Doctoral Dissertation

NEURAL CORRELATES OF SEMANTIC MEMORY: FROM NEUROPSYCHOLOGY TO NEUROIMAGING

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ABSTRACT

This thesis will describe two functional Magnetic Resonance Imaging (fMRI) experiments and one Voxel-Based Morphometry (VBM) study, each investigating how the human brain identifies objects and their associated properties. In particular, we used three different categories of objects – living (animals), nonliving (tools and nontools) and faces (famous and non-famous) – to examine the type of knowledge attribute in question: one perceptual (movement) and two semantic attributes (typical object location and biographic knowledge).

We know from neuropsychological literature that the most anterior portions of the temporal cortices critically support human conceptual knowledge. Unfortunately, the Anterior Temporal Lobe (ATL) is a challenging region for fMRI due to susceptibility artifacts, especially at high fields. For these reasons we established an optimized fMRI protocol (described in the second Chapter) by adjusting key acquisition parameters like phase-encoding gradient polarity, slice thickness, echo time, and slice angle. The protocol gave reliable Blood-Oxygen-Level Dependence (BOLD) signal sensitivity in the ATL.

Clinical data describe patients with specific semantic impairments at the level of category (living, nonliving) as well as disproportionate deficits for a modality or type of knowledge (e.g., visual/perceptual knowledge or manipulation knowledge). Functional neuroimaging studies on semantic organization with normal subjects found an “action network” specific for tools rather than living items. In the first experiment (Chapter 3) we devised an fMRI paradigm to investigate the processing of movement (action) and place (encyclopedic) features, and their influence on

category-specific activations. Within the “movement network” statistical analyses did not show any significant interaction between categories. These findings suggest that the visuomotor “action network” is not specific for tools because it is also activated when the action related knowledge is elicited for other categories, such as animals.

The second and the third experiment (Chapter 4) focus on the processing of faces. Neuropsychological literature attributes semantic and lexical retrieval deficits in patients to ATL lesions. In Part I of Chapter 4, we report data from a VBM study on patients with known lesions in the temporal lobe. Unfortunately, as far as we know, data on patients and functional neuroimaging in healthy individuals has not clarified the differential role of this area in the two mental operations because semantic and lexical processes usually occur simultaneously and automatically. In Part II, we devised an event-related fMRI activation paradigm that allowed us to study the identification (i.e., association of semantic biographical information) of celebrities, with and without the ability to retrieve the proper name. While semantic retrieval reliably activated the ATL, only more posterior areas in the left temporal and temporal-parietal junction were significantly modulated by covert lexical retrieval. These results support findings from patients with ATL lesions and suggest that their anomia is due to semantic rather than lexical retrieval impairment.

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LEGEND:
NEUROANATOMICAL LABELS

AG: ANGULAR GYRUS

ATL: ANTERIOR TEMPORAL LOBE

IFG: INFERIOR FRONTAL GYRUS

IOG: INFERIOR OCCIPITAL GURYS

IPL: INFERIOR PARIETAL LOBULE

IPS: INFERIOR PARIETAL SULCUS

ITG: INFERIOR TEMPORAL GYRUS

ITP: INFERIOR TEMPORAL POLE

ITS: INFERIOR TEMPORAL SULSUS

ITL: INFERIOR TEMPORAL LOBULE

MOG: MIDDLE OCCIPITAL GYRUS

MFG: MIDDLE FRONTAL GYRUS

MTG: MIDDLE TEMPORAL GYRUS

OTP: OCCIPITO TEMPORAL JUNCTION

OPJ: OCCIPITO PARIETAL JUNCTION

SFG: SUPERIOR FRONTAL GYRUS

SMG: SUPRAMARGINAL GYRUS

SPG: SUPERIOR PARIETAL GYRUS

STS: SUPERIOR TEMPORAL SULCUS

TP: TEMPORAL POLE

TPJ: TEMPOROPARIETAL JUNCTION

VPMC: VENTRAL PREMOTOR CORTEX

To my mother …

CHAPTER 1: BACKGROUND TO THE NEURAL ANATOMY OF OBJECTS AND FACES RECOGNITION PROCESSING

1.1 INTRODUCTION

Everyday, we are exposed to large amounts of information by interacting with people, watching animals and manipulating tools. Thanks to these experiences, we develop internal representations of objects. All of these representations are processed by the semantic memory system in form of factual knowledge of objects, faces, features, and words and their meanings.

In comparison to episodic or autobiographical memory, the semantic system consists of memories that are shared by members of a culture rather than those unique to an individual, tied to a specific time and place. Within this network, activations of specific representations are dependent on the item's meaning, not on the physical format of the stimulus denoting that object. Thus the semantic representation of a "dog" would be activated by its picture, its written word and by its name or just the simple thinking about it.

Through repeated multisensory exposure to the object, semantic memory can store both concrete and abstract concepts, such as "dish", "cat" and "love", as well as objects' features, such as "a dish can be found in the kitchen", "a cat can run" or a "house can be made of wood". There are different types of features, such as physical (perceptual) properties (how it looks, sounds, smells, feels, and tastes), functional properties (what it is used for), and the category it belongs or other encyclopedic feature (such as where it is from). Features play a central role in conceptual categorization and word meaning processing because they allow us to efficiently retrieve and produce information in the service of thought and language. They are behaviorally investigated by researchers through an experimental approach called “feature norms” in which participants are asked to list all the features of a concept that best describe it (Kremer & Baroni 2011).

One limitation of this method is that descriptions are generally collected in written or verbal form, and thus some kind of information can be transmitted more easily and with more details than other types of information. For example, information about the size of an object is quite difficult to verbalize; saying that a door is used by people is easier that saying how big it is, and features such as “is large” perhaps mean something different for ostrich that for yacht and, thus, could also be differentiated (McRae, Cree, Seidenberg, & McNorgan, 2005). Similarly, although animals can be recognized by the way they move, the particular movements are hard to verbalize, although for some animals a distinguishing, general movement can be given, e.g. “a frog jumps" (Kremer & Baroni, 2011).

A number of authors assume conceptual feature representations, such as size, movement or color, although few researchers have attempted to assess whether conceptual structures can be exhaustively decomposed into a set of primitive features. In neuropsychology, the relevance of feature representations across categories is also revealed in spontaneously occurring speech errors: for example, saying “wheel” when “foot” is intended (Garrett, 1992) suggests that shared features related to motion can be sufficiently active to induce an error in which, importantly, semantic field (category) membership is not preserved (Vigliocco, Vinson, Lewis, & Garrett, 2004). Different types of features are emphasized for different types of objects. For example, when subjects are asked to give definition of animals, they generally provide information about their visual appearance; whereas when they have to speak about tools they usually emphasize how they are used. From this assumption we might predict that the differences in the types of features that define different objects play a central role when considering disorders of semantic memory and models of how semantic memory is organized in the human brain. To investigate the neuroanatomy of conceptual processing, researchers have the possibility to draw data from patients or from neuroimaging studies about categorizations. Behind the well documented activations between these categories: animals, tools, houses and faces, we know from literature that modality-specific feature representations are assumed by a numbers of authors (Martin & Chao, 2001, Warrington & Shallice, 1984).

1.2 COGNITIVE THEORIES OF SEMANTIC MEMORY

1.2.1 The Sensory/Functional Theory

Evidence from patients demonstrates that the impairment in the living things category is sometimes characterized also by the deficit in the appreciation of perceptual features of concepts (Gainotti & Silveri 1996). According to this framework, Warrington and Shallice (1984) have suggested that object concepts may be represented in the brain as distributed networks of sensory, motor and abstract functional information. The "Sensory/Functional Theory" states in fact that semantic representations are distributed across sensory and functional semantic processing regions of the brain that are closely linked to sensory and motor input/output processing channels.

Concretely researchers argue that the ability to identify living things differentially depends on sensory knowledge, while the ability to identify nonliving things differentially depends on functional knowledge. This can be explained by the fact that during the gradual cultural development of specific man-made tools a memory system based on functional properties might have evolved for the identification of man-made objects. The results of the hierarchical cluster analyses that McRae et al. (2005) conducted during their feature norms study support this assumption. They wanted to determine which semantic categories differentially loaded on which feature types, and they concluded that visual motion and functional information were the two most important knowledge types for distinguishing living things (high on visual motion information) from nonliving things (high on functional information).

Nevertheless, as often happens in the clinic, some patients with category-related deficits do not strictly respect the boundary between living and nonliving things. If it is true that sensory knowledge is particularly salient for living things and functional knowledge for nonliving things, and if category-specific deficits are due to damage to modality-specific processing channels, then a deficit in one of the two domains should affect the accessing to that type of knowledge that is supposed to underlie the deficit. Data reported by Lambon Ralph & Patterson in 1998 showed that both living-things and sensory knowledge deficits can be found in isolation: e.g. an Alzheimer's dementia patient presented poor performance on living things but did not show any difference between visual and functional knowledge; also a Semantic Dementia (SD) patient demonstrated poor knowledge of visual features but did not show any category specific impairments for animate objects. These cases demonstrate that living-things deficits do not necessarily have to be accompanied by impairments to visual sensory knowledge. Patient JBR, reported by Warrington and Shallice (1984), showed low performance with concepts referring to living things but also to musical instruments and gemstones. In contrast, patient YOT had problems with artifacts as well as body parts (Warrington & McCarthy, 1987). The researchers argued that musical instruments and gemstones are similar to living things because they might be distinguishable in terms of perceptual features; whereas body parts and artifacts are categories of knowledge for which function is salient. However, Laiacona , Capitani, and Caramazza (2003) reported a patient who was impaired for living things but spared for sensory quality categories, and Farah and Rabinowitz (2003) mentioned the case of a patient who showed low performance for living things and was at the same time impaired for both visual and nonvisual knowledge of living things.

1.2.2 The Domain-Specific Theory

A theory that accounts for the pattern of category specificity is the “Domain-Specific Hypothesis”, presented by Caramazza and Shelton (1998), which states that semantic representations are divided into processing channels specific to animals, plants, and nonliving objects that have evolved because of evolutionary pressures to avoid predators, find plants for food and medicine, and perhaps to use tools.

Mahon and Caramazza in 2009 argued that one important aspect of the performance profile of patients with category-specific semantic impairment is that the impairment is to conceptual knowledge and not (only) to modality-specific input or output representations. According to this assumption, category-specific semantic impairments will be associated with impairments for all types of knowledge about the impaired category. However, also for this theory, there is evidence from patients that show pattern deficits that cross domain boundaries, making it unlikely that knowledge is organized by domain (e.g. impaired knowledge of animals and fruit/vegetables, musical instruments, nonliving food, and gemstones versus relatively spared knowledge of other nonliving things; Warrington and Shallice, 1984).

1.2.3 The Embodied and Disembodied Cognition Theories

There are other two theories that have tried to explain how concepts are organized in the brain: the Embodied and the Disembodied Cognition Hypothesis. According to the Embodied Cognition Theory, conceptual content is represented within the sensory and motor system. In this case there would be no interferences between the symbolic concept of an object and its sensory and motor features. For example, if we consider the situation in which a person is presented with a hammer and asked about the way to use it, from the Embodied Cognition point of view, the process of retrieving the concept *hammer* would itself be constituted by the retrieval of sensory and motor information about how to use it.

On the other hand, according the Disembodied Cognition Theory, we will first retrieve the abstract concept of the hammer and then this information will contact the motor system in order to obtain motor system information about its manipulation. Neuropsychological evidences for this theory show that patients can be impaired for using objects despite being unimpaired for naming them or recognizing the pantomimes associated with the uses of those objects (Mahon & Caramazza, 2005). These facts strongly reject the Embodied Cognition Theory because the data show that the concept of an object is abstract and qualitatively different from the motor knowledge that is compromised in the patient.

Within the embodied cognition framework, some recent assumptions of the multiple semantic approach state that conceptual entities can be grounded in sensory and motor processes (Barsalou, 2008; Damasio, H., Tranel, Grabowski, Adolphs, & Damasio, A. R., 2004; Patterson, Nestor, Rogers, 2007). In general, these theories reject the hypothesis that knowledge is represented by amodal symbols in semantic memory. Instead, the theories focus on the critical role that body cognition plays in causing cognitive states and how they are then affected by such states. When knowledge is needed to represent a category, the brain reactivates multimodal representations settled during experiences with that entity to simulate perception and action representations associated with it. Barsalou (1998) explains this concept clearly when he describes what subjects do when they generate features in a norming task. He states that they directly exploit representations that have developed through repeated interactions with the objects, and they construct a holistic simulation of the target category and then interpret this simulation by using feature and relation simulators. The fact that brain regions that mediate object-directed actions are automatically activated during the observation of manipulable objects is taken as proof in support of these theories.

1.2.4 Feature-Based Theories

McRae, Cree, Cho, and McNorgan, (2003) demonstrated that although feature types alone cannot account for all of the main trends in the patients' data, they are an important component. The Feature-Based Hypotheses concerning category specificity can be divided in two types: accounts that assume a feature type organization of semantic memory (Martin & Chao, 2001; Warrington & McCarthy, 1987; Warrington & Shallice, 1984) and accounts that underline the importance of feature properties (such as shared features, distinctiveness of features, and correlation among features) in the structure of concepts rejecting the assumptions based on modality-specific organization (Caramazza, Hillis, Rapp, & Romani, 1990; Rapp, Hillis, & Caramazza, 1993).

According to the feature type account, these features arise from our interactions with the environment (perception and action) and their organization is very similar to that of the sensorimotor systems (Warrington and Shallice, 1984). Category-specific deficits are explained by the fact that features have a different weight among specific domains. Patient RG, described by Marshall, Chiat, Robson, and Pring, (1996) can be taken as evidence compatible with a conceptual knowledge organized in terms of different types of features that are frequently associated with a particular category, but they are not limited to one. In fact, the patient showed a living-thing deficit coupled with low performance with concepts for manner of motion. This link between living things and manner of motion that is a feature classically related to nonliving things (especially tools) was taken as a confirmation of the importance of perceptual features in both domains.

The Sensory Motor Theory of Semantic Representations

Martin, Ungerleider, and Haxby, (2000) proposed the Sensory-Motor Theory of semantic representations in which they assume that the concept of an object is composed of information about that object learned through direct sensory experience and stored near sensory and motor cortices. Recently, Martin and Chao (2001) presented a new model for the semantic representation of concepts in which, while object features are represented along sensory-motor cortical networks of the brain, other regions in the left frontal and temporal lobe are responsible for the coding and the retrieval of these representations.

The authors reported critical evidence for modality-specific representations (Beauchamp, Lee, Haxby, & Martin, 2002; Chao & Martin, 1999). First, they found activations for a nonliving category (chairs) not within the areas of maximal activation for tools and houses but laterally, falling in the inferior temporal gyrus (ITG). This finding argues against a strict living-nonliving separation and is, instead, compatible with different feature compositions of the investigated categories (Vigliocco et al., 2004). Second, within the lateral temporal cortex, they found specific activations for movement properties of tools in the left posterior medial temporal gyrus (MTG), while video displays containing visual biological motion elicited greater activation in the superior temporal sulcus (STS) and in the MTG (Beauchamp, Lee, Haxby, & Martin, A., 2003). According to these results, we can argue that activations were strictly associated with the type of motion of the entities rather than their category membership. Finally, all these studies showed that category-related responses are not restricted to a single region which responds maximally for that category, but that all categories activated a largely feature-specific overlapping region, and that the profile of activation differed depending on category. From this data and more, we might conclude that object concepts are represented according to object features, rather than according to semantic categories corresponding to specific and anatomically segregated modules.

On the other hand, the second type of hypotheses relies on feature properties such as distinctive, shared and correlated features to account for category-specificity. These theories are based on the correlated structure principle assumption that states that the conceptual system has no structure that is specifically reflected in functional neuroanatomy. In line with these theories, we find the Organized Unitary Content Hypothesis.

The Organized Unitary Content Hypothesis

The Organized Unitary Content Hypothesis (OUCH) (Caramazza et al., 1990; Rapp et al., 1993) proposes the existence of a single, amodal semantic store in which structure emerges from the distribution of features across categories. Concretely, the categorical organization of knowledge arises from the differences in feature inter-correlations and shared features among members of the same category. Caramazza et al. (1990) argued that there are privileged relationships between certain types of visual representations (e.g. visual form of an object) and certain types of output representations (e.g. object manipulation). Therefore this might explain how optic aphasic patients are spared for gesturing to objects while impaired for naming them.

The authors explained category-specific deficits, arguing that problems can derive from the fact that similar things are clustered together in a semantic space according to their shared and inter-correlated features. Other researchers developed specified proposals based on the idea that features are correlated across semantic categories in different ways. For example, Tayler and Moss (2001), besides underlining the importance of feature properties like OUCH, stressed particularly the type of association between perceptual and functional features that differ for living and nonliving entities. That is, while correlated perceptual features of living things would be used with different biological functions (e.g. has legs/can move, has eyes/can see), distinctive features would not (e.g. stripes for tiger). On the other hand, the association between perceptual and functional features for artifacts would involve distinctive perceptual features (e.g. the perceptual feature *sharp-edge* and the functional feature *cuts* for knife). This means that living things have more shared features, which are highly correlated, whereas nonliving things have more distinctive features, which likewise are highly correlated.

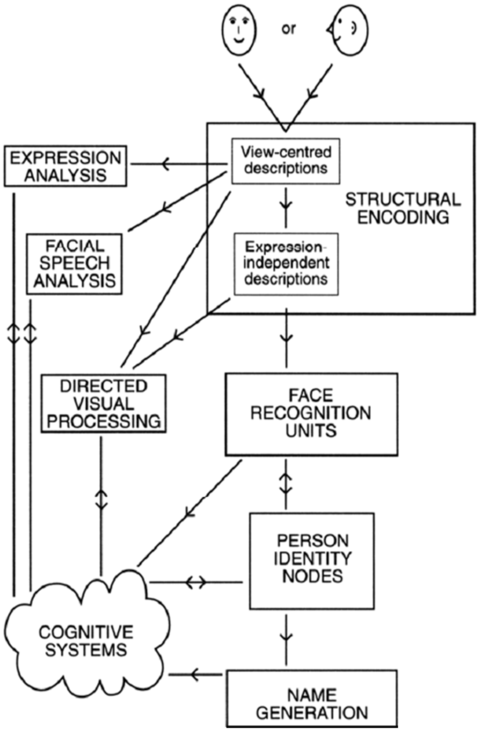
These assumptions bring to two conclusions. First, distinctive features of living things are weakly correlated with other properties, and so category-specific deficits in case of brain damage should involve primarily this class of concepts. Second, the nonliving domain might be more resistant to damage since its high correlation between distinctive perceptual features that are, for instance, critical for identification. Because theories based on the Correlated Structure Principle consider that the organization of the semantic system does not have a structure based on functional neuroanatomy, they are more appropriate to explain the patterns of progressive loss of conceptual knowledge observed in neurodegenerative diseases, such as dementia of the Alzheimer type and semantic dementia (SD). These types of diseases are in fact characterized by a diffuse and widespread deficit than can involve at different degrees selected components of the network. However, such assumptions cannot explain diseases in which manipulation dissociates from function; in fact, although manipulation knowledge ("how to use it") might be highly correlated with functional knowledge ("what for"), damage to the former does not imply damage to the latter (Buxbaum, Veramonti, & Schwartz, 2000).

1.2.5 Models on Face and Proper Name Processing

Despite the ability to recognize different species of animals or different kind of tools, our brain is incredibly efficient at processing faces. We can memorize, discriminate and identify hundreds of faces, with or without naming them (Meadows, 1974). The brain's fine-grained efficiency in recognizing a familiar face has intrigued researchers for decades and the presence of a dedicated system for this ability has been a matter of animate debate. However, retrieving the name corresponding to a known face is far more difficult. We know from literature that when shown faces of familiar people subjects are typically slower and less accurate when retrieving names than other semantic information (Burton & Bruce, 1992).

The Bruce and Young (1986) Information Processing Model has been the most influential model in the field. At the beginning of this process the sensory input is “Encoded Structurally”, allowing the recognition of a particular face. The next step occurs at the “Face Recognition Unit” (FRU) where the information of the encoded structural representation of a seen face is associated with a particular person identity node. In this node, semantic biographical information (such as the person’s profession or nationality) can be accessed. The ability to feel a sense of familiarity when presented with a familiar face is based on the degree to which a FRU is activated. Identity-specific semantic codes represent any information known about an individual except their name (e.g. the person’s profession or nationality). The Structural Encoding and FRU levels are thought to be modality-dependent and specific to faces. As seen in Figure1.1, the model states that proper names are stored separately and can only be accessed once the person’s semantic information has been recalled. Therefore, retrieval of a person’s name from a face depends on its prior identification. On the other hand, the level of storage of semantic information about known people (person-specific semantics) is thought to be amodal and accessible from any input modality.

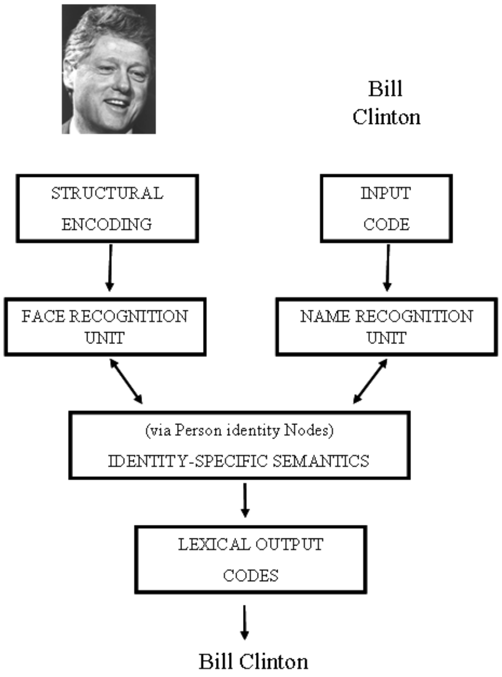
Figure 1.1 The Bruce and Young (1986) Cognitive Model of Face Processing



Valentine, Bredart, Lawson, and Ward, (1991) expanded the Bruce and Young model to encompass proper name processing (see Figure 1.2). The updated model states that proper names are a sub-class of words, since they are first recognized as words and then as proper names, and therefore present some early processing in common with word recognition (Input Code). Name Recognition Units (NRUs) are the logical equivalent of FRUs and mediate between the initial input analysis and access to identity-specific semantic information about individuals. The NRU then allows access to Person Identity Nodes and to identity-specific semantic information, which is also accessed by known faces. The stages of encoding and recognition are thought to involve face- or name-specific processing; but identity-specific semantics (biographical knowledge) and name retrieval are modality independent, and can be accessed by facial, verbal (written or heard proper names) and non-verbal (voice patterns and gait characteristics) inputs.

Within the framework of theories on object processing, the identification of famous faces is characterized by the "uniqueness" of the attributes linked to each face that are not shared by other visually similar members of the same category. People seem to have the ability to detect the unique identity of an unlimited numbers of different faces. In case of objects on the contrary, appearance alone would often be sufficient to determine membership of many categories (Rosh, 1976).

Figure 1.2 Cognitive Model of Face and Proper Name Identification (adapted from Valentine et al., 1991)



1.3 LESIONS STUDY: NEUROPSYCHOLOGY AND NEUROANATOMY

1.3.1 Principal Etiologies of Semantic Disorders

Semantic memory is characterized by a cognitive capacity that depends on a widespread network of regions (Martin, 2007; Patterson et al., 2007; Pobric, Jefferies, & Lambon Ralph, 2010) that are mostly located in the left and right temporal lobe (Binder, Desai, Graves, & Conant, 2009; Tranel, Logan, Frank, & Damasio, 1997; Lambon Ralph, Pobric, & Jefferies 2009). The principal etiologies known to produce semantic disorders are Alzheimer's disease (AD), semantic dementia, cerebral infarcts and herpes simplex virus encephalitis (HSE). All of these different causes of brain damage produce a variation in both the degree to which the anterior and inferolateral temporal regions of cortex are affected and the nature of the damage of these regions (Gainotti, 2000).

In a study of regional brain atrophy of AD, Boxer et al. (2003) demonstrated that atrophy and hypometabolism are moderately left and right symmetrical and involve parietal and temporal lobes. In SD, a subtype of frontotemporal dementia (FTD), temporal lobe atrophy is usually bilateral, but more extensive in the left hemisphere (Wilson et al., 2009). Specifically, the damage in SD has a strong focus in the anterior and inferior temporal regions, while AD patients show a damage that is more medial in the temporal lobe, i.e. hippocampus.

Neuropsychological studies in patients reveal that the right Anterior Temporal Lobe (ATL) seems to be involved in the recognition of familiar people, such as friends and relatives, or celebrities (Gainotti, Barbier, & Marra, 2003; Gorno-Tempini et al., 2004). In his review, Gainotti (2000) reported cases of herpes patients showing lesions in the anterior portions of the temporal lobe and deficits for living items; whereas stroke patients with lesions in the left dorsolateral peri-sylvian region were characterized by a selective semantic disorder for man-made objects. He also reported the involvement of left fronto parietal areas in the processing of "functional" information contributing to the semantic representation of man-made objects through processes of manual use, physical contact and concrete utilization.

1.3.2 Neuroanatomical models of semantic memory

As previously mentioned, well-documented studies of patients with semantic impairment suggest that the most anterior portions of the temporal cortices critically support human conceptual knowledge. However, to characterize the role of the anterior regions of the temporal lobes (ATLs) is quite complicated because it is not a homogeneous structure; rather it contains numerous anatomically discrete regions, each of which may play a distinct role in the acquisition, storage, and manipulation of conceptual information.

In this section I will discuss two main theories that confirm a role of the ATLs in conceptual processing. The first describes the ATLs as a semantic hub linking conceptual information that is widely distributed throughout the brain (Lambon Ralph & Patterson, 2008); the second conceives the ATLs as a repository for knowledge of unique entities such familiar people and landmarks (Damasio et al, 2004).

Semantic Hub

According to Lambon Ralph and Patterson (2008), semantic memory is not restricted to one specific and defined anatomical region but on the contrary should be represented by the activation of modality-specific information stored within a distributed network of regions. All the attribute-specific components of semantic memory (color, sound or movement knowledge) should have their independent role and defined neuroanatomical location (Martin, 2007), but the central conceptual knowledge might be slightly different. Lambon Ralph and Patterson (2008) state that the central properties of conceptual knowledge are localized in a subsystem of amodal representations. Or better, they think that all attribute-specific features of a concept are bound together in an amodal semantic hub localized in the anterior regions of the temporal lobes bilaterally.

