two control regions. The first was the right

fusiform body area (FBA) located in the right lateral fusiform gyrus and determined for each subject with the contrast Bodies >Objects at $p < 0.0001$, uncorrected (Schwarzlose et al., 2005; 2008). The second control region was defined as the voxels in FBA that did not overlap with the FFA voxels and labeled as FBA* (Schwarzlose et al., 2005).

The analysis of the fMRI-adaptation experiment was carried on a ROI basis, using data from the six core face network areas and the two fusiform control regions determined by the face localizer scan for each subject, and from the anatomically determined low-level control region at the occipital pole. The time series of the BOLD response in all the voxels for a given ROI were averaged to produce a single time series in each ROI for each subject. This single time series of the BOLD measure in image intensity units was then converted into percent signal change by subtracting each time point from the mean response during the scan, and normalized [$(x-\mu)*100/\mu$] (Davies-Thompson et al., 2009; Andrews et al., 2010). If there were more than one face responsive cluster within the expected location of an ROI, the time series of both clusters were averaged. Each stimulus block was normalized by subtracting the $t = 0$ point value for that stimulus block from the subsequent time points. The normalized data was then averaged across subjects in order to obtain the mean time course for each condition. The peak response was defined as the average value of time points 8, 10, and 12 seconds after the block onset. (Kourtzi and Kanwisher 2001).

3.1.6 Statistical Analysis

The discrimination threshold results from the ideal observer analysis were entered as the outcome variables in a repeated-measures ANOVA with Condition (whole-different, top face-half different, bottom face-half different, eyes different, mouth different, nose different) as a

factor. The efficiency scores from the human behavioral experiment were entered as the outcome variables in a repeated measures ANOVA with Condition (whole-same, whole-different, top face-half different, bottom face-half different, eyes different, mouth different, nose different) as a factor, and Subject as a random effect. The peak response from the fMRI-adaptation experiment was entered as the outcome variable in a repeated-measures ANOVA, with Condition (whole-same, whole-different, top face-half different, bottom face-half different, eyes different, mouth different, nose different), Hemisphere (left, right) and ROI(OFA, FFA, pSTS) as factors, and Subject as a random effect. Peak fMRI responses from each of the control regions were also entered as outcome variables in a repeated measures ANOVA with Condition (whole-same, whole-different, top face-half different, bottom face-half different, eyes different, mouth different, nose different) as Factors, and Subject as a random effect.

In each of these analyses, paired-samples t-tests, two-tailed for planned comparisons were used in order to explore the basis of the interactions. In order to determine which conditions showed a significant release from adaptation in the fMRI-adaptation experiment, these *a posteriori* comparisons were performed particularly between the whole-same condition and each of the "different" conditions. The alpha level was adjusted with Bonferroni correction for multiple comparisons in order to avoid an inflated Type 1 error rate. In order to determine whether the neural responses in the face responsive ROIs were parametrically correlated with the physical differences in the stimuli or the perceptual differences reported by the participants, we analyzed the correlation of the subjects' peak neural responses from the fMRI-adaptation experiment with their efficiency scores from the behavioral experiment, and the contrast discrimination threshold index from the ideal observer analysis. Since the physical and behavioral measures themselves might be correlated, we performed a partial correlation analysis

to estimate the individual contributions of these two measures. Partial correlations were run for each subject, where the contrast discrimination thresholds from the ideal observer analysis were included as a constant when correlating the peak neural response with the behavioral efficiency scores, and the behavioral efficiency scores were included as a constant when correlating the peak neural response with the contrast discrimination thresholds. Correlations were then transformed using Fisher's z-transformation and entered into two-tailed one-sample t-tests, compared to 0 with Bonferroni correction to detect significant correlations.

3.2 Results

3.2.1 Ideal Observer Experiment

The ideal observer analysis was run in order to assess the physical differences between the face pairs. For each face pair, the contrast threshold for discrimination at 82% accuracy was measured and averaged across conditions. The repeated-measures ANOVA for the six "different" conditions (whole-different, top face-half different, bottom face-half different, eyes different, mouth different, nose different) showed a significant main effect of Condition ($F(5,35) = 168.87$, $P < 0.001$) (Figure 3.2A). Across the conditions, detection of changes to the whole face required the lowest contrast threshold ($M = 165$, $SD = 13$). Paired-samples t-tests for planned comparisons (with Bonferroni correction) revealed that the contrast threshold for detecting changes to the top face-half ($M = 120$, $SD = 8.1$) was not significantly different from the contrast threshold for detecting changes to the bottom face-half ($M = 116$, $SD = 9.6$; $t(7) = 1.41$, $P = 0.20$). This confirmed that the selection of eight face images used for the study were physically similar for the top and bottom face-halves. In terms of the changes to the individual features, eye changes ($M = 115$, $SD = 8.8$) required significantly less contrast to detect than changes to the mouth ($M =$

98, SD = 9.8; t (7) = 5.52, P = 0.002) or changes to the nose (M = 70, SD = 13.1; t (7) = 9.44, P < 0.001). Mouth changes were also more easily detected than nose changes (t (7) = 4.82, P = 0.004).

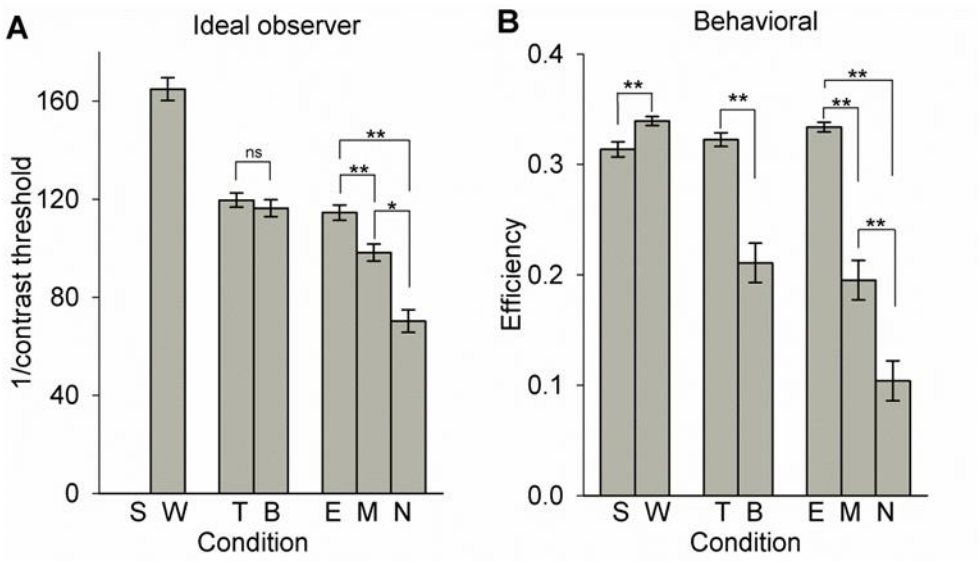


Figure 3.2 Results of (A) the Ideal Observer and (B) the Behavioral Experiment. S = whole same, W = whole different, T = top face half different, B = bottom face half different, E = eyes different, N = nose different, M = mouth different. * P < 0.01, ** P < 0.001, ns = no significant difference.

3.2.2 Human Behavioral Experiment

In order to investigate how the changes to the face stimuli were perceived by the humans, all participants performed a behavioral experiment involving a same/different task with the same stimuli set used in the Ideal Observer Analysis. The results described below includes data from 22 subjects from the original 25 subject pool after the exclusion of one subject who reported using the anomalous strategy of focusing on the mouth alone, and of two other subjects who had excessive movements during the fMRI experiment. Average accuracy and reaction times for different conditions changes are listed in Table 3.1. A repeated-measures ANOVA showed a

significant main effect of Condition F (6,126) = 67.43, P < 0.001) (Figure 3.2B). Paired-samples t-tests for planned comparisons revealed that subjects were more efficient at detecting changes to the whole face (whole-different condition) (M = 0.34, SD = 0.02) than detecting no changes to the faces (whole-same condition) (M = 0.31, SD = 0.03; t (21) = 3.28, P = 0.004). Changes to the top face-half (M = 0.32, SD = 0.03) were easier to detect than changes to the bottom face-half (M = 0.21, SD = 0.08; t (21) = 6.02, P < 0.001). In terms of the individual features, subjects were better at detecting changes to the eyes (M =0 .33, SD = 0.02) than changes to the mouth (M = 0.20, SD = 0.08; t(21) = 7.36, P < 0.001) or changes to the nose (M = 0.10, SD = 0.08; t(21) = 12.43, P < 0.001). Mouth changes were also more easily detected than nose changes (t (21) = 6.49, P < 0.001).

Condition	Accuracy (%)	Reaction time (ms)
Same	96.5 (1.1)	709.7 (23.9)
Whole	90.3 (1.6)	786.7 (36.3)
Top	92.0 (1.5)	731.9 (27.2)
Bottom	61.6 (5.1)	884.1 (39.0)
Eyes	95.1 (1.2)	723.1 (28.5)
Nose	30.6 (5.3)	916.6 (29.9)
Mouth	57.1 (5.1)	906.6 (43.3)

Table 3.1 Average Accuracy and Reaction Times and Corresponding Standard Errors of the Mean for the Behavioral Experiment for Each Condition.

3.2.3 fMRI Experiment

The six core face processing areas, the OFA, the FFA, and the pSTS bilaterally, were identified with the HVEM face localizer in most of the 23 participants who were included in the fMRI

analysis (Figure 3.3). The mean Talairach coordinates of the regions across subjects are reported in Table 3.2. The range of the ROI voxel sizes were variable across subjects, and for each region were as follows: right FFA 77- 2019; left FFA 42- 1518; right OFA 47- 1971; left OFA 18- 899; right pSTS 123- 1418; left pSTS 38- 1833. fMRI data for 2 subjects out of the original 25 subject pool were excluded from the fMRI data analysis due to excessive head motion during scanning.

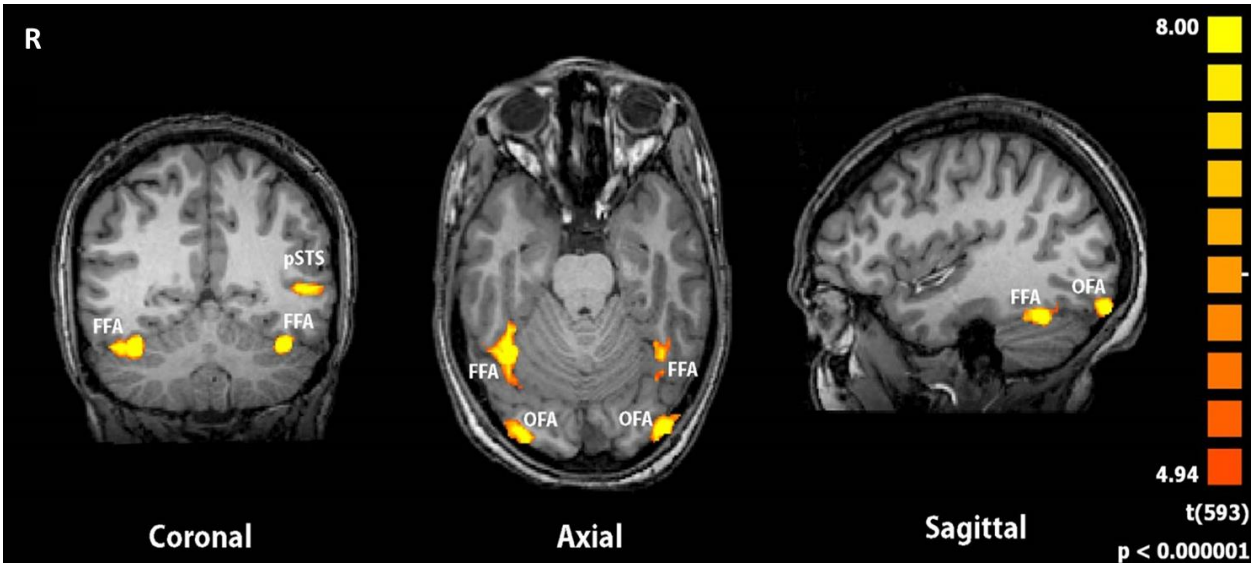


Figure 3.3 Localizer Scan Results of a Representative Subject. FFA (fusiform face area), OFA (occipital face area), pSTS(posterior Superior Temporal Sulcus) located bilaterally. Images follow radiological convention with the right hemisphere shown on the left.

The right FBA was localized in 14 subjects. Out of these 14 subjects, eight subjects had right FBA voxels which did not overlap with right FFA voxels. These voxels were defined as FBA*. The occipital pole box mask was selected anatomically for each subject. Subjects performed a size-change detection task during the adaptation experiment. A one-way ANOVA revealed no differences in response times between different conditions ($F(6,126) = 0.33$, $P =$

0.92) , suggesting that any difference measured in the neural responses across different conditions did not result from attention level differences throughout the experiment.

Region		*N*	Coordinates		
			x	*y*	*z*
FFA	Right	23	35	−48	−20
	Left	19	−38	−47	−20
OFA	Right	22	34	−72	−15
	Left	20	−34	−79	−16
pSTS	Right	22	47	−42	2
	Left	19	−50	−47	3

Table 3.2 Mean Talairach Coordinates of Face Responsive Regions of Interest Bilaterally.

The peak response was measured for each of the seven conditions in each ROI (Figure 3.4). A repeated-measures ANOVA with main factors of Hemisphere (right, left), ROI (OFA, FFA, pSTS) and Condition (whole-same, whole-different, top face-half different, bottom face-half different, eyes different, mouth different, nose different) revealed a significant main effect of ROI ($F(2,28) = 57.27$, $P < 0.001$) and Condition ($F(6,84) = 3.43$, $P = 0.004$), but not of Hemisphere ($F(1,14) = 3.91$, $P = 0.07$). There was a significant interaction between Hemisphere and ROI ($F(2,28) = 6.98$, $P = 0.003$), indicating response differences in the two hemispheres. There was no significant 3-way interaction between the Hemisphere, ROI and Condition ($F(12,168) = 0.87$, $P = 0.58$).

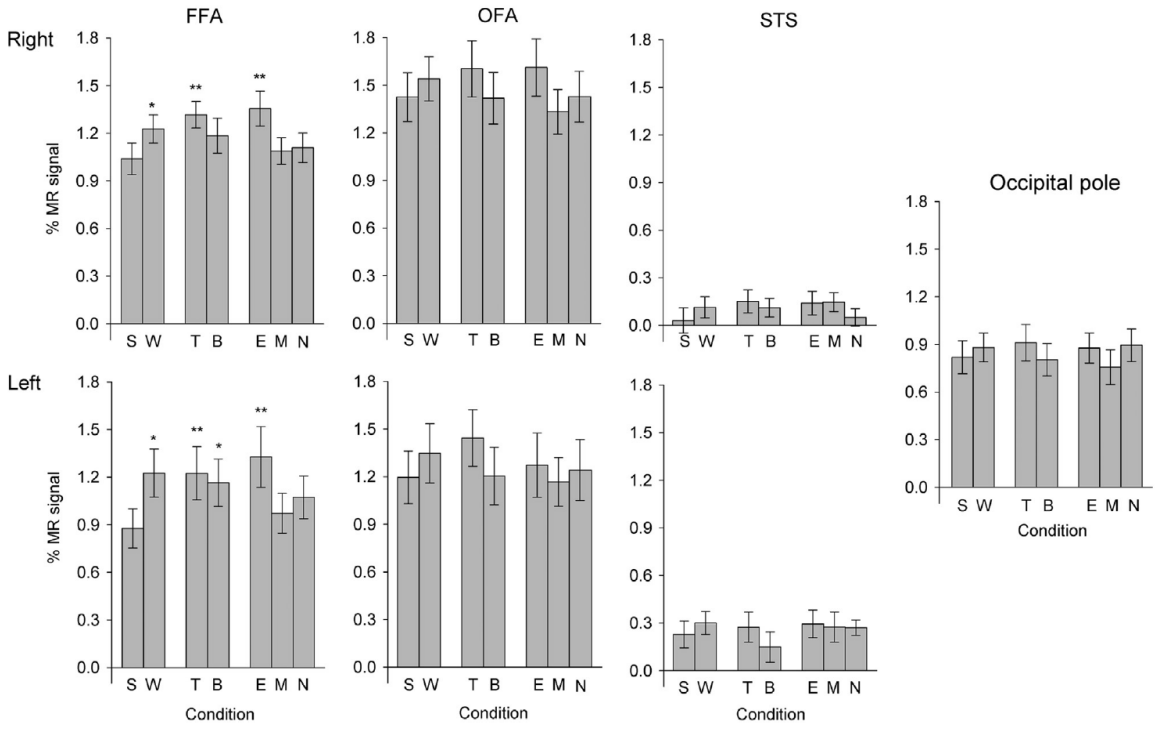


Figure 3.4. Responses in the Face Responsive Regions Bilaterally in the fMRI-adaptation Experiment as % Change in the MR Signal. FFA (fusiform face area), OFA (occipital face area), STS (Superior Temporal Sulcus), S = whole same, W = whole different, T = top face half different, B = bottom face half different, E = eyes different, N = nose different, M = mouth different. * P < 0.05, ** P < 0.01.

Paired-samples t-tests, two-tailed for planned comparisons revealed that there was a significant effect of Condition for both the right ($F(6,132) = 5.35$, $P < 0.001$) and the left FFA ($F(6,108) = 6.24$, $P < 0.001$). In the right FFA, there was release of adaptation in the top face-half different condition ($M = 1.32$, $SD = 0.40$; $t(22) = 3.94$, $P = 0.006$), the eyes different condition ($M = 1.36$, $SD = 0.53$; $t(22) = 6.09$, $P < 0.001$), and the whole-face different condition ($M = 1.23$, $SD = 0.43$; $t(22) = 3.00$, $P = 0.042$), but no release of adaptation in the bottom face-half different condition($M = 1.18$, $SD = 0.53$; $t(22) = 1.88$, $P = 0.44$), the mouth different condition ($M = 1.09$, $SD = 0.40$; $t(22) = 0.76$, $P = 0.99$) or the nose different condition ($M = 1.11$, $SD = 0.44$; ($t(22) =$

0.93, P = 0.99), compared to the whole-same condition (M = 1.04, SD =0 .48) (Figure 3.4). Similarly, the left FFA showed a release of adaptation in the top face-half different condition (M = 1.22, SD =0 .73; (t(18) = 4.18, P = 0.006), the eyes different condition (M = 1.33, SD = 0.83; (t(18) = 4.12, P = 0.006), and the whole-different condition (M = 1.23, SD =0 .66; t(18) = 3.57, P = 0.012), as well as the bottom face-half different condition (M = 1.16, SD = 0.65; (t(18) = 3.16, P = 0.03), but not for changes in the mouth different condition (M = 0.97, SD = 0.55; t(18) = 1.25, P = 0.99) or the nose different condition (M = 1.07, SD =0 .59; t(18) = 2.48, P = 0.99), all in comparison to the whole-same condition (M =0 .88, SD =0 .54).

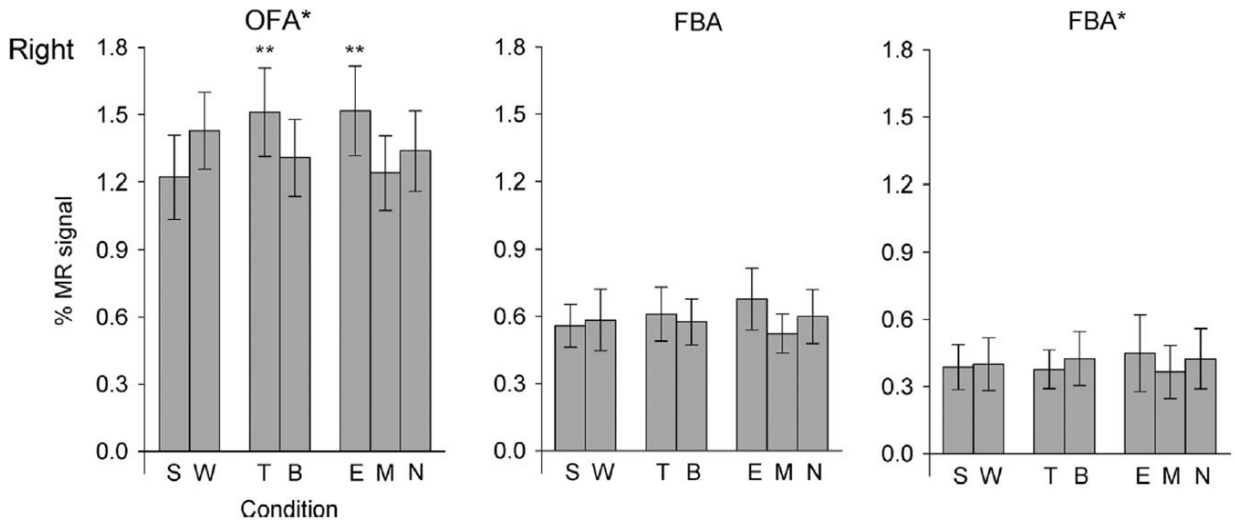


Figure 3.5 Responses of Additional Regions of Interest in the fMRI-adaptation Experiment. OFA* (occipital face area minus body responsive voxels), FBA (fusiform body area), FBA* (fusiform body area minus overlapping face responsive voxels), S = whole same, W = whole different, T = top face half different, B = bottom face half different, E = eyes different, N = nose different, M = mouth different. * P < 0.05, ** P < 0.01.

In the right OFA, Condition (F (6,126) = 2.22, P = 0.045) had a significant effect. The overall trend across conditions in the right OFA appeared similar to the right FFA. Yet, planned comparisons showed no significant release of adaptation after multiple comparison corrections.

Condition had no significant effect in the left OFA ($F(6,114) = 1.25$, $P = 0.29$). A *post hoc* analysis was run in order to explore the lack of significant adaptation aftereffects in right OFA. One possible explanation could be insufficient sample size. We had a relatively large sample size compared to previous studies. Therefore, this is unlikely to be the case. Another possibility is the inclusion of overlapping voxels from another region that are not as strongly face responsive. To test whether this is the case, within the previously defined right OFA ROIs (Faces>Objects), we localized voxels with a Faces> Bodies contrast at $P<0.05$ (Bonferroni corrected). These voxels were defined as right OFA*, and the fMRI-adaptation analysis was repeated. A repeated measures ANOVA revealed a significant main effect of Condition $F(6, 96) = 2.73$, $P = 0.017$) based on the peak responses of 17 right OFA* clusters localized. Planned comparisons in right OFA* revealed a significant release of adaptation when the top face halves ($M = 1.51$, $SD = 0.82$; $t(16) = 3.49$, $P = 0.003$), and the eyes changed ($M = 1.52$, $SD = 0.83$; $t(16) = 3.50$, $P = 0.003$) (Figure 3.5). There was also a trend of release of adaptation in the whole-different condition. There was no significant release of adaptation in the bottom face half different ($M = 1.31$, $SD = 0.70$: $t(16) = 1.08$, $P = 0.30$), nose different ($M = 1.34$, $SD = 0.73$; $t(16) = 1.01$, $P = 0.33$), or mouth different ($M = 1.24$, $SD = 0.68$; $t(16) = 0.18$, $P = 0.86$) conditions.

Neither the right ($F(6,126) = 1.24$, $P = 0.29$) nor the left ($F(6,108) = 0.87$, $P = 0.52$) pSTS showed a significant change of activation in response to different conditions. There was no significant effect of Condition ($F(6,132) = 1.38$, $P = 0.23$) in the occipital pole, suggesting that the significant effects observed in the face responsive regions did not solely reflect processing at earlier stages of the visual system (Figure 3.4). Neither the right FBA ($F(6, 108) = 1.14$, $P = 0.34$) nor FBA* ($F(6, 42) = 0.19$, $P = 0.98$) showed any differences in response to different conditions (Figure 3.5).

3.2.4 Partial Correlation Analysis

Partial correlation analysis included data from 22 subjects after the removal of the subject that had reported the strategy of focusing on the mouth throughout the behavioral experiment, and two other subjects that had excessive movements during the fMRI scan. One-sampled t-tests revealed that the peak fMRI responses in the right FFA were correlated with the human behavioral efficiency scores ($Zr = 0.34$, $t(21) = 4.67$, $P < 0.001$) but not with the ideal observer contrast thresholds for discrimination ($Zr = -0.07$, $t(21) = -0.84$, $P = 0.41$) (Figure 3.6). A paired-samples t-test showed that the peak fMRI response in the right FFA was significantly more correlated with human efficiency scores than with the ideal observer contrast thresholds for discrimination ($t(21) = 3.13$, $P < 0.01$). The left FFA showed a similar pattern, with significant correlations of the peak fMRI responses with human behavioral efficiency scores ($Zr = 0.27$, $t(17) = 2.48$, $P < 0.05$), but not with the ideal observer contrast thresholds for discrimination ($Zr = -0.02$, $t(17) = -0.15$, $P = 0.88$). In the left FFA, there was only a trend towards a significant difference between how well human efficiency and ideal observer contrast thresholds for discrimination correlated with the left FFA response ($t(17) = 1.79$, $P = 0.09$).

Peak responses in the right OFA were not correlated with either the human behavioral efficiency scores ($Zr = 0.13$, $t(20) = 1.40$, $P = 0.18$), or the ideal observer contrast thresholds ($Zr = 0.05$, $t(20) = 0.36$, $P = 0.73$). Peak responses in the left OFA were also not correlated with either the human behavioral efficiency scores ($Zr = 0.17$, $t(18) = 1.49$, $P = 0.16$) or the ideal observer contrast thresholds for discrimination ($Zr = 0.06$, $t(18) = 0.58$, $P = 0.57$). There was no difference in the correlation patterns of the right and the left OFA with the human behavioral efficiency scores and the ideal observer's discrimination thresholds (right OFA: $t(20) = 0.64$, $P = 0.53$; left OFA: $t(18) = 0.86$, $P = 0.40$). The *post hoc* analysis of right OFA* showed no

significant correlations between the peak responses in rOFA* and the human behavioral efficiency scores (Zr = 0.21, t (16) = 1.51, P = 0.15) or the ideal observer contrast thresholds for discrimination (Zr = 0.02, t (16) = 0.12, P = 0.91). There was no significant difference in the correlation patterns of the right OFA* with the human behavioral efficiency scores and the ideal observer's discrimination thresholds (t(16) = 0.63, P = 0.54) (Figure 3.7).

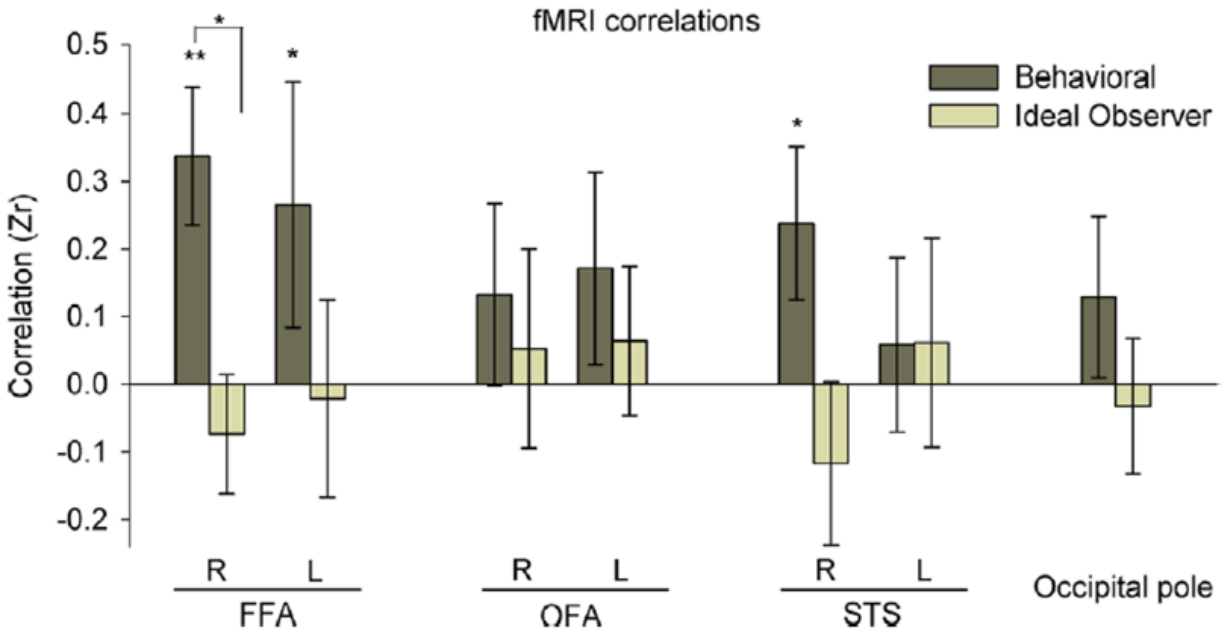


Figure 3.6 Mean Correlations of the Peak Responses of the Face Responsive Regions in the fMRI-adaptation Experiment with the Behavioral Experiment and the Ideal Observer Experiment. FFA (fusiform face area), OFA (occipital face area), STS (Superior Temporal Sulcus), * P < 0.05, ** P < 0.01.

Peak responses in the right pSTS correlated with the human behavioral efficiency scores (Zr = 0.24, t(20) = 2.19, P < 0.05), but not with the ideal observer contrast thresholds for discrimination (Zr = -0.12, t(20) = -0.97, P = 0.34). Responses in the left pSTS correlated with neither the human behavioral efficiency scores (Zr = 0.06, t (17) = 0.83, P = 0.42) nor the ideal

observer contrast thresholds for discrimination (*Zr* = 0.06, t (17) = 0.40, P = 0.70). There was no significant difference between how well these measures correlated with the neural response in pSTS (right: t (20) = 1.75, P = 0.10; left: t (17) = 0.35, P = 0.73).

Our control regions analysis showed that the peak responses in right FBA and the right FBA*were not correlated with the human behavioral efficiency scores (right FBA: *Zr* = 0.095, t(13) = 0.68, P = 0.51; right FBA*: *Zr* = - 0.077, t(7) = 0.99, P = 0.36) or the ideal observer contrast thresholds for discrimination (right FBA: *Zr* = 0.173, t(13) = -0.54, P = 0.60); right FBA*: *Zr* = - 0.19, t(7) = - 0.73, P = 0.49). There were no significant differences between the correlations of the peak responses in these control regions with the human behavioral efficiency score and the ideal observer contrast thresholds for discrimination (right FBA: t (13) = 0.65, P = 0.53; right FBA*: t (7) = 0.87, P = 0.42) (Figure 3.7). Analysis of the response patterns of the occipital pole in order to determine whether the responses of the face responsive regions were merely reflecting low-level visual processing revealed that there were no significant correlations between peak fMRI responses in the occipital pole with either the human behavioral efficiency scores (*Zr* = 0.13, t (21) = 1.31, P = 0.21) or the ideal observer contrast thresholds for discrimination (*Zr* = -0.03, t (21) = -0.33, P = 0.75).There was no difference between the human behavioral efficiency scores and the ideal observer contrast threshold for discrimination in how they correlated with the neural response in the occipital pole (t (21) = 1.02, P = 0.32).

Finally, 2X2 ANOVAs were used to examine the differences between response patterns in pairs of face responsive regions in each hemisphere and Analysis (Ideal Observer Discrimination Thresholds, Human Behavioral Efficiency Scores). In the right hemisphere, there was a significant difference between the FFA and pSTS pair (F(1,20) = 7.69, P = 0.01) and analysis (F(1,20) = 5.48, P = 0.03), but no significant interaction (F(1,20) = 0.18, P = 0.68). This

significant difference arose from the human behavioral efficiency scores having a higher correlation with the peak fMRI responses in the FFA than the pSTS ($t(20) = 2.70$, $P = 0.01$). There were no differences between the correlations of these regions with the ideal observer measures ($t(20) = 1.68$, $P = 0.11$). There were no significant effects or interactions for the left hemisphere across pairs of regions and the analysis measures.

In total, these results suggest that bilateral FFA is sensitive to the subjective perception of feature differences, but not to the physical differences in a facial image. Neural activity in the right FFA correlates more with a feature-salience hierarchy in subjective human perception than with physical image differences. The right pSTS has activity patterns that correlate with the feature-salience hierarchy revealed by human perception.

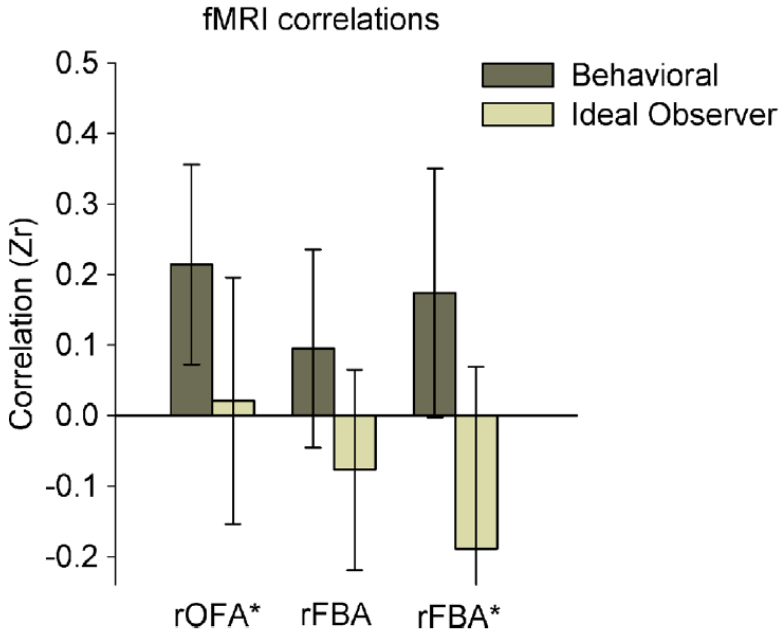


Figure 3.7 Mean Correlations of the Peak Responses of the rOFA* (right occipital face area minus body voxels), rFBA(right fusiform body area), rFBA* (right fusiform body area minus overlapping face responsive voxels) in the fMRI-adaptation experiment with the Behavioral Experiment and the Ideal Observer Experiment.

