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The specificity of visual recognition impairments following focal brain damage

Jessica Lee Wisnowski
University of Iowa

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THE SPECIFICITY AND SEVERITY OF VISUAL RECOGNITION IMPAIRMENTS
FOLLOWING FOCAL BRAIN DAMAGE

by

Jessica Lee Wisnowski

An Abstract

Of a thesis submitted in partial fulfillment
of the requirements for the Doctor of
Philosophy degree in Psychology
in the Graduate College of
The University of Iowa

December 2007

Thesis Supervisors: Associate Professor Steven W. Anderson
Professor Daniel Tranel

ABSTRACT

Although the visual system is perhaps the most well understood system in the human brain, the precise organization of the neural system whose activity gives rise to higher order functions like visual recognition remains unknown. Furthermore, the manner in which damage involving this system relates to deficit, or the extent to which other factors modulate this relationship is unknown. Building on prior research in this laboratory and elsewhere, which has related focal brain damage to deficits in visual recognition pertaining to particular categories of stimuli, the present study examined both the specificity of lesion-deficit associations, and the relation between damage to the neural systems subserving visual recognition and the severity of a patient's impairment.

In the first part, I employed a novel method to address the specificity of visual recognition impairments in relation to the categories of faces, animals, fruits/vegetables and tools/utensils. By using voxelwise logistic regression to parse out variance that could be attributed to deficits across multiple categories, I was able to identify areas that were uniquely predicted by impairment in a single category. In the second part, I examined the relation between the extent of damage in these "category-specific" regions and the severity of the recognition impairment in the same four categories, as well as potential modulating effects from various demographic (e.g., sex, handedness), neuropsychological (e.g., premorbid intellectual functioning, visual-spatial and visuoperceptual ability), and lesion (e.g., age at onset, time elapsed since onset, extent of damage in other ROIs, lesion size) variables. The findings indicated that the largest factor accounting for performance in the recognition of these entities was the extent of damage in the respective category-specific regions. However, within each of the categories, there were additional factors

that were also associated with performance, which helped explain some of the additional variance in recognition performance that could not be explained by extent of damage alone. With regard to the latter, I found that damage in certain category-specific regions was related to the severity of deficit across multiple categories, thereby reinforcing the notion of relative specialization within the visual system.

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CERTIFICATE OF APPROVAL

PH.D. THESIS

This is to certify that the Ph.D. thesis of

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Hanna Damasio

To
Amanda Green,
My Parents
&
Dr. Arthur L. Benton

As one reads accounts of prosopagnosic patients, one cannot help but be impressed
by the wide variation in their descriptions of their difficulty and in the
concomitant disabilities that they show

Arthur L. Benton
The Neuropsychology of Facial Recognition

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There are countless people who have played an instrumental role in making this thesis possible, and many of them are individuals who I have never met and whose personal contribution I will never quite know. This is largely because I had the phenomenal opportunity to work on a project that started before I started high school. Thus, for the many researchers, research assistants and patients who participated in this project before I learned where the Central Sulcus was located or what it separates, and afterward, I owe a great deal of thanks.

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I hope that I make all of you proud.

ABSTRACT

Although the visual system is perhaps the most well understood system in the human brain, the precise organization of the neural system whose activity gives rise to higher order functions like visual recognition remains unknown. Furthermore, the manner in which damage involving this system relates to deficit, or the extent to which other factors modulate this relationship is unknown. Building on prior research in this laboratory and elsewhere, which has related focal brain damage to deficits in visual recognition pertaining to particular categories of stimuli, the present study examined both the specificity of lesion-deficit associations, and the relation between damage to the neural systems subserving visual recognition and the severity of a patient's impairment.

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CHAPTER 1

INTRODUCTION

1.1 Context and questions

What factors ultimately govern which patients have a deficit and the nature of that deficit following an acquired brain injury? For more than 150 years, scientists have been reporting on the neuropsychological impairments that patients have suffered as a result of stroke or other focal brain injuries. Yet, as much as these studies have taught us about the neural systems underlying various cognitive processes, they have also demonstrated remarkable variability across patients. For example, in 1861 Pierre Paul Broca published one of the first studies to postulate a specific lesion-deficit relationship when he described a patient with a deficit affecting speech output and lesion in the third convolution of the frontal lobe (Broca, 2006). A little more than a decade later, Carl Wernicke described a different patient who had suffered damage to the posterior-superior part of the temporal lobe and displayed a defect in the comprehension of speech, and not in the ability to produce speech (Wernicke, 1977). Taken together then, these two cases suggested that the neural system underlying language can be subdivided into at least two sectors with dissociable functions and that the deficit observed in any one patient was to be a function of which of these two systems the lesion affected.

The more than a century of research that has followed the observations by Broca and Wernicke has demonstrated that brain-behavior relationships are indeed more complicated than initially described. To begin, most acquired neuropsychological disorders that follow a static brain injury are not static syndromes. That is, many patients demonstrate a degree of recovery following the initial injury, and although this period of

recovery often achieves a maximal rate during the first three months, it may continue at a lower level throughout the lifespan. Second, recovery, or compensation/reorganization as it is probably more accurately termed, appears to vary both across individuals, and across cognitive functions. Thus, the degree to which a patient demonstrates a deficit following a brain injury is likely a function of not only where the lesion is, but when it was acquired, which cognitive function is in question and where the patient falls with regard to certain psychological or possibly, even genetic factors. Finally, anatomy, both structural and functional, varies across individuals. One of the key contributions of the functional imaging literature has been to demonstrate that there can be a range across individuals with regard to where certain tasks or stimuli elicit activation in the brain. Thus, it is possible that due to inter-individual differences in the organization of the brain, identical brain injuries could produce different outcomes in different individuals.

It is within the context of all of this inter- and intra-individual variability that scientists are attempting to determine the organization of the human brain, and it is within this context that this thesis examines the nature of visual recognition impairments following focal brain injuries.

1.2 Visual recognition impairments following focal brain damage

The first case report of a patient with an acquired visual recognition impairment, later termed visual agnosia by Freud (1891), was published by Quaglino and Borelli (1867) which described an individual who, following presumed bilateral disease, was unable to recognize family and friends, in addition to having impaired color perception,

defective spatial orientation and a left homonymous hemianopia (translated by Sala & Young, 2003). Less than a decade later, Hughlings Jackson (1876) described a patient with a tumor in the posterior region of the right hemisphere and who also lacked the ability to recognize familiar persons and places (Jackson, 1932). During the next 50 years, there were several additional case reports published which helped support the existence of visual agnosia; however, it wasn't until the middle to latter half of the 20th century that visual agnosia became a focus of clinical research.

In 1946, Nielsen published a report on two cases, C.H.C. and Flora D., which would foreshadow later research on visual agnosia. The first patient, C.H.C., had a lesion in the right temporo-occipital lobe and could not recognize inanimate objects like a hat or telephone, but retained the ability to recognize living entities such as flowers. The second patient, Flora D., had a lesion in the left occipital lobe and was unable to recognize family and friends, but was able to recognize objects like a watch and a pencil. Although these findings from this study would be largely ignored for about 40 years, they illustrate a pattern (namely, impairment in the ability to recognize one category of stimuli with relative sparing of the ability to recognize another type of stimuli) that would come to be replicated numerous times during the last two decades of the 20th century.

In 1984, Warrington and Shallice published a seminal paper describing four patients, all of whom had recovered from herpes simplex encephalitis and all of whom demonstrated a marked impairment in the recognition of living entities and foods, with relatively preserved knowledge of inanimate objects. That paper revolutionized our understanding of the neural system subserving visual recognition, because it suggested that the functions necessary to carry out visual recognition were not distributed evenly

across occipital-temporal cortices, but rather were organized into discrete regions that were at least partially segregated according to the nature of the stimuli to be recognized, which the authors interpreted as reflecting differences in the cognitive processes necessary to recognize them.

The report by Warrington and Shallice (1984) has been followed by more than 75 case studies documenting patients with “category-specific deficits,” although often with limited evidence supporting the extent of the impairment or the locus of brain damage (Capitani, Laiacona, Mahon, & Caramazza, 2003). Accordingly, although these studies have provided interesting evidence regarding the possibility of category-specific deficits, their utility toward discerning the organization of the higher-order visual and association cortices is limited.

There have been a few attempts at large-scale examinations of visual recognition impairments (e.g., Capitani, Laiacona, Mahon, & Caramazza, 2003; Damasio, Tranel, Grabowski, Adolphs, & Damasio, 2004; Humphreys & Riddoch, 2003), of which the largest is a study of 139 patients with unilateral focal lesions published by Damasio and colleagues (2004). The Damasio et al. study demonstrated that impairments in the recognition of or the ability to retrieve conceptual knowledge for (based on a visual stimulus) the categories of animals, fruits/vegetables, tools/utensils, musical instruments and persons could be associated with lesions in particular areas. Using lesion difference maps, the authors found that impaired recognition animals was associated with lesions in mesial occipital cortex (mostly infracalcarine), bilaterally, and posterior IT. Impaired recognition of fruits and vegetables was associated with lesions in the right and left anterior temporal region and in the right latero-inferior IT and angular gyrus. Impaired

recognition of tools and utensils was associated with lesions in the left temporoparietooccipital junction. Finally, impaired recognition of persons was associated with lesions in the right temporal pole, angular gyrus and lateral occipital cortex.

Although the findings from the Damasio et al. study revealed much about the organization of higher-order visual and association cortices, it did not address the specificity of the lesion-deficit relations. Further, the results also suggested that there could be considerable variability in the nature or severity of visual recognition impairments following focal brain damage. For example, the behavioral data from the study indicate that the severity of performance could vary considerably across individuals, and that the extent of the recognition impairment could range from “category-specific” (meaning an impairment which was documented for a single category only) to a more generalized deficit which affected a maximum of four of the five categories that were included in the study.

1.3 General Approach

Building on the prior work by Damasio and colleagues, the present study first examines the specificity of visual recognition impairments pertaining to the recognition of persons, animals, fruits/vegetables and tools/utensils for areas of damage in the human brain, and then attempts to identify the factors that moderate the relationship between the extent of brain damage and the severity of the observed deficit.

The overall approach is based on prior neuroimaging techniques that have been developed in this laboratory (e.g., Damasio, 2000; Frank et al., 1997) and elsewhere (e.g.,

Bates et al., 2003; Karnath, Berger, Küker, & Rorden, 2004). Using a large sample of patients with focal brain lesions, all of which have been mapped onto a single, template brain, this study will first employ a voxelwise logistic regression analysis to identify areas in the brain that where damage is predicted by impaired performance in recognition for the category of interest while controlling for performance in the three remaining categories. Accordingly, the results will highlight areas of the brain where impaired performance appears to have a relatively specific¹ relationship to damage in the brain. It is hypothesized that *within visual and heteromodal association cortex, there will be regions that are more specifically associated with recognition impairments pertaining to one category compared with any other category. However, there will be overlap between the neural systems such that commonality will be observed between the lesions that are associated with recognition deficits in any two categories.*

The second part of the study will examine the relation between damage to category-related regions and the severity of the observed behavioral deficit. It will also examine additional demographic, neuropsychological and lesion variables with the aim of identifying other factors that help account for the variability in visual recognition impairments following focal brain damage. It is hypothesized that *anatomical factors (i.e., the extent of damage with in these regions of interest) would account for the greatest portion of variance in the severity of visual recognition impairments, but that additional variables including age, sex, handedness, age at onset, time elapsed since onset, contrast sensitivity, estimated premorbid IQ, and measures of visuoperceptive, visuospatial, and*

¹ Specific in the context of this study. Obviously, the four categories employed here are only a subset of a large number of categories that would be possible to study. Therefore, specific is a relative term meaning in relation to the categories employed here.

visuoconstructive abilities would also account for a small portion of the variance in recognition for faces, animals, fruits/vegetables and tools.

1.4 Relevance

As noted above, researchers in various fields have been studying the effects of focal brain lesions on visual recognition for more than 100 years; however, despite the considerable attention placed on the topic, the precise organization of higher order visual and association cortices remains unknown. Notably, there have been several key advances that have shaped current research, as well as theoretical formulations, on visual agnosia.

Perhaps the most influential, recently, have been the findings from recent functional imaging studies. Beginning with a study by Kanwisher and colleagues (1997), which demonstrated that areas within the posterior and inferior temporal-occipital cortices appeared to be more strongly activated in response to face stimuli when compared with other stimuli (e.g., animals, objects), researchers have investigated the specificity of particular patterns of cortical activation for particular types of stimuli (e.g., Gauthier, Skudlarski, Gore, & Anderson, 2000; Grill-Spector, Knouf, & Kanwisher, 2004). In turn, these findings, together with observations from lesion studies, have led researchers to postulate that the neural systems subserving visual recognition, as well as stored conceptual knowledge more generally, may be at least partially segregated either based on category or based on functions that co-vary with category membership (e.g., Caramazza & Shelton, 1998; A. R. Damasio, 1989; H. Damasio et al., 2004).

In general, research regarding lesion patients has made a limited contribution toward testing these hypotheses, because most published studies have been single case reports. Recently, the findings from studies of 79 patients with “category-specific deficits” were reviewed by Capitani and colleagues (2003), and while the authors drew conclusions regarding the behavioral aspects of the “category-specific” syndromes, they did not draw any anatomic conclusions. In general, the failure to draw anatomic conclusions reflects the paucity of neuroanatomic data available in these studies. Accordingly, the present study has the potential to make a substantial contribution to the available literature in that it will be the first to address specificity of the neural systems subserving visual recognition through an analysis of patients with focal lesions.

In addition, the translational aspect of the present study also has the potential to make a significant contribution to the available literature on visual recognition impairments. Most of the present-day, large scale analyses of patients utilize voxelwise analyses. Accordingly, the results highlight voxels in the brain that appear to be important for a particular cognitive function. Yet, cognitive functions are not carried out by individual voxels. Systems of neurons are required. However, few studies have systematically investigated the effects of varying degrees of damage to these neural systems on the observed behavioral outcome. Therefore, this study will provide important information about how the extent of damage observed on a structural scan relates to performance on a visual recognition task.

Finally, although the notion that patients demonstrate remarkable variability in outcome following a brain injury is not new, there have been surprisingly few systematic investigations aimed at identifying which factors might moderate the variability in

outcome. The little data that is available has suggested that demographic factors like sex are systematically associated with performance, at least for the category of fruits/vegetables (e.g., Capitani, Laiacona, Mahon, & Caramazza, 2003), although it is not difficult to postulate that such effects may be related to other categories of stimuli as well. The findings from the present study will be useful in determining what factors may play an important role in moderating outcome, as well as potentially, what factors may need to be considered in other investigations of brain-behavior relationships.

1.5 Visual Agnosia

As noted above, the first case reports of patients with visual recognition impairments were presented within a decade of the report by Broca linking a deficit in speech production with a lesion in the frontal lobe. Like Broca, the authors postulated that the deficits in visual recognition arose as a result of damage to discrete areas in the brain. Based on the clinical presentation (e.g., acute onset left hemiplegia and loss of vision bilaterally, both of which resolved over time), Quaglino and Borelli (1867) concluded that the damage involved the right hemisphere and affected brain tissue, “the matter of the right ventricle,” and possibly even the superior colliculi, which by this time had been identified as a “center” involved in vision. Jackson (1876), on the other hand, pathologically confirmed a tumor affecting the posterior aspect of the right hemisphere which resulted in what he termed, “imperception,” – a lack of recognition of familiar persons and places, losing one’s way in familiar surroundings, and inability to dress oneself (which today would be referred to as prosopagnosia, topographagnosia and

apraxia, respectively). Based on the above, Jackson postulated that the posterior region of the right hemisphere played a crucial role in visual recognition and memory.

Two years later, Munk (1878) presented results from animal experiments producing what he termed, “mindblindedness.” Following bilateral ablation of the upper convex surface of the occipital lobes, Munk’s dogs could still freely ambulate through their environment and even avoid obstacles by walking around them or climbing over them. However, what they lost was “an ability to appreciate the meaning of many visual stimuli” (as cited in Benton & Tranel, 1993). Munk’s dogs did not snap at a piece of meat presented in front of them, cringe at threatening gestures, or demonstrate signs of recognition for their master or other familiar persons compared to strangers. Munk interpreted the results as indicating that the lesion in the occipital lobes destroyed their “memory images” of earlier visual experience. Without these memory images, his dogs could not relate current to past experience and therefore, derived no meaning from current experience.

Following Munk’s report, there were reports of “mindblindedness” in patients leading Wilbrand (1887) to posit that there was a “visual memory center” in the peristriate cortex. However, it wasn’t until 1890 that Lissauer presented the first comprehensive theory about visual recognition. He theorized that visual recognition could be subdivided into two distinct processes. The first was conscious perception, which was held to be the role of the visual cortex itself, and the second was a linking of the conscious perception with the stored memory representations, which was held to be the role of the fibre connections (Catani & ffytche, 2005). Lissauer posited that damage to the cortex would result in an *apperceptive* type of visual agnosia whereby individuals

would manifest impairments in visual recognition due to impairments in their ability to accurately perceive visual form. In contrast, damage to the white matter (sparing the cortex) would result in intact perception, but an inability to link the percept with stored memory representations (*associative visual agnosia*)².

Overall, Lissauer's model fit well with the prevailing theory about brain organization put forth during his time—namely, that the brain was divided into discrete centers which were then interconnected through white matter association pathways (i.e., associationist models; for a review of associationist models and disconnection syndromes, see Catani & ffytche, 2005). However, not everyone was supportive, and thus, the early part of the 20th century was dominated by a debate as to whether associative agnosia was a true clinical syndrome or whether it could be explained in the context of something else, such as a personality disturbance or a deficit in visual perception, which was too subtle to be detected by typical clinical tests.

The latter point culminated in proposal by Bay (1953) which stated that visual agnosia does not exist, and that the appearance of a selective deficit in visual recognition actually resulted from a combination of two more generalized impairments. The first was a selective impairment in elementary visual functions and the second was a generalized intellectual decline. In other words, Bay (1953) argued that a mild dementia together with a degraded visual percept produced the phenomenon of visual agnosia.

Following the report by Bay, Bender and Feldman (1972) reviewed the records from a large number of neurological patients spanning a period of two decades at Mount

² Other authors have reported that Lissauer was skeptical that cases with a pure associative agnosia could exist without some concomitant perceptual deficit (e.g., Riddoch & Humphreys, 2003)

Sinai Hospital, and found very few cases of visual agnosia. Moreover, all of the patients with visual recognition impairments also displayed significant elementary visual and/or generalized intellectual impairment. Thus, the temptation was to explain recognition deficits away as a byproduct of poor visual perception.

However, an earlier study by Ettliger (1956) raised questions about the significance of perceptual deficits in patients with associative-type of visual agnosia. Using a sample of patients of whom only one had visual agnosia, Ettliger showed that visual agnosia was not caused by impaired visual perception by demonstrating that patients with more severe visual perceptual impairments could nonetheless recognize objects.

The debate regarding the existence of visual agnosia eventually gave way to more complex theoretical debates about the nature of visual recognition impairments and the associated neural system that subserves recognition. In general, this shift reflected broad-based changes in the fields of neurology, neuropsychology and neuroscience, which in turn, reflected significant advances in both theoretical formulations and in available technology. The principal shift theoretically was the resurgence of disconnection syndromes, which arose out of a seminal paper by Geschwind (1965). Taking off from Wernicke's original formulation of higher order cognitive functions arising out of an association between cortical areas storing motor and sensory information, Geschwind postulated that the organization of the human brain centered on multimodal association regions. Unlike smaller mammals, whose brains demonstrated numerous direct connections between primary sensory and motor regions, and lower-order primates, whose brains appeared to be organized around connections between primary sensory

areas and limbic regions, the human brain is organized in a manner such that all of the connections between primary sensory and motor areas course through “association” areas, which in turn were connected with limbic and other cortical/subcortical regions. Geschwind interpreted this as indicating that deficits in higher order cortical functions (like visual recognition) could arise out of damage either involving the connections (i.e., white matter) between primary sensory areas and these association regions or to the association regions themselves.³ In this sense, he provided an alternative account to how neuropsychological syndromes could arise following focal damage to the cortex (i.e., that they resulted not from damage to the center for carrying out a particular function, but rather from damage to these association regions or their connections, which were necessary to link systems of neurons together to carry out a function) and provided an impetus for decades of research with focal lesion patients. At the same time, advancements including the development of new imaging techniques (i.e., computerized tomography in the 1970s and magnetic resonance imaging in the 1980s), single unit recording and neurosurgical techniques (e.g., callosotomy) provided new ways of testing Geschwind’s theory.

Within that context, studies of visual agnosia moved away from merely positing its existence, toward the development of complex theories about the organization and function of visual and higher order association cortices. Studies by Hécean and Angelergues (1962) and Damasio, Damasio and Van Hoesen (1982) examined groups of

³ At this point in history, the known association regions included the limbic system and a region at the temporo-parieto-occipital junction. Subsequently, there have been areas in the anterior temporal lobes, the lateral frontal lobes and most recently, the mesial parietal lobes (Damasio & Parvisi, 2006), which also appear to serve as multimodal association regions.

subjects with face recognition impairments drawing conclusions about the nature of the recognition impairment and the locus of the lesions necessary to produce such deficits. Regarding the latter, Hécean and Angelergues postulated that prosopagnosia resulted from unilateral damage involving temporal and occipital cortices on the right. In contrast, Damasio and colleagues posited that associative prosopagnosia resulted from bilateral damage visual and association cortices in the ventral temporo-occipital lobe (i.e., Brodmann areas 18/19, and 37) whereas more apperceptive forms of prosopagnosia resulted from damage involving association cortices within superior and inferior aspects of the parietal-occipital lobe on the right and amnesic/associative forms of prosopagnosia resulted from damage to association areas in the anterior temporal lobe on the right.

Further, taking off from Geschwind's theory, A.R. and H. Damasio postulated that the visual and higher order association cortices are organized around what they termed *convergence zones*, which are regions that link together activity arising out of primary sensory cortices with contextual information which exists in visual and multimodal association cortices throughout the brain (e.g., Damasio & Damasio, 1994). According to their theory, deficits in recognition arise when there is damage either to the connections themselves (i.e., white matter) or to these convergence zones, which in turn disrupts the linking of perceptual information arising in primary sensory cortices with contextual information that is contained in visual and multimodal association cortices, which is necessary for recognition.

A key aspect of the Damasios' theory is that they do not hypothesize that visual recognition is carried out by particular cells in the inferior temporal lobe. Rather, what they and their colleagues postulate is that these areas function as part of a neural system

subserving visual recognition by linking together activity from multiple areas of the brain which is necessary to carry out visual recognition.

That distinction is important because subsequent research has pushed many of the dominant theoretical formulations away from a connectionist model, and back toward localizationist models, postulating instead that recognition is carried out by circumscribed areas in the ventral temporal lobe. In general, this shift stemmed from the publication of numerous case studies of patients with apparent category-specific recognition impairments (e.g., Warrington & Shallice, 1984; Warrington & McCarthy, 1987; Silveri & Gainotti, 1988) as well as subsequent functional imaging studies (e.g., Kanwisher et al., 1997). Notably, prior to this, research on visual recognition had not emphasized the distinction between visual recognition impairments pertaining to different categories of stimuli, and when it was discussed (e.g., Damasio et al., 1982), it was generally placed in the context of face recognition requiring a different level of processing (e.g., unique identity versus categorical membership).

With the publication of case reports describing category-specific recognition impairments, there was a push to now divide visual and higher order association regions into domain-specific areas.⁴ This was then further supported by functional imaging studies of neurologically-normal adults which demonstrated that certain areas of the brain are more active (interpreted from increases in the BOLD signal) when particular types of stimuli are present compared to when other types of stimuli are present (e.g., Kanwisher,

⁴ Generally speaking, the notion of domain specificity is not incompatible with an associationist model if one posits that the association areas are domain-specific (see Damasio, 1990 for an example); however, generally-speaking, most of these theories posited that recognition for stimuli within these categories was carried out by the neurons in these areas.

McDermott, & Chun, 1997, McCarthy et al, 1997, Polk & Farah, 1998, Epstein & Kanwisher, 1998, Aguirre, Zarahn, & D'Esposito, 1998). Additional work has produced retinotopic-like maps of faces, objects and other stimuli for higher order visual and association cortices based on functional imaging data (e.g., Hasson, Harel, Levy, & Malach, 2003; Levy, Hasson, Avidan, Hendler, & Malach, 2001). Perhaps the most fine-grained examples are results from studies employing single unit recordings in animals (Perrett, Rolls & Caan, 1982; Tanaka, 1997) and humans (e.g., Quiroga et al., 2005). In fact, results from the latter identified neurons within medial temporal lobes that appeared to be highly specific to a stimulus at the unique level, responding invariably to different pictures of the same person, and even to letter strings of their name.

Together, the results from these studies have been used to generate a host of theories regarding the organization of knowledge or visual recognition processes in the human brain and to fuel a prolific debate about the role of various areas in visual and association cortices with regard to stimuli from different categories (for reviews, see Aguirre & Farah, 1998; Grill-Spector & Malach, 2004; Peissig & Tarr, 2007; and for a review of conceptual knowledge in the brain, see Martin, 2007). Yet, what is common across most of these theories (e.g., sensory-functional theory by Warrington & Shallice, 1984; domain-specific model by Caramazza & Shelton, 1998) is that the areas that subserve visual recognition do so because knowledge pertaining to the stimulus is stored by those neurons. For example, Warrington and Shallice (1984) posit that damage to regions that store information about how tools are used produce tool-specific deficits (i.e., recognition and semantic impairments). Further, the debate regarding areas such as the “fusiform-face-area” centers on whether the area is the center for face processing or

whether it processes stimuli at a more unique level or that are associated with expertise (e.g., Gauthier et al., 1997; Grill-Spector et al., 2004).

What is missing from these theories is the neural system. Yes, it may be true that areas in the ventral temporal-occipital lobe respond differently depending on the stimulus (as well as the task demands, etc). It is also probable that there are even neurons (most likely within anterior temporal lobes) that respond to a single stimulus such as a face, or collectively to stimuli with particular features. However, even if that is true, that neuron is not responding in isolation; rather it is responding in conjunction with many other neurons, and in that sense, is part of a network of neurons. It may be that, for the anterior temporal lobe neurons, there is specificity such that a single neuron binds together activity from a collective group of neurons ultimately linking information about the perceived stimulus with knowledge about the entity arising from many different regions of the brain, but that is not to say that the information is “stored” in the neuron the way a historical text stores information about a past president.

In general, one constraint on all current theoretical models of visual recognition is that one particular methodology appears to dominate current research on visual recognition,—namely, functional imaging. In addition, many of the functional imaging studies utilize the same model (i.e., subtraction) and ultimately test the same question (i.e., what areas are specific to what functions, or within the visual recognition literature, in particular, what areas are specific for what categories of stimuli?). There have been virtually no attempts to validate the findings using a different methodology (e.g., lesion studies), in part, because of the constraints associated with addressing questions like the

specificity of relatively small cortical regions using lesion patients.⁵ Thus, during the last decade, research with focal lesion patients has often served to highlight dissociations among cognitive functions (e.g., face recognition versus object recognition as exemplified in a study by Moscovitch, Winocur, & Behrmann, 1997, which demonstrated intact face recognition in a patient with visual object agnosia) or to identify the underlying nature of the impairment in patients with agnosia (e.g., configural processing impairments in patients with prosopagnosia as exemplified in a study by Barton & Cherkasova, 2005, which examined spatial configuration within objects and between objects in patients with prosopagnosia). However, remarkably few studies have been examined the neural systems associated with visual recognition.

The notable exception has been the studies by Damasio and colleagues (e.g., Damasio et al., 2004). However, even in those studies, specificity, which has been at the center of most functional imaging studies, has not been addressed. Thus, by addressing the specificity of lesion-deficit associations, the findings from the present study have the potential to shed new light on the organization of the brain, as well as on current debates regarding visual recognition in the human brain.

In summary, more than 100 years of research has implicated the ventral temporal-occipital cortices as being the substrate of visual recognition processes. Early models emphasized the role of discrete processes in visual recognition (e.g., perception versus recognition) and “associations” between these percepts and stored knowledge. More recently, with the documentation of numerous case reports of patients with category-

⁵ In general, such studies require large numbers of patients with focal lesions, which would be on the magnitude of more than 50 times what is typically included in a lesion study (i.e., groups of 1-3 patients with focal lesions).

specific visual agnosias and functional imaging studies demonstrating differential patterns of activation in particular regions associated with different categories of visual stimuli, there has been a drive toward parsing the visual and higher order association cortices into discrete category-related regions. Notably, most of this has been based on data from functional imaging studies, and to date no study has examined the specificity of lesion-deficit associations across a large sample of patients with focal lesions. Such data would be very useful in helping to enhance our understanding of the neural systems subserving visual recognition.

1.6 The severity of visual recognition impairments following focal brain damage

There has been very little research aimed at understanding the factors that govern the severity of visual recognition impairments following focal brain damage. A review of the available literature using PubMed and Scholar-Google and terms such as “outcome” or “severity” coupled with “visual agnosia” or “prosopagnosia” revealed only a handful of case reports on long-term outcome in visual recognition and a single group study. As a result, most of what can be said about long-term outcome in visual recognition must be extrapolated from studies on recovery from aphasia or motor impairment, or from research on visual agnosia, more generally.

Estimates of the prevalence of visual recognition impairments following stroke or other acquired brain injury vary across studies, ranging from less than 1% (Zihl & Kennard, 1996) to more than 20% (Valentine, Powell, Davidoff, Letson, & Greenwood, 2006). In the Damasio et al. (2004) study, 100 of 139 subjects (72%) were found to

perform at least 2 SDs below the mean of the comparison sample of neurologically-normal adults in recognition for at least one of the conceptual categories. In general, the differences in prevalence estimation are not indicators that agnosia is endemic in Iowa, but rather that there can be marked differences in the manner in which impaired recognition is defined. In the studies in which there were higher estimates of prevalence, impairment is typically defined in relation to the performance of a comparison sample on a specific test. Thus, subjects who demonstrate impairment on these laboratory tests need not demonstrate a level of impairment which is sufficient to interfere with daily life. Consistent with this, estimates of visual recognition impairments based on self-report or care-giver report of impairment in daily life approximated 2% in the same sample reported above (Valenstein et al, 2006).

Within the context of trying to elucidate the neural underpinnings of visual recognition, it makes sense that patients with milder impairments (e.g., those who demonstrate impairment on laboratory tests, but who may not have sufficient impairment so as to interfere with daily life) be included, as their performance is not normal, and therefore, their lesions may impart important information about the neural system that is necessary for normal visual recognition. However, if lesions within a neural system can produce severe as well as mild impairments, then a reasonable question that follows is why? Why do some lesions result in severe deficits whereas others lead to only mild impairments?

More than 20 years ago, Damasio, Damasio and Van Hoesen (1982) postulated that “some single lesions of the right hemisphere can cause transient impairment in facial recognition (p. 335).” Notably, this hypothesis was put forth during a time when the

prevailing evidence indicated that bilateral and functionally symmetric lesions involving the ventral occipital temporal cortex were necessary to produce prosopagnosia.

Subsequently, there have been a few reports of unilateral lesions involving the temporo-parieto-occipital cortices on the right resulting in prosopagnosia (e.g., Damasio, Tranel, & Damasio, 1990; Landis, Regard, Bliestle, & Kleihues, 1988; Wada & Yamamoto, 2001), although in each of these cases, there was a notable perceptual deficit leading to the conclusion that unilateral right hemisphere lesions are associated with a more apperceptive form of prosopagnosia (Damasio, Tranel, & Damasio, 1990). Moreover, the results from the Damasio et al. (2004) study, which included patients with unilateral lesions only, indicated that 41 of 139 (29%) subjects had impairments in facial recognition.

Notwithstanding the issue regarding whether a unilateral lesion can produce prosopagnosia, the observation that a unilateral right hemisphere lesion can produce a *transient* prosopagnosia is consistent with other observations of recovery from right hemisphere strokes, which have shown that during the acute period, there can be rapid recovery from deficits such as prosopagnosia (Hier, Mondlock, & Caplan, 1983). On the other hand, the few case reports that have examined face recognition impairments across a span of up to 40 years, suggest that there is very little recovery from prosopagnosia in the chronic phase following acquired brain injury (e.g., Farah, Rabinowitz, Quinn, & Liu, 2000; Sparr, Jay, Drislane, & Venna, 1991; Young & Ellis, 1989). Additionally, the fact that patients with prosopagnosia are often studied by various laboratories over many years is de facto evidence that for many individuals, the deficit can persist in a severe form for a number of years (e.g., patient, "LH", Levine, Calvanio, & Wolf, 1980; de

Gelder & Rouw, 2000). Overall, these observations together raise questions about who recovers to “normal” performance, and what factors determine the severity of a facial recognition impairment following focal brain damage.

In regards to visual agnosia more broadly, there is even less data regarding what governs the severity of a patient’s deficit pertaining to the recognition of stimuli other than faces. In general, the studies that examine long-term outcome for visual functions following stroke or other acquired brain injury generally do not examine visual agnosia, and instead focus on lower-order functions like visual field deficits (e.g., Bosley et al., 1987) or higher-order functions like visual neglect (e.g., Samuelsson, Jensen, Ekholm, Naver, & Blomstrand, 1997; Patel, Coshall, Rudd, & Wolfe, 2003) or visuoconstructional impairments (Hochstenbach, den Otter, & Mulder, 2003). Even those studies that report outcome for prosopagnosia, do not necessarily mention outcome for recognition of other types of stimuli (Hier, Mondlock, & Caplan, 1983).

Two reports of patients with visual agnosia who were studied longitudinally suggest that recovery from visual agnosia may be minimal (Sparr et al., 1991), although compensation may be substantial (Schiavetto, Decaire, Flessas, Geoffroy, & Lassonde, 1997). In addition, similar to above, there are numerous case reports of patients with visual agnosia who were examined years after their acquired deficit, thereby suggesting that impairments in recognition may persist for years following a static injury. In contrast, there is one report of a single patient with visual agnosia resulting from a severe head injury sustained at 17 years of age, whose agnosia for real objects appeared to “resolve” by follow-up ten-years later (Wilson & Davidoff, 1993). This was in marked contrast to her ability to recognize model animals and objects from line drawings, which

continued to be impaired. The authors took these findings as evidence for a “partial recovery from visual object agnosia” and are at least suggestive that for some individuals the severity of the deficit, or more likely, compensatory mechanisms may change over time.

In general, very little can be concluded on the basis of a few case reports pertaining to a few patients who present with different ages of onset, different mechanisms of injury, and different concomitant disabilities. However, these reports do raise interesting questions regarding who might recover and what might determine severity of deficit.

1.6.1 Severity of deficit following acquired brain injury

As noted above, because there is very little information regarding severity of visual recognition impairments following focal brain injury, current hypotheses must be extrapolated from research on deficits associated with acquired brain injury more broadly. In general, there are potentially numerous factors that could influence recovery or the severity of a deficit following brain injury. A partial list is included in Table 1.1.

Of these, perhaps the factor that has received the greatest attention is age at onset. In as early as the mid-1800s, it was observed that damage to the left hemisphere incurred prenatally or in early childhood did not result in aphasia (Cotard, 1868, as cited in Benton & Tranel, 2000). Nearly 70 years later, Margaret Kennard demonstrated in a primate model that surgical lesions involving motor and premotor cortex were associated with substantially better motor outcomes when those lesions were incurred early in life

Table 1.1 Possible factors influencing outcome from brain injury.

Age at onset
Handedness
Severity of the injury
Location of injury
Number of insults
Mechanism of injury
Integrity of the rest of the brain
Individual idiosyncrasies in brain structure/organization
Premorbid abilities
Motivation
Emotional factors
Nature of the cognitive function in question
Extent to which one function can be subsumed by another function
Extent and quality of rehabilitation

Adapted, in part, from Kapur (1997)

compared to when they were incurred during adulthood (Kennard, 1938, 1940). These observations, together with further research examining outcome associated with hemispherectomy and other lesions incurred during childhood, led researchers to conclude that age of onset, at least when dichotomized into prenatal/childhood onset versus onset later in life, was an important factor in determining severity of deficit following an acquired brain injury (Wilson, 1970).

Notably, more recent research regarding outcome following childhood-onset brain injury has indicated that age of onset appears to interact with other variables, including the location of lesion or nature of the cognitive ability under consideration (Anderson et al., 2000), the etiology or severity of initial insult (Reeder, Rosenthal, Lichtenberg, & Wood, 1996), whether the lesion is focal or diffuse, and the time since acquisition of the skill or cognitive ability under consideration (Kolb, 1995). Other research has indicated that age of onset is important not only for childhood-onset injuries, but is also predictive of outcome following adult-onset injuries (e.g., Alexander, 1994; Kotila, 1986; Macciocchi, Diamond, Alves, & Mertz, 1998), including those with the most severe injuries (Jørgensen, Reith, Nakayama, Kammersgaard, Raaschou, & Ølsen, 1999), although there have also been null findings regarding age of onset and outcome (e.g., Samuelsson, Soderfuldt, & Olsson, 1996). In general, the prevailing evidence suggests that age of onset, either by direct influence or by indirect influence via interactions with other variables, is an important predictor of outcome following acquired brain injury.

Another factor that has received attention is the notion of cognitive reserve (Wilson, 1998). Cognitive reserve is a concept that has been the focus of numerous studies on dementia, particularly of the Alzheimer's type and refers to the finding that premorbid intelligence or years of education appear to have a protective effect leading to a later age of onset for dementia. This has led to the notion that patients with higher intellectual functions or more education have more cognitive resources, and therefore, are able to withstand a greater degree of neural insult before demonstrating impairment. This concept has also been applied to the recovery from a static neural injury by Basso and Farbola (1997) who noted that severity of aphasia and lesion were insufficient to explain

language functions in a group of patients with aphasia. However, as Wilson (1998) noted, it is unclear whether patients with greater intellectual functions actually demonstrate greater recovery or that they just have more residual functions. Regardless of which is true, it is quite possible that premorbid intellectual abilities play a role in determining outcome following an acquired brain injury.

Other demographic factors such as sex have also been examined, producing mixed, and, if significant, mostly small relations with outcome (for studies in which outcome appears worse for women compared to men, see Wyller, Sødning, Sveen, Ljunggren, & Butz-Holter, 1997; Roquer, Campello, & Gomez, 2003; see also, Ween et al., 1996; Macciocchi et al., 1996 for null effects). The one finding of particular relevance for this study, is that sex has been shown to be an important factor in determining whether the nature of certain category-related deficits. Owing to presumed differential experience with animals or fruits/vegetables, the findings from Gainotti (2005) indicated that men with acquired brain damage were more impaired at fruits/vegetables relative to animals and women were more impaired on animals compared to fruits/vegetables when assessed with both confrontational naming or other semantic tasks.

Several lesion factors have also received attention as possible predictors of outcome. The most crude of these is side of lesion. Several studies have found better recovery associated with left hemisphere lesions compared to right (e.g., Alexander, 1994; Macciocchi et al., 1998; Ween, Alexander, D'Esposito, & Roberts, 1996), although the findings are not consistent across all studies (e.g., Kotila, 1986). Initial stroke severity also appears to be an important predictor of outcome either independently (Cifu

& Lorish, 1994; Macciocchi et al., 1998) or via interactions with side of lesion (Alexander, 1994). Mechanism of injury also appears to be an important predictor of outcome, with slow growing lesions producing less severe deficits comparing to more rapid mechanisms (Anderson, Damasio, & Tranel, 1990).

Notably, none of the aforementioned studies examined the relation between damage within particular neural systems and the severity of the behavioral deficit. Rather, for these studies, severity of neurologic insult was measured in relation to a whole brain index (e.g., total lesion size, global neurological functioning). This is an important consideration, because prior research has suggested that both the location of the lesion and the volume of the lesion are related to outcome (Kertez, 1988), in part due to the nature of the systems involved. For example, a circumscribed lesion involving the left hippocampus is likely to have a very deleterious effect on verbal memory, while the same volume of damage incurred in the left posterior-superior parietal lobe may have no discernable effect at all. A reasonable explanation for why this may be is provided by Robertson and Murre (1999) who argues that recovery is enhanced for cognitive functions that are subserved by multiple neural circuits (e.g., language), and more limited for functions that are subserved by fewer pathways (e.g., declarative memory, visual fields).

One final consideration is the extent to which other cognitive deficits, or abilities, influence recovery. A prime example of this is anosagnosia. Patients who lack awareness of their deficits have been found to have poorer outcomes during rehabilitation (Gialanella, Monguzzi, Santoro, & Rocchi, 2005). Similarly, visual neglect is also predictive of poorer outcome following right hemisphere stroke (Cherney, Halper,

Kwasnica, Harvey, & Zhang, 2001). Regarding visual recognition in particular, to date, there have been no studies that have identified potential moderator variables for prosopagnosia or visual agnosia, more generally. However, there have been studies that have shown a relationship between prosopagnosia and impaired contrast sensitivity for high spatial frequencies, which in turn, has been hypothesized to be one mechanism by which the recognition defect in prosopagnosia can extend to other classes of object subcategorization (e.g., Barton, Cherkasova, Press, Intriligator, & O'Connor, 2004). It is not clear whether contrast sensitivity would be related to visual recognition impairments in patients without prosopagnosia, because no study has examined this issue.

In summary, although the available data are limited, the findings from studies regarding the long-term course of visual agnosia and prosopagnosia together with the findings from studies of recovery following brain injury more generally indicate that there are a number of potential moderator variables that may account for differences in the severity of patients' visual recognition impairments. Amongst these, lesion variables such as the extent of damage within a particular neural system and age of onset, as well as demographic variables such as age, sex, handedness and psychological variables like premorbid IQ or contrast sensitivity all potentially account for the severity of a patient's recognition impairment following focal damage to the cerebral cortex.

1.6.2 Mechanisms that may account for differences in severity or recovery following focal brain injury.

In considering the severity of a deficit following focal brain damage, it is important to note that differences in severity can arise out of two broad mechanisms. The

first is the extent to which damage disrupts the function in question directly leading to a behavioral deficit. The second is the extent to which patients are able to recover lost functions in the period following an injury. Notably, the latter reflects both neural processes such as plasticity and reorganization as well as behavioral processes like the development of compensatory strategies. In patients who are in the chronic state following a brain injury (i.e., ≥ 3 months following injury), it is likely that the severity of their observed deficit results from a combination of all of the above processes.

1.6.2.1 Direct Effects

There are two factors that can directly affect the extent to which damage leads to a behavioral deficit. The first is the extent of damage. It would be expected that, in general, more damage would produce a more severe behavioral deficit. Indeed, early studies by Lashley (1930) demonstrated that the degree of impairment observed in rats during a maze learning task was proportional to the amount of tissue that had been damaged. However, later studies have demonstrated even very small lesions can produce profound behavioral deficits, if the lesion is strategically placed. The hippocampus is a prime example of the latter. Anoxia/hypoxia often results in subtle changes to the hippocampus, which may only be observable with high resolution MRI, particularly if coupled with volumetric analysis (Allen, Tranel, Bruss, & Damasio, 2006). In contrast, anoxia can produce dense anterograde amnesic syndromes which are observable even without psychometric tests. Thus, as later studies have suggested, it is much more likely that the lesion volume in relation to the neural system is much more informative than the lesion volume in relation to the whole brain.

The second factor pertains to interindividual variability. Prior research has demonstrated that there are considerable differences across individuals with regard to the structural and functional organization of the human brain (Ono, Kubik, & Abernathey, 1990; Amunts, Malikovic, Mohlberg, Schormann, & Zilles, 2000). This varies from marked shifts in cortical representations, such as language dominance in the right hemisphere (Damasio & Geschwind, 1984), to more subtle variations, such as differences in the antero-posterior course of the calcarine fissure. The net result of this variation is that the same volume of damage, even if incurred within the same gyrus, may not affect the same neural systems to the same degree. Accordingly, interindividual differences in anatomy may account for some of the variation in outcome observed across large groups of patients with focal lesions.