This semantic hub is domain-general and stores information about the similarities and differences between categories, rather that peculiar property information of specific attributes (Patterson et al., 2007). It allows semantic generalization processing, supporting conceptual relations between categories (e.g. a fox and an owl both are animals, both live in a forest, both breathe air, etc.). These kinds of processes need a semantic hub and therefore when the brain regions supporting this amodal hub are lesioned the consequence will be a deficit in appropriate generalization. They do not reject the assumption that information arising in each specific modality is stored in the related specific cortical sensory or motor region, rather they claim that these regions are supported by the bilateral ATL semantic hub, a region which is well known to be highly interconnected with many modality-specific association cortices.

Convergence Zone

Another neuroanatomical model of semantic memory is represented by the convergence zone theory by Damasio et al. (2004). According to this theory, temporal poles are convergence zones, where simpler features from different modalities are brought together to define unique individuals and situations. In their Positron Emission Tomography (PET) experiment, Damasio et al. (2004) demonstrated that naming animals or tools versus persons shows activation in posterior ITG bilaterally, whereas naming persons versus animals or tools activated ATL cortices. Therefore they stated that naming unique faces (a process that require the highest disambiguation of physical details and the highest recall of the related background related to the person) are elicited by rostral temporal and frontal regions revealed by lesions data and activations sites in normal subjects. In his theoretical framework, Damasio et al. (2004) state that the system operates through images, images that represent mental patterns characterized by any sensory type (e.g. visual, auditory, somatosensory).

The cerebral regions that surround the point of entry of sensory signals are the explicit neural patterns that primarily support these images. Dispositions are the stores where the knowledge for facts and the mechanism for image and action are processed, their contents are implicit and they can construct and recall images, generate movements and regulate processes. All the evolutionary knowledge historically accumulated exists in the dispositional form and can potentially become an image or an action. Dispositions are neuroanatomically distributed in higher order cortices (limbic cortices) and when they are active they can cause the generation of images and actions elsewhere in the brain. The most important aspect is that dispositions are represented in neurons ensemble called “convergence zone” that are made of microcircuits and are distributed within convergence regions.

The particularity of these convergence regions is that they exist prior to individual experience and then they are shaped by individual experience. Convergence zones should generally be found in the same regions of the brain according to specific types of tasks, but because of the constraints of the brains' anatomical design one could expect to find them in different sites across individuals. Therefore, Damasio et al. (2004) concluded that only at a large-scale there should be an overlap of the convergence zones. He also states that PET and lesions data highlight the fact that left ATL regions are the convergence regions containing disposition for proper name retrieval. ATLs may be the convergence region where, conceptual knowledge about unique entities and entity associated words (e.g. names), which are stored outside the ATL, are linked together. Data on focal ATL damage has been associated with selective semantic memory deficits. For example, anterior temporal resection can affect recognition and naming of famous people, suggesting that the ATLs may store semantic information about unique entities rather than semantic memory generally. Consistent with the unique entity theory there are also functional neuroimaging findings. ATLs activity has been associated with viewing famous and familiar faces (Damasio et al., 2004; Gorno-Tempini et al., 1998; Leveroni et al., 2000; Nakamura et al., 2000).

Neuroanatamomical model of face processing

According to the widely accepted neuroanatomical model proposed by Haxby, Hoffman, and Gobbini (2000), faces are processed firstly by a "core system" consisting of three regions: the inferior occipital gyri (IOG), the STS and the lateral fusiform gyrus, which allow the perception of the invariant aspects of the faces (perception of unique identity) despite the changeable aspects of the face. These regions interact with the "extended system" characterized by two components, person knowledge and emotion, with each component presumably including several neural regions. Person knowledge includes biographical information (ATL), retrieval of personal traits, attitudes, and mental states (anterior paracingulate), mental states and intentions (STS, temporo parietal junction, TPJ), and retrieval of episodic memory (precuneus/posterior cingulate). The emotion components include the insula, amygdale, and striatum, which are presumably linked to emotional reactions to familiar faces.

1.3.3 Neuropsychological Data of Category-Specific Information

Unfortunately, the underpinnings of the organization of category-specific information remain now days still controversial. There are different explanations for this lack of consistency: the inadequate description of the brain pathology provided by most of the reported cases, the authors' prevailing interest for the cognitive rather than the anatomical problems of the case. And furthermore brain pathology was limited to Computerized Axial Tomography (CT) scan findings, whose spatial resolution is unsatisfactory, especially with respect to lesions involving the medial and inferior parts of the temporal lobes (Kapur et al., 1994). Another problem is the non-homogeneous nature of the cognitive deficit, which in some patients is confined to naming tasks, while in others it also involved tasks probing semantic knowledge.

The "Domain-Specific Hypothesis" and the "Sensory/Functional Theory", which are based on different assumptions, admit the existence of distinct representational areas for distributed visual, semantic, and lexical representations, arguing that category specific semantic deficits depends on selective damage to the neural substrate upon which the impaired category of items depends. However, even if direct evidence for the existence of such a network in the normal human brain has not been reported, nor have the component areas of the network been identified, cases of category-specific semantic deficits are of particular interest because regularities in patterns of impairment can be used to derive constraints on possible theories of semantic memory. In this session I will discuss the neuropsychological evidence that has inspired both the domain-specific accounts and the sensory functional theory.

Warrington and McCarthy (1983, 1987) and Warrington and Shallice (1984) were the first to describe patients with specific semantic impairments for living but not for nonliving items and also the reversed pattern. In particular, Warrington and Shallice found 4 patients who showed bilateral temporal lobe damage as a consequence of HSE. These patients were unable to identify plants or animals and showed low performance in describing living things while they performed well in visual identification and spoken description of inanimate objects. This finding suggests that the selective impairment of living things is strongly associated with a certain kind of brain pathology.

The first study that investigated which brain regions tend to be lesioned in association with category-specific deficits was by Damasio, H., Grabowski, Tranel, Hichwa, and Damasio, A.R. (1996). They assessed 127 neurological patients characterized by lesions caused by different cerebrovascular diseases, HSE and temporal lobectomy, with a recognition and naming famous faces task. Through a lesion overlap analyses they found that name retrieval impairments were associated with left temporal pole lesions. In a group study on 79 patients, Strauss et al. (2000) found that anterior temporal lobectomy has a greater effect on naming ability for living things compared to nonliving things. In another study of Tranel et al. (1997) researchers demonstrated maximal overlap of lesions site with abnormal concept retrieval for faces in the right temporal pole, animals in the right mesial occipital and ventral temporal cortex and tools in the left lateral occipito temporo-parietal (OTP) junction. In the PET study of 2004, Damasio and colleagues collected data on patients with the same cerebral diseases from the study conducted in 1996. They demonstrated that naming animals or tools versus persons shows activation in posterior inferior temporal lobe (ITL) bilaterally; whereas naming persons versus animals or tools activated ATLs. Damasio et al. (2004) stated that naming unique faces (a process that require the highest disambiguation of physical details and the highest recall of the related background related to the person) are elicited by rostral temporal and frontal regions revealed by lesions data and activations sites in normal subjects.

In the Voxel-Based Morphometry (VBM) experiment of Brambati et al. (2006), researchers found a correlation between naming living things and lesions in the right anteromesial temporal pole, and between the left posterior MTG and tools. Dissociations of abilities in patients (and of processes in models) are central to the neuropsychological approach. It has been demonstrated that the majority of reported patients have disproportionate impairments for living things compared to nonliving things (Capitani, Laiacona, Mahon, & Caramazza, 2003).

1.3.4 Neuropsychological Data of Action Knowledge

The disorder of action planning is called “apraxia”, impairment in the use of familiar objects that cannot be attributed to physical dysfunction of the limbs (Rothi & Heilman, 1997). Specifically, apraxic patients usually make errors when moving on a command, with movement imitation, in producing a coherent action sequence (e.g. preparing a cup of the) and in object use. Apraxia can be divided in three subtypes: ideomotor, ideational and conceptual. The ideomotor apraxia is characterized by problems with imitation, pantomime and tool use, and it is most commonly caused by parietal damage in the dominant hemisphere (Left Hemisphere).

In their model of ideomotor apraxia, Rothi and Heilman (1997) claimed that movement planning involves representations of limb postures associated with specific action components that are called praxicons. Praxicons are translated into the appropriate motor patterns for the desired movement via the supplementary motor area (SMA) of the right and left hemispheres. The model predicts the dissociation between the ability to produce the required action and the knowledge of action. The ideational apraxia consists in the inability to produce a coherent action sequence because both perceptual and motor tasks of action sequencing are impaired, while the ability to imitate or to produce movement on commands is spared. In the conceptual apraxia there is a profound inability to use tools in an appropriate way.

Literature provides a series of reports on patients with diminished ability to recognize and/or use tools and with damage to left inferior parietal lobule (IPL) associated with apraxia. Neuropsychological data on apraxic patients (Mahon & Caramazza, 2005) show that when patients have to process the ‘abstract’ and ‘symbolic’ concept of a hammer, they instantiate it in isolation from motor information (how to use it), because they can still recognize and name it but not mimic its use. There are data on patients that maintain knowledge of the function of common objects (Buxbaum & Saffran, 2002) but have degraded knowledge about how to move their body parts to interact with tools. Studies of SD patients suggest that the patients suffer from impaired knowledge of how to use common tools as well as their purpose (Bozeat, Lambon Ralph, Patterson, & Hodges, 2002). The degree of the patients’ object use deficit has been found to correlate with their lower scores of general semantic recognition and comprehension. In summary, the neuropsychological literature indicates that lesions to the IPL generate a specific deficit to tool manipulation knowledge while the ATL, damaged in semantic dementia patients, generates a general effect which, in the context of tool use, impacts on both function and praxis in a parallel fashion.

In a study conducted in 2003, Tranel, Kemmerer, Adolphs, Damasio, H., Damasio, A.R, were interested in the neural underpinning of the semantic knowledge of action and they assessed 90 patients with Picture Attribute and Picture Comparison tasks. They were interested in two tasks that elicit the processing of action knowledge without necessarily requiring verbal mediation. During the performance of these two tasks it was possible that subjects covertly named some of the actions, since using language to facilitate performance is an automatic and reflexive thing to do. However, it might be possible that accuracy on the responses did not absolutely depend on the retrieving of the phonological forms of the actions. They contrasted the lesions sites of the patients who presented low performance in the task with those of the patients who did not fail both tasks. The maximal overlap among lesions involved the inferior frontal gyrus (IFG), the inferior regions of the precentral and postcentral gyri, the supramarginal gyrus (SMG) and the posterior MTG. The same regions involved in the action of knowledge were found by Kemmerer et al. (2010), who used the same method to investigate the verbal and semantic knowledge of action assessing 226 brain damaged patients with focal lesions in either the left or the right hemisphere. In the same experiment, Tranel et al. (2003) also measured conceptual knowledge for concrete object categories of persons and tools asking subjects to name famous faces or tools. Through this, they compared the neural system involved in action knowledge with that involved in categories of concrete entities. Investigating the lesion profile of the subjects who had impaired tools and action concepts through a lesion overlap analyses, they found that the highest area of overlap was the left middle temporal region. In the case of famous persons, the systems are distinct since in their study just 1 person on 26 subjects presented impaired action concepts and knowledge for famous persons. This patient had right hemisphere lesion in the occipital temporal region.

1.3.5 Neuropsychological Syndromes of Faces and Naming Processing

The anatomical correlates underlying the different components in the cognitive models previously described (Bruce & Young, 1986; Valentine, 1981; Haxby et al, 2000) are still debated, and patient studies and functional imaging studies diverge. This is particularly true for semantic and lexical retrieval processes and their possible involvement of the left ATL. In particular, the strictly sequential nature of the multistage organization of the Bruce and Young model is supported by psychological studies in normal subjects and by behavioral dissociations in neurological patients. Studies indicate that a face can look familiar without being identified and biographical information can be retrieved without recollection of the corresponding name. In healthy subjects it is well known the existence of the “tip of the tongue phenomena” (TOT), an effect characterized by the difficulty in the retrieval of proper names whereby the person has the feeling to know the name but cannot access it. In literature there is evidence confirming that the TOT phenomena is a universal experience that occurs about once a week, increasing with age, and it is frequently elicited by proper names (Brown, 1991). In patient studies, these examples of semantic and lexical dissociations became clear impairments.

There are three main neuropsychological syndromes that have been reposted to correspond with deficits at three main levels of face and proper name processing: prosopagnosia, loss of knowledge about known people and proper name anomia. Prosopagnosia was first described from Bodamer (1947) and refers to the impairments if brain-damaged patients to recognize familiar faces. They do not fail in recognizing the general appearance of a face, but in the identification to whom that particular face belongs. The deficit is confined to faces since patients are able to identify known individuals by means of their voice, posture or other non-facial cues (e.g. a scar, hair style, or a particular item of clothing).

Since the 1940s, many case reports of prosopagnosia have been published (Damasio, 1985; De Renzi, 1986). If we accept the idea that prosopagnosia is really confined only to faces, we can claim to the conclusion that faces are one of the most striking example of a domain (or category)-specific neuropsychological deficit, suggesting a categorical organization not only at the cognitive, but also at the neural level.

Regarding the loss of knowledge about known people there are patients described by Ellis, Young and Critchley (1989), and Evans, Heggs, Antoun, and Hodges (1995) who show a selective impairment in identification of known people regardless of the input modality (i.e. faces and names). Kroll, Markowitsch, Knight, and Von Cramon (1997) reported cases of patients, who have a deficient semantic, show low performance in recalling information about famous people compared to other categories of objects. The crucial site for loss of biographical knowledge across all modalities seems to be the anterior temporal lobe, but the type of pathology available does not clearly indicate which hemisphere is more important.

More recently, the involvement of both ATLs has been implied from patients with neurodegenerative disease (i.e. temporal variant of FTD) or semantic dementia, who have loss of semantic memory in particular for familiar people (Mummery, Patterson, Hodges, & Price 1998). Furthermore, patients with left ATL lesions of traumatic or infective origin have been reported to lose the ability to recall information about known people, together with other aspects of semantic knowledge (Kroll et al., 1997). Therefore, the crucial lesion seems to be in the anterior portions of the temporal lobes. On the other hand, patients that present impairment at the post semantic lexical retrieval level show inability in the generation of names (McKenna & Warrington, 1980; Lucchelli & De Renzi, 1992, Semenza & Zettin, 1988). Patients who suffer from proper name anomia are unable to name a person, in response to photograph or verbal description, despite being able to provide semantic information about that person. From the date of the original report from Semenza and Zettin (1988), several cases of proper anomia have been reported (Papagno & Capitani, 1998). Papagno and Capitani (Papagno & Capitani, 2001) described a patient with degenerative disease mainly involving the left anterior temporal lobe who progressed from having a pure anomia for proper names to a severe impairment of person-specific semantic information. In contrast with the site responsible for biographical knowledge, the laterality of the lesion site in proper name anomia is more consistent. Most of the reported patients had extensive left hemisphere lesions, involving multiple regions, such as subcortical structures (thalamus), or the temporal and parietal lobes (Semenza, Mondini, & Zettin 1995).

According to the “two stage lexical access model” proposed by Levelt (1989), proper anomia should represent the result from damage at the level of the “lemma” that correspond to the conceptual representation of the word, and that activates its phonological representation (the "lexeme"). In summary, there are currently two main interpretations of face specific deficits. On one hand, faces are considered a very particular kind of stimuli and thus served by a specific dedicated cognitive system. On the other, faces and objects are processed by a shared system, but faces place different demands on the system than objects. At the perceptual level, identification of faces requires an exceptionally high level of visual discrimination since they have numerous visually similar exemplars with which humans are experts. In contrast, at the semantic/naming level, faces have unique identity, not shared by other visually similar members of the same category.

1.4 NEUROIMAGING STUDIES

Functional imaging experiments in normal subjects have given different insights of neural representation of semantic memory. First, the majority of research found left-sided activations rather than bilateral (Devlin et al., 2002; Martin & Chao, 2001). Second, results indicate that semantic knowledge is encoded within a large distributed cortical network, with different regions specialized to represent particular kind of information (Martin & Chao, 2001; Tranel et al., 1997), or particular categories of objects (Caramazza & Mahon, 2003; Perani et al., 1995). These main findings compel some researchers to suggest that no single region supports semantic abilities for all modalities and categories (Humphreys & Forde, 2001). On the contrary, we already know from previous neuropsychological studies on SD that the anterior temporal cortex in both hemispheres is critical for the semantic representation processing across all stimulus modalities and for all types of conceptual knowledge. Anterior temporal activation has been in fact associated with the processing of semantic tasks (Devlin et al., 2002; Mummery et al., 1999), but the vast majority of functional imaging studies have reported posterior temporal and/or frontal activations for semantic tasks, with no mention of the anterior temporal cortex.

In this Section, I will review the currently available functional neuroimaging data regarding the perceptual and semantic level of object recognition processing. Perceptual processing was assessed using passing viewing and match-to-sample with pictures of animals, tool and faces, while conceptual processes was evaluated using silent picture naming and a property verification task probing semantic knowledge of objects denoted by their written names. Tables 1.1, 1.2 and 1.3 summarize the results of the studies that investigated respectively the neural systems underlying tools, animals and faces processing.

1.4.1 Perceptual and Semantic Processing of Tools and Animals

In a single multi-study, Devlin et al. (2002) collected data from seven PET experiments and considered in the analyses all the following factors: stimulus type (living things and man made items), stimulus type (pictures, words) and task (perceptual, semantic, syllable decisions and word retrieval). They concluded that the only consistent finding found across studies was the activation of the left posterior MTG specific for tools presentation when the task involved semantic processing.

An example of the activation of this area is seen in the functional Magnetic Resonance Imaging (fMRI) experiment of Chao, Haxby and Martin (1999), in which they used photographs of animals, tools, faces and animals, during a reading, naming, viewing and matching task. They found that tools versus animals activated bilaterally the medial fusiform and the MTG, while living things activated the lateral portion of the fusiform gyrus, the medial and inferior occipital regions and the STS.

In a following fMRI experiment, Chao and Martin (2000) examined the areas associated with viewing and naming pictures of tools relative to other categories of animate and inanimate objects. Viewing tools rather than animals activated the left ventral premotor cortex and the left posterior parietal cortex. The authors suggested that these activations might be related to the retrieval of information about finger movements associated with the use of manipulable man-made objects. Also in the PET study of Gorno-Tempini, Cipollotti, and Price (2000) the processing of reading and naming body parts as well as manipulable objects activated an area in the posterior temporal cortex.

Chao, Weisberg and Martin (2002) sought to evaluate the effect of experience on the pattern and magnitude of the category related cortical activity using a repetition related reductions in the fMRI signal index changes in object-specific neural representations. Subjects became familiar with a subset of animal and tools pictures by performing naming and other tasks, and four days later they were scanned while naming the old and the novel pictures of animals and tools. The fronto-temporo-parietal activations found for tools and the occipito-temporal activations specific for animals found in the previous experiments were consistently obtained with this study as well.

In particular, for what concerns the ventral temporal cortex, two investigations (Chao, et al., 1999; Ishai, Ungerleider, Martin, Schouten, & Haxby, 1999) indicated that different ventral cortical regions responded preferentially to pictorial stimuli from specific categories. Biological entities (faces and animals) were associated with a greater activation in the lateral fusiform gyrus while activation for tools and houses was more medial. However, these studies showed that response to a specific object category is not restricted to the region that responds maximally for that category, but that all categories activated, to different degrees, a broad region of the ventral temporal cortex. According to these results, the representation of objects within the ventral temporal cortex appears to be organized by object features clustering together, rather than into semantic categories corresponding to specific and anatomically segregated modules. To this regard, I will include in this section some studies that investigated object categorization through associative task, asking subjects to respond to semantic tasks about objects features. Some experiments of word-generation provided evidence supporting the idea that information about different object features might be stored in different regions of the cortex. For example, Martin and Chao (2001) reported that asking subjects to generate the name of an action typically associated with an object activated the posterior region of the left MTG just anterior to sites active during motion perception. These studied therefore demonstrate that the regions of the posterior temporal cortex can be differently activated depending on the type of information retrieved.

In the PET experiment of Cappa, Perani, Schnur, Tettamanti, Fazio (1998), researchers asked subjects where a specific animal is typically found in Italy, and for words referring to nonliving objects they asked whether the object is typically used of food preparation. They focused their analysis on the main effects of category: the nonliving items versus the living items activated the left inferior temporal cortex, the left SMG, the right STS and the right thalamus. Animals versus tools activated the right middle frontal gyrus (MFG) and the right fusiform gyrus.

While the associative task versus the visual task activated the posterior cingulate cortex bilaterally.

Further, Mummery et al. (1998) introduced in their PET experiment three experimental manipulations: a semantic similarity judgment and a control task (syllable task), the object domain (words denoting living things or artifacts), and type of knowledge attribute one perceptual (color) and one associative attribute (typical object location). The regions activated in the semantic more than in the control task for both domains revealed left lateralized activation that include the left OTP junction and the medial parietal lobe. The activations specific for artifacts versus living things were found in the left posterior MTG and in the left fusiform gyrus. They did not find any specific activation associated with the processing of living things regardless of task. The activations for living things only for the location task were obtained in the left MFG and the right TOP junction.

Moreover, a network of regions involved in semantic processing of objects was studied in the meta-analysis of Binder et al. (2009). These researchers were interested in identifying brain regions that access meaning of objects. They included over 500 published fMRI and PET studies that used words to access knowledge retrieval. They found a left lateralized network for the semantic system, composed of the following regions: the angular gyrus (AG), the middle and ITG, the medial fusiform gyrus, the dorsomedial and ventromedial prefrontal cortex, the IFG and the posterior cingulated gyrus.

Neuroimaging of Function and Action

Despite the large number of researchers interested in the exploration of the neural correlates of retrieval of semantic knowledge for concrete domains (e.g. animals, tools, faces) some work focuses its attention to the neural underpinnings for the retrieval of conceptual knowledge for actions. In particular, Beauchamp (2003) showed his subjects point light displays and video displays containing visual motion (human video clips) and he found posterior STS and lateral fusiform gyrus activated for the human motion, while the MTG and inferior temporal sulcus (ITS) bilaterally involved in the processing of tools motion.

Using pictures, written and spoken words of animals and tools, Noppeney, Price, Penny, and Friston (2006) asked participants to perform a one-back task deciding whether stimuli are identical, have the same size, or perform a similar action. They found the activation of the left hemisphere in the posterior MTG, in the medial and anterior fusiform gyrus, in the SMG, in the IFG (triangular and opercular part) during the processing of tools, while the activations associate with animals have been found in the right middle occipital gyrus (MOG) and in the right fusiform gyrus.

Studying modulations in stimulus-specific repetition suppression (RS) with a rapid, event-related fMRI, Mahon et al. (2007) described a network of regions associated with motor movements and tools use. On the basis of the convergence that they found between functional and neuropsychological data, they claimed that the left medial fusiform gyrus, the left MTG and the left IPL are domain specific for tools. This means that this circuit is mainly defined by the content of the objects class that is processed, rather that the type of information (form, size, action). There is additional evidence in literature of this “action network” more activated for tools than for living items and maybe involved in the processing of action knowledge/manipulability (Chao & Martin, 2000; Canessa et al. 2008). In particular, neuroimaging data showed that familiar tools use knowledge activates the inferior parietal cortex and, furthermore, this brain area has shown greater activation for manipulation than function judgments (Boronat et al., 2005).

The Sensory Functional Theory explains the activation of these areas by tools stimuli that mediate object directed action with the critical role that functional knowledge plays in the recognition of nonliving things (Kellenbach, Brett, & Patterson, 2003; Martin et al. 2000, Noppeney et al. 2006). According to the embodied cognition the activation of the motor system would either constitute a semantic analysis of the stimulus, that is that the motor system is activated because that activation is causally involved in the semantic analysis of the sentence. Whereas from the perspective of the disembodied cognition hypothesis, stimulation of the motor system results in a cascade of activation back to the ‘abstract’ concept, and subsequently to the perceptual systems (and/or decision mechanisms) that generate.

Finally, several neuroimaging investigations of healthy participants have reported dissociable neural activations associated with either function knowledge or knowledge of manipulation of tools. Buxbaum et al. (2000) introduced a first distinction between functional and motor features when they reported a double dissociation between manipulation and function knowledge. Kellenbach et al. (2003) conducted a PET study to investigate the neural activation associated with making judgments about a tool’s function or manipulation. They found increased activation in left inferior parietal cortex when participants were asked to make binary decisions about the actions associated with familiar objects (e.g. “Does using the object involve a back-and-forth action?”) relative to when they were making judgments about the function of the same objects (e.g. “Is the object used to attach or hold objects together?”). The left intra parietal sulcus (IPS) was highly activated by explicit judgment about the type of movement engaged during the use of manipulable objects. This cortical area was not activated by either of the function judgments even relative to the control condition, suggesting that this structure is selectively activated by retrieval of knowledge concerning action.

Boronat et al. (2005) also reported similar activation in the left parietal area in an fMRI study. They presented pairs of tool pictures and asked the participants to judge whether or not the tools had the same function (e.g., matches and lighter), or if they could be manipulated in a same way (e.g., piano and computer keyboard). The comparison of the neural activations for these two tasks indicated significantly higher activation in the left inferior parietal area (extending from AG to IPS) during the manipulation-relative to the function-related judgments. Using very similar tasks, Canessa, Borgo, Cappa, Perani, and Falini (2008) found contrasting activations in parietal and inferior temporal cortices during the manipulation and function judgments, respectively. The authors reported significantly higher activation for manipulation than function task in the left IPL, premotor cortex and IPS. In contrast, the inferior temporal lobe was activated significantly more in the function judgments. These neuroimaging findings are consistent with the different neuropsychological symptoms associated with the damage in these structures (see above), implying that there is a relative division of labor across the left inferior parietal and inferior temporal areas, with respect to the knowledge and use of familiar tools.