3.3 Comments

We applied an fMRI-adaptation technique to ask whether the neural activity in the core face processing network shows a feature-salience hierarchy pattern for facial features similar to that demonstrated by human participants in behavioral experiments. We also examined whether the activity patterns of the core face processing network correlated with the physical properties of the face image, as determined by an ideal observer analysis, or the human behavioral data for discriminating the features of the face. Our results revealed that the right and left FFA show differential sensitivity to different face features, reflected by the greater release from adaptation when the upper face half or the eyes change between images. This pattern was not found in the OFA or the pSTS. A parametric analysis revealed that the pattern of release of fMRI-adaptation across different conditions correlated with the human perceptual data in the FFA bilaterally. The right FFA, where the neural signal was significantly more correlated with the human perceptual data than with the physical properties of the images, showed stronger overall correlations. There was also a significant correlation with human perceptual data in the right pSTS. Our findings suggest that the feature-salience hierarchy characteristic of human face processing is highly reflected by activity in the right and left FFA, and to a degree in the right pSTS.

The apperceptive variant of acquired prosopagnosia most commonly presents with lesions which span the fusiform gyrus, which in turn includes the FFA. A disruption of the feature salience hierarchy in prosopagnosia patients could be the crucial element of the face processing impairments. Therefore, investigation of the eye region processing deficits and whether they present selectively with fusiform gyrus lesions that abolish the function of the FFA would clarify whether the loss of FFA is indeed the main reason for the eye region processing deficits in these patients. Acquisition of neuroimaging data from acquired prosopagnosia

patients to describe their lesions and to establish the status of the face processing network in addition to extensive behavioral testing of face processing abilities of these patients is necessary to compare the patient's lesion(s) and the function of the remaining face processing network with the patient's behavioral eye region processing performances. We examined a cohort of 10 acquired prosopagnosia patients to characterize the structural damage and the behavioral deficits, and their relation to one another to establish whether the feature salience hierarchy patterns are lost in these patients due to the loss of function of the FFA. The next chapter provides detailed descriptions of the acquired prosopagnosia patients in the study cohort.

Chapter 4: Acquired Prosopagnosia Patient Cohort

The following chapters of this thesis consist of studies performed on a prosopagnosia patient cohort along with healthy controls for each respective study. The current chapter includes descriptions of the 10 patients studied in the cohort as assessed by neuropsychological and behavioral testing as well as structural neuroimaging. The status of the core face processing network in these patients was also characterized using functional neuroimaging.

4.1 Methods

4.1.1 Patients

Patients were recruited from the www.faceblind.org website. This website provides a sign-up option for the patients where they can voluntarily fill out a screening questionnaire to describe their face recognition difficulties, their brain injury and their diagnosis. All patients completed a series of experiments which included neuro-ophthalmological examination, neuropsychological assessment, structural MRI scan, functional MRI scan, and behavioral face processing experiments. Goldmann Perimetry Test for visual fields and Farnsworth-Munsell (FM) 100-Hue Color Test for color vision were administered to establish the status of the visual fields and color vision respectively. Visual acuity was measured with Snellen Eye Test Chart. All protocols were approved by the institutional review boards of UBC and VGH. Written consent was taken from all patients in accordance with the Code of Ethics of the World Medical Association, Declaration of Helsinki (Rickham 1964).

4.1.1.1 Criteria

Acquired prosopagnosia is diagnosed by confirming the patient's inability to recognize familiar and famous faces. We administer a Famous Faces Familiarity Test and calculate the patient's discrimination power for determining whether a face is famous or not, and compare that discrimination score to those of healthy controls.

The Benton Face Recognition Test has been commonly used to test perceptual deficits in face processing (Benton and Van Allen 1968, 1972). This test requires subjects to pick a matching face from an array of six images to a target face across changes in viewpoint and lighting. Some non-prosopagnosic patients have also shown to obtain abnormal results in this test (Farah 1990). Additionally, some prosopagnosia patients may achieve normal accuracy rates (Duchaine and Nakayama 2004). In some cases, the normal score achieved can be explained by long amounts of time allocated to the study of test items by the patient (Farah 1990). As a complementary test, The Cambridge Face Perception Test has been developed for testing face perception abilities (Duchaine et al., 2007). This test requires subjects to arrange six faces in order of resemblance to a target face within one minute per item.

For testing face memory and its dissociation from memory for other visual stimulus forms, such as words, Warrington Recognition Memory for Faces and Words have been commonly used (Warrington 1984). This test requires the subjects to study a total of fifty faces for three seconds per item, and then asks the subjects to pick the face they have seen previously in a forced-choice task for each item studied. It has repeatedly shown a clear dissociation of memory for faces and words in prosopagnosia patients. In addition, the Cambridge Face Memory Test has proven to be a very effective diagnostic tool for confirming face memory impairments

(Duchaine and Nakayama 2006a). This test includes both the immediate and delayed recall of six different faces studied from different viewpoints throughout the experiment.

Apperceptive and associative variants of prosopagnosia are best distinguished by the status of structural coding of faces. Apperceptive prosopagnosia is typically defined as the inability to recognize familiar faces with face perception difficulties and results from damage to the inferior occipitotemporal cortex. It can be diagnosed by confirming impairments in perceiving the differences between faces in addition to failure to recognize familiar or famous faces. This can be achieved by testing the patients with the Benton Face Recognition Test and the Cambridge Face Perception test. These same tests are also used to demonstrate intact or relatively preserved face perception in associative prosopagnosia. Associative prosopagnosia is typically defined as the inability to recognize familiar faces with intact face perception processing and impaired face memory and/or impaired access to face memory. It results from damage to the anterior temporal lobe(s), and is diagnosed by confirming impairments in face memory and/or access to face memory in addition to failure to recognize familiar or famous faces. The Warrington Recognition Test for Faces and the Cambridge Face Memory Test are used to confirm face memory impairments. Additionally, testing face imagery by asking subjects questions based on what they can recall about famous faces without the actual presentation of these faces is also used to test patients' access to face memory stores (Takahashi et al., 1995; Barton and Cherkasova 2003). It should be noted that testing of face perception in patients with anterior temporal lobe lesions can still show some perceptual deficits which are generally milder than those seen in patients with occipitotemporal damage. Patients with anterior temporal lesions are better at perceiving the spatial relations between face features, yet, some of these patients may fail to integrate these spatial relations holistically (Barton et al., 2003).

For our patient cohort, we used: 1) the Famous Faces Familiarity Test to assess face recognition, 2) Benton Face Recognition Test and the Cambridge Face Perception Test to assess perceptual face processing, 3) Warrington Recognition Memory Test for Faces and Words, the Cambridge Face Recognition Test, and the Face Imagery Test to assess face memory and access to face memory. The performances of the patients in these tests are summarized in Table 4.2.

4.1.1.2 Exclusion Criteria

Individuals with psychiatric disorders or degenerative disorders of the central nervous system and general visual agnosia or amnesia were not included in the patient cohort. Similarly, individuals with corrected visual acuity less than 20/60 were also excluded. The patient group was limited to English speaking subjects from USA and Canada. Individuals who were MRI-incompatible (metal clips, pacemakers etc.) were also excluded. Subjects were limited to ages between 20 and 70 years.

4.1.2 Famous Faces Familiarity Test

Subjects are presented a total of forty faces in random order (Barton 2001b). 20 of these belong to famous people and the other 20 belong to anonymous people. Subjects are asked to indicate which out the 40 faces are familiar. Afterwards, subjects are given a list with the 20 names of the famous people and 20 anonymous names. Famous faces whose names are not recognized by the subject are eliminated from the face analysis. Discrimination power (d') scores are calculated for each patient and compared with the mean d' of controls (2.78 ± 0.42). Critical z scores are calculated at $\alpha = 0.05$ to determine each patient's deviation from the controls.

4.1.3 Benton Face Recognition Test

This test measures the face discrimination abilities without any demand on face memory (Benton and Van Allen 1968, 1972). For the first six items of the test, subjects are given a front view face and asked to find the same face among 6 front view faces. For the next eight items, subjects are given a front view face and asked to find the 3 matches to the target face out of 6 faces with different view-points. For the last eight items, subjects are given a front view face and asked to find the 3 matches to the target face out of 6 faces presented under different lighting conditions. Items are scores per correct face out of a total of 54 and compared to the normative observations of the Benton and Van Allen study.

4.1.4 Cambridge Face Perception Test

This test investigates face discrimination abilities without memorizing any of the faces (Duchaine et al., 2007). Subjects are presented with 3/4 profile view of a target face on top middle location of the screen and 6 morphed front view faces with gradual levels of resemblance to the target face below the target face. Subjects are asked to arrange the six faces in the order of resemblance from the least like the target face to the most like the target face in 60 seconds. There are a total of 8 upright and 8 inverted trials. Scores of each item were calculated by adding the deviations of each test face from their correct position. Controls showed a mean error rate of 36.7 ± 12.2 for upright and 65 ± 9.8 errors for inverted faces. Critical z scores are calculated at $\alpha = 0.05$ to determine each patient's deviation from the controls.

4.1.5 Warrington Recognition Test for Words and Faces

This test assesses memory for faces and words separately (Warrington 1984). For the face memory, subjects are first shown 50 anonymous faces sequentially for 3 seconds per face while they are asked to perform an irrelevant subjective Pleasant/ Unpleasant task. This is followed by presentation of face pairs, a face from the previously studied faces and a distractor face that is seen for the first time. In a forced-choice task, the subjects are asked to choose the face they have seen previously in each pair. The same procedure is followed for the memory test for words, where subjects are presented with each word for 3 seconds while they perform the irrelevant subjective Pleasant/ Unpleasant task, followed by the forced-choice recognition task for 50 items. Correct answers for each test item are added for the total score out of 50 for faces and words separately. Subject's scores are compared with the normative results from the Warrington study.

4.1.6 Cambridge Face Memory Test

This test assesses the ability to memorize faces in different orientations (Duchaine and Nakayama 2006a). The test consists of 6 target male faces, with 12 different images of each identity, and a total of 46 distractors. There are four parts: practice, introduction, novel images, and novel images with noise. In the introduction part, subjects are asked to memorize a face that is shown in three different angle images sequentially. Immediately after three images, they are asked to choose the face they memorized out of 3 faces, 2 of which are distractors. There are three questions for each trial, one for each angle shown. In the novel images phase, subjects are presented a single "review" image which includes the frontal view of each target face. Following the 20s review, subjects are presented with 30 forced-choice items (6 target faces from novel

angles X 5 presentations), each item containing 3 faces, one of which is the target face. Subjects are reminded that each item will contain 1 target face. Following this, subjects are given another 20s review, and then in the final part of the test with noisy novel images, 24 forced-choice items (6 targets X 4 presentations) are presented as novel angle Gaussian-noise added images (1 target, 2 distactors). Subject score is calculated as percent correct out of 72 total items. Subject's scores are compared to the mean of the controls (57.92% ± 7.92). Critical z scores are calculated at $\alpha = 0.05$ to determine each patient's deviation from the controls.

4.1.7 Face Imagery Test

This test assesses the face imagery abilities to determine whether the subject is able to conjure up the faces of famous people and answer questions about these faces without actually seeing these faces (Barton and Cherkasova 2003). Subjects are given the names of 39 famous people pairs and asked to compare in their mind the faces of these famous people, in terms of a feature (e.g. who has the larger nose?) or the global shape (e.g. who has the rounder face?). Items in this test were selected for a 92% average correct in the control group with 95% prediction intervals at 82%. A performance less than 68% percent is below chance.

4.1.8 Neuropsychological Assessment

Each patient underwent an extensive battery of neuropsychological testing to characterize their baseline cognitive levels compared to a normative age-matched healthy population. This battery includes tests of handedness, general intelligence, executive functions, memory, attention, general visual perception, visual imagery, and language skills. The performances of the patients

in these tests are summarized in Table 4.1. If any impairment is observed, it is included under each patient's individual description.

4.1.9 Structural Neuroimaging

Patients were scanned in a Philips 3.0T scanner at the UBC MRI Research Centre. A high resolution T1-weighted anatomical image gradient echo sequence (170 axial slices, FOV 256X200mm, slice thickness 1mm, voxel size 1X1mm) was collected from each patient.

4.1.1 Functional Neuroimaging

Patients were scanned in a Philips 3.0T scanner at the UBC MRI Research Centre. T2*-weighted functional scans using echo planar imaging were used to collect data from 36 interleaved axial slices (TR 2000ms, TE 30ms, FOV 240X216mm, 3mm thickness with 1mm gap, voxel size 3X3mm, 128 reconstruction matrix, reconstructed voxel size 1.88X1.6mm). These were co-registered onto a T1-weighted anatomical image (EPI) sequence (170 axial slices, FOV 256X200mm, slice thickness 1mm, voxel size 1X1mm) from each participant.

The HVEM Dynamic Localizer scan was run on each patient to identify and characterize the status of the face-selective regions of the visual cortex (Fox et al., 2009b). This localizer consisted of grayscale video clips of faces and objects. Each stimulus block included 6 video clips lasting 1.5s separated by a 500ms blank screen. Stimulus blocks were separated by a 12s fixation cross block. Each condition was repeated 8 times per run. Attention was monitored by asking the patients to press a button on an MRI-compatible button-box when the same video was presented twice in a row. All data was analyzed using Brainvoyager QX software. The preprocessing of

Test	Max	R-IOT1	R-IOT4	L-IOT2	B-IOT-2	B-ATOT1	B-ATOT2	R-AT2	R-AT3	B-AT1	B-AT2
Visuo-perceptual											
Hooper Visual Organization	**30**	27	22	9*	22.5	17.5*	12*	28	27.5	20	28
Benton Judgment of Line Orientation	**30**	29	24	23	29	26	22	28	30	28	28
Screening Test-VOSP	**20**	20	18	20	20	20	20	20	20	20	20
Incomplete Letters-VOSP	**20**	19	19	17	19	19	19	20	19	19	19
Silhouettes-VOSP	**30**	21	18	3*	12*	9*	4.5*	18	22	10*	25
Object Decision-VOSP	**20**	16	19	13*	14	9*	10*	20	17	16	18
Progressive Silhouettes-VOSP	**20**	9	13	10	15	11	4	10	11	17*	8
Dot Counting-VOSP	**10**	10	9	10	10	10	9	10	10	10	10
Position Discrimination-VOSP	**20**	20	19	19	19	20	15*	20	19	19	20
Number Location-VOSP	**10**	10	10	10	10	10	8	9	10	10	10
Cube Analysis-VOSP	**10**	10	10	10	10	10	9	10	10	10	9
Boston Naming Test-Short or Long Form	**15/60**	15/15	15/15	2*/15	15/15	14/15	36*/60	15/15	15/15	22*/60	15/15
Imagery											
Mental Rotation	**10**	10	10	7	10	10	10	9	10	10	5*
Attention											
Star Cancellation	**54**	54	54	53	53	54	54	54	54	54	54
Visual Search	**60**	54	n/a	60	56	52	59	59	59	59	56
Memory											
Digit span-forward	**16**	12	8	10	14	12	7*	13	16	12	9
Spatial span-forward	**16**	9	10	10	8	11	8#	9	12	10	9
Word list	**48**	28	37	27	35	17*	27*	35	31	27*	23#
Executive Function											
Trails A	-	39	48#	54#	80*	24	30	21	22	18	30
Trails B	-	61	102#	117#	142*	60	93#	44	37	25	40
Faces-Identity											
Identity Discrimination, FAB	**100**	95%	90%	85%*	60%*	100%	90%	90%	95%	100%	95%
Faces-Expresssion											
Affect Discrimination, FAB	**100%**	95%	75%	65%*	80%	75%	65%*	95%	95%	85%	85%
Affect Naming, FAB	**100%**	85%	85%	75%	67%	95%	52%*	89.5%	95%	89.50%	89%
Affect Selection, FAB	**100%**	95%	90%	55%*	80%*	100%	55%*	100%	100%	100%	90%
Affect Matching, FAB	**100%**	90%	75%	60%*	60%*	85%	55%*	100%	100%	85%	90%
Reading the mind in the eyes	**36**	27	19*	11*	13*	20#	9*	23	29	24	28

Table 4.1 Summary of Patient Neuropsychological Assessments. VOSP (Visual Object Space Perception), FAB (Florida Affect Battery),* denotes impaired, # denotes borderline performance.

the fMRI data consisted of slice time correction (cubic spline interpolation), 3D motion correction (trilinear/sinc interpolation), and high-pass temporal filtering (GLM-Fourier, 2 sines/cosines). Face-selective regions were determined for each patient individually with the contrast “Faces> Objects” at $p<0.05$, Bonferroni corrected for multiple comparisons.

4.2 Patient Descriptions

Patients were classified as apperceptive or associative variants of prosopagnosia based on their anatomical damage and their results in face processing and face memory experiments. Patients with inferior occipitotemporal lobe lesions are classified as apperceptive prosopagnosics, whereas patients with anterior temporal lobe lesions are classified as associative prosopagnosics. In cases where patients presented both inferior occipitotemporal lobe and anterior temporal lobe lesions, they were classified as apperceptive since the perceptual processing stages attributed to the inferior occipitotemporal cortex precede the further face processing stages such as semantic face memory retrieval attributed to the anterior temporal cortex in the human brain (Davies-Thompson et al., 2014). Patients are given code names based on their lesions and the numbering index used in the lab; IOT denotes an inferior occipitotemporal lesion; AT denotes an anterior temporal lobe lesion.

Patient	R-IOT1	R-IOT4	L-IOT2	B-IOT-2	B-ATOT1	B-ATOT2	R-AT2	R-AT3	B-AT1	B-AT2
Face Perception										
BFRT	45	46	31	38	41	37	47	38	45	40
CFPT	62	76	74	70	100	80	40	48	52	76
Face Familiarity										
Famous Faces d'	1.96	1.29	0.00	1.31	0.00	0.15	0.65	0.90	0.36	0.68
Face Memory										
WRMT face	33	39	27	21	27	19	27	31	27	31
WRMT word	41	50	42	42	50	39	47	47	45	46
CFMT	44	27	21	24	30	24	33	31	30	31
Face Imagery %	82	84	41	86	60	48	73	49	*	50

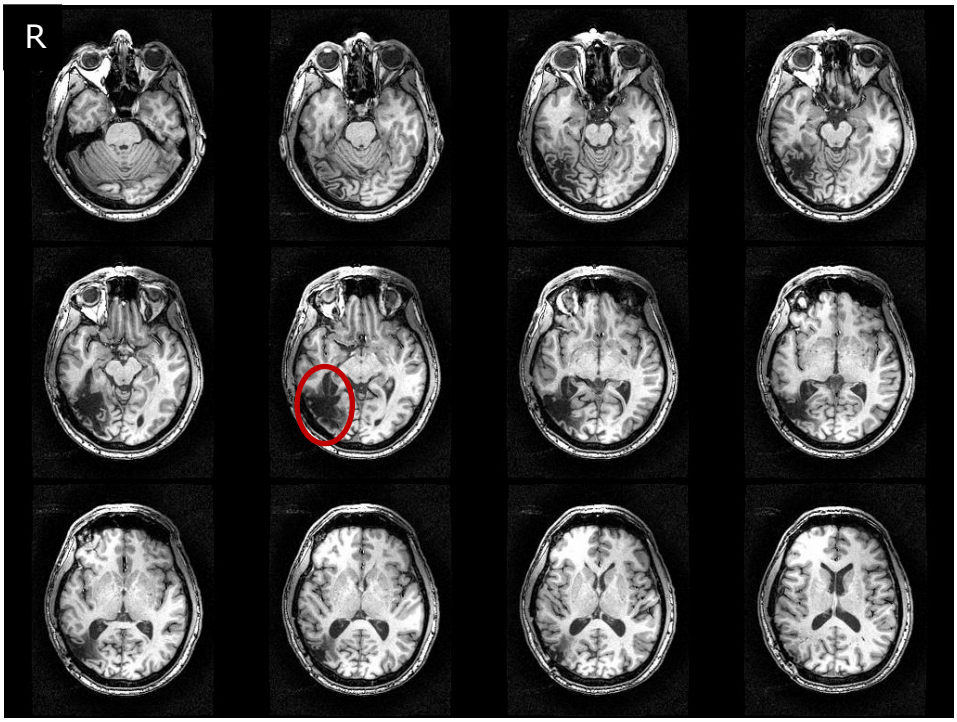
Table 4.2 Performances of Patients in the Face Perception Tests. BFRT (Benton Face Recognition Test), CFPT (Cambridge Face Perception Test), WRMT (Warrington Recognition Memory Test), CFMT (Cambridge Face Memory Test). * B-AT1 did not recognize enough celebrity names to perform the imagery test. Underlined numbers indicate abnormal result.

4.2.1 Apperceptive Prosopagnosia Group

4.2.1.1 Patient R-IOT1

Patient R-IOT1 is a 49 year old left-handed man. He suffered from an occipital hemorrhage due to an arteriovenous malformation rupture at the age of 37. Since then he has had difficulty recognizing faces. He is employed full-time. Goldmann perimetry test revealed a homonymous partial left superior quadrantanopia. His color vision is normal. His visual acuity with contact correction is 20/20 for both eyes. His performance on the Famous Faces Familiarity Test revealed impaired face familiarity (d' = 1.96). He performed within the normal range in the Benton Face Recognition Test, but he was impaired in the Cambridge Face Perception Test (62 errors). He was impaired for the face component of the Warrington Recognition Memory Test (33/50), but performed within the normal range in the Cambridge Face Memory Test. He performed within the normal range in the Face Imagery test. His performance was within the normal range for all other memory tests included in the neuropsychology battery. His neuropsychological assessment showed no other impairments. His structural scan reveals a right inferior occipitotemporal lesion (Figure 4.1A). His functional scan revealed loss of function in right OFA and FFA and preserved activation in response to faces in the left OFA, left FFA, and bilateral pSTS (Figure 4.1B).

A



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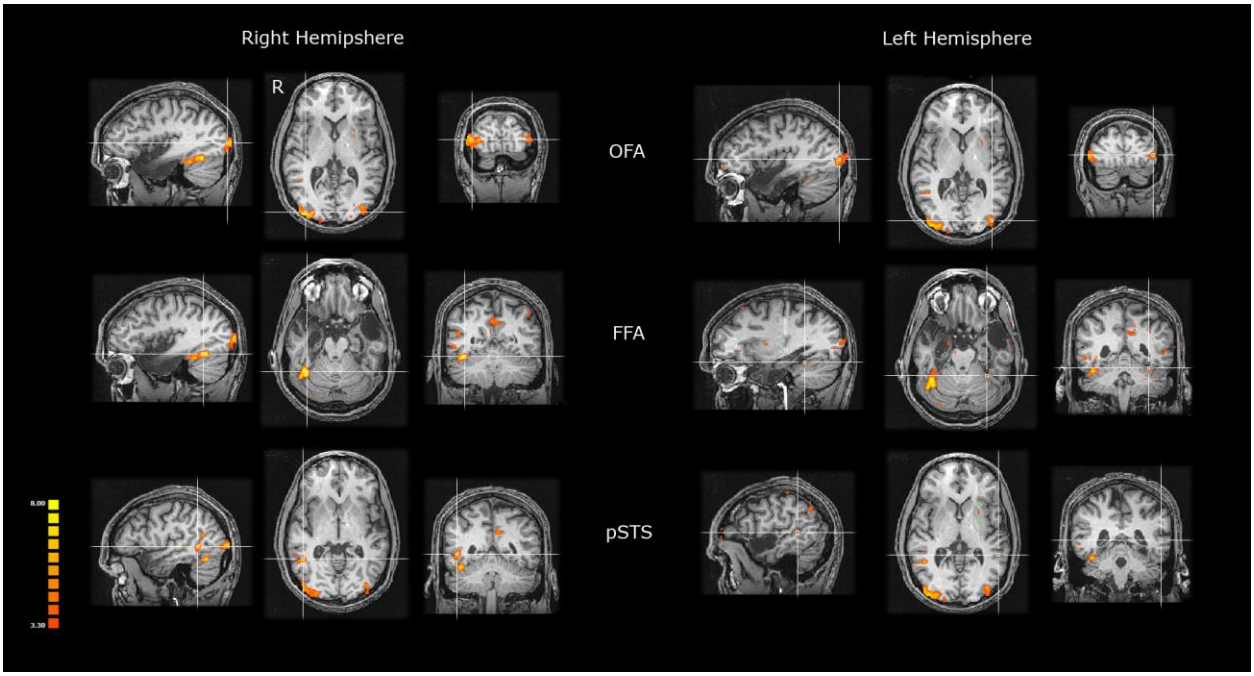
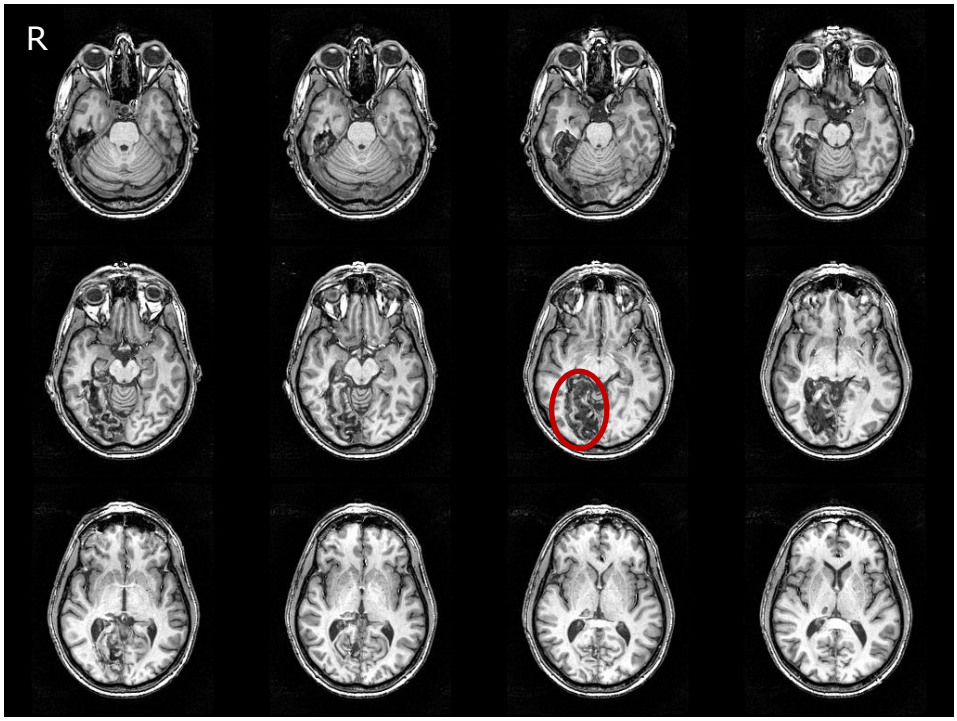


Figure 4.1 A) Structural MR Images, B) fMRI Face Localizer Scan Results of Patient R-IOT1.

4.2.1.2 Patient R-IOT4

Patient R-IOT4 is a 57 year old right-hand dominant man. He suffered from a right posterior cerebral arterial infarct associated with a fetal circulation pattern six months prior to his testing by our lab. Since then he has difficulty recognizing faces and his surroundings. Since his injury, he first switched to a part-time position from full-time employment and is currently retired. He has an incongruous homonymous left upper quadrantanopia, and a visual acuity of 20/30. His color vision is normal. He was impaired in the Face Familiarity test (d' = 1.29). He performed within the normal range in the Benton Face Recognition Test, but was impaired in the Cambridge Face Perception Test (76 errors). He performed within the normal range in the Warrington Recognition Memory for Faces, but was impaired in the Cambridge Face Memory Test (27/72). His Face Imagery results were within the normal range. His neuropsychological assessment shows mostly normal performance with delays in the Trail Making Test, which can be explained by his hemianopia. His structural scan reveals a right inferomedial occipital lesion which extends from the inferior calcarine fissure to the middle and lateral parts of the middle fusiform gyrus (Figure 4.2A). His functional scan revealed loss of right FFA activation (Figure 4.2B). All other core face processing areas (bilateral OFA, left FFA, bilateral pSTS) had preserved activation in response to faces.

A



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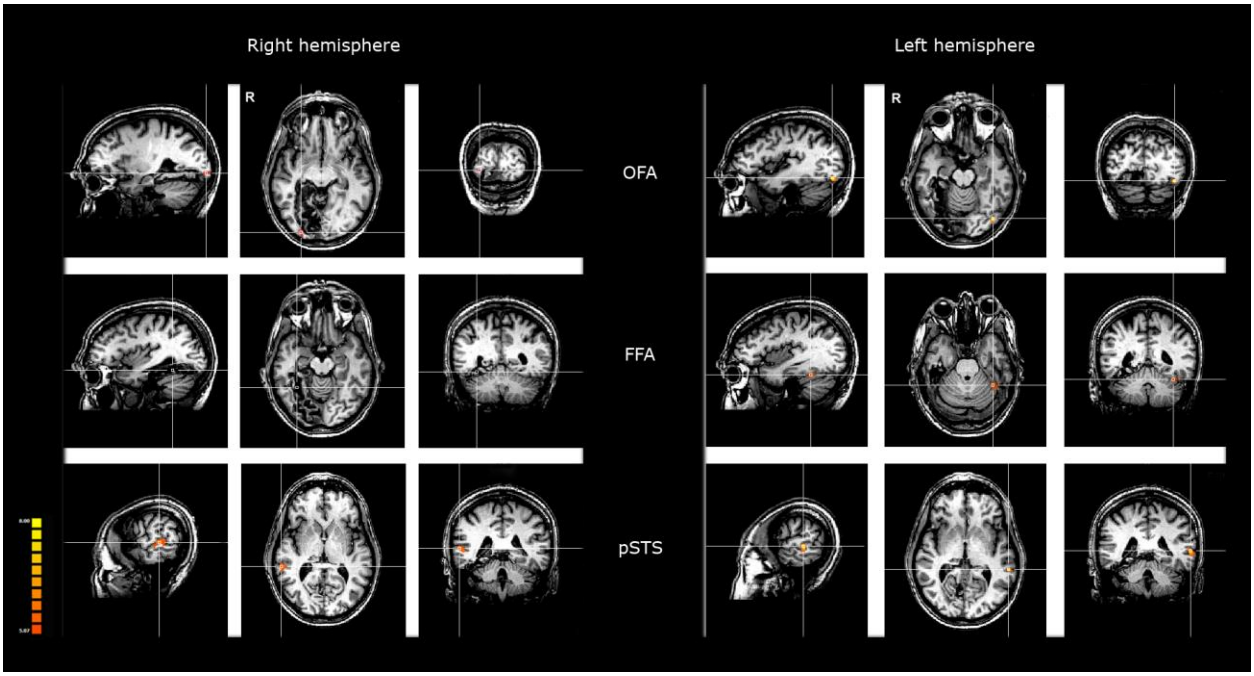
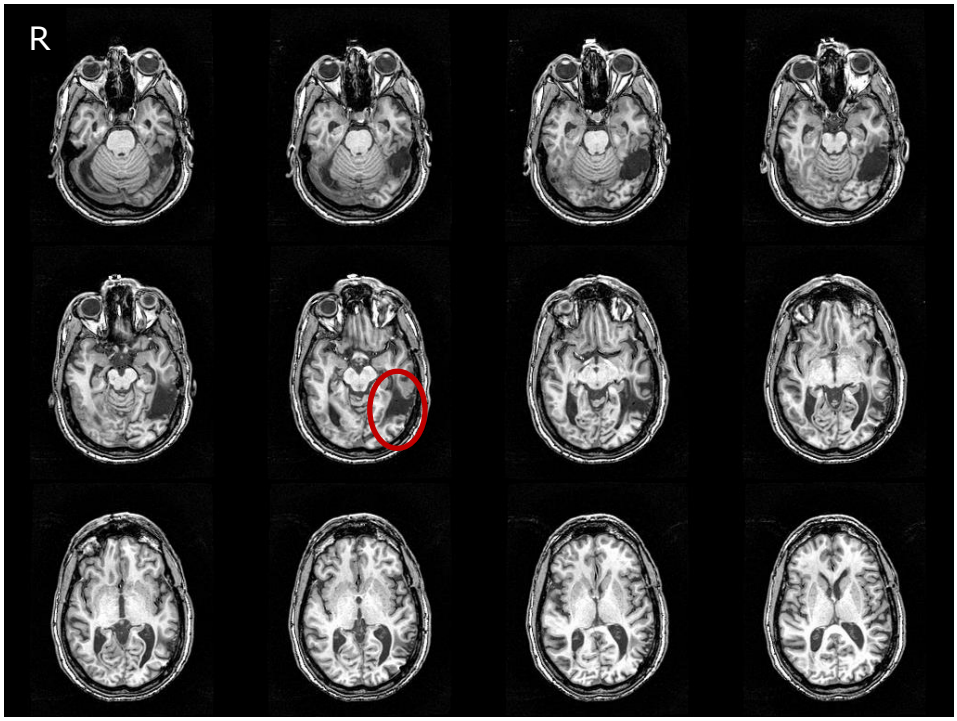


Figure 4.2 A) Structural MR Images, B) fMRI Face Localizer Scan Results of Patient R-IOT4.

4.2.1.3 Patient L-IOT2

Patient L-IOT2 is a 56 year old ambidextrous man. At the age of 41, he underwent left temporal epilepsy surgery. Since then, he has had difficulties recognizing familiar faces. He is retired on disability. He has full visual fields confirmed with Goldmann perimetry. His visual acuity with correction at far is 20/25 od and 20/40 os. FM-100 hue test score is 312, indicating low color discrimination. He was impaired in the Famous Face Familiarity Test (d' = 0.00). He was impaired in the Benton Face Recognition Test (31/54) and the Cambridge Face Perception Test (74 errors). He was impaired in the Warrington Recognition Memory Test for faces (27/50) and the Cambridge Face Memory Test (21/72). He was also impaired in the Face Imagery Test (41%). His neuropsychological assessment (Table 4.2) indicates mild defects in object recognition and naming. He also had a mild defect in the delayed recall component of complex spatial memory. He was impaired in the Trail Making Test. His structural MRI scan (Figure 4.3A) reveals a left middle fusiform gyrus lesion. His functional MRI scan revealed loss of function in the bilateral FFA. He had preserved activation in response to faces in the right OFA, right pSTS and a very small activation on the left OFA (Figure 4.3B).