1.6.2.2 Indirect effects: Plasticity, reorganization

and compensation

In the period immediately following a brain injury, there are often dramatic changes in behavior beginning initially with the loss of a certain function(s), and then sometimes, with the rapid return of some of these abilities (e.g., Carrol, 1962; Wade, Wood, & Hewer, 1985; Kelly-Hayes, Wolf, Kase, Gresham, Kannel, & D'Agostino, 1989). Notably, many of these early changes are more likely to reflect direct effects of the brain injury rather than indirect effects, either via the ongoing evolution of the infarct (Beaulieu, Crespigny, Tong, Moseley, Albers, & Marks, 1999) or via mechanisms such as reabsorption of perilesional edema (e.g., Pascual-Leone, Amedi, Fregni, & Merabet, 2005).

However, in the weeks following the injury, the pattern shifts so that the observed changes no longer reflect the direct effects of the brain injury, but rather reorganization of the neural system such that other cortical regions are able to carry out the same cognitive function. This phenomenon is a type of plasticity, which generally speaking, is a feature of the nervous system that is not limited to the lesioned brain (Kolb, 1999). Behaviorally, reorganization can be inferred by the return of certain cognitive functions in the absence of any regeneration of neural tissue (Lennenberg, 1967), as well as observed using modern functional imaging techniques which demonstrate changes in the pattern of activation associated with recovery of various functions (LieÂgeois, Connelly, Cross, Boyd, Gadian, Vargha-Khadem, & Baldeweg, 2004; Schaecter, Kraft, Hilliard, Dijkhuizen, Benner, Finklestein, Rosen, & Cramer, 2002).

With regard to the mechanism subserving reorganization, researchers in various fields have focused on dendritic arborization (e.g., Kolb & Winshaw, 1988; Jones & Shallert, 1992; Kolb, 1999), although there are potentially a multitude of mechanisms, including the recruitment of pathways that are functionally homologous to, but anatomically distinct from the damaged ones, synaptogenesis, and reinforcement of existing by functionally silent synaptic connections (Rossini, Caluitti, Pauri, & Baron, 2003). Evidence for synaptic arborization being a mechanism underlying reorganization stems from numerous studies that have shown an association between changes in dendritic branching and the extent of recovery across multiple animal models of acquired brain lesions (e.g., Kolb & Winshaw, 1989; Kolb & Gibb, 1991; Kolb & Gibb, 1993). Additionally, there is some convergent evidence from studies with humans that decreased

synaptic density is associated with mental retardation (e.g., Purpura, 1974), although more definitive research has yet to be completed.

At this point, an additional comment regarding behavioral compensation and “recovery” should be made. Until now, “recovery” has been treated like a unitary construct and implying that an organism returns to a premorbid state of functioning. However, an alternative definition would be to define recovery as “a change in behavior over time (Kolb, 1999, p. 66)” that does not necessarily result in a return to premorbid functioning. As an example, consider the performance of an animal following a unilateral lesion in the motor cortex. Over time, that animal may learn to carry out motor functions with the limb that is contralateral to the lesion, and even perform within normal limits on behavioral markers such as the number of times it is able to obtain a piece of food by reaching an arm past a barrier. However, if one examines the performance of the behavior, rather than the outcome, one would note that the behavior looks very different, even though it achieves the same endpoint (adopted from Kolb, 1999). An alternative example could be found in cases of prosopagnosia. Individuals with even the most severe face recognition impairments often report that they are able to recognize one or two individuals, owing largely to distinctive, and often non-face, features (e.g., hair style, mole). Grossly speaking, this represents intact “face” recognition, in that if presented with an image of these faces, these individuals are able to recognize them. However, the means by which they recognize these faces is markedly different than would be expected in “normal” recognition. It is possible to conceive of compensatory mechanisms as the behavioral parallel to reorganization at the neural level.

In summary, the severity of an observed deficit following a focal brain injury is likely to be a function of both direct and indirect mechanisms associated with the lesion. Direct mechanisms include the extent to which the lesion affects a given neural system thereby disrupting function, whereas indirect mechanisms include the extent to which an organism is able to recover lost functions as a result of plasticity, reorganization and behavioral compensation.

CHAPTER 2.

THE SPECIFICITY OF VISUAL RECOGNITION IMPAIRMENTS

2.1 Background

As discussed in the previous chapter, prior research in this laboratory used a large-scale sample of patients with focal lesions to test the hypothesis that the recognition of concrete entities (i.e., persons, animals, fruits/vegetables, tools) is dependent on partially segregated neural systems within visual and higher order association cortices. The findings from those studies indicated that deficits in the recognition of persons, animals, fruits, and tools, were associated with discrete patterns of lesions in temporal and occipital cortices (see Table 2.1). However, the prior study did not consider whether the areas of damage were specific to the deficits in the respective categories and examination of the results suggests that certain areas may be specific (e.g., left temporo-parieto-occipital junction) whereas other areas may be non-specific (e.g., right inferior-temporal cortex).

Further evidence that there may be unique relations between areas of damage and the nature of a patient's visual recognition impairment stems from this laboratory (e.g., Damasio, 1990) and others (e.g., Warrington & Shallice, 1984), where there have been reports of patients who present with striking dissociations between recognition performance for stimuli in some categories compared to others. The first systematic examination of the specificity of recognition impairments was conducted by Farah (1990). She reviewed the case reports of patients with recognition impairments and catalogued whether the impairments pertained to faces (prosopagnosia), objects (visual agnosia) or words (alexia). Farah found that 97 of the 99 cases reviewed conformed to

Table 2.1 Areas of maximal lesion overlap for visual recognition impairments based on lesion-difference maps for the four categories of interest (Damasio et al., 2004).

Category	Left hemisphere	Right hemisphere
Persons	-	Temporal pole into anterior IT
		Angular gyrus/lateral occipital region
	Mesial infracalcarine	Mesial occipital, mostly infracalcarine
		Mesial + inf. temporo-occipital junction
Animals	-	Mesial + inf. posterior IT
Fruits/vegetables	Temporal Pole	Latero-inferior IT into temporal pole
	Lower sector of frontal operculum	Angular gyrus
Tools/utensils	MT (temporo-occipito- - parietal junction)	

Note: results depicted here are based on their standard deviation analysis. Results from distribution analysis yielded the above, as well as an extension into the right parahippocampal gyrus for persons and left infero-lateral occipital region for animals. Additionally, results from the distribution analysis did not yield an overlap in the right mesial + inferior temporo-occipital junction for persons.

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one of the following patterns: faces alone impaired (pure prosopagnosia), words alone impaired (pure alexia), faces and objects impaired (visual object agnosia together with prosopagnosia), words and objects impaired (alexia and visual object agnosia) and faces, objects and words impaired (prosopagnosia, visual object agnosia and alexia). In no instance did she find compelling evidence for cases with prosopagnosia and alexia

without concomitant visual object agnosia or the converse, visual object agnosia without prosopagnosia or alexia. Farah interpreted these results as being evidence that there were two dissociable systems subserving visual recognition: one system that was necessary for face recognition, used for object recognition, and not used in printed word recognition, and another that was necessary for printed word recognition, used in object recognition and not used in face recognition. Although Farah's original findings have been subsequently challenged by a few reports of patients who were reported to have prosopagnosia and alexia without concomitant visual object agnosia (Buxbaum, Glosser, & Coslett, 1999) or agnosia without prosopagnosia or alexia (Humphreys & Ruminati, 1998; Ruminati, Humphreys, Riddoch, & Bateman, 1994), to date no definitive disconfirmatory evidence has been found.

A different approach to the question of specificity has been put forth in studies of visual recognition in neurologically-intact individuals. Studies by Kanwisher and colleagues (e.g., Grill-Spector, Knouf, & Kanwisher, 2004; Kanwisher, McDermott, & Chun, 1997), Gauthier and colleagues (e.g., Gauthier, Skudlarski, Gore, & Anderson, 2000), Malach and colleagues (e.g., Hasson, Harel, Levy, & Malach, 2003; Levy, Hasson, Avidan, Hendler, & Malach, 2001), amongst many others have examined patterns of brain activity (inferred from BOLD signal) in response to tasks involving faces contrasted with tasks involving many other classes of stimuli (e.g., cars, houses, birds). Based on the findings from these studies, it has been postulated that the visual and higher order association cortices can be subdivided into areas that have relative specialization for processing particular types of stimuli (although there remains considerable debate regarding what precisely these subdivisions might be). The most

well known of these hypothesized regions are the fusiform face area (Kanwisher et al., 1997), the parahippocampal place area (Epstein & Kanwisher, 1998) and the lateral occipital complex (Grill-Spector, Kourtzi, & Kanwisher, 2001).

In general, it could be said that the neuropsychological investigations of patients with visual recognition impairments and the functional imaging studies of visual recognition in neurologically-normal adults have approached the question of specificity very differently. The neuropsychological investigations of patients have largely focused on the specificity of the neuropsychological impairment while placing relatively little emphasis on the delineating the underlying neuroanatomy (with the exception being Damasio et al., 2004). In contrast, functional imaging studies of neurologically-intact adults have focused on delineating the specificity of functionally-defined neural regions for processes related to visual recognition. There has been very little research bridging the two—examining the specificity of lesion-deficit relationships—as a means of delineating the subdivisions within the visual and association cortices.

Capitalizing on the remarkable registry of patients with focal lesions at the University of Iowa and the more than 15 years of research on visual recognition and naming, the present study aims to build on prior work by examining whether impairments in the recognition of faces (i.e., persons from faces), animals, fruits/vegetables and tools/utensils has a specific association with damage to areas of the human brain.

One potential limitation in any large-scale study of patients is that “category-specific” impairments are rare. For example, out of 139 patients in the Damasio et al. (2004) study, only 37 demonstrated impairments that were specific to a particular category. However, across a large-scale sample (i.e., 180 subjects with focal lesions in

the present study), it is possible to examine patterns of deficits across a large number of lesions and determine where damage appears to be uniquely predicted by a deficit in one category, after deficits in the remaining categories have been controlled for using statistical techniques.

For the present study, it is hypothesized that *within visual and heteromodal association cortex, there will be regions that are more specifically associated with recognition impairments pertaining to one category compared with any other category. However, there will be overlap between the neural systems such that commonality will be observed between the lesions that are associated with recognition deficits in any two categories.* Based on a voxelwise logistic regression analysis, it is expected that there will be regions where damage is predicted by impaired performance in the recognition of a single category of stimuli (e.g., faces) after performance in the remaining three categories has been factored out.

2.2 Methods

2.2.1 Participants

All subjects in the patient registry at the University of Iowa, Department of Neurology, Division of Cognitive Neuroscience were screened to determine 1) whether they had completed the visual recognition battery for the categories of faces, animals, fruits/vegetables and tools, and 2) whether their lesions had been or were capable of being mapped into a common template space based on the MAP-3 procedures (see below). Over the past 15 years, 349 patients with focal brain lesions had been mapped

onto a template brain, while 423 patients completed some portion of the recognition battery and 293 completed the entire set. The number of subjects represented in both datasets (i.e., subjects for whom data regarding the entire recognition battery and a mapped lesion were available) was 169. Of these 169 subjects, 129 had previously been included in the Damasio et al. (2004) study.⁶

In addition to the subjects whose lesions had already been mapped, six of the subjects who had complete neuropsychological data were found to have a “category-specific deficit,” meaning a score that fell more than 2 SD below the mean of a comparative sample of normal adults for one category of interest, but not for any other category of interest for this study (Damasio et al., 2004). Given the relevance of these subjects in regard to the aim of this study, the anatomy pertaining to these subjects was reviewed and traced for five of them. The sixth subject could not be traced, because neuroanatomical data were not available.

Finally, six additional subjects were included after neuroanatomical data were reviewed and lesions were transferred to the template brain. Two of these subjects were the subjects for whom the lesion traces had been lost following the publication of the Damasio et al. (2004) study. These subjects were re-traced in accordance with the procedures established in the Human Neuroanatomy and Neuroimaging Laboratory, which are discussed below, and included in the present sample. Three of the subjects had also been excluded from the subsequent reanalysis of the Damasio et al. (2004) study, but were included in this study after a re-review of the anatomy and appropriate editing of the

⁶ The Damasio et al. (2004) study included 139 subjects, of whom 11 were discarded from a subsequent re-analysis (Rudrauf, et al., in press) due to data loss (n=2) or to findings of additional damage outside of the principal lesion (n=8).

lesion transfer. Finally, one subject with complaints of prosopagnosia who had been assessed extensively by this writer during the summer of 2006 was traced and also included in the final sample.

Thus, the final sample of subjects included in this study consisted of 180 subjects with focal lesions. 167 had unilateral damage involving either the left (N=104) or right (N=63) hemispheres and 13 had bilateral damage. All of the prospectively included subjects (i.e., those that were not included in prior studies) had lesion onset at age 18 or later, consistent with the methodology from the prior studies. However, upon further review of the previous data, it was noted that six of the subjects from the Damasio et al. study had lesion onset between age 10 and age 17. Consistent with the eligibility criteria utilized in the prior studies, all subjects had normal intelligence (e.g., Verbal Intelligence Quotient > 80) and the ability to attend to and perceive visual stimuli. Subjects also had language skills that were sufficient to produce verbal responses to test stimuli and to comprehend all test instructions.

2.2.2 Stimuli

The stimuli for this study included photographs and line drawings of persons and objects. Person stimuli (presented as faces) were drawn from the Iowa Famous Faces Test (n = 77) (Tranel, Damasio, & Damasio, 1995) and a modified version of the Boston Famous Faces Test (n = 56) (Albert, Butter, & Levin, 1979). Object stimuli included pictures of animals (n = 90), fruits/vegetables (n = 67), and tools/utensils (n = 104) selected from the Snodgrass and Vanderwart (1980) line drawings and from a set of photographs previously developed in this laboratory. For all categories, the same entity

(e.g., hammer) was presented only once. “Unusual” views of faces and objects were not included. All faces were presented as black-and-white photographs in normal forward-face view, with all non-face features deleted. Hair was included in the photographs. For all other categories, the stimuli were comprised of an approximately equal mix of line drawings (approximately 55% of the items), black-and-white photographs (approximately 25 % of the items) and color photographs (approximately 20% of the items). All of the stimuli were identical to those included in the H. Damasio et al. (2004) paper and that consistent with prior studies in this laboratory, no attempt was made to “equate” the categories on variables such as word length, word frequency, name agreement, familiarity or visual complexity (cf. Damasio & Tranel, 1993; Tranel, Adolphs, Damasio & Damasio, 2001 for a detailed discussion of such variables).

2.2.3 Procedures

All subjects were tested in the chronic epoch, at least three months post lesion-onset. All provided informed consent in accordance with the Human Subjects Committee of the University of Iowa prior to participation in this study.

The stimuli were shown in random order, one-by-one, with unlimited viewing time on either a Caramate 4000 slide projector in free field or on a computer monitor via *Power Point*TM Presentation. All 417 stimuli were presented to all subjects and generally across two sessions in order to avoid the confounding effects of fatigue and inattention. The primary consideration was that all participants were able to fully cooperate with the procedures and to provide sufficient effort at all times.

For each stimulus, the subject's task was to tell the experimenter who (or what) the entity is. If the subject gave a vague or superordinate level response (e.g., "an actor," "something you eat"), he/she was prompted to "be more specific; tell me exactly who [what] you think that [thing] is." Prompting was repeated if it was apparent that the subject could give a more specific answer or if a paraphasic response was produced. If subjects indicated that they could not name the entity (i.e., that they "knew what [who] it was, but could not think of the name"), subjects were instructed to "provide as much information as they could about the person [thing]" in order to determine whether the item could truly be recognized. Responses were scored by raters who were blind to the experimental hypotheses following the procedures described below.

2.2.4 Neuropsychological Data Analyses

The dependent measure for this study was a recognition score reflecting the percentage of correctly recognized items within each category. Subjects' responses were scored as correctly recognized if 1) a correct name was provided or 2) a name was not provided, but information that is sufficient to allow a blind rater to identify the object was provided. The notion that correct naming will be considered evidence of correct recognition is consistent with prior studies in this laboratory (e.g., Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996) as well as other laboratories (Warrington & Shallice, 1984). Additionally, utilizing the procedures to indicate correct recognition where individuals are unable to produce a name limits the extent to which naming impairments confound visual recognition performance.

For each subject and each category, the number of correct recognition responses were divided by the total number of stimuli in that category and then multiplied by 100 to yield a percent correct recognition score. For the purposes of determining which additional subjects could be classified as having a category-specific impairment, subjects were classified as impaired/unimpaired based on the extent to which their scores deviated from the means of a comparison group of neurologically normal adults⁷. All subjects with scores that are two or more SDs below the mean of the comparison subjects (i.e., Z scores ≤ -2.0) were classified as impaired. Subjects whose scores are no worse than 1.5 SDs below the mean of the comparison subjects (i.e., Z scores ≥ -1.5) were classified as normal. Subjects with scores between 1.5 and 2.0 SDs below the mean will be considered to fall within a borderline zone and were considered neither intact nor impaired. Therefore, the FIVE subjects whose lesions were traced because they were found to have “category-specific impairments” had Z-scores that fell below -2.0 for one category, but above -1.5 for the remaining three.

In contrast, for the purpose of the remaining analyses, subjects’ scores were transformed into standardized scores based on the mean and standard deviation within the *total sample of focal lesion patients* who have completed the visual recognition task pertaining to that particular category. This was done to normalize the distribution of data and reduce the positive skew, which would otherwise result from a Z-transformation

⁷ In prior studies, 55 neurologically-normal adults, who are matched to the brain-damaged subjects on age, education and gender distribution, completed the face and object recognition task according to the same procedures described above. The results for recognition for the four conceptual categories utilized in this study were as follows: (1) persons, 75.7 ± 6.7 ; (2) animals, 91.9 ± 2.8 ; (3) fruits/vegetables, 92.6 ± 3.9 ; (4) tools/utensils, 96.2 ± 3.3 (Damasio et al., 2004).

based on a comparison between a patient population and a neurologically-intact, normal population.

For the present analyses, raw scores (i.e., as percent correct per category) were standardized using an arithmetic inverse of the traditional Z-score. To obtain these scores, subjects individual scores were compared against the mean and standard deviation from the total population of lesion subjects who have completed this task (N=423) to yield a corresponding Z-score for each subject for each category. These Z-scores were then multiplied by (-1) to yield inverted Z-scores, such that higher numbers corresponded to greater impairment.

2.2.5 Anatomical Localization of the Lesion and Mapping onto a Template Brain

All subjects underwent neuroimaging studies contemporaneously with the neuropsychological examinations in accordance with the standard procedures of the University of Iowa Human Neuroanatomy and Neuroimaging Laboratory. For most subjects, thin-cut T1-weighted magnetic resonance images were obtained in a General Electric Signa scanner operating at 1.5 Tesla, using the following protocol: SPGR/50, TR 24, TE 7, NEX 1 matrix 256 X 192, FOV 24 cm, which yielded 124 contiguous slices in the coronal plane, 1.5 or 1.6 mm thick. These slices were then used to reconstruct a 3-dimensional image of each subject's brain using Brainvox (Damasio & Frank, 1992; Frank, Damasio, & Grabowski, 1997).

For a few subjects, different neuroimaging protocols were used either because the patient was unable to undergo magnetic resonance imaging (due to the presence of a

pacemaker or metallic clip) or because newer technology was available. Accordingly, 10 subjects underwent a CT scan in which 3 mm slices were acquired across a whole brain volume parallel to the direction of a metallic clip (if present, to minimize the effect of artifact from the clip). Additionally, for 2 patients, thin-cut T1-weighted magnetic resonance images were obtained in a Siemens Trio scanner operating at 3.0 Tesla using the 3D-MPRAGE sequence. The MPRAGE sequence is an inversion prepared gradient echo sequence with the following parameters: TR = 2530, TE = 3, TI = 800, Flip = 10, NEX = 1, FOV = 256x256, which yields 220 slices approximately 1 mm thick in the coronal plane. Overall, the use of different neuroimaging protocols should have no effect on the final results as none of the analyses were conducted in native space. Rather, all of the lesions were manually warped onto a template brain using the MAP-3 technique.

The MAP-3 technique, which is described in detail in Damasio and Damasio (2000), involves two principal steps: 1) re-orienting and re-slicing the template brain in such a manner as to create slices that have maximal correspondence with the native slices in the lesion brain, and 2) manually drawing the lesion onto the newly generated slices accounting for any anatomical differences that were not eliminated by re-slicing or re-orientating the template brain. Notably, this manner of lesion transfer takes into account the extent of damage in gray matter versus subadjacent white matter and only marks damage in regions where there has been an obvious interruption in the tissue, and not in regions where atrophy may have occurred.

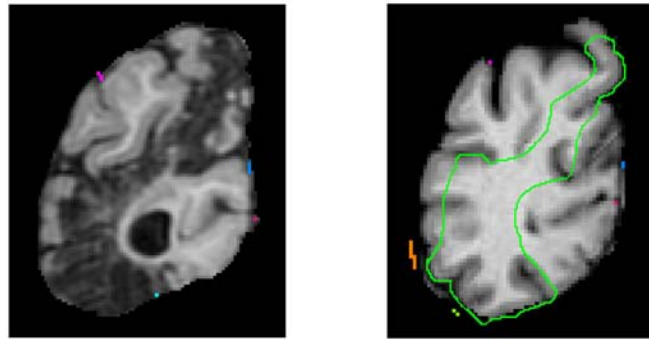


Figure 2.1 An example of a lesion manually traced on the template brain. The image on the left is a single slice from the subject's MRI scan with the skull and left hemisphere removed. The image on the right is the corresponding slice in the template brain. Note that the area contained within the green line corresponds to the area that is damaged in the lesion brain.

2.3 Statistical Analyses and Data Processing

2.3.1 Introduction

The neuroimaging procedures described above placed the lesions from each of the subjects into a common space (i.e., the “template brain”) which permitted group analyses across each voxel in the brain. The next sections present the development of a set of statistical techniques, which were ultimately used to test the study’s hypotheses.

2.3.2 Preliminary Analyses

2.3.2.1 Subjects

All of the preliminary analyses were based on a pilot sample which included the 137⁸ subjects (59 female; 78 male) who were published in the Damasio et al. (2004) study. As noted in the prior study, all of the subjects had unilateral focal lesions⁹, which were caused by either a cerebrovascular event (N=110), neurosurgical intervention (N=20), herpes simplex encephalitis (N=6) or focal head trauma (N=1). 124 subjects were right-handed (+90 or greater based on the Geschwind-Oldfield Questionnaire), 9 were mixed-handed (< +90 and > -90), and 4 were left-handed (-90 or less). All subjects had left hemisphere language dominance based on neurological, neuropsychological, and

⁸ Note, as discussed earlier, the original Damasio et al. (2004) study contained 139 subjects; however, only data from 137 of them were available due to the loss of data from 2 subjects.

⁹ As discussed earlier, during later analyses, 8 of these subjects were found to have additional damage outside of the lesion, including 4 who were found to have minor damage in the contralateral hemisphere.

for the temporal lobectomies, WADA testing. Mean estimated premorbid IQ was 104 based on a regression equation using demographic variables (Barona, Reynolds, & Chastain, 1984).

2.3.3.2 Weighted MAP-3 analysis

The analyses that were originally proposed at my prospectus on October 5, 2005 centered on a type of analysis called a weighted MAP-3 analysis, which in turn, was based on the MAP-3 technique developed by H. Damasio and colleagues (e.g., H. Damasio, 2000; Frank et al., 1997). Briefly, the MAP-3 technique requires first dividing the subjects into two groups: a deficit group and a no-deficit group, then overlapping the lesions within groups and subtracting the overlap maps across groups (forming lesion-difference maps). At a given voxel, the value of that voxel then corresponds to the number of subjects with a lesion and a deficit minus the number of subjects with a lesion and no-deficit (assuming that one is subtracting the no-deficit overlap map from the deficit map). Thus, across all of the voxels in the human brain, the MAP-3 technique provides a descriptive map revealing areas where lesions were more frequently associated with deficit than no-deficit. In general, the basic maps are descriptive; however, additional techniques have been developed that permit the use of inferential statistics as well as statistical control for the number of lesions at a given voxel (see Rudrauf, et al., submitted for further detail).

A feature of the basic MAP-3 analysis (or the modified proportional MAP-3 analysis developed by Rudrauf et al.) is that lesions are weighted equally within groups. Thus, the lesion from subject who performs at a level that is 5 standard deviations below

the mean is weighted the same as a lesion from subject who performs at a level that is 2 standard deviations below the mean (assuming a standard cutoff of Z score = -2.0 for deficit). It is possible that the differences in performance reveal important information regarding the underlying anatomical structure and therefore weighing lesions equally may mask this information. For example, if damage to the core of a neural system produced a more severe deficit whereas damage to the periphery of a neural system produced a less severe deficit then by weighing the lesions based on deficit, it may be possible to reveal central components of a neural system versus peripheral. Additionally, if larger lesions are associated with more severe deficit compared with smaller lesions due to damage to surrounding or related neural systems, then weighing lesions by lesion size may help reveal smaller, more homogenous neural systems.

Given the above, the present study initially proposed weighing lesions by the severity of deficit as well as lesion size in order to identify the regions that were most strongly associated with deficits for each of the four categories of visual stimuli.

2.3.2.2.1 Image Processing and Weighted MAP-3 Methodology: Although Brainvox allows for weighted-type analyses within the GUI interface, the lesion transfers, which are stored as “ROIs” within the Brainvox file structure were converted into PIC files, so that analyses could be run at the command line and utilizing programs other than Brainvox. This step was carried out in a C-shell utilizing a set of tal_programs (Frank et al., 1997). For those subjects whose lesions could not be warped in native PC space (i.e., those for whom lesion warping required re-orienting or re-slicing the template brain), this step also involved warping the traced lesions back into native space.

After all of the lesion ROIs were transformed into PIC files, additional steps were employed to generate weighted overlap maps. First, each subject's lesion was multiplied by that subject's standardized score (i.e., inverse Z-score) for each of the four categories: faces, animals, fruits/vegetables and tools/utensils. The weighted lesions were then summed within category to create weighted overlap maps. Notably, this is tantamount to a subtraction as some of the subjects had scores that were positive while others had scores that were negative.

Specificity for the weighted lesion-deficit associations was then examined by comparing the weighted maps across categories. To do this, the maps were first thresholded to remove all negative values (which would confound findings based on subtraction). The thresholded maps were then subtracted across categories, yielding the areas that were associated with the most frequent or most severe deficits in a particular category with the other categories factored out.

2.3.2.2.2 Weighted MAP-3 results: The results for the weighted MAP-3 overlaps are presented for each of the categories in Figure 2.2. In general, these results conform to the pattern that was observed in the Damasio et al. (2004) study, with the exception of an area of overlap in the right mesial and inferior temporal-occipital lobes for animals, which was observed in the prior study, but not in this analysis.

The results from the analysis of specificity (i.e., across category subtractions) are presented in Figure 2.3. The results yielded an area in the right temporo-parieto-occipital junction that was specific for faces, an area in the left mesial inferior temporo-occipital lobe that was specific for animals, an area in the left anterior temporal lobe that was

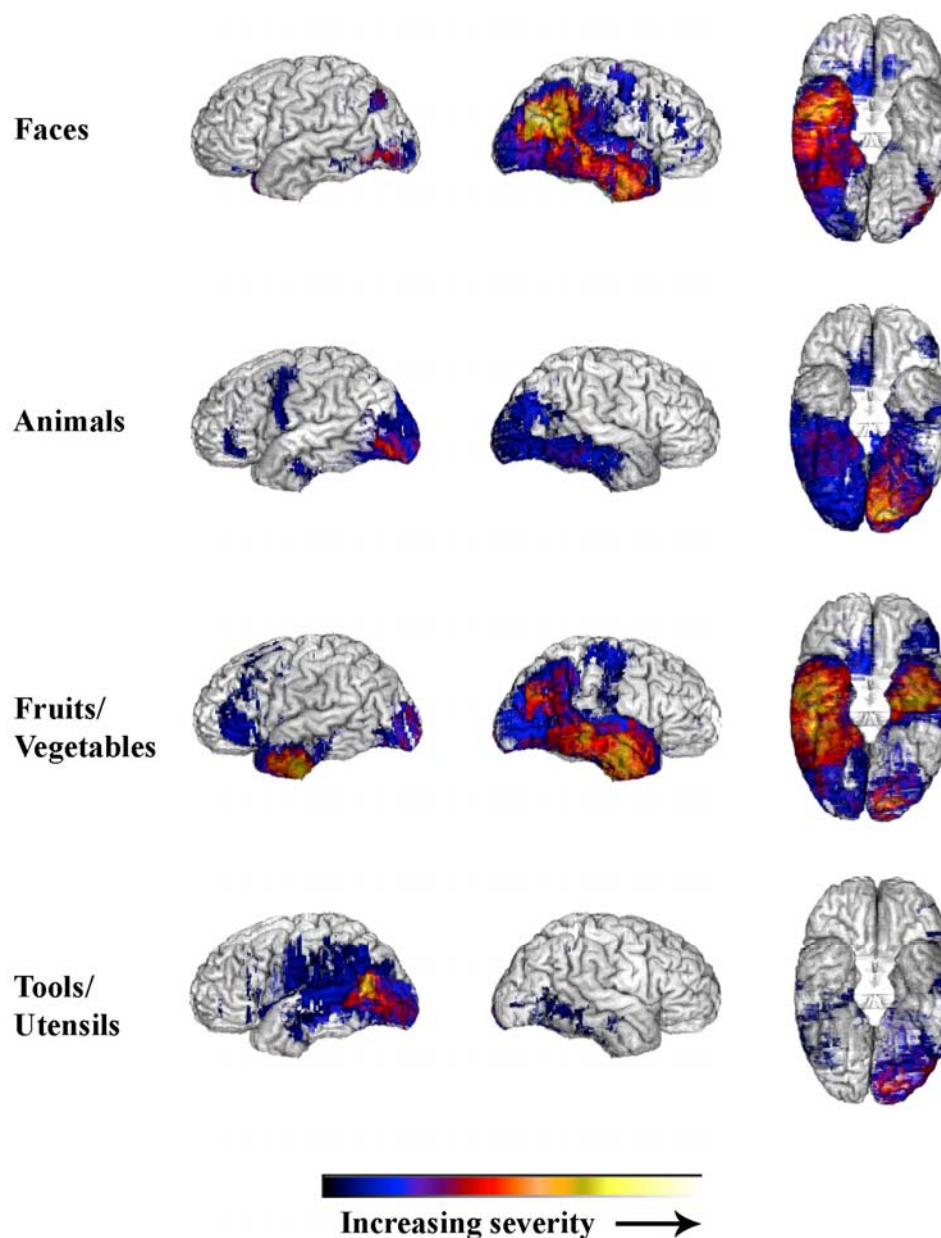


Figure 2.2 Results from Weighted MAP-3 Analysis. Unthresholded results from a weighted MAP-3 analysis overlaid on a template brain. For the purpose of display, the color bar has been set to the maximum overlap for each category (i.e., 9.87 for faces, 14.78 for animals, 11.04 for fruits/vegetables, and 19.97 for tools/utensils). Note that negative values are not displayed.

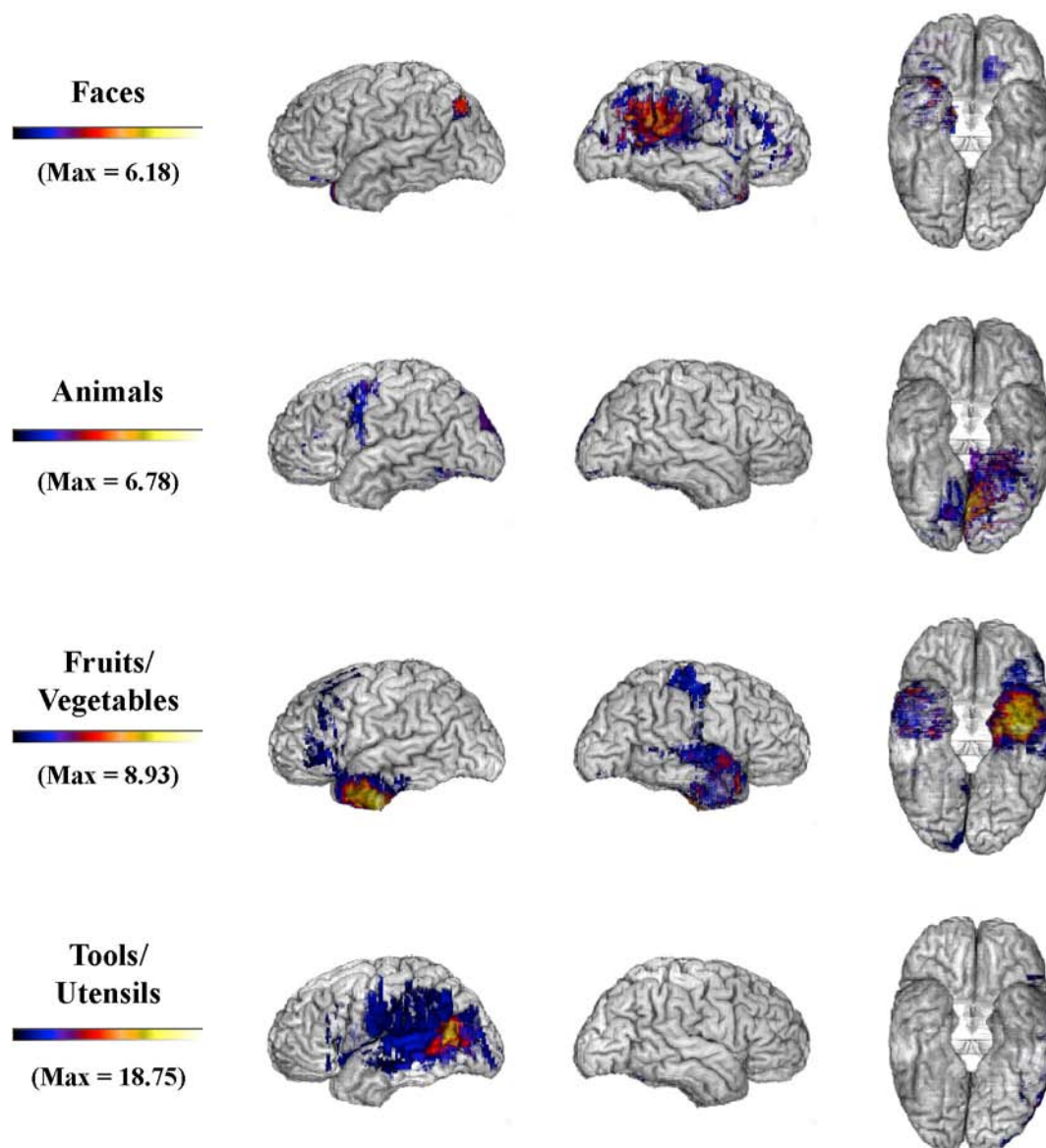


Figure 2.3 Results from specificity analysis. Areas of maximal specificity based on subtracting the weighted overlaps for the other three categories from the category of interest. Areas of maximal difference are depicted in color (see colorbar). Note that for the purpose of display, the color bar has been set to the maximum value for each analysis (i.e., 6.18 for faces, 6.78 for animals, 8.93 for fruits/vegetables, and 18.75 for tools/utensils). Negative values are not displayed.

specific for fruits and an area in the left temporo-parieto-occipital junction that was specific for tools.

One concern regarding the results from this analysis is that the subtraction is potentially confounded by differences in the range of scores across categories. As could be seen in the weighted overlaps above (see Figure 2.2), there was a range in the maximal overlaps from 9.87 for faces to 19.97 for tools/utensils. This difference has the potential to affect results from the subtraction at a voxelwise basis. Further, the use of the subtraction assumes that performance is equivocal across categories (i.e., that a score of $InvZ = 2.5$ means the same in different categories) and there are no data available to validate (or invalidate) that assumption. Given the above, as well as the fact that this analysis is very sensitive to statistical outliers, an attempt was made to develop an analysis that would not be limited by those problems.

2.3.3.3 Examination of those subjects with

“category-specific” deficits

One possible way of identifying the neural regions whose damage appeared to be most specifically related to deficits in a particular category was to examine only those subjects with “category-specific” deficits and determine their areas of overlap. Of the 137 subjects who were included in this analysis, 36 subjects were found to have deficits in the recognition of stimuli from a single category only; 5 of those had deficits in the recognition of faces only, 8 in the recognition of animals only, 19 in the recognition of fruits/vegetables only and 4 in the recognition of tools only.

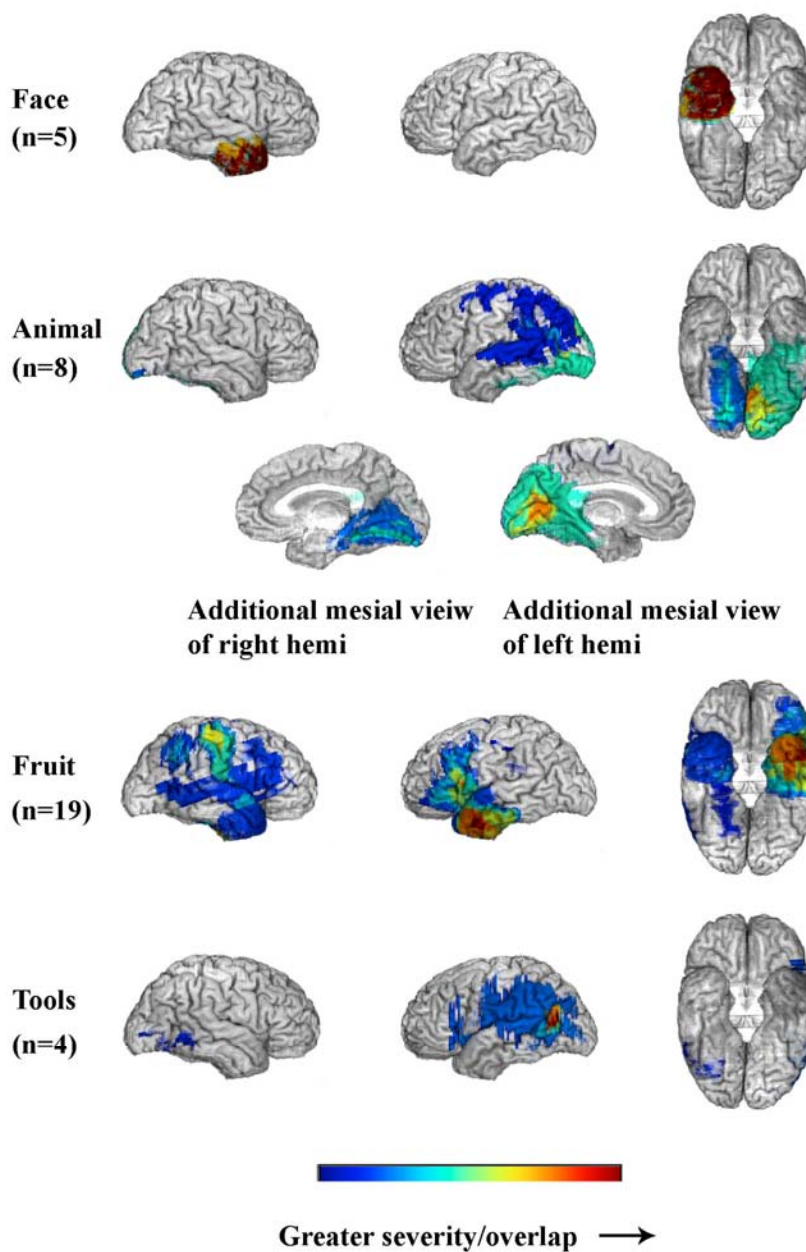


Figure 2.4 Overlap of weighted lesions for subjects with “category-specific” deficits. Colored regions represent areas that correspond to one or more category-specific lesions, with color intensity (see color bar) indicating the areas of greatest weighted overlap.

For each category, the weighted lesions corresponding to the subjects with the category-specific deficits were summed within category and presented in Figure 2.4. The findings revealed that the face-specific lesions overlapped maximally in the right temporal pole, the animal-specific lesions overlapped maximally in the mesial occipital lobe, the fruit-specific lesions overlapped maximally in the left temporal pole, and the tool-specific lesions overlapped maximally in the left temporo-parieto-occipital junction.

In general, these findings reflect a subset of the regions observed in the Damasio et al. (2004) study. However, they are based on only a quarter of the sample, and therefore, greatly limit the potential statistical power in this study. Further, it is possible that the category-specific deficits reflect anomalies or statistical outliers, and therefore, do not reflect the more typical organization of the higher-order visual and association cortices. Accordingly, it may be inappropriate to use those lesions solely when attempting to delineate the most typical organization of the human brain. Therefore, the decision was made to find an analysis that 1) would utilize the data from all of the subjects, 2) would not be very sensitive to outliers or to differences in the range of scores across categories, and 3) would permit identification of regions that appeared to be most strongly associated with deficits in a single category while controlling for deficits in the remaining three categories.

2.3.3 Final Analyses

2.3.3.1 Background

For the past two decades, functional imaging studies have been refining the analytic techniques that are available to examine brain-behavior relationships at a voxelwise level throughout the brain. More recently, researchers have begun employing similar techniques to the evaluation of brain-behavior relationships in neuropsychological investigations of patients with focal lesions (e.g., Bates et al., 2003; Karnath, Berger, Küker, & Rorden, 2003). The strength of these methods is that they allow for the use of continuous behavioral data, and employ inferential statistics. Further, because they are based on regression techniques, they are less sensitive to statistical outliers or to the differences in the range of scores observed across categories.

Given the aims of this study, it was decided to employ a voxelwise logistic regression analysis to identify areas of the brain where lesion is predicted by deficit in a single category, after deficits in other categories were taken into consideration. The strength of this approach is that it allows for the use of inferential statistics, and is not affected by the differences in range of scores across categories. More importantly, it provides a means of covarying out variance that may be explained by deficits in other categories.

2.3.3.2 Model and Implementation

This analysis utilized the following model:

$$\text{Logit} [\text{pr } Y=1] = \beta_0 + \beta_1(\text{InZ}_{\text{Face}}) + \beta_2(\text{InZ}_{\text{Animals}}) + \beta_3(\text{InZ}_{\text{Fruits}}) + \beta_4(\text{InZ}_{\text{Tools}})$$

where the binary dependent variable was lesion (1) or no-lesion (0) at that voxel, and the four independent variables were performance in the recognition of faces (InZ_{Face} ¹⁰), animals ($\text{InZ}_{\text{Animals}}$), fruits/vegetables ($\text{InZ}_{\text{Fruits}}$), and tools/utensils ($\text{InZ}_{\text{Tools}}$). As is standard in a regression equation, the model also employed an intercept term.

This logistic regression was implemented in Matlab (MathWorks, Inc., Natick, MA) utilizing the Econometrics Toolbox (Le Sage, 1999). Additionally, a binary mask was employed to restrict the analysis to the telencephalon. Similar to the manner in which other regressions are implemented in Matlab, the Logit regression utilizes a standardized “structure” for the output, and the variable of interest here was the t -statistic.

2.3.3.3 Statistical significance and thresholding

the data

The four output volumes corresponding to the results for person recognition, animal recognition, fruit/vegetable recognition and tool recognition, were then thresholded based on an uncorrected p -value of $p < .01$, one-tailed. A one-tailed value rather than a two-tailed value was utilized because I was interested in lesion-deficit relations, and had no a priori hypotheses regarding areas where deficit appeared to be predictive of no-lesion. To facilitate interpretation of the results, the thresholded volumes

¹⁰ The variable InZ refers to the arithmetic inverse of the Z score for performance in each respective category. As noted above, to obtain these scores, subjects individual scores were compared against the mean and standard deviation from the total population of lesion subjects who have completed this task ($N=423$) to yield a corresponding Z-score for each subject for each category. These Z-scores were then multiplied by (-1) to yield inverted Z-scores, such that higher numbers corresponded to greater impairment.

were then co-rendered with the template brain using Brainvox, and all significant voxels were highlighted in red.

A major challenge to any voxelwise analysis is the issue of multiple comparisons. This analysis, while run in a masked volume (i.e., only on those voxels which fall inside the telencephalon) still contains 889,583 voxels. Therefore, with an uncorrected p -value of $p < .01$, 8895 voxels were still expected to be significant by chance in each logistic regression.