Table 1.1 Activations Associated with Tools

Contrast Tools>Animals	**TASK**	**TEMPORAL LOBE**	**PARIETAL LOBE**	**FRONTAL LOBE**
Damasio et al. (1996)**	Naming task (Not available coords)	Inferior MTG		
Martin et al. (1996) *	Identifying line drawings, naming silently and out loud	MTG L -36, -50, 4 Anterior Cingulate L -6, -38, 2	SMG R 48, -50, 24	Inferior frontal cortex L -52, 10, 20 L -48, 0, 20
Cappa et al. (1998)**	Functional knowledge task with tools words: decision about utilization in food preparation	ITG L -48, -64, -8 STS R 52, -16, 16	SMG L -50, -40, 24	
Mummery et al. (1998)*	Matching words task on a specific dimension: domain (living nonliving) or associative attribute (location)	posterior MTG L -57, -56, 2 Fusiform L -31 -30 -19		
Chao et al. (1999)*	Naming task	Medial Fusiform L -28, -53, -15 R 29, -50, -18 MTG L -47, -58, 10 R 55, -55, 6		
Chao and Martin (2000)*	Viewing task		Posterior parietal L -32 -44 47	Ventral premotor cortex L -42, 4, 18
Gorno-Tempini et. al. (2000)**	Reading and naming task with objects and body parts	Inferior MTG L -54, -56, 0		
Chao et al. (2002)*	Naming task	Medial Fusiform L -26, -60, -6 R 25, -56, -5 MTG	Inferior parietal cortex L -31, -44, 49	Premotor cortex L -46, 12, 31

		L -46, -57, 4		
Devlin et al. (2002)**	Semantic decision tasks (location, color, action, and real-life size)	posterior MTG L -62, -58, 0	Anterior SMG -62, -58, 0	Ventral premotor cortex L -42, 4, 18
Noppeney (2006)*	Naming task	posterior MTG L -51, -66, -6 Medial Fusiform L -24, -57, -15 Anterior Fusiform L -33, -33, -24	SMG L -57, -30, 39	IFG (triangular part) L -48, 36, 6 IFG (opercular part) L -54, 18, 15
Mahon et al. (2007)*	Stimulus specific repetition suppression	Medial Fusiform L -25, -50, -8 R 31, -43, -12 MTG L -52, -64, -5	Caudal IPS L -15, -65, 51 R 28, -63, 41 IPL L -60, -24, 37	

**** PET studies ; *fMRI studies**

Table 1.2 Activations Associated with Animals

Contrast Animals>Tools	**TASK**	**TEMPORAL LOBE**	**OCCIPITAL LOBE**	**FRONTAL LOBE**
Damasio et al. (1996) *	Naming task (Not available coordinates)	Anterior and ITG		
Martin et al. (1996)*	Identifying line drawings, naming silently and out loud		Calcarine sulcus L -4, -80, 8	L -26, -6, 24 L -26, 28, 16
Cappa et al. (1998)**	Associative knowledge task with animals words: location decision	Fusiform R 34 -38 -24		R 30, 50, 12
Mummery et al. (1998)*	Matching words task on a specific dimension: domain (living nonliving) or associative attribute (location)		TOP R 53, -66, 30	L -31, 29, 22
Chao et al.	Naming task	Lateral Fusiform	MOG	

(1999)*		L -40, -59, -20 R 41, -56, -22 STS L -45, -65, 11 R 57, -59, 17	L -10, -100, 7 R 17, -97, 3 IOG L -37, -84, -7 R 45, -84, -8	
Gorno-Tempini et. al. (2000)**	Reading and naming task with faces, animals and maps		Cuneus L -4, -62, 20; L -10, -94, 8	
Chao et al. (2002)*	Naming task	Lateral Fusiform L -40, -61, -9 R 40, -60, -10 STS R 48, -39, 19	Calcarine sulcus L -12, -92, 9 R 22, -90, 9 MOG L -38, -77, 6 R 43, -75, 5	
Devlin et al. (2002)**	Semantic decision tasks (location, color, action, and real-life size)	Anterior MTG R 24, 8, -24 Insula L -28, 8, -8		
Noppeney (2006)*	One-back semantic task (identity, size, action) with pictures and words	Fusiform R 39, -60, -21	MOG R 51, -78, 0	

**** PET studies; *fMRI studies**

1.4.2 Perceptual and Semantic Processing of Faces

In this section, I report functional neuroimaging data regarding the perceptual and semantic level of face processing of famous and non-famous persons. In previous imaging studies, the term “famous” consistently refers to faces of well known celebrities, while the term “familiar” has been used for faces that were previously seen only once during the experimental setting, or to faces belonging to friends and acquaintances. In this thesis, the term “familiar” will only be used to indicate faces of people personally known by the subject, while the term “previously seen” refers to faces to which subjects have been previously exposed to but do not possess any associated semantic or episodic memory, and the term “unknown faces” refers to faces of anonymous people.

At a perceptual level of analysis, PET and fMRI studies on viewing and matching unknown faces has evoked activation in the middle portion of the lateral fusiform gyrus, usually bilaterally. This region has been labeled as the Fusiform Face Area (FFA) in the experiment of Kanwisher, Dermott, and Chun (1997) because it responds significantly more strongly to passive viewing of faces than scrambled faces, and to photos of faces than photos of houses or human hands. In particular, the FFA is considered to be involved in analyzing the more static aspects of face perception, such as feature configuration, which are more useful for face identification (Haxby et al., 2000).

In addition to the fusiform gyrus, other regions have been shown to be involved in particular aspects of face processing. Particularly, a region in the lateral IOG, labeled by Kanwisher et al. (1997) by the name of Lateral Occipital Complex (LOC), and which seems to be related to more general analysis of object shape (Kourtzi & Kanwisher, 2000). The STS (Chao et al., 1999), which responds during perception of averted gaze and lip movements (Hoffman & Haxby, 2000), and the amygdala, which has been frequently activated in response to facial expression depicting negative emotions (Gorno-Tempini et al., 2001a).

This data confirms the clear role of the fusiform region in the perceptual processing of faces. In any case, the precise role of this region in the stages of the face identification following the perceptual processing is still a matter of much debate. In particular, it is not clear whether this region is implicated in recognizing a face as familiar and/or famous and thus whether fame has an effect on FFA activation. In addition, it is still unclear whether the FFA activation in response to unfamiliar faces is really specific to faces, or also shared by other categories of objects. Table 1.3 summarizes the results from both PET and fMRI experiments of the studies that investigate the neural systems underlying famous and familiar face processing. In particular, some researchers have investigated the semantic stage of face processing during the differential responses to famous or familiar faces (Damasio et al., 1996; Kapur, Friston, Young, & Frith, 1995; Leveroni et al., 2000) and their results are not completely convergent. In these studies, famous faces have either been compared to other categories of objects, or to unfamiliar faces.

Sergent and Signoret (1992) carried out the first PET study that investigated the neural basis of famous face processing. They compared a categorization task on famous face with gender decision task on unfamiliar faces. The processing of famous faces in this contrast activated the fusiform gyrus, the temporal pole bilaterally and the more lateral portion of the left anterior MTG. In the same study, researchers asked subjects to perform a categorization task on objects (living/nonliving judgments). They later compared this condition with the viewing of gratings and they found activations in the left anterior MTG, but not in the temporal poles. A direct comparison between famous faces and objects was not performed.

Damasio et al. (1996) contrasted naming famous faces and objects with a task where subjects had to respond “up” if unknown faces were presented in the correct way up and “down” if they were upside down. Enhanced activity for famous faces was again found in the bilateral temporal poles and the left sided activation extended to the anterior portion of the lateral MTG. The authors attributed the response of the right ATL to the process of recognizing the identity of the face and the left sided activation to a face-dedicated lexical retrieval system. In fact the ATL activations were not found for naming tools or animals when compared to the same control condition. Few fMRI studies have attempted to investigate the brain responses to famous faces. In the experiment of Sergent and Signoret (1992) it was impossible to attribute the activation to the identification process alone since not only the type of stimuli (famous versus unfamiliar) but also the cognitive task (semantic versus perceptual) varied across conditions. Instead, during a familiarity judgment task, Leveroni and co-workers (2000) carried out an fMRI study that compared activation obtained from famous faces, faces seen once before and unknown faces. The anterior lateral MTG showed greater activation to famous faces compared to both previously seen and unfamiliar faces. Significant activations for famous faces were also found in the prefrontal and mesial temporal lobes bilaterally (hippocampus and parahippocampus). Also Henson, Shallice and Dolan (2000) comparing famous and non-famous faces in the context of a priming experiment found an effect of fame in the left anterior MTG.

Therefore, the available functional imaging data suggests a possible role of the fusiform gyri in the perceptual analysis of faces and of anterior temporal lobe in the identification of famous faces. However, when subjects view a famous face, retrieval of semantic and lexical (proper name) occurs together automatically, and therefore it is not possible to disentangle identification from lexical retrieval process. This fact was confirmed by results obtained by Campanella et al. (2001), who tried to localize the brain structures allowing the retrieval in long-term memory of a face on the basis of a related name and of a name on the basis of a related face. In their experiment subject’s task consisted in deciding whether the pairs of stimuli referred correctly to a previously learned couple. The processing of face associations relative to name and rest condition produced, in line with previous findings, a large increase of activity in the right fusiform gyrus. Whereas they did not find any specific activation for the name condition relative to the face condition, assuming that name processing was automatically activated during face presentation.

At this point, neuroimaging studies have been primarily devoted to studying famous and non-famous stimuli, and only a small number of studies have examined the direct contrast between famous faces and famous names. At this regard, in the PET experiment of Gorno-Tempini et al. (1998), researchers investigated the neural system involved in face, proper name and common name processing during a same different task with pairs of stimuli. Specifically, they used faces and names of famous and non famous people as stimuli, and within the category of names they involved proper and common names. The control conditions were scrambled faces for pictorial stimuli and strings of consonant for verbal stimuli. Activity in the fusiform gyri bilaterally (particularly in the right) and in the right lingual gyrus was found for the processing of faces relative to names and scrambled faces. In particular, the activations of the fusiform gyri were common for famous and unfamiliar faces, suggesting that perceptual analysis is equivalent when subjects perform the same task on both types of stimuli. Whereas Sergent and Signoret (1992), after having found the fusiform gyri to be more active on a semantic categorization task with familiar faces relative to a gender decision on unfamiliar faces, claimed that this region "*performs perceptual operations particularly well adapted to the process of facial identity*".

The most interesting demonstration of functional segregation in the study of Gorno-Tempini et al. (1998) was the activation in the left lateral anterior middle temporal cortex, which responded more to famous faces than to famous names, and to famous names more than to common object names. Therefore, the area specific to famous proper names appeared to be enhanced by semantic processing of person knowledge. This finding contrasts with that of Damasio et al. (1996), which associated the left anterior temporal cortex with a face dedicated lexical retrieval system. Gorno-Tempini and Price (2001b) explained that there might be a discrete region in the left ATL that is specific to person specific semantic or lexical attributes. As a matter of fact, this conclusion is in line with patients having anterior temporal damage and loss of person specific semantic, but at the same time it is not consistent with the neuroimaging studies that have shown activation of the anterior MTG when retrieving specific semantic features related to objects. A possible explanation for these contrasting results is that naming or matching famous faces elicits more activation than object naming in areas associated with the retrieval of semantic features due to the uniqueness of semantic associations evoked by famous faces and not shared by other items of the same category.

In their PET experiment, Gorno-Tempini and Price (2001b) tried to test this hypothesis with a matching task involving famous and non-famous faces and buildings. They found equivalent responses for both famous faces and buildings in the left anterior MTG, confirming that processing unique items increased the demand in this semantic area. Also in this experiment, they demonstrated the role of the FFA in the perceptual stage of face recognition, confirming that this area is unaffected by fame when subjects attend to the perceptual features of unfamiliar as well as famous faces. Previous studies that found a differential role of fame in the FFA did not control for task (Sergent & Signoret, 1992), or used passive viewing (Henson, Shallice, & Dolan 2000) or familiarity decision (Leveroni et al. 2000) paradigms, in which more attention could have been engaged by the subjects when the stimuli were familiar. However, the problem that arises with famous stimuli is that when subjects are exposed to them identification and lexical retrieval occurred together automatically. Therefore we cannot exclude the possibility that this region is involved in pure lexical retrieval processes (Damasio et al. 1996).

In a recent study, Nielson et al. (2010) tried to identify the unique and shared regions associated with accessing name and face familiarity. Subjects were asked to undergo a fame discrimination task on faces of famous and non-famous persons and names of famous and non-famous individuals. They found that famous faces produced greater activity than famous names in the fusiform gyrus, right cuneus and right inferior temporal gyrus (ITG). Famous names instead produced more activity than famous faces in a set of regions including the cuneus and the precuneus and in the left SMG. They found a common area of activation for both famous faces and famous names in the area of the left ATL, which did not extend out to the temporal pole as reported by Gorno-Tempini et al. (1998). It is undeniable that future studies, combining neuropsychological and neuroimaging data, are necessary to solve this issue.

Table 1.3 Activations Associated with Famous, Familiar and Previously seen Faces

	TASK	**FUSIFORM**	**ANTERIOR TEMPORAL LOBE**	
Famous Faces			**LATERAL MTG**	**TEMPORAL POLE**
Sergent *et al.* (1992)**	Categorization of famous faces - gender decision on unknown faces	L -37, -60, -12 R 37, -55, -11	L -52, -9, -9	L -36, 9, -27
Kapur *et al* (1995)**	Categorization of famous faces - gender decision on unknown faces			R 37, 20, -32
Damasio et al. (1996) **	Naming famous faces – saying “up” or “down” to upright or inverted unknown faces		L -56, -14, -9	L -37, 3, -33

Gorno-Tempini et al. (1998) **	Matching: famous faces - non-famous faces; proper names - common object names		L -60, 2, -24	
Gorno-Tempini et al. (2000) **	Reading – Naming Famous faces		L -66, -14, -8	
Leveroni et al. (2000)*	Familiarity decision on famous – unknown faces		L -52, -15, -12 R 52, -5, -16	
Leveroni et al. (2000)*	Familiarity decision on famous – newly learned faces	R 32, -46, -16	L -51, -11, -13 R 52, -6, -18	
Henson et al. (2000)*	Viewing famous – unknown faces (primed and not primed)	L -36, -60, -15	L -63,-6,-24	
Gorno –Tempini et al. (2001) **	Matching task Famous faces relative to non-famous faces and scrambled faces		L -64, 0, -16 R 62, -2, -14	
Ishai et al. (2005)*	Passive viewing of black and white line drawings of unknown faces - famous faces - unknown faces – emotional faces	L -42, -58, -18 R 40, -57, -17	L -54, -48, 4 R 53, -45, 7	
Brambati et al. (2010)*	Decisions on specific role (president) versus general profession (politician)		L -54 -8, -4	
Nielson et al. (2010) *	Fame discrimination task on famous – unfamous faces	R 40, -47, -60		
Familiar Faces				
Nakamura at al. (2000)**	Familiarity decision on familiar fixation or face discrimination			R 37, 23, -27
Previously seen faces				
Kim (1999)**	Previously seen faces versus gender decision	Not available		

Leveroni et al (2000)*	Familiarity decision on previously seen – unknown faces	R 32, -43, -15		
Campanella et al. (2001) **	Deciding whether the pairs of stimuli referred correctly to a previously learned couple (names-faces pairs)	R 44, -81, -15 R 40, -59, -15		

**** PET studies; *fMRI studies**

In summary, two main consistent findings emerge from cognitive neuropsychological research. First, patients have been reported with disproportionate impairments for a modality or type of knowledge (e.g., visual/perceptual knowledge or manipulation knowledge). Second, category-specific semantic deficits are associated with impairments for all types of knowledge about the impaired category.

Analogues to those two facts are also found in functional neuroimaging. First, features and attributes of some categories of objects (e.g., tools) are differentially represented in modality-specific systems (i.e., motor systems). Second, within a given modality-specific system (e.g., ventral visual pathway), there is functional organization by semantic category (e.g., living animate versus nonliving).

CHAPTER 2: FUNCTIONAL MRI GENERAL METHODS

2.1 BOLD SIGNAL AND NEURONAL ACTIVATION

The Blood-Oxygen-Level-Dependent (BOLD) contrast is considered a measure of the functional changes in brain activity since it represents the mechanism that connects neural activity to the measured T2* value. The physiological basis of the BOLD signal lies in the fact that T2* weighted images, that form the basis for BOLD contrast, are sensitive to the amount of deoxygenated hemoglobin present in the blood flow which changes according to the metabolic demands of active neurons. More specifically, as we can infer from its extended definition, the BOLD signal depends on the oxygenated level of blood, or better it exploit the different magnetic properties of the oxygenated and the deoxygenated hemoglobin and the fact that the proportions of the two types of hemoglobin change because of the increase of the neural activity. The deoxygenated hemoglobin, that is paramagnetic, generates inhomogeneities in the strong magnetic field of the scanner, these disomogeneities provoke a spin-dephasing of the hydrogen nuclei in the tissue and a following signal loss from that tissue and a correspondent decrease in the MR signal. Neuronal activity causes an increase in the metabolic demand and therefore an increase in the blood flow and in the oxygen consumption, but the fact is that there is not a correspondence between oxygen metabolism and blood-flow increase. In fact, the oxygen consumption increases less than the blood flow. The increase of oxygenated hemoglobin due to the increase of the blood flow exceed largely the decrease of oxygenated hemoglobin due to its conversion in the deoxygenated form because the oxygen consumption. This process reflects the net increase in the relative concentration of oxygenated hemoglobin and thus an increase in the BOLD signal. In fact, if we consider the time course of the BOLD contrast we see how the oxygenated hemoglobin reaches it s positive peak about 5 or 6 s after stimulus onset, on the contrary deoxygenated hemoglobin increases rapidly at stimulus onset, peaking at about 2 s and then it declines to its minimum value after 4 s. This fact can be explained by the initial oxygen extraction before the later compensatory response of blood flow. When the blood volume increase because the oxygen consumption is finished, due to the cessation of neuronal activity, blood flow decrease more rapidly than blood volume, so the amount of the deoxygenated hemoglobin will be greater and the MR signal will be reduced. This phenomenon explains the low results on the fMRI BOLD hemodynamic response.

2.2 LIMITS OF FUNCTIONAL NEUROIMAGING

Within the framework of semantic categorization we think that fMRI can be contribute to disentangle theoretical interpretations and give new explanations to anatomical constraints of these cognitive processes. However the use of this technique with normal subjects gave different insights rather than patients about the neural representation of semantic memory: there is in fact no evidence of a distributed network responsible for different aspects of semantic processing in the ATL. We know that ventral temporal regions are difficult to study with fMRI because the proximity of bone and air-filled cavities with very different magnetic susceptibilities leads to geometric distortions and signal loss, well recognized limitations of echo planar imaging (EPI), particularly with high-field MRI (Devlin et al., 2002; Ojemann et al. 1997; Robinson, Windischberger, Rauscher, & Moser, 2004). Therefore, the use of standard EPI may preclude the detection of task-related activity in the ATL. Studies using more sophisticated image acquisition techniques (Binney, Embleton, Jefferies, Parker GJ, & Ralph 2010; Simmons, Reddish, Bellgowan & Martin, 2010; Visser, Jefferies & Lambon Ralph, 2010) succeeded in finding ATL activation for semantic representations. For this reason we optimized BOLD sensitivity of 4 T gradient echo EPI in ATL areas, considering slice thickness, echo time, polarity of the phase-encode gradient, slice angle and shimming. Time-series signal-to-noise ratio (tSNR) in the resultant protocol, a good index for BOLD sensitivity (Triantafyllou et al., 2005), was compared with that achieved with a standard EPI protocol used for whole-brain imaging.

2.3 SUBJECTS AND GENERAL METHOD

We first optimized and evaluated a single-shot gradient-echo EPI protocol for 4 T fMRI in the ATL. This optimized protocol (for parameters see below) was used to characterize semantic and lexical retrieval in the temporal lobes.

All participants were right-handed, had normal or corrected-to-normal vision, and none reported a history of head injury or other neurological problems. Specific demographics are indicated below, separately for the three groups of subjects used in the optimization of the EPI protocol, in the movement and place experiment (Chapter 3) and in semantic and lexical retrieval (Chapter 4) experiment. All participants gave written informed consent for their participation in the study. The ethical committee for experiments involving humans at the University of Trento approved the experimental procedures.

2.4 OPTIMIZED EPI PROTOCOL FOR ATL AT 4 TESLA

The following parameters were investigated to minimize susceptibility-loss effects in the ATL, and to increase time-series signal-to-noise ratio (tSNR), a good index for BOLD sensitivity (Triantafyllou et al. 2005). We tested different TE (Bandettini, Wong, Jesmanowicz, Hinks, &

Hyde, 1994; Gati, Menon, Ugurbil, & Rutt, 1997; Kruger, Kastrup, & Glover, 2001), slice thickness and orientation (Deichmann, Gottfried, Hutton, & Turner, 2003), polarity of the phase-encoding gradient and shimming (De Panfilis & Schwarzbauer 2005), following previous evidence at lower field strength (Robinson et al. 2004). Voxel-wise tSNR was assessed in 10 healthy volunteers (mean age: 32.9 years, range: 24-45 years) in our standard EPI protocol (TE = 33 ms, 3 mm isotropic voxels, TR = 2000 ms, flip angle= 750, 37 axial AC-PC oriented slices, slice gap = 0.45 mm) and the optimized EPI protocol (TE = 21 ms, 3x3 mm2 in-plane voxels, 2 mm slice thickness, 43 axial slices oriented approximately -200 relative to the AC-PC plane (approximately parallel to the longitudinal axis of the temporal lobes), slice gap = 0.3 mm). Each volunteer underwent a 10 minutes resting state scan with each EPI protocol. Full brain coverage was not possible with the optimized EPI protocol. Approximately the upper 2 cm of the brain were not included while the main areas of interest were covered, including the entire temporal lobes, the inferior parietal regions as well as the occipital and most of the frontal lobes.

Images were preprocessed in SPM5 using standard methods (see below). The tSNR was used as a metric of BOLD sensitivity, and was calculated as follows. Low-frequency signal changes (such as drift) were removed by subtracting a second-order polynomial fit to total slice signal. tSNR was calculated by dividing the voxel-wise detrended signal mean by the standard deviations. Comparison between the optimized and standard EPI protocols using paired t-test and thresholding with a false discovery rate (FDR) of 0.05 revealed significant increases in tSNR with the optimized EPI protocol in bilateral ATL. Further, tSNR distributions within the bilateral ATL were calculated over all subjects. The ATL was defined as the volume of the temporal lobes anterior to the limen insula (approximately defined as the anteroposterior position of y = 4mm in the MNI template space (Insausti et al. 1998) excluding the parahippocampal formation and amygdalae. The distributions showed higher tSNR with optimized EPI (mean tSNR = 156) compared with the standard protocol (mean tSNR = 111). The mean tSNR improvement in the ATL was 41%. Results are illustrated in the Figure 2.1.

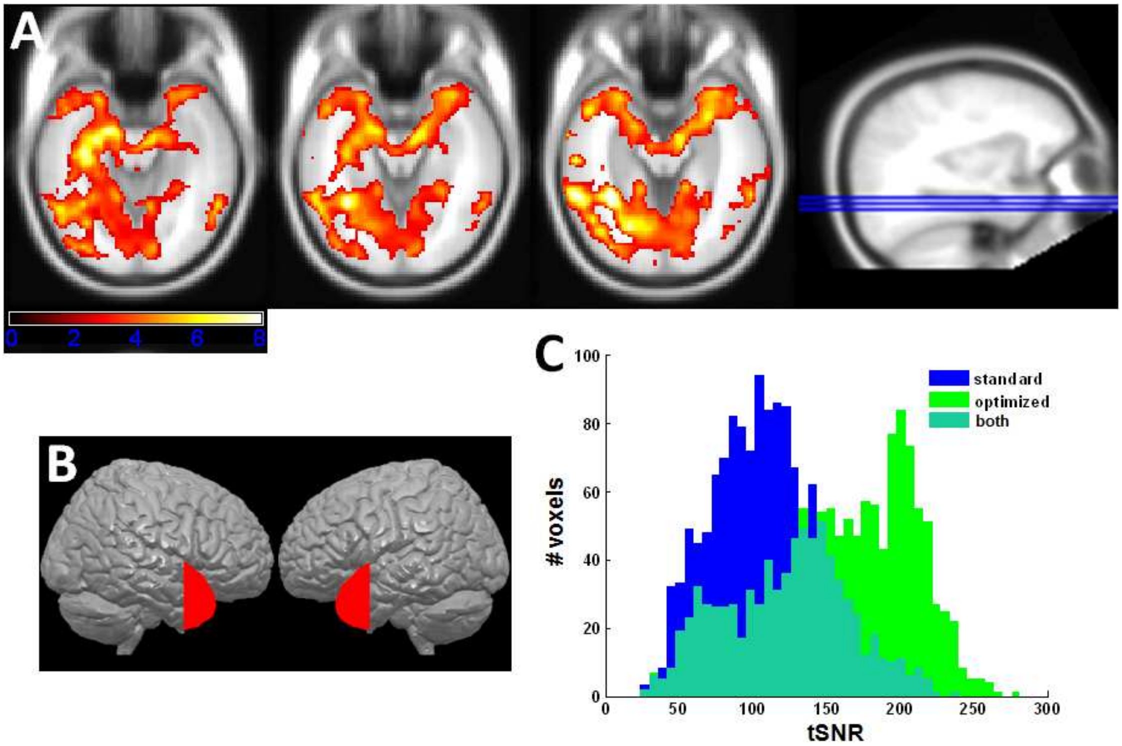


Figure 2.1 Comparison between optimized and standard EPI protocols. (A) Statistical map showing regions, in which the optimized protocol yields significantly higher tSNR. The shown axial slices are oriented parallel to the longitudinal axes of the temporal lobes, corresponding to the orientation of slices acquired with the optimized EPI protocol. The blue lines in the sagittal view on the right side indicate their position. (B) Extension of the anatomically defined ATL in the left and right hemisphere (red) overlaid on the rendered MNI template. The distribution of tSNR values in these regions is shown for both protocols (C).

2.5 fMRI DATA ACQUISITION AND PREPROCESSING

Functional and structural images were acquired with the parameters listed in the methods description of the optimization study. Only optimized EPI was used for functional scanning runs. For both functional runs 405 volumes were acquired. A point-spread function (PSF) scan was acquired prior to each functional run for distortion correction (Zaitsev, Hennig, & Speck, 2004; Zeng & Constable, 2002). The first 5 volumes of each run were discarded to allow T_1 equilibrium to be established. Further preprocessing was performed with SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5) (Friston, Ashburner, Kiebel, Nichols, & Penny, 2007), including slice time correction and motion correction. The mean functional image was coregistered with the structural image using a rigid body transformation. Structural images were segmented, bias corrected and spatially normalized to Montreal Neurological Institute (MNI) space using a unified segmentation procedure (Ashburner & Friston, 2005). Functional images were normalized to MNI space, using the same parameters, and spatially smoothed with a Gaussian kernel of 8 mm FWHM.