A



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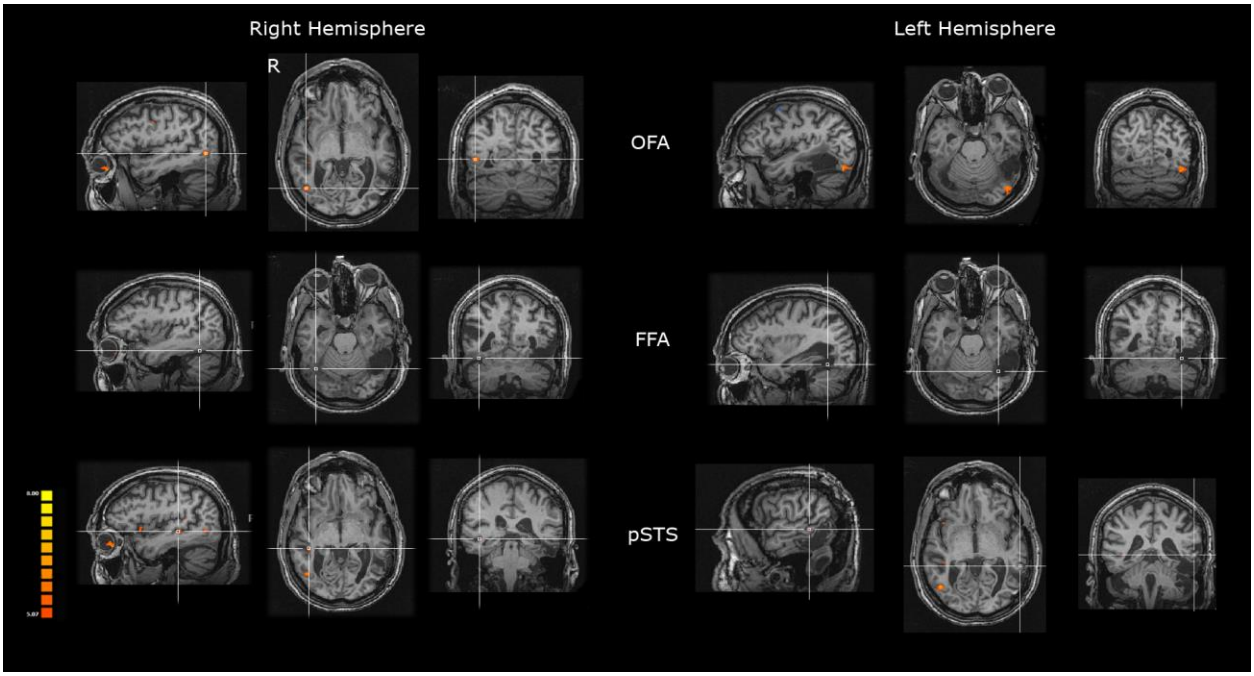
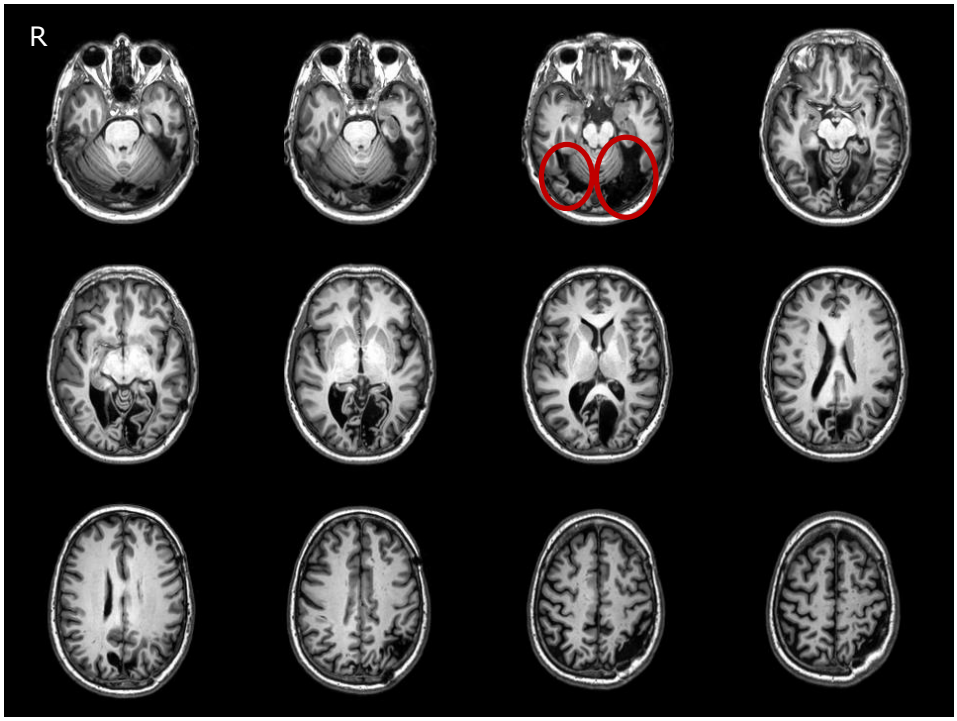


Figure 4.3 A) Structural MR Images, B) fMRI Face Localizer Scan Results of Patient L-IOT2.

4.2.1.4 Patient B-IOT2

Patient B-IOT2 is currently a 60 year old right-handed man. He suffered from a subdural hematoma following a head injury at the age of 26. Since then he has had difficulties in recognizing faces and places. He is currently retired. Goldmann perimetry test revealed severe field defects with a constricted left inferior homonymous island of vision. His color vision is impaired. His visual acuity with correction is 20/15 for both eyes. He was impaired in the face familiarity test (d' = 1.31). His face perception is also impaired as revealed by poor performances on the Benton Face Recognition Test (38/54) and the Cambridge Face Perception Test (70 errors). He was impaired in the Warrington Recognition Memory Test for faces (21/50) and the Cambridge Face Memory Test (24/72). His face imagery was within the normal range. His neuropsychological assessment reveals a mild impairment in the delayed recall of verbal memory with normal performance in all other memory tests. He was also impaired in the Face Identification, Affect Perception, and Affect Judgment subtests of the Florida Face Affect Battery. His structural scan reveals bilateral occipitotemporal lesions (Figure 4.4A). His functional MRI scan revealed loss of bilateral FFA and left OFA with preserved right OFA and bilateral pSTS activation in response to faces (Figure 4.4B).

A



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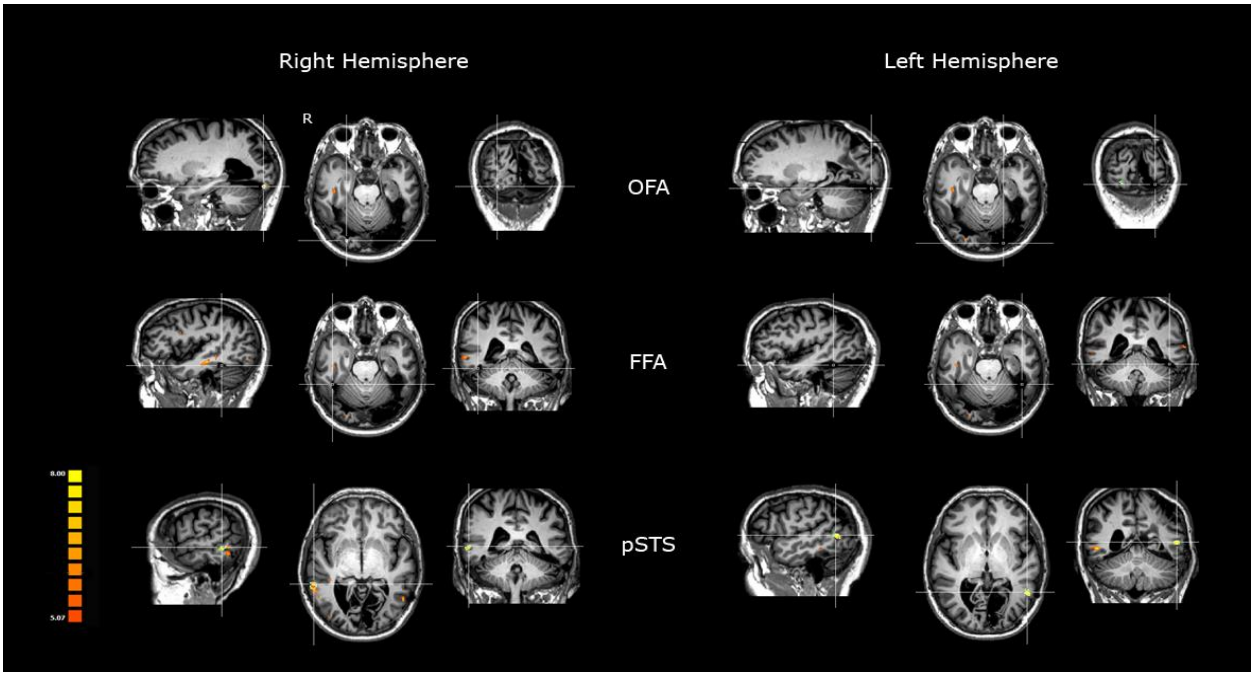
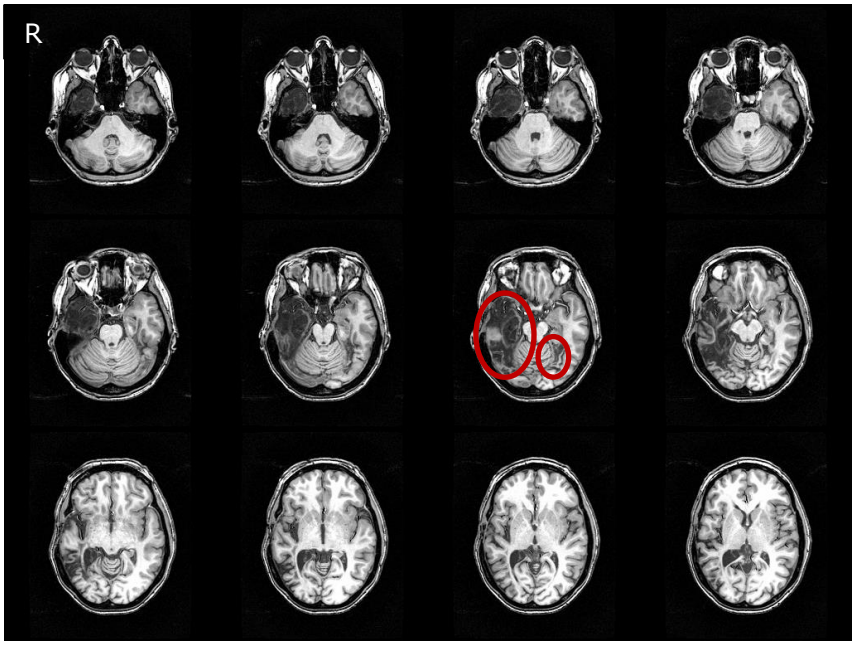


Figure 4.4 A) Structural MR Images, B) fMRI Face Localizer Scan Results of Patient B-IOT2.

4.2.1.5 Patient B-ATOT1

Patient B-ATOT1 is a 39 year old left-hand dominant woman. She suffered from herpes simplex encephalitis at the age of 14. Since then she has had difficulty recognizing faces. She completed a university degree and works full-time. Her Goldmann perimetry test showed a subtle left upper quadrantic field defect outside the central 30^{o}. She has impaired color vision in the left, indicating left hemiachromatopsia. Her visual acuity is 20/15 for both eyes. She was impaired in the Famous Face Familiarity Test (d' = 0.00). She was in the normal range for Benton Face Recognition Test, but she was impaired in the Cambridge Face Perception Test (100 errors). She was impaired in the Warrington Recognition Memory Test for faces (27/50) and the Cambridge Face Memory Test (30/72). She was also impaired in the Face Imagery Test (60%). Her neuropsychological assessment shows impaired memory for the delayed recall component of complex spatial memory. She also has mild object perception deficits as revealed by impaired performance on the Silhouettes and Object decision subtests of the Visual Object and Space Perception Battery and the Hooper Visual Organization Test. Her structural scan reveals a right anterior temporal lobe lesion that extends and spreads all the way to the fusiform gyrus and past that to the right occipital lobe, and a smaller left inferomedial fusiform gyrus lesion (Figure 4.5A). Her functional MRI scan revealed loss of function of right FFA with preserved activation in response to faces in the left OFA, left FFA, and bilateral pSTS as well as a small right OFA activation(Figure 4.5B).

A



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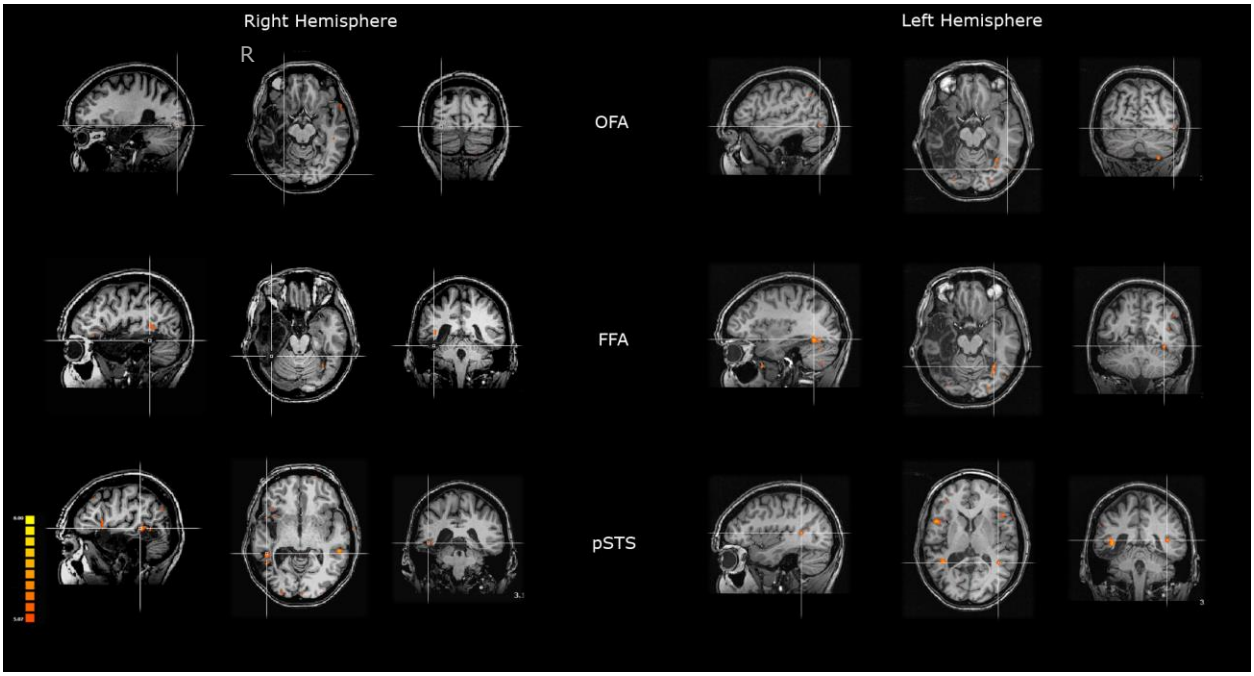
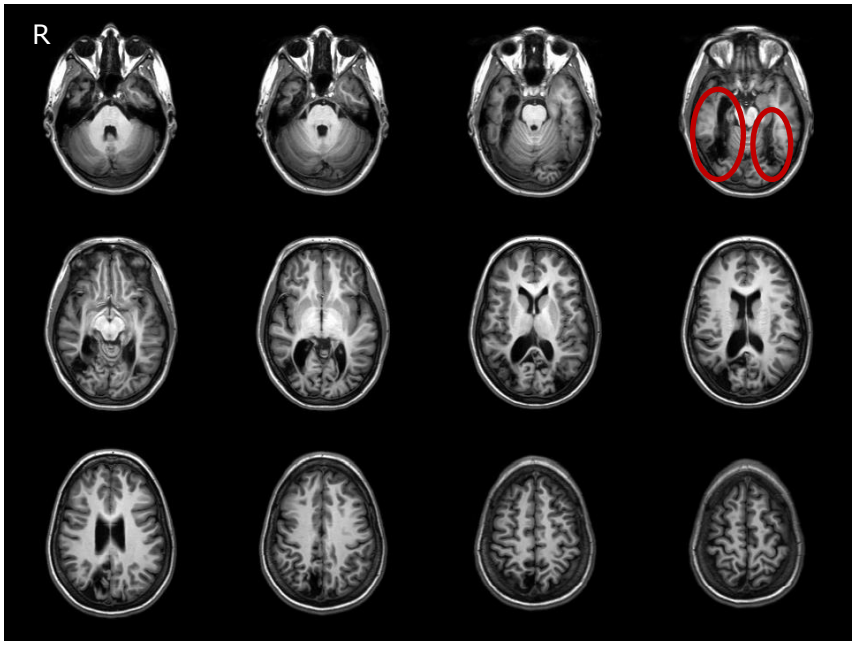


Figure 4.5 A) Structural MR Images, B) fMRI Face Localizer Scan Results of Patient B-ATOT1.

4.2.1.6 Patient B-ATOT2

Patient B-ATOT2 is currently a 22 year old right-handed woman. She suffered from herpes simplex encephalitis at the age of 10. Since then, she has had difficulties in recognizing faces and places, and understanding emotional expressions. She is currently a college student. She has full visual fields with visual acuity of 20/20 for both eyes. Her color vision is impaired. She was impaired in the Famous Face Familiarity Test (d' = 0.15). She was impaired in the Benton Face Recognition Test (37/54) and the Cambridge Face Perception Test (80 errors). She was impaired in the Warrington Recognition Memory Test for faces (19/50) and the Cambridge Face Memory Test (24/72). She was also impaired for Face Imagery (48%). Her neuropsychological assessment reveals borderline performance for word memory. She showed borderline performance in all but one of the rest of the memory tests in the neuropsychology battery. She was impaired for the delayed recall component of complex spatial memory. Object recognition and naming were also impaired as revealed by the poor performances in Visual Object and Space Perception Battery, the Hooper Visual Organization Test, and the Boston Naming Test. In addition her face affect discrimination was also impaired as revealed by abnormal performances the Florida Face Affect Battery. Her structural scan reveals a right anterior temporal lobe lesion and bilateral occipitotemporal lesions (Figure 4.6A). Her functional MRI scan reveals loss of function of right FFA with preserved activation in response to faces in the left OFA and bilateral pSTS in addition to very small left FFA and right OFA activations (Figure 4.6B).

A



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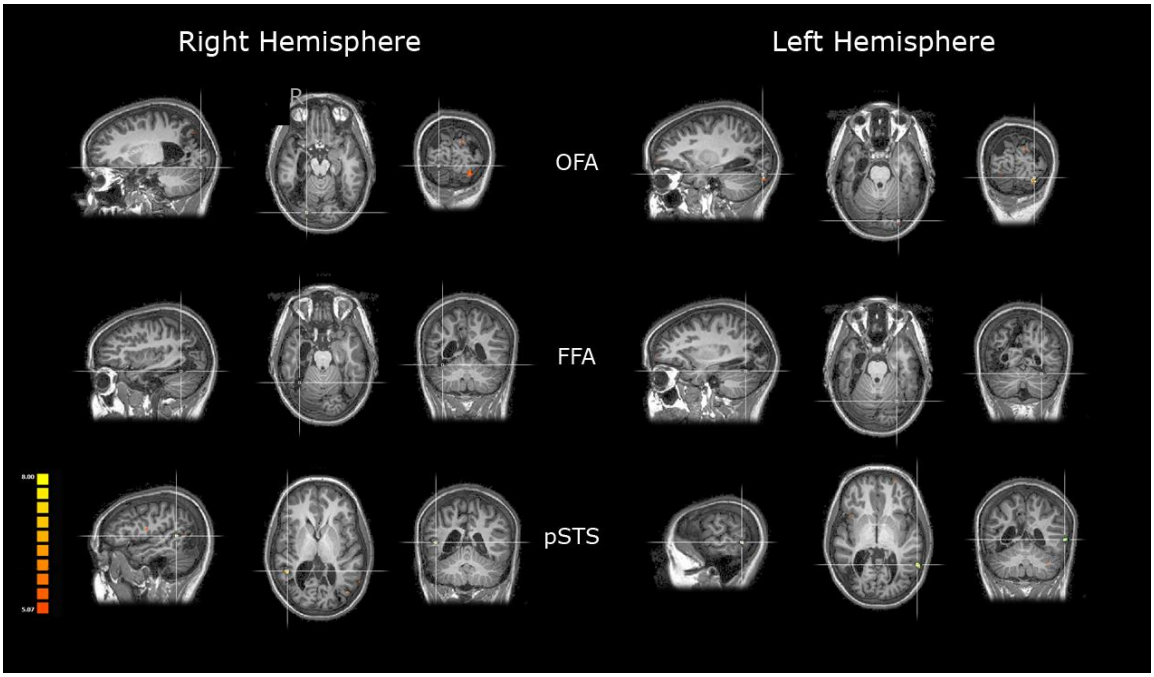


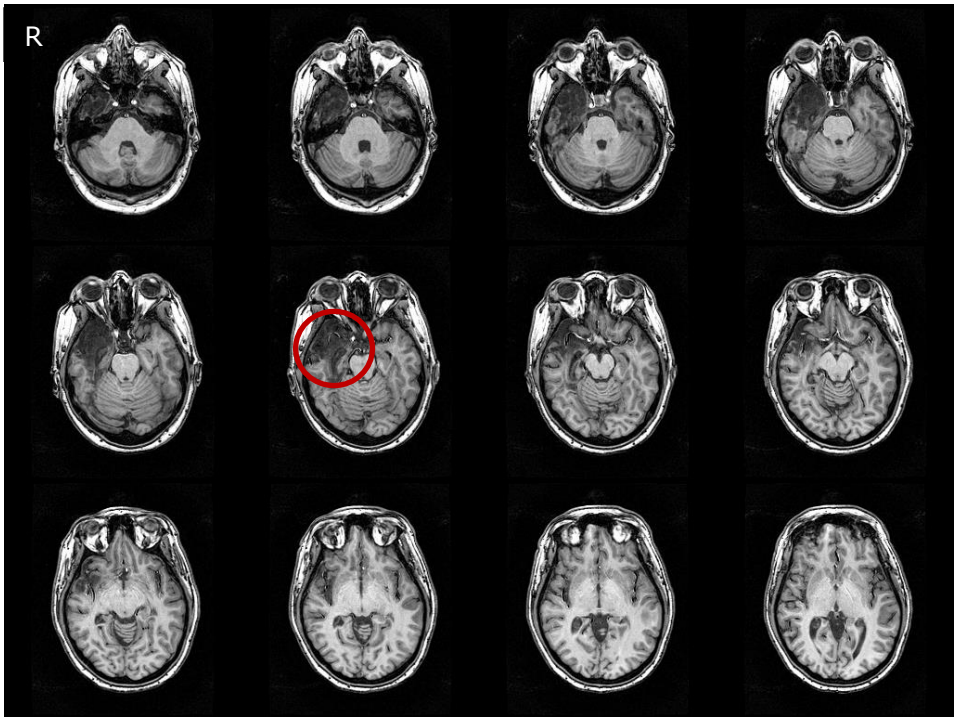
Figure 4.6 A) Structural MR Images, B) fMRI Face Localizer Scan Results of Patient B-ATOT2.

4.2.2 Associative Prosopagnosia Group

4.2.2.1 Patient R-AT2

Patient R-AT2 is a 30 year old left-hand dominant woman. She suffered from herpes simplex encephalitis at the age of 25. Since then she has had difficulties recognizing faces and places. She is employed full-time. Her visual fields and color vision are both normal. Her visual acuity is 20/15 in both eyes. She was impaired in the Famous Face Familiarity Test (d' = 0.65). She performed within the normal range on the Benton Face Recognition Test and the Cambridge Face Perception Test. She was impaired in the Warrington Recognition Memory Test for faces (27/50) and the Cambridge Face Memory Test (33/72). She was also impaired in the Face Imagery Test (73%). Her neuropsychological assessment revealed impaired memory for the delayed recall component of complex spatial memory. Her structural MRI reveals a right anterior temporal lobe lesion extending into the right fusiform gyrus (Figure 4.7A). Her functional MRI scan revealed preserved activation in all regions of the core face processing network (Figure 4.7B).

A



B

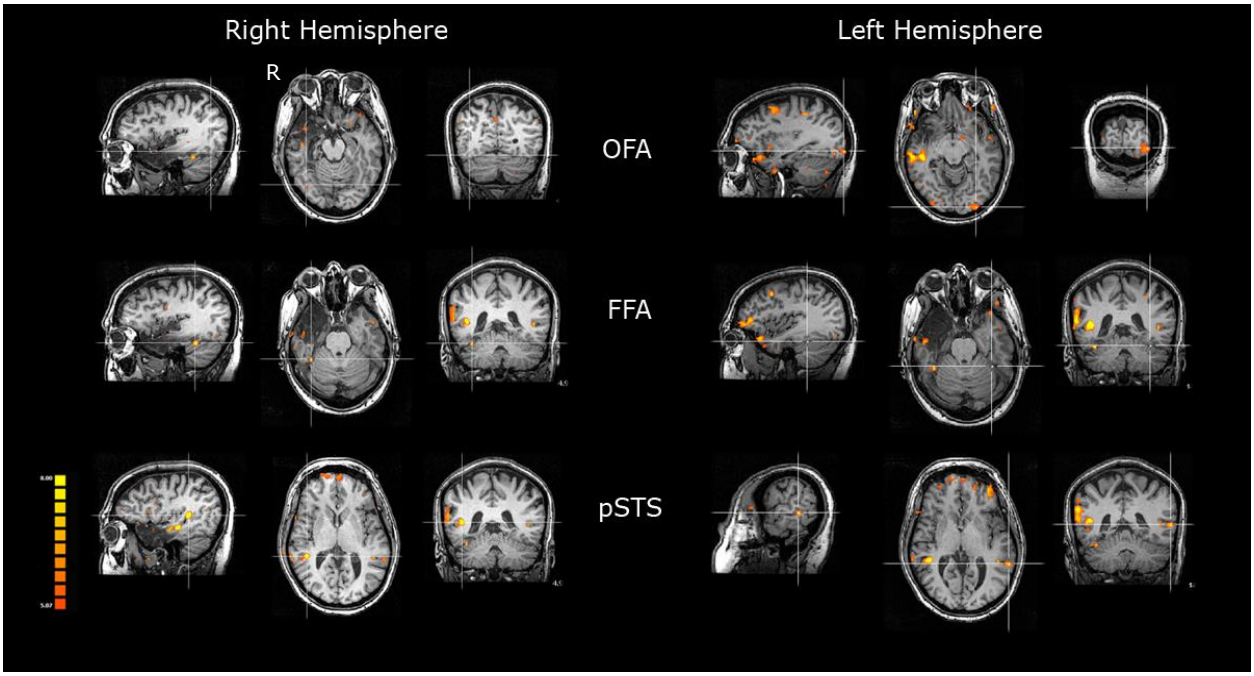
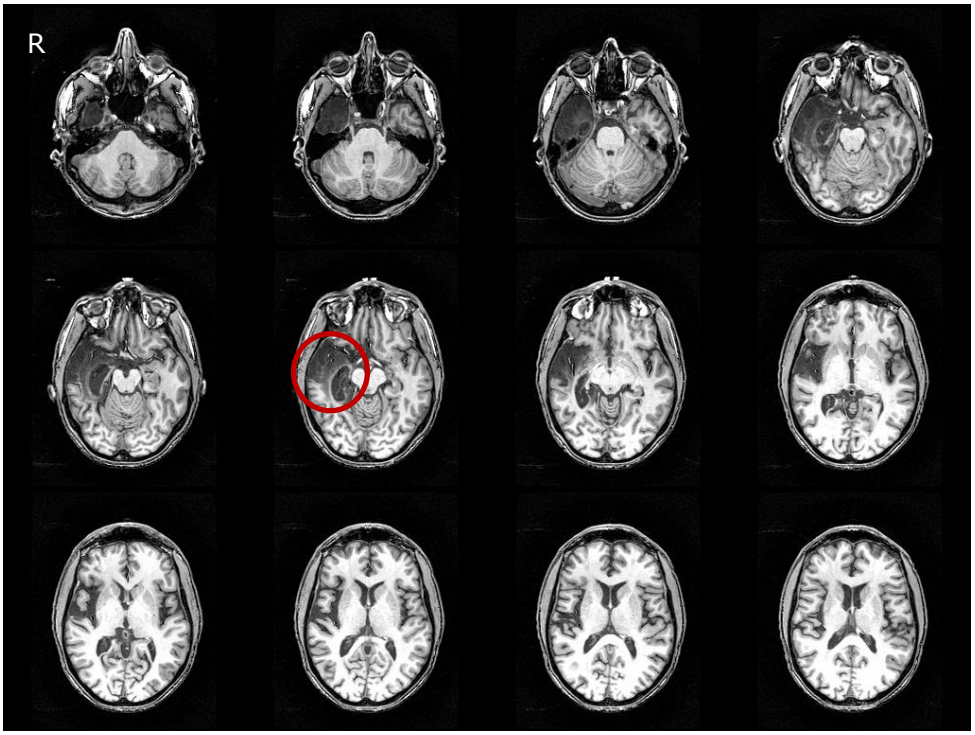


Figure 4.7 A) Structural MR Images, B) fMRI Face Localizer Scan Results of Patient R-AT2.

4.2.2.2 Patient R-AT3

Patient R-AT3 is a 37 year old right-handed man. At the age of 30, he suffered from herpes simplex encephalitis. Since then he has had difficulty in recognizing faces, but he can recognize people with whom he has regular daily contact with. He works full-time. He has full visual fields and normal color discrimination. His visual acuity is 20/15 for both eyes. He was impaired in the Famous Face Familiarity Test (d' = 0.90). He was moderately impaired in the Benton Face Recognition Test (38/54), but performed within the normal range in the Cambridge Face Perception Test. He was impaired in the Warrington Recognition Memory Test for faces (31/50) and the Cambridge Face Memory Test (31/72). He was impaired for Face Imagery (49%). His neuropsychological assessment shows impairments in the delayed recall of verbal memory and complex spatial memory, and in the immediate recall of episodic memory with normal-range delayed recall of episodic memory. His structural scan reveals a right anterior temporal lobe lesion (Figure 4.8A). His functional MRI scan reveals preserved core face processing network bilaterally (Figure 4.8B).

A



B

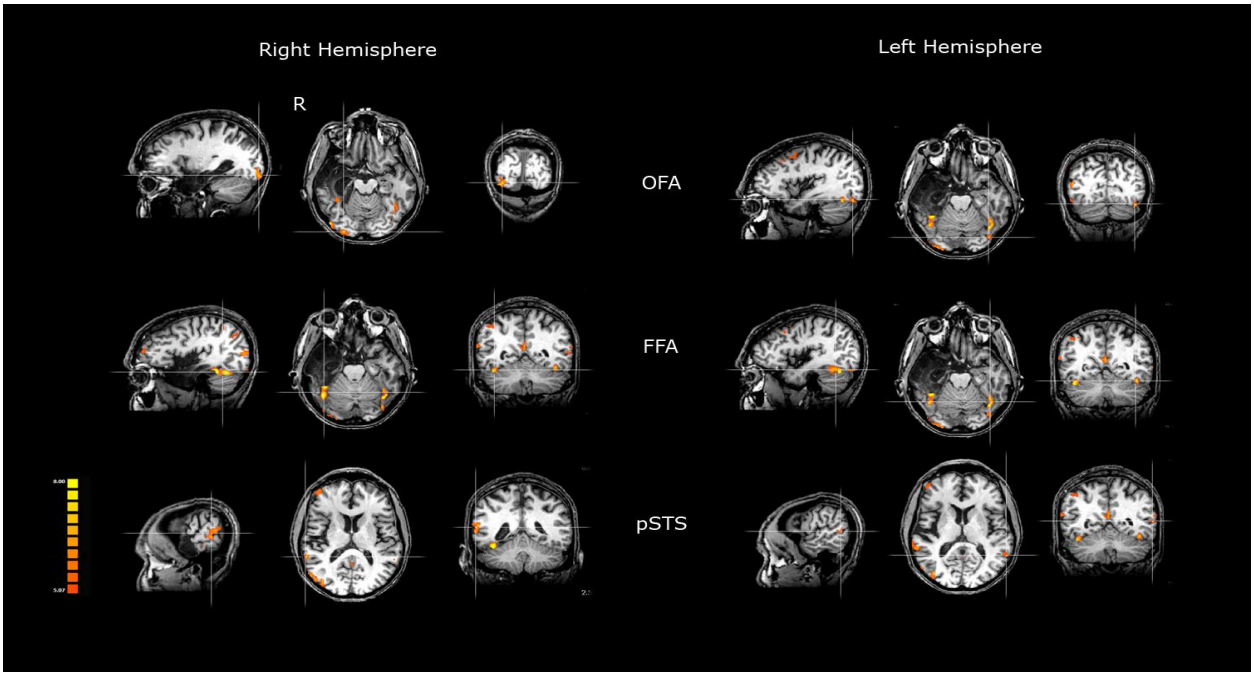
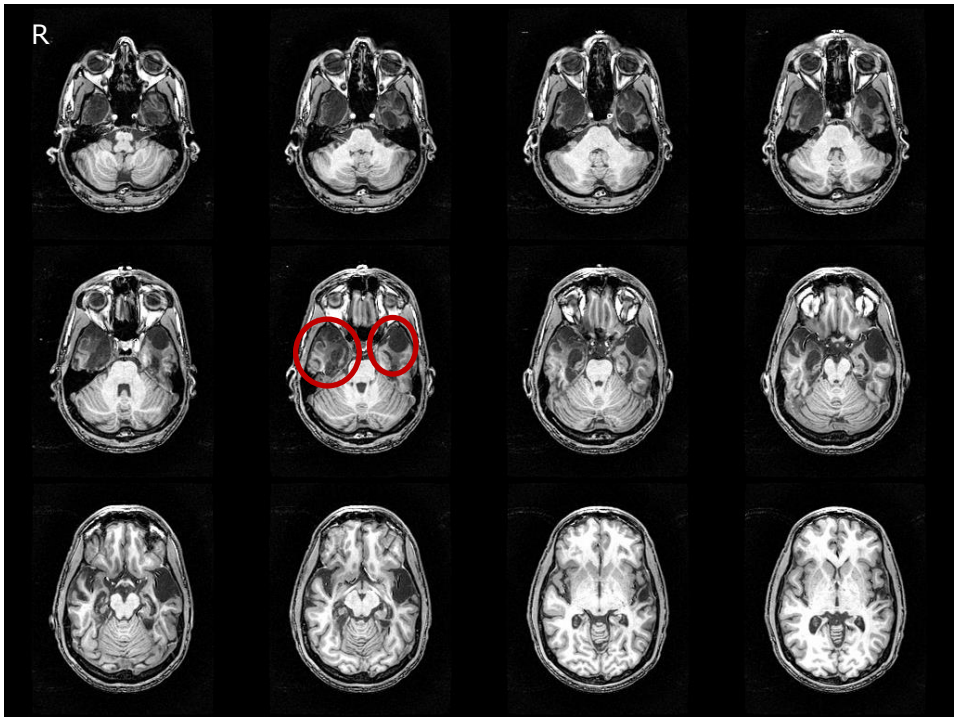


Figure 4.8A) Structural MR Images, B) fMRI Face Localizer Scan Results of Patient R-AT3.