Previous research has handled the issue of multiple comparisons in a number of different manners, although to date, no definitive solution has been established. In their 2004 study, Karnath and colleagues used a Bonferroni correction for their first voxelwise analysis, which utilized a chi-square, but applied an uncorrected threshold of $p < .05$ in a later analysis, which utilized logistic regression. Bates and colleagues (2003) used a similar Bonferroni correction in their study, which utilized a t-test as the basis for comparison across each voxel.

One concern regarding the use of the Bonferroni correction is that it assumes statistical independence across voxels (i.e., “ n independent tests”). However, the nature of data—namely, that it is lesion data—makes that prospect highly untenable. For any subject, if one voxel is lesioned, the probability that an adjacent voxel is lesioned is extremely high. In a group, this is even more problematic as most subjects in any lesion study acquired their lesions via a cerebrovascular accident and therefore, across subjects, there is a relatively high probability that if certain voxels are damaged, others are damaged as well. Therefore, the use of a statistical correction like the Bonferroni will actually result in overcorrection, and consequently, will substantially decrease power.

An alternative to the Bonferroni correction is to apply spatial smoothing and clustering algorithms, which can eliminate isolated voxels and leave the largest and most robust clusters of significant voxels intact. Notably, these algorithms have been previously applied to functional imaging data and shown to reduce the possibility of type I error while increasing power by as much as five-fold over methods like the Bonferroni correction (Forman, Cohen, Fitzgerald, Eddy, Mintun, & Noll, 1995)

For the present study, uncorrected results were first smoothed using a radius of 3 voxels using a program called tal_smooth (Frank et al., 1997). The 3-voxel radius was chosen based on results from a prior study by Fiez, Damasio and Grabowski (2000), which demonstrated that the mean standard deviation of the distance between MAP-3 lesion transfers by two independent, expert tracers was ± 3 voxels.

After smoothing, a cluster analysis was performed and a spatial extent threshold of 1000 voxels was applied. Prior functional imaging studies have applied a spatial extent threshold of 11 contiguous voxels (e.g., Graves, Grabowski, Mehta, & Gordon, 2007; McDermott, Petersen, Watson, & Ojemann, 2003); however, such a threshold would be inappropriate in this case given the size of the lesions. Assessment of the maximal clusters indicated that the largest cluster for faces was 30,348 voxels, for animals was 17,945, for fruits/vegetables was 5,789, and for tools was 23,669 (see Table 2.2). Further, there were only two clusters less than 1000 voxels in size. Therefore, thresholding the clusters at a spatial extent of >1000 voxels appeared to be a reasonable decision.

Table 2.2 Largest clusters for all significant results for the four-category logistic regression

	Cluster Number	Size (in voxels)
Faces	1	30343
	2	13797
	3	4522
	4	1510
	5	3
Animals	1	17945
	2	197
Fruits/Vegetables	1	5789
Tools/Utensils	1	23669

Note: Clusters of less than 2 voxels in size are not included.

2.3.3.4 Specificity and Overlap

The results from the logistic regression indicated areas that were predicted by a deficit in a single category, while factoring out covariance that could be attributed to impairments in other categories. It was still possible, however, for a voxel to be predicted by deficits in two or more categories, if there was sufficient unique explanatory variance for each variable. Given that the aims of this study were to identify areas that appeared to have the most specific, or unique, relationship with a deficit in a single category, it did not seem appropriate to refer to voxels that were predicted by deficits in multiple categories as being specific.

Accordingly, to identify areas that appeared to be uniquely or specifically related to deficits in a particular category (within the context of the four categories examined here), the voxels that overlapped across categories needed to be removed from the results.

To do this, masks representing the significant voxels were created for each category, and then each category was subtracted from each other category, pairwise. The results for the three subtractions for each category were then multiplied together, so that any voxel that was not significant in each was reduced to zero. Finally, for the purposes of display, masks representing the specific results for each category were multiplied by a different number (yielding different colors) and then overlaid together on the template brain using Brainvox.

2.3.3.5 Non-specificity and overlap

To this author's knowledge, this is the first study to use voxelwise logistic regression and a large sample of patients with focal lesions to try to identify specific lesion-deficit relationships amongst closely related cognitive functions. In this study, the issue of specificity was largely handled statistically, as relatively few patients in the sample actually presented with "category-specific" deficits. The assumption behind this approach is that the patients who do present with deficits across multiple categories do so because their lesions span multiple neural systems. However, an alternative explanation is that the patients present with deficits in multiple categories, because the same neural system is used to carry out cognitive functions related to both categories. Although this study cannot truly address which underlying assumption is actually true, it is helpful to compare the findings associated with specificity with those that are obtained when one examines which regions appear related to a deficit, regardless of specificity.

To do this, a parallel set of analysis were run without covarying out deficits in other categories. In this case, four logistic regressions were run, each with a binary

dependent variable, lesion (1) or no-lesion (0) at that voxel, and one independent variable, performance in the category of interest, in addition to the intercept term. Procedures for determining statistical significance, smoothing, and applying a spatial extent threshold were as described above.

A final set of analyses examined overlap across categories. For this, conjunction analyses were performed by multiplying the results for each of the four categories in each possible logical combination in pairs, triplets, and in the quartet. By multiplying, voxels that are not significant in each analysis are removed yielding only those voxels that are significant in all of the relevant results.

2.3.3.6 Results

2.3.3.6.1 Lesion Coverage: Figure 2.5 depicts the lesion coverage for the final sample. The most robust coverage was in the Middle Cerebral Artery territory and in the anterior temporal lobes. In contrast, coverage was much less extensive along the mesial surface of the frontal and parietal lobes, bilaterally, and along the ventral surface of the frontal lobes.

2.3.3.6.2 Analysis of Specificity: As hypothesized, there were regions where damage appeared to have a relatively specific relationship with deficits in faces, animals, fruits and tools (see Figure 2.6). These included an area in the left mesial occipital cortex (mostly lingual gyrus) that was specific for animal deficits, a small area in the right inferior temporal gyrus that was specific for fruits/vegetables, an area in the left lateral

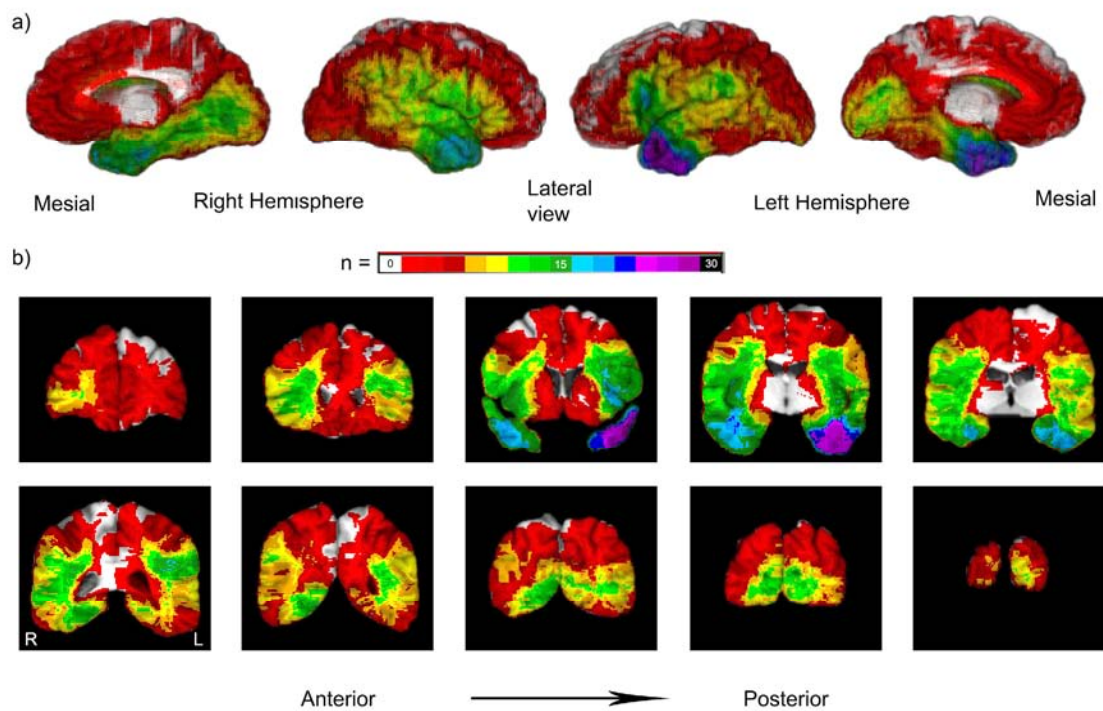


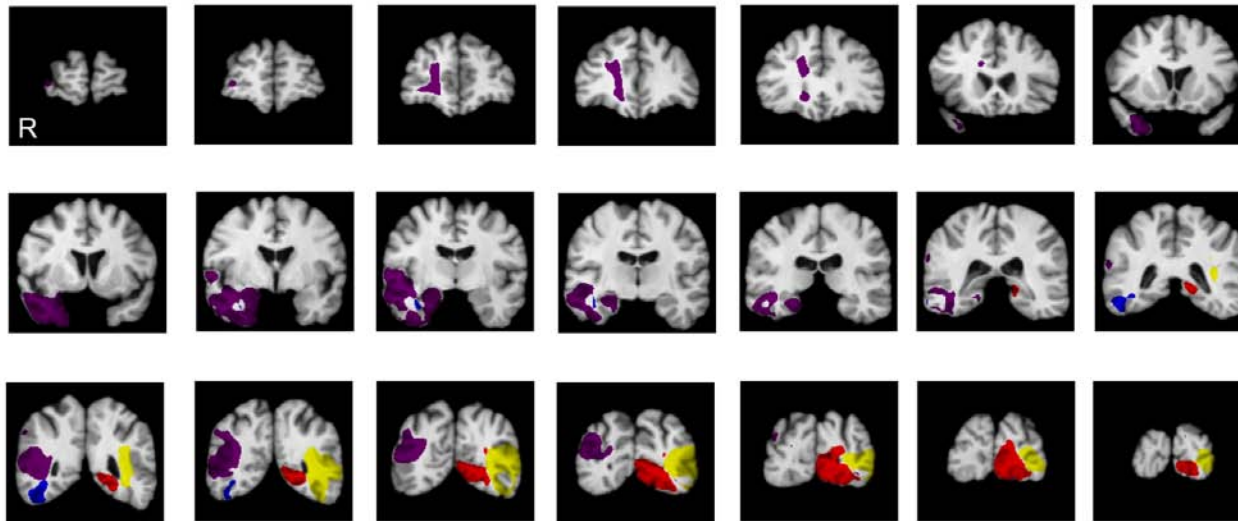
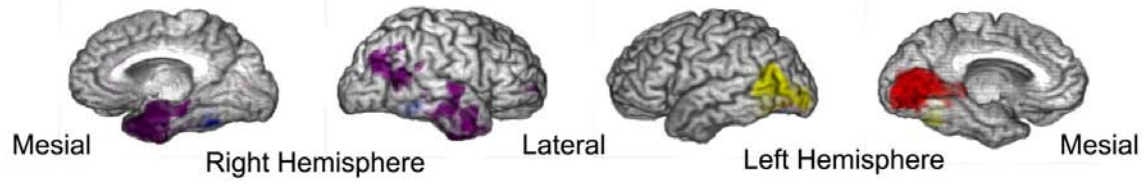
Figure 2.5 Lesion Coverage. MAP-3 overlap of lesions included in the final sample (N=180) represented on a) lateral and mesial views of the left and right hemispheres, and b) representative 2D slices. Color bar corresponds to number of overlapping lesions with cooler colors representing greater overlap.

occipital cortex that was specific for tools/utensils and a large area that included the right anterior temporal lobe, which then extended caudally through the white matter into the temporal-parietal-occipital junction and rostrally through the white matter core in the frontal lobe, for faces.

Compared to the regions that were identified in the 2004 study as well as in the parallel analysis that did not co-vary out deficits in other categories, these areas generally represent a subset of the regions that were identified by the other analyses (see Figure 2.7). However, it is also noteworthy that some of the most robust findings from the prior analyses do not appear to be regions that are specific to the categories of interest. For example, in the Damasio et al. (2004) study, there was a large area in the right mesial and inferior temporal-occipital cortex that was related to deficits in the recognition of animals, but was not found to be specific to animals in this analysis. Similarly, there was an area in the left temporal pole that was related to deficits in the recognition of fruits and vegetables in the prior study, but was not found to be specific to recognition of fruits/vegetables in this study. Further, the results from the second logistic regression where performance in fruits/vegetables was considered alone (i.e., without co-varying out deficits in other categories) also did not yield an association between performance in the recognition of fruits/vegetables and damage to the left anterior temporal lobe.

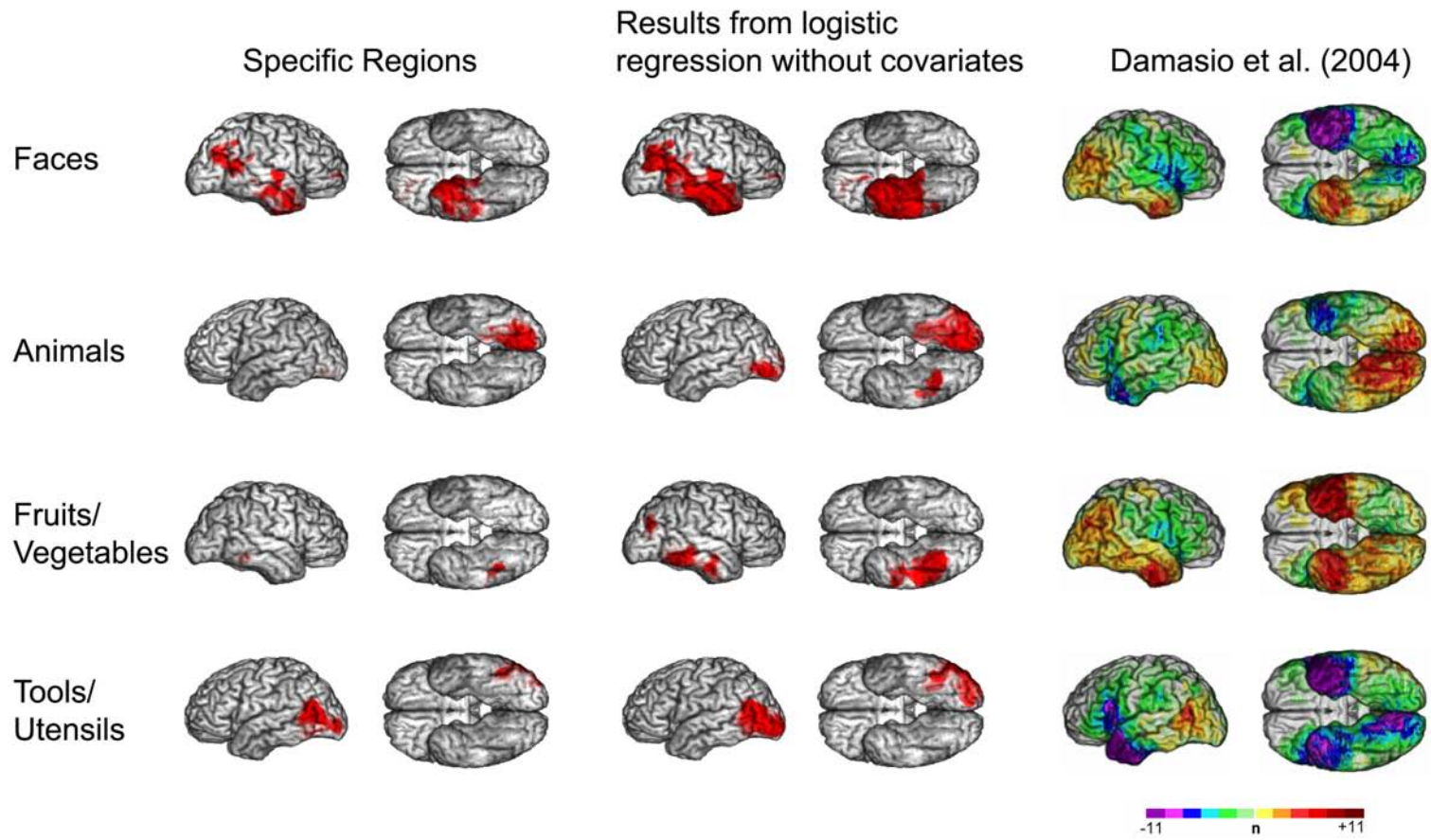
Notably, there has been a re-analysis of the data from the Damasio et al. (2004), which applied inferential statistics to traditional MAP-3 methods (Rudrauf, Mehta, Bruss, Tranel, Damasio, & Grabowski, in press). This study also addressed a common problem in lesion analysis, namely that there are different numbers of lesions represented at each voxel in the brain, by developing a “proportional MAP-3” statistic. Comparisons

Figure 2.6. Areas of relatively specific lesion-deficit associations. Purple indicates area of specificity for deficits in face recognition, red indicates area of specificity for deficits in animal recognition, blue indicates area of specificity for deficits in fruit/vegetable recognition (see bottom row, right hemisphere, 1st and 2nd slices, for example) and yellow indicates area of specificity for deficits in tool recognition. Findings are based on results from a voxelwise logistic regression which included lesion (1) or not (0) as the dependent variable and performance in recognition for each of the four categories as independent variables. Data were thresholded at $p < .01$, uncorrected, with a smoothing radius of 3-voxels and a spatial extent threshold of 1000 contiguous voxels. To identify areas of specificity, all voxels that were significant for multiple categories were removed from the respective results.



Anterior  Posterior

Figure 2.7 Comparison of findings from present study with those from the Damasio et al. (2004) study. For the results from the present study, red indicates significance after all smoothing and thresholding procedures were applied. For the prior study, positive results (see color bar) indicate areas where there were a greater number of lesions in the deficit group as compared to the no-deficit group. Note that results for the prior study were provided by David Rudrauf (Rudrauf, Mehta, Bruss, Tranel, Damasio, & Grabowski, in press) and are based on 129 subjects who were included in the re-analysis by Rudrauf et al. Data are reproduced with permission from D. Rudrauf and H. Damasio.



between the findings between this study and the re-analysis are presented in Figure 2.8.

Regarding the extent of overlap between the areas associated with deficits in each of the categories, overlap between the “specific” areas could not be examined due to the manner in which specificity was defined. However, conjunction analyses based on the results from the four-category logistic regression indicate that there was relatively little overlap pairwise in the areas that were predicted by performance in each of the categories after variance that could be attributed to impairments in other categories was factored out (see Table 2.3 and Figures 2.9). There were no areas of overlap across three or more categories.

Table 2.3 Overlap across categories for the results from the four-variable logistic regression.

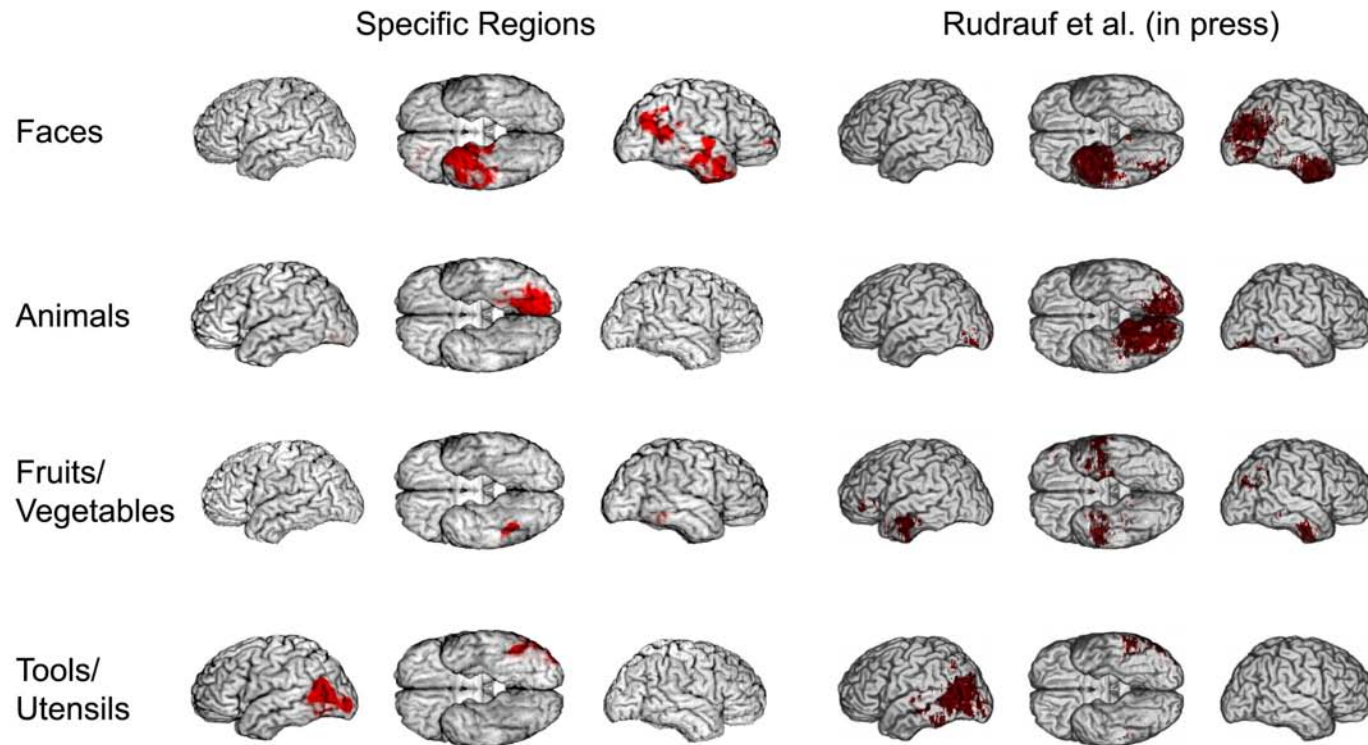
Category	Face	Animals	Fruits/Vegetables	Tools
Face ($N_{\text{total}} = 50172$)	n/a	0	2992	1483
Animals ($N_{\text{total}} = 17945$)		n/a	0	244
Fruits/Vegetables ($N_{\text{total}} = 5789$)			n/a	0
Tools/Utensils ($N_{\text{total}} = 23669$)				n/a

Note: Numbers indicate the number of overlapping voxels between each of the categories, examined pairwise. There were no overlapping voxels across three or more categories.

N_{total} refers to the size of the resultant volumes, in voxels, after thresholding as above.

N/a refers to not applicable.

Figure 2.8 Comparison of findings from this study with findings from Rudrauf et al. (in press). Red indicates areas of significant results in both the present analysis, and the analysis by Rudrauf et al. (in press), which utilized the “proportional MAP-3 statistic.” Results reproduced with permission from first author.



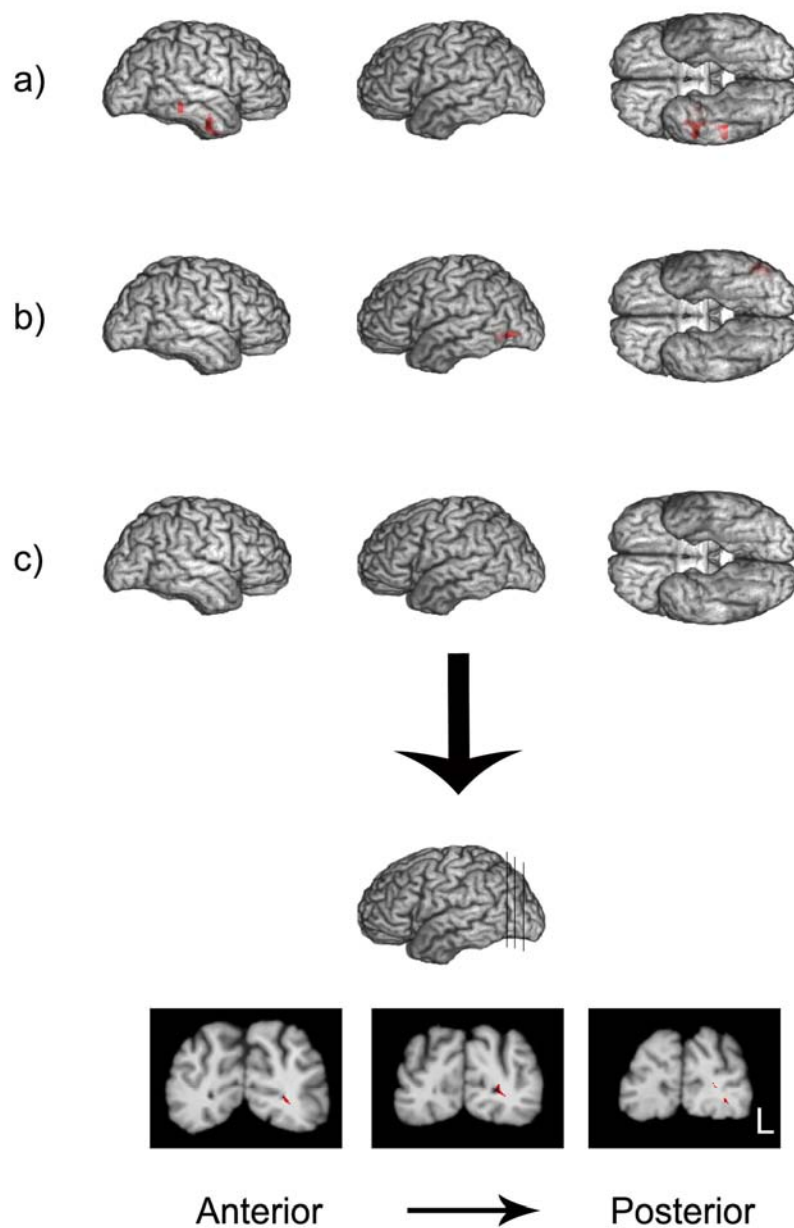


Figure 2.9 Areas of overlap across categories for the results from the four-variable logistic regression. Red indicates voxels that were significant in the conjunction analysis for a) faces and fruits/vegetables, b) faces and tools, and c) animals and tools. Note that the overlapping voxels for animals and tools are displayed on both a 3D rendering of the template brain, and for c) on representative 2D-slices due to their location.

Areas of damage that appear to be common to deficits across multiple categories were identified through conjunction analyses based on the results from single-category logistic regressions (see Table 2.4). The findings indicated that there was an area of overlap common to the three categories of Faces, Animals, and Fruits/Vegetables, which was located in the inferior temporal-occipital cortex (see Figure 2.10). There was no area of overlap common to deficits in all four categories, nor were there areas of overlap for any of the other three combinations of three categories (i.e., Faces, Animals and Tools/Utensils; Faces, Fruits/Vegetables, and Tools/Utensils; Animals, Fruits/Vegetables, and Tools/Utensils).

Table 2.4 Results from the conjunction analysis indicating overlaps between regions based on the four, single-category logistic regressions.

Category	Face	Animals	Fruits/Vegetables	Tools
Face ($N_{\text{total}} = 87,278$)	n/a	1837	19217	0
Animals ($N_{\text{total}} = 38,753$)		n/a	4888	16868
Fruits/Vegetables ($N_{\text{total}} = 25,740$)			n/a	0
Tools/Utensils ($N_{\text{total}} = 35,416$)				n/a

Note: Numbers indicate the number of overlapping voxels between each of the categories, examined pairwise.

N_{total} refers to the size of the resultant volumes, in voxels, after thresholding as above.

N/a refers to not applicable.

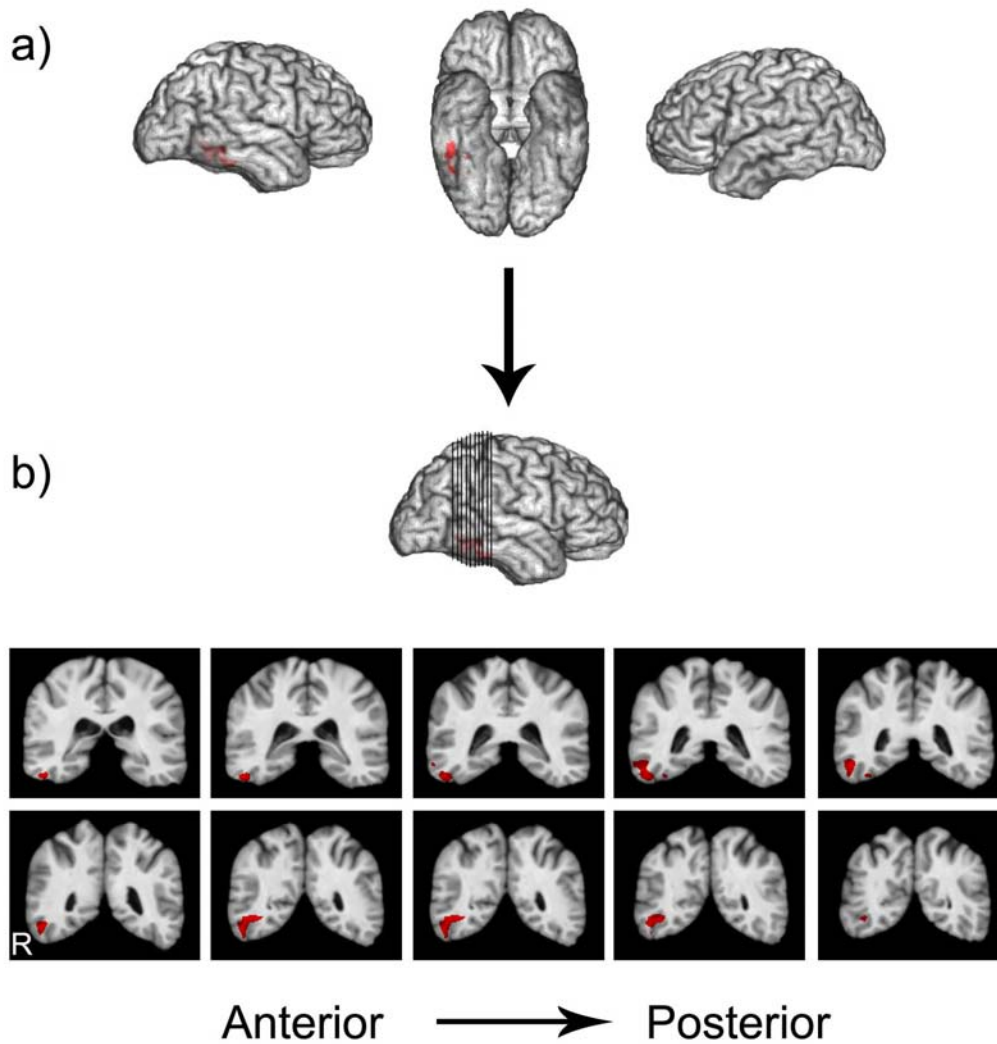


Figure 2.10 An area that appears to be related to deficits in the recognition of “natural entities.” Results from the conjunction analysis indicating an area (red) that appears to be related to deficits in the ability to recognize faces, animals and fruits.

2.4 Discussion

The prevailing models regarding visual recognition hold that the neural system subserving visual recognition can be subdivided into at least partially dissociable subsystems or subregions (e.g., Caramazza & Shelton, 1998; Damasio & Damasio, 1990; Farah, 1990), although the principle by which these subsystems are organized remains under considerable debate. In the past, evidence for this has been provided by case studies of patients who, following a stroke or other brain injury, display striking dissociations in their ability to recognize visual stimuli pertaining to different classes of stimuli (e.g., natural entities versus artifacts). Additionally, numerous functional imaging studies have shown that different patterns of neural activity are associated with processing different classes of visual in neurologically normal adults (e.g., Kanwisher et al., 1997).

The only large scale investigation of focal lesion patients aimed at identifying the neural systems subserving visual recognition was conducted in this laboratory, and it examined the lesion deficit associations between impairments in the ability to recognize faces (i.e., persons from faces), animals, fruits/vegetables and tools/utensils, as well as musical instruments (Damasio et al., 2004). Notably, this prior study did not examine the specificity of the lesion-deficit relations, and given the numerous functional imaging studies which have suggested that activity in different regions may be modulated based on the type of stimuli present as well as the case studies of patients who display “category-specific” visual recognition impairments, it is important to examine the specificity of these lesion-deficit relations across a large-scale sample of focal lesion patients.

To address this, the present study utilized a voxelwise logistic regression to parcel out variance that could be attributed to deficits across multiple categories of stimuli and identify areas of damage that were predicted by impairment in the category of interest. In this study, specific lesion-deficit relations were examined for the categories of faces, animals, fruits/vegetables and tools/utensils. As hypothesized, there were regions in visual and higher order association cortices where damage appeared to be more specifically associated with deficits in a particular category, than in any of the other categories. These regions included an area in the left mesial occipital cortex (mostly lingual gyrus) that was specific for animal deficits, a small area in the right inferior temporal gyrus that was specific for fruits/vegetables, an area in the left lateral occipital cortex that was specific for tools/utensils and a large area that included the right anterior temporal lobe, which then extended caudally through the white matter into the temporal-parietal-occipital junction and rostrally through the white matter core in the frontal lobe, for faces.

Compared to the findings from the Damasio et al. (2004), these areas represent a subset of the regions that were previously identified as being related to deficits in the respective categories. However, there are some notable differences. For example, in the prior study, in every category except tools, the regions that were identified as being related to the respective deficit were bilaterally distributed. Here, the areas that are specific are generally unilateral (with the possible exception of a small area in the contralateral hemisphere for faces). Additionally, some of the areas that appeared to be most robustly related to deficits in a particular category (e.g., left anterior temporal pole

for fruits/vegetables, right mesial and inferior IT for animals) were not found to be specific for these categories of deficit in the analyses presented here.

It is possible that the discrepancies in the findings between the two studies result from the fact that certain areas, while being necessary to carry out particular functions, are not specific for those functions. For example, the failure to find specific relations between deficits in any of the categories and damage to the posterior sector of the inferior temporal cortex suggests that this area may not be specific to the processing of stimuli from any one category.¹¹ This explanation is further supported by the results of the conjunction analysis, which indicated that there was an area in the posterior inferior temporal gyrus and temporal occipital gyrus that was related to deficits in the recognition of faces, animals, and fruits/vegetables.

2.4.1 The Category of Faces

Of the categories addressed in this study, the one that has received the most attention by researchers from various fields is faces. This is most likely the result of both the biological significance of this category as well as the patient reports themselves (i.e., it's much more common to hear a patient complain about an inability to recognize cherished family members than an inability to recognize berries of various sorts). As a result, research on prosopagnosia and the neural system subserving face recognition has been going on for more than 100 years.

¹¹ An alternative explanation is that there are areas within this region that are specific, but that they are too small in relation to the resolution that can be obtained in the present study to be identified with these analyses.

Current models of prosopagnosia posit that face recognition impairments arise from bilateral damage affecting the ventral temporal-occipital cortices (Damasio et al., 1982) or a unilateral lesion affecting parieto-occipital cortices on the right (DeRenzi, Perani, Carlesimo, Silveri, & Fazio, 1994) although, the latter is often purported to result in a more apperceptive form of prosopagnosia (Damasio et al., 1990). Additionally, data from a large scale study of focal lesion patients suggests that damage to the anterior temporal lobe or the angular gyrus on the right is also associated with face recognition impairments (Damasio et al., 2004). In contrast, current theories regarding the neural underpinnings of visual recognition in neurologically normal adults posit two areas as being involved in face processes more than object processes: the “fusiform face area” (e.g., Kanwisher et al., 1997; Grill-Spector et al., 2004) and the lateral occipital complex (Grill-Spector, Kourtzi, & Kanwisher, 2001).

Notably, these two lines of research focus on largely different regions—one being a widely distributed network in the ventral occipital cortex, and the other being a handful of voxels in two discrete areas. One possibility for these differences is that they are an artifact of methodological differences. In other words, it is possible that most of face processing is carried out by a few voxels in the ventral occipital temporal lobe, but that lesion subjects fail to demonstrate this because lesions are large relative to the size of the fusiform face area, and because most lesion studies don’t address specificity. In fact, this is supported by a single case report which demonstrated that a hematoma occupying the fusiform gyrus and lateral occipital region was sufficient to disrupt face recognition

(Wada & Yamamoto, 2001).¹² An alternative explanation is that the fusiform face area is not the *locus* of face recognition.

To examine this, I compared the face-specific region identified in this study with the fusiform face area (FFA) that has been defined through functional imaging studies, using the mean center of activation and a one standard deviation radius as reported in Grill-Spector et al. (2004). Notably, because I did not define the fusiform area based on functional data, I cannot be certain that the area truly encompasses what would have been FFA in every subject. However, based on the 1 SD radius and the distribution within the normal curve, I would expect the fusiform face areas for 74% or more of the subjects to fall within these bounds.

As is evident in Figure 2.11, the face-specific region identified in this study does not correspond to the FFA. In fact, the two regions are perfectly non-overlapping. Comparison with the face related area (see Figure 2.12) suggests that it is part of a network related to face processing, which at this point, has been well-established through the results of functional imaging studies and a century of lesion studies. However, it does not appear to be related to the areas where damage is specifically predicted by impairment in face recognition.

Given the above, an obvious question at this point is what is the FFA if it is not the locus of face recognition? To answer that, one must begin with how the FFA is defined. Recall that the FFA is an area that is more active (inferred from increased BOLD signal) when subjects view faces compared to when they view objects. Generally

¹² On the other hand, another case report of a patient with a large lesion in the lateral occipital area bilaterally, but without damage to the fusiform gyrus, and impairments in face recognition suggests that the fusiform face area is not sufficient for face processing.

speaking, this does not mean that the region is not active when subjects view objects, just that it is more active when subjects view faces. This difference in level of activity has been interpreted as reflecting the specificity of this area for face processing. An alternative explanation, however, is that face processing places higher demands on certain aspects of a neural system, most likely due to the nature of the task. In other words, if one begins with the hypothesis that processing faces is more demanding than processing animals, fruits, etc., because one not only needs to identify the item as a face (or a berry, etc), but that one needs to be able to link that face with stored knowledge about the person's identity, then it follows that such processing may require a greater recruitment of neurons to facilitate a more robust representation of the face or because it will be associated with or need to generate more widespread activation. There are many possibilities as to why. The key is that the difference in level of activation may not represent the specificity of the neural system, just the degree to which neurons in this area are recruited to facilitate processing.

Before shifting to the remaining categories, it is worth discussing one additional face-specific area. This is an area on the lateral surface of the temporal-occipital lobe, although its precise location has varied somewhat across studies. In the initial report of this area by Puce and colleagues (1995), the authors indicated that an area in the lateral occipital-temporal cortex caudal to the superior and inferior temporal sulci was activated for faces more than scrambled faces. More recently, although not the focus of their paper, Grill-Spector and colleagues (2004) reported findings about two additional areas that responded more strongly when subjects viewed faces compared to when they viewed objects. These included an area in the lateral occipital region that appeared to be in the

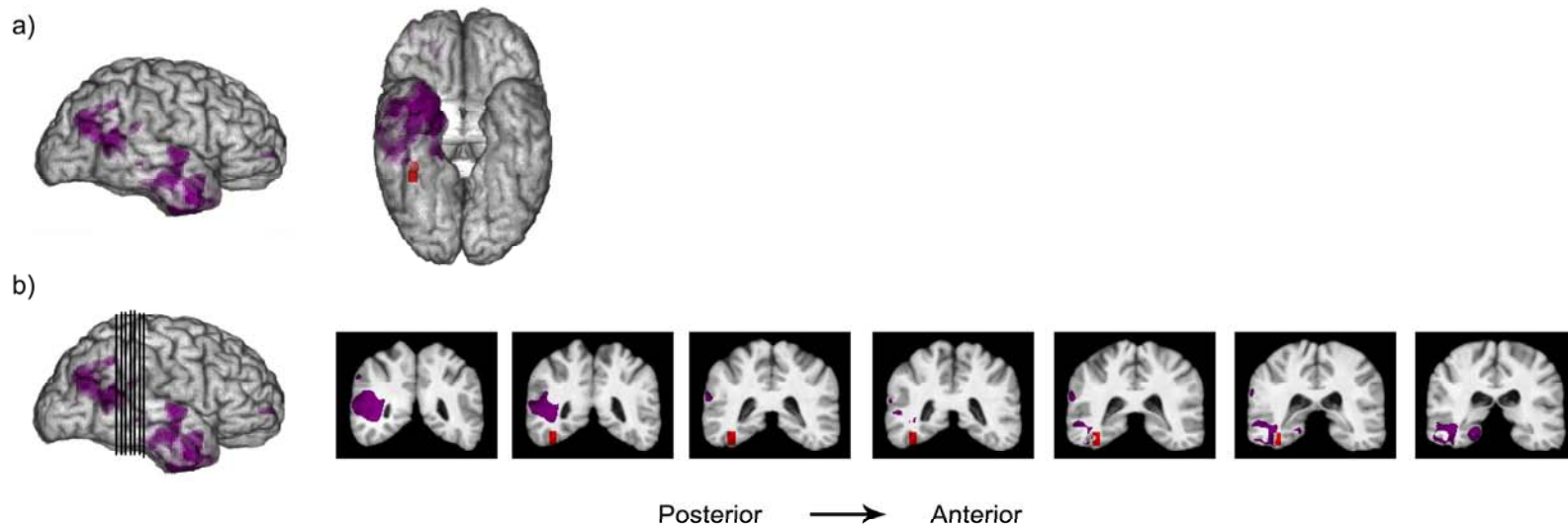


Figure 2.11 The “fusiform face area” overlaid with the “face-specific” region. Purple indicates the voxels that are specific for face recognition impairments, as defined in this study. Red indicates the probable fusiform face area mapped on the template brain based on the coordinates published in Grill-Spector et al. (2004): X, Y, Z; Mean + 1 SD.

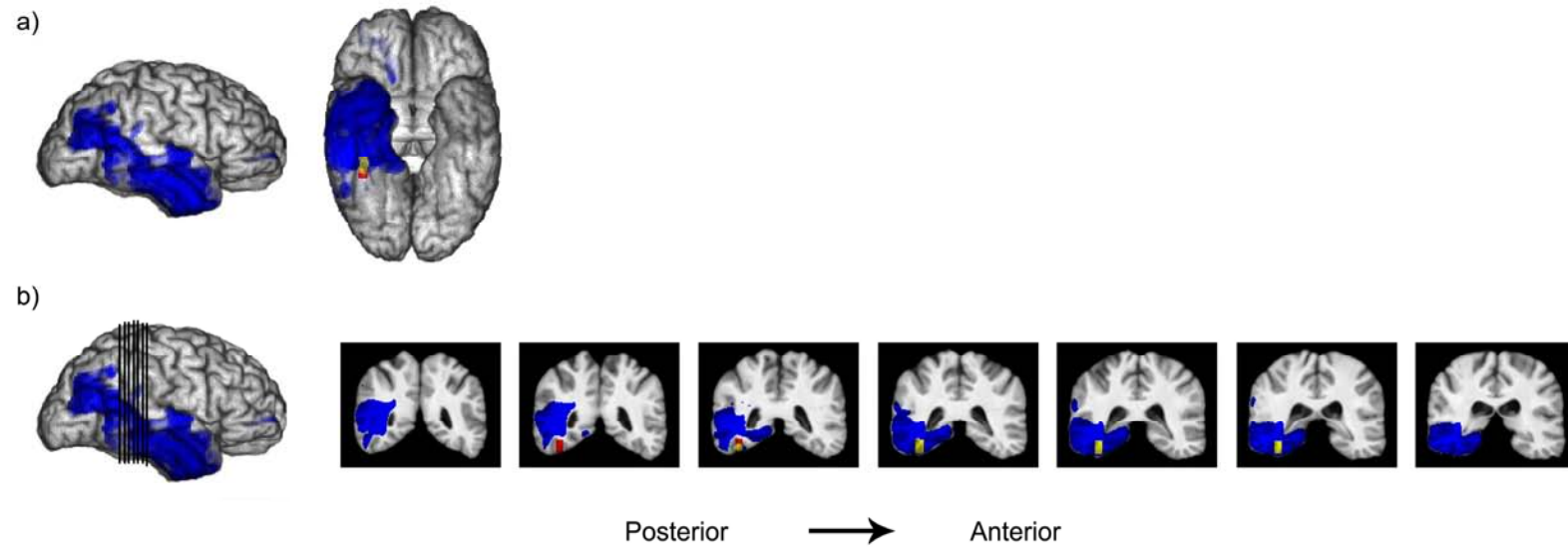


Figure 2.12 The “fusiform face area” overlaid with the “face-related” region. Blue indicates the voxels that are related to face recognition impairments, as defined in this study. Red indicates the probable fusiform face area mapped on the template brain based on the coordinates published in Grill-Spector et al. (2004): X, Y, Z; Mean + 1 SD. The area in yellow indicates the overlap between the FFA and the face-related region.

grey matter just caudal to the anterior occipital sulcus and an area that they refer to as posterior superior temporal sulcus (STS). Activation in the lateral occipital was associated with greater activation on face-detection hit trials than on misses; however, activation in the posterior STS was not. Grill-Spector and colleagues interpreted the latter as indicating that the area in the STS was not involved in recognition.