CHAPTER 3: FIRST FMRI EXPERIMENT “INVESTIGATION OF MOVEMENT AND PLACE FEATURES IN OBJECT RECOGNITION”

3.1 AIMS OF THE EXPERIMENT

With the present study we intend to investigate the anatomical correlates of place and movement features using living and nonliving items. The place feature (encyclopedic knowledge) was chosen as an associative attribute that equally applies to living things and artifacts, whereas the perceptual feature of action is typically associated to objects (tools in particular).

First, we chose three categories of objects, maintaining the well-established distinction between animals and tools (Chao & Martin, 2000; Caramazza & Shelton, 1998; Warrington & Shallice, 1984) and introducing, within the category of nonliving things, the nontools category. Since the majority of the studies on categorization and features focuses their analyses on the contrast between tools and living things (e.g., faces, animals), we might assume that their conclusions are also driven by the different involvements of properties used for their identification (perceptual for animals and functional for tools). For example, the hammer, the reflex hammer and the gavel are similar in weight and shape, but the semantic system will processes the hammer differently from the other similar tools primarily by its unique properties connected to nails and the common movement associated to its use instead of its physical properties or its typical location. Therefore, to control for all the nuances of the movement feature, without them being masked by the already established perceptual and functional difference between animals and tools, we introduced the category of nontools objects, which belong to the nonliving category but have a proper mechanical movement rather than tools.

Second, with the purpose to isolate activations associated with movement, rather than other associative aspects related to functional knowledge, we tried to dissociate manipulation knowledge from the context of use knowledge, which has mainly been used to investigate function (Martin & Chao 2000). For example, to investigate action and functional knowledge, Canessa and colleagues (2008) asked subjects whether two objects in a pair had the same manipulation pattern or whether they were found in the same context based on their function.

The feature of movement and specifically the activations in the IPL have always been studied in relation to tools; whereas in the present experiment we want to extend the most important property for the recognition of tools (movement) also to other categories which belong to nonliving, like nontools (i.e. vehicles) and living items (i.e. animals). From literature, we are aware of the existence of an “action network” involving the left medial fusiform gyrus, the left MTG and the left IPL, which are more activated for tools rather for living items and may be involved in the processing of action and manipulability (Canessa et al., 2008; Mahon et al., 2007; Noppeney et al., 2006; Boronat et al., 2005). These findings are consistent between functional neuroimaging studies on normal and neuropsychological studies.

In particular, damage to left IPL is associated with apraxia, a disease characterized by impairment in the use of familiar objects without any physical dysfunction of the limbs. These patients maintain knowledge of the function of common objects (Buxbaum & Saffran, 2002) but have degraded knowledge of how to move their body parts to interact with tools. Studies on SD patients demonstrate impaired knowledge of how to use common tools as well as their purpose (Bozeat et al., 2002). Specifically, in their study, Hodges, Bozeat, Lambon Ralph, Patterson and Spatt (2000) found that low performance in a conceptual knowledge task about tools correlates with the impairment of the knowledge of their use. Hence, the neuropsychological literature shows the involvement of the IPL in tools manipulation knowledge, while the ATL is responsible for a more general effect that affects both function and praxis.

3.2 METHODS

3.2.1 Subjects

Thirteen right-handed, native Italian-speaking volunteers took part in the study (4 males and 9 females; mean age: 27 years; st.dev.: 7,37; range: 19-47 years). All participants had normal or corrected-to-normal vision, and none reported a history of head injury or other neurological problems. All participants gave written informed consent for their participation in the study. The experimental procedures were approved by the ethical committee for experiments involving humans at the University of Trento.

3.2.2 Stimuli

We presented black and white photos of animals (n=204), tools (n=215), and nontools (n=215). Our definition of tools and nontools is not necessarily based on their purpose, but rather on the typical nature of their movements. With “tools” we refer to objects whose movement depends, from initialization to completion, on the manipulative interaction with humans and particularly with human hands (e.g. hammer, pencil, and scissors). With “nontools” we refer to objects moving mainly on the basis of intrinsic mechanisms. The initialization of their movements may depend on the interaction with humans as well, but they would maintain their movement after being started, like the spinning of a washing machine or carousel, or the swinging of a pendulum. We removed the background from all images and selected only static representations of objects and animals, to avoid cuing of the semantic attributes of interest (place, and movement). We composed pictures with pairs of animals (n=40), tools (n=40), and nontools (n=40), which should elicit either a same response in the "place" task and a no response in the "movement" task, or vice versa. Figure 3.1 shows example stimuli for each condition and all the object pairs are listened in Appendix A, Table 1.

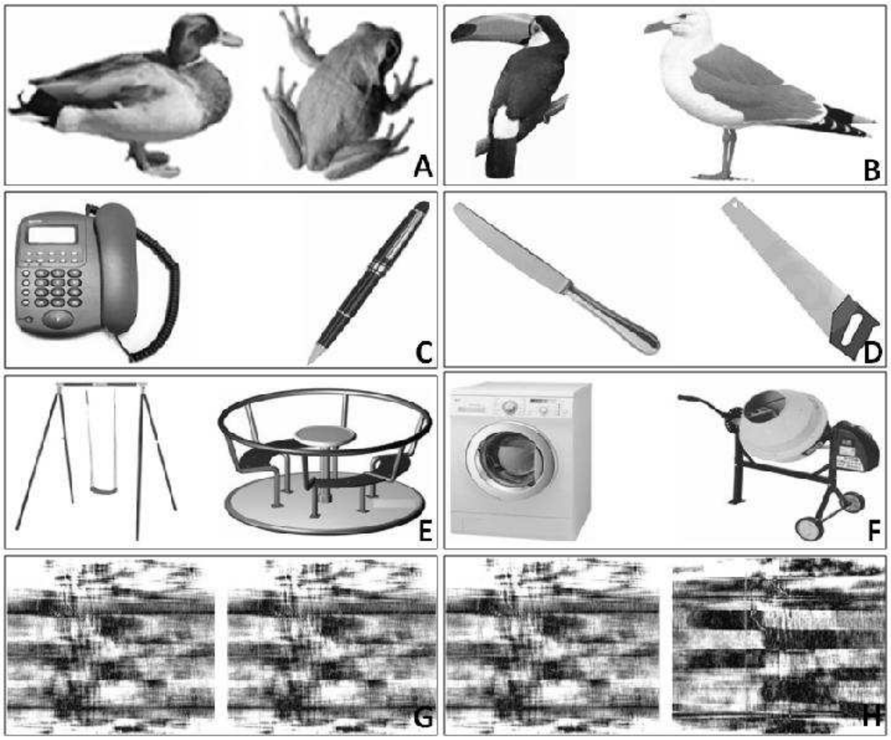


Fig. 3.1: Examples of stimulus pairs for the seven conditions: same place animals (A), same movement animals (B), same place tools (C), same movement tools (D); same place nontools (E), same movement nontools (F) same scrambled picture (G) and different scrambled picture (H).

Standardization and Stimulus Selection

In order to select the best stimuli for our experiment and to have the possibility of controlling for confounding factors, we presented all pictures first individually and then as pairs to a group of 40 subjects (16 males and 24 females; mean age: 26,13; st. dev.: 4,53 years, range: 20-40 years). For each individual picture, subjects had to report their familiarity (likert scale from 1 to 5: 1=low familiarity; 5=high familiarity) and visual complexity (likert scale from 1 to 5: 1=low visual complexity; 5=high visual complexity). For each picture pairs, subjects had to rate the visual similarity between them (likert scale from 1 to 5: 1=low visual similarity; 5=high visual similarity), and whether the two objects are typically found in the same “place”, and whether they typically “move” in the same way. Instructions were given to the subjects in the form of the following questions:

Familiarity: “How familiar are you with the object the picture refers to?” “How frequently do you come into contact with the stimuli, both directly (meeting the real exemplar of the object) or indirectly through media (from TV or newspapers)?”

Visual Complexity: “Assess the amount of details, lines and points in the picture.” (McRae, et al., 2005)

Visual Similarity: “How similar are the two objects presented in each pair?”

Place: “Do the two objects/animals are found in the same place/environment?”

Movement: “Do the two objects/animals move in the same way?”

How we created the object pairs for the standardization

The pairs with animals were chosen through a behavioral study in which 20 subjects took part (7 males and 13 females; mean age: 26; st. dev.: 4,13; years, range: 20-40 years). Participants were shown each stimulus on a computer screen and they were asked to state all the places they thought the animal could be found. Similarly, they had to state all the possible ways they thought that animal could move. This questionnaire allowed us to verify for the most common places and movements associated with each object. Instructions were given to the subjects in the form of the following questions:

Environment: In which environment or country do you think this animal is found more frequently? *(e.g. camel-desert, lion- savana, pig- farm)*

Movement: How do you think this animal moves in real life? *(e.g. eagle-fly, cow-walk, frog- jump)*

We adopted this questionnaire just for the animal category, rather than tools and nontools, since living things are on average less familiar, more visually complex, and designated by less frequent words (Funnell & Sheridan, 1992). Additionally, a number of feature listing studies found that living things concepts on average share more features with other category members than nonliving concepts (McRae et al., 2003).

Based on the results from the standardization, for each object we selected category 20 picture-pairs judged by at least 70% of participants to be typically found in the same place, and by less than 40% of participants to move in the same way. Similarly, we selected another set 20 picture pairs judged by at least 70% of participants to move in the same way, and by less than 40% to be found in the same place. In this way we received a final set of 40 object pairs per category. The same set of objects was used for both tasks, since half of the pairs were expected to elicit the “same place” response and the other half was expected to elicit the “same movement” response. We averaged familiarity ratings and visual complexity ratings across the pictures of each pair. The resulting average familiarity and visual complexity ratings, as well as the visual similarity ratings were compared between object categories using paired t-tests and Bonferroni correction (respectively 3 tests per measure).

Visual Stimulation

Stimuli were back-projected onto a screen with a liquid-crystal projector at a frame rate of 60 Hz and a screen resolution of 1,280 x 1,024 pixels. Participants viewed the stimuli binocularly via an adjustable mirror mounted on the head coil. Stimulation was programmed using the in-house software ‘‘ASF’’ (available from jens.schwarzbach@unitn.it), based on the MATLAB Psychtoolbox-3 for Windows.

3.2.3 Procedure

All subjects were screened by a neurologist to assess not fMRI compatibility, and then trained with the experimental task and familiarized with the MRI environment. Participants were then brought into the scanner, supine and head first. One structural scan was acquired, lasting 6 minutes, and 4 functional scanning runs with the experimental task, each lasting 10min.

3.2.4 Tasks

The task consisted in a semantic same/different judgment regarding object pairs, presented as pictures in the scanner. We used a 3 x 2 full factorial design, resulting in six conditions. The first factor was the “category” of the presented objects – either “animals”, “tools” or “nontools”. The second factor was the “kind” of task. In the “place” task, subjects were asked whether the two objects presented are found typically in the same environment or geographical habitat. In the “movement” task, subjects were asked whether the two objects move typically in a similar way. In the following text, the six resulting conditions will be referred to by “animals–place” (Ap), “animals-movement” (Am), “tools-place” (Tp), “tools-movement” (Tm), “nontools-place” (Np), “nontools-movement” (Nm). An additional “scrambled” control condition (Sc) was included, showing pairs of scrambled images, and subjects were asked whether they were identical or not. Subjects were instructed to press a key with their right index finger to indicate a “Yes” response, and to press a key with the left index finger to indicate a “No” response.

Training

Subjects were familiarized with the task prior to the experiment using a separate set of stimuli. They were instructed to respond as quickly as possible, and to respond even if they were unsure about their decision. Regarding the “place” task, they were instructed to think about the general environment (e.g. workshop, office, kitchen, garden) or the geographical habitat (e.g. desert, forest) in which objects are typically found. For the movement task, they were asked to consider the common movement associated with the objects and, in the case of tools, the common manipulative movements related to them. We told them not to be too specific since the same objects can be found in one or more different places and can move in different ways (e.g. a sheep can be found both in a lawn or farm, and it can both walk or run).

Design

In each condition, 40 trials were presented, with half of them being congruent in the relevant attribute-dimension (i.e. place, movement in the semantic conditions Ap, Am, Tp, Tm, Np, and Nm; and visual identity in the control condition with scrambled images). The experimental conditions were behaviorally blocked to avoid confusion of the tasks by frequent switching. However, trials were jittered using inter-trial intervals between 2 and 7 seconds. In each of the 4 runs, 2 blocks with respectively 5 trials were presented for each of the 6 conditions (Ap, Am, Tp, Tm, Np, and Nm). The order of these conditions was counterbalanced across blocks and participants.

One second before the start of each block, written instructions were given to remind the participants of the task: “Same Place” anticipated the conditions involving the place task (conditions Ap, Tp and Np); “Same Movement” anticipated the conditions involving the movement task (conditions Am, Tm and Nm). Between each of these blocks, either two or three trials with scrambled images (condition Sc) were presented. In each trial the grayscale pictures of 2 objects were presented simultaneously on a white background for 3.5 seconds. A black fixation cross was presented in the centre of a white screen for the duration of inter-trial intervals and before/after the first/last trial of each run. The fixation period before/after the first/last trial lasted 20 and 16 seconds respectively.

3.2.5 Behavioral Data

Subject responses were collected with fMRI compatible button boxes for the left and right hand (Lumina LU400-PAIR, Cedrus, United States). Respectively, the first response and reaction times were measured. Accuracy and mean reaction times were calculated for the different conditions and compared using two-way repeated measures ANOVA. Post-hoc analysis was performed using t-tests and Bonferroni correction. We did not exclude trials with incorrect responses from the statistical model of the BOLD response (see below) because we expected a similar degree and pattern of BOLD signal changes during these trials. This idea was motivated by on the assumption that, even if a subject came to a conclusion different from that predicted on the basis of our standardization, the subject should still have analyzed the object features corresponding to the particular task. Consequently, we included incorrect trials also in the analysis of reaction times to have a better idea of the possible effect of reaction times on the BOLD signal.

3.2.6 fMRI Statistical Analysis

Effects on the subject level were estimated by fitting a General Linear Model (Friston et al., 1995) for each voxel using SPM5. The four functional runs for each subject were concatenated. The design matrix consisted of one explanatory variable (EV) per experimental condition and run. The EVs were created by convolving a box-car function (corresponding in duration to the stimulus presentation) with a canonical hemodynamic response function (HRF). To control for differences in visual complexity and familiarity of the object pairs shown in the different trials of conditions Ap, Am, Tp, Tm, Np, and Nm, we created one additional EV in analog manner that modeled the events of all these 6 conditions. This EV was then modulated parametrically by the familiarity and visual complexity ratings received during the standardization procedure. For each trial, the parameters for the modulation were chosen by averaging the ratings of the two objects presented. Each run included 6 additional regressors, corresponding to the head motion parameters estimated during the realignment step, and one variable encoding the mean.

Model parameters were estimated using Restricted Maximum Likelihood (ReML) using an autoregressive AR(1) model to correct for non-sphericity arising from serial correlations. The data and model were high-pass filtered with a cut-off frequency of 1/128 Hz.

Contrast images calculated at the single subject level were entered in a random effects analysis to infer effects on the population level. This second level of analysis was conducted using the flexible-factorial design implemented in SPM5. Average reaction times were calculated for each subject and condition, and entered as a covariate. Contrasts at the second level were calculated at the single voxel level, correcting for Familywise Error (FWE) at $P<0.05$. Based on a priori hypotheses, we recalculated certain contrasts using a region of interest (ROI) approach using Marsbar software.

All results were displayed with MRIcron (Version 7 July 2009, Chris Rorden, http://www.mricro.com), overlaying functional data on the provided single-subject T1 template. Anatomical labels were determined based on visual inspection of the data with reference to the atlas of Duvernoy (1999).

To visualize the size of cognitive effects on the BOLD signal, the percent signal change was plotted in certain activation clusters.

Hypothesis Testing

The first analysis aimed at determining category-specific effects. To this end, we contrasted respectively both conditions involving one particular object category against the two conditions of one of the other categories (e.g. Tp and Tm for tools). In this way, each object category was tested against each other (i.e. animals against tools; animals against nontools; tools against nontools; and vice versa). We created a region of interest analyses (ROI) on the basis of the coordinates found by Devlin et al., (2002), Mahon et al., (2007) and Noppeney et al., (2006) for the contrast tools against animals and tools against nontools.

The second analysis aimed at determining the effect of the task (i.e. movement, place). Contrasting all conditions involving the movement task against the place task, and vice versa, identified this effect.

The third analysis tested interactions between object category and task.

3.3 RESULTS

3.3.1 Behavioral Data

Behavioral results

No significant differences were found for the accuracy of response (Fig. 3.2A). Reaction times (Fig. 3.2B) differed significantly across object categories [F(2)=11.825, p=0.0003] and tasks [F(2)=6.685, p=0.0239]. Also, the interaction between both factors was statistically significant [task*category F(2)=7.198, p=0.0036].

Standardization

Figure 3 summarizes the results of the standardization in the final stimulus set. There was no significant difference in familiarity ratings (Fig. 3.3A) between animals and tools [t(69)= -0.6399; p=1.5723], but there was a significant difference between animals and nontools [t(67)= 2.9365; p=0.0136] and between tools and nontools [t(77)= -3.0764; p=0.0087]. We obtained significant differences in visual complexity (Fig. 3.3B) for all the categories, animals and tools [t(63)= 5.5834; p<0.001], animals and nontools [t(58)= -5.0452; p<0.001], and tools and nontools [t(76)= -8.5289; p<0.001]. For visual similarity (Fig. 3.3C), there was no significant difference between animals and tools [t(73)= -1.0633; p=0.8733] or between animals and nontools [t(76)= 1.8109; p=0.2223]. Only the difference between tools and nontools was significant [t(69)= -2.6611; p=0.0294].

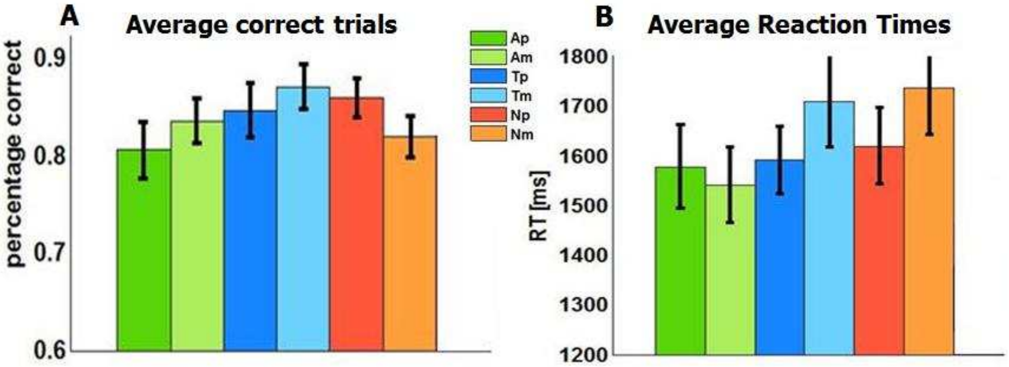


Fig. 3.2 Mean accuracy (A) and reaction times (B) in the six experimental conditions. Error bars show standard error of mean. For abbreviations of conditions see text.

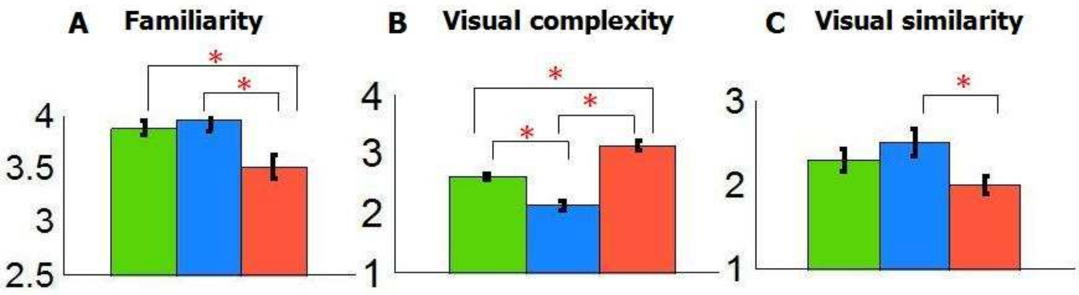


Fig. 3.3 Mean and SEM are shown for familiarity (A), visual complexity (B), and visual similarity ratings (C), collected during standardization.

3.3.2 Imaging Data

fMRI Data: Effect of category irrespective of task

Animals: the task of comparing animals versus tools (see Fig. 3.4A, Table 3.1) revealed activity in several cortical regions, including the fusiform gyrus bilaterally, the MOG bilaterally and the right MTG. Animals compared to nontools (Fig. 3.4B, Table 3.1) revealed activations in the IOG) bilaterally in the left MOG, in the fusiform gyrus bilaterally and in the right cuneus and precuneus.

Tools: the comparison of tools (Table 3.1) versus animals revealed greater activity in the fusiform gyrus bilaterally.

Nontools: for the contrast of nontools versus animals (Fig. 3.4C, Table 3.1), activations were observed in the fusiform gyrus bilaterally and in the left lingual gyrus, and the MOG bilaterally.

Comparing nontools against tools (Fig. 3.4D, Table 3.1) revealed activations in the fusiform gyrus bilaterally, in the left MOG, and in the right calcarine.

Table 3.1: Category Specific Effects

Contrast	**Brain area**	**MNI coordinates**			**Extend mm^3**	**P (FEW-cor)**	**Max T**
		x	**y**	**z**			
Animals>Tools							
	Right middle occipital	45	-75	-6	4266	<0.001	10.41
	Right middle temporal	57	-60	18		0.007	
	Right middle temporal	42	-63	15		0.013	
	Left middle occipital	-21	-99	6	2079	<0.001	6.46
	Right Fusiform	42	-51	-21	648	<0.001	6.74
	Left middle occipital	-45	-81	6	378	0.001	5.39
	Right middle temporal	51	-42	12	972	0.002	5.33
	Left fusiform	-39	-51	21	162	0.012	5.4
Animals>Nontools							
	Right inferior occipital	45	-75	-6	4698	<0.001	11.6
	Left inferior occipital	-45	-78	-6	2295	<0.001	8.15
	Left middle occipital	-18	-99	6	1782	<0.001	7.6
	Right Fusiform	42	-51	-24	891	<0.001	7.5
	Left Fusiform	-42	-51	24	729	<0.001	6.71
	Right middle temporal	54	-42	12	135	0.016	5.31
	Right precuneus	6	-57	24	108	0.022	5.21
	Right cuneus	6	-75	30	54	0.043	5.01
	Right precuneus	3	-69	24	27	0.047	4.97
Tools>Animals							
	Left fusiform	-27	-63	-12	2511	<0.001	8.32
	Right fusiform	30	-60	-9	1890	0.004	7.31

Nontools>Animals							
	Right Fusiform	27	-48	-12	7884	<0.001	13.55
	Left lingual gyrus	-27	-60	-9	6696	<0.001	12.46
	Left middle occipital	-36	-84	15	1620	<0.001	6.91
	Right middle occipital	36	-81	21	405	0.006	5.6
	Left fusiform	-21	-84	-9	27	0.047	4.97
Nontools>Tools							
	Right fusiform	27	-45	-12	2592	<0.001	7.28
	Right fusiform	33	-36	15		<0.001	
	Right cerebellum	24	-30	-24		0.001	
	Right calcarine	21	-57	15	243	0.003	5.76
	Left middle occipital	42	-78	27	243	0.009	5.49
	Left fusiform	-27	-33	-21	162	0.019	5.25
	Left middle occipital	-39	-84	18	27	0.045	4.00

Table 3.1 Effect of category: P-values (P) and maximum T statistics (Max T) are reported for the local maximum of each cluster. P-values were controlled for FWE (13 subjects: FWHM = 13.2mm 13.6mm 12.7mm; Volume = 46415 voxels = 487.2 resels). For single clusters, which clearly extended into several areas of the brain, the local maxima in these additional areas are indicated in italics.

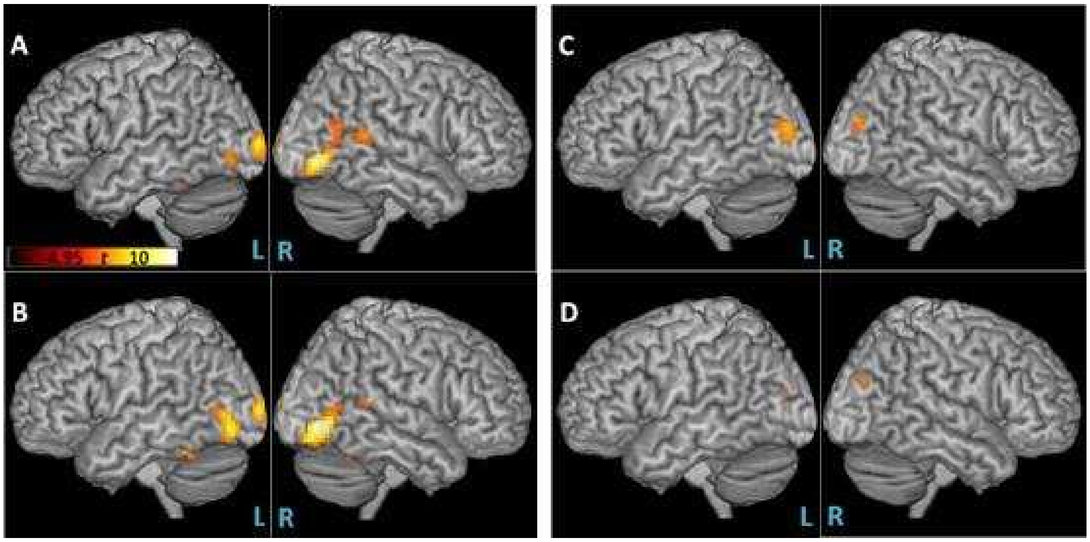


Figure 3.4: Surface rendering of the parametric maps of t-statistic in 13 subjects. Overall effect of processing living things (A, contrast Animals vs. Tools; B, contrast Animals vs. Nontools); and effects due to processing of nonliving things (C, contrast between Nontools vs. Animals; D, contrast between Nontools vs. Tools). Height threshold and scale of t-statistic is indicated for the 13 subjects in A.

fMRI Data: ROI Analyses

We did not find any activation in the comparison between tools and nontools (tools>nontools), while in the contrast between tools and animals (tools>animals) we obtained the activation of the fusiform gyrus bilaterally and not the inferior parietal gyrus as it is generally reported in literature. We created a ROI for the inferior parietal area (IPL; MNI coordinates-61 -25 37), defined by the average calculated in the Devlin et al., (2002), Mahon, et al., (2007) and Noppeney et al., (2006) and studies. The responses in the ROI were significant for both the contrasts of tools versus animals ($p < 0.01$) and tools versus nontools ($p < 0.05$) 0.0012.

fMRI Data: Effect of task irrespective of category

Movement: processing the "action knowledge" (Fig. 3.5A, Table 3.2) in the movement condition activated bilaterally, the SMG including the left IPL, the posterior ITG and the posterior IFG. Lateralized left activations were found in the precentral gyrus and for the right hemisphere in the superior parietal gyrus (SPG) and in the right MTG.