4.2.2.3 Patient B-AT1

B-AT1 is a 24 year old right-handed man. He suffered from herpes simplex encephalitis at the age of 21. Since then he has had difficulty recognizing faces, but he can recognize some of his family members. He attends college and is employed full-time. His visual fields and color vision were both normal and his visual acuity was 20/15 in both eyes. He was impaired in the Famous Face Familiarity Test (d' = 0.36). He was given a modified version of the face familiarity test with stimuli consisting of personally familiar faces, since he had poor general knowledge of celebrities. He performed within the normal range in the Benton Face Recognition Test, and the Cambridge Face Perception Test. He was impaired in the Warrington Recognition Memory Test for faces (27/50) and the Cambridge Face Memory Test (30/72). His neuropsychological assessment revealed impaired immediate recall of verbal memory with normal performance on all other memory tests. He also has mild topographagnosia and mild anomia for uncommon objects with preserved semantic knowledge about these objects. Structural MRI scan showed bilateral anterior temporal lobe damage extending into the fusiform gyri (Figure 4.9A). His functional MRI scan reveals preserved core face processing network bilaterally (Figure 4.9B).

A



B

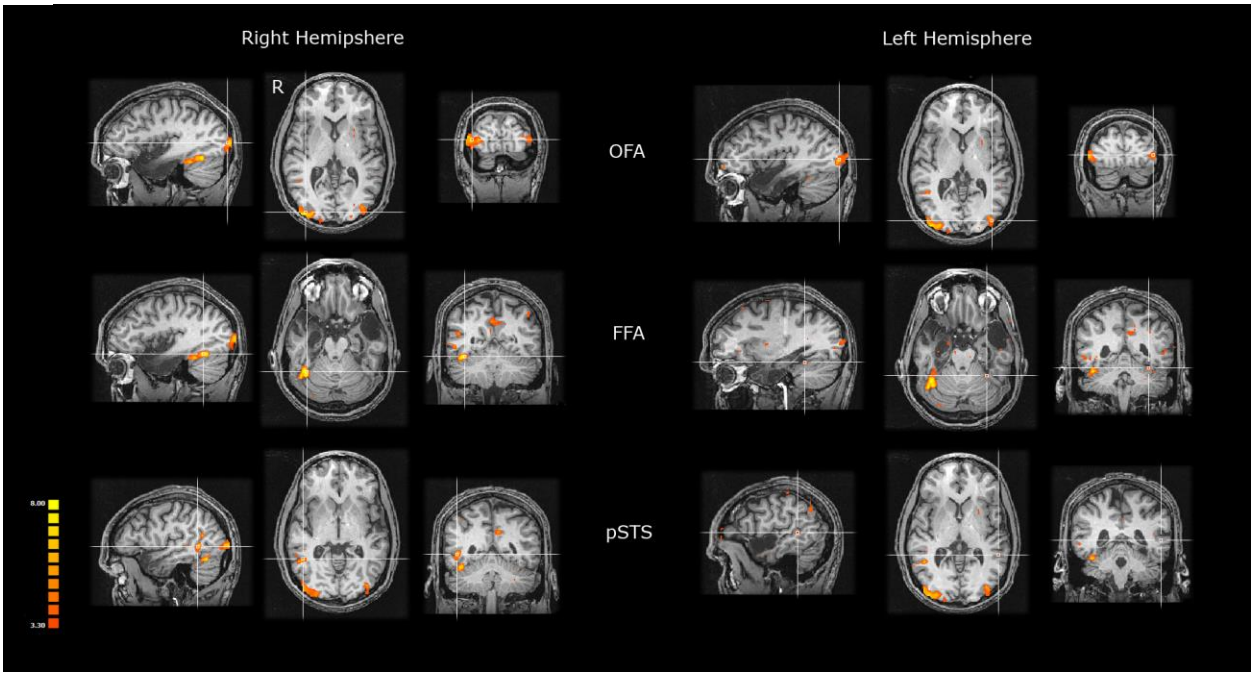
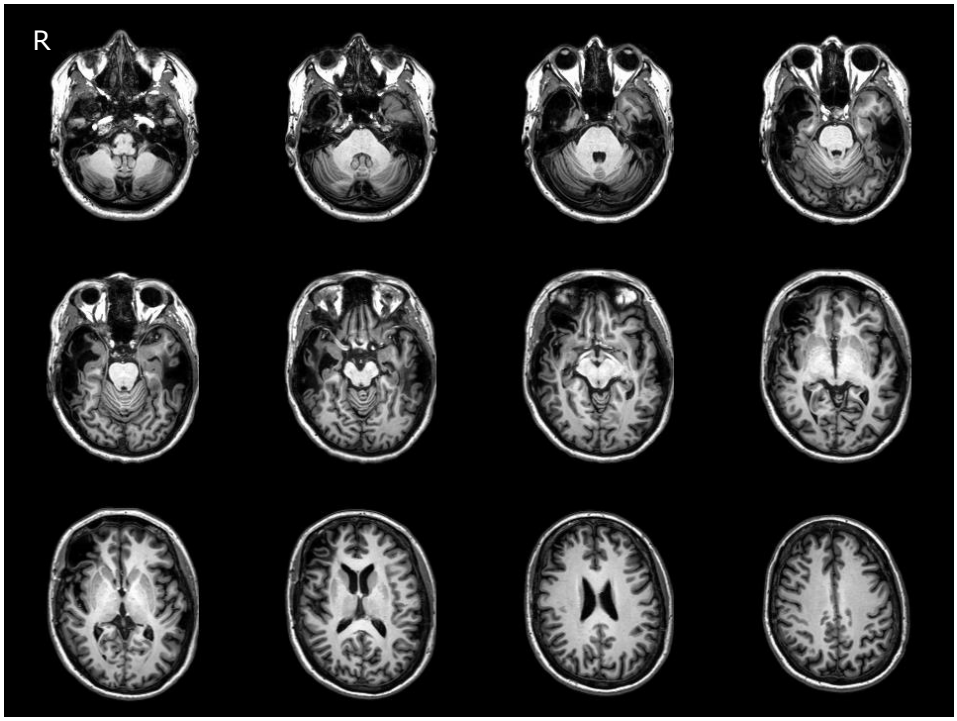


Figure 4.9 A) Structural MR Images, B) fMRI Face Localizer Scan Results of Patient B-AT1.

4.2.2.4 Patient B-AT2

Patient B-AT2 is currently a 47 year old right-hand dominant woman. Following a head injury that caused basilar skull fractures and contusions to the right and left temporal lobes and the right inferior frontal lobe, she had a right anterior temporal lobectomy as a decompression for cerebral edema at the age of 24. Since then she has difficulty in recognizing faces and complaints of memory. She works part-time and volunteers. She has full visual fields and normal color discrimination. Her visual acuity is 20/15 od and 20/400 os. She performed within the normal range in the Benton Face Recognition Test, but was impaired in the Cambridge Face Perception Test (76 errors). She was impaired in the Warrington Recognition Memory Test for faces (31/50) and the Cambridge Face Memory Test (31/72). Her neuropsychological assessment reveals borderline performance in the delayed recall component of verbal memory. She was also impaired on the Mental Rotation Test. Her structural scan reveals bilateral anterior temporal lobe lesions as well as a right frontal lobe lesion (Figure 4.10A). Her functional MRI scan reveals preserved core face processing network bilaterally (Figure 4.10B).

A



B

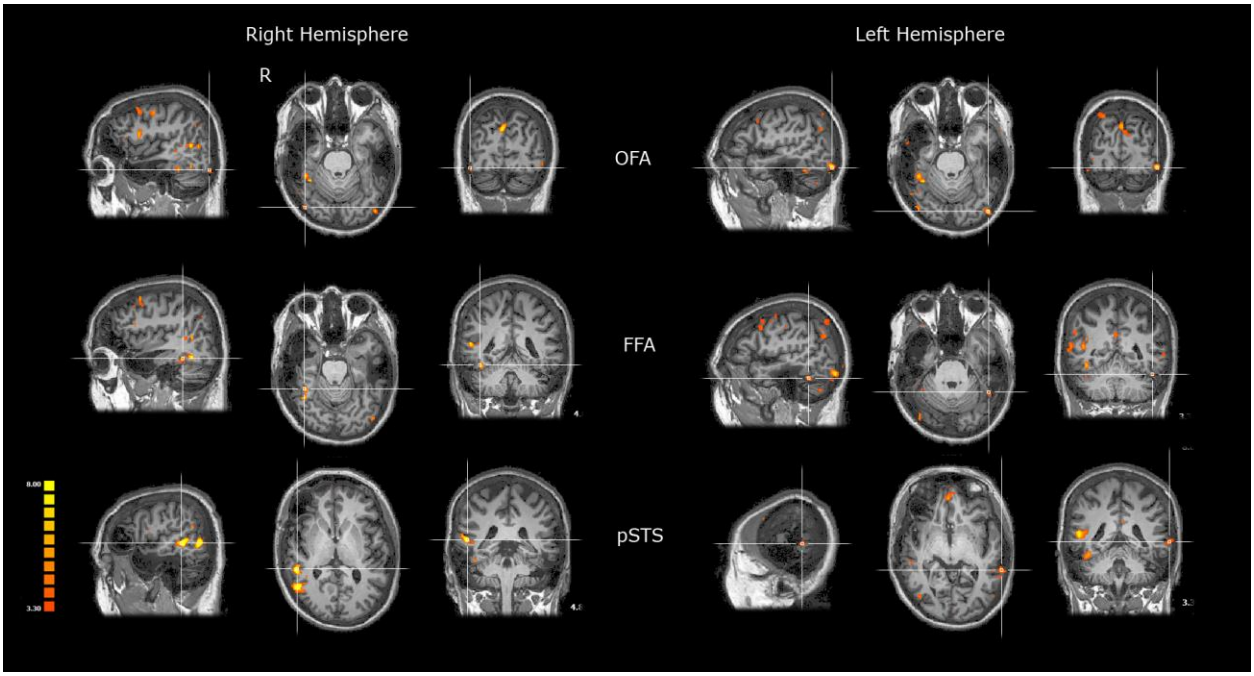


Figure 4.10 A) Structural MR Images, B) fMRI Face Localizer Scan Results of Patient B-AT2.

Chapter 5: Processing of Eye Region Information in Acquired Prosopagnosia

The apperceptive variant of prosopagnosia is suggested to involve impairments of structural encoding of faces, whereas the associative variant is suggested to involve problems of face imagery and semantic face memory (Barton 2008a, 2011a; Davies-Thompson et al., 2014). Cases of the apperceptive variant of acquired prosopagnosia generally demonstrate difficulties in perceptual face processing. Our studies investigating the neural correlates of the feature salience hierarchy in healthy subjects show the involvement of FFA bilaterally in this perceptual characteristic of human face processing. The involvement of FFA suggests that the patients with fusiform lesions that encompass the location of the FFA may present greater difficulties in processing eye region specific information and therefore may show larger impairments in tasks involving changes to the eye region of faces.

Our cohort of 10 patients includes patients with both the apperceptive and the associative variants of acquired prosopagnosia. In our cohort, we characterized the structural face feature processing deficits. We hypothesize that patients with the apperceptive variant of prosopagnosia which results from inferior occipitotemporal lobe lesions will have impairments in processing eye region of faces, whereas patients with the associative variant of prosopagnosia which results from anterior temporal lobe lesions will not have significant difficulties in processing eye region information. However, the feature salience hierarchy may be the consequence of activity of a network of brain regions in addition to the FFA, as indicated by the significant correlation of the human behavioral performance with the activity pattern of the pSTS in our neuroimaging study. In that case, the eye region processing difficulties may also be observed in the associative prosopagnosia patients with anterior temporal lobe lesions.

In order to discover the type of structural information not being properly processed in our patient cohort, we utilized a series of feature change detection tests which examined the individual feature processing and the second-order spatial processing of face features. These tests measured the ability of the patients in detecting changes to different structural components of a face in order to dissect the face feature or second-order relation that is not properly processed.

5.1 Methods

5.1.1 Participants

Healthy individuals and prosopagnosia patients participated in the experiments. Descriptions of patients with acquired prosopagnosia who participated in the study are given in Section 4.2. All protocols were approved by the institutional review boards of UBC and VGH. Written consent was taken from all patients and healthy participants in accordance with the Code of Ethics of the World Medical Association, Declaration of Helsinki (Rickham 1964).

5.1.2 Feature Processing Experiments

Face processing is suggested to involve second-order configural processing of facial features as an essential component (Diamond and Carey 1986; Rhodes 1988; Maurer et al., 2002). With the main goal of characterizing the eye region processing deficits in our patient cohort, we utilized face perception experiments where we introduced modifications to different face features individually or to their second-order relations. By this method, we aimed to dissect the type of structural information that is not properly processed in our patients. Across the experiments administered, we introduced changes to feature color (eye or mouth), to feature shape (eye or mouth elongated vertically), to the external contour (chin or forehead contour), and to the

second-order relations (inter-ocular distance, vertical mouth position) (Figure 5.1). In Experiment 1, all these changes were tested in order to explore the feature that was not being properly processed by the patients. Experiment 2 focused on the eyes and the mouth in order to explore the first- and second-order spatial relations in detail.

Mean scores and standard deviations were measured for the control participants. In order to compare the results of each patient with the results of controls, we used the modified t-test of Crawford and Howell for single-case studies with a one-tailed 0.05 p value (Crawford and Howell 1998). Consequently, all scores associated with a p value under 0.05 were considered to reflect an abnormal result. Analyses were conducted on a computerized version of the Crawford and Howell's method: SINGLIMS.EXE: Point estimate and confidence limits on the abnormality of a test score (Crawford and Garthwaite 2002). This modified t-test gives slightly different values than the z-scores. Therefore, the values reflecting z-scores in the tables and figures may be slightly different than the individual t-stat values reported in the results section. However, the significance requirements are met in both cases.

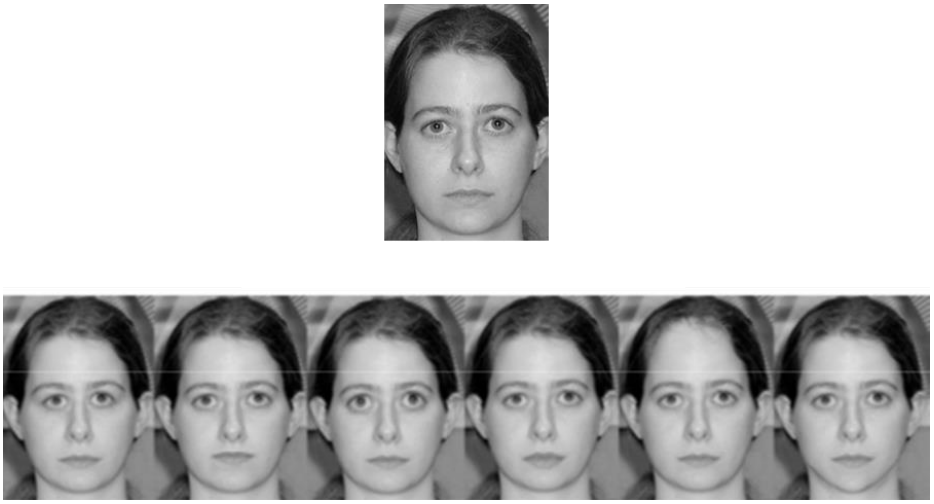


Figure 5.1 Changes to Individual Face Features and Second-order Relations of Features. Top face shows the intact face.

5.1.2.1 Feature Processing Experiment 1

This experiment presented a change to one aspect of the face features at a time in order to assess the processing of different types of facial structure, including second-order spatial relations, feature shape and external contour (Malcolm et al., 2004). Faces of three males and three females were used to create the stimuli. Horizontal inter-ocular distance was reduced by moving the eyes closer together by 16 pixels. Vertical mouth position was altered by moving the mouth up closer to the nose by 10 pixels. These were the two changes to the second-order spatial relations. Changes in feature shape were a vertical elongation of either the eyes or the mouth. Changes in external contour were either an elevation in hairline or a narrowing of the chin. Subjects were shown three faces simultaneously, with the left face 7% larger and the right face 14% larger than the top face of the triangular arrangement. One of the three faces was altered in one of the six ways described, and the subject's task was to indicate the altered face in an oddity paradigm. Participants were allowed unlimited duration to complete each trial.

This test additionally manipulated processing difficulty and attention demands by varying the number of changes possible in the target within a block of trials. In the first version, there were 6 blocks. In each block only one possible target change could occur so the subjects could focus their attention on the specific feature where the change would occur. In the second version, there were two blocks, one with changes to the eye region (spatial relation or eye size), and the other with changes to the mouth region (spatial relation or mouth size). This version allowed subjects to focus their attention on one facial region, although the type of change was not specified. Finally, in the last version, all 6 changes were possible in the same block, and these were given in random order. Therefore, the subjects did not know which type of facial change to expect on any given trial, and had to monitor the images for all possible changes. In all of the

versions, subjects were instructed in advance what type of changes would occur in a particular block. There were a total of 9 blocks. Each type of change had 18 items, with a total of 18 items in the single change version; 36 items in the two change version, and 108 items in the all-six-change version.

The subject's task throughout the experiment was to detect the modified face and report via a keyboard button press. Both accuracies and reaction times were measured. The scores were also converted into an inverse efficiency score using the formula: Inverse Efficiency = log (latency)/accuracy (Townsend and Ashby 1983; Morein-Zamir et al., 2007). This combined efficiency score takes into consideration both the latency and the accuracy of the response and therefore is a better measure of performance. However, for patients with visual field defects, accuracies rather than latencies may be a better measure of the perceptual impairments since their visual field defects may have a substantial effect on their latencies. Therefore, we calculated and analyzed both the raw accuracies and the combined inverse efficiency scores for each patient. In the results section, in cases where the patient had a field defect, this is reported and the raw accuracy scores are emphasized. Additionally, the accuracies and the patient z-scores for Experiment 1are listed in Table 5.1.

In addition to our prosopagnosia cohort, twelve healthy participants (8 females; mean age= 38, age range = 25-55) with no history of neurological disease or cognitive complaints were tested.

5.1.2.2 Feature Processing Experiment 2

Experiment 2 assessed the processing of second-order spatial relations and feature luminance separately for the upper and the lower face (Barton et al., 2001a, 2002). One male and one female face were used to create four types of modifications. The horizontal inter-ocular distance

was reduced by 16 pixels. The mouth was moved up closer to the nose by 10 pixels. These were the two changes made to the second-order spatial relations. Eye color and mouth color were lightened by 15% in order to create the two changes made to feature color. All modifications to the faces were made using Adobe Photoshop.

In each trial, three faces, one of which is the modified target face, were presented simultaneously. The faces differed in size, with the top face 10% larger than the left face, and the right face 10% larger than the top face. There were two blocks; the viewing time was limited to 2 seconds in the first block, and it was unlimited in the second block. The subject's task was to detect the modified face. Each block consisted of 72 items, with 18 items per condition. In the 2-second viewing duration block, accuracies were measured. In the unlimited viewing duration both the accuracies and reaction times were measured.

In addition to our prosopagnosia cohort, fifteen healthy participants (mean age = 38, age range = 21-70) with no history of neurological disease or cognitive complaints participated in the experiment.

5.1.3 Comparison of Patient Data at the Group Level

Accuracy scores for the eye position and the mouth position changes in the six-change block of Experiment 1 were averaged across the two patient groups (Apperceptive and Associative) to compare the performance of the patients with the performance of the controls at the group level. This particular comparison was chosen since the 6-change block is the most valid condition with similarity to real life challenges where patients do not know where to focus for any informative cues. Two-sample one-tailed t-tests for unequal sample size were used to compare the patient group's performance with the controls.

5.2 Results

5.2.1 Controls

5.2.1.1 Feature Processing Experiment 1

The mean accuracy score of the control group was at or above 94% for all subtests of Experiment 1. When one of the all six changes were possible, the changes to the eye horizontal position were detected with 99% ± 2.34 accuracy and changes to the eye shape were detected with 98.5% ± 2.71 accuracy. The changes to the mouth vertical position were detected with 95.7% ± 5.93 accuracy, while the changes to the mouth shape were detected with 94.8% ± 6.83 accuracy. The changes to the chin were detected with 95.7% ± 4.23 accuracy, while the changes to the forehead were detected with 96.7% ± 6.89 accuracy. When the average latencies of 3-4 seconds were also taken into consideration, the mean inverse efficiency scores for the healthy subjects in the all-six-change block varied between 3.6-3.8 for the different features. In the two-change blocks, healthy subjects had a mean accuracy score of 99% for all four changes (eye horizontal position, eye shape, mouth vertical position, mouth shape). In the one-change-only blocks where the subjects were informed of the type of change to occur in advance, the healthy subjects had mean accuracy scores of 96% and above for all conditions.

5.2.1.2 Feature Processing Experiment 2

In the unlimited duration block of Experiment 2, the mean accuracy scores of the healthy subjects were 100% for all four conditions with mean reaction times of 2335ms ± 1103 for the horizontal eye position changes, 3163ms ± 2904 for the eye color changes, 2618ms ± 706 for the vertical mouth position changes, and 6915ms ± 3952 for the mouth color changes. In the 2 second viewing duration block, the mean accuracies for the healthy subjects were 98.5% ± 3.30

for eye horizontal position changes, 95.5% ± 7.34 for eye color changes, 94.8% ± 5.35 for mouth vertical position changes, and 78.5% ± 17.03 for mouth color changes.

5.2.2 Patient Results

5.2.2.1 Patient R-IOT1

In Experiment 1, in terms of efficiency, Patient R-IOT1 performed well in the 1-change and two-change blocks except for eye position condition (one change: $t= 3.330$, $p<0.01$; 2-changes: $t= 7.856$, $p<0.0001$) (Figure 5.2). In the 6-changes block, he was impaired for all conditions except for changes to the chin. Patient R-IOT1 had a left partial left superior quadrantanopia which could result in increased latencies. In terms of accuracy, Patient R-IOT1 performed within the normal range for the 1-change condition (Table 5.1). In the two-change condition, he was impaired in detecting the changes in the eye position ($t = 8.713$, $p < 0.0001$). In the 6-changes block, he was impaired for all conditions except for detecting changes to the chin, and all these impairment were with $p < 0.0001$. However, his z-score was 25.74 for the eye position and 7.64 for the eye shape changes. The z-score of 25.74 shows more than a three-fold deviation for the eye position change compared to the z-score of eye shape. The rest of the significantly impaired scores were at about 4 standard deviations away from the mean. These results indicate that Patient R-IOT1 is significantly impaired in detecting changes to the individual features and the second-order relations of the features. Furthermore, he is severely impaired in detecting changes to the eye position, even when he is informed about the change location beforehand.

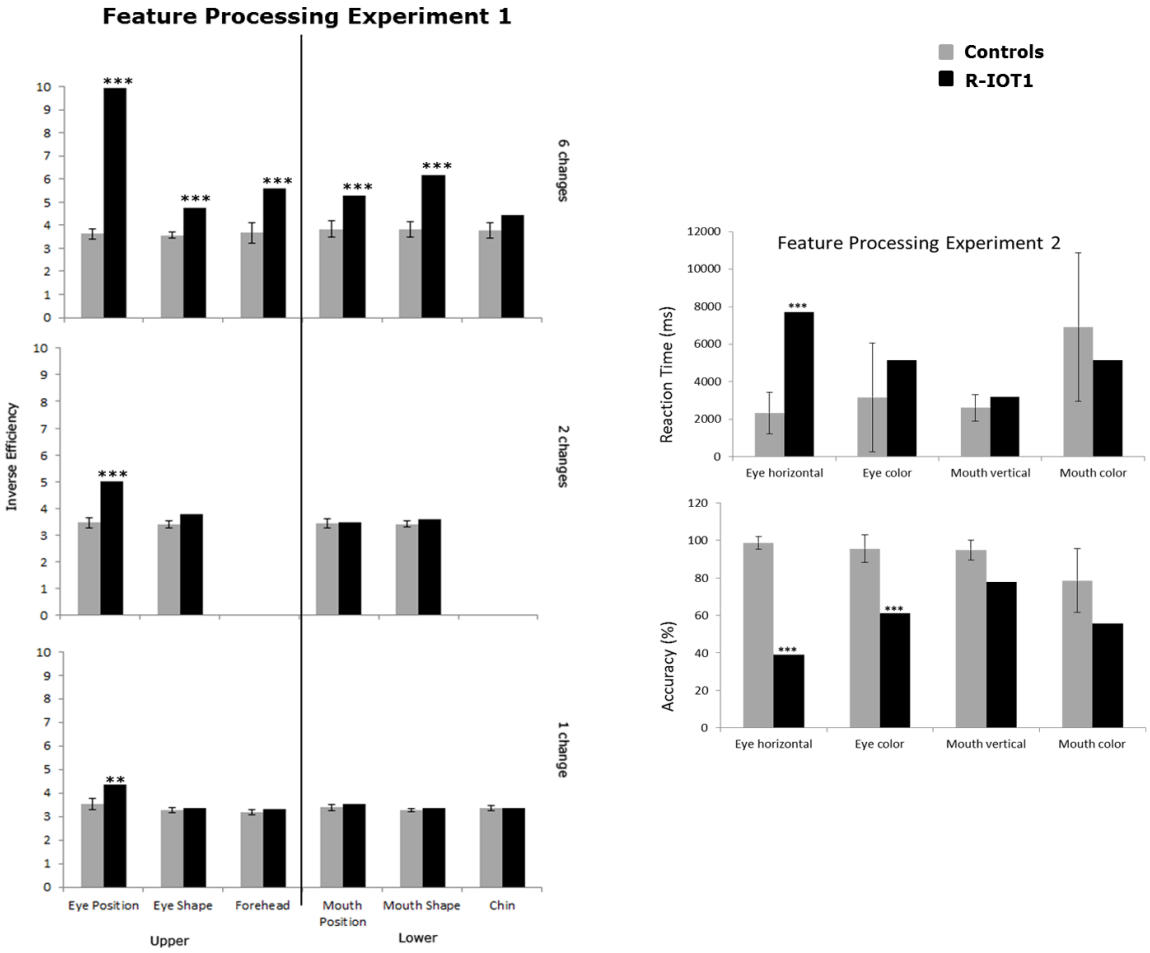


Figure 5.2 Feature Processing Results of Patient R-IOT1. ** p < 0.01, *** p < 0.001.

In Experiment 2, in the unlimited viewing duration block, he was significantly slower for detecting eye position changes (t= 4.679, p<0.001) but achieved 100% accuracy like the controls. In the 2s limited viewing duration block, his accuracies were significantly lower than controls for eye position (t= 17.339, p<0.0001) and eye color (t= 4.501, p<0.001) conditions (Figure 5.2).

5.2.2.2 Patient R-IOT4

In Experiment 1, in terms of efficiency, R-IOT4 was impaired for all facial aspects, under all three block conditions, with the exception of changes to eye position and chin shape in the 1-change block (Figure 5.3). R-IOT4 has a left superior quadrantanopia which could result in increased latencies. In terms of accuracy, Patient R-IOT4 performed within the normal range for the one-change condition except for the mouth shape ($t = 16.05$, $p < 0.0001$) (Table 5.1). In the 2-changes condition, he was impaired in detecting the changes in the eye position ($t = 7.899$, $p < 0.0001$), and the mouth position ($t = 5.259$, $p < 0.001$). In the 6-change block, he was impaired for both the eye position ($t = 7.899$, $p < 0.0001$) and the eye shape changes ($t = 3.048$, $p < 0.05$).

In Experiment 2, in the unlimited viewing block, R-IOT4 performed with 100% accuracy for all facial aspects but was significantly slower than controls for all changes (eye position, $t=18.188$, $p<0.001$; eye color, $t=4.079$, $p<0.001$; mouth position, $t=12.734$, $p<0.001$; mouth color, $t=6.384$, $p<0.001$). In the 2s limited viewing duration block, R-IOT4 was impaired for all facial aspects (eye horizontal, $t=15.742$, $p<0.001$; eye color, $t=5.961$, $p<0.001$; mouth vertical, $t=9.042$, $p<0.001$; mouth color. $t=1.922$, $p<0.05$) (Figure 5.3).

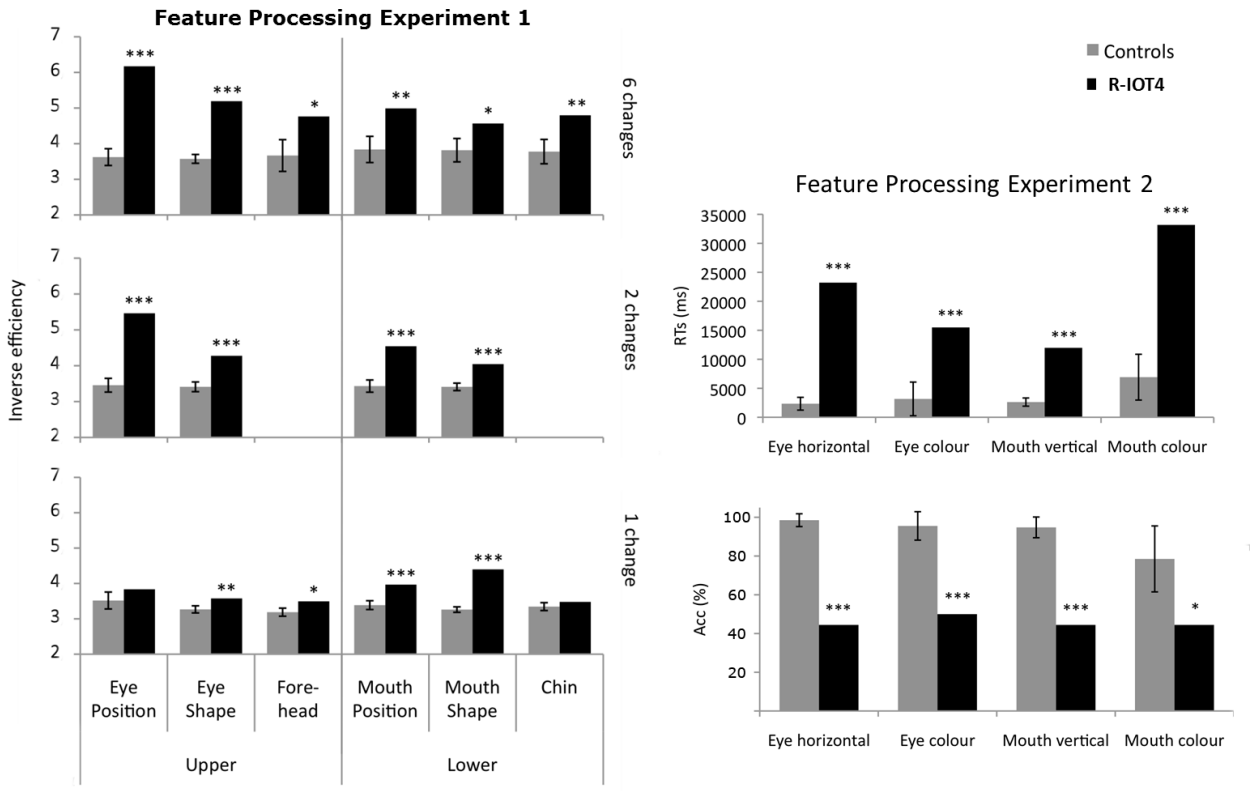


Figure 5.3 Feature Processing Results of Patient R-IOT4. * p < 0.05, ** p < 0.01, *** p < 0.001.

5.2.2.3 Patient L-IOT2

In Experiment 1, in terms of efficiency, Patient L-IOT2 was severely impaired for all six conditions in all three blocks of the experiment except for changes to the chin in the 6-changes block (Figure 5.4). His performance indicated severe face processing impairments for all face regions and features all with $p < 0.0001$. Patient L-IOT2 did not have any visual field defects. In terms of accuracy, he was severely impaired for changes to the eye position, eye shape, mouth position, and the mouth shape in all three blocks of the experiment with $p < 0.0001$ for all face regions and features (Table 5.1). In the all 6-changes condition, his z-scores for the changes to

the eye position (28.13) and the eye shape (21.96) were more than three folds of his z-score for mouth position (7.72) and mouth shape (4.12).