Similar to above, I compared the findings for my face-specific region to the lateral occipital complex as defined based on the findings from Grill-Spector et al., (2004) (see Figures 2.13 and 2.14). Just as above, I found no overlap between the face-specific area and the lateral occipital complex, and interestingly, no overlap between the face-related area and the lateral occipital complex, although the areas are adjacent in both cases. Again, these findings raise questions about how one interprets differences in level of activation during various tasks as assessed by functional imaging.

2.4.2 The category of tools/utensils

Following faces, the category that has received the most attention is tools/utensils. In the 1980s, it was shown that there could be dissociations in the recognition of tools versus the recognition of natural or living entities (which includes faces, animals, fruits/vegetables). For example, in the initial study by Warrington and Shallice (1984), all four patients, who were survivors of herpes simplex encephalitis, demonstrated intact tool recognition, while demonstrating impairments for living things. A few years later, Warrington and McCarthy (1994) described a patient with the opposite pattern: impaired visual recognition of common objects with intact recognition of animals following bilateral, but asymmetric infarcts in the right parietal lobe and left occipitotemporal

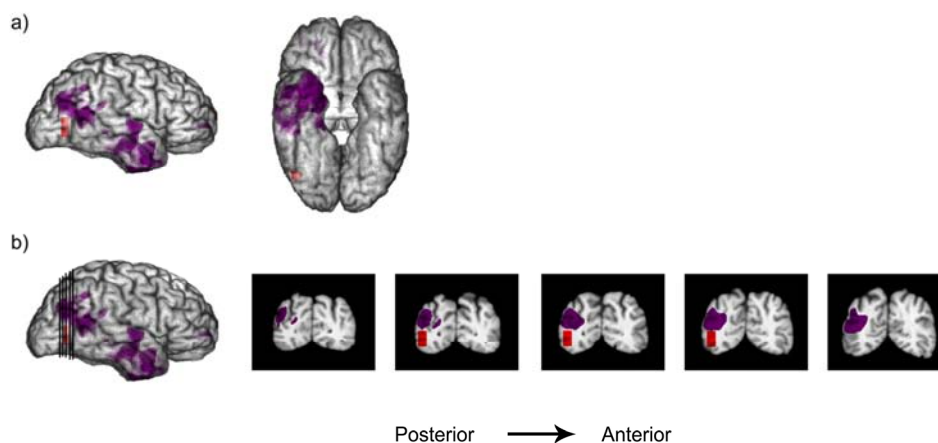


Figure 2.13 The lateral occipital complex overlaid with the “face-specific” region displayed on a) lateral and ventral views of a 3D-rendering of the template brain, and on b) representative 2D-slices. Purple indicates the voxels that are specific for face recognition impairments, as defined in this study. Red indicates the probable lateral occipital complex mapped on the template brain based on the coordinates published in Grill-Spector et al. (2004): X, Y, Z; Mean + 1 SD. Note that there is no overlap between the two regions.

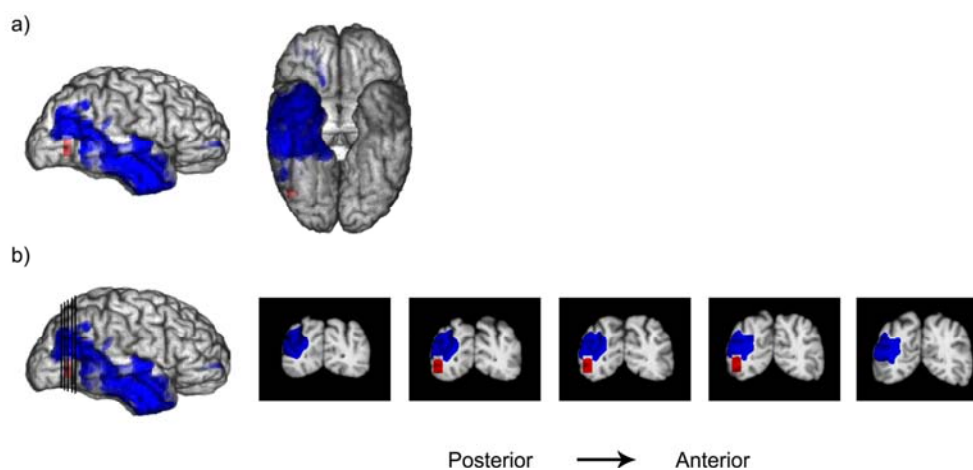


Figure 2.14 The lateral occipital complex overlaid with the “face-related” area displayed on a) lateral and ventral views of a 3D-rendering of the template brain, and on b) representative 2D-slices. Blue indicates the voxels that are related to deficits in face recognition, as defined in this study. Red indicates the probable lateral occipital complex mapped on the template brain based on the coordinates published in Grill-Spector et al. (2004): X, Y, Z; Mean + 1 SD. Note that there is no overlap between the two regions.

region.

Reviews of the published case studies pertaining to category-specific disorders suggest that damage involving the left frontal, temporal, parietal, or occipital lobes is associated with category-specific impairments for tools (Capitani, Laiacona, Mahon, & Caramazza, 2003; Gainotti, 2004). Additionally, as noted above, the only large-scale investigation of lesion patients, which was conducted by Damasio and colleagues (e.g., Damasio et al., 2004; Tranel et al., 1997) has indicated that the left temporo-parieto-occipital junction is part of a network which subserves tool recognition. Overall, the findings from the present study, which include that an area in the left temporo-parieto-occipital junction extending posterior-laterally into occipital cortices was specifically related to impairments in tool recognition converge well with prior case studies of patients with impairments in the recognition of tools or other artifacts.

With regard to the results from prior functional imaging studies, activation associated with perceiving or recognizing tools has been found in the middle temporal gyrus (e.g., Chao, Haxby, & Martin, 1999), fusiform gyrus mesial to the face-related activations (e.g., Chao et al., 1999), dorsal and ventral premotor cortices (Chao & Martin, 2000) and posterior parietal cortex (Chao & Martin, 2000). It has been noted that the functional imaging studies pertaining to tool recognition have often produced inconsistent results across studies and that the discrepancies may be attributable to methodological differences across the studies (e.g., Devlin et al., 2002, Moore & Price, 1999).

With the latter point in mind, the results from the present study do not converge well with results from prior functional imaging studies. For the category of tools, the findings from the present study revealed an area that includes the temporo-parieto-

occipital junction extending laterally into the occipital cortex as being specifically related to impaired performance in tool recognition. In general, the lack of convergence between this study and prior functional imaging studies could reflect the same problem that underlies the lack of convergence in functional imaging studies more broadly (namely, methodological differences pertaining to the task, stimuli, etc.); however, similar to the FFA, it also raises concerns about what is reflected by areas that are more active when viewing one particular class of stimuli versus another.

2.4.3 The category of animals

Relative to the above, the locus of animal-recognition processes have received considerably less attention in the literature. Case reports of patients with animal-specific deficits are rare, and generally speaking represent a mix of both recognition, naming and semantic impairments. Nonetheless, a review by Gainotti (2000) indicated that impairments pertaining to the category of animals or “plants” (i.e., fruits/vegetables) were associated with damage involving the posterior cerebral artery territory impinging on the mesial temporal-occipital cortices either restricted to the left hemisphere or bilaterally. Notably, the findings from this study of a relatively animal-specific area involving the mesial occipital lobe on the left (i.e., lingal gyrus) and an animal-related area involving the mesial occipital lobe on the left and ventral temporo-occipital areas on the right is generally consistent with the areas identified by Gainotti (2000).

With regard to prior findings from functional imaging studies, animal-related areas of activation have been found in the lateral fusiform gyrus, bilaterally, (Chao, Haxby, & Martin, 1999; Grill-Spector et al., 2004, for birds only) and left anterior-medial

temporal pole (Devlin et al., 2002), although it is also well documented that areas are often not replicated across studies (e.g., Aguirre & Farah, 1998). Kanwisher and colleagues investigated the specificity of activations pertaining to mammals, fish, birds, insects, spiders and microbes (amongst a total of 20 categories) and found no areas that were specific to these subcategories relative to each other. The finding in the present study of an area in the left mesial occipital lobe that was specific for impairment in animal recognition was therefore generally not consistent with the findings from the functional imaging literature and therefore raises questions about which areas are involved in animal recognition.

2.4.4 The category of fruits/vegetables

Of the four categories included in this study, the category whose inclusion was most questionable from the beginning was fruits/vegetables. This is due, in part, to the fact that category-specific impairments pertaining to fruits/vegetables are extremely rare in the literature (e.g., Hart, Brendt, & Caramazza, 1985; Samson & Pillon, 2003), and that functional imaging studies have not identified areas whose activity is specifically associated with the recognition of fruits/vegetables. However, rather than summarily discount the category of fruits/vegetables, I decided to include it and let the data determine whether there was support for specificity between performance in the recognition of fruits/vegetables and damage in the human brain.

Overall, the results indicated that there was a small area situated in the posterior aspect of the inferior temporal gyrus and lateral fusiform gyrus where damage appeared to be predicted by performance in the recognition of fruits/vegetables above and beyond

performance in the other four categories. Thus, at the outset, it appears that the results from this study are at least supportive of there being an aspect of a neural system subserving visual recognition that appears most strongly related to processing fruits/vegetables. However, qualitatively, the results for fruits/vegetables are much less compelling than for the remaining three categories.

First, compared to the very large regions that were identified for the remaining three categories (i.e., >17,000 voxels) the findings for fruits and vegetables revealed a very small region (5,789 voxels) that is less than a third of the size of the next smallest category-specific area. Although size per se should not discount the results, given the proximity of this region to other areas involved in visual recognition processes, it is concerning whether this area would hold under replication.

Second, the result for the category-specific area for fruits/vegetables differed markedly from the area that is most commonly associated with category-specific recognition impairments for fruits/vegetables, which is found maximally in the left temporal pole or left frontal operculum (see overlap of subjects with category-specific deficit for fruits/vegetables in Figure 2.3). This disparity raises concerns both about the validity of the category-specific region for fruits/vegetables, and the validity of the category-specific impairments for recognition of fruits/vegetables themselves. Regarding the latter, the fact that the patients who display “fruit/vegetable-specific” recognition impairments have damage most commonly outside of the fruit-specific area suggests that the patients with fruit-specific impairments may be outliers and that there may be alternative explanations for their deficits. Given the proximity of the lesion overlaps, one plausible explanation is that the subjects have some degree of language or naming

impairment, which in turn, affect performance on this task. Notably, the task was designed to minimize the effects of naming on recognition by accepting both correctly named responses and accurate conceptual information (e.g., “snunk” or “small animal that sprays a foul-smelling liquid when scared” as correct recognition for skunk). However, the nature of the items in the category of fruits/vegetables makes them harder to describe compared to animals like a skunk. For example, how would one describe a raspberry with sufficient detail as to differentiate it from a strawberry or a blackberry based on the verbal description alone? Thus, it is possible that patients who display naming impairments for these stimuli may look as if they have recognition impairments, because in the absence of the correct name, it may be difficult to provide enough verbal information to demonstrate recognition.

Overall, the results from the present study could be interpreted as providing mild support for there being aspects of a neural system that appear to be specific for processing fruits/vegetables, and suggest that further research should be done to elucidate this.

2.4.5 Natural versus Manmade Entities

In studies of patients with brain damage, one of the most robust dissociations has been between natural and artifactual or man-made stimuli. Starting with the earliest case reports (e.g., Nielsen, 1946; Warrington & Shallice, 1984), the most common description involves a deficit in recognizing types of natural stimuli (i.e., faces, animals, foods) with relative sparing of the ability to recognize tools or other manmade objects. There have also been a number of reports detailing the opposite—patients who have impairments in

the ability to recognize man-made stimuli (e.g., Warrington & McCarthy, 1994). In contrast, there have been remarkably few reports that demonstrate a dissociation between types of natural stimuli (e.g., animals and fruits).

In fact, this pattern was so common, that it led to numerous theories that centered on there being a division between the system subserving the recognition of natural entities versus the system subserving the recognition of artifactual stimuli (e.g., Warrington & Shallice, 1984; Martin & Caramazza, 2003). While the findings from the present study cannot be used to test these theories, it is striking that an area of convergence was observed for deficits in the recognition of faces, animals, and fruits. These findings suggest that there is a region in the posterior inferior temporal cortex which is necessary for the recognition of all three types of stimuli. It follows that if this area were damaged, deficits in the recognition for all three types of stimuli would occur, which may be the basis for the impairment in the recognition of “natural” entities.

2.5 Summary

The findings from the present study suggest that there are aspects of the neural system subserving the recognition of concrete entities that are most specifically involved in the processing of faces, animals, fruits/vegetables and tools/utensils and that when damaged appear to have relatively specific relations with deficits in the aforementioned categories. Although numerous questions remain (e.g., Can these areas be replicated? How can the findings from the functional imaging literature be reconciled with the findings from the present study?), one pertinent question, which will be addressed in the next section is how does damage to these area relate to severity of the clinical deficit?

CHAPTER 3

THE SEVERITY OF VISUAL RECOGNITION IMPAIRMENTS

3.1 Background

As discussed in the introduction, there has been remarkably little research aimed at understanding the factors that govern the severity of visual recognition impairments following focal brain damage. Available research does indicate that there can be considerable variability across patients in the severity of the observed deficit, with some patients demonstrating an almost complete loss of function, and others showing only mild impairments on laboratory tests. However, the precise factors that determine this are unknown.

Longitudinal data, albeit limited, suggest that there is likely only slight recovery of visual recognition functions during the chronic phase following a brain injury (e.g., Young & Ellis, 1989; Sparr et al., 1991), although possibly a greater degree of recovery acutely (Damasio, Damasio, & Van Hoesen, 1982; Hier, Mondlock, & Caplan, 1983). However, such data do not address the degree to which a given patient, examined cross-sectionally, displays a deficit.

Research pertaining to long-term outcome more generally, or to cognitive functions other than visual recognition, suggests that the degree of impairment may be a function of a number of factors, including age of onset, handedness, sex, premorbid abilities, as well as lesion characteristics, such as the mechanism of injury and location and size of the lesion. In particular, regarding to the latter, current research suggests that more fine grained estimates (e.g., extent of damage within a region) are more closely

related to deficit compared to gross indices like total lesion volume, owing to a more precise estimation of the disruption of the neural systems involved in a function.

Having identified areas where damage appeared to be specificity associated with deficits in the ability to recognize faces, animals, fruits/vegetables and tools/utensils, the present study examined the relationship between the extent of damage in these regions of interest, and the severity of the observed recognition impairment. Additionally, a number of demographic and neuropsychological variables were examined as possible moderators, with the overall aim being to identify the best models to account for the severity of a deficit in visual recognition following focal brain damage.

It was hypothesized that *anatomical factors (i.e., the extent of damage with in these regions of interest) would account for the greatest portion of variance in the severity of visual recognition impairments, but that additional variables including age, sex, handedness, age at onset, time elapsed since onset, contrast sensitivity, estimated premorbid IQ, and measures of visuoceptive, visuospatial, and visuoconstructive abilities would also account for a small portion of the variance in recognition for faces, animals, fruits/vegetables and tools.*

3.2 Method

3.2.1 Participants

The subjects that were included in this study were the same subjects that were included in the previous study (see section 2.2.1). Briefly, the sample consisted of 180 subjects with focal lesions, of which 167 had unilateral damage involving either the left

(N=104) or right (N=63) hemispheres, and 13 had bilateral damage. All except 6 had lesion onset at age 18 or later, and all had normal intelligence (e.g., Verbal Intelligence Quotient > 80) and the ability to attend to and perceive visual stimuli. Although some subjects had residual aphasias, all were able to produce verbal responses and to comprehend test instructions sufficient to complete the test.

3.2.2 Stimuli and procedures for assessing visual recognition

The stimuli and procedures used to assess visual recognition were the same as in the first study (see sections 2.2.2 – 2.2.4). As described above, subjects were shown photographs and line drawings of famous persons and ordinary objects (animals, fruits/vegetables, tools/utensils) and asked to indicate who or what they were. Subjects' responses were scored as correctly recognized if 1) a correct name was provided (e.g., "skunk" for skunk) or 2) a name was not provided, but information that is sufficient to allow a blind rater to identify the object was provided (e.g., "small animal that squirts foul-smelling liquid when scared" for skunk). The number of correct responses was then calculated for each subject and transformed into an inverse Z score, by comparing the subject's score to the mean and standard deviation for the total population of lesion patients and then multiplying by (-1). The latter ensured that positive numbers would be indicative of greater impairment.

3.2.3 Neuropsychological variables

Data regarding patient characteristics and performance on neuropsychological indices were coded from patient files, which are maintained as part of their participation in the Anatomical Substrates of Complex Behavior. Age of onset referred to the patient's age when they acquired their lesion and was coded based on age or date of onset as reported in their file. Notably, for some patients, the exact date was not available, and therefore, in those instances, age was based on the midpoint of the month and year corresponding to their lesion onset. Time elapsed between lesion-onset and when the recognition tests were completed was coded in years based on the date of lesion-onset and the date that the recognition battery was completed. Age referred to the subject's age at the time s/he completed the recognition tests. Handedness was coded from -100 to +100 and was based on the Geschwind-Oldfield Questionnaire. Contrast sensitivity (OD/OS or OU) was assessed using a wall chart viewed at standard distance (Pelli et al., 1988). Visuospatial, visuoconstructive, and perceptual discrimination functions were coded based on scores on the Judgment of Line Orientation test (Benton, des Hamsher, Varney, & Spreen, 1983), Block Design test (Wechsler Adult Intelligence Test-Revised or Third Edition; Wechsler, 1981; Wechsler, 1997), and Benton Facial Recognition Test (Benton, des Hamsher, Varney, & Spreen, 1983), respectively. Note that in instances where tests were repeated, data from the test that was administered closest in time to when the recognition battery was completed.

In contrast to the above, premorbid IQ was estimated based on demographic variables using the regression equation developed by Barona and colleagues (e.g., Barona

et al., 1984). For this study, the equation for estimating full scale IQ was used, which is as follows:

$$\text{Estimated FSIQ} = 54.96 + 0.47 (\text{age}) + 1.76 (\text{sex}) + 4.71 (\text{race}) + 5.02 (\text{education}) + 1.89 (\text{occupation}) + 0.59 (\text{region}).$$

In the above equation, values for the equation are determined from the following:

Age: 16-17 years = 1; 18-19 = 2; 20-24 = 3; 25-34 = 4; 35-44 = 5; 45-54 = 6; 55-64 = 7; 65-69 = 8; 70-74 = 9

Sex: Female = 1; Male = 2

Race: African American = 1; other = 2; Caucasian = 3

Education: 0-7 years = 1; 8 years = 2; 9-11 years = 3; 12 years = 4; 13-15 years = 5; 16+ years = 6.

Occupation: Unskilled laborers (e.g., farm workers) = 1; Semiskilled (e.g., farmers, service workers) = 2; not in the labor force = 3; skilled workers (e.g., craftsmen, foremen) = 4; managers, clerical, sales workers = 5; professional and technical = 6.

Region: South = 1; North Central = 2; West = 3; Northeast = 4.

The rationale for utilizing this to estimate premorbid IQ, is that the Barona index is not dependent on reading ability, and thus it ought not to be affected by reading impairments (e.g., alexia) or aphasia. Additionally, research by Powell, Brossart, and Reynolds (2003) found that estimates based on demographic variables alone were actually better predictors of premorbid IQ than estimates that combined current

performances on tests with demographic factors in a sample of patients who sustained brain injury.

3.2.4 Neuroimaging Methods

3.2.4.1 Anatomical Localization of the Lesion and

Mapping onto a Template Brain

For each subject, anatomical localization of the lesion was based on structural neuroimaging data (i.e., thin-cut T1-weighted images, or CT-scan) in accordance with the procedures in the Laboratory for Computational Neuroimaging, which are described in Chapter 2 (see section 2.2.5). All lesions were manually warped onto a template brain using the MAP-3 technique and subsequent analyses were based on these warped volumes (Frank et al., 1997; see also section 2.2.5).

3.2.4.2 Regions of interest

For this study, one of the key variables was extent of damage within a priori defined regions of interest (ROI). In this case, the ROIs were the category-specific regions that were derived in the first study. Accordingly, if the findings from the first study identified voxels that were specifically related to deficits in the recognition of faces, animals, fruits/vegetables and tools/utensils, this study investigated whether there was a linear relationship between the number of voxels that were damaged in these regions and the severity of the observed recognition impairment.

To generate the actual ROIs which were used in the analyses, the final results¹³ from the first study were overlaid on the template brain using Brainvox. Then, using features within the Brainvox software, the volumes were converted into ROIs using an automated technique. The final step involved manually editing the ROIs to ensure that none of the procedures altered the ROI with regard to key anatomical structures. Regarding the latter, the resultant ROI was reviewed in regards to six major sulci: Interhemispheric Fissure, Sylvian Fissure, Superior Temporal Sulcus, Central Sulcus, Collateral Sulcus, and Calcarine Fissure, as well as the lateral ventricles, and in any instance in which the resultant ROI crossed these boundaries in a manner that differed from the original results (prior to smoothing, etc.) the ROI was edited to back to reflect the original boundaries. Additionally, with regard to the grey matter at the surface of the brain, in many areas, the ROI included all of the grey matter except for that which fell within the lateral-most voxel, as a result of smooting procedures. Accordingly, in all areas where the bounds of the ROI differed from the surface of the brain by a distance of 3 voxels or less (i.e., the smoothing radius), the ROI was edited so that it included the full extent of the grey matter to the surface of the brain. (See Figure 3.1 for further details regarding manual editing procedures, and Figure 3.2 for example of resultant ROI.).

Following all of these procedures, the ROIs were converted into PIC files so that they could be used in subsequent analyses in programs outside of Brainvox (see section 2.3.2.2.1 for further details about how data were transformed into PIC files).

¹³ This corresponds to the specific regions, which resulted from the logistic regression controlling for deficits in the three categories that weren't of interest, with all thresholding and smoothing procedures applied as described in Sections 2.3.3.2 – 2.3.3.4.

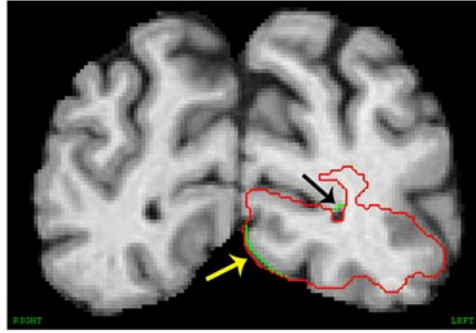


Figure 3.1. Examples pertaining to the manual editing procedures that were used in determining regions of interest. The red line represents the final ROI and the green lines represent the boundaries as generated through the automated procedure described in section 3.2.4. The black arrow indicates where the ROI was edited to remove the voxels that correspond to the lateral ventricle. The yellow arrow indicates where the ROI was edited so as to include all of the grey matter to the surface of the brain.

To examine the relation between damage to areas that appear to be related to deficit (but not necessarily specific), a parallel set of procedures was used to convert the results corresponding to the areas that are related to deficit (i.e., the results from the single category logistic regressions) into ROIs. A final set of ROIs were created based on a parcellation of the category-related ROIs into grey matter and white matter ROIs; however, data indicated that the extent of damage in the grey matter and white matter ROIs correlated $>.90$ with the extent of damage in the whole ROI, and thus grey matter and white matter ROIs were not used in the subsequent analyses.

3.2.5 Control Regions

To further demonstrate that it is extent of damage within these regions that matter and not just extent of damage within a more circumscribed area of the neocortex, two control regions were generated: a left hemisphere control region (which included the left

inferior and middle frontal gyri) and a right hemisphere control region (which included the right inferior and middle frontal gyri) (see Figure 3.4). These regions were chosen because they had adequate lesion coverage, were in the Middle Cerebral Artery territory (as were most of the subjects' lesions) and were comparable with regard to the size of the ROI. However, because these regions were outside of the regions that were found to be related to visual recognition impairments in the first study, they were not hypothesized to relate to the severity of visual recognition deficits for any of the four categories.

3.2.6 Calculating the extent of damage within the ROI

To calculate the extent of damage within the ROI, binary masks were made corresponding to each of the regions of interest. Damage in the ROI was then calculated by computing the volume of lesion within each ROI for each subject using tal_stat, a customized software program that computes both local and global statistics for three-dimensional volumes (Frank et al., 1997). This procedure was repeated for each of the ROIs as well as the whole brain volume, which allowed for the calculation of total lesion size.

3.3 **Statistical analyses**

3.3.1 Basic Analyses

To examine the relations between the extent of damage in the regions of interest and the severity of the recognition impairment, basic correlations were first computed between each of the ROIs and recognition performance in each of the categories using

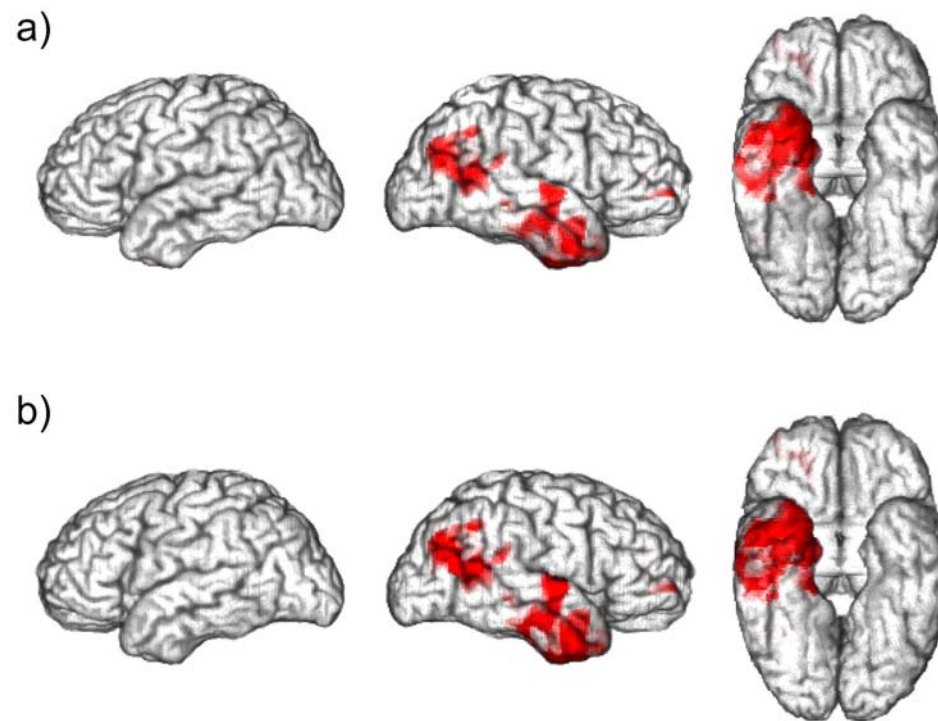


Figure 3.2 Example of an ROI. The results for the face specific region from chapter 2 are displayed in a) and the corresponding face-specific ROI is displayed in b). Note that there are areas in b) where the area in red is darker than the comparable area in a) (representing where the voxels at the surface of the brain were edited into the ROI), but that the overall pattern is nearly identical between a) and b), indicating the procedures for generating the ROI did very little to alter the volume.

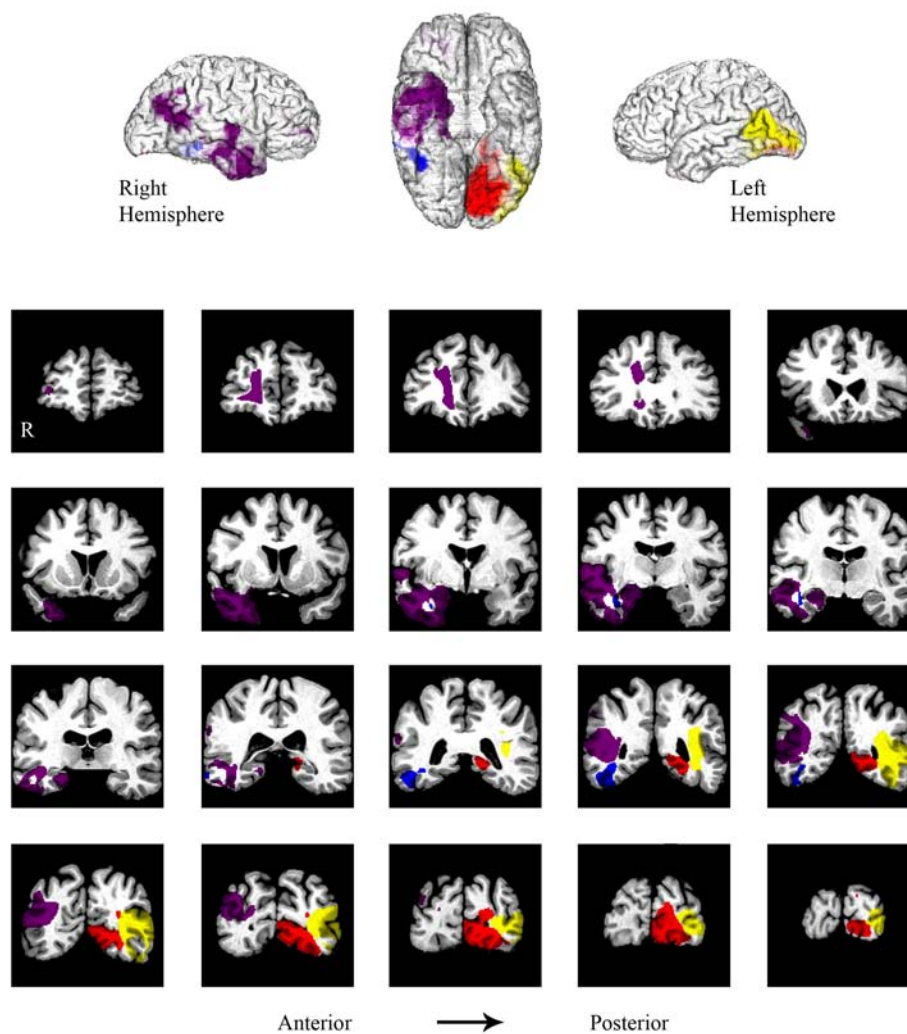


Figure 3.3 Category specific regions of interest depicted on lateral and ventral views of the template brain, and on representative 2D slices. Purple denotes the face-specific ROI, red denotes the animal-specific ROI, blue denotes the fruit/vegetable-specific ROI and yellow denotes the tool-specific ROI.

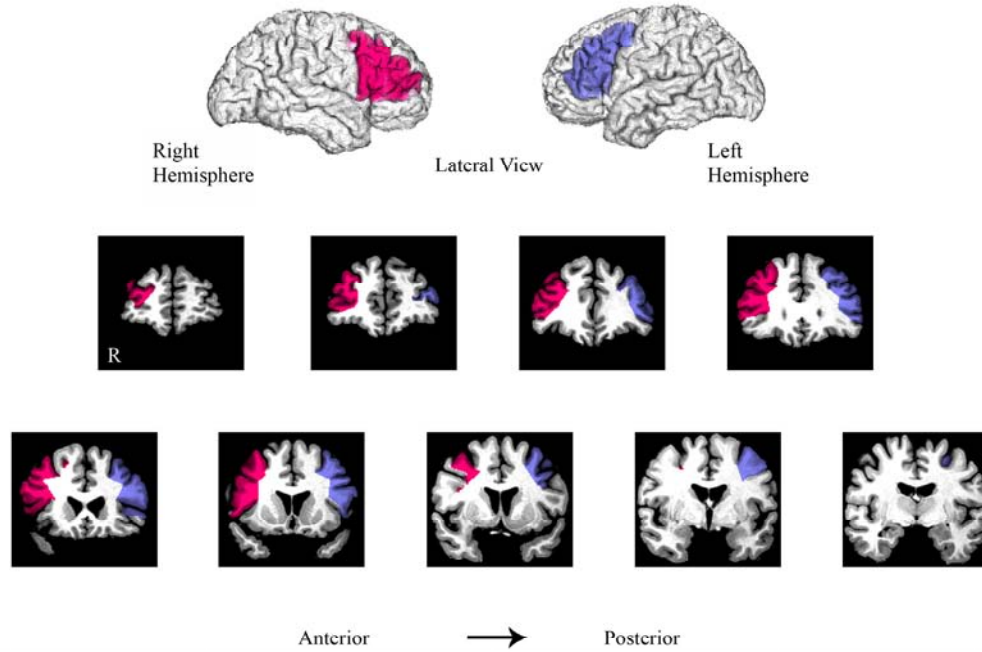


Figure 3.4 Control regions are depicted on lateral views of the template brain and on representative 2-D slices. Pink denotes the right hemisphere control region and blue denotes the left hemisphere control region.

SPSS[®] for Windows version 12.0. This procedure was then repeated across categories, so that the correlations between the extent of damage in one category and performance in the remaining three categories were computed. In general, these procedures provided validation of the specificity of the regions as it was expected that the correlation between the category-specific region and the respective category would be greater than the correlation between the category-specific region and performance in the remaining three categories.

Next, because I was interested in whether additional variables might help explain the variability in performance following focal brain damage, I examined the relations between various demographic demographic (i.e., handedness, sex), neuropsychological (i.e., estimated premorbid IQ, contrast sensitivity, and aspects of visual perception measured as performance on these neuropsychological tests: Block Design, Benton Facial Recognition Test, and Judgment of Line Orientation) and lesion variables (i.e., age of onset, time elapsed since onset) and performance in visual recognition. To do this, I computed partial correlations between these variables and performance in recognition for the four categories while controlling for the extent of damage in the category-specific ROI and overall lesion size.

Finally, because the overall framework for the present study posited that the neural systems subserving the visual recognition of faces, animals, fruits/vegetables and tools/utensils were partially overlapping, I tested the cross-category relations between damage and performance in recognition while controlling for the damage in the principal category-specific ROI and overall lesion size (e.g., meaning that for faces, I tested whether damage in the animal-specific, fruit-specific or tool-specific ROI were related to

performance on the face recognition task, after controlling for the extent of damage in the face-specific ROI). Note that for these analyses, the control regions were also included.

3.3.2 Testing moderator effects

Overall, the above analyses addressed whether various demographic, neuropsychological, and lesion variables were associated with performance in the recognition of faces, animals, fruits/vegetables, and tools/utensils, across the broad population of lesion patients. One possibility, however, is that these variables are only important for subjects who have damage to the neural systems that subserve visual recognition (i.e., that they *interact* with damage in the ROI). In other words, for the average subject without a lesion in the temporal-occipital cortices, it may be that performance on a test of visual discrimination, the Benton Facial Recognition Test (BFRT) has no bearing on performance on the recognition of animals task (i.e., that everyone falls within a narrow range of “normal” performance and that high-average or low-average is not dictated by BFRT performance); however, for those subjects with damage in this region, visual perceptual abilities may modulate visual recognition performance.

To test for this possibility, potential moderation effects were examined using hierarchical linear regression following the procedures outlined by Holmbeck (1997) and Baron and Kenny (1986). These procedures required mean centering the predictor variables (i.e., subtracting the mean value from each subject’s score) in order to minimize the correlation between predictor variables and potential interactions and maximize the likelihood of detecting significant effects (Aiken & West, 1991).

For the hierarchical regressions, all potential neuropsychological variables and lesion variables (i.e., extent of damage within the ROI, total lesion size), as mean-centered variables, were entered first. Interactions (i.e., moderating effects) were then tested individually, by adding them to the model containing neuropsychological and lesion variables alone, and then computing the change in R^2 associated with the new model compared to the old. Significance was set at $p < .05$, uncorrected for multiple comparisons. Notably, for many of the subjects data regarding one or more of the neuropsychological variables was missing, and rather than exclude these cases from the analyses, mean values were substituted for the missing values using standard procedures in SPSS. Follow-up analyses were conducted to facilitate interpretation of the interactions.

In addition to examining the potential moderating effects of various neuropsychological variables, this study also examined potential moderating effects of damage to additional regions of interest. Therefore, each potential ROI by ROI interaction was tested in accordance with the procedures outlined above.

The last step in the statistical procedures was to identify the best model to account for performance in the visual recognition of faces, animals, fruits/vegetables and tools. Notably, this analysis was not included in the original proposal, and thus, it should be considered exploratory. However, after examining the above variables individually, it seemed appropriate to try to develop a comprehensive model to account for severity for each of the aforementioned analyses. To do this, all candidate variables, which included the demographic, neuropsychological and lesion variables noted above, were entered into a stepwise regression. Notably, in the case where there were interactions between

damage to the principal region of interest and other variables, this was done separately for the group with damage in the principal ROI and the group without damage to the principal ROI. Forward selection procedures were then used to build the best model to account for performance in visual recognition. The forward selection model was chosen because it did not require the model to be specified a priori. Rather, the model is built based on the strength of the relationship between the independent variables, and the dependent variable, visual recognition performance. To do this, the computer selects the variable with the highest correlation with the dependent variable and enters it into the regression first (calculating overall F statistic for the model, etc.). Assuming the overall model is significant, the computer then computes partial correlations for the remaining variables (controlling for the variable that has already been entered into the regression) and then selects the variable with the highest partial correlation to be entered next. At this point, R^2 change is computed by comparing the R^2 for the new model with the R^2 for the previous model, and the new variable is retained if the addition of the variable caused a significant increase in R^2 ($p < .05$). The process is then repeated for all remaining variables until the entry of a variable no longer increases R^2 in a statistically significant manner, or until no variables remain.

3.4 Results

3.4.1 Relations between ROIs and severity of deficit

As hypothesized, the extent of damage in each of the specific regions of interest was related to recognition performance for each of the categories (see Table 3.1).

Further, the strength of the relationship was much greater within category than across category, lending support for the “specificity” of the ROIs, although notably, not all cross-category correlations were non-significant.

For “related”-areas, a strong association was again observed between the extent of damage in the ROIs and recognition performance. Similar to above, this relationship was generally stronger for within category associations than across category associations, and not observed for the control categories (all p 's > .20). Notably, at this point, a large correlation between the extent of damage in the fruit-related region and performance in face recognition was observed. This was likely due to the fact that the fruit-related area largely overlaps with the face-related and face-specific areas.

One concern that could be raised regarding correlations between damage and the severity of the deficit, is that the correlation actually reflects a separation between poor performance by those subjects who sustained damage in the ROI and good performance by those subjects who did not. To address this, correlations were recalculated only for those subjects who sustained damage in the ROI (see Tables 3.3 and 3.4). In general, by restricting the calculation to only those subjects who sustained damage in the ROI, the magnitude of the correlations increased, while maintaining the general pattern for all of the regions except for the ones pertaining to fruits. Regarding the latter, for the subjects who sustained damage in the fruit-specific ROI, a large correlation was observed between the extent of damage in that ROI and performance in animal recognition. Similarly, for the fruit-related area, large correlations between the extent of damage in the fruit-related area and recognition performance for faces and animals were observed.

To further examine the relations between the extent of damage in the ROI and the

Table 3.1 Correlations between damage in the category-specific regions of interest and impairment in recognition of faces, animals, fruits/vegetables and tools/utensils.

		Regions of Interest			
		Face-specific	Animal-specific	Fruit-specific	Tool-specific
Recognition	Faces	.404**	-.023	.247**	.030
	Animals	.097	.397**	.221**	.180*
	Fruits/vegetables	.216**	.103	.354**	.036
	Tools/utensils	-.048	.224**	.047	.539**

Note the correlations along the diagonal (in **bold**). These represent within category correlations and should be higher than across category correlations (see corresponding column or row).

* $p < .05$. ** $p < .01$. N=180.

Table 3.2 Correlations between damage in the category-related regions of interest and impairment in the recognition of faces, animals, fruits/vegetables, and tools/utensils.

		Regions of Interest				Control Regions	
		Face-related	Animal-related	Fruit-related	Tool-related	Right MFG/IFG	Left MFG/IFG
Recognition	Faces	.397**	.084	.355**	.049	.092	-.086
	Animals	.128	.477**	.220**	.324**	-.073	.011
	Fruits/vegetables	.237*	.216**	.335**	.116	-.031	.032
	Tools/utensils	-.045	.379**	.018	.568**	-.062	.011

** $p < .01$

severity of the observed deficit, the extent of damage was plotted against severity for only those subjects who sustained damage in the ROI for category-specific as well as category-related ROIs (see Figures 3.5 – 3.12).

In general, the plots suggested that there was a linear relationship between the extent of damage within an ROI and the severity of a patient's deficit. At the same time, careful examination of the plots also indicated that not every patient appeared to obey the linear trend (notwithstanding the variability amongst those that did follow the trend as well). Further, there appeared to be two different types of potential outliers: those who appeared to perform better than would be expected based on the extent of their lesion and those who performed worse than would be expected based on the extent of their lesion. This raised interesting questions about who these individuals might be, and whether there would be commonalities amongst them that might be revealing to the studies aims. Therefore, post-hoc analyses were done to examine these potential outliers.

3.4.2 Examination of the outliers

Basic demographic and lesion data are provided for the outliers in Tables 3.5-3.8. Additionally, because one potential explanation for the outliers is that their lesions were anomalous with regard to the ROIs (e.g., missing the core and affecting only peripheral voxels), the subjects' lesions (traced as volumes on the template brain) were overlaid with the specific ROIs and displayed on the template brain (see Figures 3.13 – 3.33).

In general, a careful examination of the data did not reveal one factor that appeared to account for the outliers across all four categories. However, within category, the data revealed some commonalities amongst the subjects which may account for their

Table 3.3 Correlation between damage in the ROIs and severity of deficit based only on those subjects who sustained damage in the ROI.

		Regions of Interest			
		Face-specific	Animal-specific	Fruit-specific	Tool-specific
Recognition	Faces	.576**	.008	.280	.165
	Animals	.299*	.428**	.588**	.157
	Fruits/vegetables	.348**	.038	.568**	.040
	Tools/utensils	.020	.053	.175	.496**

Note that n= 63 for the face-specific ROI, n=53 for the animal-specific ROI, n=37 for the fruit-specific ROI, and n=52 for the tool-specific ROI.

* $p < .05$. ** $p < .01$

Table 3.4 Correlations between damage in the category-related regions and the severity of the deficit based only on those subjects who sustained damage in the ROI.

		Regions of Interest				Control Regions	
		Face-related	Animal-related	Fruit-related	Tool-related	Right MFG/IFG	Left MFG/IFG
Recognition	Faces	.565**	.083	.549**	.177	-.006	-.213
	Animals	.336**	.477**	.625**	.363**	-.142	.218
	Fruits/vegetables	.375**	.193	.580**	.167	-.111	.221
	Tools/utensils	.022	.307**	.143	.544**	.003	.074

Note that MFG = Middle Frontal Gyrus and IFG = Inferior Frontal Gyrus.

Note that n=68 for the face-related ROI, n=82 for the animal-related ROI, n=52 for the fruit-related ROI, n=61 for the tool-related ROI, n=25 for the right IFG/MFG control region, and n=33 for the left IFG/MFG control region.