Place: in the contrast between place and movement (Fig. 3.5B, Table 3.2), only the left hemisphere was activated. The analyses elicited widespread activity in the medial inferior occipital lobe (calcarine), the AG, the anterior MTG, and the fusiform gyrus.

Table 3.2: Task Specific Effects

Contrast	**Brain area**	**MNI coordinates**			**Extend mm³**	**P (FEWcor)**	**Max T**
		x	**y**	**z**			
Mov>Place							
	Left supramarginal	-60	-36	36	16281	<0.001	9.95
	Left inferioir parietal	-42	-42	45		<0.001	
	Left inferioir parietal	-33	-48	45		<0.001	
	Left precentral gyrus	-48	6	24	4131	<0.001	8.63
	Right supramarginal	63	-27	39	6129	<0.001	8.47
	Left inferior temporal	-57	-57	-6	3402	<0.001	7.37
	Right superior parietal	18	-60	51	1215	<0.001	6.75
	Right inferior frontal	48	12	18	891	<0.001	6.35
	Right inferior temporal	51	-54	-3	540	0.005	5.62
	Left inferior frontal	-45	42	6	189	0.00	5.48

	Right middle temporal	66	-45	12	27	0.038	5.04
Place>Mov							
	Left Calcarine	-9	-54	6	3375	<0.001	7.26
	Left angular gyrus	-42	-75	30	1863	<0.001	7.13
	Left middle temporal	-54	-3	-21	1080	<0.001	6.57
	Left fusiform gyrus	-24	-33	-21	531	0.001	6.24

Table 3.2 Effect of task: P-values (P) and maximum T statistics (Max T) are reported for the local maximum of each cluster. P-values were controlled for FWE (13 subjects: FWHM = 13.2mm 13.6mm 12.7mm; Volume = 46415 voxels = 487.2 resels). For single clusters, which clearly extended into several areas of the brain, the local maxima in these additional areas are indicated in italics.

fMRI Data: Interaction between object category and task

We found no interaction between object category and task. For visualization, we show the percent signal change in two representative clusters respectively revealed by the contrasts between Movement versus Place (Fig. 3.5B: left SMG; MNI coordinates: -60, -36, 36; and Fig. 3.5C: left ITG; MNI coordinates: -57, -57, -6; only voxels within 10mm around the peak voxel), and between Place versus Movement (Fig. 3.6B: left AG; MNI coordinates: -48, -72, 30; only voxels within 10mm around the peak voxel).

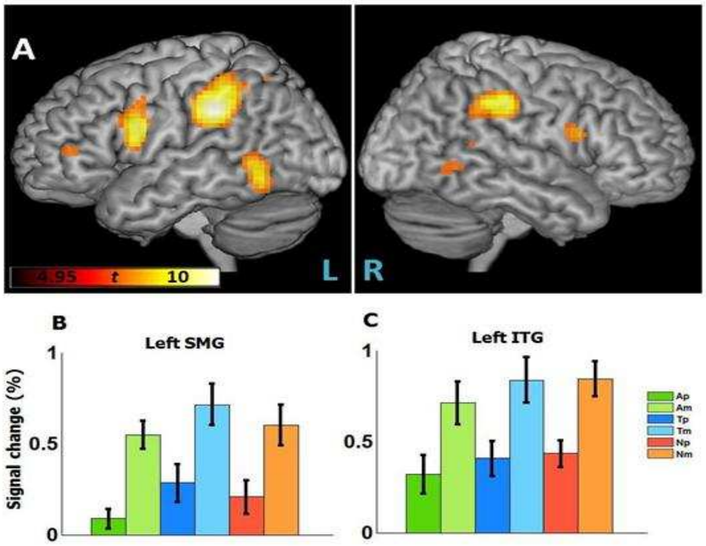


Figure 3.5: Surface rendering of the parametric maps of t-statistic in 13 subjects. Overall effect of processing the movement feature (A, contrast Movement vs. Place); Height threshold and scale of t-statistic is indicated for the 13 subjects in A. Percent signal change is shown for two representative clusters defined by the contrast Movement>Place (B,left SMG; C,left ITG).

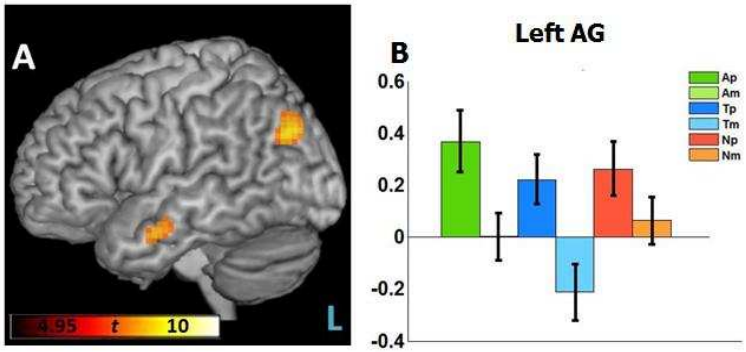


Figure 3.6: Surface rendering of the parametric maps of t-statistic in 13 subjects. Overall effect of processing the place feature (A, contrast between Place vs. Movement). Height threshold and scale of t-statistic is indicated for the 13 subjects in A. Percent signal change is shown for one representative clusters defined by the contrast Place>Movement (B, left AG).

3.4 DISCUSSION OF RESULTS

The present experiment aims to investigate the neural correlates of two semantic features: one related to the encyclopedic knowledge which investigates the typical environment of objects, and one related to the perceptual knowledge of action. By asking subjects to make same/different judgments on a recognition task about object pairs, we identified two neural networks involved in the place and in the movement feature.

fMRI Data: Effects of category

Activations based on the effects of category-specific for living items are consistent with previous neuroimaging studies. Specifically, compared to pictures of tools, pictures of animals elicited greater bilateral activity in the lateral fusiform gyrus (Cappa et al., 1998; Chao et al., 1999, 2002; Noppeney, et al., 2006;), in the MOG, and in the right MTG (Chao et al., 1999; 2002; Noppeney et al., 2006; Perani et al., 1995). Note that these activations are consistent with studies that focused their research particularly on feature investigations. For example, using pictures of animals and tools in an fMRI experiment, Noppeney et al., (2006) asked subjects to decide whether subsequent stimuli within a block were identical, performed a similar action or were a similar size in real life. She found the right MOG and the right fusiform to be involved in the processing of animals rather than tools.

Previously, we mentioned the divergence between neuroimaging studies and data on patients with regards to the lack of activations in the ATL. According to our results, we might assume that the temporal lobe activation specific for living items could find a confirmation on the VBM correlation analyses of Brambati and colleagues (2006). Even though they reported more anterior activations, we can claim that within this context, our findings, consistent with literature, that some regions respond more strongly to animals than tools in the ventral temporal pole (right fusiform) and in the right MTG may provide a neural basis for selective semantic deficits for animals following temporal lobe lesions. At the same time, we cannot yet claim a full understanding of the constraints under which concepts from the domain of living things do not produce regional activation in the anterior temporal pole in functional investigations.

Finally, consistent with recent reports on nonliving items, the comparison of tools versus animals showed activations in the medial part of the fusiform gyrus bilaterally (Chao et al., 1999, 2002; Noppeney et al., 2006). Despite the well-documented relation of the IPL during the processing of tools, we did not find any activation in this area with a corrected threshold (FEW $p<0.05$). However, the ROI analyses calculated in the Devlin et al., (2002), Mahon et al., (2007) and Noppeney et al., (2006) studies revealed significant results confirming the supremacy of the tools category over both animals and nontools. Note that the difference between living nonliving was in our experiment an implicit focus of the task, in fact we tried to drive subjects' attention specifically on the difference between attribute types: place and movement, rather than the comparison between objects category, then explaining therefore the lack of activations in the IPL area. Activations related to nontools were elicited in the fusiform gyrus and in the right and left medial IOG.

Clearly the fact that we obtain distinct activations for different categories of objects fits with the dramatic deficit specific to object domains that have been reported in neuropsychological literature (Warrington & Shallice, 1984). However, it is important to point out that differences found in object domain activations were smaller than those related to differing types of knowledge. This same pattern of results was also found in another experiment about features by Mummery et colleagues (1998), in which they could not find any activations in the contrast between animals versus tools, irrespective of task condition.

fMRI Data: Effects of tasks

Place: the processing of the place feature elicited a left lateralized widespread activity in the medial inferior occipital lobe and in the AG (Cappa et al., 1998; Mummery et al., 1998;). Other activations were found in the left anterior MTG and in the fusiform gyrus. In the study of Cappa and colleagues (1998), researchers used a PET experiment to investigate visual and associative knowledge about animals and tools words. In particular, for the semantic task, they asked subjects where a specific animal is typically found and whether a specific tool is typically used in food preparation. In the main effect of the task, they found the left MFG and the occipito parietal junction (OPJ) bilaterally (MNI -41 -74 30) were more active during the processing of animals location. Mummery and colleagues (1998) carried out another study that investigated object features. They specifically ran a PET experiment using object names as stimuli, and they asked subjects to respond to a matching task investigating object domain (living versus nonliving) and type of knowledge attributes, one perceptual (color) and one associative (location). The regions activated in the semantic task, more so than in the control task, were the MTG, more posterior than our activations, and the TPJ (MNI 42 -72 34), very close to the coordinates of our cluster in the AG. As a matter of fact, our results are confirmed by neuroimaging studies on semantic features and specifically by studies that focused their attention on the location property.

Movement: judgments about object movement relative to place were associated with enhanced activation of the SMG, including the left inferior parietal gyrus (Boronat et al., 2005; Canessa et al., 2008; Kellenbach et al., 2003). Other activated areas were the right SPG, the right posterior MTG (Beauchaump et al., 2003), the posterior inferior temporal pole (ITP), the medio lateral, and posterior inferior regions of the frontal lobe.

Canessa and colleagues (2008) found the inferior parietal regions more involved in action knowledge and the lateral anterior inferior temporal cortex more active during functional knowledge. They explicitly dissociate the action/manipulation knowledge ("how" objects are used) from the functional knowledge ("what for" objects are used) with two different conditions. Note that the functional properties of object was investigated by explicitly asking participants a judgment relative to the context of use, a property that does not belong to the perceptual or the motor domains. On the contrary, we tried to focus the subject's attention on the general concept of movement, including any movement classified as biological independent movement (animals), mechanical proper movement (nontools) and manipulation (tools), contrasting it with an encyclopedic knowledge related to location, avoiding referring to any functional property of the object.

Literature consistent with an "action network" suggests that the areas involved in it are more activated for tools than for living items and are possibly involved in the processing of action knowledge/manipulability (Canessa et al., 2008; Chao & Martin, 2000; Mahon et al., 2007). With the present study we want to determine whether category-specific activations for nonliving (tools and nontools) depend on this action network, and nevertheless to investigate a possible role of this network during the processing of action knowledge related to other categories of objects, like animals. If the brain organizes information about objects according to their features and attributes, we might expect motor-based properties to be more important when identifying manipulable man-made objects that are strongly associated with specific hand movements (i.e., tools). Our results demonstrate that, although we cannot exclude that this feature remains the most important for tools recognition, there are no significant interaction between category and task neither in the place nor in the movement networks. This suggests that these areas are not more activated for tools than they are for either animals or nontools. We could argue that the areas we found to be involved in the movement task might be responsible for a general and more global meaning of movement, which includes not only the action related to manipulation but also the independent biological motion of animals and the intrinsic mechanical motion of nontools.

Also in their PET study, Kellenbach and colleagues (2003) investigated action and functional knowledge in the form of questions tasks, using manipulable and nonmanipulable objects. They found that the ventral premotor cortex (VPMC) and the left posterior MTG are activated by all kinds of objects, both nonmanipulable and manipulable relative to the control condition, with a greater activation for manipulable objects. Note that in our experiment we specifically found a widespread activation in the bilateral areas of the posterior ITG and the involvement of the right posterior MTG instead of the left posterior MTG, this last activation might be explained by the fact that we also included the category of animals.

On the other hand, there were two studies by Chao et al., (1999) and Chao and Martin (2000) that compared tools against another kinds of man-made objects (i.e. houses). The authors found that the left VPMC and the posterior MTG were activated during the comparison between tools and the control condition (scrambled objects), whereas no such activations were found for buildings. They explained this finding by suggesting that these regions of the temporal lobe support some aspects of the manipulation of objects rather than artifacts in general. Note that Chao et al., (1999) and Chao and Martin (2000) asked their subjects to watch carefully and name the pictures of objects, while we focused participants' attention on the movement judgment. Thus the activity found for nontools and animals in our experiment and in the Kellenbach et al., (2003) study might represent the result of stressing the feature of action in the non-manipulable object category.

Moreover, our results surprisingly showed an activation in the IPL for all categories, areas that have always been claimed to be selectively activated by tools stimuli and therefore reflecting the nature of motor properties related to the representation of these objects. The lack of interaction between category and task make us conclude that the processing of movement cannot be attributed solely to the processing of tools. The finding that specific regions, assumed to be involved in storing information about object motion, were not significantly active for the processing of tools with respect to other categories could mean that motion information might be critical also for distinguishing between objects that do not belong to the tools category. Furthermore, our results seem to confirm the neuropsychological data and theory that account for a feature type organization of semantic memory that argues that features are generally associated with a particular category but they are not limited to one.

3.5 CONCLUSION

The fMRI data presented confirms the importance of a network of regions involved in the semantic processing of place and movement features, but also reveals category-specific activations that were consistent across individual subjects and processing tasks. By applying a semantic categorization task related to movement (action) and place (encyclopedic) knowledge to three different categories of objects (animals, tools and nontools), we were able to identify the networks involved in the processing of the two semantic features.

The processing of place activated a network of left anterior temporal and inferior parietal regions**,** whereas the processing of movement elicited a bilateral network of the inferior parietal, inferior frontal and posterior ITG. These regions form a common network for the retrieval of semantic action knowledge and place, regardless of stimulus category. We have shown that, when normal adults make semantic judgments on place and movement feature, a network of cortical areas is activated, remarkably consistent with those found in other studies using pictures of objects. Furthermore, we demonstrated that within these regions statistical analyses did not show any significant interaction between categories. These findings suggest that this visuomotor “action network” is not more specialized for tools than for nontools or animals, and therefore that it is active not only when people process the meaning of graspable objects.

CHAPTER 4: "ATL IN SEMANTIC AND NAMING" A VBM STUDY ON PATIENTS AND AN fMRI STUDY WITH NORMAL SUBJECTS

The following chapter describes two experiments: Part I will present the Voxel-Based Morphometry (VBM) study with patients, while Part II will report an fMRI experiment with normal subjects. These studies aim at the investigation of the anatomical organization of processing famous faces, in particular, the functional investigation allowed to disentangle between semantic and lexical retrieval processing.

PART I: VBM STUDY ON PATIENTS

4.1 AIM OF THE EXPERIMENT

In the present study, we wanted to investigate the anatomical organization of processing famous faces distinguishing brain regions responsible for recognition, semantic association and naming. To do this we used VBM on structural MRI images, a structural neuroimaging technique that is not affected by artifacts in the anterior temporal lobe, and we included patients with known damage to this region, such as SD patients.

4.2 METHODS

VBM is a technique that converts structural MRI data into spatially normalized images of gray matter density, and makes inferences about the differences between normal subjects and patients in a regionally specific and quantitative fashion.

In this study we correlated accuracy scores obtained by patients in three tasks that differentially separated the three steps – recognition, semantic association, and naming – in the face-processing cascade. This technique allowed us to avoid confounding artifacts produced in BOLD imaging of the anterior temporal lobes. We expected that differential scores on each of these tasks might correlate with unique gray matter volumes in the temporal lobes in such a way as to localize the neuroanatomic correlates of familiarity-checking, personal identity retrieval, and naming.

4.2.1 Subjects and Patients assessment

We collected MRI images from a group of 107 patients (44 male, 64 female, mean age: 62,88, range 47-79) with both varying degrees of impairment and different patterns of gray matter atrophy.

The patients were recruited through the Memory and Aging Center (MAC) at the University of California, San Francisco (USCF) and were diagnosed with Alzheimer Dementia (AD), Primary Progressive Aphasia (PPA) and its three variants: Semantic Dementia (SD), Progressive Nonfluent Aphasia (PNFA) and Logopenic Progressive Aphasia (LPA) (Gorno-Tempini et al. 2011); The behavioral variant of Fronto-Temporal Dementia (FTD), Dementia with predominant motor symptoms: Corticobasal Degeneration (CBD), Lewy Bodies Dementia (DLB), Progressive Supranuclear Palsy (PSP); as well as Amyotrophic Lateral Sclerosis (ALS), Mild Cognitive Impairments (MCI) and clinically normal subjects (NC). All these diagnosis were based on published criteria by a multi-disciplinary team of neurologists, neuropsychologists, neuropsychiatrists and nurses after a comprehensive evaluation including neurological history and examination, and neuropsychological testing of memory, executive function, visuospatial skills, language and mood. The different neurodegenerative diseases are characterized by distinct cognitive and neurological symptoms that reflect the specific patterns of gray matter atrophy involved (Boxer et al., 2006; Gorno-Tempini et al., 2004).

During the neuropsychological screening battery that patients underwent, general intellectual function was assessed using Mini Mental State Examination (MMSE) and functional status was tested using the Clinical Dementia Rating scale (CDR). The study was approved by the UCSF committee on human research. All subjects provided written informed consent before participating. Patients that were included in the analyses (66 subjects) were required to score at least 11 out of 30 on the Mini-Mental Status Exam (MMSE), 1 at the Naming Test, 5 at the Facial Recognition Test and 10 at the Semantic Task Triplets Test. Demographic and clinical variables are reported in Table 4.1.

Tab. 4.1 Demographic characteristics of the subjects included in the VBM study

	NC (*n=16*)	*AD* (*n=8*)	*CBD/PSP/DLB* (*n=7*)	*FTD* (*n=6*)	*MCI* (*n=3*)	*PPA* (*n=14*)	*AD* (*n=5*)	*ALS* (*n=2*)	*MNRC* (*n=5*)
Age	68.25	59.25	66.42	58	65.3	66.28	66.6	55	58.2
M/F	4/12	4/4	3/4	4/2	1/2	4/10	4/1	2/0	2/3
MMSE	29.56	23.5	27.57	25.5	29	22.28	27	29.5	28.75

Table 4.1 Means of Age and means of MMSE scores are reported for each clinical group. NS = clinically normal subjects; AD = Alzheimer's disease; PSP/CBD/DLB = patient with dementia and predominant motor symptoms (progressive supranuclear palsy, corticobasal degeneration, dementia with Lewy bodies); FTD = frontotemporal dementia; MCI = mild cognitive impairment; MNRC = patients that did not meet any research criteria; PPA = primary progressive aphasia (only patients with and with LPA and PNFA have been included in this group); SD = semantic dementia; MMSE = Mini-Mental State Examination.

4.2.2 Stimuli

All subjects were administered with three tests consisting of a set of 20 black-and-white photographic stimuli of celebrities, i.e. entertainers, politicians, royalty, and athletes. The photographs were reproduced on white horizontally oriented sheets of paper and were presented one-at-a-time to the participants. Participants were given as much time as they needed to respond.

4.2.3 Famous Faces Task

Famous faces processing was tested using an experimental battery comprising three different tests: 1) The Recognition Test: in which subjects were asked to make a famous face familiarity judgment, pointing to the familiar face among three unfamiliar distracters; 2) The Famous Faces Semantic Association Test: in which subjects needed to match two famous faces, among three choices, according to profession; and 3) The Famous Faces Confrontation Naming Test: in which subjects were asked to name each face. Figure 4.1 shows example stimuli for each test.

Fig. 4.1 Examples of stimuli used in the: Famous Faces Confrontation Naming Test (A); Famous Faces Semantic Association Test (B); Recognition Test (C).

4.2.4 Image Acquisition and Preprocessing of Structural Data

MRI scans were obtained on a 1.5T Magnetom Vision System (Siemens, Iselin, NJ), a standard quadrature head coil and previously described sequences to obtain scout views of the brain for positioning subsequent MRI slices, proton density and T_2-weighted MRIs and T_1-weighted (MP-RAGE) images of the entire brain. MP-RAGE images were used in the analysis.

4.2.5 Voxel-Based Morphometry Analysis

VBM analysis included two steps: spatial preprocessing (normalization, segmentation, Jacobian modulation and smoothing) and statistical analysis. Both steps were implemented in the SPM2 software package (Wellcome Department of Imaging Neuroscience, London: http://www.fil.ion.ucl.ac.uk/spm) running on Matlab 6.5.1 (MathWorks, Natick, MA). *Ad hoc* templates and *a priori* images were created by averaging 30 age-matched normal control scans that had been normalized and segmented in the MNI (Montreal Neurological Institute) stereotaxic space. A two-step segmentation procedure was then applied to the scans in this analysis. First, T1-weighted images were segmented in native space. Each gray matter image was then normalized to the gray matter template. The parameters obtained from the gray-matter normalization were then applied to the original T1 images. Finally, the normalized images were segmented again into gray matter, white matter and cerebrospinal fluid. Gray matter voxel values were multiplied by the Jacobian determinants derived from the spatial normalization step (Jacobian modulation), in order to preserve the initial volumes. Modulated gray matter images were then spatially smoothed with a 12 mm FWHM isotropic Gaussian kernel.

All subjects were entered as a single group. Age and gender were entered as nuisance covariates. We accounted for global levels of atrophy by scaling each image by its total intracranial volume. The significance of each effect of interest was determined using the theory of Gaussian fields. We accepted a statistical threshold of $p<0.05$, (SPM family-wise error – FWE, corrected for multiple comparisons).

In order to investigate whether there were significant differences in anatomic localization and lateralization between familiarity judgments and processes that require the activation of transmodal "semantic" neurons, we entered naming, recognition, and association scores as covariates in three separate analyses. Three different statistical models were implemented to assess the global effect of total recognition score (General Recognition Effect), of total semantic score (General Semantic Effect) and the naming score (General Naming Effect). All subjects were entered as a single group regardless of clinical diagnosis.

To look for a general naming effect, we used the sum of naming scores of all subcategories as a single covariate. The general naming effect was tested using a t contrast, assuming that decreasing naming abilities would be associated with decreased gray matter volumes. We calculated the recognition and the semantic effect in an analog way.

4.3 RESULTS

4.3.1 Behavioral Data

Means of accuracy obtained at the three Famous Faces tasks are reported separately (Table 4.2) for each category of patients. Statistical analyses were conducted to test for group differences in total naming accuracy. We used a univariate analysis of variance (General Linear Model), in which we entered the sum of scores across diagnostic groups (NC, AD, CBD/PSP/DLB, FTD, MCI, PPA, SD, ALS, MNRC) as a fixed factor. Total naming scores varied significantly across groups [F(8,99) = 14,228, $p < 0.001$]. Bonferroni's method was used for post doc pair-wise group comparisons. Post hoc analysis revealed that the naming performance of SD patients was significantly lower when compared to all the other groups, apart from the AD group.

Tab. 4.2 Means and Standard Deviations of Recognition/Semantic/Naming Tests Grouped by Clinical Diagnosis

	NC (n=16)	***AD (n=12)***	***CBD/ PSP/DLB (n=10)***	***FTD (n=13)***	***MCI (n=3)***	***PPA (n=16)***	***SD (n=28)***	***ALS (n=2)***	***MNRC (n=7)***
REC	18 (1.7)	15.6 (2.2)	14.7 (3.7)	14.77 (6.1)	16.3 (2.8)	16.37 (3.8)	12 (4.6)	19 (1.4)	13.72 (4.9)
SM	18.12 (0.8)	16.42 (2.6)	18.3 (3.8)	14 (3.9)	18 (1)	16.5 (3)	12.71 (3.1)	16.5 (3.5)	15.36 (4.2)
NM	13.75 (3)	4.5 (5.4)	7.3 (4.6)	8.30 (6.8)	11 (3.6)	8.81 (6.3)	0.35 (1.8)*	13.5 (3.5)	5.63 (5)

Table 4.2 Means of accuracy for the total scores obtained by the overall group of patients (107) at the three behavioral tests with famous faces: REC=Recognition Test; SM=Semantic Association Test; NM= Confrontation Naming.

*** $p < 0.01$ vs. each of the other groups in pairwise comparisons, except AD.**

4.3.2 Voxel-Based Morphometry Data

General Recognition Effect

There was a significant positive correlation between accuracy in recognition scores and gray matter volumes (Tab. 4.3, Fig. 4.2A) in the bilateral MTG, ITG and middle temporal pole, left superior temporal pole, left IOG and right hippocampus and left fusiform ($p < .05$, FWE corrected for multiple comparisons).

General Semantic Effect

There was a significant positive correlation between accuracy in recognition scores and gray matter volumes (Tab. 4.3, Fig. 4.2B) in the right MTG, bilateral ITG, left middle temporal pole, right superior temporal pole, bilateral superior frontal gyri (SFG), left MFG and right fusiform right anterior cingulum ($p < .05$, FWE corrected for multiple comparisons)

General Naming Effect

There was a significant positive correlation between accuracy in scores and gray matter volumes (Tab. 4.3, Fig. 4.2C) in the bilateral ITG, the left superior temporal pole, the right fusiform and the right hippocampus and in the left amigdala and bilateral cerebellum.