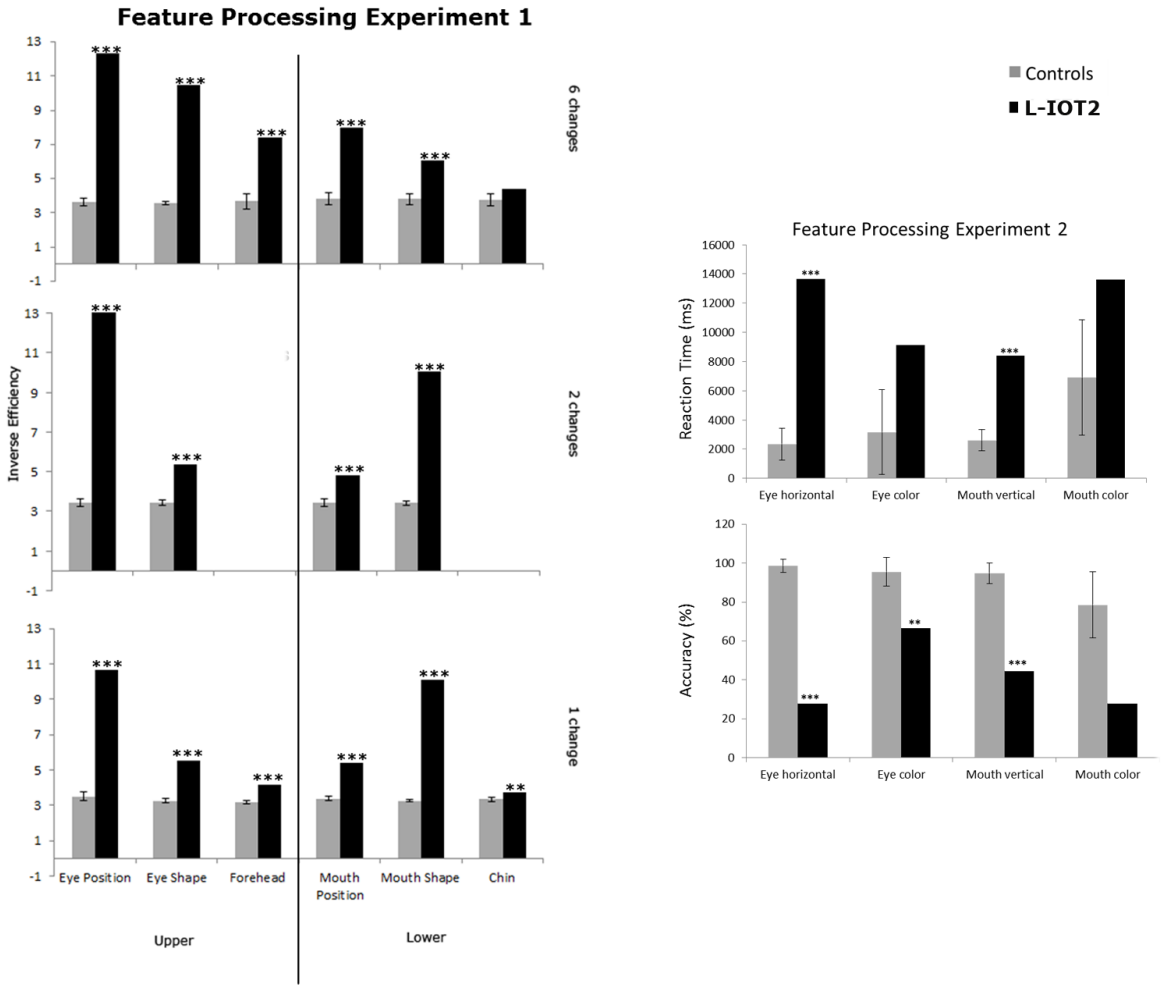


Figure 5.4 Feature Processing Results of Patient L-IOT2. ** p < 0.01, *** p < 0.001.

In Experiment 2, he achieved 100% accuracy, but was significantly slower than controls for the eye ($t = 9.877$, $p<0.0001$) and mouth ($t = 7.860$, $p<0.0001$) position changes in the unlimited viewing duration block. He was severely impaired in detecting changes to the eye position in the 2s limited viewing duration block ($t = 20.587$, $p<0.0001$). He was also impaired

for the mouth position ($t = 9.048$, $p<0.0001$) and eye color ($t = 3.775$, $p<0.01$) changes in this block (Figure 5.4).

5.2.2.4 Patient B-IOT2

In terms of efficiency, Patient B-IOT2 was impaired for the eye position and eye shape changes in all three blocks of Experiment 1 with $p < 0.0001$(Figure 5.5). He had a rather selective impairment for the eye region except for an impaired score for the mouth shape in the 2-changes block ($t = 3.47$, $p < 0.01$) and an impaired score for the forehead in the 6-changes condition ($t = 5.017$, $p < 0.001$). Patient B-IOT2 has severe visual field defects with only a constricted left inferior homonymous island of vision. In terms of accuracy, he was within the normal range for all features in the 1-change block (Table 5.1). He was impaired for the eye position ($t = 6. 434$, $p < 0.0001$) and the eye shape ($t = 6.435$, $p < 0.0001$) in the 2-changes block. He was impaired for the eye position ($t = 10.995$, $p < 0.0001$), the eye shape ($t = 11.285$, $p < 0.0001$), and the forehead ($t = 4.192$, $p < 0.005$) changes in the 6-changes block.

In Experiment 2, in the unlimited viewing duration block, he was significantly slower than the controls for all conditions yet he achieved 100% accuracy like the controls. In the 2s limited viewing duration block, he was impaired for the eye position ($t= 20.592$, $p <0.0001$) and eye color ($t= 6.689$, $p <0.0001$) changes (Figure 5.5).

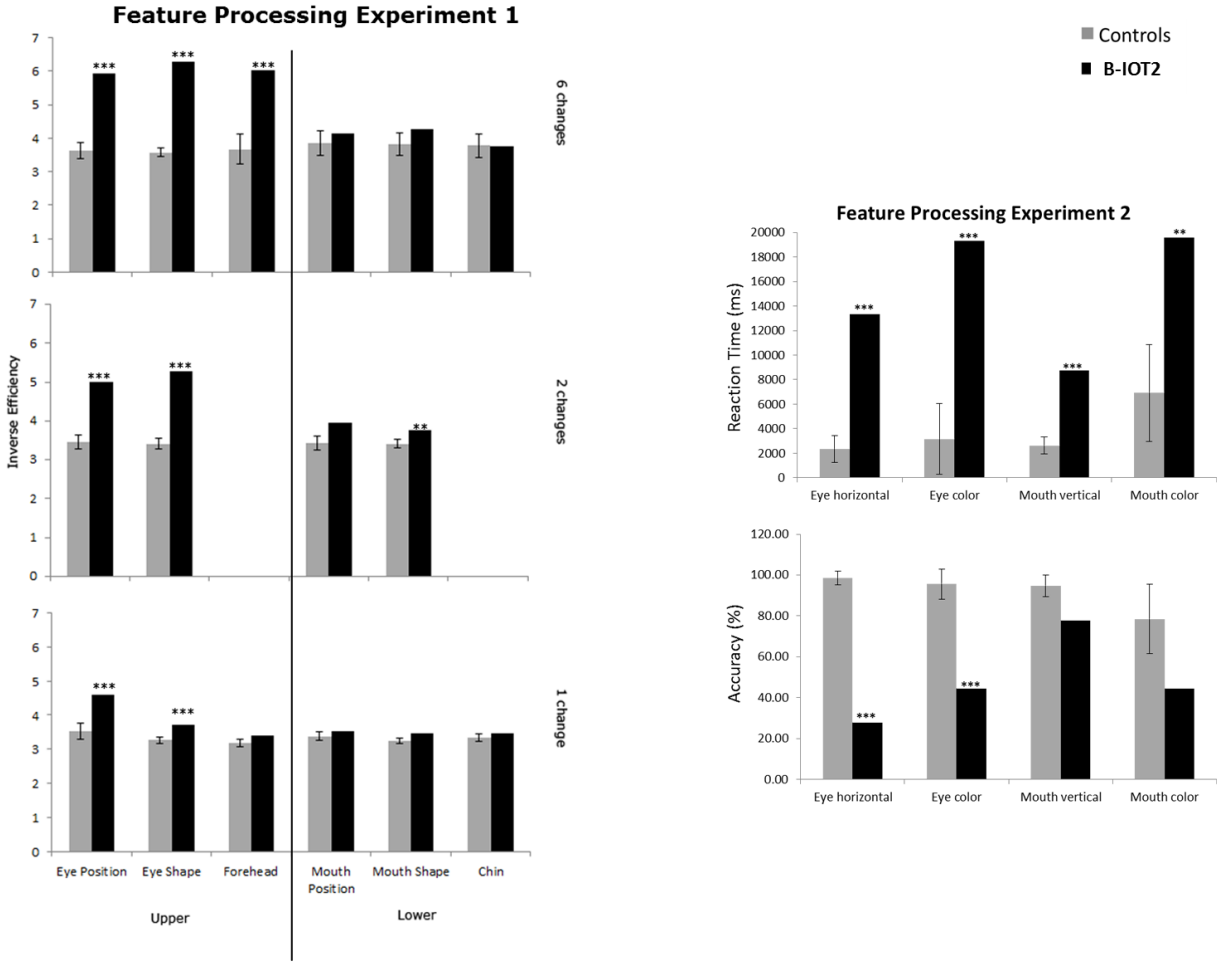


Figure 5.5 Feature Processing Results of Patient B-IOT2. * p < 0.05, ** p < 0.01, *** p < 0.001.

5.2.2.5 Patient B-ATOT1

In Experiment 1, in terms of efficiency, Patient B-ATOT1 was severely impaired for eye position and eye shape changes in all three blocks with $p < 0.0001$ (Figure 5.6). In the 1-change block she was also impaired in detecting changes to the chin ($t = 4.280$, $p < 0.005$). In the 6-changes ($t = 10.698$, $p<0.0001$) and 2-changes ($t = 4.719$, $p<0.001$) blocks she was also impaired for mouth shape changes. Patient B-ATOT1 has a subtle left superior quadrantanopia outside the central

30°. In terms of accuracy, she was severely impaired for the eye position and eye shape changes in all three blocks with $p < 0.0001$. Her accuracy scores also revealed impairment for the chin in the 1-change block ($t = 5.892$, $p < 0.001$) and for the mouth shape in the 6-changes ($t = 5.530$, $p < 0.005$) block (Table 5.1).

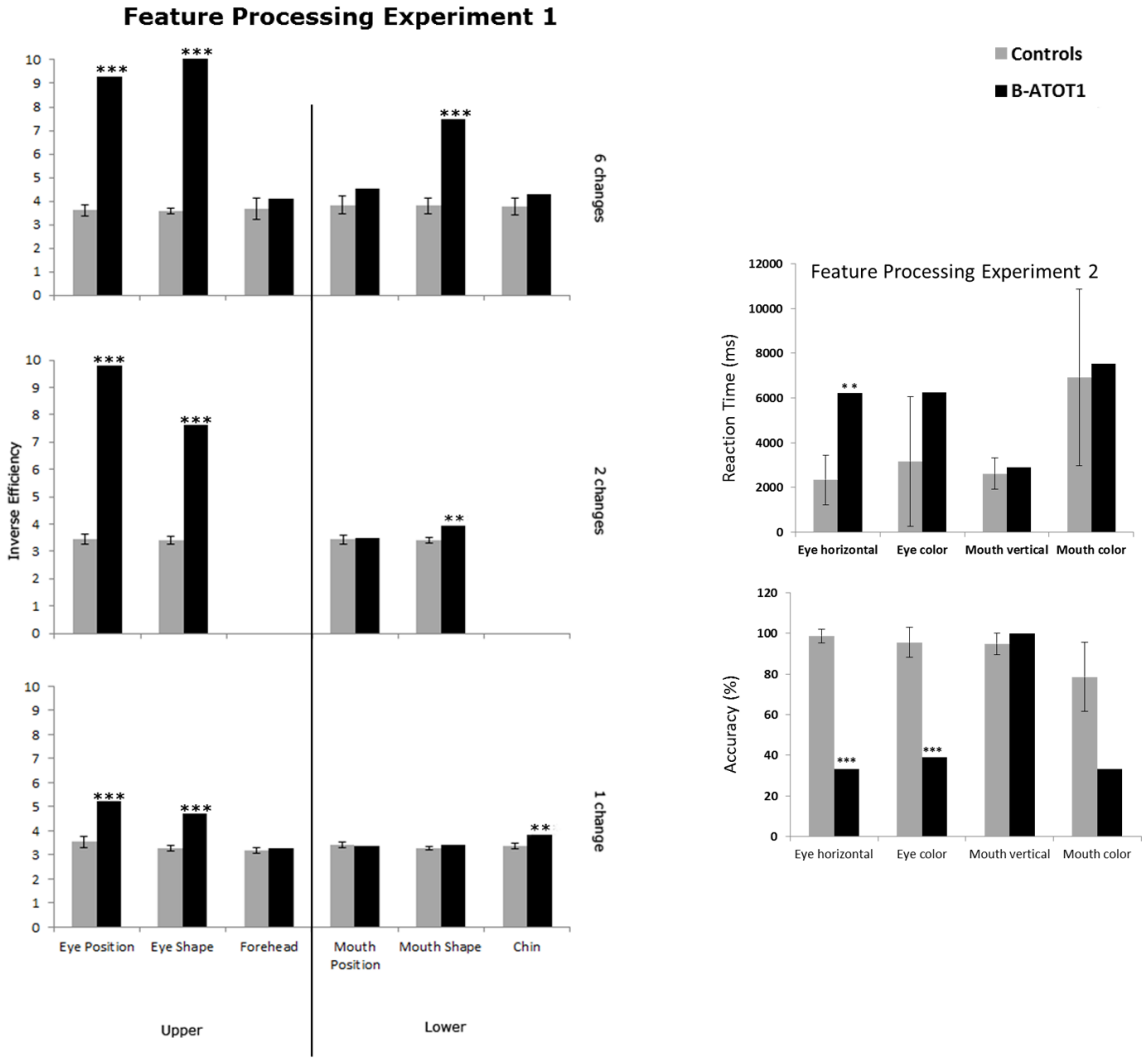


Figure 5.6 Feature Processing Results of Patient B-ATOT1. ** $p < 0.01$, *** $p < 0.001$.

In Experiment 2, she was impaired in detecting changes to eye position ($t= 18.958$, $p<0.0001$) and eye color ($t= 7.414$, $p<0.0001$) in the 2s limited viewing condition. She was 100 % accurate but significantly slower in detecting changes to the eye position ($t=3.372$, $p<0.01$) in the unlimited viewing condition (Figure 5.6).

5.2.2.6 Patient B-ATOT2

In Experiment 1, in terms of efficiency, Patient B-ATOT2 was impaired for all feature changes in the 6-changes and the 2-changes blocks with $p < 0.0001$ for the eye position and eye shape changes (Figure 5.7). She was impaired for the eye position ($t= 40.272$, $p<0.0001$), eye shape ($t= 6.629$, $p<0.0001$) and mouth shape ($t= 5.164$, $p<0.001$) changes in the 1-change only block. Patient B-ATOT2 does not have any visual field defects. In terms of accuracy, similar to her efficiency scores, her results show impairment in all feature changes in the all 6-changes block (Table 5.1). She was also severely impaired for all changes except for the mouth shape in the 2-changes block. In terms of accuracies in the 1-change block, she was severely impaired for the eye position, eye shape, and the mouth shape changes.

In Experiment 2, in the unlimited viewing duration block, she was significantly slower than controls for eye ($t= 4.252$, $p<0.001$) and mouth ($t= 5.664$, $p<0.0001$) position change conditions but she achieved 100% accuracy like the controls. In the 2s limited viewing duration block, she was impaired for the eye color ($t= 8.143$, $p<0.0001$), eye position ($t= 20.592$, $p<0.0001$), and mouth position ($t= 7.045$, $p<0.0001$) changes (Figure 5.7).

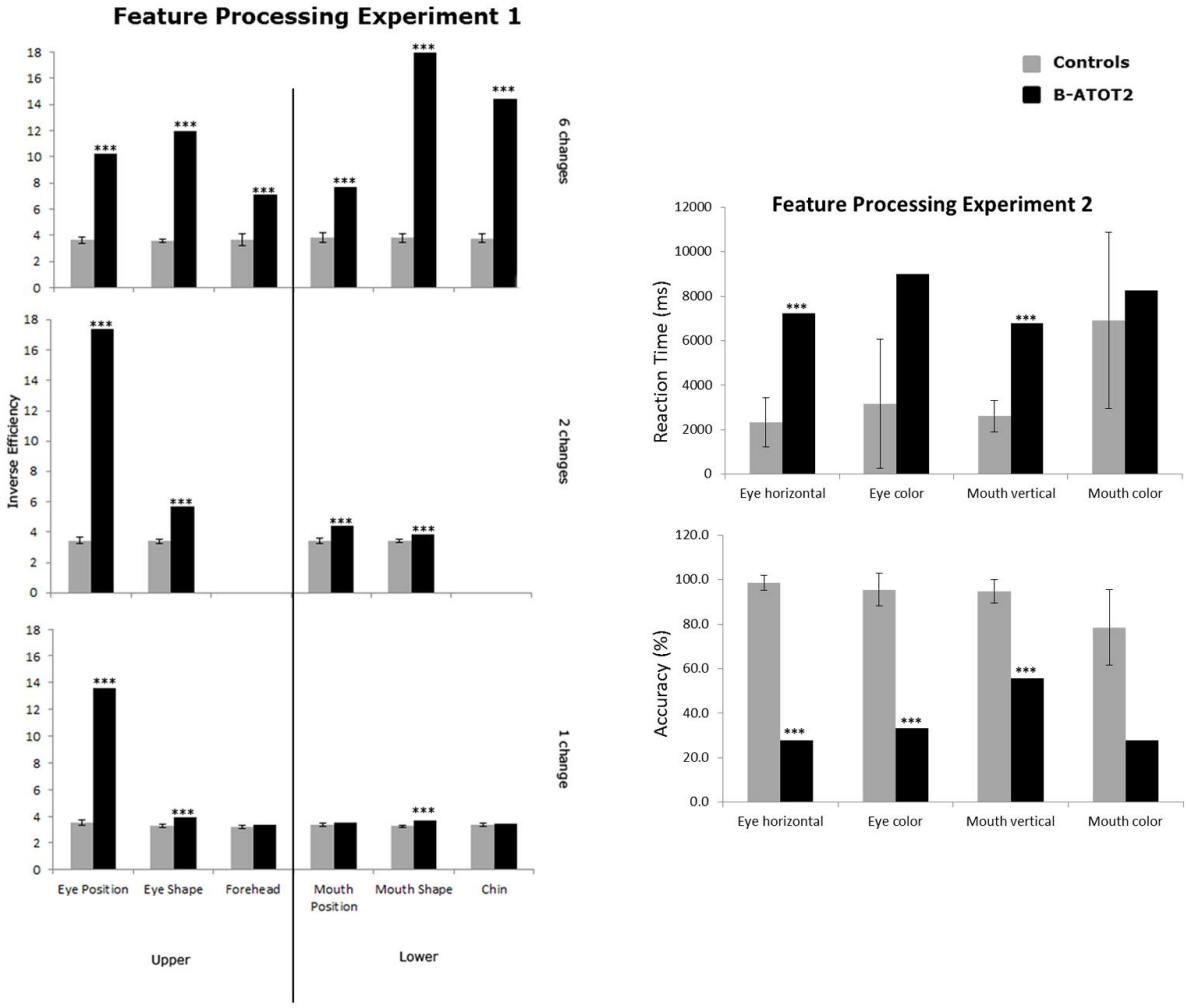


Figure 5.7 Feature Processing Results of Patient B-ATOT2, * p < 0.05, *** p < 0.001.

5.2.2.7 Patient R-AT2

Patient R-AT2 performed well in all three Feature Processing Experiments. In Experiment 1, her inverse efficiency scores show that her performance was not significantly different than those of the control participants (Figure 5.8). She does not have any visual field defects. In terms of accuracy, she was impaired for the eye position change in the 6-changes block (t = 4.106, p <

0.005) (Table 5.1). For both blocks of Experiment 2, she performed within the normal range (Figure 5.8).

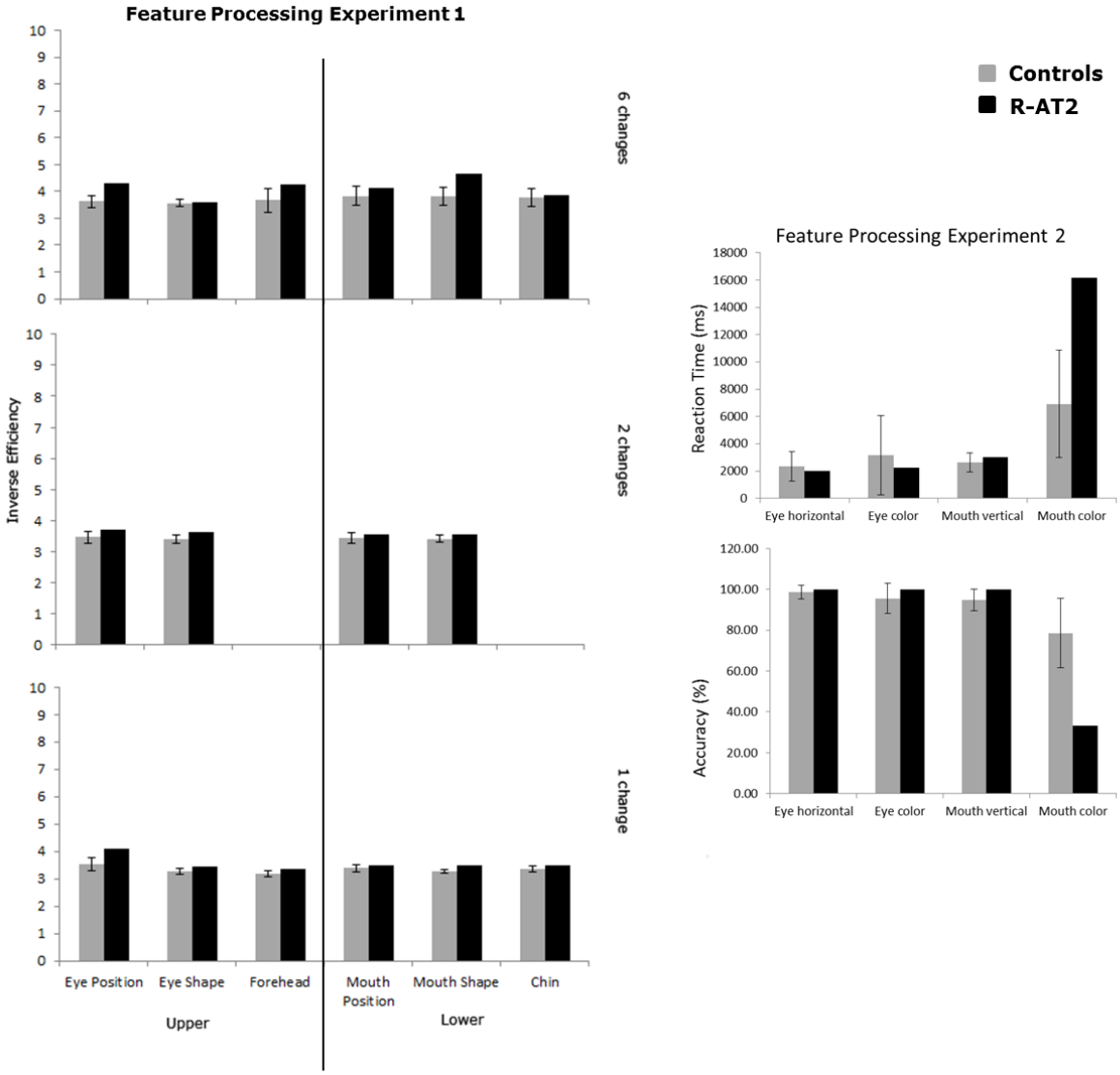


Figure 5.8 Feature Processing Results of Patient R-AT2. No significant differences.

5.2.2.8 Patient R-AT3

Patient R-AT3 performed well in Experiment 1 in terms of efficiency, except for the eye shape ($t= 15.132$, $p<0.0001$), and forehead ($t= 11.209$, $p<0.0001$) changes in the 6-changes block

(Figure 5.9). He does not have any field defects. In terms of accuracy, he was impaired for the eye shape in the 6-changes block (t = 9.324, p < 0.0001) (Table 5.1).He performed within the normal range for all conditions of Experiment 2 (Figure 5.9).

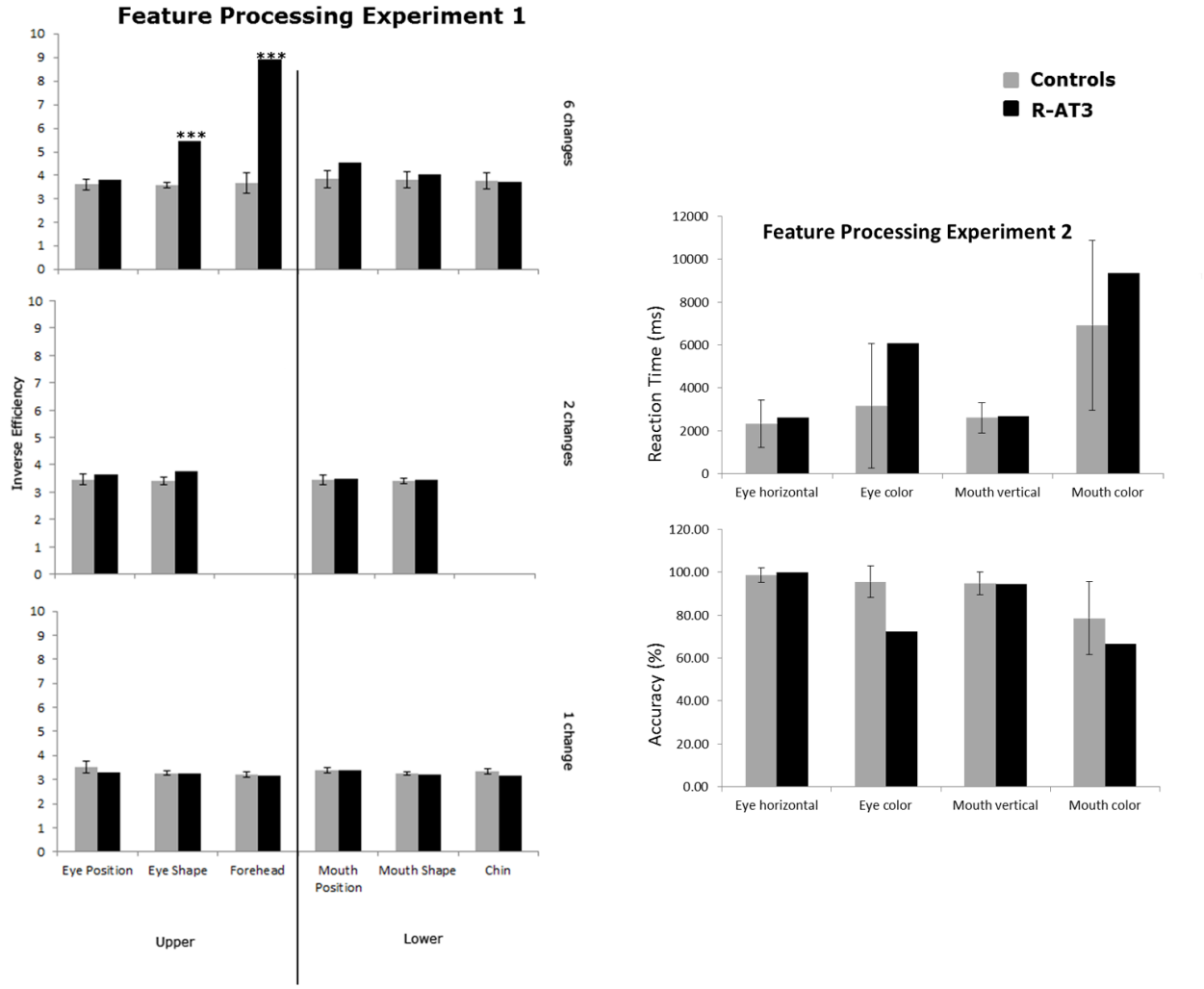


Figure 5.9 Feature Processing Results of Patient R-AT3. * p < 0.05, ** p < 0.001,* p < 0.001.**

5.2.2.9 Patient B-AT1

Patient B-AT1 completed only Experiment 1. In terms of efficiency, he was impaired for eye shape (t=5.293, p<0.001) and eye position (t = 3.726, p<0.05) changes as well as mouth position

changes in the 2-changes block (t = 5.677, p<0.0001) (Figure 5.10). He was also impaired for the forehead change in the 6-changes block (t= 3.395, p < 0.01). Patient B-AT1 does not have any visual field defects. In terms of accuracy, he performed mostly within the control range with the exception of eye position (t= 4.159, p<0.001) and mouth position (t= 6.678, p<0.0001) changes in the two-changes block (Table 5.1).

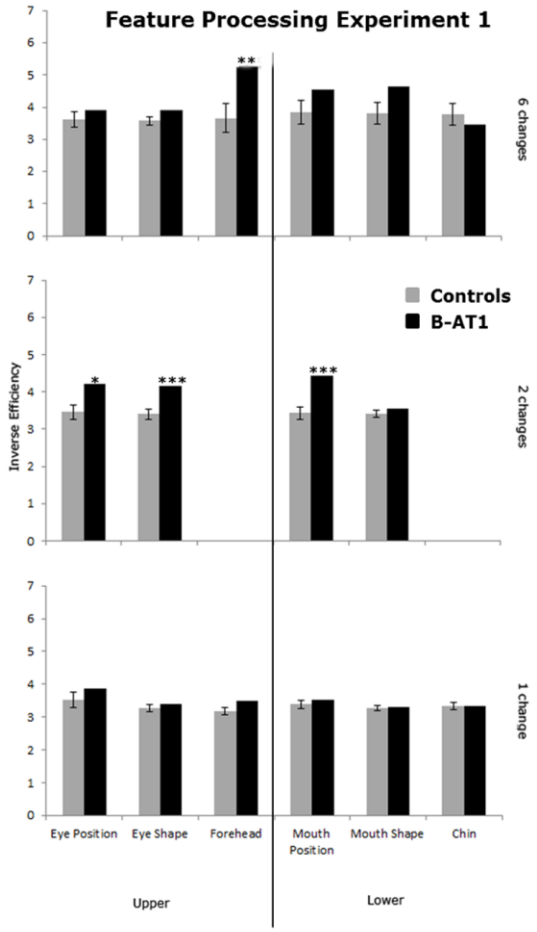


Figure 5.10 Feature Processing Results of Patient B-AT1. * p < 0.05, ** p < 0.001,* p < 0.001.**

5.2.2.10 Patient B-AT2

In Experiment 1, in terms of efficiency, Patient B-AT2 performed similar to controls except for the eye shape condition (t= 5.604. p<0001) in the 6-changes block (Figure 5.11). She does not

have any field defects. In terms of accuracy, she was impaired in the eye shape condition in the 6-changes block ($t = 5.378$, $p < 0.001$) (Table 5.1). She performed within the range of the controls in Experiment 2 (Figure 5.11).