** $p < .01$

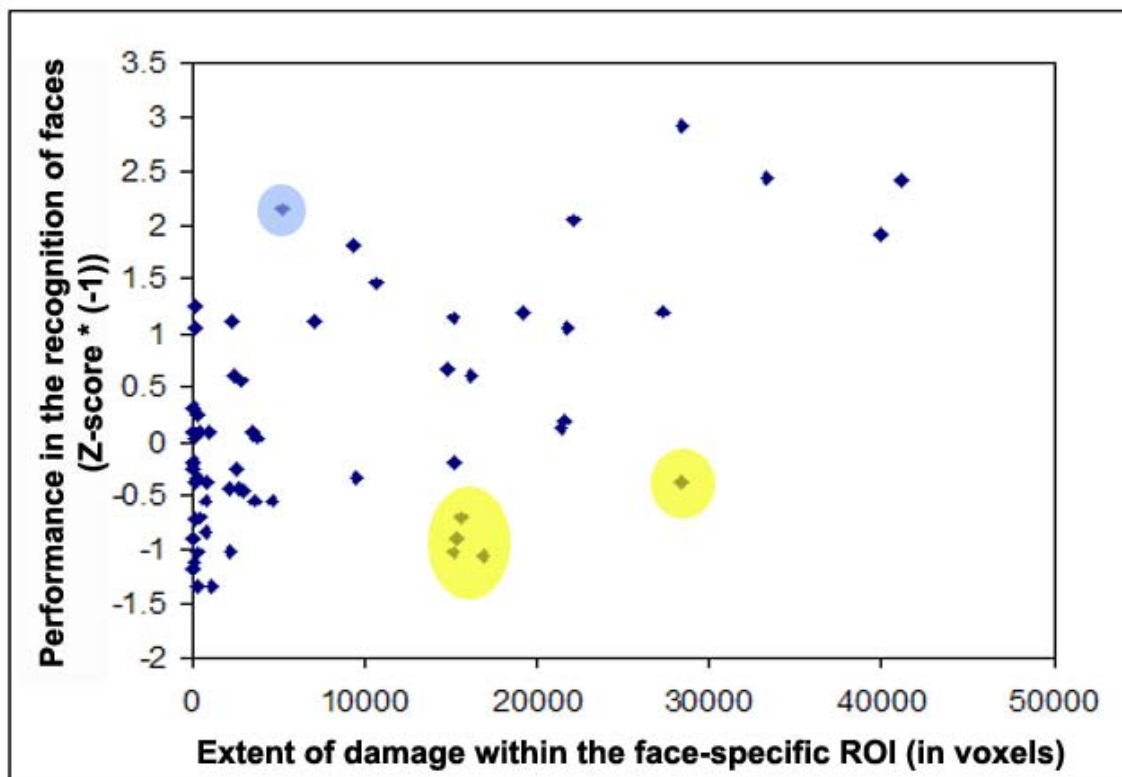


Figure 3.5 The relationship between damage in the face-specific ROI and the severity of the face recognition impairment. The scores for individual subjects ($n=63$) are plotted as individual points in dark blue. In general, there was a linear relationship between the extent of damage in the face-specific ROI and recognition of famous faces ($r = .576, p < .01$). However, note the potential outliers who are highlighted in light blue and yellow. The subject in light blue represents a case where the severity of the deficit appears to be greater than would be expected based on the extent of damage in the ROI. The subjects in yellow represent cases where the severity appears to be less than would be expected based on the extent of damage in the ROI.

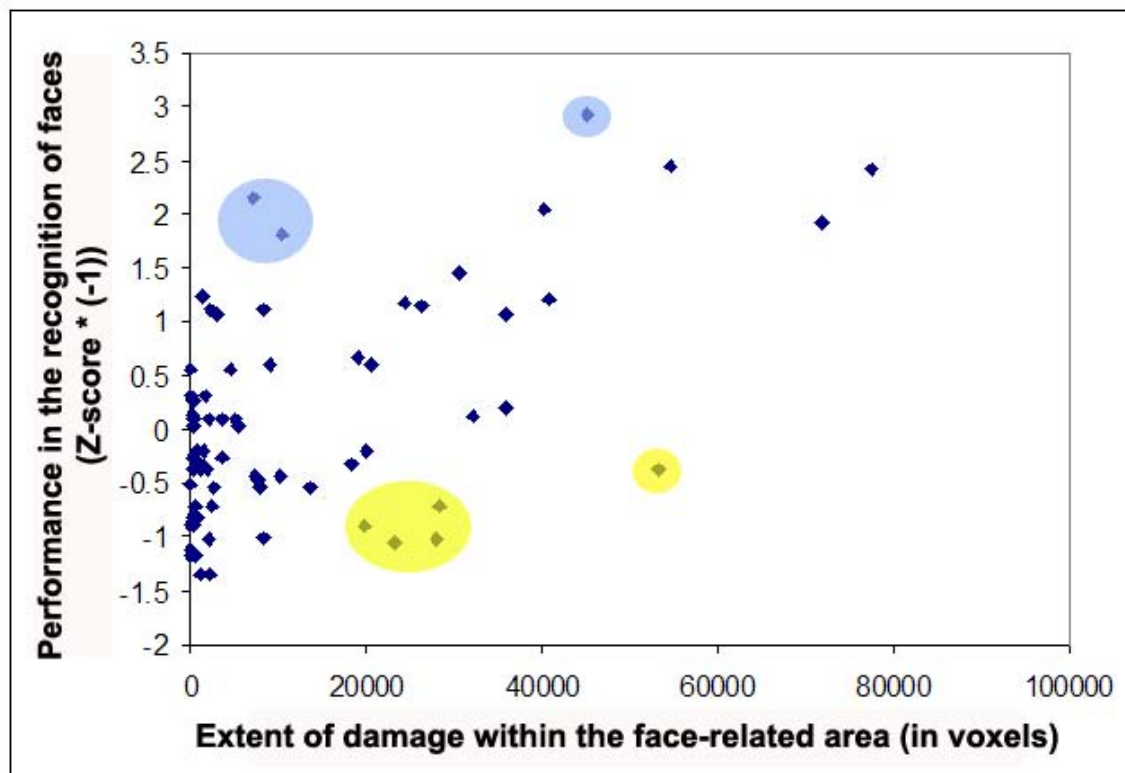


Figure 3.6 The relationship between damage in the face-related area and the severity of the face recognition impairment. The scores for individual subjects ($n=68$) are plotted as individual points in dark blue. In general, there was a linear relationship between the extent of damage in the face-related area and recognition of famous faces ($r = .565, p < .01$). However, note the potential outliers who are highlighted in light blue and yellow. The subjects in light blue represent cases where the severity of the deficit appears to be greater than would be expected based on the extent of damage in the ROI. The subjects in yellow represent cases where the severity appears to be less than would be expected based on the extent of damage in the ROI.

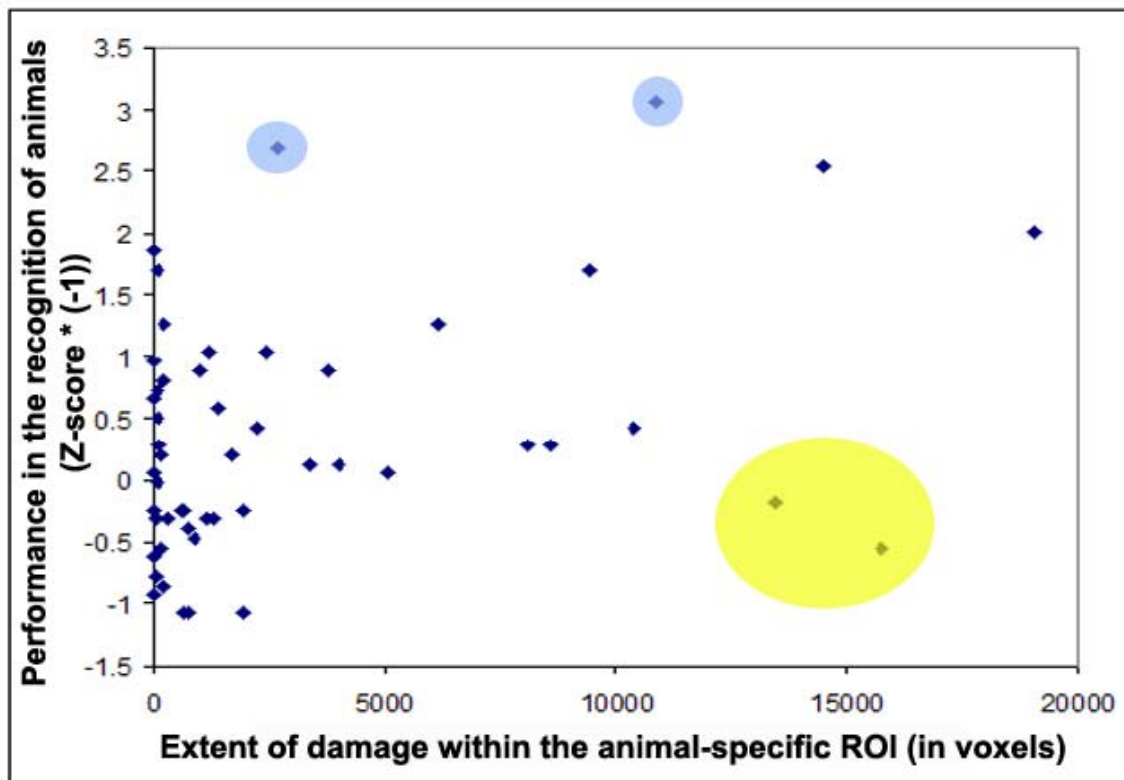


Figure 3.7 The relationship between damage in the animal-specific ROI and the severity of the animal recognition impairment. The scores for individual subjects ($n=53$) are plotted as individual points in dark blue. In general, there was a linear relationship between the extent of damage in the animal-specific ROI and recognition of animals ($r = .428, p < .01$). However, note the potential outliers who are highlighted in light blue and yellow. The subjects in light blue represent cases where the severity of the deficit appears to be greater than would be expected based on the extent of damage in the ROI. The subjects in yellow represent cases where the severity appears to be less than would be expected based on the extent of damage in the ROI.

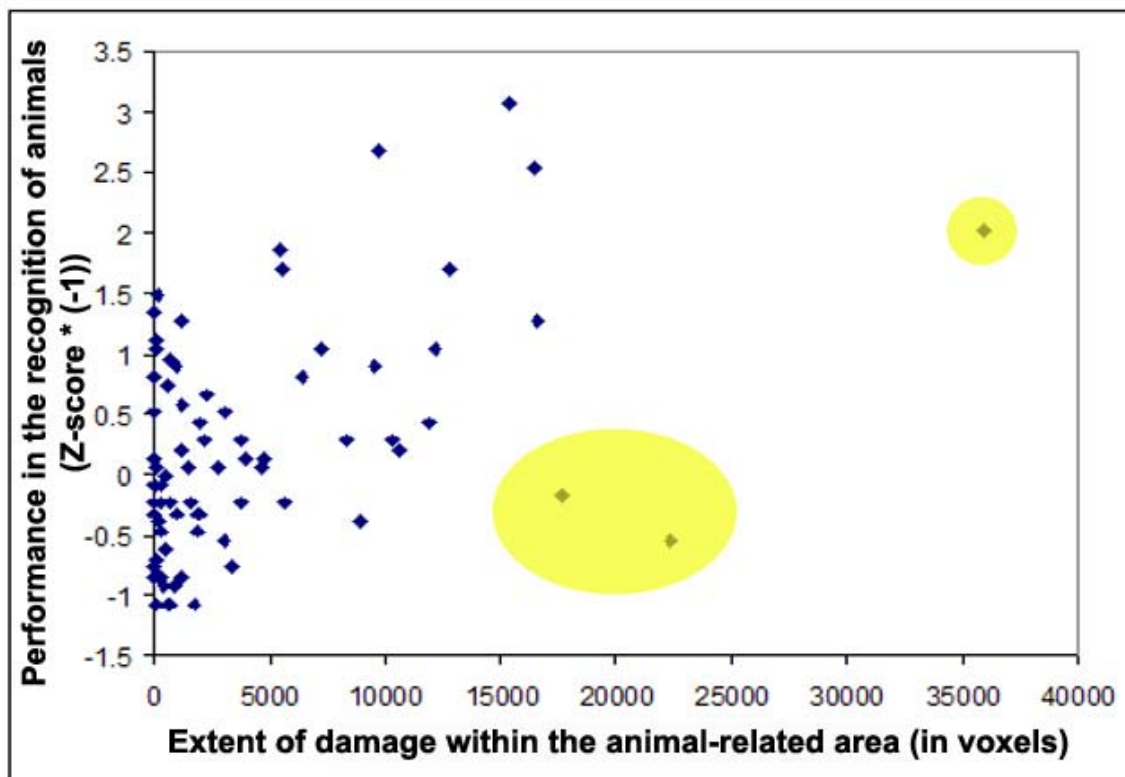


Figure 3.8 The relationship between damage in the animal-related area and the severity of the animal recognition impairment. The scores for individual subjects ($n=82$) are plotted as individual points in dark blue. In general, there was a linear relationship between the extent of damage in the animal-related area and recognition of animals ($r = .477, p < .01$). However, note the potential outliers who are highlighted in yellow. They represent cases where the severity appears to be less than would be expected based on the extent of damage in the ROI.

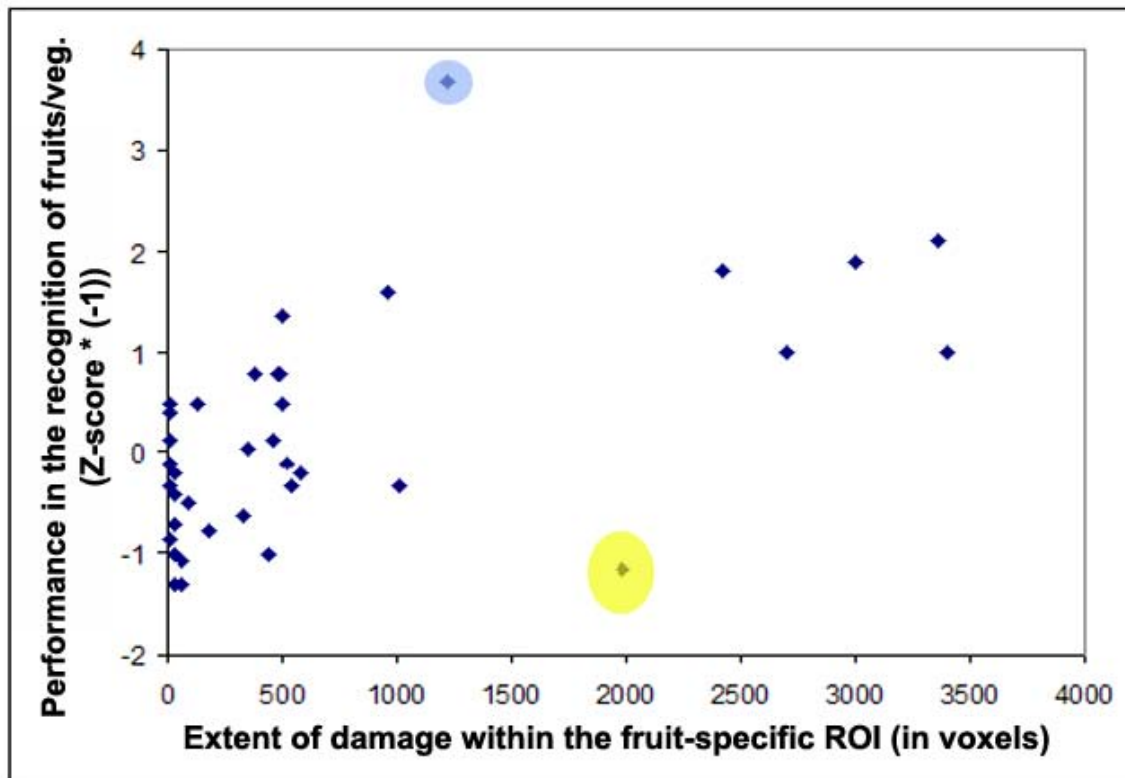


Figure 3.9 The relationship between damage in the fruit/vegetable-specific ROI and the severity of the fruit/vegetable recognition impairment. The scores for individual subjects ($n=37$) are plotted as individual points in dark blue. In general, there was a linear relationship between the extent of damage in the fruit-specific ROI and recognition of fruits/vegetables ($r = .568, p < .01$). However, note the potential outliers who are highlighted in light blue and yellow. The subject in light blue represents a case where the severity of the deficit appears to be greater than would be expected based on the extent of damage in the ROI. The subject in yellow represents a case where the severity appears to be less than would be expected based on the extent of damage in the ROI.

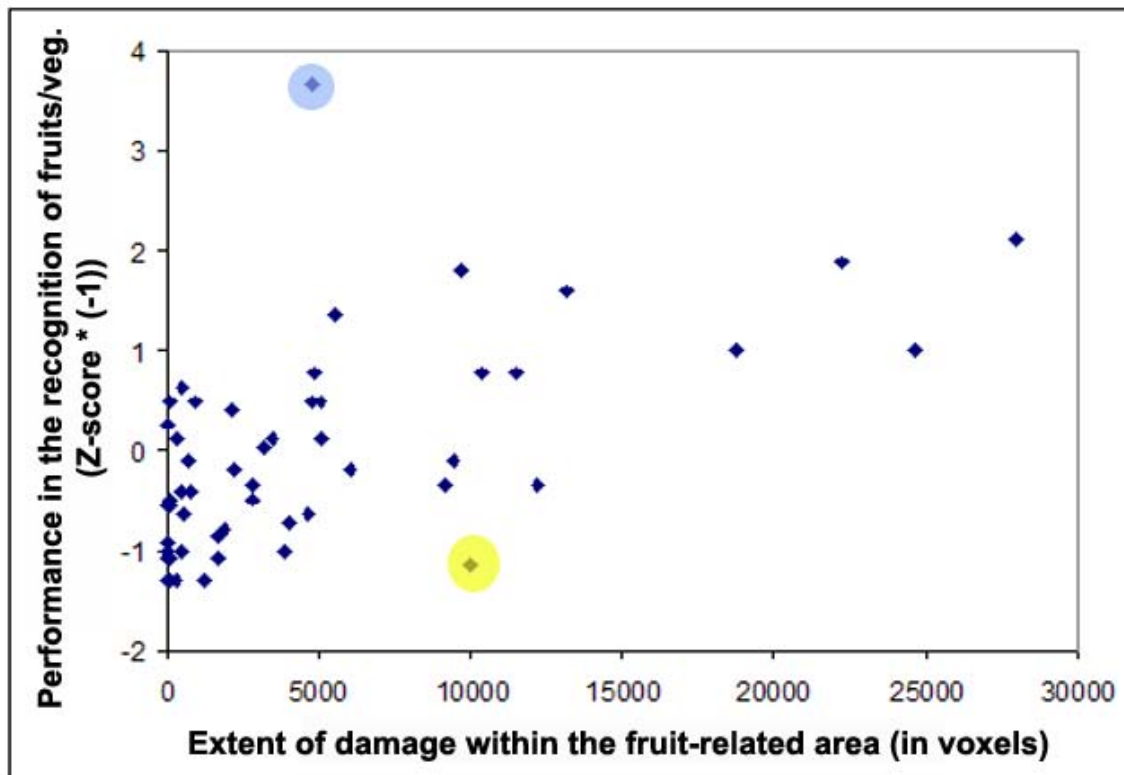


Figure 3.10 The relationship between damage in the fruit/vegetable-related area and the severity of the fruit/vegetable recognition impairment. The scores for individual subjects ($n=52$) are plotted as individual points in dark blue. In general, there was a linear relationship between the extent of damage in the fruit-related area and recognition of fruits/vegetables ($r = .580, p < .01$). However, note the potential outliers who are highlighted in light blue and yellow. The subject in light blue represents a case where the severity of the deficit appears to be greater than would be expected based on the extent of damage in the ROI. The subject in yellow represents a case where the severity appears to be less than would be expected based on the extent of damage in the ROI.

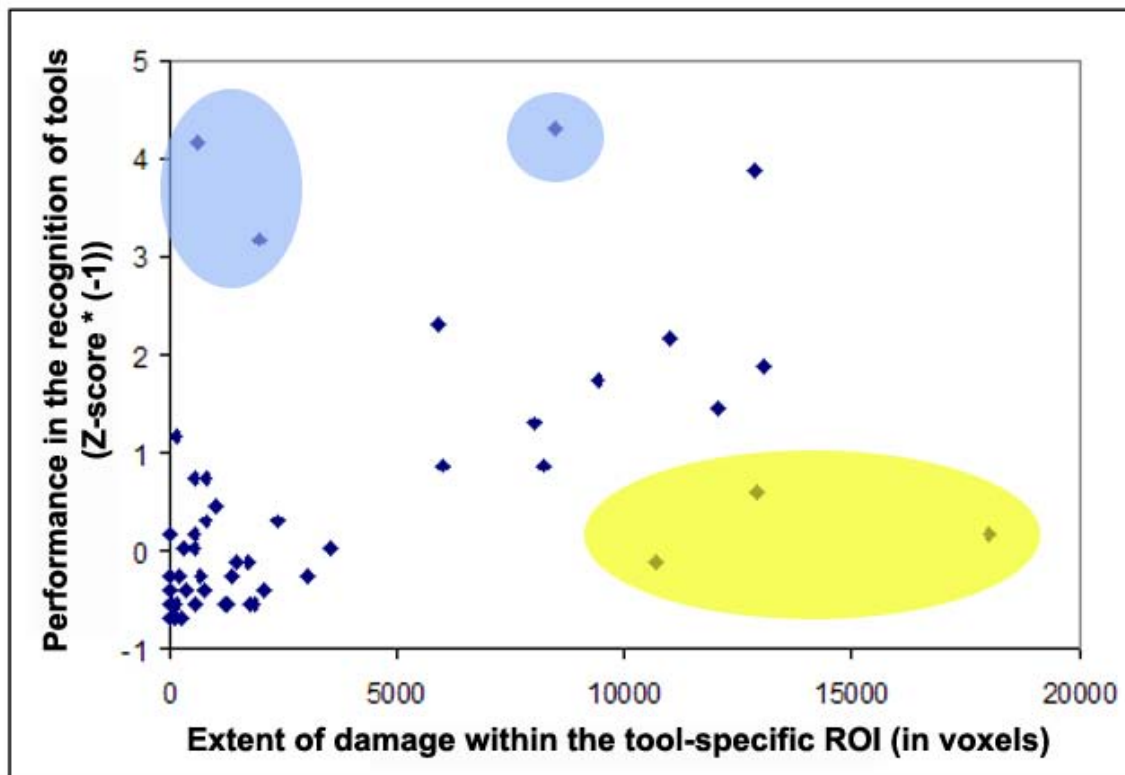


Figure 3.11 The relationship between damage in the tool-specific ROI and the severity of the tool recognition impairment. The scores for individual subjects ($n=52$) are plotted as individual points in dark blue. In general, there was a linear relationship between the extent of damage in the tool-specific ROI and recognition of tools/utensils ($r = .496, p < .01$). However, note the potential outliers who are highlighted in light blue and yellow. The subjects in light blue represent cases where the severity of the deficit appears to be greater than would be expected based on the extent of damage in the ROI. The subjects in yellow represent cases where the severity appears to be less than would be expected based on the extent of damage in the ROI.

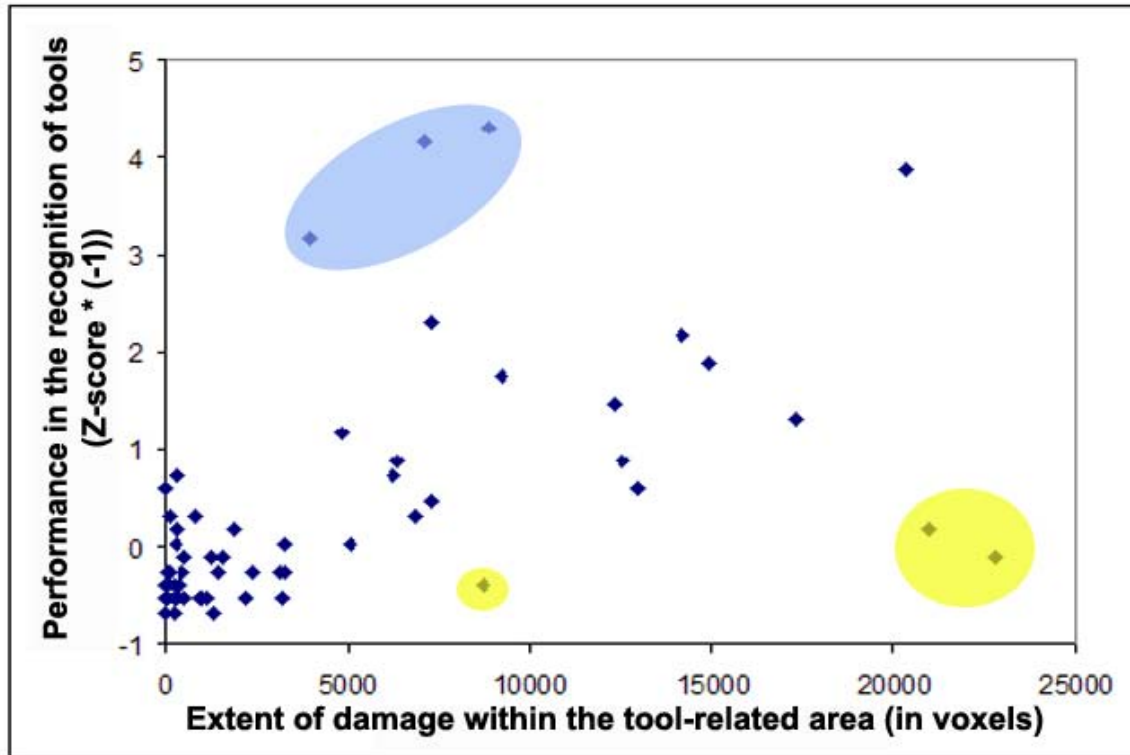


Figure 3.12 The relationship between damage in the tool-related area and the severity of the tool recognition impairment. The scores for individual subjects ($n=61$) are plotted as individual points in dark blue. In general, there was a linear relationship between the extent of damage in the tool-related area and recognition of tools/utensils ($r = .544, p < .01$). Note the potential outliers who are highlighted in light blue and yellow. The subjects in light blue represent cases where the severity of the deficit appears to be greater than would be expected based on the extent of damage in the ROI. The subjects in yellow represent cases where the severity appears to be less than would be expected based on the extent of damage in the ROI.

Table 3.5 Demographic, neuropsychological and lesion data are presented for the outliers for face recognition.

	Sub- ject	Imp. Cats	<u>Demographics</u>			<u>Neuropsychological variables</u>					<u>Lesion Variables</u>		
			Hand- edness	Sex	Occupation	Est. IQ	BD	BFRT	JLO	CS	Age of Onset	Mechanism	Vol in ROI
Performed better than expected	747	0	+100	M	Medical records	111.16	10	41	23	1.65	25.01	CVA	15084
	1580	An, Fr	+100	M	College student	105.97	8	45	25	--	19.73	HSE	28298
	1603	0	+100	F	Nursing home adm.	108.46	13	43	25	1.95	21.19	ATL	15346
	1711	0	+100	F	Day care provider	103.26	6	39	15	1.95	28.22	CVA	15559
	2268	Fr	-100	M	Factory worker	100.00	10	37	21	--	33.11	ATL	16901
Performed worse than expected	1336	Fa, An, Fr	+100	M	Appliance sales/repair	102.53	8	41	24	--	70.76	Tumor resection	5211
	1465	Fa	+100	M	Electrician	109.74	16	48	28	1.95	60.27	HSE	9314
	3268	Fa, An	+100	M	Wilderness guide	111.40	14	43	30	1.80	29.78	HSE	28458

Imp. Cats = Categories for which subject demonstrated impairment relative to a comparison sample of neurologically normal adults (i.e., traditional definition of impairment). An = Animals, Fr = Fruits/vegetables, Fa = Faces, BD = Block Design, BFRT = Benton Facial Recognition Test, JLO = Judgment of Line Orientation, CS = Spatial contrast sensitivity, CVA = cerebrovascular accident, ATL = anterior temporal lobectomy, and HSE = herpes simplex encephalitis.

Lesion size and volume of damage in the ROI are measured in voxels.

Vol in ROI = the extent of damage in the category-specific ROI.

Table 3.6 Demographic, neuropsychological and lesion data are presented for the outliers for animal recognition.

	<u>Sub- ject</u>	<u>Imp. Cats</u>	<u>Demographics</u>			<u>Neuropsychological variables</u>					<u>Lesion Variables</u>		
			Hand- edness	Sex	Occupation	Est. IQ	BD	BFRT	JLO	CS	Age of Onset	Mechanism	Vol in ROI
Performed better than expected	1133	0	+100	M	Nursing home volunteer	101.42	8	39	16	--	10.23	Meningitis/ abscess/ CVA	15740
	1645	0	+15	M	Farmer	101.41	10	36	24	--	68.63	CVA	13469
Performed worse than expected	1976	An, Fr, To	+100	M	Radiator repairshop owner/mgr	106.61	7	42	25	.45	62.77	CVA	10861
	2061	Fa, An, Fr, To	+100	F	Book- keeper	105.32	10	43	24	1.65	66.01	CVA	2672

Note that the subjects who perform worse than expected have poor contrast sensitivity and display impairments for at least 3 of 4 categories.

Imp. Cats = Categories for which subject demonstrated impairment relative to a comparison sample of neurologically normal adults (i.e., traditional definition of impairment). An = Animals, Fr = Fruits/vegetables, Fa = Faces, To = Tools/utensils, BD = Block Design, BFRT = Benton Facial Recognition Test, JLO = Judgment of Line Orientation, CS = Spatial contrast sensitivity, and CVA = cerebrovascular accident. Lesion size and volume of damage in the ROI are measured in voxels.

*The subjects who are included above as performing worse than expected are based on the results for the animal-specific ROI only (see Figure 3.7) as the results for the animal-related ROI did not yield apparent outliers.

Vol in ROI = the extent of damage in the category-specific ROI.

Table 3.7 Demographic, neuropsychological and lesion data are presented for the outliers for fruit recognition.

	<u>Sub- ject</u>	<u>Imp. Cats</u>	<u>Demographics</u>			<u>Neuropsychological variables</u>					<u>Lesion Variables</u>		
			Hand- edness	Sex	Occupation	Est. IQ	BD	BFRT	JLO	CS	Age of Onset	Mechanism	Vol in ROI
Better	975	0	+100	F	Secretary	104.85	1	--	--	--	63.45	CVA	1987
Worse	2206	An, Fr, To	-50	M	Writer/law. business owner	116.65	14	41	30	1.95	58.86	CVAs	1222

Note that 975 was not impaired on any category, whereas 2206 demonstrated impaired performances for animals, fruits and tools.

Imp. Cats = Categories for which subject demonstrated impairment relative to a comparison sample of neurologically normal adults (i.e., traditional definition of impairment). An = Animals, Fr = Fruits/vegetables, To = Tools/utensils, BD = Block Design, BFRT = Benton Facial Recognition Test, JLO = Judgment of Line Orientation, CS = Spatial contrast sensitivity and CVA = cerebrovascular accident.

Lesion size and volume of damage in the ROI are measured in voxels.

Vol in ROI = the extent of damage in the category-specific ROI.

Table 3.8 Demographic, neuropsychological and lesion data are presented for the outliers for fruit recognition.

	Sub- ject	Imp. Cats	<u>Demographics</u>			<u>Neuropsychological variables</u>					<u>Lesion Variables</u>		
			Hand- edness	Sex	Occupation	Est. IQ	BD	BFRT	JLO	CS	Age of Onset	Mechanism	Vol in ROI
Performed better than expected	983	An	+100	F	Home- maker	96.05	5	33	26	--	56.61	CVA	19048
	988*	An	+100	F	Semi- skilled labor	89.61	7	46	18	--	63.87	CVA	12913
	1133	0	+100	M	Nursing home volunteer	101.42	8	39	16	--	10.23	Meningitis/ abscess/ CVA	15740
	2496	Fa, An, Fr	-100	F	Hospital volunteer	106.09	4	35	20	1.95	53.97	ATL	18026
Performed worse than expected	1366	To	+100	M	Business owner	112.10	14	46	25	.90	61.14	CVA	8480
	1976	An, Fr, To	+100	M	Radiator repairshop owner/mgr	106.61	7	42	25	.45	62.77	CVA	10861
	2061	Fa, An, Fr, To	+100	F	Book- keeper	105.32	10	43	24	1.65	66.01	CVA	2672

Imp. Cats = Categories for which subject demonstrated impairment relative to a comparison sample of neurologically normal adults (i.e., traditional definition of impairment). An = Animals, Fr = Fruits/vegetables, Fa = Faces, To = Tools/utensils, BD = Block Design, BFRT = Benton Facial Recognition Test, JLO = Judgment of Line Orientation, CS = Spatial contrast sensitivity, CVA = cerebrovascular accident, and ATL = anterior temporal lobectomy. For the neuropsychological variables, better performance is indicated by higher numbers. Lesion size and volume of damage in the ROI are measured in voxels. Vol in ROI = the extent of damage in the category-specific ROI. *Subject is included based on the results for the tool-specific ROI only.

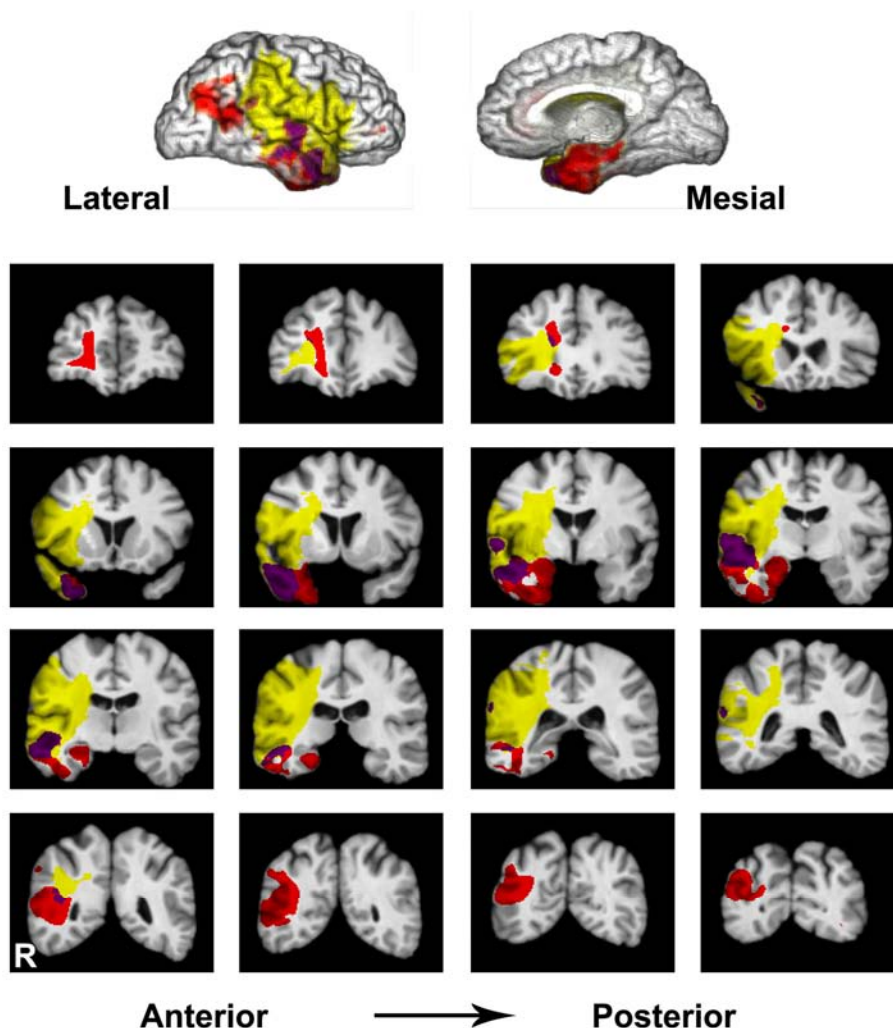


Figure 3.13 Subject 0747's lesion (in yellow) is overlaid with the face-specific ROI (in red) on the template brain and displayed on lateral and mesial views of the right hemisphere and on representative 2D slices. Purple voxels represent overlap between the subject's lesion and the ROI. This subject performed within normal limits (based on mean and SD of a normal comparison sample) on the task of famous face recognition. Note that the lesion spares both the posterior aspect of the ROI (the area near the lateral temporal-occipital junction) and the mesial sector in the temporal pole and along the parahippocampal gyrus.

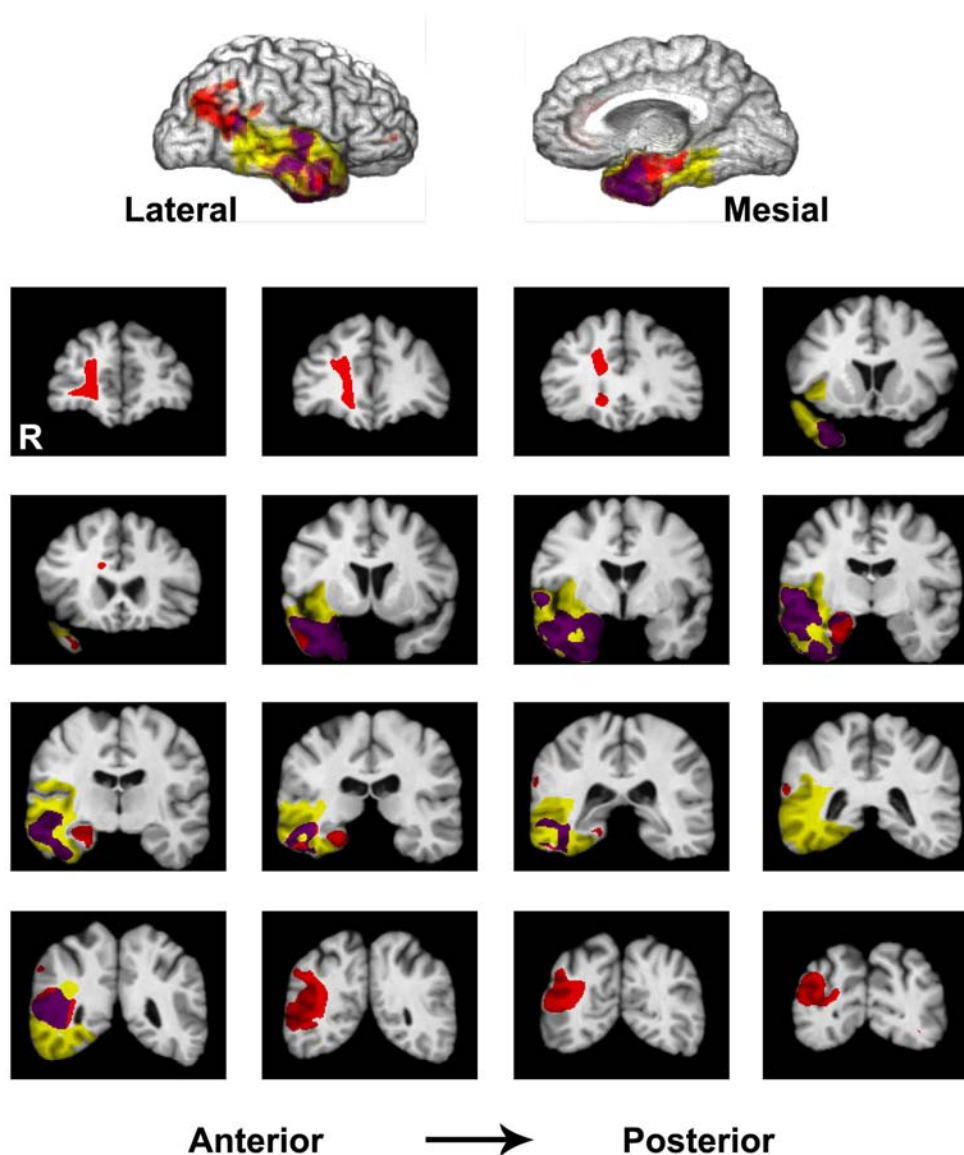


Figure 3.14 Subject 1580's lesion (in yellow) is overlaid with the face-specific ROI (in red) on the template brain and displayed on lateral and mesial views of the right hemisphere and on representative 2D slices. Purple voxels represent overlap between the subject's lesion and the ROI. This subject performed within normal limits (based on mean and SD of a normal comparison sample) on the task of famous face recognition. Note that the lesion encompasses most of the anterior portion of the ROI within the temporal lobe, but spares the posterior sector as well as the anterior sector within the frontal lobe.

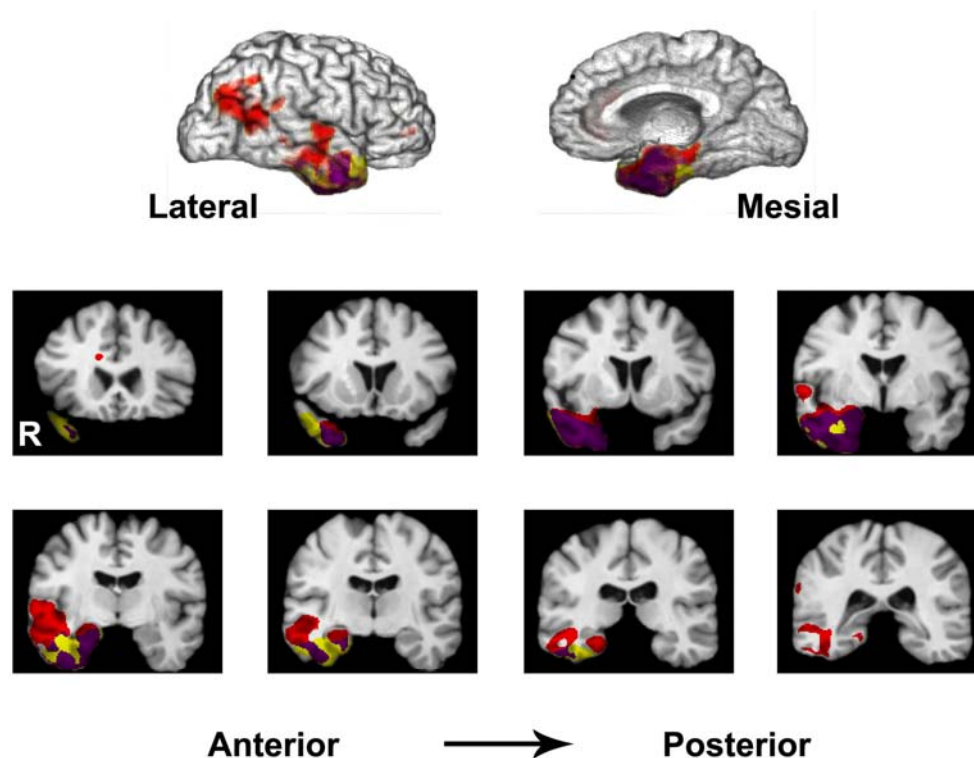


Figure 3.15 Subject 1603's lesion (in yellow) is overlaid with the face-specific ROI (in red) on the template brain and displayed on lateral and mesial views of the right hemisphere and on representative 2D slices. Purple voxels represent overlap between the subject's lesion and the ROI. This subject performed within normal limits (based on mean and SD of a normal comparison sample) on the task of famous face recognition. Note that the similar to above, the lesion encompasses most of the anterior portion of the ROI within the temporal lobe, but spares the posterior sector as well as the anterior sector within the frontal lobe.