Table 4.3 Results of the VBM Correlation Analysis

	Brain area	**MNI coordinates**			**Extend (mm^3)**	**P**	**Max T**
		x	**y**	**z**			
General Recognition Effect							

	Right middle temporal	64	-6	-16	7782	<0.001	7.52
	Right middle temporal	66	-14	-16			7.09
	Right middle temporal	52	-6	-18			7.05
	Right Hippocampus	30	-12	-12	1020	<0.001	6.44
	Left inferior temporal	-60	-18	-28	2244	0.001	6.17
	Right inferior temporal	58	-58	-16	309	0.001	6.08
	Left superior temporal pole	-40	6	-20	255	0.008	5.5
	Left middle temporal	-46	-2	-14			5.23
	Left middle temporal pole	-36	2	-42	303	0.009	5.48
	Left inferior temporal	-40	-12	-38			5.36
	Right middle temporal pole	42	16	-38	114	0.01	5.46
	Left inferior temporal	-60	-54	-10	57	0.018	5.28
	Left inferior occipital	-50	-66	-16	24	0.029	5.13
General Semantic Effect							
	Right Fusiform	30	-8	-46	10878	<0.001	8
	Right middle temporal						7.13
	Left inf temporal	-60	-10	-30	15537	<0.001	7.62
	Left middle temporal pole	-46	-8	-42			7.3
	Left middle frontal	-24	52	28	72	0.004	5.72
	Right cerebellum	50	-48	-40	33	0.016	5.3
	Right superior temporal pole	54	12	-14	48	0.02	5.25
	Right superior frontal	24	44	40	9	0.024	5.18
	Left inferior temporal	-52	-66	-18	39	0.029	5.14
	Left superior frontal	-22	64	12	21	0.029	5.13
	Right inferior temporal	56	-56	-18	21	0.03	5.12
	Right middle temporal	70	-24	-4	18	0.033	5.09
	Right anterior cingulum	4	34	22	6	0.034	5.08
	Right superior temporal pole	34	18	-28	6	0.039	5.04
	Left superior frontal	-16	46	40	3	0.04	5.04
	Right fusiform	42	-34	-26	3	0.043	5.01
	Right superior temporal pole	34	22	-30	3	0.049	4.97
General Naming Effect							
	Left amigdala	-22	-6	-14	18543	<0.001	8.4
	Left inferior temporal	-56	-8	-34			7.68

	Left inferior temporal	-42	-2	-18			7.59
	Left superior temporal pole	-42	26	-20	225	<0.001	6.43
	Right inferior temporal	40	6	-46	1083	<0.001	6.37
	Right Fusiform	30	-8	-44			5.5
	Right Fusiform	20	2	-40			5.17
	Right Cerebellum	26	-76	-54	456	0.001	5.99
	Right Hippocampus	24	-10	-12	732	0.002	5.93
	Left Cerebellum	-28	-74	-56	558	0.003	5.81
	Right Fusiform	42	-12	-40	27	0.037	5.06

Table 4.3 Note: P-values (P) and maximum T statistics (Max T) are reported for the local maximum of each cluster. P-values were controlled for FWE (in the group of 64 subjects: FWHM = 13.1 mm 14.4 mm 13.1 mm; Volume = 182193 voxels = 518.3 resels. For single clusters, which clearly extended into several areas of the brain, the local maxima in these additional areas are indicated in italics

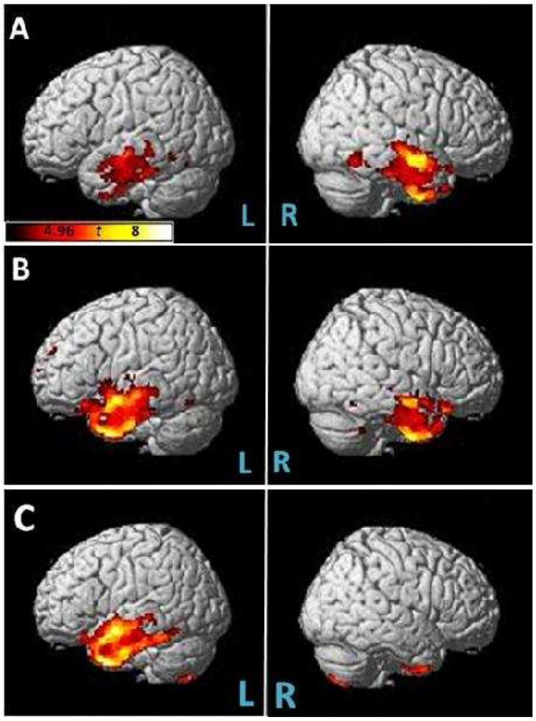


Figure 4.2: Surface rendering of the parametric maps of t-statistic for VBM analyses. General Recognition effect (A), General Semantic Effect (B), General Naming Effect (C). Height threshold and scale of t-statistic is indicated in A.

4.4 DISCUSSION OF RESULTS

We correlated accuracy in recognition, semantic and naming retrieval of different categories of faces with voxelwise gray matter volumes in 66 patients with neurodegenerative diseases using VBM.

Our data supports two conclusions: first, we identified that the semantic retrieval system elicits a network within the anterior inferior and middle temporal pole bilaterally; second, that within the left temporal lobe, naming occur more superiorly than semantic association, eliciting activations in the most posterior part of the inferior temporal lobe.

These data are consistent with previous studies which state that semantic and lexical processing of faces involved mainly temporal regions (Gorno-Tempini & Price 2001b; Perani et al. 1999) and in particular left temporal areas are crucial for naming (Howard 1995; Howard & Gatehouse 2006; Lambon Ralph, Sage, & Roberts, 2000). Studies by Damasio and colleagues (Damasio et al. 1996; Damasio et al. 2004; Tranel 2006) with a large population of patients with focal lesions suggest that the left anterior temporal lobe (ATL) is crucially involved in naming faces while the right ATL is crucial for recognizing famous faces (Tranel et al. 1997). Regardless, in order to claim the conclusions that we derived from our data we would need a linear comparison between semantic and naming processing.

Unfortunately, the procedure implemented for the VBM study does not allow us to understand the differential role of areas implicated in the processing of proper names versus biographical knowledge (i.e. semantics), because in our patient population we do not have enough patients who identify and do not name and the effect is likely to come from the SD patients who have lesions in the ATL and present impairment at the level of semantic retrieval and therefore they show inability in the generation of names (McKenna & Warrington, 1980; Semenza & Zettin, 1988; Lucchelli & De Renzi, 1992). In the behavioral analysis, SD patients showed a significantly lower performance in naming compared to the other groups (Table 4.2). Thus, the scores obtained at the Naming task by the SD group may not represent a pure measure of their deficit and therefore become useless data to put in the correlation VBM analyses.

With the fMRI experiment described in Part II, we tried to disentangle semantic and naming processes. Based on previous studies we predicted that semantic and lexical retrieval are characterized by different neural correlates.

PART II: "ATL IN SEMANTIC AND NAMING"

THE SECOND fMRI EXPERIMENT

4.5 AIMS OF THE EXPERIMENT

The occasional failure to name well-known people is a common experience in healthy individuals and suggests that naming is a process somehow independent from the identification of a person. In aphasia and in normal aging, this difficulty to retrieve names can become pathological and is called "anomia". Anomic subjects can show preserved semantic knowledge of items they cannot name, thus suggesting that, even in pathological situations, the processes of lexical and conceptual knowledge retrieval can dissociate. In these cases, anomia can be caused by lexical and phonological deficits (Howard 1995; Howard & Gatehouse 2006; Lambon Ralph et al. 2000). The dissociation between semantic knowledge and naming is not a double dissociation, though, since patients who have semantic deficits invariably show lexical retrieval impairments as well (Butterworth, Howard, & McLoughlin, 1984; Gainotti, Silveri, Villa, & Miceli, 1986; Hodges, Patterson, Oxbury, & Funnell, 1992). This finding is consistent with a serial, although interacting, naming model in which name retrieval follows semantic processing (Bruce & Young 1986; Valentine et al. 1996).

Despite the behavioral distinction between semantic and naming processes, the identification of the anatomical correlates of the two processes has been difficult and is still debated. Single case studies in which semantic and lexical retrieval processes have been studied in detail suggest that left temporal and temporo-parietal areas are crucial for naming but the precise anatomical location of the lesion was usually not detailed in these reports (Howard 1995; Howard & Gatehouse 2006; Lambon Ralph et al. 2000). Group studies (Damasio et al. 1996; Damasio et al. 2004; Tranel 2006) on a large population of patients with focal lesions suggest that the left anterior temporal lobe (ATL) is crucially involved in naming faces while the right ATL is crucial for recognizing famous faces (Tranel et al. 1997). The presumptive role of the left ATL in naming was then explained by Damasio and colleagues (Damasio et al. 2004) in their “convergence zone” account. According to this account, the left ATL would hold the “dispositions for naming”. Dispositions are the potentiality to produce the explicit mental representation of the word or its written and spoken patterns. Together, this evidence suggests that the left temporal lobe and the left inferior parietal region are involved in semantics and naming, but the specific role of each region is still not clarified.

Recent evidence from patients with PPA (Gorno-Tempini et al. 2004; Gorno-Tempini et al. 2011; Mesulam 1982, 2007;) has suggested a functional distinction between posterior temporo-parietal areas on the one hand, and the ATL on the other. Patients with left posterior temporal and parietal damage have logopenic PPA and anomia but not a multimodal semantic deficit (Gorno-Tempini et al. 2011; Henry & Gorno-Tempini 2010), whereas patients with ATL atrophy due to semantic variant PPA typically have naming problems but also a multimodal semantic deficit (Patterson et al. 2007).

While patient studies suffer from uncertainty regarding the precise anatomical location of the lesion responsible for the cognitive impairment, functional imaging studies on semantics and naming have to meet two different challenges. Firstly, semantics and name retrieval occur usually simultaneously and automatically and are difficult to dissociate in cognitive tasks (Gorno-Tempini et al. 2000; Gorno-Tempini et al. 1998; Mummery et al. 1998). However, as initially mentioned, the failure to retrieve proper names is relatively frequent in healthy individuals (Brown 1991). In this study we therefore used a paradigm involving famous people. This gave us the opportunity to dissociate semantics and lexical processing, an opportunity we would not have had with categories of non-unique objects (e.g. animals, tools, vehicles) and common names.

Secondly, the ATL is a region of the brain that is difficult to investigate with fMRI. The proximity of bone and air-filled cavities with very different magnetic susceptibilities leads to geometric distortions and signal loss, well-recognized limitations of EPI, particularly with high-field MRI (Devlin et al. 2000; Gorno-Tempini et al. 2002; Ojemann et al. 1997; Robinson et al. 2004; see Visser et al. 2010b for review). Therefore, the use of standard EPI may preclude the detection of task-related activity in the ATL, especially when using a higher field magnet. Studies using more sophisticated image acquisition techniques (Binney et al. 2010; Simmons et al. 2010; Visser et al. 2010a) succeeded in finding ATL activation for semantic representations.

The main aim of this study was to characterize the role of the left temporal and inferior parietal regions in semantics and name retrieval using blood-oxygen-level-dependent (BOLD) fMRI. To address this, we first optimized BOLD sensitivity of 4 T gradient echo EPI in ATL areas, considering slice thickness, echo time, polarity of the phase-encode gradient, slice angle and shimming. We then used the optimized fMRI protocol to study semantic-biographical and proper name retrieval in a group of 21 healthy subjects. We asked subjects to perform a semantic (profession) same-different matching task in the scanner to ensure subjects' performance and attention to semantic information. The ability to identify and name the famous faces that were shown was assessed individually in a post-scanning behavioral test, presenting all famous faces once again.

Based on this post-scanning assessment, we were able to compare the BOLD response during trials in which celebrities could be correctly identified and named, to trials in which faces were correctly identified without the name being recalled. Based on previous findings in PPA (Gorno-Tempini et al. 2008; Gorno-Tempini et al. 2011; Patterson et al. 2007), we predicted that a network of regions, including bilateral ATL, left posterior temporal and the inferior parietal regions, would be activated by the semantic matching task but that the more posterior left lexical and phonological regions would show greater response for name retrieval.

4.6 METHODS

4.6.1 Subjects and Procedure

Twenty-one native Italian-speaking volunteers took part in the study (7 males; mean age: 28.4 years, range: 19-49 years). All participants were right-handed, had normal or corrected-to-normal vision, and none reported a history of head injury or other neurological problems.

4.6.2 Stimuli

Three types of stimuli were used: famous faces, unknown faces, and scrambled faces. Black and white photographs of 105 famous faces of Italian and internationally known celebrities were selected. Their names are listed in Appendix B, Table 2. Thirty-six healthy controls (ages ranging from 25-70) were asked to identify, name and rate the faces for familiarity. All of the celebrities belong to one of the following categories: politics, entertainment, sports, clergy, royal family, journalism, and business. The famous faces were then assembled in pairs of celebrities belonging to the same category (65 picture pairs: 15 pairs of women, and 50 pairs of men) or belonging to different categories (65 picture pairs: 16 pairs of women, and 49 pairs of men). We selected pictures in order to maximize attention and FF semantic processing. See figure 4.3 A,B for example pairs, and Appendix B, Table 2 for a complete list of pairs.

In order to create picture pairs of unknown faces, we chose 150 grayscale pictures of unfamiliar faces (74 females and 76 males) from the “Multiracial Faces” database created by the Tarrlab at Brown University (*Stimulus images courtesy of Michael J. Tarr, Center for the Neural Basis of Cognition, Carnegie Mellon University, http://www.tarrlab.org/*). Four types of picture pairs were created: same females, same males, different females and different males. Picture pairs of the same person were taken from slightly different perspectives and showed the person with slightly different facial expressions. In contrast, picture pairs of different persons were selected to be as similar as possible (for example pairs see figure 4.3 C, D). This allowed us to increase task difficulty, matching it as closely as possible to the level of difficulty in the condition FF. Unfamiliar faces were matched with famous faces for age, nationality and confounding factors such as position of the face, expressions, luminosity and the presence of glasses or earrings. We selected 80 picture pairs (i.e. 20 of each type) that were most consistently perceived as the same or different person in tests with a sample of 18 healthy subjects.

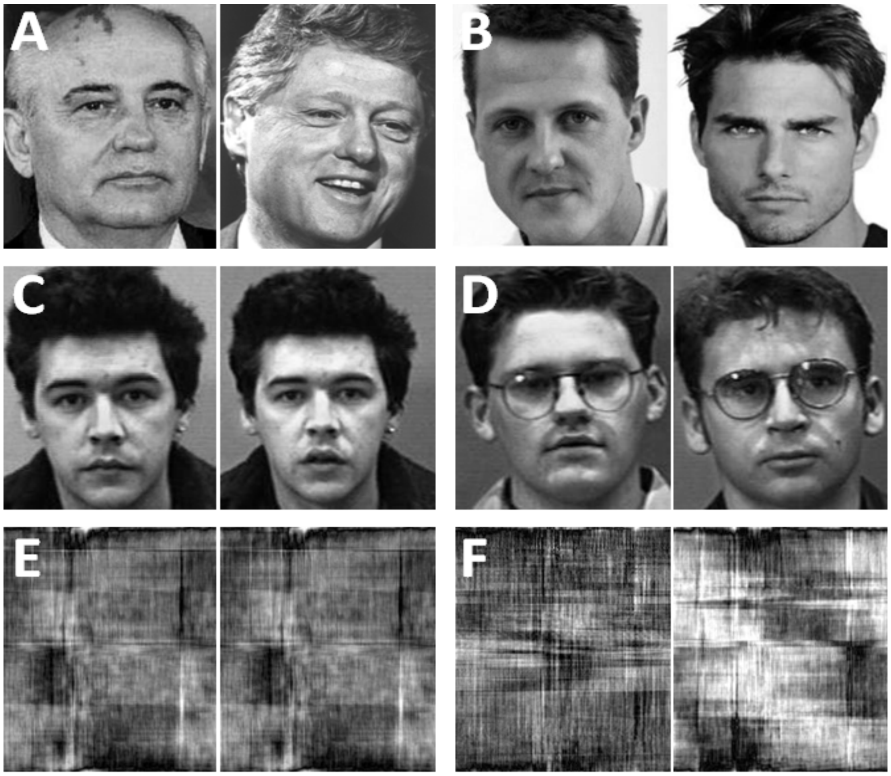


Figure 4.3 Examples of stimulus pairs for the three conditions FF (A,B), UF (C,D), and SF (E,F). Subjects had to do a same/different judgment regarding the persons' profession (condition FF), the identity of the faces (condition UF), or the identity of the images (condition SF). Respectively one matched pair (A,C,D) and one unmatched pair (B,D,F) is shown for each condition. For details see text.

The stimuli for the control condition SF were created by scrambling both types of faces, i.e. famous and non-famous faces (see Fig 4.3 E,F). To maintain a constant spatial frequency power density spectrum in these scrambled faces, the manipulation was performed on the phases of each spatial frequency in the image. The phase of each lower frequency component, starting from the lowest frequency, was swapped with the phase of a corresponding higher frequency component, starting with the highest. A pattern was obtained that was no longer recognizable as a face. The scrambled faces were arranged in 20 pairs of different pictures and 20 pairs of identical pictures.

All pictures were scaled to 315 x 260 pixels (visual angle: 6.05° x 4.85°). Pairs of pictures were displayed next to each other, in the centre of the visual field and on a black background.

Visual Stimulation

Stimuli were back-projected onto a screen with a liquid-crystal projector at a frame rate of 60 Hz and a screen resolution of 1,280 x 1,024 pixels. Participants viewed the stimuli binocularly via an adjustable mirror mounted on the head coil. Stimulation was programmed using the in-house software ‘‘ASF’’ (Schwarzbach in press), based on the MATLAB Psychtoolbox-3 (Brainard 1997) for Windows.

4.6.3 Procedure

All participants underwent 2 functional scanning runs with the task, each of 14.2 minutes duration. After the scanning session, subjects were presented with each famous face to assess identification and naming scores.

4.6.4 Tasks

A mixed blocked/event-related design was used. There were three different conditions, which were presented in blocks. At the start of each block, a written instruction was shown for 2 seconds to inform subjects of the upcoming task (“famous faces” or “unknown faces”). Within each block, trials were jittered to allow analysis based on different responses. Each condition involved the presentation of pairs of pictures. In the first condition, two famous faces were presented and subjects were asked to perform a semantic task, deciding whether the people shown had the same profession (condition FF). In the second condition, two unknown faces were presented and subjects were asked to perform a same-different visual matching task, deciding whether the images were of the same person (condition UF). In the third condition, two scrambled faces were presented and subjects were asked to perform a perceptual task, deciding whether the two images were identical (condition SF). Subjects were instructed to press a key with their right index finger to indicate a “Yes” response, and to press a key with the left index finger to indicate a “No” response. Response times were collected using in-house software ‘‘ASF” (Schwarzbach 2011), based on the MATLAB Psychtoolbox-3 (Brainard 1997) for Windows.

Of the 21 subjects, 13 were scanned with 80, 80 and 40 trials respectively in the conditions FF, UF, and SF. The remaining 8 subjects were presented with 130, 40, and 40 picture pairs in the same conditions. In this second group, the larger number of picture pairs was used for the FF condition because trials in this condition were to be subdivided in the analysis according to the naming and identification abilities of each individual subject, assessed after the scanning session (see below for details).

Each picture pair was presented at the centre of the screen on a black background, for 3.5 seconds. Inter-trial-intervals were jittered in a range of 2-7 seconds (mean = 4.5 seconds). A black screen with a fixation-cross in the centre was shown during these periods. Each scanning run contained 15 blocks: 5 in each condition. Each block of a given condition type contained the same number of trials.

Subjects were familiarized with the task before the experiment using a separate set of stimuli. They were instructed to respond as quickly as possible, and to respond even if they were unsure about their decision. For famous faces, they were asked to concentrate on the semantic task without thinking about the name of the person.

Post-scanning behavioral assessment of identification and naming ability

After the scanner session, subjects were again presented with all the famous faces they had been shown in the fMRI experiment. Each face was presented on a computer screen for a maximum of 5 seconds, and subjects were asked to state the proper name and the profession/category of the person shown. A face was considered as identified correctly if the profession/category was stated correctly. These data were used to categorize trials of condition FF individually for each subject, depending on their ability to name and identify the faces shown in the corresponding picture pair. This categorization was critical for testing our main hypothesis on semantic and lexical processing and is explained in detail below.

4.6.5 Behavioral Data

Subject responses were collected with fMRI-compatible response pads for the left and right hand (Lumina LU400-PAIR, Cedrus, United States). Reaction time and accuracy of response was calculated for the different conditions and compared among conditions using one-way repeated measures ANOVA. Post-hoc analysis was performed using t-tests and Bonferroni correction.

4.6.6 Trial Splitting and Hypothesis Testing

The aim of our study was to reveal, in a first analysis, brain areas involved in the processing of famous faces in general. In a second analysis, we attempted to distinguish areas contributing to lexical retrieval. Both these analyses required the classification of trials in the FF condition depending on the subjects' ability to correctly identify and/or name the famous faces in the post-scanning behavioral assessment. Although we collected behavioral responses to the profession-matching task in the scanner, we considered the post-scanning explicit description as a more specific index of semantic knowledge. Furthermore, naming could only be assessed post-scanning. The schemes of trial splitting for our two major analyses are described below.

Trial Splitting for Analysis 1 (Famous Faces Network):

In the first analysis, we were interested in revealing the overall effect of semantic processing, independent of lexical retrieval. To do so, we isolated trials in which subjects knew both famous faces, and therefore had access to the related semantic information. In order to do this, trials in condition FF were split into two groups: trials in which both faces were correctly identified in the post-scanning assessment (FF-known); and trials in which subjects could not identify both faces correctly (FF-unknown). Contrasting FF-known against condition SF would then reveal the overall network involved in processing famous faces. The range of processes captured by this contrast would include high level visual processing specific to faces as well as semantic and lexical retrieval processes. A conjunction of this contrast, i.e. FF-unknown vs SF, with the contrast of condition UF versus SF would allow isolation of high level visual processing common to both tasks. A third contrast, between FF-known and condition UF, could finally reveal all semantic and lexical processes which go beyond the pure visual processing of faces.

Trial Splitting for Analysis 2 (Naming Effect):

In the second analysis, we were interested in identifying networks contributing to lexical retrieval processes. In order to study lexical retrieval, without confounding it with different levels of semantic processing or the task performed in the scanner, we included only trials in which both faces could be correctly identified (i.e. FF-known), but split these trials further into two subgroups: trials in which both faces were correctly named in the post-scanning testing (FF-named); and trials in which subjects could not name both faces (FF-unnamed). The ability to retrieve proper names could then be captured by contrasting FF-named against FF-unnamed. In order to avoid effects being compromised by noise, we conducted this second analysis only for subjects who had at least 16 trials of each type. There were 12 subjects who met this criterion and were therefore included in the second analysis.

Since FF trials were classified as known, unknown, named or unnamed based on the post-scanning session we included in the analyses also trials in which subjects gave an “incorrect” performance in the scanner. Since post-scanning performance showed that subjects actually knew the celebrities, these “incorrect” responses on the semantic matching task in the scanner were really atypical categorizations since celebrities can have more than one profession (e.g. actor and singer). Similarly, FF trials in which subjects did not identify both faces post-scanning were classified as FF-unknown and excluded from the analyses, regardless of performance in the scanner.

4.6.7 fMRI Statistical Analysis

Effects at the individual subject level were estimated by fitting a General Linear Model for each voxel using SPM5. The two functional runs for each subject were concatenated. The design matrix consisted of one explanatory variable (EV) per experimental condition and run. The number of EVs was different for our two analyses, depending on the scheme of trial splitting in condition FF (see above). For the first analysis, 4 EVs were used, corresponding to the conditions FF-known, FF-unknown, UF, and SF. The EV for condition FF-unknown was included in the model as an effect of no interest. For the second analysis, 5 EVs were used, corresponding to the conditions FF-named, FF-unnamed, FF-unknown, UF, and SF. Here, only the first two EVs were of interest for the experimental hypothesis. All of these EVs were created by convolving a boxcar function (corresponding in duration to the stimulus presentation) with a canonical hemodynamic response function (HRF). For each run, 6 additional regressors were included, corresponding to the head motion parameters estimated during the realignment step, and one variable encoding the mean of the run. Model parameters were estimated through restricted maximum likelihood (ReML) using an autoregressive AR(1) model to correct for non-sphericity arising from serial correlations. The data and model were high-pass filtered with a cut-off frequency of 1/128 Hz.

Contrast images calculated in the first level of analysis were entered in a random effects analysis, to infer effects on the population level. This second level of analysis was conducted using the flexible-factorial design implemented in SPM5. Contrasts at the second level were calculated at the single voxel level and corrected for multiple comparisons. For the Analysis 1 (i.e. semantic contrast), we corrected for Family-Wise Error (FWE) at $P<0.05$, taking advantage of the ability of FWE to detect small clusters that are reliably activated. For the Analysis 2 (i.e. lexical contrast), we did cluster size correction because we did not anticipate strong effects given that naming was an implicit process, and given the lower number of trials. Following a whole brain uncorrected voxel-wise with a threshold at $p<0.01$, we only activations surviving at $p<0.05$ (FWE) at the cluster level were accepted as significant. We also performed a small volume correction to reduce the risk of false negative results in the left temporal lobe. The ATL volume included the temporal pole and extended posteriorly to the -10mm MNI coordinate, in order to include also the MTG cluster found in the semantic contrast between conditions FF versus UF

All results were displayed with MRIcron (Version 7 July 2009, Chris Rorden, http://www.mricro.com), overlaying functional data on the provided single subject T1 template. Anatomical labels were determined based on visual inspection of the data with reference to the atlas of Duvernoy (1999).

4.7 RESULTS

4.7.1 Behavioral Data

Based on the post-scanning performance, we first sorted FF trials in FF-known and FF-unknown (Analysis 1, overall famous faces network). For the lexical retrieval analysis (Analysis 2, naming effect), we split the FF-known trials in FF-named and FF-unnamed (see methods above for more details). The number of FF-known trials ranged from 79-130. FF-unknown trials were generally fewer and even absent for some subjects and were not included in the analyses. After splitting FF-known further, we had enough FF-named (range from 16-97) and FF-unnamed (range from 16-63) trials for twelve subjects. The proportions of FF-named and FF-unnamed trials are shown for these 12 subjects in figure 4.4B.

Performance in the scanner was analyzed for trials split based on the post-scanning results described above. Subjects responded faster and more accurately during trials of type FF-known compared to trials of type FF-unknown (Fig. 4.4A). This finding was to be expected since subjects' performance on the trials in which they do not know the celebrities should depend mainly on guessing, i.e. "real errors". Compared to trials of type FF-known, subjects reacted faster in conditions UF [$t(20)=-12.14$, $p<0.001$] and SF [$t(20)=-11.21$, $p<0.001$]. Accuracy was also higher in UF [$t(20)=4.82$, $p<0.01$] and SF [$t(20)=3.28$, $p=0.02$] when compared to FF-known. Since FF-known were correctly recognized post-scanning, "errors" in this condition are likely due to "atypical" categorization of celebrities with multiple professions (see methods). These findings nevertheless indicate that the UF and SF conditions were less effortful. No significant difference was found between conditions UF and SF.