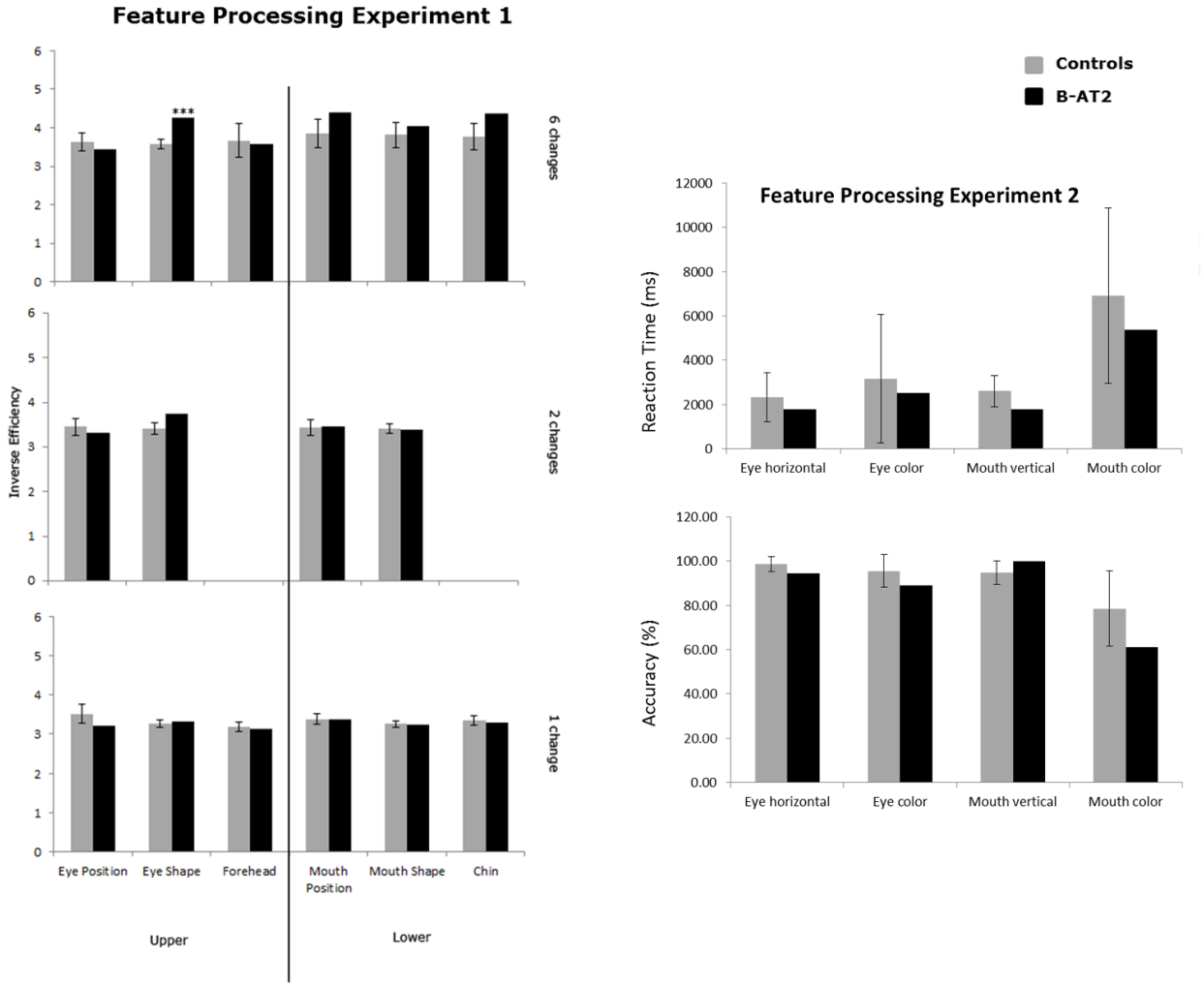


Figure 5.11 Feature Processing Results of Patient B-AT2. * p < 0.05 ,* p < 0.001.**

PATIENT Apperceptive	ACCURACY %	1 change	2 change	6 change	z-score 1 change	2 change	6 change
R-IOT1	Eye Position	88.89	77.78	38.89	-1.41	**-9.09**	**-25.74**
	Eye Shape	100.00	94.44	77.78	0.29	-1.46	**-7.64**
	Forehead	100.00		66.67	0.29		**-4.37**
	Mouth Position	100.00	100.00	72.22	0.55	0.43	**-3.97**
	Mouth Shape	100.00	100.00	61.11	0.00	0.43	**-4.94**
	Chin	100.00		83.33	0.29		-2.92
R-IOT4	Eye Position	100.00	77.80	78.00	-0.69	**-8.30**	**-8.22**
	Eye Shape	100.00	100.00	89.00	-0.32	0.32	**-3.17**
	Forehead	100.00		89.00	-0.32		-2.47
	Mouth Position	94.00	89.00	89.00	1.45	**-5.48**	-0.96
	Mouth Shape	83.30	100.00	94.00	**-16.70**	0.47	-0.05
	Chin	100.00		89.00	-0.32		-1.80
L-IOT2	Eye Position	38.90	11.10	33.30	**-10.42**	**-37.64**	**-28.13**
	Eye Shape	72.20	72.20	38.90	**-15.76**	**-8.47**	**-21.96**
	Forehead	94.40		55.60	-2.94		**-5.97**
	Mouth Position	72.20	77.80	50.00	**-9.69**	**-9.40**	**-7.72**
	Mouth Shape	38.90	38.90	66.70	**-11.00**	**-25.73**	**-4.12**
	Chin	100.00		88.90	0.29		-1.60
B-IOT2	Eye Position	88.89	83.33	72.22	1.41	**-6.71**	**-11.47**
	Eye Shape	100.00	77.78	66.67	-0.29	**-6.71**	**-11.73**
	Forehead	100.00		66.67	-0.29		**-4.37**
	Mouth Position	100.00	94.44	94.44	-0.55	-2.03	-0.22
	Mouth Shape	100.00	100.00	94.44	0.00	0.43	-0.06
	Chin	100.00		100.00	-0.29		1.02
B-ATOT1	Eye Position	72.22	38.89	44.44	**-4.42**	**-25.74**	**-23.36**
	Eye Shape	77.78	50.00	27.78	**-12.54**	**-15.46**	**-26.06**
	Forehead	100.00		94.44	-0.29		-0.33
	Mouth Position	100.00	100.00	88.89	-0.55	-0.43	-1.16
	Mouth Shape	100.00	94.44	55.56	0.00	-1.95	**-5.76**
	Chin	88.89		88.89	**-6.13**		-1.60
B-ATOT2	Eye Position	27.78	22.22	38.89	**-12.43**	**-32.88**	**-25.74**
	Eye Shape	88.89	66.67	33.33	**-6.13**	**-10.21**	**-24.02**
	Forehead	100.00		55.56	0.29		**-5.98**
	Mouth Position	100.00	83.33	50.00	0.55	**-6.95**	**-7.72**
	Mouth Shape	94.44	94.44	22.22	**-6.60**	-1.95	**-10.64**
	Chin	100.00		27.78	0.29		**-16.06**

PATIENT Associative	ACCURACY %	1 change	2 change	6 change	z-score 1 change	2 change	6 change
R-AT2	Eye Position	88.89	100.00	88.89	-1.41	0.43	**-4.33**
	Eye Shape	100.00	100.00	100.00	0.29	0.29	0.55
	Forehead	100.00		88.89	0.29		-1.14
	Mouth Position	100.00	100.00	94.44	0.55	0.43	-0.22
	Mouth Shape	100.00	100.00	77.78	0.00	0.43	-2.50
	Chin	100.00		100.00	0.29		1.02
R-AT3	Eye Position	100.00	94.40	94.40	0.59	-1.97	1.97
	Eye Shape	100.00	94.40	72.20	0.29	-1.47	**-9.69**
	Forehead	100.00		44.40	0.29		**-7.60**
	Mouth Position	100.00	100.00	83.30	0.55	0.43	-2.10
	Mouth Shape	100.00	100.00	94.40	0.00	0.43	-0.07
	Chin	100.00		94.40	0.29		-0.30
B-AT1	Eye Position	94.44	88.89	100.00	-0.41	**-4.33**	0.43
	Eye Shape	100.00	88.89	100.00	0.29	**-3.21**	0.55
	Forehead	94.44		77.78	-2.92		-2.75
	Mouth Position	100.00	83.33	88.89	0.55	-6.95	-1.16
	Mouth Shape	100.00	100.00	83.33	0.00	0.43	-1.69
	Chin	100.00		100.00	0.29		1.02
B-AT2	Eye Position	100.00	100.00	100.00	0.59	0.43	0.43
	Eye Shape	100.00	94.44	83.33	0.29	-1.46	**-5.59**
	Forehead	100.00		100.00	0.29		0.47
	Mouth Position	100.00	100.00	83.33	0.55	0.43	-2.10
	Mouth Shape	100.00	100.00	94.44	0.00	0.43	-0.06
	Chin	100.00		88.89	0.29		-1.60

Table 5.1 Accuracy and z-scores of Patients for Eye and Mouth Position Changes in Experiment 1. Impaired z-scores are indicated in red.

5.2.3 Comparison of Patient's Data at the Group Level

Patients in the Apperceptive Group (R-IOT1, R-IOT4, L-IOT2, B-IOT2, B-ATOT1, B-ATOT2) showed impairments for changes to different features and the second-order relation of features. These impairments were not limited to the eyes, but they showed significantly larger deviations from the control group for changes to the eyes (Table 5.1). Accuracy results for the eye and the mouth changes in 1-change, 2-changes and 6-changes blocks of the Feature Processing Experiment 1 show that all patients except for L-IOT2 perform similar to controls in detecting changes to the mouth in the 1-change block (Figure 5.12). Patients L-IOT2, B-ATOT1 and B-ATOT2 are impaired in detecting changes to the eye position even in the 1-change block when the subjects were informed where the change on the face would take place, and none of these patients have significant visual field defects. When there are two changes possible at a time and the subjects are informed where in the face the change would take place, e.g. eye changes or mouth changes, patients perform worse. In fact, all apperceptive patients fall below the control range for eye position change. Except for Patients R-IOT4 and B-ATOT1, all Apperceptive patients fall below the control range also for mouth position changes. Except for B-AT1, all Associative prosopagnosia patients (R-AT2, R-AT3, B-AT2) perform within the normal range.

Increases in the difficulty level of the experiment in the 6-changes block, when subjects are not informed where the change will take place on the face, results in large deviations from the control performance in the Apperceptive patient group. The Associative group patients also show a decrease in performance, yet to a lesser degree compared to the Apperceptive group. Comparison of the eye position and mouth position processing at the group level shows a significant difference between the controls and the Apperceptive group for both for the eye ($t(5) = 6.130$, $p < 0.001$) and the mouth ($t(5) = 2.584$, $p < 0.005$) changes (Figure 5.13). There is also

a significant difference between the Apperceptive and Associative patients in detecting changes to the eye region ($t(6) = 5.438$, $p < 0.001$).

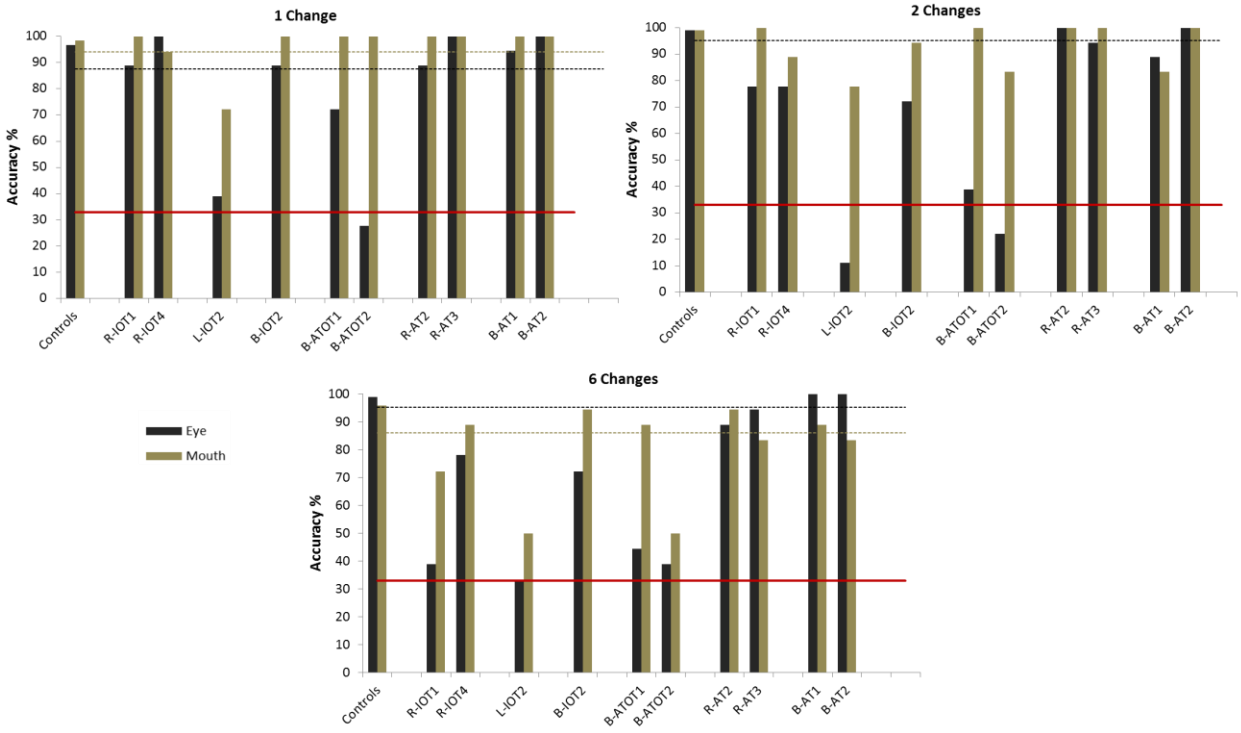


Figure 5.12 Accuracies for the Eye and the Mouth Position Change in the 1-Change, 2-Changes, and the 6-Changes Blocks of Experiment 1. Dotted lines indicate 95% prediction limits derived from the control data; red line indicates 33% correct at change level.

Finally, the eye region processing impairments of the patients are contrasted with their performance on the Warrington Recognition Memory Test for Faces, which is the most consistent predictor of face processing impairments. Apperceptive Prosopagnosia Patients for the most part, demonstrate bigger impairments for both eye position discrimination and face memory (Figure 5.14).

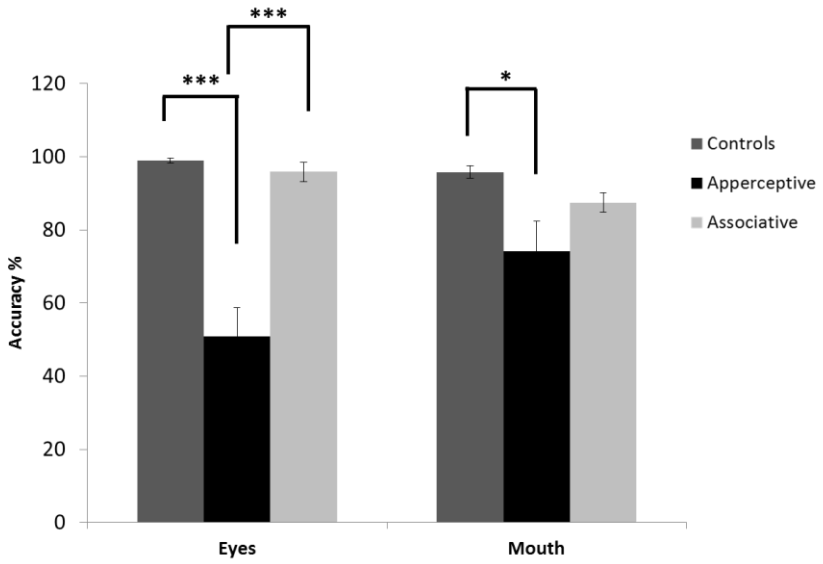


Figure 5.13 Comparison of Eye and Mouth Change Scores of Apperceptive and Associative Patients. * p < 0.05, *** p < 0.001.

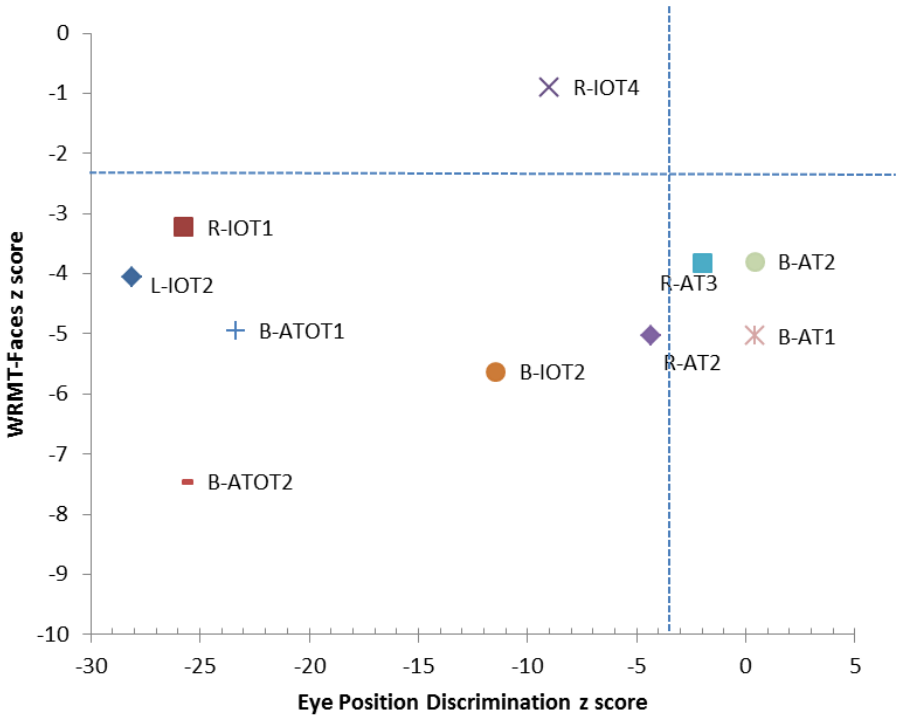


Figure 5.14 Correlation of the Eye Position Discrimination Scores and the Warrington Recognition Memory Test-Faces. Blue lines indicate critical z-scores for 95% confidence intervals.

5.3 Comments

Results for healthy controls from Experiment 1 and 2 are in agreement with previous studies indicating better performance for the eye region (Bukach et al., 2008; Barton 2008a) supporting the feature salience hierarchy. Individual patient data in Experiment 1 indicate that although the patients are impaired for both the eyes and the mouth, the impairments for the eye region are more severe than the impairments for the mouth region. In addition, patients with inferior occipitotemporal lesions consistently demonstrate bigger impairments in the eye region processing compared to patients with anterior temporal lobe lesions. In certain cases, such as Patient B-IOT2, larger latencies can be explained by the visual field defects. However, even when we allow for this, he was still impaired for accuracy in most eye change conditions selectively. In some cases, the higher demand of attending to all possible six-changes at different face locations has been reflected in impaired performances. However, for patients who demonstrated severe impairments such as L-IOT2, the total number and location of possible changes in a block did not reveal an improvement of performance with 1-change or 2-change blocks with lower task demands than the 6-change block. In Experiment 2, all Apperceptive patients demonstrated impairments. Patients R-IOT1, B-IOT2, and B-ATOT1 had impairments selectively for detecting changes to the eye region, whereas Patients R-IOT4, L-IOT2, and B-ATOT2 revealed impairments in detecting both the eye and the mouth region changes. It is important to note that none of the patients revealed selective mouth region impairments with preserved eye region change detection. All associative patients tested performed within the normal range in Experiment 2, except for B-AT1 who did not perform this experiment. These experiments establish the eye region impairments in the Apperceptive variant of prosopagnosia as the largest feature processing deficit in our patient cohort, in agreement with previous studies

(Bukach et al., 2006, 2008; Barton et al., 2002; Barton 2008a). The functional face localizer scans of all of these patients reveal loss of function of the right FFA (Chapter 4), confirming the relation of eye processing and damage to the FFA in agreement with previous studies which have indicated a link between the fusiform damage and impaired second-order feature relation processing (Sergent and Signoret 1992; Barton et al., 2002; Joubert et al., 2003; Barton 2008a; Riddoch et al., 2008; Busigny et al., 2010).

The next question is whether these impairments in eye region processing are accompanied by face scanning abnormalities. The next chapter examines the face scanning patterns in a learning and memory task in order to investigate how the behavioral bias for the eye region is reflected in the face scanning patterns in healthy subjects, and whether this pattern is altered in prosopagnosia patients who demonstrate the loss of the advantage and the bias for the eye region in face identity experiments.

Chapter 6: Face Scanning Patterns in a Learning and Memory Task

Previous eye movement studies indicate that healthy subjects look more at the eyes when identifying faces (Vinette et al., 2004; Henderson et al., 2005; Barton et al., 2006). Henderson and colleagues have reported that healthy participants spent 4-10 seconds on average in the eye region of the face when learning a new face, whereas all other regions of the face were fixated on for less than a second each. It has also been reported that some prosopagnosia patients have lost this normal preference of fixating on the eyes (Barton et al., 2007b), and have lost the ability to deduce accurate information from the eyes and base their face identity decisions on information from the mouth region of faces (Caldara et al., 2005; Bukach et al., 2008). In addition, prosopagnosia patients have more problems perceiving changes in the eyes than in the mouth region (Barton 2008a).

As described in Chapter 5, feature processing experiments administered in our current prosopagnosia cohort have shown that prosopagnosia patients are more challenged in detecting changes made to the eye region of a face, in agreement with previous studies (Barton 2008a). In addition, patients with inferior occipitotemporal lobe lesions, classified as apperceptive prosopagnosia, are significantly more impaired than patients with anterior temporal lobe lesions, classified as associative prosopagnosia, in detecting changes to the eye region of a face.

In order to investigate whether the eye region processing difficulties in prosopagnosia patients occur with abnormal face scanning patterns, we examined the face scanning patterns while the participants performed a face learning and memory task. We tested both healthy subjects and prosopagnosia patients performing a face learning and memory task while we recorded their eye movements. By measuring the number of fixations and the durations of

fixations in a given face region both in the learning and the recognition phases of the experiment, we were able to compare the scanning patterns for a novel face versus an already seen and learned face in the healthy subjects and test how the face scanning patterns of the prosopagnosia patients differed from those of healthy subjects. In particular, we tested whether the patients: 1) scanned faces for similar durations to controls when given unlimited time, 2) searched the lower face half/ mouth region more than the upper face half/ eye region.

6.1 Methods

6.1.1 Participants

Twenty healthy subjects (10 female; mean age = 34.4, range 18-66) with no history of neurological disease or cognitive impairments participated in the experiment. All subjects had normal or corrected-to-normal vision and viewed all the stimuli with both eyes.

Eight patients from the prosopagnosia cohort (R-IOT4, L-IOT2, B-IOT2, B-ATOT2, R-AT2, R-AT3, B-AT1, and B-AT2) whose case descriptions are given in Chapter 4 participated in the study. The experiment protocol was approved by the institutional review boards of Vancouver General Hospital and the University of British Columbia. Written consent was obtained from all participants in accordance with the declaration of Helsinki.

6.1.2 Stimuli

Thirty male faces from the KDEF face database (Lundqvist et al., 1998) were used as stimuli for the experiment. Five faces were randomly selected as Target identities. Two images of each target identity were used in the learning phase, resulting in a total of 10 learning phase faces. The two different images of the same individual identity had different expressions. One of these two

images was always neutral, and the second image had either a sad or happy expression. The two images of the same identity were shown in succession in the Learning phase of the experiment. The rest of the face images of 25 different identities were randomly assigned as Distractors and were randomly selected with different facial expressions (6 neutral, 4 happy, 5 sad, 4 surprised, 4 angry, 1 afraid). All images were converted to grey scale and matched for luminance using Photoshop. Faces were cropped to remove all external features. Faces were cropped with a straight line on the top, and with the face's natural contour for the rest. Faces were adjusted in size in order to ensure that the final size of each image would roughly have similar sizes for each region of interest of the face. Final size of all stimuli was set at 320 pixels in width and 376 pixels in height. On the display, all faces were centered in the middle of the screen with the tip of the nose as the center point.

6.1.3 Experimental Procedure

Subjects sat in a room with dim lighting standardized across subjects, positioned 34cm away from the computer display. Head position was maintained by a chin rest. Eye movements were recorded by an Eyelink 1000 binocular system (SR Research Ltd, Mississauga, Canada). Stimuli and trials were programmed in SR Research Experiment Builder 1.10.165. Stimuli were displayed on a white background on a high refresh rate monitor at 140Hz with a 1024 X 768 pixel resolution. The fixation cross was created as a text object '+' in Times New Roman font, size 30, spanning 1.43° visual angle at location (512,100) on the screen. Subjects performed 2 blocks: the Learning and Recognition phases of the test. Subjects started with a camera calibration where the range of each subject's eye movements was assessed using a 9 point grid. After this, subjects started the first (Learning) phase, where they were shown 10 images of faces

with different expressions. There were 5 identities, with 2 consecutive images being shown for each identity, one of which was with a neutral expression. Subjects were instructed to memorize the identity of these Target faces and that they would be tested on their face memory (Figure 6.1). Subjects were shown each image for an unlimited time, and they had to press the space bar to go to the next image when they were ready. Followed by this, subjects were informed that the "test" part of the experiment would start next. Subjects were allowed a short break (maximum of 60 seconds), and they were instructed to press the space bar to start the "test" part when they were ready. Subjects were shown a total of 35 images of faces in the Recognition phase. 10 of these images belonged to the Target (Learned) identities. The same images of Target faces presented during the Learning phase were used in the Recognition phase. The rest were Distractor (Novel) faces not presented during the Learning phase. Subjects were asked to press the left arrow key on the keyboard if they had seen that person in the Learning phase and the right arrow key if it was a new face identity not presented during the Learning phase. Subjects were not told the total number of targets that would be presented in the "test".

In the Learning phase, each trial began with a fixation cross on the screen at location (512, 100) spanning approximately 1.43° visual angle above the location where the face image would appear (approximately 3° visual angle). Subjects had to fixate within 2° of the cross, determined by a box at location (501, 89) top left corner with 22 pixel width and 22 pixel height, for at least 100ms for the trial to progress. After an interval of 1050ms, the face appeared at the center of the screen. When the subject pressed the space bar, the face disappeared and the fixation cross appeared. Following fixation within 2° of the cross for at least 100ms, and a delay of 1050ms, the second image of the same identity was shown. When the subject pressed the space bar for the second time, the trial was terminated and subject had to fixate before moving to

the next identity. Failure in fixation resulted in exit from the trial loop and calibration. After calibration, subject resumed testing in the trial where fixation was unsuccessful. In the Recognition phase, each trial began with a fixation cross above the image of the face (approximately 3° visual angle). Subjects had to fixate within 2° of the cross for at least 100ms for the trial to progress. After an interval of 1050ms, the face appeared at the center of the screen. The face stayed on until subjects pressed the left arrow or right arrow key on the keyboard. In this block, the trials were randomized. If subjects did not fixate successfully in the beginning of the trial, subjects were redirected to a calibration after which they resumed testing. After subjects had seen all 35 faces, a "Thank you" screen came up after which the experiment was complete.

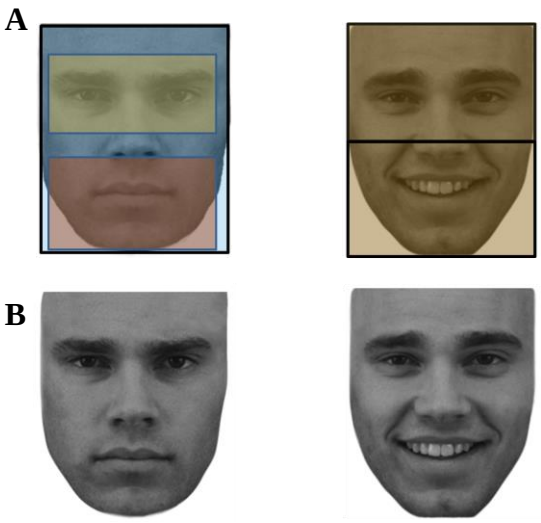


Figure 6.1 Region of Interests Overlayed on Face Stimuli. A) shows the regions of interest Eyes, Mouth, and Whole Face on the left, Upper Face and Lower Face Half on the right. B) shows representative pair of stimuli from the Learning Phase where two different images of the same individual are presented sequentially.

6.1.4 Data Analysis

Data was analyzed with SR Research Eyelink Data Viewer 1.10.1. Latencies for response for each image were recorded as the time between image onset on the screen and keyboard press (space bar for the Learning phase, left or right arrow key for the Recognition phase). All eye movement data was analyzed in this interval for all the blocks. The effect of condition (learning target, recognition target, recognition distractor) on fixation patterns was analyzed, in addition to the distribution of fixations in the face by specific regions of interest. Fixation reports for all fixations made in the latency period (subject response time – image onset time) for all the subjects were generated. The average duration of fixations in each interest area and total number of fixations made within this area were multiplied for each subject. The interest areas were: Eyes (X= 360-660, Y= 243-369 pixels), Mouth (X= 378-647, Y= 423-571 pixels), Lower Face Half (X= 352-672, Y= 384-572 pixels), Upper Face Half (X= 352-672, Y= 196-384 pixels), and the Whole Face (X= 352-672, Y= 196-572 pixels) (Figure 6.1). The areas of the Upper Face and Lower Face Half were the equal in size and together equaled the Whole Face interest area. The areas of the Eyes and the Mouth were also similar with the Mouth area (39812 pixels) being slightly larger than the Both Eyes area (37800 pixels). All subsequent analysis was done at the subject average level to deal with the sampling issue (the number of fixations made in each trial was highly variable within and between subjects). The duration spent in each region of interest was analyzed in terms of the condition, normalized by trial number in each condition.

All statistical analysis was performed with JMP 10 (www.jmp.com). For the control group, the time spent (total number of fixations X average duration of fixations) in an interest area for each subject was entered as the outcome variable in ANOVA with subject as random effect, and Condition (learning target, recognition learned, recognition distractor) and Face Half

Interest Area (Upper Face, Lower Face) as main factors. Planned linear contrasts were used to explore the basis of interactions. A separate ANOVA was run for the time spent (total number of fixations X average duration of fixations) in an interest area for each subject as the outcome variable, Condition (learning target, recognition learned, recognition distractor) and Face Part Interest Area(Eye, Mouth) as main factors and the subject as random effect. An Upper/Lower Face Index with the formula (Upper-Lower)/ (Upper + Lower)/2, and an Eye/Mouth Index with the formula (Eye-Mouth)/ (Eye + Mouth)/2 was calculated for each subject with the total time spent values. Results for the patients were compared with the control group results for the whole face fixations, the Upper/Lower Face fixation ratio, and the Eye/Mouth Index.

Responses from the face memory task in the Recognition phase of the experiment were measured with true (Hits) and false (False Alarm) rates, and discrimination ability (d') and criterion bias (c') were calculated . The results of the patients and the controls were compared in a two-sample t-test for unequal sample size.

6.2 Results

6.2.1 Face Memory Task

The F- test for the equality of variances of the controls and the patient group showed that these were not different for hits ($F(18,6) = 0.97$, $p = 0.56$), false alarms ($F(18,6) = 0.82$, $p = 0.66$), d' ($F(18,6) = 2.11$, $p = 0.18$), or c' ($F(18,6) = 0.83$, $p = 0.65$). Hence we used 2-sample t-tests for samples with equal variance to contrast the control and prosopagnosic groups.

Comparing the two groups, the prosopagnosic group had more false alarms (43% versus 25%, $t(24) = 2.26$, $p<0.034$), and a trend to fewer hits (70% versus 81%, $t(24) = 1.98$, $p = 0.059$) than the controls (Figure 6.2). This resulted in significantly lower discriminatory power for the

prosopagnosic group (mean d' = 0.52 versus 1.79, t(24)=3.08, p<0.0052). However, the mean criterion bias did not differ between the groups (mean c' =0.07 versus 0.07, t(24) = 0.006, p = 0.99).

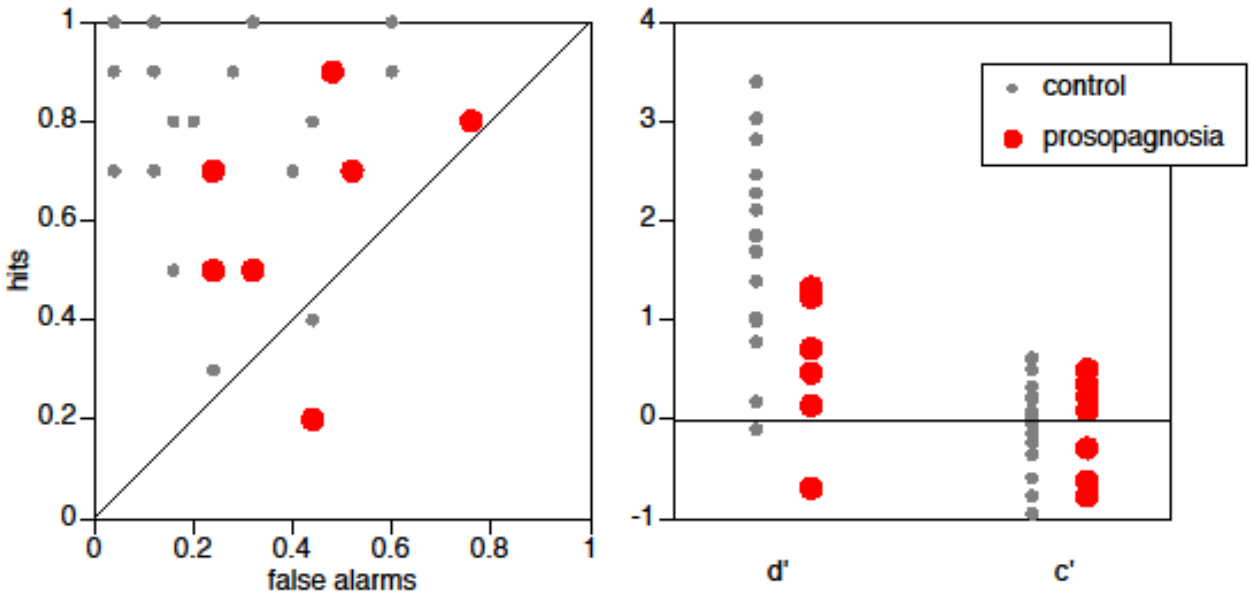


Figure 6.2 Face Memory Task Results Showing A) correct hits versus false alarms, B) d'and c'.

6.2.2 Controls

In the analysis of Face Halves, ANOVA showed a main effect of phase ($F(2,95) = 7.26$, $p < 0.0012$). Linear contrasts showed that controls spent more time looking at distractor faces in the recognition phase than at target faces in the learning phase ($F(1,95) = 14.5$, $p < 0.0002$). There were trends for control subjects spending more time with target faces in the recognition phase than in the learning phase ($F(1,95) = 3.86$, $p = 0.053$), and more time on distractor than target faces in the recognition phase ($F(1,95) = 3.41$, $p = 0.068$). There was also a main effect of face

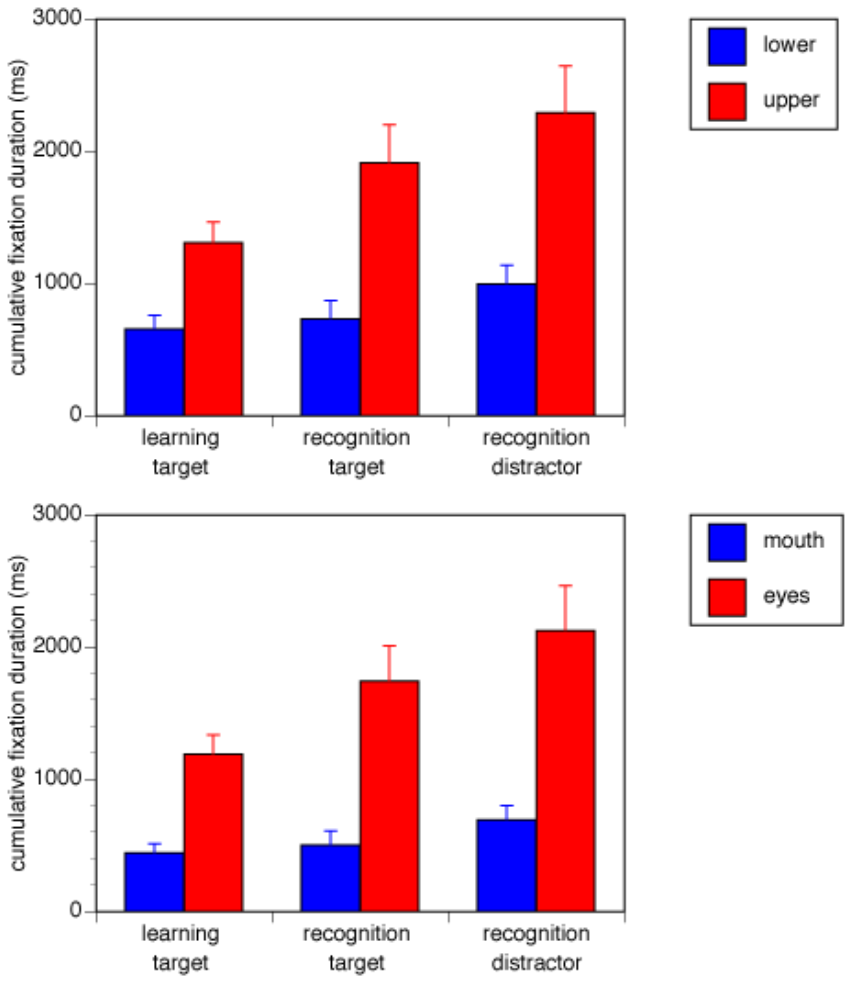


Figure 6.3 Cumulative Fixation Durations of the Controls in Upper/Lower and Eyes/Mouth Interest Areas.

half ($F(1,95) = 53.9$, $p < 0.0001$), with control subjects spending more time on the upper half (Figure 6.3). However, there was no interaction between phase and face half.