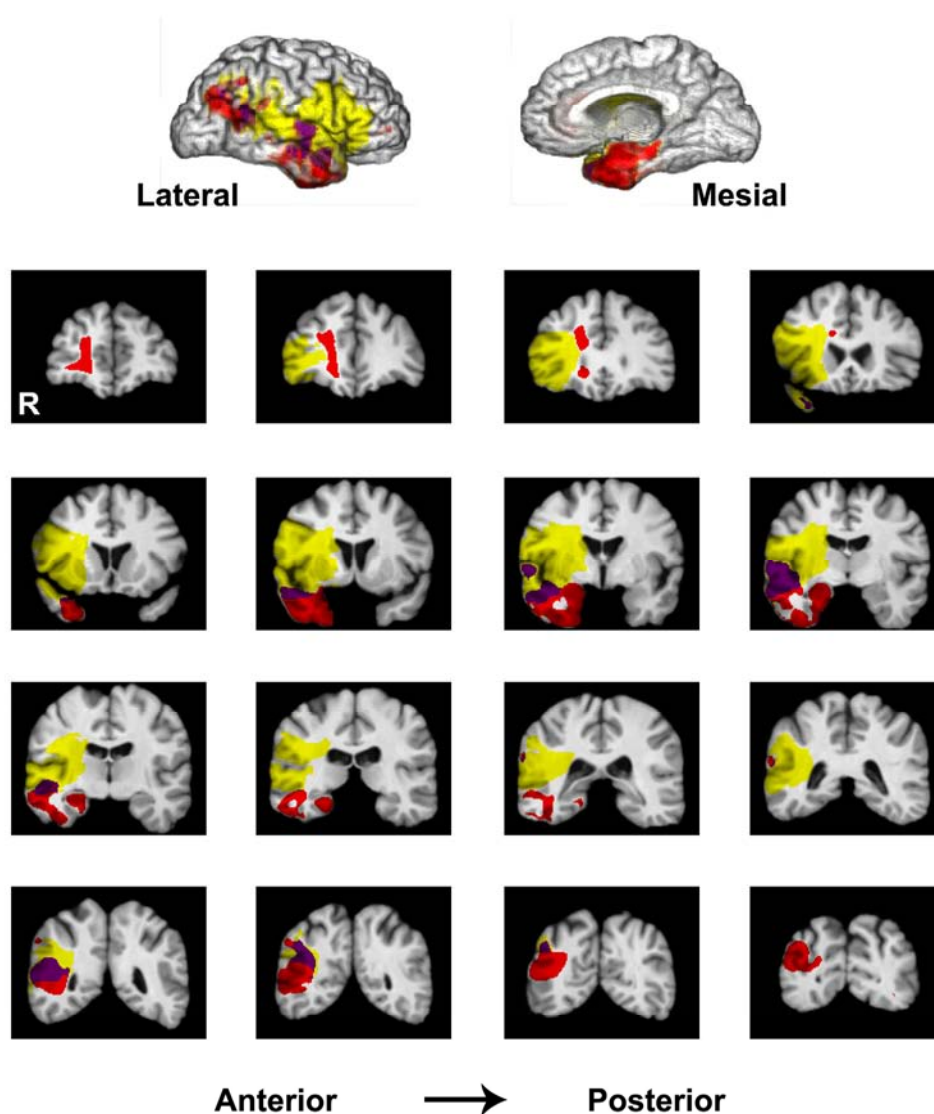


Figure 3.16 Subject 1711's lesion (in yellow) is overlaid with the face-specific ROI (in red) on the template brain and displayed on lateral and mesial views of the right hemisphere and on representative 2D slices. Purple voxels represent overlap between the subject's lesion and the ROI. This subject performed within normal limits (based on mean and SD of a normal comparison sample) on the task of famous face recognition. Note that this lesion is very similar to subject 0747's lesion, which is displayed above. Like 0747's, this lesion is a large lesion affecting widespread aspects of the lateral frontal, temporal and parietal cortices. With regard to the ROI, it appears to affect widespread areas superiorly and laterally within the temporal lobe, including the posterior aspect near the temporal-occipital junction, but spares the mesial sector in the temporal pole and along the parahippocampal gyrus as well as the portion anteriorly within the frontal lobe

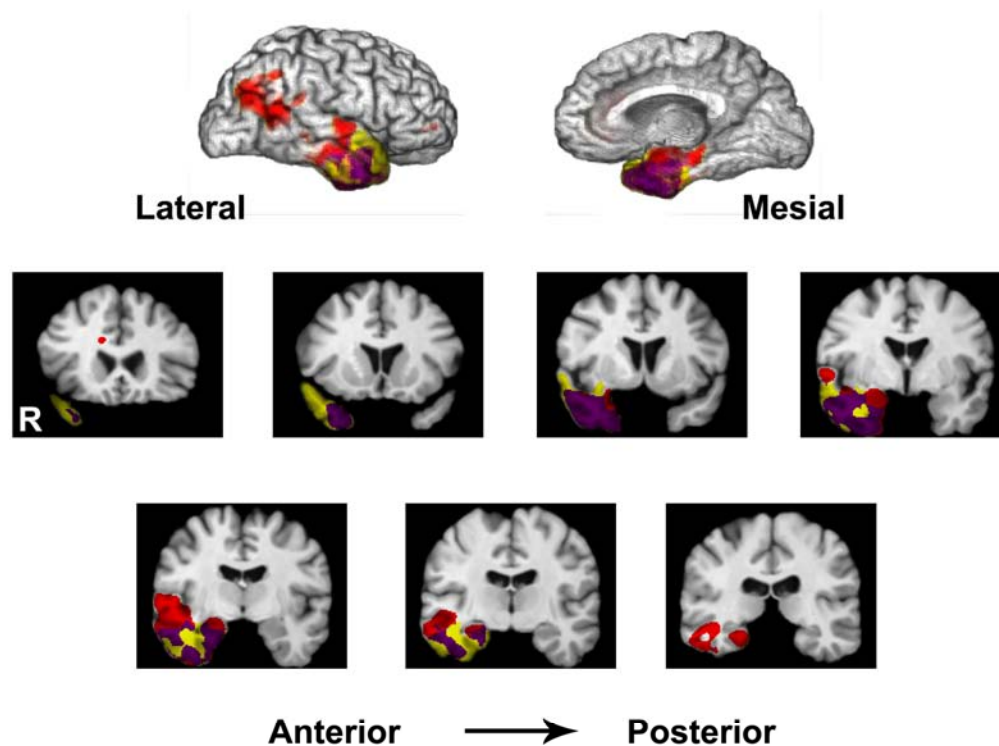


Figure 3.17 Subject 2268's lesion (in yellow) is overlaid with the face-specific ROI (in red) on the template brain and displayed on lateral and mesial views of the right hemisphere and on representative 2D slices. Purple voxels represent overlap between the subject's lesion and the ROI. This subject performed within normal limits (based on mean and SD of a normal comparison sample) on the task of famous face recognition. Note that this lesion is very similar to that belonging to 1603. (Both are the result of anterior temporal lobectomies.) As in 1603, this is a very circumscribed lesion affecting most of the anterior portion of the ROI within the temporal lobe, but sparing the posterior sector as well as the anterior sector within the frontal lobe.

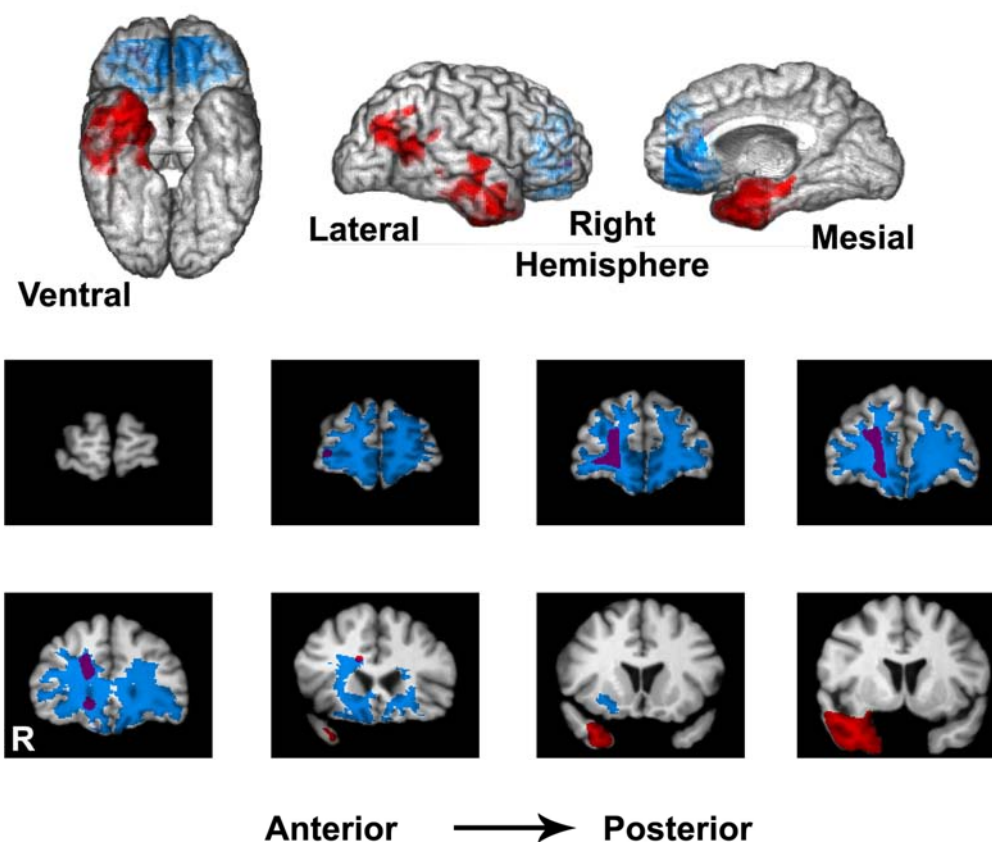


Figure 3.18 Subject 1336's lesion (in blue) is overlaid with the face-specific ROI (in red) on the template brain. Purple voxels represent overlap between the subject's lesion and the ROI. Note that this lesion is bilateral, and therefore displayed on a ventral view of the whole brain, as well as on lateral and mesial views of the right hemisphere and on representative 2D slices. This subject performed markedly below expectations on the task of famous face recognition based on the extent of his lesion within the ROI. Note that the lesion actually spares all of the tissue in the temporal, parietal and occipital lobes. Interestingly, relative to a comparison sample of neurologically-normal adults, this subject's Z-scores for Faces, Animals, and Fruits/Vegetables fall well within the impaired range ($Z = -6.37, -6.39, \text{ and } -5.54$, respectively).

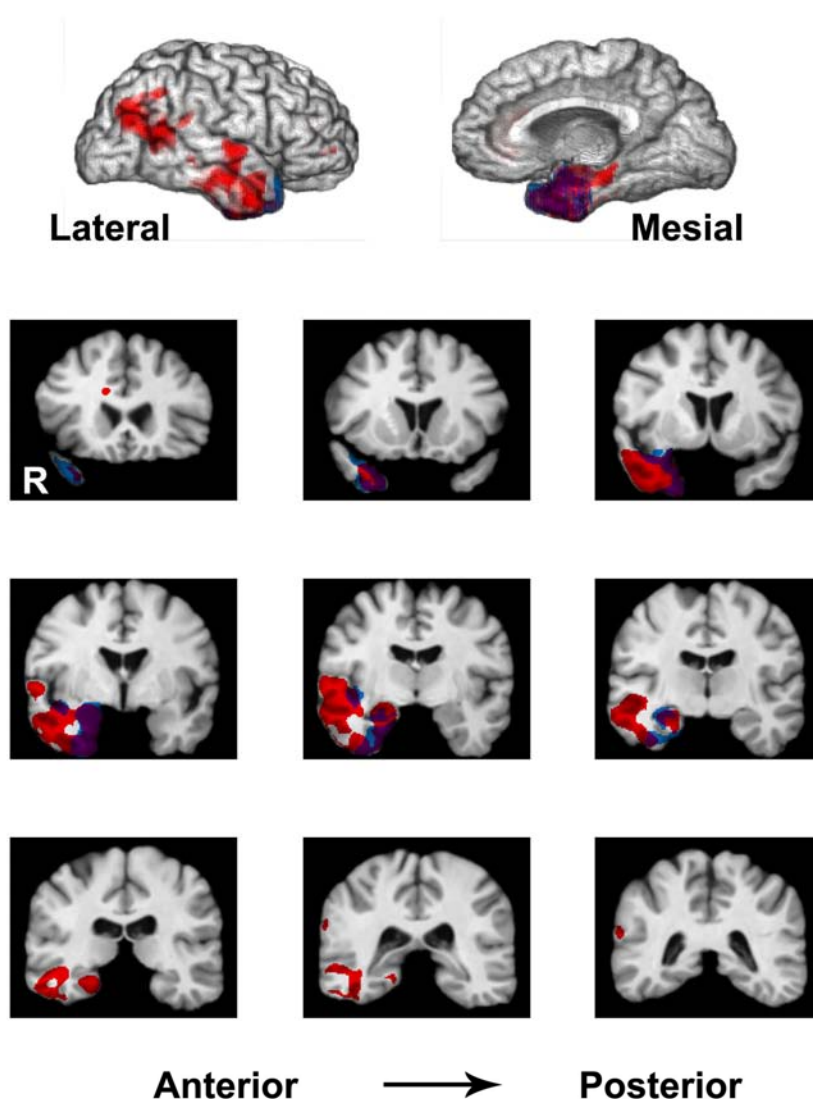


Figure 3.19 Subject 1465's lesion (in blue) is overlaid with the face-specific ROI (in red) on the template brain and displayed on lateral and mesial views of the right hemisphere and on representative 2D slices. Purple voxels represent overlap between the subject's lesion and the ROI. This subject performed in the impaired range ($Z = -5.48$, based on mean and SD of a normal comparison sample) on the task of famous face recognition. Note that this lesion is relatively circumscribed affecting only polar and mesial sectors of the right anterior temporal lobe. However, what is not depicted above, is that the MRI also reveals atrophy (but not lesion, per se) in the homologous areas in the left hemisphere, suggesting a degree of bilateral pathology, which may explain the relatively severe deficit associated with relatively little involvement in the face-specific ROI.

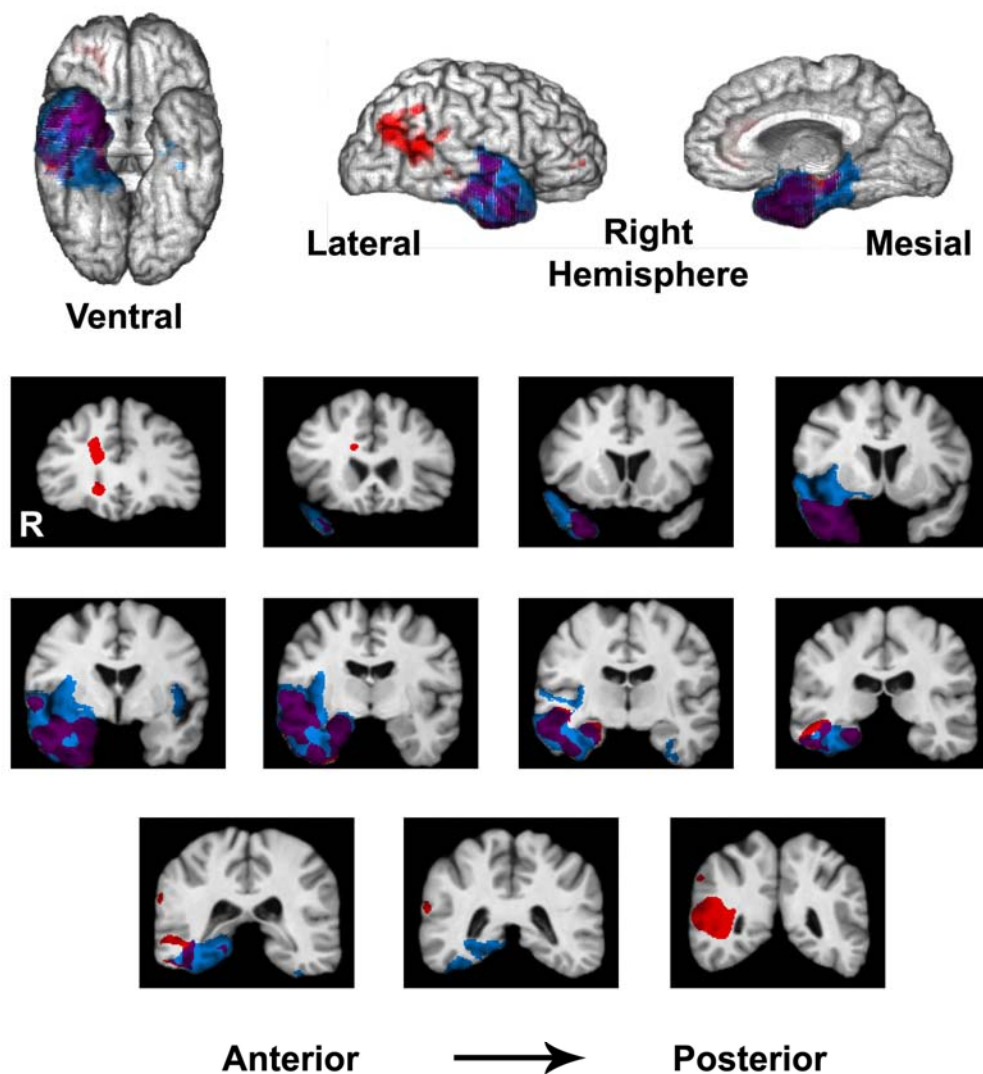


Figure 3.20 Subject 3268's lesion (in blue) is overlaid with the face-specific ROI (in red) on the template brain. Purple voxels represent overlap between the subject's lesion and the ROI. Note that this lesion is bilateral, and therefore displayed on a ventral view of the whole brain, as well as on lateral and mesial views of the right hemisphere and on representative 2D slices. This subject performed in the impaired range ($Z = -6.4$, based on mean and SD of a normal comparison sample) on the task of famous face recognition. Note that this lesion affects bilateral areas ($R \gg L$) in the anterior and ventral aspects of the temporal lobes, and in the insula. The lesion does not affect the right temporo-occipital junction.

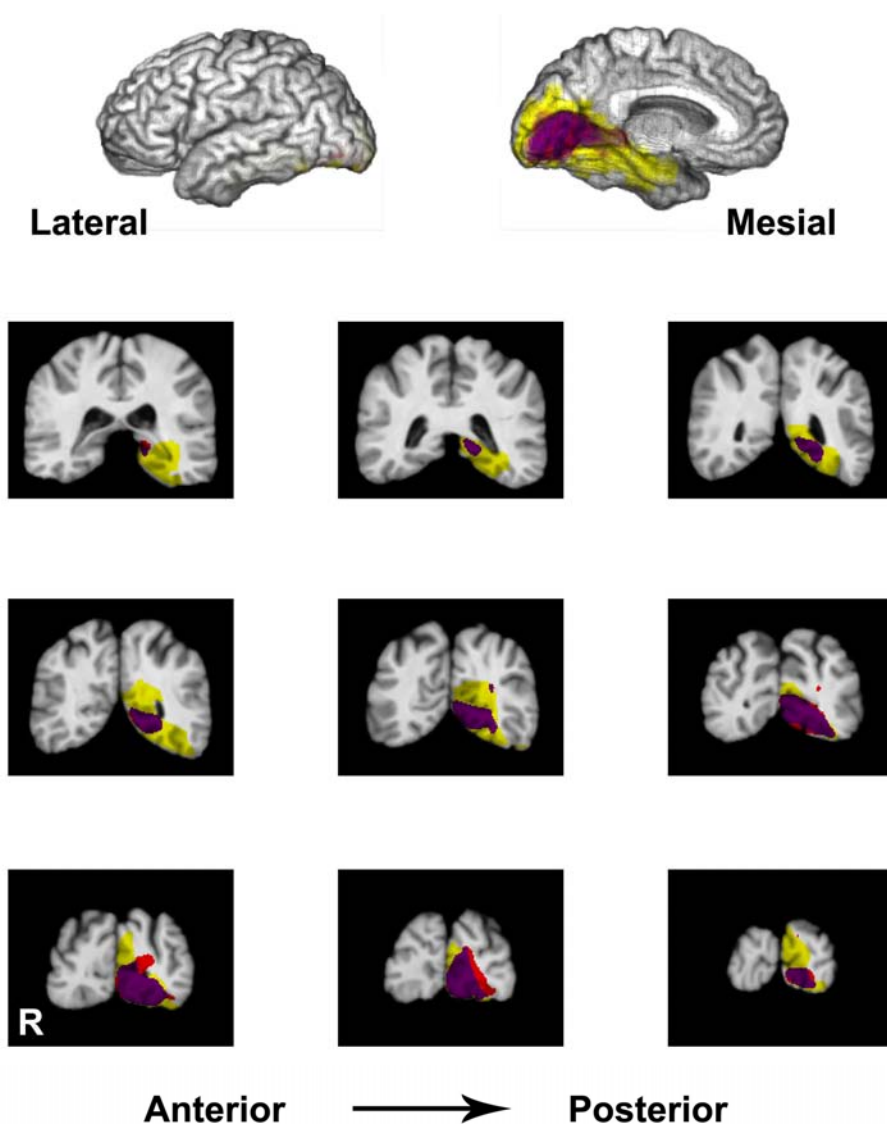


Figure 3.21 Subject 1133's lesion (in yellow) is overlaid with the animal-specific ROI (in red) on the template brain and displayed on lateral and mesial views of the left hemisphere and on representative 2D slices. Purple voxels represent overlap between the subject's lesion and the ROI. This subject performed within normal limits (based on mean and SD of a normal comparison sample) on the task of animal recognition. Note that this lesion is large and encompasses nearly all of the animal-specific region; thus, it is unlikely that the lesion missed key, animal-specific areas of the ROI. However, this lesion was acquired early in life (i.e., age 10), and thus, it is possible that a substantial amount of re-organization has allowed this subject to recognize animals despite significant damage to the neural system that subserves normal function in this domain.

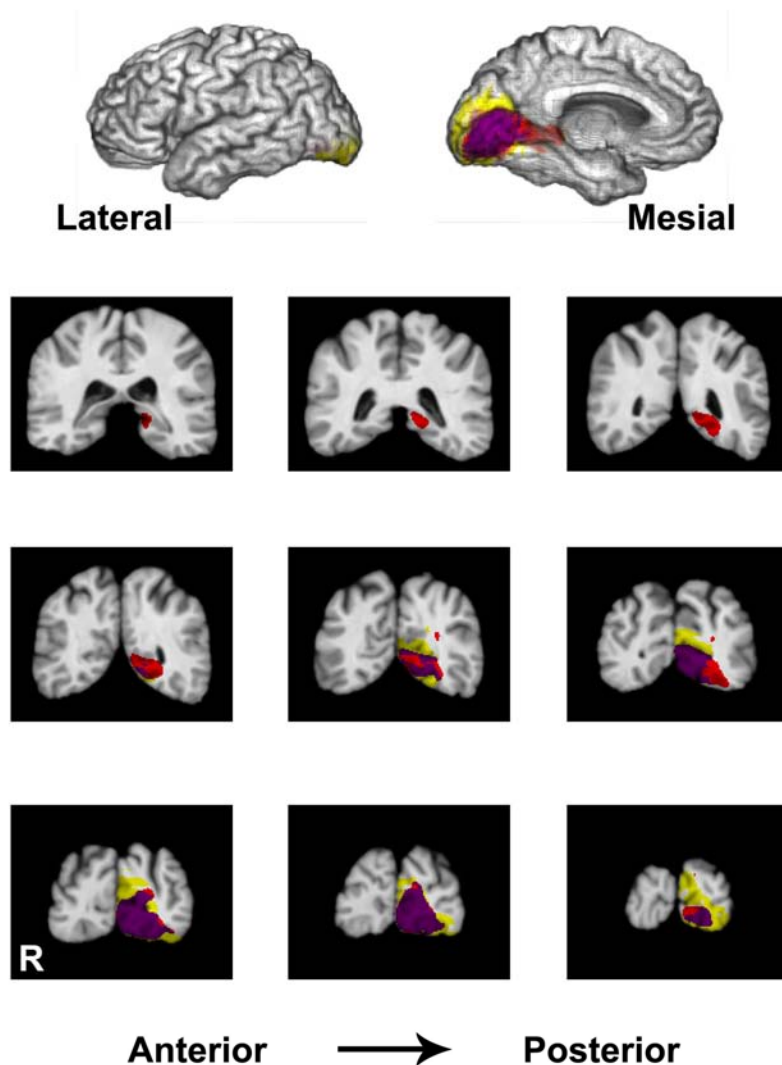


Figure 3.22 Subject 1645's lesion (in yellow) is overlaid with the animal-specific ROI (in red) on the template brain and displayed on lateral and mesial views of the left hemisphere and on representative 2D slices. Purple voxels represent overlap between the subject's lesion and the ROI. This subject performed within normal limits (based on mean and SD of a normal comparison sample) on the task of animal recognition. Note that this lesion is very similar to the above (i.e., 1133), albeit smaller and acquired later in life. It is possible that similar to the above, plasticity or reorganization has allowed for normal performance. Alternatively, this subject was a farmer during his adult life, and it is possible that that experience has enhanced his performance either because he had higher abilities premorbidly, or because the neural system subserving animal recognition is more robust (i.e., larger, or more distributed) as a result of prior learning.

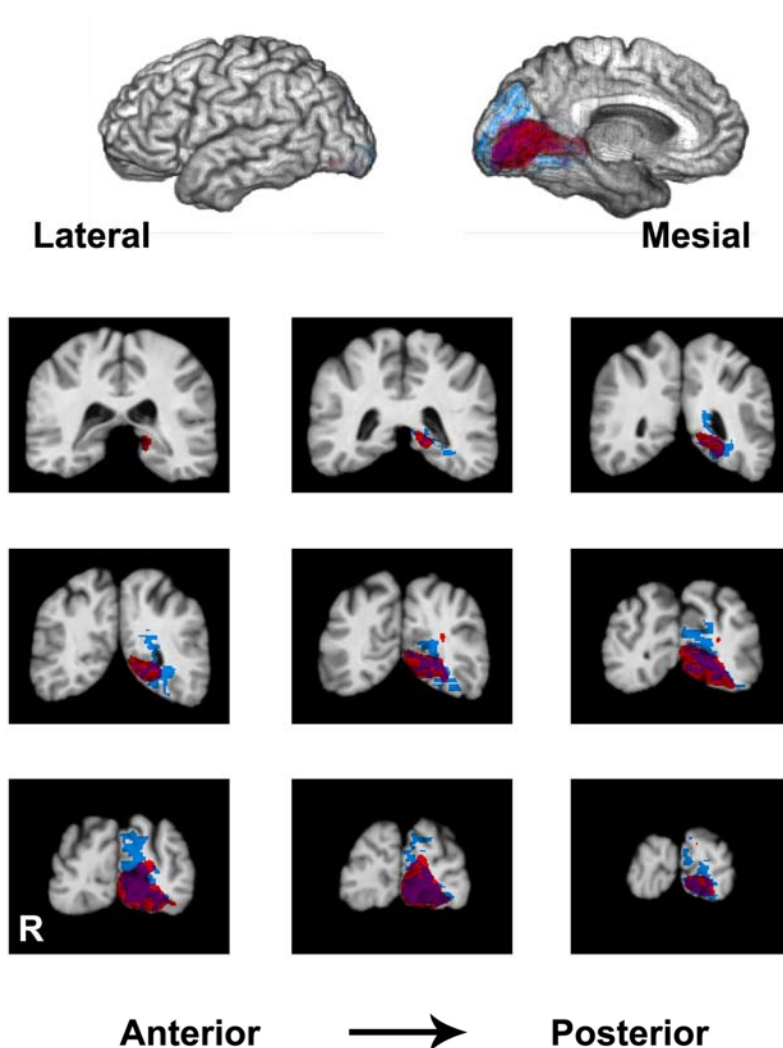


Figure 3.23 Subject 1976's lesion (in blue) is overlaid with the animal-specific ROI (in red) on the template brain and displayed on lateral and mesial views of the left hemisphere and on representative 2D slices. Purple voxels represent overlap between the subject's lesion and the ROI. This subject performed within the impaired range ($Z = -17.11$ based on mean and SD of a normal comparison sample) on the task of animal recognition. Note that this lesion is very similar to both of the lesions described above (i.e., 1133 & 1645), but that unlike the previous two which are associated with spared performance, this lesion is associated with severely impaired performance.

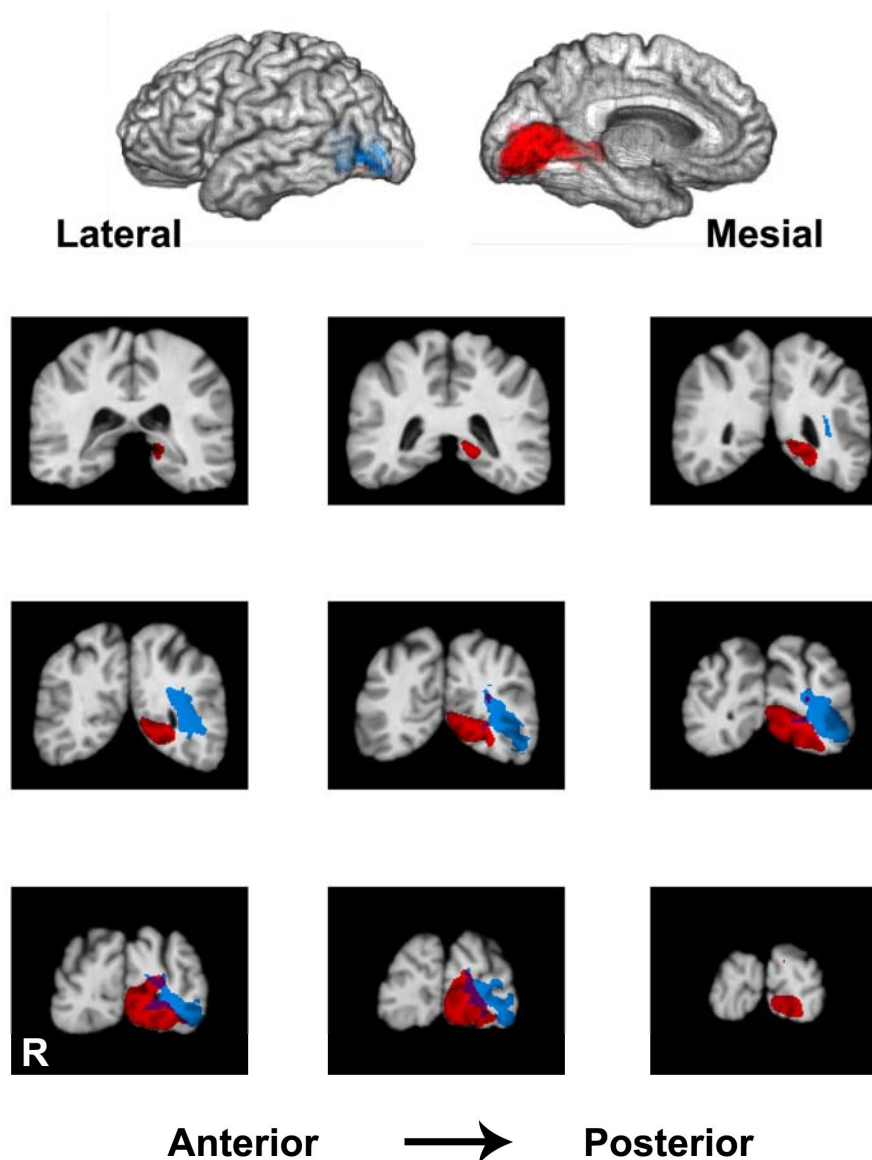


Figure 3.24 Subject 2061's lesion (in blue) is overlaid with the animal-specific ROI (in red) on the template brain and displayed on lateral and mesial views of the left hemisphere and on representative 2D slices. Purple voxels represent overlap between the subject's lesion and the ROI. This subject performed within the impaired range ($Z = -15.32$ based on mean and SD of a normal comparison sample) on the task of animal recognition. Note that this affects very little of the animal-specific ROI, but does affect the white matter adjacent to the tissue. It is possible that the damage to the white matter affects connections between this ROI and other regions, which in turn accounts for the patient's impaired performance.

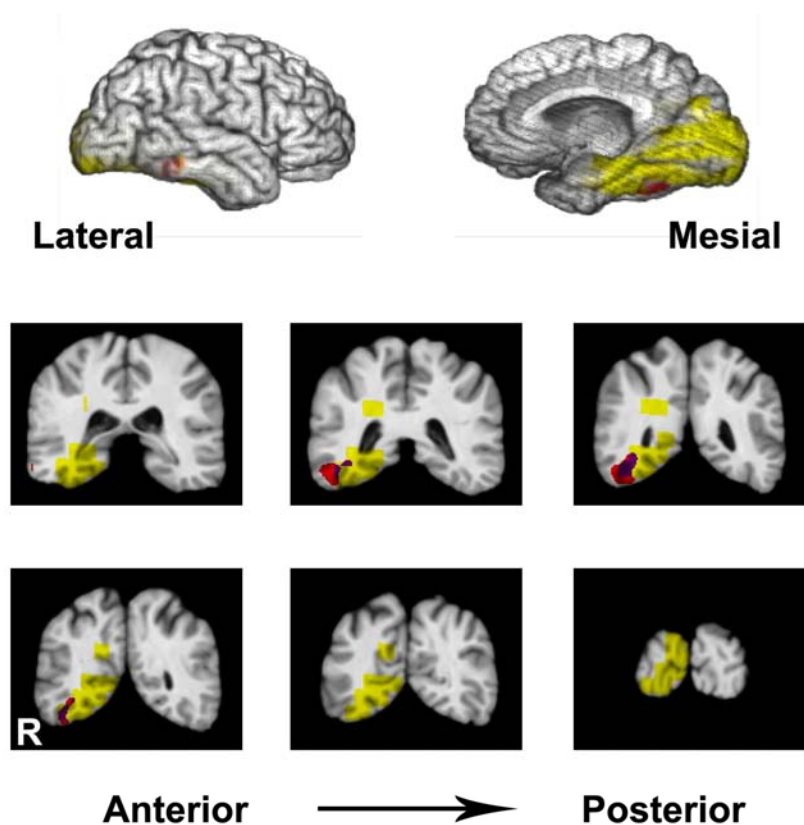


Figure 3.25 Subject 975's lesion (in yellow) is overlaid with the fruit-specific ROI (in red) on the template brain and displayed on lateral and mesial views of the right hemisphere and on representative 2D slices. Purple voxels represent overlap between the subject's lesion and the ROI. This subject performed within normal limits (based on mean and SD of a normal comparison sample) on the task of fruit/vegetable recognition. In fact, this subject performed within normal limits in recognition for all four categories.

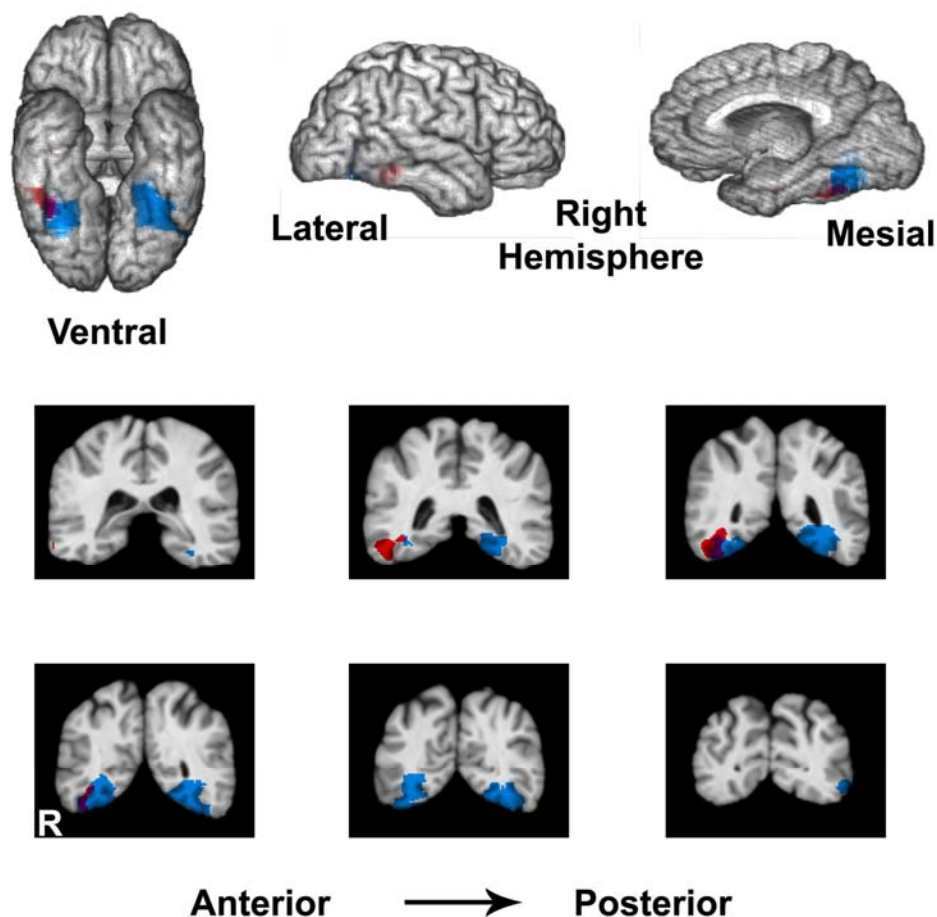


Figure 3.26 Subject 2206's lesion (in blue) is overlaid with the fruit-specific ROI (in red) on the template brain. Purple voxels represent overlap between the subject's lesion and the ROI. Note that this lesion is bilateral, and therefore displayed on a ventral view of the whole brain, as well as on lateral and mesial views of the right hemisphere and on representative 2D slices. This subject performed in the impaired range for animals, fruits/vegetables and tools, ($Z = -7.46, -15.28, \text{ and } -7.03$, respectively, based on mean and SD of a normal comparison sample). Note that unlike the case described above which had a large, unilateral lesion, this subject has incurred damage bilaterally. In general, the total volume of damage in this case is considerably less, but the fact that it was incurred bilaterally and symmetrically, may account for why this subject displays moderately severe recognition impairments across multiple categories.

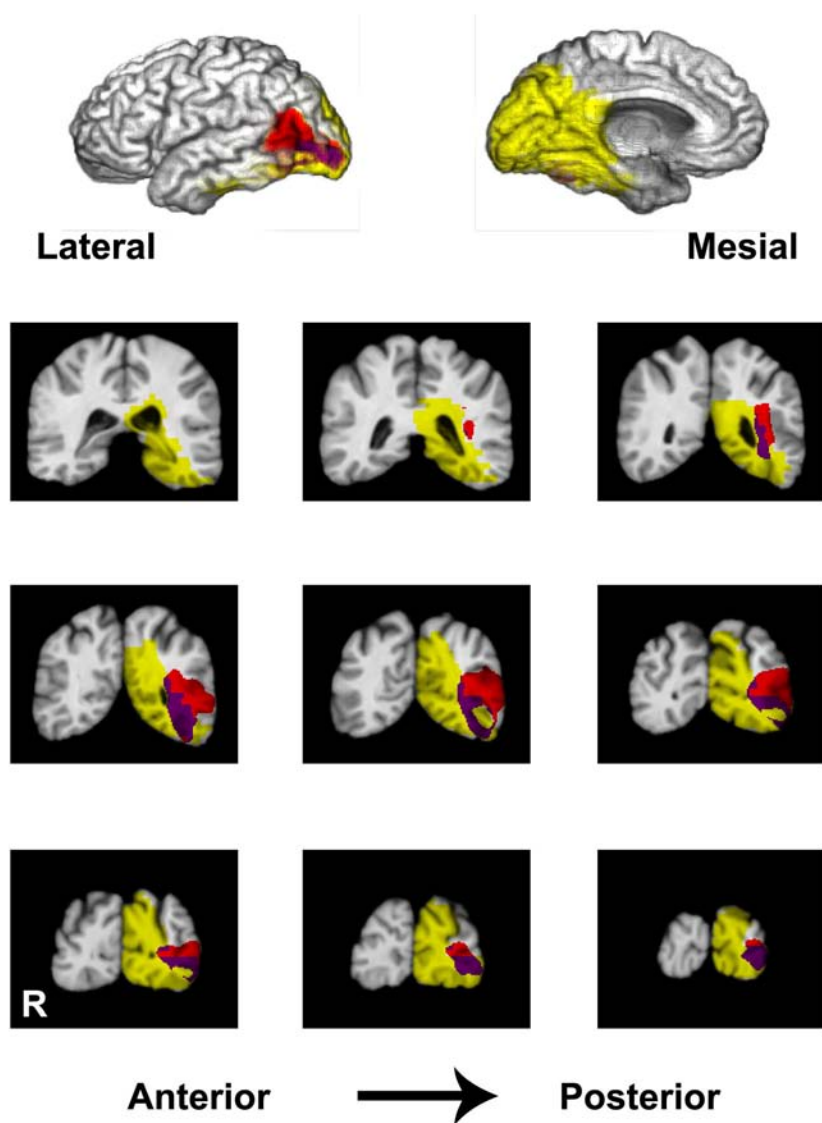


Figure 3.27 Subject 983's lesion (in yellow) is overlaid with the tool-specific ROI (in red) on the template brain and displayed on lateral and mesial views of the left hemisphere and on representative 2D slices. Purple voxels represent overlap between the subject's lesion and the ROI. This subject performed within normal limits (based on mean and SD of a normal comparison sample) on the task of tool recognition, although she was impaired on animal recognition. Note that this lesion is very large, but mostly spares the lateral cortex, which may explain why this subject is able to perform normally on tool recognition.

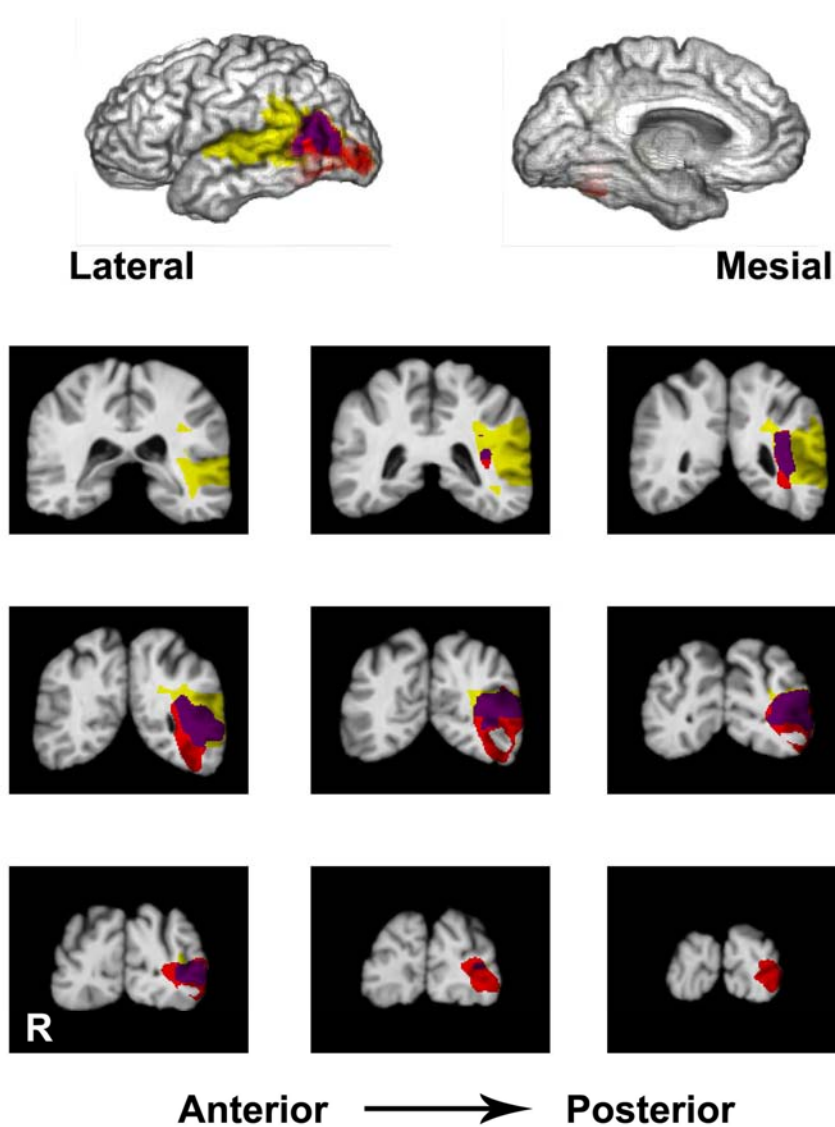


Figure 3.28 Subject 988's lesion (in yellow) is overlaid with the tool-specific ROI (in red) on the template brain and displayed on lateral and mesial views of the left hemisphere and on representative 2D slices. Purple voxels represent overlap between the subject's lesion and the ROI. This subject performed within normal limits (based on mean and SD of a normal comparison sample) on the task of tool recognition. Note that this lesion is very different from the previous in that it does affect the lateral temporal-parietal cortex. However, this lesion affects only the anterior-most part of the ROI, which may explain why this subject performs normally on tool recognition.