For analysis 2 (Fig. 4.4C), there was no significant difference in accuracy during scanning for the FF-named and FF-unnamed [t(11)=2.07, p=0.38], but reaction times were significantly faster [t(11)=-3.83; p=0.016] for FF-named. This finding suggests greater effort for the FF-unnamed trials. As a consequence, we argue that any positive effect of naming on the functional data (i.e. FF-named > FF-unnamed) cannot simply be explained by task difficulty, which has the opposite sign.

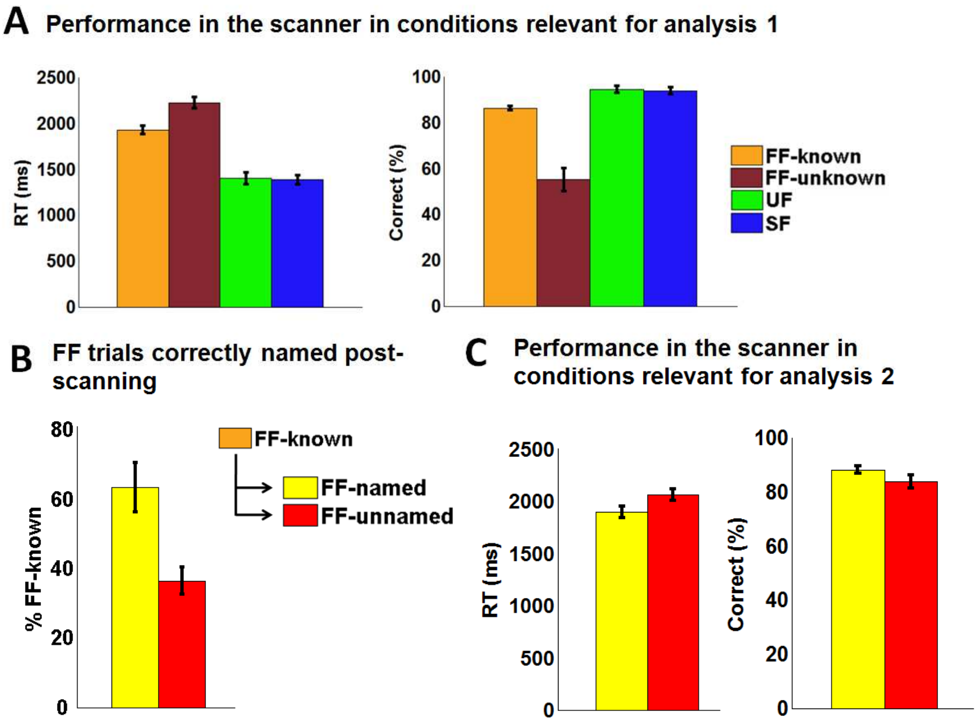


Figure 4.4 Reaction times and accuracy in the scanner is shown in panel A for all 21 subjects and in all conditions (i.e. conditions FF, UF, and SF). According to the post-scanning assessment, trials of condition FF were split individually for each subject into a first group in which subjects knew the pair of presented famous faces (FF-known) and a second group, in which they did not know both faces (FF-unknown). The second group of trials was considered "real" errors, since subjects could do the semantic matching task inside the scanner only on guessing. Consequently, these trials were excluded from the analysis of functional data. Analysis 1 investigated the overall famous faces network. For Analysis 2 which investigated the naming effect, the trials with known famous faces were further split into two subgroups (i.e. FF-named, FF-

unnamed) according to subjects' ability to name them in the post-scanning assessment. Panel B shows the percentages of FF trials falling in these subgroups for the 12 subjects included in Analysis 2. Panel C shows for the same subjects the performance in the semantic matching task done during the scanning session. For details see text.

4.7.2 Functional Data

Table 4.4 Activations Associated with the different contrasts performed for Analysis 1

Contrast	**Brain area**	**MNI coordinates**			**Extend (mm^3)**	**P**	**Max T**
		x	**y**	**z**			
FF vs. SF (including 21 subjects)							
	Right fusiform	42	-51	-24	15282	0	15.56
	Right inferior occipital	42	-78	-12			13.78
	Right middle temporal	45	-53	15			9.17
	Left precuneus	-3	-54	15	54756	<0.001	12.98
	Left amygdala	-21	-6	-12			10.25
	Left thalamus	-6	-9	3			9.88
	Right amygdala	24	-6	-15			8.97
	Right hippocampus	33	-12	-18			8.72
	Left caudate	-12	9	6			8.72
	Left hippocampus	-30	-15	-15			7.99
	Right caudate	12	12	6			7.08
	Left inferior frontal (pars triangularis)	-45	24	21	12150	<0.001	11.84
	Left fusiform	-42	-72	-18	7749	<0.001	10.92
	Left inferior occipital	-42	-81	-15			10.68
	Left occipito-parietal junction	-36	-75	42	4644	<0.001	9.67
	Right inferior frontal (pars orbitalis)	33	33	-12	1296	<0.001	9.05
	Left temporal pole	-39	12	-33	1215	<0.001	9.04
	Right middle temporal	54	-9	-21	1701	<0.001	8.2
	Left middle temporal	-57	-6	-18	1269	<0.001	7.65
	Right medial frontal	6	42	-18	1944	<0.001	7.43
	Right temporal pole	36	12	-33	405	0.001	6.87

	Right inferior frontal (pars triangularis)	45	24	21	648	0.003	6.42
Conjunction(FF vs. SF; UF vs. SF) (including 21 subjects)							
	Right fusiform	42	-51	-24	9450	<0.001	15.56
	Right inferior occipital	42	-78	-12			13.78
	Right middle temporal	48	-66	12			6.83
	Left fusiform	-42	-72	-18	5940	<0.001	10.92
	Left inferior occipital	-42	-81	-15			10.68
	Right amygdala	24	-6	-15	2889	<0.001	8.97
	Left amygdala	-21	-6	-15	1728	<0.001	8.96
	Right inferior frontal (pars orbitalis)	36	33	-15	324	<0.001	6.97
	Right inferior frontal (pars triangularis)	45	27	18	405	0.004	6.29
FF vs. UF (including 21 subjects)							
	Left precuneus	-3	-54	12	128466	<0.001	15.91
	Left caudate	-12	6	6			12.27
	Left thalamus	-9	-6	6			11.87
	Left posterior cingulum	-3	-36	30			9.48
	Left inferior frontal (pars triangularis)	-39	27	6			9.3
	Right caudate	18	21	-3			9.18
	Left inferior frontal (pars orbitalis)	-36	33	-12			7.86
	Left temporal pole	-39	15	-33			7.53
	Left temporo-parieto-occipital junction	-33	-72	39	9450	<0.001	11.48
	Left middle temporal	-60	-6	-18	2403	<0.001	8.56
	Right middle temporal	60	-3	-15	1809	<0.001	7.54
	Left medial orbitofrontal	-3	60	-9	2025	<0.001	7.18
	Right temporo-parieto-occipital junction	45	-66	30	2457	<0.001	7.08
	Left superior frontal	-21	57	0	270	<0.001	7.01
	Left middle temporal	-54	-39	-6	918	0.004	6.25
	Right lingual gyrus	18	-45	-9	324	0.005	6.23
	Right hippocampus	36	-12	-18	81	0.02	5.72
	Right middle temporal	48	6	-27	54	0.026	5.63

FF vs. UF (including 12 subjects)							
	Left cuneus	-6	-66	27	38664	<0.001	12.81
	Left precuneus	-6	-57	12			12.61
	Left posterior cingulum	-3	-39	30			7.63
	Left inferior frontal (pars triangularis)	-42	24	24	2160	<0.001	8.6
	Left cingulum	-9	-18	27	351	<0.001	8.16
	Right middle temporal	60	0	-15	729	<0.001	8.04
	Left parieto-occipital junction	-33	-72	42	2889	<0.001	7.65
	Left temporal pole	-42	15	-33	540	0.001	7.08
	Right angular	51	-66	27	729	0.004	6.57
	Left middle temporal	-57	-6	-18	405	0.005	6.47
	Left superior frontal	-24	54	3	108	0.005	6.46
	Right putamen	15	15	-3	567	0.008	6.27
	Left medial orbitofrontal	-3	54	-12	837	0.01	6.18
	Left inferior frontal (pars triangularis)	-39	27	3	81	0.019	5.93
	Left inferior frontal (pars orbitalis)	-39	33	-12	54	0.026	5.81
	Left caudate	-6	9	3	297	0.029	5.77

Table 4.4 Note: P-values (P) and maximum T statistics (Max T) are reported for the local maximum of each cluster. P-values were controlled for FWE (in the whole group of 21 subjects: FWHM = 12.1 mm 12.5 mm 11.6 mm; Volume = 42101 voxels = 566.7 resels; in the subgroup of 12 subjects: FWHM = 13.0 mm 13.4 mm 12.3 mm; Volume = 43152 voxels = 478.1 resels). For single clusters, which clearly extended into several areas of the brain, the local maxima in these additional areas are indicated in italics.

Consistent with previous studies, perceptual processing of faces involved mainly the fusiform and occipital cortex (Kanwisher et al. 1997; McCarthy et al. 1997), while semantic and lexical processing went well beyond these visual association regions, including our temporal and parietal regions of interest (Gorno-Tempini & Price 2001b; Perani et al. 1999).

As stated above, we included only 12 subjects in our second analysis on lexical retrieval. However, we first wanted to show that the subgroup was a representative sample of the whole group. For this reason, we calculated the contrast between trials of type FF-known and condition

UF again for the subgroup (Table 4.4). The overall pattern of activation in this contrast was similar, although some clusters were activated to a lesser extent. Most importantly, stable activation clusters were still present in the left temporal pole, the bilateral anterior MTG, and the bilateral TPJ. These were areas predicted to be involved in famous face processing (Gorno-Tempini et al. 1998), and our particular aim was to disambiguate the role of these areas in semantic and lexical processing respectively.

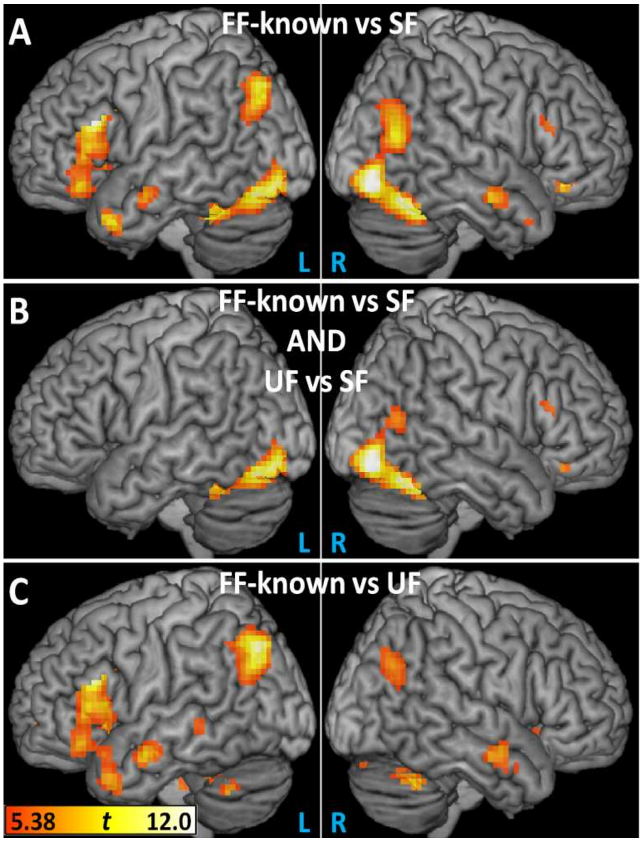


Figure 4.5 Surface rendering of the parametric maps of t-statistic for Analysis 1. Overall effect of processing famous faces in 21 subjects (A, contrast FF-known vs. SF); effects due to high level visual processing of faces in 21 subjects (B, conjunction between FF-known vs. SF, and UF vs. SF); and effects due to semantic and/or lexical processes in 21 subjects (C, contrast FF-known vs. UF). Height threshold and scale of t-statistic is indicated in C. For details see text.

Results of Analysis 2 (Naming Effect)

The aim of the second analysis was the identification of brain areas that would show greater activation for implicit naming. For this purpose, we compared the BOLD signal for FF-known trials that were named in the post-scanning session (FF-named) versus the ones that were correctly identified but not named (FF-unnamed) post-scanning. Data from 12 subjects were included in this analysis (for explanation see ‘behavioral results’). Using cluster size correction (see methods) this analysis revealed one large cluster (size = 269 voxels = 7263 mm^3), comprising areas in the left inferior parietal (TPJ) and in the left posterior MTG (Fig. 4.6A). To reduce the risk of a false negative result in the left ATL caused by signal noise, we used also a small volume correction including only the left ATL. This analysis confirmed the absence of any effect in that region.

In order to visualize the size of the lexical retrieval effect, BOLD signal was calculated within two regions of interest (ROI) centered at the local maxima of the activation cluster in the posterior MTG (Fig. 4.6B, MNI coordinates: x -63; y -54; z 6) and in the TPJ (Fig. 4.6C; MNI coordinates: x -42; y -60; z 48). ROIs were defined as all voxels within a 10 mm sphere around the local activation maximum, and being located within the overall activation cluster.

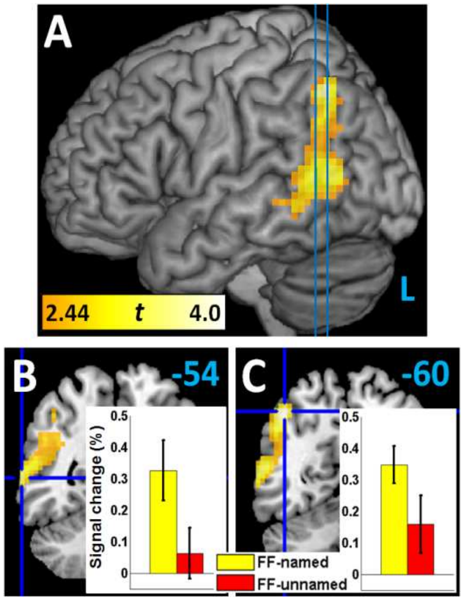


Figure 4.6 Effect of naming (Analysis 2). Surface rendering of the significant cluster revealed by cluster thresholding at p=0.01 (A). Blue lines indicate the anterior-posterior position of coronal sections shown in panel B and C. The local maxima in the MTG (B) and in the TPJ (C) are indicated by blue cross-hairs. Percent signal change is shown for masked 10 mm spheres in both local maxima.

Post-Hoc Analyses Results of Analysis 1 (Famous Faces Network)

To identify the overall effect of famous face processing (e.g. perceptual processing, structural encoding, face recognition, semantic, lexical and phonological retrieval, emotional processing) we contrasted FF-known versus SF (Fig. 4.5A, Table 4.4). The areas revealed by this contrast were bilateral fusiform and IOG, left occipito parietal junction (OPJ), left precuneus, bilateral amygdala and hippocampus, bilateral caudate, bilateral IFG, right MFG, bilateral MTG, and bilateral temporal pole (TP).

To isolate further the effect of visual processing of faces, we calculated the conjunction of contrasts FF-known versus SF, and UF versus SF (Fig. 4.5B, Table 4.4). Since semantic processing of UF is not possible, this conjunction should identify perceptual areas. Common activations were present in bilateral fusiform and IOG, right MTG, bilateral amygdala, and right IFG.

Finally, to identify the effect of semantic and covert lexical processes, we contrasted FF-known versus UF (Fig. 4.5 C, Table 4.4). Areas revealed by this contrast were left IFG, left TP, bilateral TPJ, bilateral MTG, left precuneus, thalamus, and posterior cingulum, bilateral caudate, left medial orbitofrontal gyrus, left SFG, right lingual gyrus and hippocampus.

A supplementary analysis was carried out to investigate how FF familiarity could contribute to the naming effect. Familiarity ratings were collected during stimulus assembly (see above). The average familiarity rating of the two FF shown in each trial was covaried out at the single subject level by adding an additional explanatory variable. The clusters in the MTG and TPJ were still activated for FF-named versus FF-unnamed, though their volumes were reduced (4023 mm3 and 891 mm3 respectively). Only the MTG survived correction for multiple comparisons at the cluster level. So, familiarity might have contributed to the effect found in the MTG and TPJ, but could not explain it entirely.

We measured BOLD sensitivity in the ATL (because of EPI protocol optimization), MTG and in the TPJ to investigate whether the lack of a significant ATL effect in naming could be explained by lower overall signal in the ATL. This is actually unlikely since ATL optimization is expected to reduce BOLD signal in areas where there is no susceptibility artifact, such as the MTG and TPJ. We nevertheless investigated this possibility by comparing tSNR in three ROIs along the left temporal-parietal lobes. The first ROI was the left ATL, defined anatomically as for the optimization study. The other two ROIs were the MTG and TPJ clusters. The tSNR was calculated from resting state data collected during the optimization study. The average tSNR value in the ATL ROI was significantly higher than that in the other two ROIs (Figure 4.7). Thus, the lack of significant lexical retrieval effect in the ATL cannot be explained by lower BOLD sensitivity in this area.

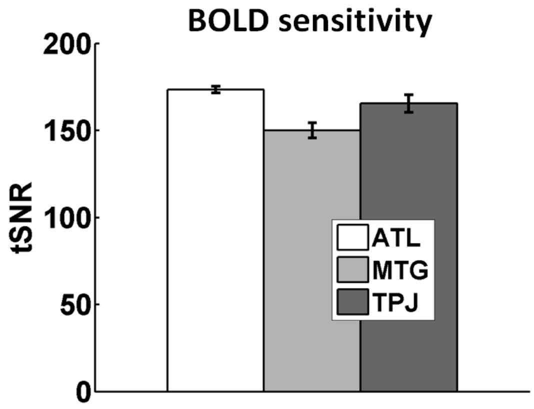


Figure 4.7 Average tSNR values and standard errors are shown for 3 ROIs along the anterior-posterior axis of the left temporal lobe. For details see text.

4.8 DISCUSSION OF RESULTS

The main goal of our study was to identify the differential role of the ATL and posterior temporo-parietal regions in processing semantic (biographical information) and lexical (proper names) information. We applied an ATL-optimized fMRI protocol and showed that a network of regions in the bilateral temporal lobes is involved in recognizing, identifying and naming famous people. The ATL bilaterally was mainly involved in semantic processing, while more posterior left temporo-parietal regions were modulated by lexical retrieval processes. Here we discuss the implications of our results for understanding the functional neuroanatomy of semantic processing and lexical retrieval.

We found that the ATL was involved in semantic processing irrespective of whether or not names could be retrieved for the identified famous faces. Both the left and right ATL responded to processing semantic information, regardless of naming ability, suggesting a major role of both ATLs in person-related semantic processing. Patients with semantic variant PPA (or semantic dementia) and ATL atrophy indeed have severe problems identifying objects, including people. While most patients with semantic variant PPA have bilateral or left greater than right ATL atrophy and show deficits for objects and people (Patterson et al. 2007), some patients with greater right ATL atrophy show greater difficulty in processing biographical information regarding people (Evans et al. 1995; Gainotti et al. 2003).

Our results support the view that both hemispheres play an important role in retrieving person-specific semantic information, although they do not exclude that different types of information are processed by each hemisphere (for related literature see Brambati, Benoit, Monetta, Belleville & Joubert 2010; Gainotti 2007). Connectivity of the ATL with visuo-spatial and emotional networks in the right and language areas in the left hemisphere might determine a preferential role of this region in processing visual, verbal and social information (Gainotti 2007). Further, our results can be accommodated in relation to recent cognitive models of ATL function. One prominent model states that the ATL acts as a semantic hub, forming amodal semantic representations, which would enable semantic generalization on the basis of conceptual structure rather than modality-specific features (Lambon Ralph & Patterson 2008; Patterson et al. 2007). Another prominent account claims that the ATL supports social conceptual knowledge in general (Simmons et al. 2010). Our study supports a central role of the bilateral ATL in semantic processing. Differences in emotional valence between famous and non-famous faces might have contributed to the activation in the ATL.

We found that covert naming modulated activation in more posterior parts of the left temporal lobe and TPJ. These findings are consistent with a role of these regions in the retrieval and encoding of phonological forms of lexical items. A view, suggested by Benson (1979) and Geschwind (1967) in their seminal descriptions of different types of anomia and their neural correlates. Also, the finding that these areas are often damaged in patients with Wernicke's aphasia or transcortical sensory aphasic, who evolve to anomic aphasia (Albert et al. 1981), is consistent with this idea.

There is no detailed study of semantic memory in the old cases, but patients with aphasia due to vascular posterior left perisylvian damage do not usually report object or face identification deficits in everyday life. Similarly, patients with logopenic PPA show impaired naming, but relatively spared nonverbal semantic association abilities (Gorno-Tempini et al. 2004; Henry and Gorno-Tempini 2010). Given their atrophy being most prominent in posterior temporal and inferior parietal areas, the symptoms of these patients give further support for the role of these areas in lexical-phonological processing.

However, many functional neuroimaging studies, including ours, have shown activations in the left inferior parietal regions in semantic tasks and a role of this region in semantics has been postulated (Binder et al. 2009;). Most of these studies were not designed to differentiate regions that would respond preferentially to naming and semantic categorization. When we performed this specific contrast the left TPJ was most involved in naming. Our results therefore suggest that the left inferior parietal region (together with the ATL, the IFG, medial frontal and subcortical areas) is part of the semantic network but that, within this network, it is particularly involved in name retrieval.

Additional roles in language processing have been suggested for other regions of the inferior parietal lobe. For example, the ventral SMG might have a role in articulation and higher phonological processing (see Price 2010 for review). This area was not activated in our experiment, possibly because the covert retrieval of proper names did not reach the phonological/articulatory level.

One of the strengths of our study was the idea to utilize famous people as stimuli. Famous faces indeed allowed us to dissociate semantics and naming in healthy subjects, as lexical retrieval failure for proper names is common. This would not have been possible with other object categories (e.g. animals, tools, etc.) and common names. However, dissociations between semantic and name retrieval processes for common and proper names have been reported (see Semenza 2006 for review). Whether our findings generalize to all lexical items remains to be established.

A limitation of our study might be that naming abilities could be tested only after the scanning session. The naming ability outside the scanner might have been slightly better due to the repeated presentation of all stimuli, or a bit worse due to fatigue. Misclassification of faces as either named or unnamed might have slightly weakened the statistical contrast between these trials. It cannot be excluded that increasing sensitivity could reveal an effect for naming also in the anterior temporal lobe. However, we suggest that in this case the effect in the posterior temporal and parietal areas would increase as well. The main conclusion that the posterior temporal and parietal areas play the predominant role in the retrieval of proper names would then remain valid.

We want to emphasize however that our results do not imply that these posterior areas exclusively accomplish lexical processing. For instance, earlier stages of lexical processing involving intermediate representations between semantic and phonological levels (termed *lemmas* by some researchers) may depend on more anterior temporal regions (Damasio et al. 1996; Damasio et al. 2004). In a recent study using voxel-based lesion-symptom mapping, Schwartz and colleagues (Schwartz et al. 2009) found that damage to anterior and middle temporal regions was predictive of semantic naming errors (e.g. naming a cat as “dog”), suggesting a role in lemma retrieval (though cf. Tsapkini, Frangakis, & Hillis, 2011) who did not find an anterior temporal locus for semantic errors in acute stroke patients. If anterior and mid temporal regions are involved in intermediate stages of lexical access, such regions would likely be undetected by our paradigm because they may be activated even when the phonological form of a name cannot be retrieved.

In summary, our data suggest that the ATL is mainly involved in semantic processing, while lexical retrieval is attributed mainly to areas in the posterior-temporal lobe and the temporo-parietal junction. One can therefore speculate a cascade of processes in the temporal lobe network, starting with semantic integration in the ATL, and leading further to the activation of lexical representations in the posterior portion of the MTG and phonological assembly in the posterior superior and TPJ.

4.9 CONCLUSION

Using an imaging sequence optimized for the ATL and considering the participants' ability to identify and name famous faces, we were able to study the neural basis of semantic memory and lexical retrieval and in particular the differential roles of anterior and posterior temporal regions in these processes. Our findings indicate that the ATL is involved in semantic processing while more posterior left temporal and temporo-parietal regions are involved in lexical retrieval processes.

CHAPTER 5: OVERALL DISCUSSION AND CONCLUSION

5.1 AIMS OF THE THESIS

Most current theories assume that conceptual knowledge is represented in a large distributed network, but the underlying organizational principles of semantic memory remain controversial.

The experiments presented in this thesis investigated the neural underpinnings of features processing (movement and place). In particular we tried to extend our understanding of how action concept is represented and processed in the human brain and we designed a procedure to differentiate regions that would respond preferentially to naming and semantic processing.

One prominent neural model of semantic knowledge states that the ATL acts as a semantic hub, storing information about the similarities and differences between categories rather than peculiar property information of specific attributes (Lambon Ralph & Patterson 2008; Patterson et al., 2007). Furthermore, neuropsychological data on patients with semantic impairments suggest that the most anterior portions of the temporal cortices critically support human conceptual knowledge.

Unfortunately, because of its different magnetic susceptibilities, ATL represents a difficult region to investigate with fMRI. Therefore, in this thesis we established an optimized ATL sensitive fMRI acquisition protocol at 4T (Chapter 2), applying an event-related paradigm to minimize susceptibility-loss effects in the ATL and to increase time-series signal-to-noise ratio (tSNR).

With the first fMRI experiment (Chapter 3), we investigated the processing of movement and place features manipulating stimulus category – animals, tools and nontools – with the aim to stress action knowledge for those categories of objects to which the movement feature is not typically associated with (i.e. animals and nontools).

In the second study (Chapter 4), we used a paradigm involving famous faces (unique entities) to investigate the cerebral substrates of semantic biographical and proper name retrieval. Considering data on patients (Part I) and on normal subjects (Part II), we tried to identify the differential role of the anterior temporal lobe (ATL) and posterior temporo-parietal regions in processing semantic (biographical information) and lexical (proper names) information.

The results of the first experiment suggested that the retrieval of encyclopedic (place) and perceptual (movement) knowledge activates two different networks, involving temporo-parietal regions, that are elicited when subjects are asked to think about objects features regardless of the specific category (tools, nontools, animals) to which they belong. With the second fMRI experiment, we demonstrated that the ATL is more involved in semantic processing, while more posterior left temporal and temporo-parietal regions are involved in the lexical retrieval processes.