Results were highly similar if we narrowed the analysis to the eye and mouth regions specifically. ANOVA showed a main effect of phase ($F(2,95) = 6.56$, $p < 0.0022$). Linear contrasts showed that control subjects spent more time looking at distractor faces in the recognition phase than at target faces in the learning phase ($F(1,95) = 13.1$, $p< 0.0005$). There were trends for control subjects spending more time with target faces in the recognition phase

than in the learning phase (F(1,95) = 3.48, p = 0.065), and more time on distractor than target faces in the recognition phase (F(1,95) = 3.08, p = 0.083). There was also a main effect of face part (F(1,95) = 72.4, p< 0.0001), with control subjects spending more time on the eyes (Figure 6.3). However, there was no interaction between phase and face part (F(2,95) = 2.32, p=0.10).

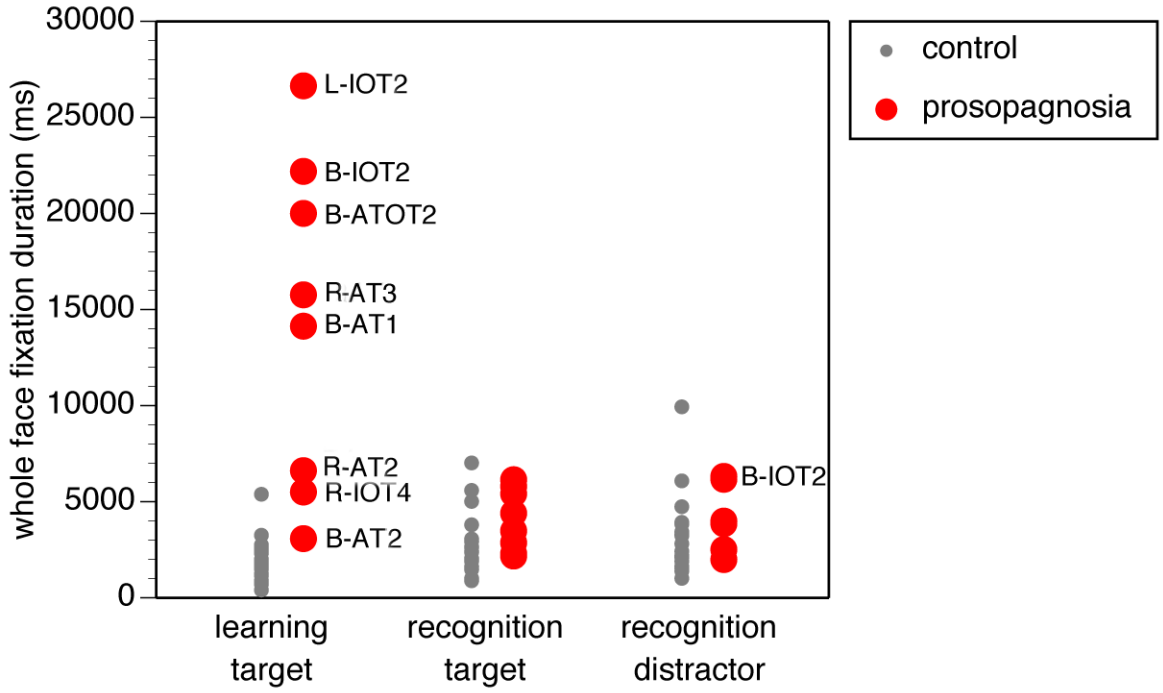


Figure 6.4 Whole Face Fixation Durations of Controls and Patients during the Learning and Recognition Phases.

6.2.3 Patients

When we assessed cumulative fixation durations on the entire face, all but one prosopagnosic subject (B-AT2) took longer to inspect faces during the learning phase, in three cases (L-IOT2, B-ATOT2, B-IOT2) as much as 10 times longer than the control mean. However, during the recognition phase, prosopagnosic subjects were comparable to the controls, with the only exception being slightly longer fixation duration by B-IOT2 on distractor faces (Figure 6.4).

For the index of fixation duration on the upper versus lower face, control subjects spent about 20% longer looking at the upper face in all phases (Figure 6.5). The majority of the prosopagnosic subjects were no different. The only exceptions were B-IOT2 for target faces and B-AT1 for distractor faces, both in the recognition phase, with more time spent looking at the lower than the upper face. Similarly, the index for eyes versus mouth showed that controls spent 24-28% more time looking at the eyes than the mouth region. Again, most prosopagnosic subjects behaved similar to the controls. The exceptions, with more time looking at the mouth than the eyes, were the same two patients. B-IOT2 demonstrated this for both target and distractor faces in the recognition phase, while B-AT1 showed this pattern for target faces in the learning phase and distractor faces in the recognition phase (Figure 6.5).

6.3 Comments

Our face scanning experiment revealed that healthy subjects spent about 2 seconds on average fixating on the faces during a learning phase, but took more time during the recognition phase, particularly when eliminating distractor faces as unfamiliar. They displayed the pattern of spending more time on the upper half of the faces, and in particular the eye region and this did not differ between learning and recognition phases, or between targets and distractors. These results are consistent with previous studies that have shown similar scanning patterns for healthy subjects (Barton et al., 2006; Malcolm et al., 2008) and strengthen the previous suggestions that healthy individuals base their decisions on diagnostic information from the upper face half and the eye region of faces.

Patient data shows that almost all prosopagnosic subjects spent significantly more time

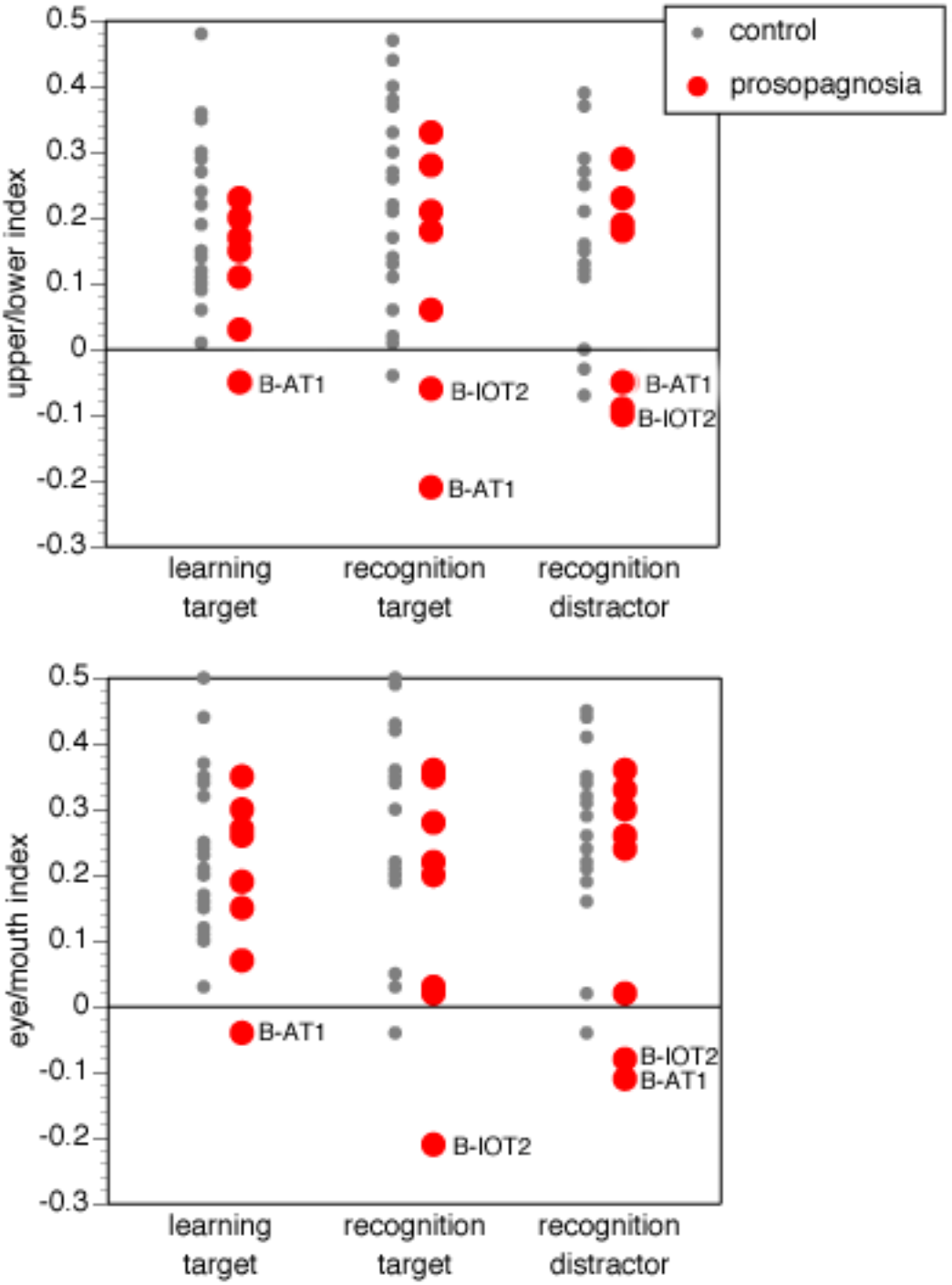


Figure 6.5 Relative Scanning Times of Upper/Lower Faces and Eye/Mouth Face Parts for Controls and Patients.

than controls fixating faces when learning the targets; however, with the exception of two subjects (B-IOT2 and B-AT1) all showed a normal pattern of emphasizing the upper half and the eyes of the face. B-AT1 showed an abnormal face scanning pattern and scanned the lower face and the mouth during the learning phase. In addition to B-AT1's anomalous strategy in the learning phase, B-IOT2 scanned the lower face and the mouth region more in the recognition phase. For the rest of the patients, this relatively normal scanning pattern indicates that a failure to inspect the upper face or the eye region with the fovea is not the cause of the pattern of perceptual deficits showing greater problems discriminating features and spatial relations in the eye region. In terms of total fixation durations, patients showed a similar pattern to the healthy controls in the recognition phase, where they spent less time for faces they had already seen in the learning phase. These results indicate that when given unlimited viewing time, prosopagnosia patients show scanning patterns similar to controls for the upper and lower halves of faces; however they spend significantly longer durations than healthy controls when given unlimited time. During the learning phase, patients make tremendous efforts to observe the faces for very long durations allocating their gaze to all different areas of the face. Yet, during the recognition phase where they have to perform the memory task, they act faster, similar to controls where they try to scan the face and give their answer as soon as they can, despite the fact that they were not explicitly told they would be scored on how fast they performed the task.

The next chapter examines the performances of healthy controls and prosopagnosia patients in a memory task for faces with the aim of exploring whether healthy subjects are better at learning and remembering upper halves of faces than lower halves of faces, and whether prosopagnosia patients perform in a different way than healthy controls in this task, where each face stimulus is presented on the screen for a fixed amount of time.

Chapter 7: Feature Salience Hierarchy in a Half- Faces Memory Task

Our behavioral adaptation aftereffects experiment on healthy subjects showed significant identity aftereffects for the upper face half and the eye region, whereas the lower face half alone was not able to generate a significant identity aftereffect, indicating differential neural representation of the upper and lower faces (Chapter 2). Additionally, the patient cohort results in the feature processing experiments show that patients may be impaired in detecting changes to both the eye and the mouth regions of faces (Chapter 5). However, patients with the apperceptive variant of prosopagnosia are significantly worse in detecting eye region changes than other changes to the face parts. When we examined how this eye region deficit was reflected in the face scanning patterns of the patients while we recorded and analyzed their eye movements, we found that most of these patients actually scanned the upper face and the eyes for longer durations than the lower face and the mouth similar to the healthy controls in a learning and memory task with unlimited viewing time (Chapter 6). These results show that patients allocate ample time studying the upper half of a face when given unlimited study duration. Therefore, the significantly larger accuracy impairments of detecting changes to the eye region in feature processing experiments are unlikely to be a result of avoidance of the eye region as demonstrated by their face scanning patterns.

With the avoidance of directing gaze at the eye region ruled out as the cause of larger impairments of the eye region processing in acquired prosopagnosia, and the feature salience hierarchy confirmed for healthy controls in the adaptation aftereffects paradigm, we next aimed to investigate whether healthy controls perform better for memory of upper face halves and whether prosopagnosia patients perform better for memory of lower face halves relative to upper faces halves.

Subjects learned the upper and lower halves of faces separately in separate blocks with limited viewing durations. Then we tested the participants' memory with presentation of full face test items corresponding to the face halves studied along with full face distractor items.

We hypothesized that 1) healthy subjects will perform significantly better for memory of upper face half than the lower face half, and 2) apperceptive prosopagnosia patients with significant impairments of the upper face and eye region information with mildly impaired or relatively preserved processing of the lower face and the mouth region in feature processing tasks will have larger impairments in upper face memory compared to lower face memory.

7.1 Methods

7.1.1 Participants

Twenty-four healthy participants (13 female; mean age = 36, range 25-67) with no history of neurological disease history or cognitive complaints participated in the experiment. All subjects had normal or corrected-to-normal vision.

Seven patients from the prosopagnosia cohort (R-IOT4, L-IOT2, B-IOT2, B-ATOT2, R-AT2, R-AT3, and B-AT2) whose descriptions are given in Section 4.2 participated in the study. The protocol was approved by the institutional review boards of Vancouver General Hospital and the University of British Columbia. Written consent was obtained from all participants in accordance with the declaration of Helsinki.

7.1.2 Stimuli

60 female faces and 60 male faces with "Happy" expressions were selected and combined from the Karolinska Directed Emotional Faces (Lundqvist et al., 1998), the NimStim Database

(Tottenham et al., 2009), and the HVEM Face Database. The faces were matched in pairs for physical similarity as determined by similarity ratings evaluated by 4 healthy individuals. External cues were removed with an elliptical mask in Photoshop. Faces were converted to gray scale and matched for luminance using Photoshop. Half of the faces were randomly assigned as Target Stimuli, and the other half were designated as the Distractor Stimuli. Full faces were sized at 350 pixels width and 530 pixels height at a resolution of 72 pixels per inch. Each image of the Target Stimuli set was separated into upper and lower face halves at the midline, above the tip of the nose. Target Stimuli were randomly assigned as Upper Face or Lower Face targets, and were used only once either as Upper Face or Lower Face stimulus. Each distractor face was also used only once. Half faces were 350 pixels in width and 250 pixels in height. There were 30 (15 female, 15 male) Upper Face and 30 (15 female, 15 male) Lower Face stimuli with a total of 60 (30 female, 30 male) full face target stimuli matches and 60 (30 female, 30 male) distractor images (Figure 7.1). The size of the faces on the choice screen which included one target full-face and one distractor full-face were set to 400 pixels in width and 600 pixels in height.

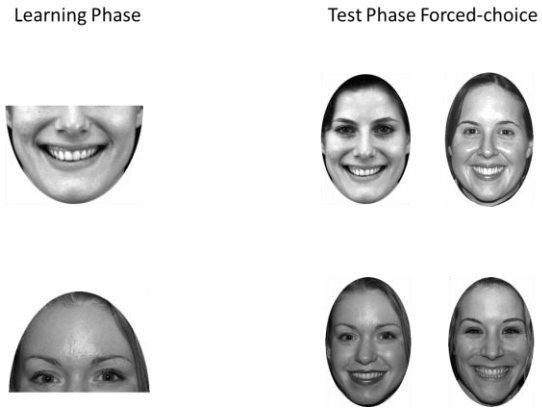


Figure 7.1 Representative Stimuli from the Learning and Test Phase. Upper and Lower Face Halves were presented in a separate Learning Phase. The Test Phase presented a full face match of the half face from the Learning Phase and a full distractor face.

7.1.3 Experimental Procedure

A Toshiba Tecra A8 notebook with 1280X800 pixels resolution at a refresh rate of 60Hz was used to display the stimuli at a viewing distance of 57cm in a dimly lit room. The experiment was designed and conducted using E-Prime software (www.pstnet.com). Subjects were instructed that they were going to perform a learning and memory task, where they would first view and memorize face halves and then be immediately tested for their memory for these faces in a full-face context. The experiment consisted of 4 blocks; Female Upper Face Halves, Female Lower Face Halves, Male Upper Face Halves, Male Upper Face Halves. Each block contained a Learning Phase and a Test Phase. In each block, 15 corresponding face halves were presented for 3s each while the subjects were learning them. Stimuli were separated by a 1s grey mask screen. Following the Learning Phase, subjects were presented with the 15 choice screens of the Test Phase. Each choice screen displayed a Target Face and a Distractor Face in a two-alternative force choice task for unlimited duration, and the subjects were asked to report the full face which corresponded to one of the 15 half faces learned. Subjects reported their choices with a key press. Accuracies were measured for each block, and combined for Upper Face and Lower Face blocks.

7.1.4 Data Analysis

Accuracies were calculated as percent correct for the total of 30 (15 per each block) upper face and 30 lower face items. A repeated measures ANOVA with Face Half (Upper, Lower) and Stimuli Gender (Female, Male) as main factors, and Subject as random effect was run for the control accuracy scores. Paired-sample t-tests were run to compare Face Half conditions. Bonferroni corrections were applied for multiple comparisons.

To compare the results of each patient with the results of controls, we used the modified t-test of Crawford and Howell (1998) for single-case studies with a one-tailed 0.05 p value. Consequently, all scores associated with a p value under 0.05 were considered to reflect an abnormal result. Analyses were conducted on a computerized version of the Crawford and Howell's method: SINGLIMS.EXE: Point estimate and confidence limits on the abnormality of a test score (Crawford and Garthwaite 2002).

7.2 Results

7.2.1 Controls

The repeated measures ANOVA with Face Half and Stimuli Gender as main factors and Subject as random effect revealed that there were no significant effects of Face Half ($F(1,23) = 5.0108$, $p = 0.120$) or Stimuli Gender ($F(1,23) = 5.9035$, $p = 0.076$) on the performances. Paired-sampled t-test revealed that the performances for the Upper and Lower face halves were not significantly different ($F(1, 23) = 2.628$, $p = 0.060$), although there was a trend. The control group had a mean accuracy score of 79.30% ±6.67 for the Top Face Halves and 83.61% ± 6.66 for the Bottom Face Halves.

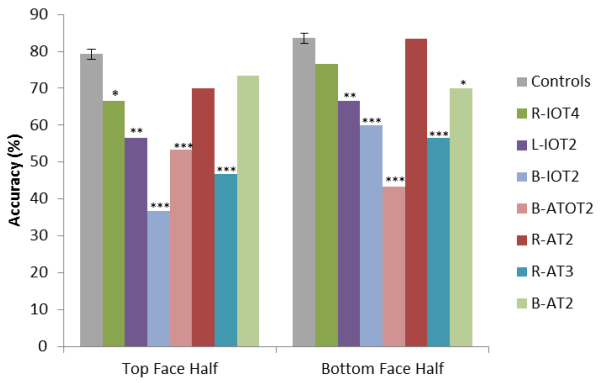


Figure 7.2 Accuracy Scores for the Top Face Half and Bottom Face Half Memory.

7.2.2 Patients

All patients tested except for R-AT2 performed significantly worse than controls for at least one face half.

Patient R-IOT4 performed significantly worse than controls in the Top Face Half ($t = 1.924$, $p<0.05$). Therefore, he was selectively impaired for memory for the Top Face Half.

Patient L-IOT2 performed significantly worse than controls both in the Top Face Half ($t = 3.431$, $p<0.01$) and the Bottom Face Half ($t = 2.911$, $p<0.01$) conditions.

Patient B-IOT2 performed significantly worse than controls in both the Top Face Half ($t = 6.444$, $p<0.0001$) and the Bottom Face Half ($t = 4.036$, $p<0.001$) conditions.

Patient B-ATOT2 performed significantly worse than controls in both the Top Face Half condition ($t= 3.943$, $p<0.001$) and the Bottom Face Half ($t = 6.840$, $p<0.0001$).

Patient R-AT2 performed no different than controls for both the Top and the Bottom Face Half conditions.

Patient R-AT3 performed significantly worse than controls both in the Top Face Half ($t = 4.937$, $p<0.0001$) and the Bottom Face Half ($t = 4.590$, $p<0.0001$) conditions.

Patient B-AT2 performed significantly worse than controls in the Bottom Face Half condition ($t= 2.357$, $p<0.05$).

7.3 Comments

These results indicate that control subjects perform similarly for memory of isolated upper and lower face halves without an advantage for the upper face half in a memory task with immediate recall after 15 items. All but one patient (R-AT2) demonstrated impaired memory for face halves. Patients in general were impaired in memorizing both the upper and the lower halves of

faces. One apperceptive prosopagnosia patient (R-IOT4) was impaired selectively for the upper face half memory and within normal range for the lower face half memory, which was more like the hypothesized outcome. Interestingly, one associative prosopagnosia patient (B-AT2) was impaired selectively for the lower face half memory with normal performance in the upper face half memory task. Individual patient's data for patients impaired in both the upper and lower face memory show that the degree of abnormality reflected in the probability values is similar for the upper and lower face halves.

These results are consistent with other face memory experiments, the Cambridge Face Memory Test and the Warrington Recognition Memory Test for Faces, (Warrington 1984; Duchaine and Nakayama 2006a), and show that most of the patients were impaired for both the upper and lower face memory.

We had hypothesized that the severe impairments in processing upper face and eye region information with relatively preserved processing of the lower face and the mouth region in feature processing tasks would be reflected in differential performance for memory of upper and lower face halves, whereby apperceptive prosopagnosia patients would have more significant impairments for the upper face memory compared to the lower face part. Surprisingly, only one patient (R-IOT4) showed the expected dissociation.

Chapter 8: Conclusion

Face processing is an extensively studied example of complex visual information processing in the human brain, and provides insights to the functional organization of the human visual system and the human brain. The holistic model of face processing suggests that faces are represented holistically in the human brain. On the other hand, various behavioral studies have demonstrated the superiority of the eye region in identifying faces, indicating a feature salience hierarchy (Garneau 1973; Shepherd 1981; Gosselin and Schyns 2001; Vinette et al., 2004). Moreover, some prosopagnosia patients do not demonstrate this bias for the eye region and have more problems detecting changes made to the eye region of a face than changes to other face regions (Barton 2008a). These findings suggest that there may be differences in the processing of upper and lower region of faces. Despite the large number of studies of face processing in the literature, it is not established whether the behavioral manifestation of the feature salience hierarchy in face perception has neural substrates beyond just processing of low-level physical properties of the visual face stimulus, and if so, where this bias for the eyes emerges in the human brain. The aim of this thesis was to investigate the neural correlates of the feature salience hierarchy in healthy individuals and to determine the relationship between the eye region processing deficits and the anatomical damage in acquired prosopagnosia patients.

8.1 Behavioral Measures of the Feature Salience Hierarchy

In order to investigate the neural representations underlying the behavioral manifestation of the feature salience hierarchy, we utilized an adaptation aftereffects paradigm where we presented upper and lower face halves as adaptor stimuli separately with the goal of obtaining a quantifiable behavioral measure of the feature salience hierarchy through the adaptation

aftereffects generated by these face halves (Chapter 2). Adaptation aftereffects paradigms provide a useful tool for studying face processing mechanisms in the human brain (Clifford et al., 2007; Webster and MacLeod 2011). Since adaptation to a certain stimulus is considered to alter the responses of the neural population that is involved in encoding that particular stimulus, observation of the adaptation aftereffects created by different adaptor stimuli allows 1) to confirm the sensitivity, hence the involvement, of the neural population to that particular aspect of the stimulus that creates the aftereffect, and 2) to infer the processing characteristics of the neural population by measuring the degree of the aftereffect by varying the properties of the adaptor stimuli. Adaptation aftereffects have been demonstrated for various properties of faces, such as identity, expression, gender, and ethnicity (Leopold et al., 2001; Webster et al., 2004). Previous work from our laboratory has also utilized this paradigm in various studies including the dissociation of face identity and face expression processing (Fox et al., 2008). In the current study, we used upper and lower face halves separately as adaptors to investigate their contributions to identity aftereffects.

In the whole face presentation, the eyes could have higher saliency merely due to their higher physical contrast levels compared to other features of the face (Gilad et al., 2008). Therefore, we investigated the ability of the upper and lower face halves to create adaptation aftereffects on the perception of a full face test stimulus when they are presented separately. The full face adapting condition in our experiment generated significant adaptation aftereffects in agreement with previous studies (Webster et al., 2004; Fox et al., 2008). The upper face adapting condition also generated significant adaptation aftereffects in the perception of a full face test stimulus, confirming the feature salience hierarchy for the upper face/the eye region (Figure 2.5). The lower face adapting condition did not generate a significant adaptation aftereffect in the

perception of a full face test stimulus, indicating that even when presented in isolation without any saliency competition from the upper face and the eyes, the lower face half is still not able to generate adaptation aftereffects. In agreement with the holistic face processing models, this result suggests that the identity processing in the human brain is based on the upper face half rather than a homogenous summation of different face parts integrated into the whole face gestalt. Therefore, the dominance of the eye region confirmed by the upper face half's ability to create identity aftereffects for a whole face stimulus suggests that the upper face/eye region contributes the most to the holistic face identity processing. Furthermore, the lack of any significant adaptation aftereffects by the isolated presentation of the lower face half supports the idea that the dominance of the eye region in a full face cannot be explained by its low-level physical properties such as higher contrast compared to other face parts. If that had been the case, then the lower face half should have been able to generate aftereffects on its own when there were no other higher contrast factors competing. An important point to mention is that a low-level image matching is unlikely to be responsible for the aftereffects created by the upper face halves since the sizes of the test stimuli were different than the size of the adapting stimuli throughout the experiment.

After confirming the significant identity aftereffects created by the upper face halves, we next asked whether the eye region itself without the forehead and the face contour would be able to generate identity aftereffects. The eye-band region alone as an adaptor resulted in significant identity aftereffects. However, this identity aftereffect generated by the eye-band region was significantly smaller than the identity aftereffect generated by whole adapting faces. These results show that the eye-band region itself cannot achieve the full range of adaptation aftereffects generated by the whole face, suggesting a crucial but partial contribution of the eye

region to face processing. A question for future investigation is what other face part/feature is necessary to achieve full face level aftereffects. Possibly, the presence of the forehead and the whole face contour is necessary. Our results indicate that there must be partial and differential contribution of different face features or regions in a non-linear additive form. A full parametric, pixel by pixel analysis of aftereffect magnitudes for face parts starting from a single eye with increasing bands of face pixels reaching the full face could prove useful in determining the exact level of contribution of each face part.

In the current study, we instructed subjects to observe the adapting stimulus for as long as it stayed on the screen (5s) without fixating on a particular spot of the face stimulus. However, we did not use eye-tracking to confirm that the subjects did indeed explore all parts of the adapting stimulus. The test stimulus was on the screen only for 500ms, which is a rather short duration to allocate multiple fixations. In order to observe the natural face processing patterns of subjects during the experiment, we did not limit the subjects by forced fixations to a particular location on the stimulus, other than presenting a fixation cross at the center of the screen for 150ms before the test stimulus onset. Additional eye-tracking could be used in the future studies to record the participant's fixation location on the test face stimulus to confirm whether overall uniform observation of the adapting stimuli occurs.

Our findings of differential contribution from the eye region to the identity aftereffects for a face stimulus suggests that there are partial and differential contributions of separate face features to face processing, in agreement with other behavioral studies that indicate better discrimination performance for the eye region of faces (Shepherd 1981; Haig 1985; Fraser et al., 1990; Bukach et al., 2008).

8.2 Neural Correlates of the Feature Salience Hierarchy

In order to characterize the neural correlates of the feature salience hierarchy and the contribution of different face features to the neural signal, we next used an fMRI-adaptation paradigm (Chapter 3). We combined the fMRI-adaptation experiment with a behavioral face perception task in order to confirm the behavioral feature salience hierarchy in our participants. We also used an ideal observer task based on contrast thresholds in order to examine the effect of the low-level visual properties of the face stimuli on the neural signal. The behavioral experiment and the ideal observer analysis were conducted to also investigate whether the neural activity pattern correlated more with the behavioral performance of human subjects or the physical properties of the face stimuli.

Using the fMRI-adaptation technique, we investigated whether the core face processing network regions in the human brain show a feature salience hierarchy similar to that observed in human behavioral studies. We also studied whether the activity pattern in the core face processing regions correlated with the human behavioral performance or the physical properties of the image determined by an ideal observer analysis based on contrast thresholds for discrimination. The results of the fMRI-adaptation experiment reveal that the right and the left FFA show differential sensitivity to different face features. There was a greater release of adaptation when the eyes and the upper face were changed between alternating images. Neither the OFA nor the pSTS showed this sensitivity. The human behavioral performance using the exact same stimuli presented in the fMRI-adaptation experiment showed the expected feature salience hierarchy pattern in a same/different task, where the participants were better in discriminating faces differing in the top half than the bottom half, and better in discriminating changes to the eyes than the mouth. The pattern of release from adaptation for different

conditions in the bilateral FFA was significantly correlated with the human behavioral data, with stronger correlations in the right FFA. The neural signal in the right FFA was significantly more correlated with the human behavioral data than with the low-level physical properties of the images. The right pSTS also showed significant correlations with the human behavioral data. These findings suggest that the feature salience hierarchy demonstrated by human behavioral performance is reflected by the activity patterns of bilateral FFA, and to some extent the right pSTS.

Previous studies had shown that the low-level physical properties such as higher contrast around the eyes contribute to face processing (Gilad et al., 2008), and that responses in the FFA reflect these low-level physical properties (Yue et al., 2011). Another study examining the response properties of FFA has shown that FFA has a generalized response to faces with very different low-level properties and has argued that its response patterns cannot be due to low-level properties of faces but rather to more broad categorical properties of faces (Tong et al., 2000). Using the Bubbles technique to determine whether the human behavioral bias towards the eye region of faces may be due to larger physical differences in the upper half of faces, one study showed that the ideal observer patterns and the human performance were only partially correlated despite the fact that the eye region had the most diagnostic information for face identity for both the human participants and the ideal observer (Gosselin and Schyns 2001). This suggests that the bias for the eye region demonstrated by behavioral performance cannot be solely reflecting the physical properties of the visual face image, in agreement with our findings for the upper and lower halves of faces. Even when the top and bottom halves of faces were equated for physical contrast levels by the ideal observer, our participants were still better in discriminating changes to the top half of a face, indicating a larger perceptual sensitivity to the

aspects of the upper face which cannot be explained completely by the low-level physical properties of the stimulus face. In the fMRI-adaptation experiment, our aim was to reveal the neuroanatomical correlates of the feature salience hierarchy demonstrated by human behavioral performance. While there are other studies that show fMRI-adaptation by individual face features or face parts (Andrews et al., 2010; Harris and Aguirre 2010; Liu et al., 2010), the relative contribution of each face part to the neural signal and how this relates to the behavioral performance and the physical stimulus properties has not been studied previously.

Previous studies have established that the core face processing network regions show adaptation in response to the repeated presentation of the same face image (Grill-Spector and Malach 2001; Schiltz and Rossion 2006; Fox et al., 2009a; Andrews et al., 2010). Two studies reported a release of adaptation in the right FFA when either the top or the bottom half of the face changed (Schiltz and Rossion 2006; Schiltz et al., 2010). In our study, in terms of the upper and lower face conditions, we found release of adaptation in the right FFA when the top half of the face changed and in the left FFA when the top or the bottom half of the face changed. Methodological differences might have caused these inconsistent results. In the two studies by Schiltz and colleagues, subjects were required to fixate on the top face half while performing a composite face task. In our study, subjects were free to fixate where they liked on the faces. In terms of individual face features, we found a release of adaptation in the FFA bilaterally when the eyes changes but not when the nose or the mouth changed. These findings are consistent with a previous finding of greater release of adaptation in response to changes to the eyes than to the mouth (Harris and Aguirre 2010).

We did not find any adaptation effect in the OFA in response to repetition of any condition including the same whole face in our initial analysis. Therefore, we performed a *post*

hoc examination of the more face-specific voxels in the right OFA, which showed a release of adaptation when the eyes or the top face half changed. This indicates that effects similar to those observed in the FFA might also occur in the OFA, and the lack of robust adaptation effects in the OFA could be due to the specific fMRI- adaptation paradigm we used where we presented alternating stimuli with the same face and the different condition in each block (ABABABAB) based on the findings from Davies-Thompson et al., that two alternating images are sufficient to obtain adaptation (Davies-Thompson et al., 2013). This could have resulted in weak adaptation since the same stimuli was not repeated continuously for the whole block which was the case in most previous protocols (Grill-Spector et al., 2006). A recent study reported sensitivity in the OFA but not in FFA for face parts, which was highest for the two-eye stimuli (Arcurio et al., 2012). This finding is not consistent with other studies (Liu et al., 2010; Harris and Aguirre 2010) and our study. It should be noted that the Arcurio study presented the isolated features embedded in a gray background, whereas our study as well as others present face parts in the oval whole face contour background. This could be an important factor indicating that the FFA requires a whole face contour shape for optimal response, whereas OFA is more sensitive to isolated presentation of face parts as indicated by other studies (Liu et al., 2010).

In our study, the pSTS also did not show any adaptation effects. In fact, the BOLD signal changes were very low in pSTS to begin with. Given the fact that our faces differed in identity rather than expression, this is consistent with other studies which show that the pSTS is not sensitive to changes in face identity (Andrews et al., 2010) unless the subjects are involved in a face expression task (Fox et al., 2009a). There were also no adaptation effects in the fusiform controls regions FBA and the FBA*, suggesting that the activity pattern changes observed in

FFA for the eyes and the upper face half is not due to the general neural processing properties of the fusiform gyrus.