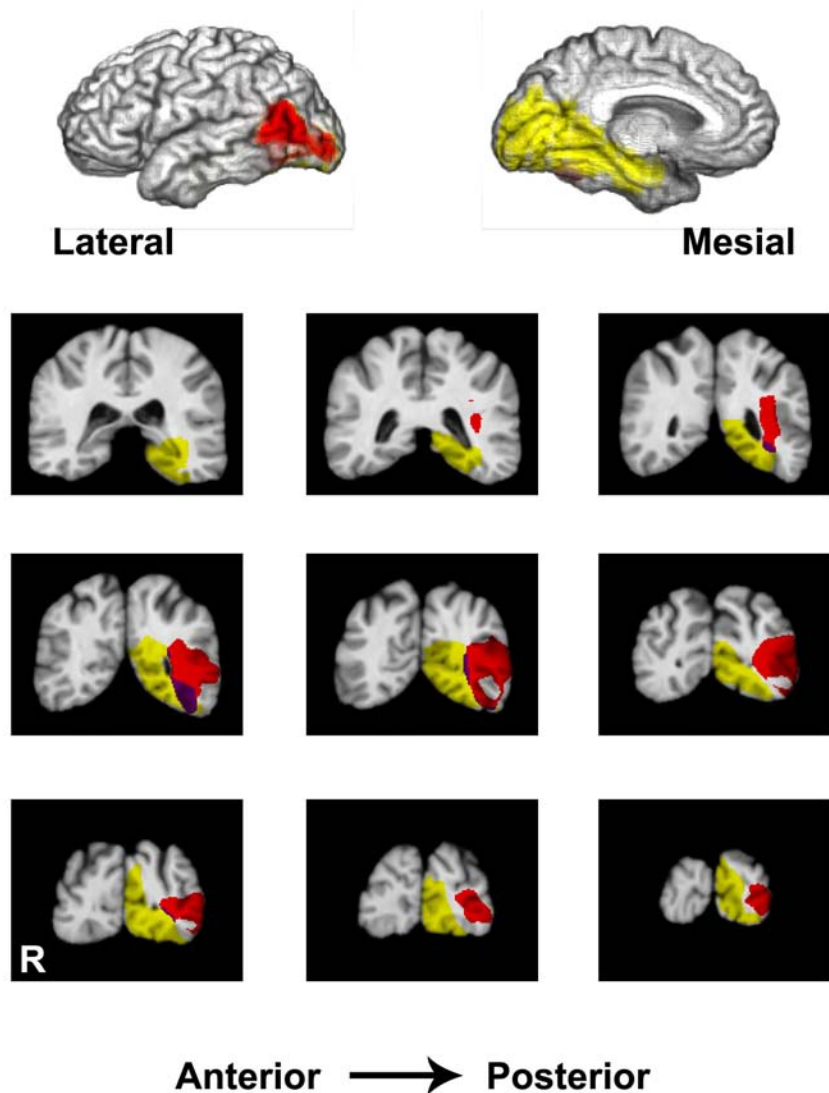


Figure 3.29 Subject 1133's lesion (in yellow) is overlaid with the tool-specific ROI (in red) on the template brain and displayed on lateral and mesial views of the left hemisphere and on representative 2D slices. Purple voxels represent overlap between the subject's lesion and the ROI. This subject performed within normal limits (based on mean and SD of a normal comparison sample) on the task of tool recognition. Note that this lesion is very similar to that in subject 983, and thus, this subject may have sparing of performance in tool recognition for the same reasons as subject 983 (i.e., that the lesion spares the areas on the lateral surface).

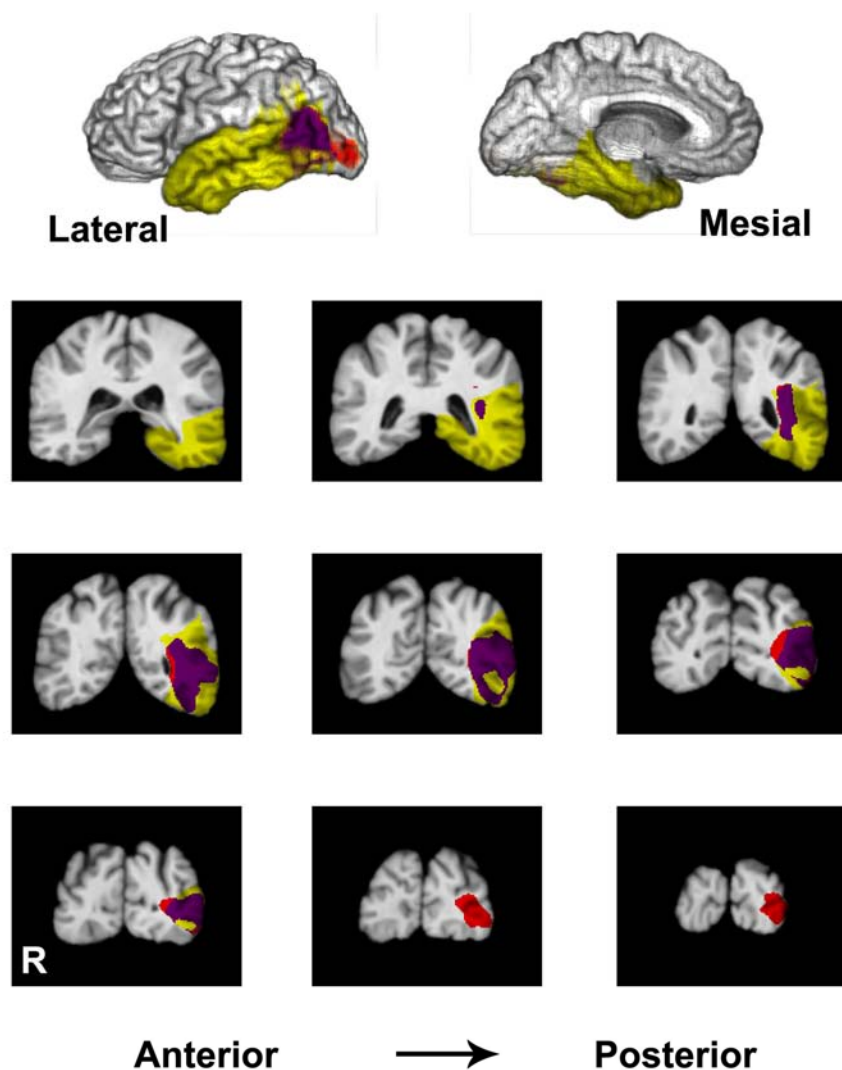


Figure 3.30 Subject 2496's lesion (in yellow) is overlaid with the tool-specific ROI (in red) on the template brain and displayed on lateral and mesial views of the left hemisphere and on representative 2D slices. Purple voxels represent overlap between the subject's lesion and the ROI. This subject performed within normal limits (based on mean and SD of a normal comparison sample) on the task of tool recognition (although was impaired in recognizing faces, animals, and fruits/vegetables). Note that this lesion is similar to that in case 988, although much larger, and affecting nearly all of the tool-related ROI. Notably, this subject is left handed (-100) and has a history of seizures, and given that, as well as the fact that her pattern of impairments across all four categories is generally the opposite of what would be expected, it is quite possible that atypical laterality explains her relatively spared performance in tool recognition.

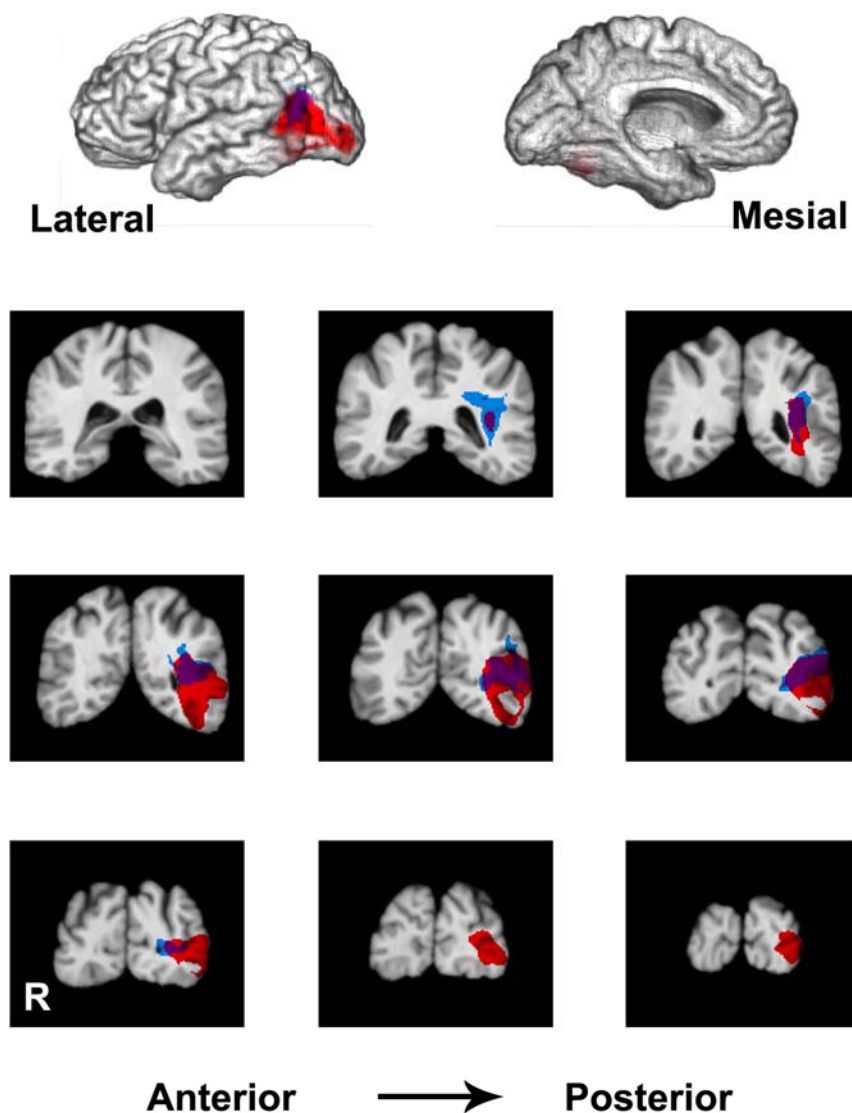


Figure 3.31 Subject 1366's lesion (in blue) is overlaid with the tool-specific ROI (in red) on the template brain and displayed on lateral and mesial views of the left hemisphere and on representative 2D slices. Purple voxels represent overlap between the subject's lesion and the ROI. This subject performed within the impaired range ($Z = -9.45$ based on mean and SD of a normal comparison sample) on the task of tool recognition. Note that this affects very little of the tool-specific ROI, but does affect the region at the temporo-parieto-occipital junction, as well as subadjacent white matter. It may be the strategic location of this lesion that accounts for the relatively severe deficit associated with a relatively small volume of damage within the ROI.

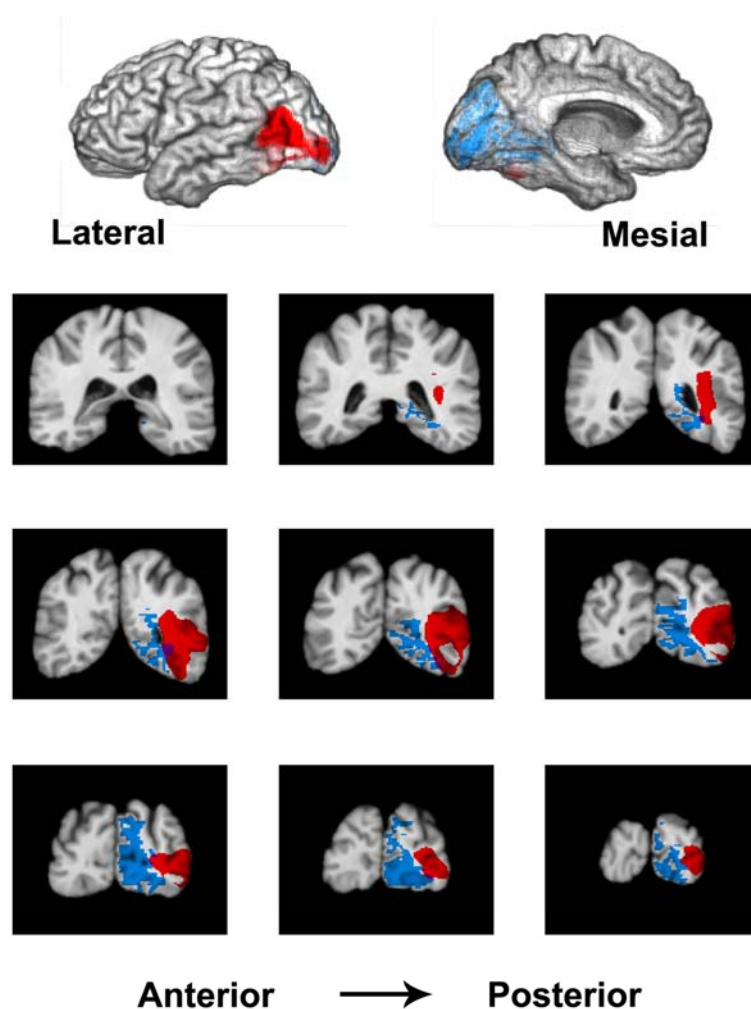


Figure 3.32 Subject 1976's lesion (in blue) is overlaid with the tool-specific ROI (in red) on the template brain and displayed on lateral and mesial views of the left hemisphere and on representative 2D slices. Purple voxels represent overlap between the subject's lesion and the ROI. This subject performed within the impaired range for animals, fruits/vegetables and tools ($Z = -17.11, -10.67, \text{ and } -9.15$, respectively, based on mean and SD of a normal comparison sample). Notably, this lesion affects very little of the tool-specific ROI, but is associated with deficits across several categories, as well as impairments in contrast sensitivity. It is possible that this subject's deficit is more global, affecting aspects of basic visual functions (e.g., fields, contrast sensitivity) and resulting in more global visual recognition impairments. (Although, if this were true, one would expect severe impairments in face recognition, in particular, and this subject performed normally on the test of famous face recognition)

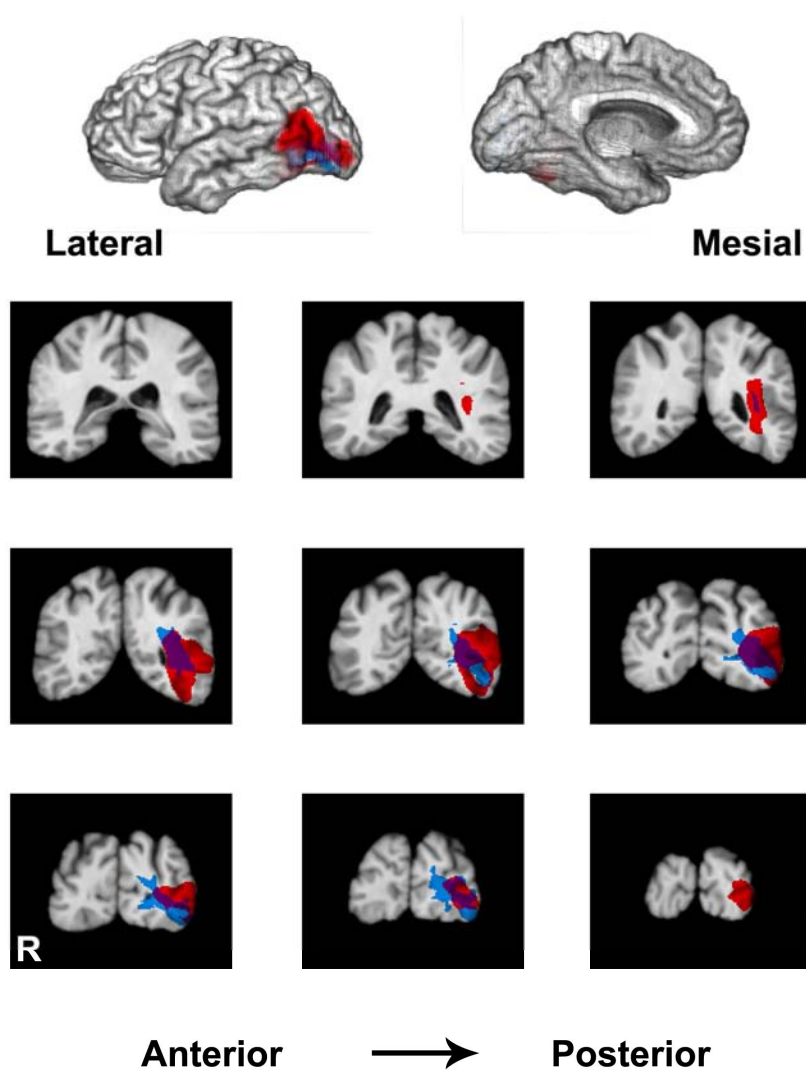


Figure 3.33 Subject 2061's lesion (in blue) is overlaid with the tool-specific ROI (in red) on the template brain and displayed on lateral and mesial views of the left hemisphere and on representative 2D slices. Purple voxels represent overlap between the subject's lesion and the ROI. This subject performed within the impaired range for all four categories ($Z = -9.81, -15.32, -5.28,$ and -2.18 for faces, animals, fruits/vegetables and tools, respectively, based on mean and SD of a normal comparison sample). Note that this very circumscribed lesion affects a small, and potentially key part of the tool-specific ROI, but is associated with deficits in all four categories (and least so for tools). In general, this pattern raises concerns about whether there is not something else (e.g., neurodegenerative process), which explains all of the patient's deficits.

performance. For the category of faces, two factors appeared to stand out. The first was that the subjects who performed better than would be expected based on lesion variables alone all had young ages of onset (mean age of onset = 25.45) compared to 2 of 3 subjects who performed worse than would be expected and had much older ages of onset. Interestingly, one subject who performed worse also had a relatively young age of onset, but also displayed a feature which also appeared common amongst those who performed worse—i.e., that there was evidence of bilateral damage. Taken together, these results suggest that early age of onset may convey some sort of protective factor, but only for those cases involving unilateral damage.

For the category of animals, three of the four outliers had lesions that appeared to remarkably similar to each other and involved most of the animal-specific ROI (see subjects 1133, 1645 and 1976). Two of these subjects performed within normal limits on the test of animal recognition while the third performed in the impaired range. In general, it did not appear that the lesions themselves could account for the differences among the subjects. In fact, there did not appear to be one factor that separated the two subjects who performed well from the subjects who performed poorly, although there were potential factors that could account for subjects performances individually. Thus, for the case of animals, it may be that more idiosyncratic factors explain performances by the outliers.

For the category of fruits/vegetables, there were only two outliers: one subject who performed better than would be expected and one who performed worse. Based on the two subjects, there was one key factor which may have accounted for the differences in their performance. Similar to the category of faces, the subject who performed worse

had bilateral damage, whereas the subject who performed better had unilateral damage. While it is unlikely the unilateral damage alone explains why the one subject did better, it is very possible that the presence of two lesions affecting homologous regions in the two hemispheres account for why a relatively small volume of tissue loss produced such a severe behavioral impairment.

For the category of tools/utensils, there were several outliers, and like the category of animals, no one factor appeared to explain their differences. For two subjects, relative sparing of the tissue on the lateral surface may explain their intact performance (see subjects 983 and 1133). For at least one additional subject, the lesion appeared to affect only the anterior-most aspects of the ROI, and it may be that preservation of the more posterior sector allows for normal performance (see subjects 988 & 2496); however, for the latter subject, a more plausible hypothesis is that atypical laterality explains her relatively intact performance. With regard to the subjects who performed worse than would be expected based on the extent of their lesions within the tool-specific ROI, two of the subjects had very small lesions that primarily affected cortex or subadjacent white matter in the vicinity of the temporo-parieto-occipital junction. Notably, this same area also appeared to be damaged in several of the subjects who had relatively intact performance, and thus it seems likely that damage to these structures alone explains their deficit. All three who performed worse did have subnormal contrast sensitivity, with two of the subjects displaying markedly abnormal performances. Thus, it is possible that for at least two subjects, deficits in primary visual perceptual processes affected their performances.

3.4.2.1 Elimination of Outliers

In general, a review of the potential outliers raised concerns that there may be two classes of outliers represented above. The first class of outliers would be the subjects for whom additional variables explain their performance. In this sense, they are the subjects whose data may be most informative toward the study's aim of understanding what factors, collectively, account for severity. Further, these subjects are not expected to be different from the population at hand; rather, given their more extreme presentations, they highlight potentially important relations in the data. The second class, however, would be the subjects who truly do not fit with the population—who truly are outliers. In this sense, their data only add noise to the analyses, because they contribute information that is probably not relevant for the population that is of interest in this study. Accordingly, these subjects would best be removed from the subsequent analyses.

With the latter point in mind, a review of the data pertaining to the outliers suggested that four subjects should be removed due to the fact that they most likely are true outliers from the population. The first is subject 2496. The data above suggested that this subject has atypical cerebral organization, which was further supported by a thorough review of her neuropsychological data presurgically (which was interpreted as indicating atypical lateralization). Given the above, this subject should have never been included in the analyses in the first place.

The next two subjects were 1366 and 1976. Both subjects had markedly impaired contrast sensitivity, and given the study's inclusion criteria which state that basic visual processes were broadly intact, these subjects should also have never been included. The final subject is subject 975. This subject's performance on Block Design, a measure of

visuoconstructional ability, was at the floor of the test suggesting some degree of visual processing impairment, and given that (with no other data to qualify visual perceptual abilities) and the study's inclusion criteria noted above, this subject was also removed from all subsequent analyses. Accordingly, all analyses from this point forward were run using the remaining sample of 176 subjects.

3.4.3 Relations between demographic, neuropsychological, and lesion variables and the severity of the observed deficit.

To address the question, do the various demographic, neuropsychological or lesion variables help explain performance in visual recognition above and beyond the extent of damage alone, partial correlations were examined for each of the potential variables controlling for the extent of damage in the region of interest and lesion size. The results from this analysis (see Table 3.9) indicated that after controlling for lesion size and extent of damage within the face-specific ROI, performance on the Benton Facial Recognition Test, Contrast Sensitivity and Age at Onset were all associated with performance on the famous face recognition task, when considered individually as variables. For the category of animals, the results indicated that after controlling for lesion size and the extent of damage in the animal-specific ROI, sex was associated with performance on the animal recognition task. For fruits/vegetables, the results indicated that none of the variables were associated with performance on the fruit/vegetable recognition task, after controlling for lesion size and the extent of damage in the fruit-specific ROI. For tools/utensils, the results indicated that after controlling for lesion size

Table 3.9 Partial correlations between each neuropsychological variable and performance in the categories of faces, animals, fruits/vegetables and tools/utensils controlling for extent of damage in the face-specific, animal-specific, fruit/vegetable-specific, and tool-specific ROIs, respectively, and lesion size.

		Faces	Animals	Fruits/ vegetables	Tools/ Utensils
Demo.	Handedness	.067	-.105	-.058	-.111
	Sex	-.036	.277**	.063	-.211**
Neuropsychological variables	Est. IQ	-.067	.017	-.078	.080
	Block Design	.018	-.053	-.148	-.025
	BFRT	-.221**	-.073	-.128	-.018
	JLO	-.010	-.016	-.070	-.023
	Contrast Sensitivity	-.235*	-.098	-.083	-.033
Lesion Variables	Age at Onset	.238**	.145	.067	.099
	Time elapsed since onset	-.038	-.118	-.121	-.153*

* $p < .05$. ** $p < .01$.

Note $n=176$ for all variables except BD ($n=175$), BFRT ($n=170$), JOL ($n=168$), and CS ($n=88$). For faces, the partial correlation between BFRT and face recognition indicates that as performance on the BFRT improves performance on the famous face recognition task improves. Similarly, the partial correlation between contrast sensitivity and facial recognition indicates that as contrast sensitivity increases, performance on the face recognition task improves. The partial correlation between age of onset and face recognition indicates that as age of onset increases performance on the face recognition task decreases. For the category of animals, the partial correlation between sex and animal recognition indicates that as sex moves from female to male performance on animal recognition improves (i.e., being a male is associated with doing better). For the category of tools, the partial correlation between sex and tool recognition indicates that as sex moves from female to male performance on tool recognition gets better. The partial correlation between time elapsed since onset and tool recognition indicates that as time elapsed since onset increases performance on tool recognition gets better.

and the extent of damage in the tool-specific ROI, sex and the length of time elapsed after the injury were associated with performance on the tool recognition task.

The above analyses were repeated controlling for the category-related ROIs instead of the category-specific ROIs, and generally-speaking, the overall pattern of results did not differ from what was obtained controlling for the category-specific ROIs (see Table 3.10).

Within the context of an overall framework that posits that the neural systems subserving visual recognition are only partially dissociable, one question to ask is does the extent of damage in other category-specific regions relate to severity after accounting for damage in the principal area (e.g., for faces, does damage in the animal-specific, fruit-specific or tool-specific ROI further account for performance on the face recognition task, after controlling for the extent of damage in the face-specific ROI)? To address this question, partial correlations were examined for the remaining three category-specific ROIs, while controlling for the extent of damage in the principal ROI and total lesion size. Note that for these analyses, the control regions were also included.

In general, the results from the partial correlation analysis examining the relations between the other category-specific areas and performance in faces, animals, fruits/vegetables and tools/utensils controlling for damage in the principal category-specific region yielded fewer significant results than were expected (see Table 3.11). Notably, these results were not restricted to only those subjects who sustained damage to the category-specific ROI. Rather, these analyses included all subjects, and thus, across all of the subjects, after controlling for damage in the principal ROI and total lesion size, damage to other regions did not appear to be significantly related to performance (with

Table 3.10 Partial correlations between each neuropsychological variable and performance in the categories of faces, animals, fruits/vegetables and tools/utensils controlling for extent of damage in the face-related, animal-related, fruit/vegetable-related, and tool- related ROIs, respectively, and lesion size.

		Faces	Animals	Fruits/ vegetables	Tools/ Utensils
Demo.	Handedness	.065	-.112	-.070	-.100
	Sex	-.033	-.272**	.065	-.202**
Neuropsychological variables	Est. IQ	-.072	.036	-.066	.090
	Block Design	.025	-.046	-.136	-.005
	BFRT	-.217**	-.048	-.111	.034
	JLO	-.007	-.013	-.049	-.031
	Contrast Sensitivity	-.225*	-.090	-.087	-.032
Lesion Variables	Age at Onset	.221**	.133	.075	.092
	Time elapsed since onset	-.036	-.103	-.117	-.146

* $p < .05$. ** $p < .01$.

Note $n=176$ for all variables except BD ($n=175$), BFRT ($n=170$), JOL ($n=168$), and CS ($n=88$). For faces, the partial correlation between BFRT and face recognition indicates that as performance on the BFRT improves performance on the famous face recognition task improves. Similarly, the partial correlation between contrast sensitivity and facial recognition indicates that as contrast sensitivity increases, performance on the face recognition task improves. The partial correlation between age of onset and face recognition indicates that as age of onset increases performance on the face recognition task decreases. For the category of animals, the partial correlation between sex and animal recognition indicates that as sex moves from female to male performance on animal recognition improves (i.e., being a male is associated with doing better). For the category of tools, the partial correlation between sex and tool recognition indicates that as sex moves from female to male performance on tool recognition gets better. In general, the pattern of results for the related ROIs does not differ from the pattern for the specific ROIs with the exception that the partial correlation between time elapsed and tool recognition is not significant when controlling for the tool-related ROI ($p < .10$).

Table 3.11 Partial correlations between damage in the category-specific ROIs and performance in the recognition of faces, animals fruits and tools, controlling for the extent of damage in the principal ROI and lesion size.

	Faces	Animals	Fruits/ Vegetables	Tools/ Utensils
Face-specific ROI	--	.052	-.089	.064
Animal-specific ROI	.034	--	.082	.020
Fruit-specific ROI	-.009	.242**	--	.180*
Tool-specific ROI	.040	.117	.046	--
Right-hemi Control	-.049	-.215**	-.097	-.025
Left-hemi Control	-.029	.026	.077	.065

Note: For animals, the partial correlation between damage in the fruit-specific ROI and performance in animal recognition indicates that after controlling for the extent of damage in the animal-specific ROI, damage in the fruit-specific ROI had a positive relationship with impairment in animal recognition (meaning that increasing damage was associated with worsening performance). The negative correlation between the right hemi control and animals, indicates that after controlling for the extent of damage in the animal ROI, damage in the right hemi control region was associated with better performance in animal recognition. The partial correlation between the fruit-specific ROI and tools indicates that after controlling for the extent of damage in the tool-specific ROI, damage in the fruit-specific ROI was positively associated with poorer performance in the recognition of tools.

the exception being the fruit-specific ROI, which will be discussed below). One possibility is that damage to the other ROIs only matters when you also have damage in the principal ROI (i.e., that damage to the principal ROI leads to deficit while damage in the other ROIs modulates the severity of the deficit), and this will be tested below with the analysis of moderator effects. However, an alternative is that these other specific regions represent the non-overlapping parts of the “partially overlapping neural systems” and thus, have little relation to performance in the other categories.

As noted above, the exception was the fruit-specific ROI. Damage in the fruit-specific ROI was associated with deficits in animals and tools, after controlling for deficits in the principal ROIs, respectively. As described previously, the fruit-specific ROI was the smallest of the ROIs, encompassing a tiny area in the ventral temporal lobe (inferior temporal gyrus/fusiform gyrus) on the right. Based on the size of the ROI itself, it is quite surprising that it was correlated with performance, (especially in relation to the very large face-specific ROI). However, it is very likely that the location of the fruit-specific ROI is the key. For more than a century, the ventral temporal-occipital lobe on the right has been widely implicated in processes associated with visual recognition. Additionally, findings from this very study indicated an area just rostral and lateral to the fruit-specific area that was associated with performance in three categories. Thus, it is possible that the association between the fruit-specific ROI and performance in animals and tools, reflects the importance of the right ventral temporal-occipital lobe in visual recognition.

3.4.4 Testing for Moderator Effects

The above analyses addressed whether various demographic, neuropsychological, and lesion variables were associated with performance in the recognition of faces, animals, fruits/vegetables, and tools/utensils, across the broad population of lesion patients. One possibility, however, is that these variables are only important for subjects who have damage to the neural systems that subserve visual recognition (i.e., that they *interact* with damage in the ROI). In other words, for the average subject without a lesion in the temporal-occipital cortices, it may be that ability to visually discriminate like items, as measured by the Benton Facial Recognition Test (BFRT), has no bearing on performance on the recognition of animals task (i.e., that everyone falls within a narrow range of “normal” performance, and that high-average or low-average is not dictated by the ability to visually discriminate similar items); however, for those subjects with damage, subtle differences in the ability to visually discriminate similar items may modulate the severity of the deficit. To test for this possibility, hierarchical linear regressions were used to test for significant interactions by comparing the effects of a model that includes an interaction term with a model that does not include the interaction term. Notably, for these analyses interactions for ROIs by handedness were not included due to inadequate cell size (i.e., there were few subjects with less than complete right handedness and even fewer with damage in an ROI versus no damage in an ROI). The results from the hierarchical linear regressions are provided in Table 3.12. There were no significant interactions for the face-specific or fruit-specific ROIs by any of the demographic or neuropsychological variables. However, for the category of animals, the results from the hierarchical linear regressions revealed two significant interactions. The

first was between performance on the Judgment of Line Orientation Task and the extent of damage in the animal-specific ROI. To further illustrate this interaction, performance on the Judgment of Line Orientation Task was plotted against performance in animal recognition for the subjects with lesions in the animal-specific ROI and for those without lesions in the animal-specific ROI (see Figure 3.34). In general, this revealed that the two groups were trending in opposite directions. However, within each of the groups (i.e., those with damage and those without), there did not appear to be a significant relation between performance on Judgment of Line Orientation and performance on the animal recognition task.

For the category of animals, there was also an interaction between the time elapsed since onset and damage in the animal-specific ROI. To illustrate this interaction, the extent of damage in the animal-specific ROI was plotted against performance on the animal recognition task for three groups: those who were still relatively close to onset (i.e., less than 1 year out), those who were moderately far out (i.e., greater than or equal to 1 year but less than 5 years) and those who were very far out from their injury (i.e., greater than 5 years). The results (see Figure 3.35) indicated that this interaction was due to a spurious association between time since onset and size of lesion (i.e., that the group who were nearer to onset also happened to have smaller lesions in the animal-specific ROI).

For the category of tools, there were significant interactions between damage in the tool-specific ROI and several of the neuropsychological variables as well as damage in the tool-specific ROI and sex. To begin, to further examine the interactions between the tool-specific ROI and the neuropsychological variables, estimated premorbid IQ and

Table 3.12 Results from the hierarchical regressions testing the effects of potential moderators.

		Faces	Animals	Fruits.	Tools
Demo.	Handedness x ROI	n/a	n/a	n/a	n/a
	Sex x ROI	.004	.014	.003	.016*
Neuropsychological variables	Est. IQ x ROI	.008	.015	.015	.032**
	Block Design x ROI	.004	.008	.003	.107**
	BFRT x ROI	.001	.013	.000	.009
	JLO x ROI	.016	.032**	.003	.018*
	CS x ROI	.005	.000	.000	.005
Lesion Var.	Age at Onset x ROI	.006	.010	.012	.022
	Time elapsed x ROI	.000	.019*	.006	.011

Note: For each of the tests, the interactions were added last to a model containing all of the demographic (i.e., sex, handedness), neuropsychological (estimated premorbid IQ, contrast sensitivity, and performance on the Block Design subtest, Benton Facial Recognition Test, and the Judgment of Line Orientation Test) and lesion variables (i.e., extent of damage in the ROI, total lesion size, age at onset and time elapsed since onset) and R^2 change was computed. Values in the table above represent R^2 change, which can be interpreted as the amount of variance in the dependent variable which is explained by the interaction. Thus, for tools, for example, 10.7% of the variance in tool recognition performance can be explained by the interaction between the extent of damage in the tool-specific ROI and Block Design Performance. Overall, the significant effects noted above generally constitute moderate effects (Cohen, 1982).

* $p < .05$. ** $p < .01$. Significant values are highlighted in **bold**.

performance in Block Design and Judgment of Line Orientation, the neuropsychological variable was plotted against performance in tool recognition for the group of subjects with damage in the tool-specific ROI (n=49) and the subjects without damage in the tool-specific ROI (n=127). These results are presented together on Figure 3.36. Contrary to what was expected, the results indicated that the interactions were actually driven by an association between the neuropsychological variable and performance in tool recognition for the subjects who did not sustain damage in the tool-specific ROI and not the subjects who did sustain damage in the tool-specific ROI! (The potential meaning of this will be discussed later).

For the interaction between the tool-specific ROI and age at onset, performance in tool recognition was plotted against age at onset for those subjects who sustained damage in the tool-specific ROI and those subjects who did not (see Figure 3.37). The results from this suggested that there was a trend toward a positive relationship between age at onset and tool recognition (such that those with later age at onset performed worse) for those subjects who sustained damage in the tool-specific ROI.

The final interaction was between the tool-specific ROI and sex. For this interaction, the extent of damage in the tool-specific ROI was plotted against performance in tool recognition separately for female and male subjects (see Figure 3.38). Here, the graphs suggested that the extent of damage was associated with performance in tool recognition for both groups, but that this may be due a linear relationship for the females and a dichotomization for the males (although it is equally possible that there are a couple of outliers in the male subjects leading to a false conclusion).

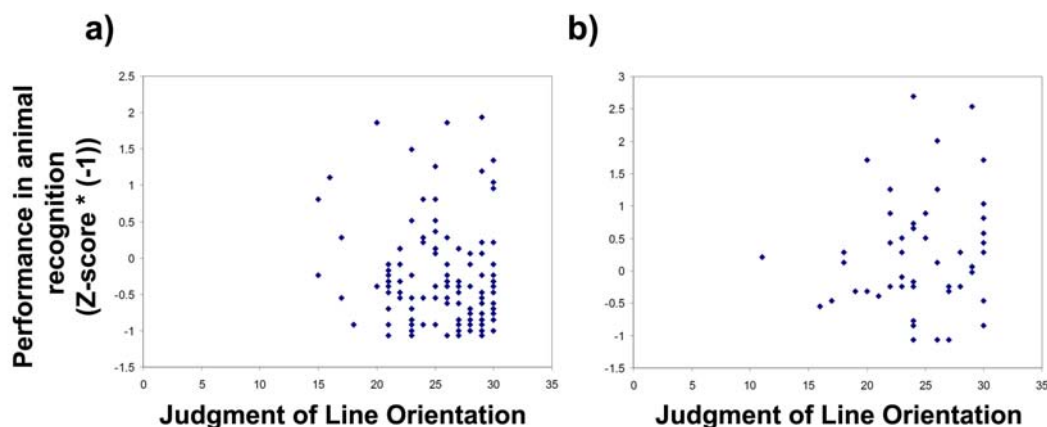


Figure 3.34 Performance in animal recognition is plotted against scores on the Judgment of Line Orientation Test for a) subjects without damage in the animal-specific ROI ($r = -.117$, n.s.; $n=119$) and b) subjects with damage in the animal-specific ROI ($r = .150$, n.s.; $n=48$). For the subjects without damage in the animal-specific ROI, there is a trend ($p < .25$) toward a negative relationship between the two variables indicating that worse performance on Judgment of Line Orientation may be associated with worse performance on the animal recognition task. For the subjects with lesions in the animal-specific ROI, there is a no relation between performance on Judgment of Line Orientation and the animal recognition task. Additionally, it is noteworthy that several subjects with damage in the Animal-specific ROI displayed very aberrant performances on the animal recognition task, but normal performance on JLO (raw score >25).

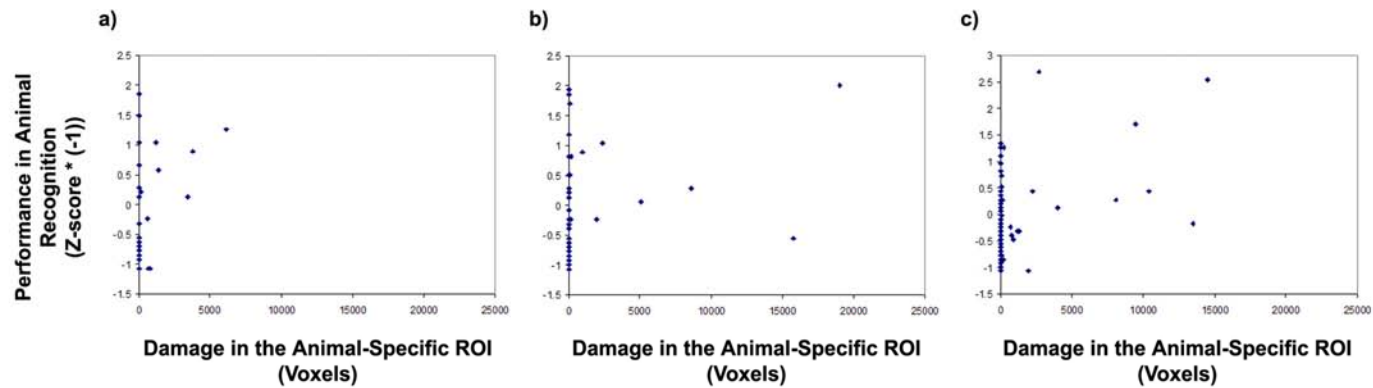
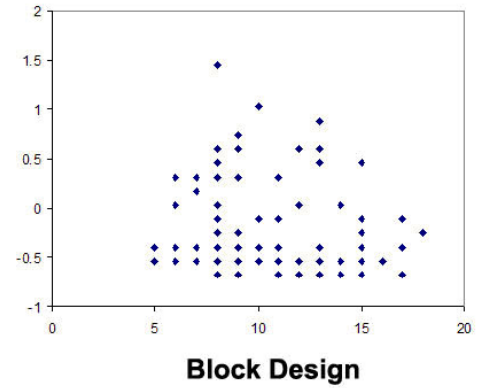
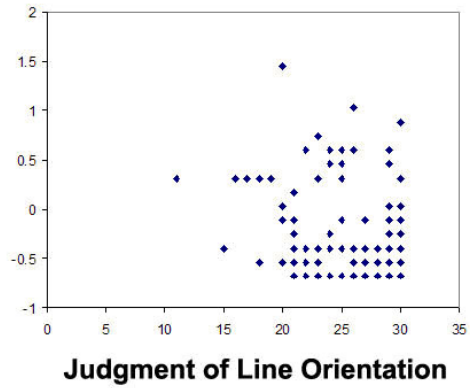
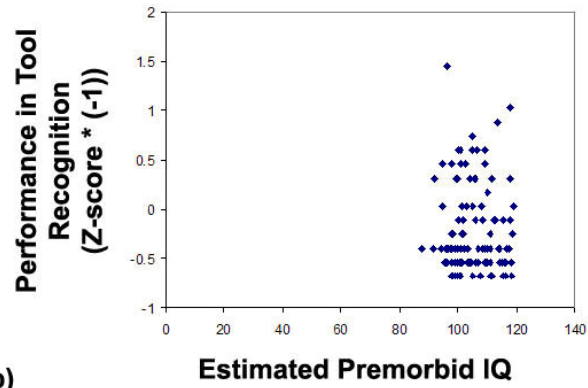


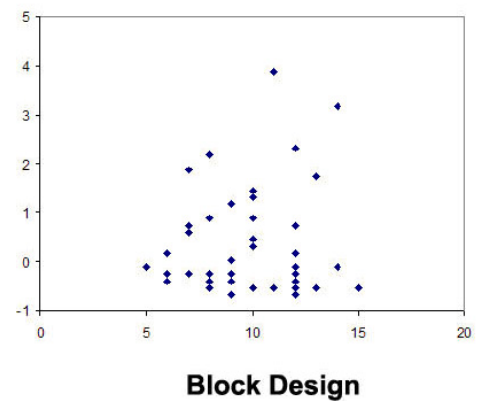
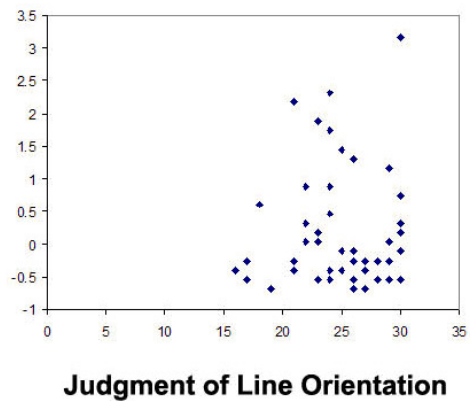
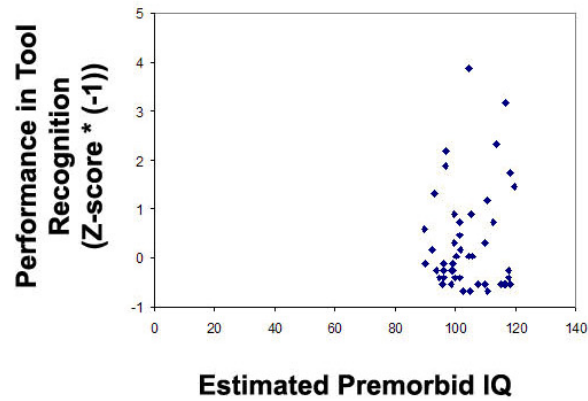
Figure 3.35 Damage in the Animal-Specific ROI is plotted against performance on Animal Recognition for those subjects a) who are near to onset (i.e., less than 1 year), b) who are moderately far from onset (i.e., ≥ 1 year but < 5 years), and c) who are very far from onset (i.e., ≥ 5 years). The results suggested that the interaction between the animal-specific ROI and time elapsed since onset was due to the fact that those who were nearer to onset also happened to have smaller lesions (when there was damage at all).