5.2 OBJECT DOMAINS AND FEATURE ACTIVATIONS

In the first fMRI experiment, we asked subjects to make same/different judgments on pairs of different categories of objects (animals, tools and nontools) with respect to two different semantic features (place or movement). Through the use of a property verification task, we tested conceptual knowledge of living and nonliving objects, driving subjects' attention specifically on the difference between attribute types rather than between the comparisons of object categories.

As previously described in Chapter 1, neuropsychological and functional studies reported evidences in favor of living thing-artifact dissociations. One account suggests a categorical organization of semantic information in the brain; that is, living things and artifacts might be so genuinely different that knowledge about the two domains is separately implemented (Caramazza & Shelton, 1998). An alternative theory argues that there are substantial differences in the types of semantic features that constitute the core meaning in instances of these two broad categories. The dissociation between living and nonliving things in this case derived from the fact that animals are distinguished primarily by their perceptual features (mainly visual) and artifacts are more often specified by functional/associative attributes, such as how objects are used and where they are found (Warrington & Shallice, 1984).

Besides this theoretical background, there is some clinical and functional evidence in literature that confirms the important role action knowledge plays in the processing of tools. In particular, it has already been established that there exists an "action network" which is more activated for tools rather for living items and may be involved in the processing of action and manipulability. This established network involves the left medial fusiform gyrus, the left MTG, and the left IPL. This neural circuit has been claimed to be "domain-specific", in the sense that the network can be defined with respect to the content of the object class that is processed, independently of the different types of information (form, motion) that are processed by different component of the circuits.

Another prominent account assumes a feature type organization of semantic memory (Martin & Chao, 2001). According to this account, object features are represented along sensory-motor cortical networks of the brain, while other regions in the left frontal and temporal lobe are responsible for the coding and the retrieval of these representations. All the attribute-specific components of semantic memory (color, sound or movement knowledge) should have their independent role and defined neuroanatomical location (Martin, 2007)

Category-Specific Activations

Driving subjects' attention to feature processing did not prevent us from obtaining category-specific activations. The processing of living things elicited activations in the ventral temporal lobe (lateral fusiform gyrus) and in the medial part of the occipital and temporal regions (Cappa et al., 1998; Chao et al., 1999; 2002; Noppeney et al., 2006; Perani, 1995). Ventral temporal areas, specifically in the medial part of the fusiform gyrus, were activated for the processing of tools, but not for the processing of animals. Large non-manipulable objects elicited independent activation in the fusiform and in the medial inferior part of the occipital region.

Feature Processing Activations

Differences found in the object domain activations were smaller than those related to different types of knowledge. Specifically the processing of place activated a network of left anterior temporal and inferior parietal regions (Cappa et al., 1998; Mummery et al., 1998)**,** whereas the processing of movement elicited a bilateral network of the inferior parietal, inferior frontal and posterior ITG (Boronat et al., 2005; Canessa et al., 2008; Kellenbach et al., 2003). Our findings are consistent with studies on semantic processing (Devlin et al, 2002; Mummery et al., 1998) and action knowledge investigation (Canessa et al. 2008; Chao & Martin, 2000; Mahon et al.,2007; Noppeney et al., 2006).

In our experiment the statistical analyses did not reveal any interaction between task and categories, suggesting the existence of specialized brain regions involved in the processing of semantic properties in which nor living neither nonliving things can be considered domain-specific. Indeed, within the action network we might have expected motor-based properties to be more important for the identification of manipulable man-made objects that are strongly associated with hand movements. At this regard we have to highlight the fact that in our experimental procedure we stressed movement feature in order to make it the most important one also for animal category. We might argue that the action knowledge does not depend strictly on the type of object that is processed. Rather, we suggest that the action network depends on the type of feature which is asked to be processes (thinking to movement rather than place). Obviously with tools category the processing of movement feature occurs more automatically. In fact, as suggested by our results the ROI analyses calculated in the IPL, an area known to be involved in the motor commands associated with tools use (Mahon et al., 2007), suggested a supremacy of this region for tools. Therefore, we cannot exclude that this feature remains the most important for tools recognition. Either way, we might argue that the brain organizes information according to features and attributes that might also be critical for distinguishing among objects that do not belong to the same category, but this again occurs more automatically for tools.

In conclusion, our data supports accounts that suggest a categorical organization of semantic information in the brain (Caramazza & Shelton, 1998), due to the fact that we obtained category-specific activation even if the cognitive task was focused on the difference between attribute types. But we want to emphasize that our findings are not completely incompatible with the functional-sensory assumptions (Warrington & Shallice, 1984). That is, tools might be more specified by action knowledge (functional associative property) rather than living things. Finally, our study showed that category-related responses are not restricted to a single region that responds maximally for that category; but that all categories activated a largely overlapping network elicited by the processing of specific features. From this data, we might conclude that object concepts are represented according to object features, rather than according to semantic categories corresponding to specific and anatomically segregated modules.

Neuropsychological Data

Our finding of category specificity for tools and animals in the ventral temporal cortex is in line with the neuropsychological evidence, which report the inability to identify visually presented objects after ventral stream damage. In addition, the supremacy for tools category found with the ROI analyses in the IPL is consistent with the impairments for object-directed grasping after damage to these posterior parietal regions.

The fact that we obtained distinct activations for different categories of objects fits with the dramatic deficit specific to object domains that have been reported in neuropsychological literature (Warrington & Shallice, 1984). Specifically, the category-specific activations that we found for animals can provide a neural basis for selective semantic deficits for animals following temporal lobe lesions; but at the same time we cannot yet claim a full understanding of the constraints under which concepts from the domain of living things do not produce regional activation in the anterior temporal pole in functional investigations.

Furthermore, our results seem to confirm the neuropsychological data and theories (Martin & Chao, 2001) that claim a feature type organization of semantic memory. These accounts argue that features are generally associated with a particular category but they are not limited to one. An example is given by the patients described by Marshall et al. (1996), who showed a deficit for living things coupled with low performance with concepts for manner of motion. This link between living things and manner of motion, which is a feature classically related to nonliving things (especially tools), was taken as a confirmation of the importance of perceptual features in both domains.

5.3 ANTERIOR TEMPORAL LOBE IN SEMANTIC AND LEXICAL RETRIEVAL

The vision of a celebrity’s face invokes a cascade of neural processes that integrate the visual perception of a face, the recognition of the person, perhaps an associated hit song or a movie plot, and, finally, the name. A mixture of “semantic” information, the type of encyclopedic information we use to identify the meaning and identity of objects, people, and words, comes to our consciousness, but exactly how the brain makes these connections remains largely obscure. Most of the studies agree on the idea that a diverse set of cognitive operations and a distributed neural network mediate the person recognition and identification process, but several questions about the structure and organization of the person identity system remain unresolved. Another topic of debate is the degree of hemispheric lateralization for faces and names, and the identification of shared and unique regions. Last, but not least, neuroimaging studies have primarily restricted their investigation on studying famous and non-famous face stimuli, but only a few studies have examined the direct contrast between famous faces and famous names.

In the current manuscript, we conducted a VBM study (Chapter 4, Part I) in which we correlated accuracy in recognizing, retrieving biographical information and naming famous faces, with voxelwise gray matter volumes in 64 patients with neurodegenerative diseases. We then collected data on normal controls (Chapter 4, Part II) with an fMRI experiment aimed at the identification of regions selectively associated with accessing name and biographic information. This idea arose from the consistency found in literature about the dissociation between lexical and conceptual knowledge retrieval (Bruce & Young, 1986; Valentine et al. 1996). Specifically, the failure to retrieve people's names, represented by the Tip-of the-Tongue phenomena, is a common experience in healthy individuals (Brown, 1991), suggesting that naming is independent from identification. In both aphasia and normal aging, difficulty in retrieving names can become pathological (anomia), but anomic patients can maintain the semantic knowledge of items they cannot name. Unlike object processing, faces were used in these experiments because they can be classified not only with respect to their physical properties (e.g. sex, race) but also according to their applicable semantic categorization (e.g. politician), and, furthermore, participants can have access to famous people's biographical details without being able to retrieve their proper name.

VBM Study on Patients

With the VBM study, we found that greater accuracy in retrieving semantic information about famous people corresponds to greater gray matter volume in the anterior temporal lobe, bilaterally; better performance in naming famous faces positively correlates with the amount of gray matter in the left temporal areas largely overlapping to the ones involved in the semantic task. This result is consistent with previous studies which state that semantic and lexical processing of faces mainly involves temporal regions (Gorno-Tempini & Price 2001b; Perani et al. 1999), as well as studies on groups of patients with deficit in naming who have left anterior temporal lobe damage (Damasio et al. 2004; Tranel 2006). However, behavioral results pointed out the fact that patients with semantic deficits showed lexical retrieval impairments as well, although the crucial role in the disease is played by the access to the semantic level rather than the lexical retrieval. Putting together all this evidence suggests that dissociation between semantic knowledge and naming is not a double dissociation because you cannot have patients who name and cannot recognize, and therefore with this type of experimental procedure the specific role of each region is still not clarified.

fMRI Experiment on Normal Subjects

In normal subjects, semantics and name retrieval usually occur simultaneously and automatically, thus making it difficult to dissociate in cognitive tasks (Gorno-Tempini et al., 2000). Therefore, we used a functional paradigm using famous faces that allowed us to disentangle between semantic biographical and proper name retrieval. Subjects had to perform a semantic (professions) same-different matching-task in the scanner and name the famous face individually in a post-scanning behavioral test. This permitted us to disentangle regions involved in high-level visual processing specific to faces, semantic and lexical retrieval processes.

Specifically, for the analyses on lexical retrieval we compared the BOLD response during trials in which celebrities could be correctly identified and named to trials in which faces were correctly identified without being named. Consistent with previous studies, we found that the visual processing of faces mainly involved areas in parts of the fusiform and occipital cortex, while both ATL regions were crucial for processing of semantic information, regardless of naming ability. The fact that the both hemispheres play an important role in retrieving person-specific semantics is information previously obtained also by our VBM study, with the only important difference being that in the correlations study it was impossible to know whether the left ATL activations were responsible for the naming or the semantic retrieval. Whereas with the fMRI study we concluded that covert naming modulated activation in more posterior parts of the left temporal lobe and TPJ.

In conclusion, the evidence from the first experiment reported in this thesis demonstrated that distinct regions activated by action knowledge are elicited by the processing of nonliving and living categories as well, indicating that the action network derived from the processing of movement feature rather than the processing of a specific category (tools, nontools, animals). The evidence of the second study demonstrated that bilateral ATL is preferentially involved in retrieving semantic information while most posterior temporal and parietal regions are involved in lexical retrieval. We might therefore speculate a cascade of processes in the temporal lobe network, starting with semantic integration in the ATL, and leading further to the activation of lexical representations in the posterior portion of the MTG and phonological assembly in the posterior superior and TPJ.

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APPENDICES

APPENDIX A – Stimuli used in the first fMRI Experiment (Chapter 3)

Table 1: List of all object pairs shown during the scanning session

objects		**category**	**same/different**
left picture	**right picture**		
dog	zebra	animal	same movement/different place
elephant	panda	animal	same movement/different place
kangaroo	frog	animal	same movement/different place
beaver	dromedary	animal	same movement/different place
horse	tiger	animal	same movement/different place
eel	cobra	animal	same movement/different place
boar	pig	animal	same movement/different place
parrot	pigeon	animal	same movement/different place
hen	ostrich	animal	same movement/different place
cat	cheetah	animal	same movement/different place
cat	lion	animal	same movement/different place
parrot	eagle	animal	same movement/different place
toucan	gull	animal	same movement/different place
reindeer	rhino	animal	same movement/different place
owl	pigeon	animal	same movement/different place
giraffe	donkey	animal	same movement/different place
moose	zebra	animal	same movement/different place
tiger	cow	animal	same movement/different place
dog	lion	animal	same movement/different place
penguin	hen	animal	same movement/different place
sheep	chick	animal	different movement/same place
octopus	starfish	animal	different movement/same place
lobster	octopus	animal	different movement/same place
crab	cuttlefish	animal	different movement/same place
hare	cockroach	animal	different movement/same place
donkey	rabbit	animal	different movement/same place
anaconda	panther	animal	different movement/same place
chimpanzee	toucan	animal	different movement/same place
deer	owl	animal	different movement/same place
mussel	crab	animal	different movement/same place
seahorse	starfish	animal	different movement/same place
owl	fox	animal	different movement/same place
duck	frog	animal	different movement/same place
eagle	ibex	animal	different movement/same place
polar bear	penguin	animal	different movement/same place
crocodile	hippopotamus	animal	different movement/same place
jellyfish	shark	animal	different movement/same place

seahorse	sea urchin	animal	different movement/same place
sloth	parrot	animal	different movement/same place
camel	snake	animal	different movement/same place
hammer	small hammer	manipulable	same movement/different place
iron	plane	manipulable	same movement/different place
vice	meat chopper	manipulable	same movement/different place
eyebrow tweezers	pliers for food	manipulable	same movement/different place
mouse	sponge	manipulable	same movement/different place
watering can	teapot	manipulable	same movement/different place
hammer	gavel	manipulable	same movement/different place
scissors	shears	manipulable	same movement/different place
carpet beater	racket	manipulable	same movement/different place
meat chopper	axe	manipulable	same movement/different place
knife	saw	manipulable	same movement/different place
meat chopper	gavel	manipulable	same movement/different place
landing net	skimmer	manipulable	same movement/different place
stick	club	manipulable	same movement/different place
trowel	spatula for cakes	manipulable	same movement/different place
rake	scrub brush	manipulable	same movement/different place
meat chopper	rubber stamp	manipulable	same movement/different place
grater	wire brush	manipulable	same movement/different place
stitcher	nutcrecker	manipulable	same movement/different place
stitcher	pliers	manipulable	same movement/different place
window washer	spray	manipulable	different movement/same place
phone	pen	manipulable	different movement/same place
lawnmower	shears	manipulable	different movement/same place
pliers	hammer	manipulable	different movement/same place
toothbrush	soap dispenser	manipulable	different movement/same place
paddle	fishing rod	manipulable	different movement/same place
stitcher	rubber stamp	manipulable	different movement/same place
nutcrecker	skimmer	manipulable	different movement/same place
ladle	meat chopper	manipulable	different movement/same place
eyebrow tweezers	nail file	manipulable	different movement/same place
anchor	rudder	manipulable	different movement/same place
watering can	shears	manipulable	different movement/same place
nutcrecker	centrifuge	manipulable	different movement/same place
supermarket cart	turnstile	manipulable	different movement/same place
wheelbarrow	watering can	manipulable	different movement/same place
scissors	hairdryer	manipulable	different movement/same place
spoon	knife	manipulable	different movement/same place
keyboard	ink rubber	manipulable	different movement/same place
brush	shaver	manipulable	different movement/same place
fork	pepper-grinder	manipulable	different movement/same place
windmill	ceiling fan	non manipulable	same movement/different place
ceiling fan	panoramic wheel	non manipulable	same movement/different place

ambulance	tank	non manipulable	same movement/different place
drawbridge	truck	non manipulable	same movement/different place
bumper car	quad	non manipulable	same movement/different place
windmill	fan	non manipulable	same movement/different place
forklift	freight elevator	non manipulable	same movement/different place
roulette	record player	non manipulable	same movement/different place
water wheel	windmill	non manipulable	same movement/different place
train	coach	non manipulable	same movement/different place
washing-machine	cement mixer	non manipulable	same movement/different place
tractor	jeep	non manipulable	same movement/different place
bell	perpetuum-mobile	non manipulable	same movement/different place
top	disco ball	non manipulable	same movement/different place
bell	pendulum	non manipulable	same movement/different place
motorsled	motorboat	non manipulable	same movement/different place
wheel	record player	non manipulable	same movement/different place
train	tractor	non manipulable	same movement/different place
washing-machine	cement mixer	non manipulable	same movement/different place
ceiling fan	roulette	non manipulable	same movement/different place
seesaw	swing	non manipulable	different movement/same place
cement mixer	forklift	non manipulable	different movement/same place
crane	scraper	non manipulable	different movement/same place
rocking horse	toy scooter	non manipulable	different movement/same place
escalator	turnstile	non manipulable	different movement/same place
hedge trimmer	lawn tractor	non manipulable	different movement/same place
panoramic wheel	bumper car	non manipulable	different movement/same place
cruise ship	buoy	non manipulable	different movement/same place
drill	flat roller	non manipulable	different movement/same place
swing	carousel horses	non manipulable	different movement/same place
gate	automatic gate	non manipulable	different movement/same place
jack in the box	carillon	non manipulable	different movement/same place
balloon	helicopter	non manipulable	different movement/same place
fan	rocking chair	non manipulable	different movement/same place
wall clock	office chair	non manipulable	different movement/same place
bumper car	carousel horses	non manipulable	different movement/same place
fighter plane	montgolfier	non manipulable	different movement/same place
shuttle	satellite	non manipulable	different movement/same place
tricycle	swing	non manipulable	different movement/same place
level crossing	train	non manipulable	different movement/same place

APPENDIX B – Stimuli used in the second fMRI (Chapter 4)

Supplementary Table 2: List of all famous face pairs shown during the scanning session			
full names		**category**	
left picture	**right picture**	**left picture**	**right picture**
Fiorello (Rosario Fiorello)	Sylvester Stallone	entertainment	entertainment
Richard Gere	Bud Spencer (Carlo Pedersoli)	entertainment	entertainment
Antonio Di Pietro	C. Azeglio Ciampi	politics	politics
Romano Prodi	Massimo D'Alema	politics	politics
Zinedine Zidan	Michael Schumacher	sports	sports
Carlo d'Inghilterra (Prince Charles)	Felipe di Spagna (Felipe de Borbon y Grecia)	royal family	royal family
Jacques Chirac	Silvio Berlusconi	politics	politics
Bruno Vespa	Michele Santoro	journalism	journalism
Albano Carrisi	Tom Cruise	entertainment	entertainment
Beppe Grillo (Giuseppe Grillo)	Luciano Pavarotti	entertainment	entertainment
Giulio Tremonti	Oscar Luigi Scalfaro	politics	politics
Alessandro Del Piero	Pelé (Ediso Arantes do Nascimento)	sports	sports
Christian De Sica	Pippo Baudo	entertainment	entertainment
Paolo Bonolis	Fonzie (Arthur Fonzarelli)	entertainment	entertainment
Adriano Celentano	John Travolta	entertainment	entertainment
Bettino Craxi	Fidel Castro	politics	politics
Ignazio La Russa	Vladimir Putin	politics	politics
Piero Fassino	George W.Bush	politics	politics
Dalai Lama	Padre Pio	clergy	clergy
Woody Allen	Roberto Benigni	entertainment	entertainment
Elvis Presley	Mike Bongiorno (MichaelBongiorno)	entertainment	entertainment
Walter Veltroni	Michail Gorbaciov	politics	politics
Nicolas Sarkozy	Nelson Mandela	politics	politics
Roberto Baggio	Alberto Tomba	sports	sports
Piero Angela	Enzo Biagi	journalism	journalism
Roberto Calderoli	Tony Blair	politics	politics
Angela Merkel	Condoleeza Rice	politics	politics
Orietta Berti	Milly Carlucci (CamillaCarlucci)	entertainment	entertainment
Maria De Filippi	Naomi Campbell	entertainment	entertainment
Livia Turco	Margaret Thatcher	politics	politics
Carolina di Monaco(Carolina Grimaldi)	Lady Diana	royal family	royal family
Monica Bellucci	Lorella Cuccarini	entertainment	entertainment
Alessandra Mussolini	Emma Bonino	politics	politics
Mike Bongiorno (MichaelBongiorno)	Elvis Presley	entertainment	entertainment

Vittorio Gassmann	Maurizio Costanzo	entertainment	entertainment
Francesco Rutelli	George W.Bush	politics	politics
Luca Cordero di Montezemolo	Gianni Agnelli (GiovanniAgnelli)	business	business
Paul Newman	Alberto Sordi	entertainment	entertainment
Silvio Berlusconi	Boris Eltsin	politics	politics
Gianfranco Fini	Bill Clinton	politics	politics
Giorgio Napolitano	Kofi Annan	politics	politics
Alberto Tomba	Michael Schumacher	sports	sports
Woody Allen	Albano Carrisi	entertainment	entertainment
Roberto Benigni	Sean Connery	entertainment	entertainment
Barak Obama	Umberto Bossi	politics	politics
Felipe di Spagna (Felipe de Borbon y Grecia)	Prince Ranieri (Ranier Grimaldi)	royal family	royal family
Enzo Biagi	Emilio Fede	journalism	journalism
Paolo Bonolis	Richard Gere	entertainment	entertainment
Francesco Cossiga	Tony Blair	politics	politics
Dalai Lama	Papa Giovanni Paolo II	clergy	clergy
Pelé (Ediso Arantes do Nascimento)	Francesco Totti	sports	sports
Pippo Baudo	Tom Cruise	entertainment	entertainment
Jacques Chirac	Giulio Tremonti	politics	politics
Ronald Reagan	Fidel Castro	politics	politics
Piero Fassino	Nicolas Sarkozy	politics	politics
Enrico Mentana	Bruno Vespa	journalism	journalism
Padre Pio	Papa Benedetto XVI	clergy	clergy
Valeria Marini	Gina Lollobrigida (Luigina Lollobrigida)	entertainment	entertainment
Hillary Clinton	Livia Turco	politics	politics
Marilyn Monrooe	Sofia Loren	entertainment	entertainment
Queen Elizabeth	Carolina di Monaco (Carolina Grimaldi)	royal family	royal family
Alessandra Mussolini	Margaret Thatcher	politics	politics
Raffaella Carrà	Monica Bellucci	entertainment	entertainment
Rosy Bindi (Maria Bindi)	Condoleeza Rice	politics	politics
Queen Elizabeth	Lady Diana (Diana Spencer)	royal family	royal family
Enrico Mentana	Giulio Tremonti	journalism	politics
Pippo Baudo	Silvio Berlusconi	entertainment	politics
Nicolas Sarkozy	Roberto Benigni	politics	entertainment
Alberto Sordi	Ronald Reagan	entertainment	politics
Piero Fassino	Fonzie (Arthur Fonzarelli)	politics	entertainment
Padre Pio	Sean Connery	clergy	entertainment
Bill Gates	Paolo Bonolis	business	entertainment
Tom Cruise	Michael Schumacher	entertainment	sports
Emilio Fede	Paul Newman	journalism	entertainment
Claudio Baglioni	Francesco Rutelli	entertainment	politics

Carlo d'Inghilterra (PrinceCharles)	Richard Gere	royal family	entertainment
Enzo Biagi	Umberto Bossi	journalism	politics
Fabrizio Del Noce	Bill Clinton	entertainment	politics
Tony Blair	Luca Cordero di Montezemolo	politics	business
Mike Bongiorno (MichaelBongiorno)	Papa Giovanni Paolo II	entertainment	clergy
Elvis Presley	Alberto Tomba	entertainment	sports
Jacques Chirac	Bruno Vespa	politics	journalism
Barak Obama	Pelé (Ediso Arantes do Nascimento)	politics	sports
Woody Allen	Francesco Cossiga	entertainment	politics
Vittorio Gassmann	Fidel Castro	entertainment	politics
Papa Benedetto XVI	Boris Eltsin	clergy	politics
Gianfranco Fini	Albano Carrisi	politics	entertainment
Giorgio Napolitano	Dalai Lama	politics	clergy
George W.Bush	Gianni Agnelli	politics	business
Hillary Clinton	Raffaella Carrà	politics	entertainment
Lilli Gruber (DietlindeGruber)	Monica Bellucci	journalism	entertainment
Valeria Marini	Alessandra Mussolini	entertainment	politics
Fiona May	Condoleeza Rice	sports	politics
Queen Elizabeth	Rosy Bindi (Maria Bindi)	royal family	politics
Margaret Thatcher	Rita Levi-Montalcini	politics	science
Gina Lollobrigida (Luigina Lollobrigida)	Livia Turco	entertainment	politics
Marilyn Monrooe	Lady Diana	entertainment	royal family
Walter Veltroni	Paolo Bonolis	politics	journalism
Michail Gorbaciov	Bruno Vespa	politics	journalism
Tom Cruise	Zinedine Zidane	entertainment	sports
Adriano Celentano	Antonio Di Pietro	entertainment	politics
Silvio Berlusconi	Roberto Benigni	politics	entertainment
Albano Carrisi	Romano Prodi	entertainment	politics
Christian De Sica	Carlo d'Inghilterra (Prince Charles)	entertainment	royal family
C. Azeglio Ciampi	Papa Giovanni Paolo II	politics	clergy
Luca Cordero di Montezemolo	Piero Fassino	business	politics
Woody Allen	Enzo Biagi	entertainment	journalism
Padre Pio	Fidel Castro	clergy	politics
John Travolta	Nicolas Sarkozy	entertainment	politics
Oscar Luigi Scalfaro	Mike Bongiorno (Michael Bongiorno)	politics	entertainment
Richard Gere	Tony Blair	entertainment	politics
Piero Angela	George W.Bush	journalism	politics
Fiorello (Rosario Fiorello)	Alberto Tomba	entertainment	sports

Roberto Calderoli	Michele Santoro	politics	journalism
Elvis Presley	Alessandro Del Piero	entertainment	sports
Jacques Chirac	Pippo Baudo	politics	entertainment
Bill Gates	Giulio Tremonti	business	politics
Dalai Lama	Bettino Craxi	clergy	politics
Sylvester Stallone	Vladimir Putin	entertainment	politics
Ignazio La Russa	Roberto Baggio	politics	sports
Nelson Mandela	Pelé (Ediso Arantes do Nascimento)	politics	sports
Michael Schumacher	Fonzie (Arthur Fonzarelli)	sports	entertainment
Carolina di Monaco(Carolina Grimaldi)	Monica Bellucci	royal family	entertainment
Angela Merkel	Mara Venier	politics	entertainment
Naomi Campbell	Condoleeza Rice	entertainment	politics
Orietta Berti	Livia Turco	entertainment	politics
Maria De Filippi	Lady Diana	entertainment	royal family
Lorella Cuccarini	Federica Pellegrini	entertainment	sports
Milly Carlucci (CamillaCarlucci)	Alessandra Mussolini	entertainment	politics
Queen Elizabeth	Margaret Thatcher	royal family	politics

Note: For each picture pair, shown during the experiment, the proper names and the semantic categories are shown. The indicated semantic categories were used as a criterion to assemble matched and unmatched famous faces pairs.