Whether the neural signals in the core face processing network reflect the feature salience hierarchy demonstrated by human behavioral performance, and how they correlate with the human behavioral data and the physical properties of faces has not been studied previously. In the current study, combining fMRI data with the behavioral data from the same subjects who participated in the fMRI experiment and the ideal observer contrast threshold data based on the low-level physical properties of faces, we conducted a parametric correlation analysis. This correlation analysis suggests that the feature-salience hierarchy is generated by activity in a network of regions, which includes the FFA bilaterally and the right pSTS, rather than by activity in one single region. Peak responses in the bilateral FFA were correlated with the human behavioral efficiency scores, but not with the ideal observer contrast thresholds for discrimination. The right pSTS activity was also correlated with the human behavioral efficiency scores, suggesting that the feature salience hierarchy effects demonstrated by human perceptual performance are evident in the face processing network. This is consistent with previous studies which showed release of adaptation in the right FFA only when the changes to the face image were perceived by the subjects as changes in face identity (Rotshtein et al., 2005; Fox et al., 2009a).

The fact that stronger correlations with the human behavioral efficiency scores were observed in the right FFA compared to the left FFA is consistent with a converging body of evidence for right hemisphere dominance in face processing (Sergent and Bindra 1981; Gazzaniga and Smylie 1983). Neuroimaging studies show that activation in response to faces is larger in area, more statistically significant, and more consistently identified across subjects in

the right than in the left hemisphere (Kanwisher et al., 1997; Fox et al., 2009b). Acquired prosopagnosia also results mainly from damage to the right or bilateral occipitotemporal cortex (de Renzi 1986; Barton 2008a). On the other hand, our study also revealed significant correlations between the left FFA and the human behavioral efficiency scores. The left FFA also showed an adaptation effects pattern similar to the right FFA reflecting the feature salience hierarchy. As a result, it is not clear whether the feature-salience hierarchy is also a product of this right hemisphere dominant core face processing network, or a product of feature-based strategies that may lateralize to the fusiform regions in the left hemisphere (Hillger and Koenig 1991; Rossion et al., 2000).

An interesting question for future neuroimaging study is which regions of a face has to change in order to achieve release from adaptation in the core face processing network. It should be noted that similar to our behavioral adaptation aftereffects study, in our combined fMRI-adaptation and behavioral study, subjects were free to fixate on any part of the face during both the behavioral and the fMRI experiments. Yet, fixation preference itself is an important component of the human perceptual experience of faces. Therefore, allowing subjects to move their eyes as they wish is ecologically the most valid approach. Fixed, forced, or randomly placed fixation on a face could interfere with natural perception of faces. Nevertheless, if fixation patterns were responsible for the feature salience hierarchy patterns observed in our neuroimaging data, the same patterns would be expected in the occipital pole activations. Since this region represents foveal vision, fixation on the eyes alone would have meant that the eyes were the dominant input in this retinotopic region, and hence we would have seen this reflected in the MR signal for the occipital pole. Our studies do not show any such differential signal for the eyes in the occipital pole.

Our study is the first systematic comparison of the fMRI-adaptation responses in the core face processing network across changes to face parts while correlating this signal to both the physical and perceptual properties of the face stimuli. Our behavioral study confirmed the feature salience hierarchy for human face perception, in which the top half of the face is more salient than the bottom half, and the eyes are more salient than the nose and mouth. Our fMRI-adaptation experiment found that activity in the FFA reflected the human behavioral data, but not the low-level physical properties of the face stimuli. There was also a correlation of the right pSTS with human behavioral performance. These results suggest that the feature-salience hierarchy reflects activity within a network of face responsive regions and points to the right hemisphere dominance of the face processing network.

8.3 Task Dependency of the Feature Salience Hierarchy

The mechanisms that generate the feature salience hierarchy in the FFA and in behavioral performance remain unclear. Results from our neuroimaging study show that the low-level physical differences across face regions cannot totally account for the feature salience hierarchy. Attention or other top-down processes may play a role, particularly since there is considerable evidence that the relative importance of different face regions varies according to the task (Malcolm et al., 2008). Healthy individuals observing faces scan faces in a task dependent manner. They look at the eyes and the upper face half while performing a face identity task (Henderson et al., 2005; Barton et al., 2006), and shift their gaze to other face regions when the task involves judgments of expression (Smith et al., 2005; Malcolm et al., 2008) or other types of judgments such as gender (Schyns et al., 2002). This task dependency may be stimulus-dependent beyond the type of the task performed. For example, a recent study examining the eye

movement patterns of healthy individuals watching videos of faces revealed that the gaze of the participants were dynamically directed to the eyes, the mouth, or the nose (Vo et al., 2012). They suggested that the gaze is allocated to different parts of a face in a task and activity dependent manner. If a face in a video was seen to be speaking, then the viewers directed their gaze to the mouth. Another study argued that fixations to the eyes in social scenes are explained by the drive to deduce social information rather than the overall saliency values within the scene (Birmingham et al., 2009).

There are other types of highly diagnostic and socially salient information from the eye region of faces beyond just face identity. A very strong example is the detection of fear from the eyes (Adolphs et al., 2005). Adolphs and colleagues have shown that the inability to make use of information from the eye region in a patient with bilateral amygdala damage results in failure to recognize fearful faces. This patient is able to recognize fear when she is explicitly instructed to look at the eyes. Furthermore, the mere presence of masked fearful eye whites is enough to cause large activations in the amygdala (Whalen et al., 2004). Similarly, for social interactions, detection of gaze direction is equally important as demonstrated by the difficulties experienced by individuals with autism (Leekam et al., 1998; Tanaka and Sung 2013). Previous studies have indicated the STS as the neural correlate of gaze direction detection (Allison et al., 2000; Hoffmann and Haxby 2000). An interacting network of regions which includes top-down mechanisms may have resulted in the feature salience hierarchy for a multipurpose problem solving rather than just for face identity in the human brain.

In terms of top-down processes, an elegant demonstration of their recruitment for face processing was demonstrated in a prosopagnosia patient who has an intact right FFA but damaged right OFA (Righart et al., 2010). This study showed that the patient's right FFA was

activated in response to noise-only images without the presence of face stimuli by merely instructing the patient to detect faces. Another elegant study reveals the involvement of the frontal eye field on the activation of motion responsive area hMT+ and the FFA in a task-dependent manner (Heinen et al., 2013). When the right frontal eye fields of subjects were stimulated by transcranial magnetic stimulation, there was an increase of the BOLD signal in the hMT+ during attention to the motion and in the FFA during attention to the faces while viewing moving dots superimposed on face stimuli. Another study aiming to examine the top-down face mechanisms via illusory face detection revealed activation of the core and extended face processing regions, and additionally the left anterior cingulate cortex, bilateral orbitofrontal cortex, and the left dorsolateral prefrontal cortex (Li et al., 2009). Taken together, these studies support the involvement of a network of brain regions in top-down modulation of face perception. Future studies are needed to disclose the specific role of these regions in the feature salience hierarchy.

8.4 Insights from Acquired Prosopagnosia

Prosopagnosia is defined as the inability to recognize familiar faces (Bodamer 1947; Barton 2003). Right-hemisphere or bilateral damage to the inferior occipitotemporal cortex or to the anterior temporal cortex can result in acquired prosopagnosia. The apperceptive variant of acquired prosopagnosia involves impairments of mainly structural encoding of faces, whereas the associative variant involves mainly problems of face imagery and face memory (Damasio et al., 1990; Barton 2008a; Davies-Thompson et al., 2014). The apperceptive variant of acquired prosopagnosia is commonly caused by damage to the fusiform gyrus which may span the FFA (Damasio et al., 1990; Barton et al., 2002; Barton 2008a). The significant correlation of the

feature salience hierarchy demonstrated by healthy human observers with the activity in the FFA in our fMRI-adaptation experiment suggests that the FFA may play an important role in the feature salience hierarchy. Involvement of FFA in the feature salience hierarchy in turn suggests that acquired prosopagnosia patients with fusiform lesions which encompass the FFA will present difficulties in processing eye region specific information. Given the likelihood of loss of FFA function in apperceptive prosopagnosia patients with fusiform damage, the disruption of the feature salience hierarchy could be the crucial element of their face processing impairments. Previous studies have shown that the structural face processing deficits in apperceptive prosopagnosia are manifested by impaired integration of the spatial arrangements of face features (Barton et al., 2002; Joubert et al., 2003; Barton 2008a), as well as impaired holistic face processing (Bukach et al., 2006, 2008; Busigny and Rossion 2011). Some apperceptive prosopagnosia patients have demonstrated poor discrimination performance for the eye region of faces (Caldara et al., 2005; Bukach et al., 2006, 2008; Barton 2008a; Rossion et al., 2009). We studied a cohort of 10 acquired prosopagnosia patients with inferior occipitotemporal cortex damage and anterior temporal cortex damage and characterized the anatomical damage, status of the core face processing network, neuropsychological profile, face perception and face memory abilities, face feature processing, and face scanning patterns in order to establish the relationship between the anatomical damage and the functional face processing deficits.

The acquired prosopagnosia patients in the study cohort were recruited through the www.faceblind.org website. We confirmed their face recognition deficits on a Famous Faces Familiarity Task (Chapter 4). Additionally, we classified the patients as apperceptive or associative prosopagnosic based on their performances on the face perception and face memory tests, and ultimately on their lesion types. In agreement with previous suggestions, the

apperceptive patients in our cohort presented with impaired performance on the face perception tests such as the Benton Face Recognition Test and the Cambridge Face Perception Test. Most of the apperceptive patients were also impaired in the face memory tasks. This is expected, since current face processing models suggest a hierarchical processing stream for faces which starts with the structural encoding of faces, and continues with stages of face identity and face expression processing followed by stages of face memory integration (Haxby et al., 2000). Therefore, proper encoding of the structural properties of faces is required for face memory. When we tested the apperceptive patients for their face imagery abilities, they generally performed well similar to controls, indicating intact face memory stores, except for the situations where there were additional anterior temporal lesions on top of the inferior occipitotemporal lesions, such as the case of Patient B-ATOT1 and Patient B-ATOT2. The associative prosopagnosia patients in our cohort performed relatively well on the face perception tests, but they were impaired in the face memory tests. When we tested their face imagery, they were all impaired, indicating impaired access to face memory stores.

Previous studies indicate that the second-order configural processing of face features are a crucial component of face processing in healthy individuals (Diamond and Carey 1986; Rhodes 1988). Studies have indicated that impaired perception of the second-order relations of facial features occurs as a result of damage to the fusiform gyrus in prosopagnosia (Sergent and Signoret 1992; Barton et al., 2002; Joubert et al., 2003; Barton 2008a; Riddoch et al., 2008; Busigny et al., 2010). In order to discover the type of structural information and feature that is not properly processed by each patient in the cohort, we conducted feature change detection tests (Chapter 5). These tests examined the feature processing and the second-order relation processing of face features, measuring the ability of the patients to detect changes to different

structural components of a face in order to dissect the face feature or second-order relation that is not properly processed. In our first face feature experiment, we tested individual changes to face features (eye shape and position, mouth shape and position, chin shape, forehead shape) in order to explore the features that were not being properly processed by the patients. Additionally, we manipulated task difficulty and demand by varying the number of changes possible in a block. In the first version, only one change type was possible and the patients were informed what change was possible before they started the experiment so that they could focus on that feature. Results from our patient cohort for the 1-change condition show that, all of the apperceptive prosopagnosia patients are impaired in detecting changes to the eyes even when they were informed where the change on the face would take place. R-IOT1, B-IOT2, and B-ATOT1 were selectively impaired for the changes to the eyes with normal range performance in detecting changes to all the other features, but R-IOT4, L-IOT2, and B-ATOT2 were also impaired for the mouth changes in the 1-change condition. None of the associative prosopagnosia patients had any impairment in detecting changes to face features in the 1-change only block. When we presented two changes at a time with possible changes either to the eye region (eye shape or eye position) or to the mouth region (mouth shape or mouth position), all of the apperceptive prosopagnosia patients were impaired in detecting changes in both the eye and the mouth region, except for R-IOT1 who was selectively impaired for the eye region changes with preserved mouth change detection. Again, no impairments were measured for the associative prosopagnosia patients except for B-AT1 who was impaired in detecting changes to the eye and mouth. These results indicate that having to process two possible changes at a time was already overloading the processing abilities of the apperceptive prosopagnosia patients, and challenging some of the associative prosopagnosia patients. Finally, when the difficulty of the task was

increased by presenting any of the six possible changes at different face locations in the 6-changes condition, all apperceptive prosopagnosia patients were impaired for eye and mouth changes, except for B-IOT2 who showed selective impairment for detecting changes to the eyes. For the 6-changes condition, two of the associative prosopagnosia patients were also impaired. These results indicate that when there is a larger task demand, all apperceptive patients fail to detect feature changes on different regions of a face. However, this is mostly true for the apperceptive patients with milder deficits such as R-IOT1 who showed selective impairments for detecting changes to the eye position in 1- and 2-change conditions; the total number and the location of possible changes in a block did not alter the outcome of the performances of apperceptive patients with more severe deficits such as L-IOT2, as they were impaired in all blocks of the experiment for detecting changes to the eyes. Associative prosopagnosia patients were still mostly within the normal range for detecting the changes, except for R-AT3 who failed to detect changes to the eye shape and position, and B-AT1 who failed to detect changes to the forehead.

In our second feature processing experiment, we examined the processing of the second-order relations of face features and feature luminance separately for the upper and lower face in order to further explore the eye region specificity of the impairments as indicated by previous studies (Caldara et al., 2005; Barton 2008a; Bukach et al., 2008). All patients in the apperceptive prosopagnosia group were impaired in detecting changes to the relative positions of the two eyes. Some apperceptive patients were also impaired in detecting changes to the relative position of the mouth with respect to the nose. All patients in the associative prosopagnosia group performed well for detecting the changes to the second-order relations of the face features.

Results from the face feature processing experiments for individual patient data indicate that the patients are impaired in processing both the eyes and the mouth, yet the impairments for the eye region are more severe than the impairments for the mouth region. When the tests were administered in an unlimited duration version, patients were able to obtain high accuracy levels similar to the controls. However, in order to obtain accuracies similar to healthy controls, they spent significantly longer periods of time per trial. Patients with inferior occipitotemporal cortex lesions consistently demonstrate larger impairments in the eye region processing compared to patients with anterior temporal lobe lesions. In certain cases, such as Patient B-IOT2, visual field defects could have had an effect on the latencies since the patient may require additional time to observe the whole stimulus. However, even when we allow for this effect on the latencies, Patient B-IOT2 was still impaired for accuracy in the eye change conditions selectively. At the group level, patients with inferior occipitotemporal lesions classified as apperceptive prosopagnosia performed significantly worse than the healthy controls for both the eye and the mouth changes, whereas the patients with anterior temporal lesions did not perform significantly worse than the healthy controls. The apperceptive prosopagnosia patients were also significantly worse than the associative prosopagnosia patients for detecting changes to the eyes. The eye region impairments of the apperceptive prosopagnosia patients were also significantly larger than their mouth region impairments. Our behavioral feature processing studies in our prosopagnosia cohort confirmed the general larger deficiency the patients have in processing changes to the eye region, and established the significantly larger eye region processing impairments in the apperceptive variant of prosopagnosia. These results are consistent with previous studies of prosopagnosia (Barton et al., 2002; Bukach et al., 2006, 2008; Barton 2008a; Rossion et al., 2009) and extend them to a relatively large cohort of prosopagnosia. Overall, the inability of

prosopagnosia patients to process changes to the eye region of a face was associated with their lesion location, whereby the apperceptive prosopagnosia patients with occipitotemporal cortex damage and loss of FFA function demonstrated significant impairments and the associative prosopagnosia patients with anterior temporal cortex damage performed similar to controls.

Previous eye movement studies have indicated that healthy subjects look more at the eyes while identifying faces (Henderson et al., 2005). It has also been reported that some prosopagnosia patients have lost this normal preference for fixating on the eyes (Caldara et al., 2005; Barton et al., 2007b; Van Belle et al., 2010). We studied the face scanning patterns in healthy controls and in our patient cohort in a face learning and memory task while we recorded their eye movements in order to investigate how the behavioral bias for the eye region is reflected in the face scanning patterns in healthy subjects, and whether this pattern is altered in prosopagnosia patients who demonstrate deficits in processing the eye region of faces. Consistent with previous studies, our face scanning experiment revealed that healthy subjects spend significantly more time looking at the upper halves and the eyes of faces than the lower halves and the mouth when the task is either to learn or to recognize faces (Barton et al., 2006; Malcolm et al., 2008). These results strengthen the previous evidence that healthy individuals base their face identity decisions on diagnostic information from the upper face half and the eye region of faces (Garneau 1973; Fisher and Cox 1975; Shepherd 1981; Vinette et al., 2004). Our patient data shows that they spend more time studying upper regions of faces similar to the scanning patterns of the healthy controls, yet they tend to spend significantly more amounts of total time studying the faces when they are given unlimited time. All patients except for B-AT1 scanned the upper face significantly more than the lower face in the learning phase. These relatively normal face scanning patterns indicate that a failure to inspect the upper face or the eye

region with the fovea is not the cause of the greater problems in discriminating features and spatial relations in the eye region. In terms of total fixation durations, patients showed a similar pattern to the healthy controls in the recognition phase, where they spent less time for faces they had already seen in the learning phase. In the recognition phase, in addition to Patient B-AT1, Patient B-IOT2 also showed the abnormal pattern of scanning the mouth region more than the eyes. These results are not fully consistent with previous reports of abnormal face scanning patterns in prosopagnosia (Barton et al., 2007b; Orban de Xivry et al., 2008; Van Belle et al., 2010) and show that in a learning and memory task with unlimited viewing durations, patients scan the faces similar to healthy controls with a bias for the upper face/eye region. There could be possible effects of task and analysis differences. For example, previous studies which showed differences in scanning patterns involved a task of famous versus unfamiliar discrimination (Barton et al., 2007b) or personally familiar face identification (Orban de Xivry et al., 2008; Van Belle et al., 2010) where patients may have resorted to the lower face scanning strategy. In our experiment, we used unfamiliar faces in a learning and memory task. We also allowed the patients to scan the faces for as long as they wished. This might have had an overall normalizing effect of scanning patterns. Alternatively, a lower face scanning pattern may be an individual strategy adopted by some patients such as B-AT1 in our current study and PS in Van Belle and colleague's study (Van Belle et al., 2010), but may not be shared by all prosopagnosia patients. Additionally, except for the Barton study, in these studies the scanning patterns were analyzed only for the correct trials when the patients identified the faces successfully (Orban de Xivry et al., 2008; Van Belle et al., 2010). The memory task of our face scanning experiment showed that patients had a lower discrimination power than the controls for the learned faces, despite the fact that they studied the faces for significantly longer durations than the controls in the learning

phase of the experiment. Therefore, the differences between the findings are most likely due to the task and analysis differences. When given unlimited time, patients study all regions of faces and allocate more fixations to the upper face and the eye region similar to the controls, yet they spend significantly longer amounts of time to study the faces. This longer duration of studying stimuli is also observed in the unlimited versions of the feature processing experiments where they obtain accuracies similar to those of controls when they are allowed unlimited viewing durations (Chapter 4). However, in the face learning and memory task, the bias for the upper face and the eye region and long durations of studying does not have any positive affects for their memory accuracy and they still have significantly lower discrimination power compared to the controls. On the other hand, when they are given only limited viewing durations in other experiments, patients may develop the strategy of studying the mouth region. In fact, anecdotally almost all of our patients report that the eyes are not very informative and that they make the most use of hair or other distinct characteristics such as a big nose or a mole in their attempts to identify faces in real life.

Despite the fact that they allocate more time studying the upper half of a face when given unlimited study duration, the apperceptive prosopagnosia patients show larger impairments selectively for the eyes in feature change detection tasks. These results suggest that the eye region processing impairments are unlikely to occur due to the disruption of top-down attention mechanisms which cause the patients to avoid the salient eye region of faces, but are more likely caused by the inability to integrate information from the eye region of faces due to defects or the total loss of function of FFA and its interactions within the face processing network. It has been previously suggested that the patients may develop the strategy of looking at other features or the lower face with the hopes of finding cues that could be used as identifiers since the most

informative area of the face that is used for optimal face processing in healthy individuals is not useful to the patient (Ramon and Rossion 2010). Our results support this view showing that the patients are not inherently avoiding the eye region but they may resort to other face regions as a part of a task-dependent strategy. Our patients looked at the upper face half and the eyes in the eye-tracking experiment, yet in the face feature processing experiments they still failed to detect changes to the eyes even when they were informed where the changes on the face would take place. For the future, it would be more informative to simultaneously record the eye movements of the patients in both the limited and unlimited viewing duration versions of the face feature processing experiments in order to compare the eye region processing deficits and the scanning patterns directly.

Feature salience hierarchy demonstrated by the healthy individuals was reflected in our behavioral adaptation aftereffects experiment where the upper face halves and the eye region of faces were able to generate significant identity aftereffects, but the lower face halves were not (Chapter 2). Finally, we examined the performances of healthy controls in a memory task for half faces in order to explore whether healthy subjects are better in learning and remembering upper halves of faces than the lower face halves. Additionally, some prosopagnosia patients have been reported to have preserved mouth region processing, and our results from the feature processing experiments in our patient cohort confirmed this relatively preserved or relatively mildly impaired mouth region processing of faces (Chapter 5). Furthermore, our face scanning experiment demonstrated that acquired prosopagnosia patients do show the normal pattern of looking at the upper half/eye region of face when they are asked to study faces, indicating that the pattern of perceptual deficits showing greater problems discriminating features and spatial relations in the eye region does not stem from a failure to inspect the upper face or the eye region

with the fovea in these patients. Therefore, in the half faces memory task we also asked whether the preserved lower face and mouth region processing in the patients could be an advantage for the lower face in a face memory task administered separately for upper and lower face halves. Results from our control group showed that subjects perform similarly for memory of upper or lower face halves. All but one patient (R-AT2) had impaired half face memory. Most of the patients were similarly impaired for upper and lower face half memory. These results show that apperceptive patients in general do not perform better for lower face half memory and suggest that despite their larger impairments for the processing of eye region information, patients are equally impaired in integrating identity information from the lower half of faces.

Given the rarity of acquired prosopagnosia, our study is an extensive examination of a relatively large acquired prosopagnosia cohort of 10 patients with neuropsychological, behavioral, and neuroimaging experiments. We compared the patients' structural neuroimaging, functional neuroimaging, face feature processing, face scanning pattern, half face memory performance results with their face perception and face memory scores in order to reveal any links between the lesions, the loss of functional face processing network, and the behavioral face processing and memory scores (Table 8.1). Our studies revealed that the apperceptive prosopagnosia patients with inferior occipitotemporal cortex lesions which include the fusiform gyrus are in general impaired in feature processing and processing of the second-order spatial relations of face features. However, they present with significantly larger impairments for the eye region of faces. All of our patients with occipitotemporal lesions have severe eye region processing deficits and loss of function of the right FFA. This is the first study to show that the second-order feature processing deficits and specifically larger eye region processing deficits are consistently associated with damage to the fusiform gyrus and loss of function in the right FFA.

This is strong evidence for the dissociation of the two variants of prosopagnosia and for designating the right FFA as the primary neural substrate of second-order feature relation processing of the eye region. That said, it should be noted that the dissociation of the feature processing patterns of the two variants is not absolute, and some associative prosopagnosia patients may demonstrate minor face processing deficits beyond their face memory deficit. All of our associative prosopagnosia patients with anterior temporal lobe lesions had significant activation in the FFA in response to faces. Despite preserved FFA activation, some of these patients still demonstrated minor eye region processing deficits, especially when the task demand was high. Recent studies which acquired functional neuroimaging data at a higher resolution of 1.5.mm voxel size revealed the consistent presence of two differentiable clusters in the fusiform gyrus, a mid-fusiform cluster and a posterior fusiform cluster in healthy subjects, as opposed to a single FFA cluster generally localized with data acquired at 3mm slice thickness (Weiner and Grill-Spector 2010, 2013). Future studies acquiring functional face localizer data at the higher resolution of 1.5mm voxel size would be useful to differentiate whether the associative prosopagnosia patients who have intact FFA activation have both of these anterior and posterior clusters or only the posterior cluster intact in order to establish a link between the functional status of their FFA clusters and their mild deficits in second-order feature relation processing under high task demand. Additionally, findings from developmental prosopagnosics also indicate a similar eye region deficit despite the lack of any brain damage in these individuals (DeGutis et al., 2012). The face processing difficulties experienced by developmental prosopagnosics has been suggested to result from network connectivity deficits (Thomas et al., 2009). Furthermore, there is recent evidence indicating involvement of other anterior temporal (Kriegeskorte et al., 2007; Nasr and Tootell 2012) and even prefrontal cortex areas in face processing (Chan and

Downing 2011). A recent study using multivariate pattern analysis has confirmed the FFA's role in face identity, and has showed the involvement of a network of cortical regions in a face individuation task (Nestor et al., 2011). Another recent study examining the face processing network in developmental prosopagnosia has revealed decreased activation of the anterior temporal cortex with intact activations in the posterior core face processing regions in these individuals, emphasizing the importance of the anterior temporal cortex and its connections to the posterior core face processing areas in face identification (Avidan et al., 2014). Therefore, future studies examining the extended face processing network in addition to the core face processing network in more detail in healthy individuals and in individuals with developmental prosopagnosia are necessary in order to establish the network connectivity patterns for face processing in the human brain and to specify the activity distribution in the network for tasks requiring eye region processing.

Our face scanning experiment shows that the patients do not have a general issue of avoiding the eye region of faces, yet they are impaired in the discrimination and encoding of the second-order spatial relations of the eye region of faces. Therefore, they would not benefit from a training regimen that forces them to look more at the eyes which could be beneficial for children with autistic spectrum disorders (Tanaka and Sung 2013). However, training programs targeting the perception of inter-ocular distance may be useful to patients with occipitotemporal lesions since this is the principal severe deficit demonstrated consistently by these patients as previously suggested (Barton 2008a) and confirmed in our current study. Our laboratory is currently developing such perceptual learning programs for both acquired and developmental prosopagnosics. Given the relatively preserved second-order feature and eye region processing in

PATIENT / TEST	R-IOT1	R-IOT4	L-IOT2	B-IOT2	B-ATOT1	B-ATOT2	R-AT2	R-AT3	B-AT1	B-AT2
Lesion	right inferior occipitotemporal	right inferior occipitotemporal	left middle fusiform gyrus	bilateral occipitotemporal	right anterior temporal & occipital; left fusiform gyrus	right anterior temporal; bilateral occipitotemporal	right anterior temporal & fusiform gyrus	right anterior temporal	bilateral anterior temporal & fusiform gyrus	bilateral anterior temporal & right frontal
Visual Fields	left superior quadrantanopia	left superior quadrantanopia	full OU	severe defects with left inferior central island of vision	subtle left superior paracentral quadrant defect	full OU	full OU	full OU	full OU	full OU
right FFA	**damaged**	**damaged**	**damaged**	**damaged**	**damaged**	**damaged**	intact	intact	intact	intact
left FFA	intact	intact	**damaged**	**damaged**	intact	low activation	intact	intact	intact	intact
right OFA	**damaged**	intact	**damaged**	intact	low activation	low activation	intact	intact	intact	intact
left OFA	intact	intact	intact	**damaged**	intact	intact	intact	intact	intact	intact
Face Perception BFRT	normal	normal	**impaired**	**impaired**	normal	**impaired**	normal	**impaired**	normal	normal
Face Perception CFPT	**impaired**	**impaired**	**impaired**	**impaired**	**impaired**	**impaired**	normal	normal	normal	**impaired**
Face Memory WRMT_F	**impaired**	normal	**impaired**	**impaired**	**impaired**	**impaired**	**impaired**	**impaired**	**impaired**	**impaired**
Face Memory CFMT	normal	**impaired**	**impaired**	**impaired**	**impaired**	**impaired**	**impaired**	**impaired**	**impaired**	**impaired**
Eye Region Processing Low task demand	**impaired**	**impaired**	**severely impaired**	**impaired**	**severely impaired**	**severely impaired**	normal	normal	**slightly impaired**	normal
Eye Region Processing High task demand	**severely impaired**	**impaired**	**severely impaired**	**severely impaired**	**severely impaired**	**severely impaired**	**impaired**	**impaired**	normal	**impaired**
Other Feature Processing Low task demand	normal	**impaired**	**severely impaired**	normal	**impaired**	**impaired**	normal	normal	**slightly impaired**	normal
Other Feature Processing High task demand	**impaired**	**impaired**	**impaired**	normal	**impaired**	**severely impaired**	normal	normal	normal	normal
Half Face Memory Upper	-	**impaired**	**impaired**	**impaired**	-	**impaired**	normal	**impaired**	-	normal
Half Face Memory Lower	-	normal	**impaired**	**impaired**	-	**impaired**	normal	**impaired**	-	**impaired**
Face Scanning Learning	-	normal long scan time	normal long scan time	normal long scan time	-	normal long scan time	normal long scan time	normal long scan time	**abnormal** long scan time	normal
Face Scanning Recognition	-	normal	normal	**abnormal** long scan time	-	normal	normal	normal	**abnormal**	normal

Table 8.1 Summary of Experiments and Patient Profiles.

patients with anterior temporal lobe lesions, other training programs may need to be developed for their rehabilitation.

8.5 Future Directions

One limitation that is common in most face perception studies including ours is the utilization of static stimuli in the laboratory setting. Application of face recognition tests using dynamic face stimuli may significantly improve our understandings of face processing both in healthy individuals and prosopagnosia patients. Our laboratory and many others already use dynamic functional face localizers which consistently achieve better activation of the face processing network than static localizers in neuroimaging (Fox et al., 2009b). Extending this to behavioral face processing tests is already in progress in our laboratory in a face recognition task that combines dynamic and static face presentation blocks in order to investigate whether information from the dynamic presentation of faces can provide face identity cues for prosopagnosia patients (Raboy et al., 2010). Using dynamic face stimuli for the investigation of face scanning patterns in prosopagnosia can also be more informative than using static face stimuli.

As mentioned in Section 8.2, another very important functional role of the eye region of faces is evident for detection of gaze direction which is linked to activity in the STS (Allison et al., 2000; Hoffman and Haxby 2000). In our neuroimaging study investigating the neural correlates of feature salience hierarchy, we observed significant correlations between the right pSTS activity patterns and the human behavioral perceptual data. However, since our stimuli were varied in the identity domain of faces, we obtained only low level of activation in the pSTS. Yet, the significant correlation of the right pSTS activity indicates an involvement in the feature salience hierarchy, most likely via top-down mechanisms. In order to investigate the top-down

modulation of the feature salience hierarchy, face responsive areas in the ventral temporal cortex and the frontal cortex should be further examined using neuroimaging (Kriegeskorte et al., Nasr and Tootell 2012), perhaps with the application of an illusory eye detection (Li et al., 2009) in order to activate the top-down mechanisms involved without engaging the bottom-up mechanisms which are expected to be activated only in response to presence of real stimulus. Combining neuroimaging studies with EEG studies in order to obtain the temporal pattern of these activations would help explore the top-down mechanisms of the feature salience hierarchy.

As already mentioned in Section 8.3, acquisition of functional data at a higher resolution of 1.5mm voxel size may be more suitable for investigating the status of the face processing network in acquired prosopagnosia patients and other aspects of face processing such as the neuroanatomic correlates of the feature salience hierarchy that cannot be clarified by functional data acquisition at a resolution of 3mm in healthy individuals (Weiner and Grill-Spector 2013). Given the promising results from recent studies revealing the involvement of a network of cortical regions in addition to the FFA in a face individuation task using multivariate pattern analysis (Nestor et al., 2011), future studies examining the core and the extended face processing using multivariate pattern analysis in combination with high resolution fMRI data in healthy individuals and in individuals with developmental prosopagnosia are necessary in order to establish the network activation patterns for face processing in the human brain and deciphering the activity distribution in this network for tasks requiring eye region processing. Additionally, diffusion tensor imaging based on white matter imaging is also proving to contribute to our improved understanding of the connectivity of the cortical visual areas involved in face processing (Thomas et al., 2009; Scherf et al., 2013; Avidan et al., 2014). Despite the fact that the presence of lesions limit the application of certain neuroimaging methods in prosopagnosia

patients currently, improvements in white matter and macromolecular tissue volume imaging are very encouraging for possible applications of these methods in patients with brain lesions in the future (Phillips et al., 2012; Mezer et al., 2013).

Results from our patient cohort reveal significantly more impaired eye region processing in patients with FFA damage. These results suggest that different strategies for rehabilitative face training of patients with different lesion types and functional loss may be necessary. Patients with inferior occipitotemporal lesions and the functional loss of FFA may benefit from perceptual learning paradigms aiming to improve processing of the face features and their spatial relations. Currently, there are no specific training programs for patients with anterior temporal lesions. Based on our results revealing relatively preserved feature processing and second-order feature relation processing in these patients, new rehabilitation programs aimed at targeting different aspects of face processing other than feature processing need to be developed.

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Appendices

Appendix A : Neuropsychological Battery

Handedness A version of the Edinburgh Handedness Inventory was used to assess the laterality of handedness (Oldfield, 1971).
General Intelligence Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) Verbal IQ, Performance IQ, Full scale IQ
Executive Function Trail Making Test (Tombaugh, 2003) Trails A, Trails B
Memory Verbal memory Word List (Wechsler, 1997) Immediate recall, Delayed recall (20 mins) Digit span (Wechsler, 1997) Forward, Backward Episodic memory Story A (Wechsler, 1997) Immediate recall, Delayed recall (20 mins) Spatial memory Corsi Block Test (Wechsler, 1997) Forward, Backward
Attention Visual Search (Spinnler and Tognoni, 1987) Stars Cancellation Test (Wilson et al., 1987)

Visual-perceptual abilities

Visual Object and Space Perception battery (Warrington and James, 1991)

Object perception

Screening test, Incomplete letters, Silhouettes, Object decision, Progressive silhouettes

Space perception

Dot counting, Position discrimination, Number location, Cube analysis

Judgement of line orientation (Benton et al., 1983)

Hooper Visual Organization Test (Hooper, 1983)

Boston Naming Test – Short and Long Form (Kaplan et al., 1983)

Face Perception

Florida Affect Battery Facial perception (Bowers et al., 1992)

Identity Discrimination, Affect Discrimination, Name Affect, Select Affect, Match Affect

Imagery abilities

Mental Rotation Test (Grossi, 1991)

Road Map Test (Money et al., 1965)