Figure 3.36 Performance on three neuropsychological measures is plotted against tool recognition for a) the subjects who did not sustain damage in the tool-specific ROI and b) the subjects who did sustain damage in the tool specific ROI (b). For the subjects who did not sustain damage in the tool-specific ROI there was a consistent negative relation between performance on the two visual spatial tasks, but not estimated premorbid IQ, and performance in recognition such that poorer performance on the neuropsychological measure was associated with poorer performance on tool recognition (Estimated Premorbid IQ: $r = -.063$, n.s.; Judgment of Line Orientation (JLO): $r = -.202$, $p < .05$; Block Design (BD): $r = -.190$; $p < .05$). For the subjects who sustained damage in the tool-specific ROI, there was no relation between performance on the neuropsychological task and tool recognition (all p 's $> .3$). The negative correlation between JLO and tool recognition performance indicates that better performance on JLO was associated with better performance on the tool recognition task in the subjects who did not sustain damage within the tool-specific ROI. Similarly, the negative correlation between BD and tool recognition indicates that better performance on BD was associated with better performance on tool recognition for the subjects who did not sustain damage within the tool-specific ROI.

a)



b)



Finally, the above analyses were also repeated for the related-areas instead of the category-specific ROIs. Consistent with the results above, there were no significant interactions between the principal ROI and any of the neuropsychological variables for the categories of faces and fruits. However, the category of animals yielded numerous significant interactions. Notably, three of these were between the animal-related area and the neuropsychological measures pertaining to visual spatial/visual perceptual abilities (i.e., Block Design, Benton Facial Recognition Test, Judgment of Line Orientation) and in each case, when the interaction was examined further, it was found that it was due to the subjects with very large lesions (i.e., $\geq 10,000$ voxels) performing well on the neuropsychological measures, but poorly on the animal recognition test. There was no association between performance on the neuropsychological measures and performance in animal recognition for the subjects with none to moderate damage in the ROI (i.e., $<10,000$ voxels). In general, this likely represents a spurious association whereby the patients with large lesions and poor performance in animal recognition also had good performance on these neuropsychological measures.

There was also a significant interaction between the extent of damage in the animal-related area and age at onset; however, further examination indicated that this was due to a single subject who had a very early age of onset (i.e., 10) and good performance (See subject 1133, who was discussed in the outliers above). When this subject was removed from the analysis and the analysis was repeated, the interaction between age at onset and damage in the ROI was no longer significant ($p > .8$).

Finally, there was a significant interaction between the animal-related area and time elapsed since onset. However, further examination of that interaction revealed the

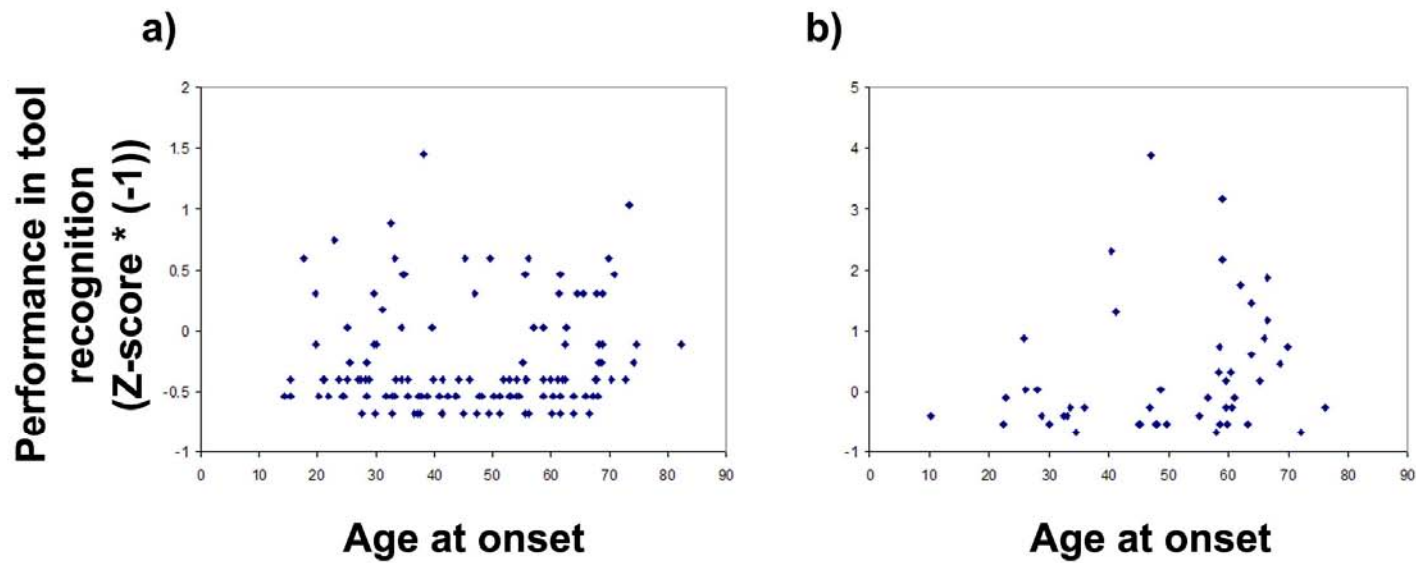


Figure 3.37 Performance in tool recognition is plotted against age at onset for a) the subjects who did not sustain damage in the tool-specific ROI, and b) the subjects who did sustain damage in the tool-specific ROI. The results did not indicate significant relations for either group; however, for the group who sustained damage in the ROI, there was a trend toward later onset being associated with worse performance ($p < .15$)

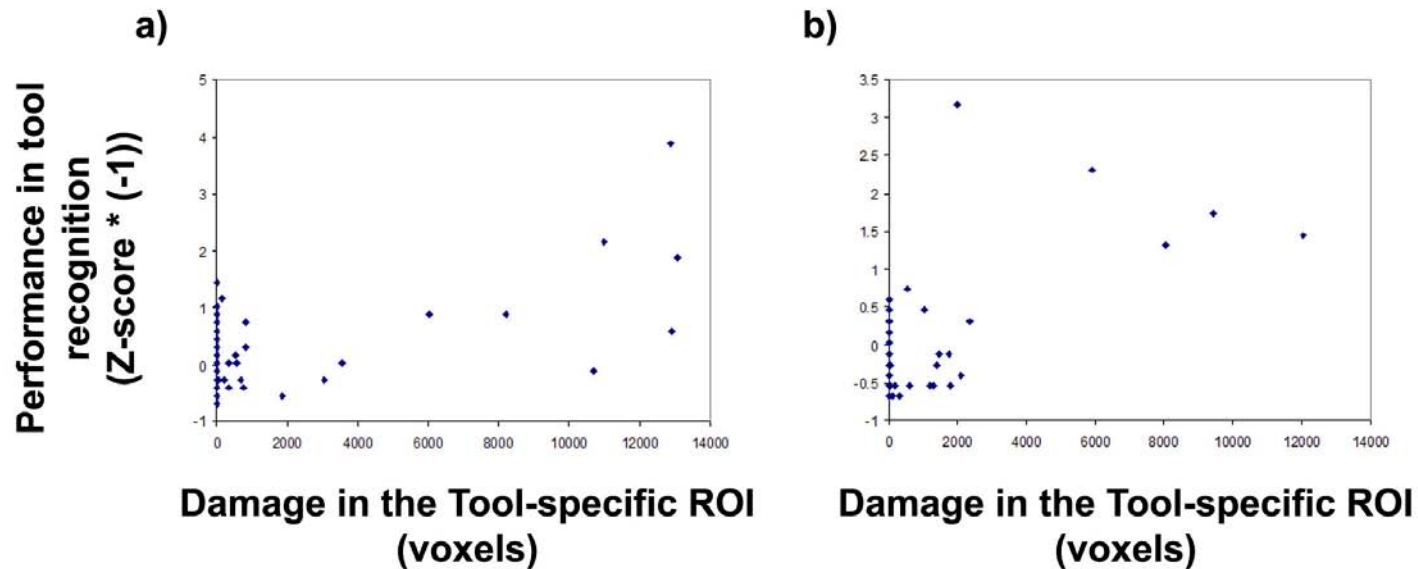


Figure 3.38 Performance in tool recognition is plotted against the extent of damage in the tool-specific ROI separately for female (a) and male (b) subjects. For both groups of subjects, there was a significant association between the extent of damage in the ROI and performance in tool recognition ($r = .606, p < .001$ for females, and $r = .658, p < .001$ for males). However, inspection of the data indicated that there was a relatively consistent trend for the women, but a separation between two groups of subjects for the men (i.e., those with little or no damage performing well, and those with larger lesions performing extremely poorly). At this point, it is unclear if this is due to a few outliers within the group of men, or whether this represents what happens in the population.

same spurious association between time elapsed and size of the lesion that was observed for the animal-specific ROI, such that those who were further out also had larger lesions (see above for further discussion).

For the category of tools, there were significant interactions between the tool-related area and the neuropsychological variables, Block Design, Benton Facial Recognition Test, and estimated premorbid IQ. In each case the relations between these variables and performance trended in different directions for the subjects who sustained damage in the ROI compared to the subjects who did not. However, none of the associations were significantly greater than 0, although the association between block design performance and tool recognition approached significance for the group without damage in the tool-related area ($r = -.176$; $p < .06$).

Additionally, for the category of tools, the interaction between the tool-related area and time-elapsed-since-onset was also significant. This interaction is illustrated in Figure 3.39. As illustrated in the figure, the association between damage in the tool-related area and performance in tool recognition was stronger for those subjects who were further out than for those subjects who were less than one year out from their injury.

In general, the pattern of significant interactions that were observed for the category-related areas were similar to what was observed for the category-specific ROIs. Finally, please note that ROI by ROI interactions were not examined for the category-related areas, because the category-related areas were not non-overlapping.

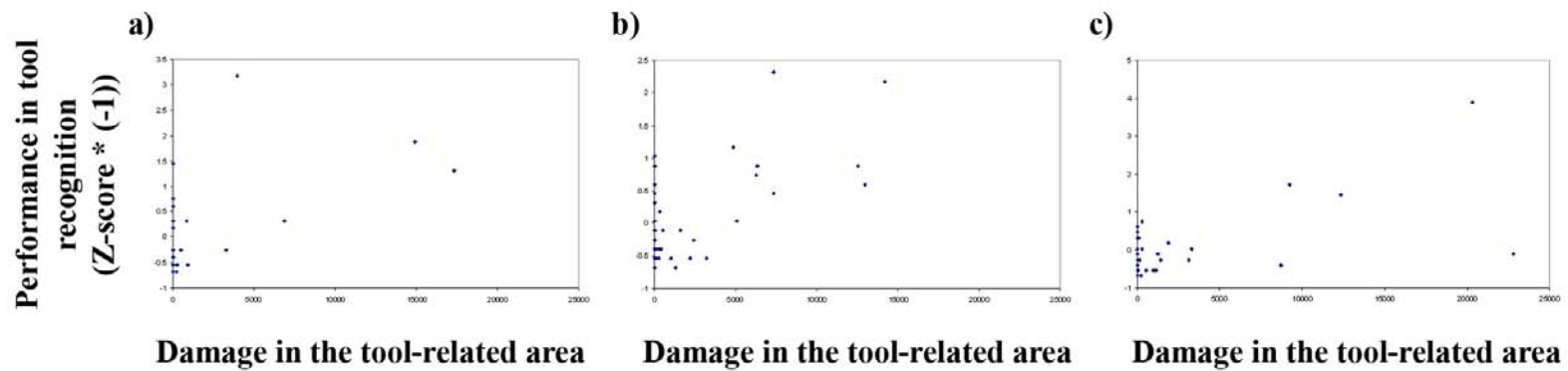


Figure 3.39 Performance in tool recognition is plotted against damage in the tool-related area for subjects who are a) near to onset (i.e., < 1 year out), b) moderately far from onset (i.e., ≥ 1 year but < 5 years) and c) very far from onset (i.e., ≥ 5 years). As can be seen from the graphs, the strongest association appeared for the group that was moderately far out.

3.4.5 Testing for Interactions between ROIs

To address the question, does damage in the other category-specific ROIs relate to recognition performance in the category of interest differently for those subjects who sustain damage to the principal ROI compared to those subjects who do not sustain damage in the principal ROI, (e.g., for face recognition, does damage the animal-specific, fruit-specific or tool-specific ROI relate to performance in face recognition differently for the subjects who have sustained damage in the face-specific ROI compared to those subjects who have not sustained damage in the face-specific ROI?), I examined whether there were moderator effects pertaining to ROI by ROI interactions. The results indicated that for the categories of faces and fruits/vegetables, there were no ROI by ROI interactions. For the category of animals, there was a significant interaction between damage in the animal-specific ROI and damage in the fruit-specific ROI, which accounted for 4.4 % of the variance in animal recognition performance. To illustrate this interaction, the extent of damage in the fruit-specific ROI was plotted against performance in animal recognition for those subjects who sustained damage in the animal-specific ROI and for those subjects who did not sustain damage in the animal specific ROI (see Figure 3.40). The results indicated that there was a positive association between damage in the fruit-specific ROI and animal recognition for the subjects who did not have damage in the animal-specific ROI, but not for the subjects who did sustain damage in the animal-specific ROI.

For the category of tools, there was a significant interaction between the tool-specific ROI and the animal-specific ROI. To illustrate the interaction, damage in the animal-specific ROI was plotted against performance in tools for the subjects who did not

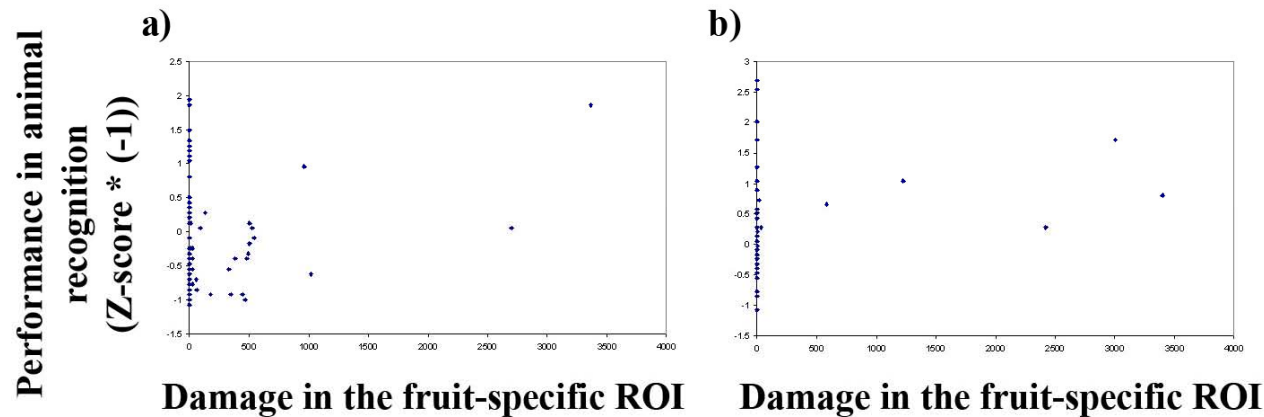


Figure 3.40 Damage in the fruit-specific ROI is plotted against performance in animal recognition for a) those subjects who did not sustain damage in the animal-specific ROI and b) those subjects who did sustain damage in the animal-specific ROI. The results indicated that for subjects who did not sustain damage in the animal-specific ROI, there was a positive association between the extent of damage in the fruit-specific ROI and worsening performance in animal recognition ($r = .248, p < .01$). However, for the subjects who sustained damage in the tool-specific ROI, increasing extent of damage in the fruit-specific ROI did not seem worsen performance on animal recognition. (Note that the animal- and fruit-specific ROIs are in different hemispheres, so the subjects who have damage to both are bilateral cases).

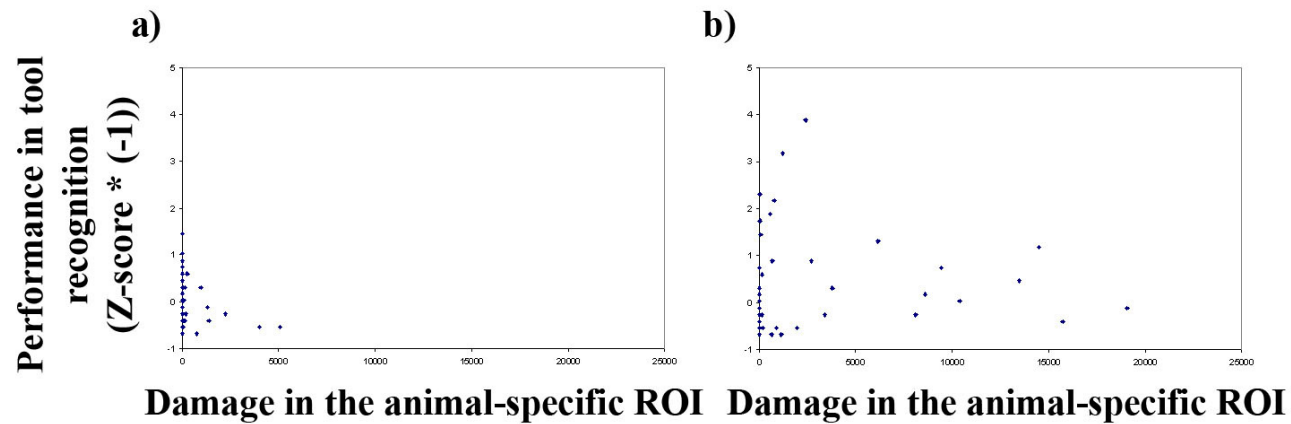


Figure 3.41 Damage in the animals-specific ROI is plotted against performance in tool recognition for a) those subjects who did not sustain damage in the tool-specific ROI and b) those subjects who did sustain damage in the tool-specific ROI. The results indicated that the association between damage in the animal-specific ROI and tool recognition is significant for neither group, but trending in different directions.

sustain damage in the tool-specific ROI and the subjects who did. (see Figure 3.41).

Overall, there was no significant association between damage in the animal-specific ROI and tool recognition performance either for the subjects who sustained damage in the tool-specific ROI or those who did not.

3.4.6 Building a model to account for the severity of a visual recognition impairment following focal brain damage

The final step was an exploratory analysis to identify the best model to account for the severity of visual recognition impairments in the categories of faces, animals, fruits/vegetables and tools/utensils. This was carried out using a forward stepwise regression in which the maximum model included all demographic (i.e., sex, handedness), neuropsychological (i.e., Contrast Sensitivity, Block Design, Benton Facial Recognition Test, Estimated Premorbid IQ) and lesion variables (i.e., age at onset, time elapsed since onset, lesion size, and extent of damage in the Face-specific ROI, Animal-specific ROI, Fruit/vegetable-specific ROI, and Tool/utensil-specific ROI).¹⁴ The final model then included the variable with the largest association with the variable of interest (namely performance in recognition) as well as any additional variables whose contribution significantly enhanced the overall fit of the model. Notably, because the analysis of potential moderator effects indicated that there were significant interactions between category-specific ROIs and neuropsychological variables for the categories of animals and tools, for those

¹⁴ Because it was postulated that damage in the other category-specific areas could be related to deficit in the category of interest, all category-specific ROIs were included amongst the possible variables available for the model.

categories, separate models were built for those subjects who sustained damage in the category-specific ROI, versus those subjects who did not.

For the category of faces, the results from the forward step-wise regression indicated that performance in face recognition could be best accounted for by the extent of damage in the Face-specific ROI, age at injury and the ability to visually discriminate faces, as measured by performance on the Benton Facial Recognition Test, in accordance with the following model (Adjusted $R^2 = .231$; $p < .001$ for the full model):

$$Y = .423 (\text{Face-spec ROI}) + .203 (\text{Age at Injury}) + (-.173)(\text{BFRT}),$$

where Y = performance in face recognition (Z-score * (-1)) and Face-spec ROI = extent of damage in the face specific ROI, Age at Injury = Subject's age at time of injury, and BFRT = Benton Facial Recognition Test. Note that the variables Face-spec ROI, Age at Injury and BFRT are all in units of standard scores, so that holding everything else constant, a 1 SD increase in the extent of damage in the Face-Spec ROI results in an increase of .423 in the patient's score.

For the category of fruits/vegetables, the results from the stepwise regression indicated that performance in fruit/vegetable recognition could best be accounted for by the extent of damage in the fruit-specific ROI and performance on the Block Design test, in accordance with the following model (adjusted $R^2 = .175$; $p < .001$ for the model):

$$Y = .414 (\text{Fruit-spec ROI}) + (-.136)(\text{Block Design})$$

where Y = performance on fruit/vegetable recognition (Z-score * (-1)) and Fruit-spec ROI and Block Design are both expressed in terms of standard scores.

For the category of animals, recall that there were significant interactions between the damage in the animal-specific ROI and other neuropsychological variables. As a result,

models were created separately for the subjects without damage in the animal-specific ROI and the subjects with damage in the animal-specific ROI. For those subjects without damage in the animal-specific ROI, performance in animal recognition was best accounted for by sex and the extent of damage in the fruit-specific ROI in accordance with the following model (adjusted $R^2 = .118$; $p < .001$ for the model):

$$Y = (-.266)(\text{Sex}) + .253(\text{Fruit-spec ROI})$$

where Y = performance in the recognition of animals (Z -score * (-1)) and sex and fruit-specific ROI are both expressed in terms of standard scores. Note that sex was dummy coded as females equaling 1 and males equaling 2 so the negative β -weight indicates that being a woman was associated with worse performance.

For the subjects with damage in the animal-specific ROI, the results indicated that performance in animal recognition was best accounted for by damage in the animal-specific ROI, damage in the fruit-specific ROI and sex, in accordance with the following model (Adjusted $R^2 = .258$; $p < .01$ for the model):

$$Y = .409 (\text{Animal-spec ROI}) + .397 (\text{Fruit-spec ROI}) + (-.296)(\text{Sex})$$

where Y = performance in animal recognition and Animal-spec ROI, Fruit-spec ROI and Sex are all expressed as standardized scores. As above, the negative β -weight for sex indicates that being a male is associated with better performance.

For the category of tools/utensils, models again were calculated separately for the subjects without damage in the tool-specific ROI and for the subjects with damage in the tool-specific ROI. For the subjects without damage in the tool-specific ROI, performance in tool recognition was best accounted for by the extent of damage in the Fruit-specific ROI and sex, in accordance with the following model (Adjusted $R^2 = .153$, $p < .001$ for the model):

$$Y = (-.385)(\text{Sex}) + .188(\text{Fruit-spec ROI})$$

where Y = performance in tool recognition and sex and Fruit-spec ROI are expressed as standard scores. Note that the negative β -weight associated with Sex indicates that being male is associated with better performance.

For the subjects with damage in the tool-specific ROI, performance in tool-recognition was best accounted for by the extent of damage in the tool-specific ROI and the extent of damage in the fruit-specific ROI (Adjusted $R^2 = .616$; $p < .001$, for the model):

$$Y = .686 (\text{Tool-spec ROI}) + .427 (\text{Fruit-spec ROI})$$

where Y = performance in the recognition of tools and Tool-spec ROI and Fruit-spec ROI are expressed as standardized scores.

3.5 Discussion

There has been remarkably little research examining the factors that determine the severity of a patient's visual recognition impairment following focal brain damage. Until now, most of what could be said would have been based on a few longitudinal case studies of patients with visual agnosia or based on extrapolation from outcomes for stroke or brain injury more generally. Those data would have suggested that factors such as age of onset, handedness, gender or premorbid abilities are potentially important. Additionally, studies of patients with prosopagnosia and visual agnosia have indicated that mild visual perceptual impairments may be present even in patients with more "associative" forms of agnosia, and thus, it is possible that these factors, in turn, modulate recognition performance. The aim of this study was to examine the relations between the extent of damage in the neural systems

subserving visual recognition and recognition performance and to determine whether additional factors modulate that relationship.

As hypothesized, the findings from the present study indicate that the most important factor in determining the severity of visual recognition impairments pertaining to faces, animals, fruits/vegetables or tools/utensils, is the extent of damage in the neural system that carries out that function. This is not surprising given that damage in these areas had been previously found to be predicted by impairment in the aforementioned categories. What is notable is that there is generally a linear relationship between extent of damage in the region and performance. While a linear relation was hypothesized, it was certainly possible that other more complex relations existed, such as stepwise relationship (whereby upon crossing some threshold damage is associated with deficit, but that below or above that severity is relatively constant in relation to the size of lesion) or nonlinear relationship (whereby the relationship between damage and severity increases as a function of the extent of damage). The finding of a linear relationship suggests that these regions function as part of broad neural systems and that there is not just one key spot that when damaged, produces a deficit. This latter point is further supported by the finding that damage outside of the category-specific areas is also associated with deficit (e.g., that damage in the fruit-specific area is associated with deficits in the recognition of tools and animals, as well as fruits). Thus, these broad neural systems do not necessarily include only these category-specific regions (a point to which I will return in Chapter 4).

With regard to the other variables (e.g., demographic variables, neuropsychological variables), overall, the findings were only weakly supportive of the hypothesis that these variables would also relate to severity of performance. Certainly, as evidenced by the outlier

analysis, there are numerous examples where extent of damage does not appear to predict performance accurately, thereby suggesting that some other factor accounts for severity. However, systematic analysis of these effects across the entire group revealed relatively few significant effects.

For example, the analysis of potential moderator effects revealed significant interactions between the extent of damage in the principal region of interest and several demographic and neuropsychological variables for the categories of animals and tools. However, further analysis revealed that this was often the result of either differences in non-significant trends between those with damage in an ROI and those without, or to spurious associations (such as when the size of lesion happens to be correlated with time elapsed since onset). When the interaction did appear to reflect a significant relationship for one group, while not the other group, it was often the group without lesion for whom the demographic or neuropsychological variable accounted for performance. Notably, the latter is not inconsistent with the hypothesis that neuropsychological or demographic factors would account for a small portion of the variance, but that relation was presumed to arise because these variables would help account for variability in performance in the subjects with a lesion in the principal area.

There were several variables that accounted for performance across all subjects, regardless of whether they had a lesion in the category-specific ROI or not. Specifically, in the case of face recognition, age at onset and the ability to discriminate between similar faces (measured as performance on the Benton Facial Recognition Test) were related to performance after controlling for lesion size and extent of damage in the face-specific ROI. Similarly, for fruits/vegetables, performance on a measure of visuoconstructional ability,

Block Design, was retained in the model accounting for severity (in conjunction with damage in the fruit-specific ROI). Finally, sex was found to relate to performance in animal recognition in both the subjects who sustained damage in the animal-specific ROI and those who did not, and to relate to tool-recognition performance in the subjects who did not sustain damage in the tool-specific ROI. However, factors such as premorbid intellectual functioning, handedness and contrast sensitivity were generally not found to relate to performance across any of the four categories.

In general, the failure to find many moderating effects or main effects for demographical or neuropsychological variables could be construed as a good result from the perspective of lesion analysis. Presently, most lesion studies do not control for potential confounding factors such as time elapsed since onset or estimated premorbid IQ, and for visual recognition at least, this appears to not be a large concern. On the other hand, had this study found large effects for a number of neuropsychological or demographic variables, it would have suggested that not controlling for these factors could lead to invalid conclusions at least in some circumstances.

With regard to the association between damage to the “other” ROIs and performance in the category of interest, one robust finding is that the extent of damage in the fruit-specific ROI not only related to performance in the recognition of fruits/vegetables, but also to animals and tools. There are several possible interpretations for this finding. First, given that the animal-specific and tool-specific ROIs are both in the left hemisphere while the fruit-specific ROI is in the right hemisphere, it is possible that this finding reflects the added contribution of bilateral damage. Indeed, the fact that the fruit-specific ROI is included in models predicting severity of deficit in animal and tool recognition for subjects with damage

in the animal-specific and tool-specific ROIs respectively, indicates that additional damage involving this area (i.e., bilateral damage, because subjects who have damage to both of these ROIs necessarily have bilateral damage) is associated with worse performance when compared to subjects with unilateral lesions alone. However, the fact that damage to the fruit-specific ROI is also associated with performance in the recognition of animals and tools/utensils for the subjects without damage involving the animal-specific and tool-specific ROIs, respectively, indicates that damage involving this region alone is associated with a decrement in performance. The latter point is particularly important because it indicates that the neural system subserving the recognition of entities is not limited to the category-specific areas, which were identified here, but involves a broad network of neurons in visual and association cortices. Furthermore, as the concept of relatively greater activation which has been robustly demonstrated in functional imaging studies, it suggests that these category-specific areas are only relatively specific, and may very well be involved in the processing of many different stimuli, albeit potentially to different degrees.

3.6 Summary

Overall, the results from the present study provide strong support for the lesion method by demonstrating that the lesion is still the most important determinant of performance. However, they also reveal that other variables (i.e., certain demographic characteristics, neuropsychological variables and lesion variables) may also be related to performance and that understanding these variables may help us better understand what determines the severity of a patient's deficit following focal brain damage.

CHAPTER 4

GENERAL DISCUSSION

4.1 Summary of findings

Although the visual system is perhaps the most well understood system in the human brain, the precise organization of the neural system whose activity gives rise to higher order functions like visual recognition remains unknown. More than a century's worth of research with focal lesion patients has led to the conclusion that posterior cortices, particularly ventral temporal-occipital cortices subserve visual recognition. Yet, are those regions equipotential? Are there subsystems within the temporal-occipital cortices that are specialized for processing particular types of stimuli? Several researchers who study patterns of neural activity in neurologically normal individuals would almost certainly respond yes to the second question (e.g., Kanwisher et al., 1997; Grill-Spector et al., 2004). Additionally, there is some convergent evidence from patients with focal lesions who display marked impairments in the ability to recognize certain stimuli while retaining the ability to recognize other types of stimuli (e.g., Warrington & Shallice, 1984; Warrington & McCarthy, 1994; Moscovitch et al., 1997). However, the question is far from answered.

First, most of the evidence regarding the specificity of any subsystem within visual and association cortices comes from research utilizing functional imaging paradigms, and as such, all of the evidence is correlational. Thus, researchers infer specificity based on the association between BOLD signal and some component of the task (e.g., stimulus class, task demands); however, without directly affecting the brain (via permanent lesion or temporary disruption such as in transcranial magnetic stimulation) one cannot truly test the specificity of these supposedly specific areas.

Second, those studies that do test specificity by directly affecting the brain mostly do so in the context of a single case design. Thus, these studies raise the possibility that certain functions can be dissociated in the human brain at least within an individual, but leave open the possibility that these cases do not represent the most standard examples of cerebral organization. To truly examine whether functions can be dissociated, they need to be examined across large numbers of subjects.

As noted in the introduction, there have been a few attempts to examine specificity by reviewing case studies of patients with visual agnosia and other types of category-specific semantic deficits; however, these have not yielded firm conclusions regarding the underlying neuroanatomy, because the neuroanatomical data has often been quite limited. There has also been a large scale examination of visual recognition impairments conducted previously in this laboratory (e.g., Damasio et al., 2004; Tranel et al., 1997); however, those studies did not address the specificity of the lesion-deficit associations. Thus, building on the results from prior studies in this laboratory, the present study examined the specificity of lesion-deficit relations pertaining to the categories of faces, animals, fruits/vegetables and tools.

In addition, the present study also examined the relation between the extent of damage involving the neural system subserving visual recognition and the severity of the observed recognition deficit as well as the potential relation between severity and other neuropsychological variables. This component of the study was motivated by both a desire to further understand the underlying neural system and a desire to link the basic research with the clinical behavior. Regarding the latter, it is obvious clinically, that there can be variability amongst patients with some individuals doing remarkably well following a focal

brain injury and others doing quite poorly. However, the reasons why patients display markedly different outcomes is not well understood at all.

Building on a research database that has spanned more than 15 years, as well as neuroimaging techniques that have been developed in this laboratory and elsewhere, this study employed a novel approach to address the specificity of visual recognition impairments following focal brain damage by using voxelwise logistic regression to parse out variance that could be attributed to deficits across multiple categories and identify areas that were uniquely predicted by performance in the category of interest. Then, based on the findings from the first part of the study, the relation between the extent of damage in these “category-specific” regions and the severity of the recognition impairment for faces, animals, fruits/vegetables and tools/utensils was examined, as well as potential modulating effects from various demographic (e.g., sex, handedness), neuropsychological (e.g., premorbid intellectual functioning, visual spatial ability, visual perceptual ability, visuoconstructional ability), and lesion (e.g., age at onset, time elapsed since onset, extent of damage in other ROIs, lesion size) factors.

Regarding the first aim, the results from the present study revealed regions in visual and higher order association cortices where damage appeared to be more specifically associated with deficits in a particular category, than in any of the other categories. These regions included an area in the left mesial occipital cortex (mostly lingual gyrus) that was specific for animal deficits, a small area in the right inferior temporal gyrus that was specific for fruits/vegetables, an area in the left lateral occipital cortex that was specific for tools/utensils and a large area that included the right anterior temporal lobe, which then extended caudally through the white matter into the temporal-parietal-occipital junction and rostrally through the white matter core in the frontal lobe, for faces.

When compared with the results from prior studies (e.g., Damasio et al., 2004, Rudrauf et al., in press) as well as the results from present analyses which did not parcel out areas that are potentially common to deficits across multiple categories, the category-specific regions identified here appear to reflect a subset of a much larger network which is involved in visual recognition more broadly (see below for further discussion of the neural system subserving visual recognition).

In regards to the second aim, I found that the largest factor accounting for performance in the recognition of faces, animals, fruits/vegetables and tools/utensils, was the extent of damage in the respective category-specific regions. However, within each of the categories, there were additional factors that were also associated with performance, which helped explain some of the additional variance in recognition performance that could not be explained by extent of damage alone. Notably, for some categories, these factors explained performance across the whole population of lesion subjects; however, for other categories I observed ROI by variable interactions, such that the factors exerted different associations with performance within the group of subjects who sustained damage in the category-specific ROI compared to those who did not. Accordingly, in instances where I observed the latter, performance was modeled separately for those subjects who sustained damage in the ROI from those subjects who did not.

Specifically, for the category of faces, performance in recognition was best accounted for by the extent of damage in the face-specific ROI, age at onset and performance on the Benton Facial Recognition Test (a measure of fine-grained perceptual discrimination). There were no significant face-specific ROI by variable interactions. Similarly, for the category of fruits/vegetables, performance in recognition was best accounted for by the extent of damage

in the fruit-specific ROI and performance on the Block Design test (a measure of visuoconstructional ability). There were also no fruit-specific ROI by other variable interactions.

In contrast, for the categories of animals and tools/utensils, there were significant interactions between the category-specific ROI and other variables so the performance was modeled separately for those with damage in the ROI and those without. Accordingly, for the subjects without damage in the animal-specific ROI, performance in animal recognition was best accounted for by the extent of damage in the fruit-specific ROI and sex (with being male associated with better performance). For the subjects with damage in the animal-specific ROI, performance in animal recognition was best accounted for by the extent of damage in the animal-specific ROI, the extent of damage in the fruit-specific ROI and sex. For the subjects without damage in the tool-specific ROI, performance in tool recognition was best accounted for by the extent of damage in the fruit-specific ROI and sex. Finally, for subjects with damage in the tool-specific ROI, performance in tool-recognition was best accounted for by the extent of damage in the tool-specific ROI and the extent of damage in the fruit-specific ROI.

Notably, the extent of damage in the fruit-specific ROI was related to not only performance in the recognition of fruits/vegetables, but also performance in the recognition of animals and tools/utensils. This suggests that although damage here is predicted by impairment in the recognition of fruits/vegetables above and beyond performance in the recognition of anything else, damage involving this region is predictive of performance in the recognition of other entities. In other words, fruit-specific is not fruit-exclusive, even in the small universe of four categories.

Additionally, the results from the first study revealed an area in the inferior temporal gyrus on the right (overlapping with the fruit-specific ROI, but extending posteriorly and lateral to the fruit-specific region) which was associated with performance in recognition for three categories: faces, animals, and fruits/vegetables. Taken together, then, the results suggest that the inferior temporal cortex on the right is part of a large network necessary to subserve visual recognition of a wide range of stimuli rather than exclusive to a particular category of stimulus.

4.2 Anatomical and theoretical perspectives

A key question is how do the findings from this study relate to broader theories on visual recognition and what do they tell us about the neural systems subserving visual recognition? The findings from the first study revealed areas in the ventral temporo-parieto-occipital cortex that were specifically related to deficits in the recognition of faces, animals, fruits/vegetables, and tools/utensils. These areas, which were distributed across a large expanse of cortex, bilaterally, were in turn part of an even larger network that appears to subserve process related to visual recognition more broadly. However, within this seemingly wide-ranging network, there appear to be organizing principles, which in turn, may structure the system underlying visual recognition.

The first principle pertains to the “uniqueness” of the entity and an anterior-posterior axis along ventral temporal-occipital cortices. Comparison of the face-specific region with the remaining category-specific regions reveals that the face-specific area extends far more rostrally than any of the remaining three areas. This suggests that the recognition of faces, and more likely, unique identity in general, requires input from anterior temporal regions as

well as potentially, areas within frontal cortices, particularly on the right. In the words of A. R. Damasio, H. Damasio and colleagues, this is because recognition at a unique level requires the coactivation of the ongoing percept with contextual information about that entity, which is contained in visual and multimodal association cortices throughout the brain. However, that coactivation, in turn requires coordination or the ability to bind the activation, which is also carried out in relatively discrete regions, mostly in higher order association cortices (e.g., Damasio, Damasio, & Van Hoesen, 1982; Damasio, 1990).

The findings from this study, as well as prior studies in this laboratory (e.g., Damasio et al., 2004) and elsewhere implicate the anterior temporal lobe on the right as being the locus for where this binding might occur. Furthermore, converging evidence is provided by electrophysiological studies employing single cell recordings in both animals and humans, which have identified cells in the superior temporal sulcus (e.g., Perrett, Rolls, & Caan, 1982) and inferior temporal cortex (TE) in monkeys (e.g., Tanaka et al., 1997), and mesial temporal lobes (e.g., hippocampus, amygdala, entorhinal cortex and parahippocampal gyrus) in humans that respond selectively to visual stimuli from different categories (Kreiman et al., 2000), and even to different pictures of the same person or letter strings of their name (e.g., Quiroga, et al., 2005). I am not saying that mesial temporal lobe structures are sufficient for visual recognition at the unique level or that activity from a single neuron which is attuned to a particular stimulus is sufficient to support the sense of familiarity one achieves when recognizing a previously known stimulus. I hold that the latter is only possible through the robust coactivation of this contextual information, which leads to the conscious experience of recognition. Further, this coactivation will almost certainly include information that is dependent on the engagement of earlier visual cortices, such as ventral occipital-temporal

cortices. However, a key component of the network subserving face recognition, and unique recognition more generally, is the need to involve aspects of the neural system which are located more anteriorly in order to link the perceptual information arising from early visual cortices with knowledge which provides context for the stimulus.

This is in contrast to recognition at a non-unique level as was observed for the categories of animals, fruits/vegetables and tools. Notably, none of these categories uniquely predicated damage in the right temporal pole. Further, according to the findings from the second study, damage involving the face-specific region (which included the right temporal pole) was only weakly associated with recognition impairments in the remaining three categories. This suggests that these more anterior regions are only weakly engaged, and potentially not necessary, when categorizing stimuli pertaining to animals, fruits/vegetables and tools/utensils at a non-unique level. However, if the recognition pertaining to these categories was at a unique level (such as when one recognizes one's own pet), I would postulate that the anterior cortices would become essential.

With regard to the distribution of the animal-specific, fruit-specific and tool-specific regions within the posterior temporal-occipital cortices, as noted above, these are relatively-specific areas, with the relative specificity varying across categories. Of these, the most, relatively specific appeared to be the animal and tool regions, and the least specific, the fruit-region. There are a number of important implications for these findings. First, the weak evidence for the specificity of the fruit-specific area, in conjunction with its location (i.e., right inferior temporal cortex) and its proximity to other areas which appear related to deficits in multiple categories (i.e., the results from the conjunction analysis) suggest that the right inferior temporal lobe may be widely involved in visual recognition processes of all

sorts. This hypothesis would be consistent with the more than 100 years of study of patients with focal lesions, many of whom have displayed impairments in recognition of faces or living entities following damage that the right posterior inferior temporal occipital lobe (and in most cases, also damage to homologous areas on the left).

However, this hypothesis is generally inconsistent with the notion that the mid-fusiform gyrus is the locus of face recognition, or specific to face processing, in general. As discussed in Chapter 2, the notion that the mid-fusiform gyrus is specific for face processes is generated primarily from studies that have shown that activity in this area is greater when subjects view faces, than when they view most other types of stimuli. However, the precise meaning of greater activation is not known. It is inferred that it reflects the specificity of the tissue, although alternate explanations are possible. In the context of the present theoretical formulation, it is possible that this area is involved in evoking aspects of the contextual information associated with visual stimuli, and that in order to achieve recognition at a unique level this information must be accessed to a greater degree than is necessary to categorize a stimulus with regard to some non-unique aspect.

With regard to tools, interestingly, results from prior studies in this laboratory as well as elsewhere have implicated more left hemisphere areas in tool recognition than right hemisphere areas. While the findings here do not refute this, the finding that damage in the right hemisphere (i.e., fruit-specific ROI) is related to performance in tool recognition reiterates the notion that the left temporal-occipital areas are part of a network of regions that are involved in recognizing tools.

4.3 Conclusion

The question posed in this thesis is: what is the relationship between damage in the human brain and the specificity and severity of visual recognition impairments pertaining to faces, animals, fruits/vegetables and tools/utensils? Overall, the results indicate that there are relatively specific relations between performance in the respective categories and damage involving particular areas within the temporal and occipital cortices. Further, there appears to be a linear relationship between the extent of damage in these areas and the severity of the observed recognition impairment, although there is also evidence that this relation may be affected by other variables. Additionally, by accounting for some of these variables, I am able to explain a greater proportion of the variability in performance, which in turn may be used toward making predictions about long-term outcome in the future.

4.4 Limitations

As in any graduate thesis or even faculty research project, there are limitations to the presented study. One of the limitations in this study is the reliance on primarily archival data, which in turn, limited the types of questions that could be addressed or the hypothesis that could be tested. For example, given the various structure-function hypotheses, it would have been interesting to examine whether a voxelwise logistic regression for deficits involving an inability to recall information pertaining to the structure or function of particular stimuli would have led to a similar pattern of lesions or whether including both information regarding the semantic knowledge for structure-function and visual recognition impairments would fail to yield any unique areas at all.

Another limitation pertains to lesion coverage. Although this study employed one of the largest samples of patients with focal lesions, their lesions were not evenly distributed across the telencephalon (as is the case with all human lesion studies). This limits both the power that can be observed at certain voxels and the independence of the voxels relative to each other. Thus, if this sample could be doubled, there might be the possibility to both enhance the spatial resolution of the results, as well as detect aspects of the network which could not be observed here due to limited power. Finally, a limitation of the present study is its reliance on cross-sectional data. Ideally, examination of the factors that account for severity would be conducted longitudinally, in order to have proper baseline data on all subjects and to look for evidence of change over time. Obviously, such longitudinal examinations were not possible here, but provide impetus for future studies.

4.5 Future Directions

It has been said that the evidence that has been obtained from studying patients with focal lesions is “powerful, but limited in anatomical specificity” (Kanwisher et al., 1997, p. 4302). In contrast the present study demonstrates that anatomical specificity can be addressed by studying focal lesion patients. Employing analytic techniques that have been developed in this laboratory (e.g., Frank et al., 1997; Damasio, 2000) and elsewhere (e.g., Bates et al., 2003; Karnath et al., 2004), the present study utilized a voxelwise logistic regression to identify regions where damage appeared to have a relatively specific relation to impairments in the recognition of faces, animals, fruits/vegetables and tools/utensils. Because this is a first study of this type, it will be important for future studies to replicate the findings using an independent sample. However, it also indicates that questions of

specificity can be addressed with focal lesion patients and encourages the development of additional analytic techniques to further develop the lesion method.

With regard to future studies, given the cross-sectional nature of the present study, an important follow-up will be to examine these variables longitudinally. For example, does age of injury influence performance in face recognition over time (i.e., do young patients demonstrate greater improvement over time, or are they just less severely impaired from the beginning)? Alternatively, do basic visual perceptual abilities, measured acutely, predict long-term outcome, e.g., 10 years later? By addressing questions such as these, I may be able to better understand the factors that govern recovery of functions and long-term outcome, and ultimately shape rehabilitation programs to maximize outcome for individuals who sustain focal brain injuries.

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